Clinical Trial Protocol

	Document Number:	**c33919902-05**
EudraCT No. **EU Trial No.**	2020-004527-16	
BI Trial No.	1425-0003	
BI Investigational Medicinal Product(s)	BI 706321	
Title	A Phase IIa, randomised, double-blind, placebo-controlled trial to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BI 706321 orally administered for 12 weeks in patients with Crohn`s Disease (CD) receiving ustekinumab induction treatment	
Lay Title	A study to test whether BI 706321 combined with ustekinumab helps people with Crohn’s Disease	
Clinical Phase	IIa	
Clinical Trial Leader	[redacted] Phone: + Fax: + Email:	
Coordinating Investigator	[redacted] Phone: Email:	
Status	Final Protocol	
Version and Date:	**Version: 5.0**	**Date: 04 Aug 2023**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim Pharma GmbH & Co. KG
Protocol date	26 Apr 2021
Revision date	27 Jul 2023
BI trial number	1425-0003
Title of trial	A Phase IIa, randomised, double-blind, placebo-controlled trial to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BI 706321 orally administered for 12 weeks in patients with Crohn's Disease (CD) receiving ustekinumab induction treatment
Coordinating Investigator	[redacted] Phone: [redacted] Email: [redacted]
Trial site(s)	Multi-center trial
Clinical phase	IIa
Trial rationale	Crohn's disease (CD) is characterized by transmural inflammation with ulcerative lesions affecting any site within the gastrointestinal tract, with most frequent involvement of the terminal ileum, often combined with inflammation in the colon. CD incidence and prevalence have been rising in all ethnic groups, the unmet medical need in patients with moderate to severe CD is the highest. The modest efficacy of the current drugs which address different components of the dysregulated inflammatory response in patients with CD suggests that multiple pathologic pathways need to be targeted in tandem to make major progress in treatment of this often severe and disabling disease. Combination treatments of established anti-inflammatory drugs with new medicines with a novel and differentiated mode of action might offer greater efficacy, in particular if such a combination partner would be orally available, safe and tolerable. BI 706321 may be such a candidate drug.
Trial objective(s)	The main objectives of this trial are to investigate a first signal of efficacy, safety and tolerability of BI 706321 in combination with ustekinumab treatment compared to placebo with ustekinumab treatment in patients with moderately to severely active CD at 12 weeks. The primary objective is to estimate the difference in change from baseline in Simple Endoscopic Score for Crohn's disease (SES-CD) after 12 weeks. The primary treatment comparison will be between treatment groups while on treatment during the 12 week induction period.

Trial endpoints	Primary endpoint Absolute change from baseline in Simple Endoscopic Score for Crohn's disease (SES-CD) at week 12. Secondary endpoints • Percent change in SES-CD from baseline at Week 12 • Endoscopic response (defined as >50% SES-CD reduction from baseline, or for an induction baseline SES-CD of 4, at least a 2 point reduction from induction baseline)) at Week 12 • Endoscopic response (defined as >50% SES-CD reduction from baseline, or for an induction baseline SES-CD of 4, at least a 2 point reduction from induction baseline)) at Week 48 • Endoscopic remission (defined as SES-CD score of ≤2) at week 12 • Endoscopic remission (defined as SES-CD score of ≤2) at week 48. • Biological remission, defined as C-reactive protein (CRP) < 5 mg/L and faecal calprotectin (FCP) < 250 ug/g at week 12 • Biological remission, defined as CRP < 5 mg/L and FCP < 250 ug/g at week 48 • Clinical remission at week 12, defined as a Crohn's Disease Activity Index (CDAI) score of <150 • Clinical remission at week 48, defined as a CDAI score of <150 • Clinical response at week 12, defined by a CDAI reduction from baseline of at least 100 points, or a CDAI score of <150 • Number of patients with treatment-emergent adverse event (TEAE) through end of treatment (EoT) and the residual effect period (REP) (i.e. through Visit 9)
Trial design	Multicentre, randomised, parallel, double-blind (patient, investigator), placebo-controlled trial with a 12 week BI 706321 treatment period in combination with a backbone ustekinumab induction regime
Total number of patients randomised	50 (*up to 76 – if applicable, ref to Section 7.2.7*)
Number of patients on each treatment	25 (*up to 38 – if applicable, ref to Section 7.2.7*)
Diagnosis	Crohn`s disease
Main in- and exclusion criteria	Key inclusion criteria: • Male or female patients. • ≥ 18 – ≤ 75 years, at date of signing informed consent.

	• Diagnosis of CD for at least 3 months prior to Visit 1, as confirmed at any time in the past by endoscopy and/OR radiology, and supported by histology. • Elevated CRP (≥ 5 mg/L) OR elevated fecal calprotectin (≥ 250 µg/g) • Symptomatic CD defined as CDAI ≥ 150 • Presence of mucosal ulcers in at least one segment of the ileum or colon and a SES-CD score ≥ 7 (for patients with isolated ileitis ≥4). • Patients who are experienced to at least 1 tumor necrosis factor (TNF) antagonist at a dose approved for CD. Patients may have stopped TNF antagonist treatment due to primary or secondary non-responsiveness, intolerance, or for other reasons. • May be receiving a therapeutic dose of the following: o Oral 5-aminosalicylic acid (5-ASA) compounds must have been at a stable dose for at least 4 weeks prior to randomisation and must continue on this dose until week 12 and/or o Oral corticosteroids if indicated for treatment of CD must be at a prednisone equivalent dose of ≤ 20 mg/day, or ≤ 9 mg/day of budesonide, and have been at a stable dose for at least 2 weeks immediately prior to randomisation and must continue on this dose until week 12. and/or o Azathioprine (AZA), mercaptopurine (MP), 6-thioguanine (6-TG), or methotrexate (MTX), provided that dose has been stable for the 8 weeks immediately prior to randomisation and must continue on this dose until week 12. Key exclusion criteria: • Have any current or prior abscesses, unless they have been drained and treated at least 6 weeks prior to randomisation and are not anticipated to require surgery. Patients with active fistulas may be included if there is no anticipation of a need for surgery and there are currently no abscesses present based on investigator`s judgement. • Have complications of CD such as strictures, stenosis, short bowel syndrome, or any other manifestation that might require surgery, or could preclude the use of SES-CD/CDAI to assess response to therapy, or would possibly confound the evaluation of benefit from treatment with BI 706321 (based on investigator's judgement). • Patient with an inflammatory bowel disease (IBD) diagnosis other than CD.

	• Have had any kind of bowel resection or diversion within 4 months or any other intra-abdominal surgery within 3 months prior to Visit 1. Patients with current ileostomy, colostomy, or ileorectal anastomosis are excluded. • Treatment with: o any non-biologic medication for IBD (e.g. tacrolimus or mycophenolate mofetil, systemic corticosteroids), other than those allowed per inclusion criteria, within 30 days prior to randomisation o any biologic treatment with a TNF-alpha antagonist (adalimumab, infliximab, golimumab, certolizumab pegol) or vedolizumab (or a biosimilar of these drugs) within 4 weeks prior to randomisation. (If drug level testing for previously used biologic treatment confirms no detectable drug level before randomisation, patient can be enrolled despite not having completed 4 weeks from last treatment.) o any previous treatment with ustekinumab (or a biosimilar of this drug) o any previous treatment with an investigational (or subsequently approved) non-biologic/biologic drug for CD (including but not limited to JAK inhibitors [e.g. upadacitinib], S1P modulators, interleukin (IL)-23 inhibitors [e.g. risankizumab], anti-integrins). o any investigational drug for an indication other than CD during the course of the actual study and within 30 days or 5 half-lives (whichever is longer) prior to randomisation. o any prior exposure to rituximab within 1 year prior to randomisation. • Increased risk of infectious complications (e.g. recent pyogenic infection, any congenital or acquired immunodeficiency (e.g. human immunodeficiency virus [HIV]), past organ or stem cell transplantation (with exception of a corneal transplant > 12 weeks prior to screening) or have ever received stem cell therapy (e.g., Prochymal). Prior treatment with a somatic cell therapy product (e.g. Alofisel) is not excluded, provided it was administered > 8 weeks prior to randomisation. • Live or attenuated vaccination within 4 weeks prior to randomisation. • Presence of clinically significant acute or chronic infections not otherwise listed, including viral hepatitis, COVID-19, or others based on investigator's judgement.

	• Pathological safety lab parameters (one retesting is allowed): o Haemoglobin < 8.5 g/dL o White blood cell (WBCs) < 3,500 cells/mm3 o Neutrophils < 1,500 cells/mm3 o Platelets < 100,000 /mm3 o Estimated glomerular filtration rate (eGFR) ≤ 60 ml/(min*1,73 m²) o Aspartate aminotransferase (AST) OR Alanine aminotransferase (ALT) > 2 times the Upper Level of Normal (ULN). Total bilirubin > 2 x ULN with ratio of direct/indirect >1 (patients with Gilbert's syndrome are not excluded), o Troponin: > ULN • A marked baseline prolongation of QT/QTc interval (such as QTcF intervals that are greater than 450 ms for men, 470 ms for female) or any other relevant electrocardiogram (ECG) finding at screening. Both have to be confirmed by repeated ECG recording.
Test product(s)	BI 706321
dose	8 mg daily
mode of administration	oral
Comparator product(s)	Placebo matching BI 706321
dose	Not applicable
mode of administration	oral
Duration of treatment	12 weeks
Criteria for Pharmacokinetics:	Population pharmacokinetics from plasma concentrations of BI 706321 sampled during the treatment period
Statistical methods	Primary endpoint analysis: Restricted maximum likelihood estimation based ANCOVA model will be used to obtain adjusted means for the treatment effect. This model will include treatment and baseline corticosteroid use as discrete fixed effects along with baseline SES-CD score as a continuous covariate. The primary treatment comparisons will be the contrast between the two treatments at 12 weeks.

FLOW CHART

Trial Periods	**Screening[H]**	**Induction Treatment [H]**							**Follow-up period [H]**							
Visit	**1[G,U]**	**2***	**3[P]**	**4**	**5**	**6**	**7**	**8 EOT** End of Treatment/Early EoT[R]	**8A**	**8B**	**8C**	**9[R]**	**10**	**11**	**12**	**13 EOS** End of study/early EoS
Days	**-28 to -1**	**1[E]**	**4**	**8**	**15**	**29**	**57**	**85**	**86**	**89**	**91**	**113**	**169**	**224**	**281**	**336**
Weeks		**0**	**0**	**1**	**2**	**4**	**8**	**12**	**12**			**16**	**24**	**32**	**40**	**48**
Time window for visits (days)		±0	+1	±2	±2	±2	±5	±5	+1	±1	±1	±5	±7	±7	±7	±7
Fasted (f) / not fasted (nf)[T]	**nf**	**f**	**nf**	**nf**	**nf**	**f**	**f**	**f**	**nf**	**nf**	**nf**	**f**	**nf**	**nf**	**nf**	**nf**
Informed consent[A]	X															
Demographics, medical history, baseline conditions	X															
Review of in-/-exclusion criteria	X	X														
Physical examination (full)	X	X		X		X	X	X				X				X
Physical examination (symptomatic-driven)			X		X				X	X	X		X	X	X	
Vital signs[D, S] (incl. height at Visit 1 only)	X	X	X	X	X	X	X	X				X		X		X
Laboratory tests (blood/urine/stool)[C]	X	X	X	X	X	X	X	X				X	X	X	X	X
Infection testing[F]	X															
Infection testing for SARS-CoV-2 in case of symptoms and if locally required before trial procedures (*locally done*)		X[Z]														
Test previously used biologic treatment (*if applicable*)[Y]	X															
Pregnancy Test[M]	X	X				X	X	X				X				
DNA Sampling (Blood, pre-specified)[I]		X														

Trial Periods	**Screening[H]**	**Induction Treatment [H]**							**Follow-up period [H]**							
Visit	**1[G,U]**	**2***	**3[P]**	**4**	**5**	**6**	**7**	**8 EOT** End of Treatment/Early EoT[R]	**8A**	**8 B**	**8C**	**9[R]**	**10**	**11**	**12**	**13 EOS** End of study/early EoS
Days	**-28 to -1**	**1[E]**	**4**	**8**	**15**	**29**	**57**	**85**	**86**	**89**	**91**	**113**	**169**	**224**	**281**	**336**
Weeks		**0**	**0**	**1**	**2**	**4**	**8**	**12**	**12**			**16**	**24**	**32**	**40**	**48**
Time window for visits (days)		±0	+1	±2	±2	±2	± 5	±5	+1	±1	±1	±5	±7	±7	±7	±7
Fasted (f) / not fasted (nf)[T]	**nf**	**f**	**nf**	**nf**	**nf**	**f**	**f**	**f**	**nf**	**nf**	**nf**	**f**	**nf**	**nf**	**nf**	**nf**
[redacted]																
12-lead ECG (central reading)[D]	X	X[V]		X	X	X[V]	X	X[V]				X				
Ileocolonoscopy for SES-CD (and CDEIS) assessment (centrally read), incl. biopsies (Ribonucleic acid (RNA) in colonic and/ileal tissues, IHC, histology)[R]	X[G]							X *(at V8 or V8A plus one day, i.e. at the latest 2 days after last IMP intake)*								X
Crohn's Disease Activity Index (CDAI, Diary)[Q]	X	X		X	X	X	X	X				X	X	X	X	X
Body weight (for CDAI)	X	X		X	X	X	X	X				X	X	X	X	X
IBDQ		X					X	X				X	X	X	X	X
Dispense Patient Diary[K]	X															
Collect & Review Patient Diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Contact IRT	X	X		X	X	X	X	X								

Trial Periods	**Screening[H]**	**Induction Treatment [H]**							**Follow-up period [H]**							
Visit	**1[G,U]**	**2***	**3[P]**	**4**	**5**	**6**	**7**	**8 EOT** End of Treatment/Early EoT[R]	**8A**	**8 B**	**8C**	**9[R]**	**10**	**11**	**12**	**13 EOS** End of study/early EoS
Days	**-28 to -1**	**1[E]**	**4**	**8**	**15**	**29**	**57**	**85**	**86**	**89**	**91**	**113**	**169**	**224**	**281**	**336**
Weeks		**0**	**0**	**1**	**2**	**4**	**8**	**12**	**12**			**16**	**24**	**32**	**40**	**48**
Time window for visits (days)		±0	+1	±2	±2	±2	± 5	±5	+1	±1	±1	±5	±7	±7	±7	±7
Fasted (f) / not fasted (nf)[T]	**nf**	**f**	**nf**	**nf**	**nf**	**f**	**f**	**f**	**nf**	**nf**	**nf**	**f**	**nf**	**nf**	**nf**	**nf**
Intake of trial drug at the site		X[O]		X	X	X	X	X								
Dispense trial drugs for intake at home		X		X	X	X	X									
Drug accountability check			X	X	X	X	X	X								
Administer ustekinumab i.v.[B]		X[O]														
Administer ustekinumab s.c. [B]							X					X	X	X	X	[W]
Ustekinumab serum level[N]		X				X	X	X					X			X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event (AE)[X]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Completion of patient participation																X

SES-CD: Simple Endoscopic Score for Crohn's Disease; CDEIS: Crohn's Disease Endoscopic Index of Severity

* Day of Randomisation / Day of first intake of randomised medication

A Subject must be informed and written informed consent obtained prior to starting any screening procedures. For the biobanking samples a separate informed consent (*optional*) will be taken.

B Treatment with ustekinumab in the trial will follow current version of SmPC/US PI and cost will be covered by Sponsor. For more information refer to Section 3.1.
The ustekinumab intravenous (i.v.) administration has to be done at the site under the supervision of a trained site personal.
The ustekinumab s.c. administration should be done during the visit at the site.

C Laboratory tests include clinical chemistry, haematology, coagulation, and urinalysis as well as CRP, fecal calprotectin and fecal entric pathogens, and will be performed centrally. Patients who have a laboratory test value that makes their participation uncertain may have the test repeated once to determine eligibility; however, the result must be available prior to Visit 2. See Section 5.2.3 for a complete list and timepoints of testing required.

D Assessment of vital signs (ref. Section 5.2.2) and ECG measurements should always precede blood sampling and drug administration. All ECGs will be evaluated by the investigator or a designee.

E During the observation period patients are receiving ustekinumab treatment alone and in an open-label fashion.

F Infection testing includes TB screening, hepatitis B, hepatitis C, and HIV assessments, as well as SARS-CoV-2

G Screening procedures have to be performed within 28 days before randomisation and can be done at different days. The here described order should be followed: first all non-ileo-colonoscopy / non-CDAI assessments have to be performed. Only if these assessments show that patients are eligible, the CDAI eligibility has to be checked (i.e. investigator is defining the 7 days for calculation of the CDAI score). Only patients who also meet the CDAI eligibility criterion have to undergo ileo-colonoscpy in a last step.
Screening period could be extenended for additional 21 days, if this is required due to logistical reasons (e.g. delay in lab assessment) and approved by sponsor.

H In the follow-up period, if the decision is made for a patient to permanently discontinue ustekinumab treatment early but between V8 and V9, V9 should be performed as the last trial visit at least 16 days after the last BI 706321/placebo dose. In the follow-up period, if a patient permanently discontinues ustekinumab treatment early but after V9, early EoS visit should be performed within 14 days after decision has been made to discontinue ustekinumab treatment. Over-night stays within the site-unit due to logistical reasons are allowed and not considered as SAE (*applicable for the whole trial*).

I Pre-specified PGx sample is mandatory.

J PK sampling timepoints at each visit are given in Table 10.1: 1. The 6-hours sample of Visit 2 can also be taken as late as appr. 24 h after first dosing at the next day to allow flexibility.

K The patient has to document the date and time of the Investigational Medicinal Product (IMP) intake at home in the patient medication diary.

L Fecal studies: Stool samples will be aliquotted for miRNA and microbiome analysis, exploratory protein biomarkers analysis and for biobanking. This exploratory protein biomarker analysis will only be performed at Visit 2, Visit 6, Visit 8 and Visit 13. Stool samples for Fecal calprotectin and Fecal lactoferrin analysis will be collected at V1, V2, V6, V7, V8, V9, V10, V11, V12 and V13. Ref. to Section 5.2.3. Stool sampling can be done any time during a visit or 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.

M Pregnancy test: Serum pregnancy test (performed at screening). Urine pregnancy tests will be performed at all other visits indicated. Urine pregnancy testing should be done prior to study drug administration. Study drug should only be administered in case of a negative test result. In case of a positive urine pregnancy test, a serum pregnancy test will be done.

N Done as part of clinical monitoring with a provided test kit. At Visit 2 pre-dose to assess for pre-existing anti-drug antibody.

O Trial drug (BI 706321 or Placebo) and ustekinumab are recommended to be given simultaneously.

P Visit at the site or done at patient`s home (by site personnel at patient´s home), as appropriate.

Q The patient will have to complete the CDAI symptom score in a Diary every day (i.e. compliance reason) after dispensing the Diary to the patient at V1. The 7 days preceding a visit (scheduled and unscheduled) will be taken for the CDAI calculation. The score will be displayed to the investigator to judge treatment efficacy. For details see Section 5.1.2 and Appendix 10.5.

At screening: After all non-ileo-colonoscopy assessments have shown that a patient is eligible, the investigator is defining 7 days for the CDAI assessment. After the CDAI eligibility is confirmed the patient will undergo the ileo-colonoscopy.

Visit 8/Visit 13: the day before the ileo-colonoscopy assessment will not be used for the CDAI calculation.

R Patients who discontinue BI 706321/placebo trial treatment and/or ustekinumab treatment before completing 10 weeks of treatment in the induction treatment period should undergo the procedures of the early end of treatment (EoT) visit within 14 days after the last BI 706321/placebo dose and Visit 9 (4 weeks after early EoT visit). If Visit 9 is performed as the last visit in the trial, ustekinumab should not be administered at this Visit 9 as the part of the trial. Further CD treatment has to be defined by the investigator. If a patient discontinues BI 706321/placebo trial treatment after completing 10 weeks of treatment in the induction treatment period (early EoT visit has to be performed) and if it is medically appropriate to continue treatment with ustekinumab, the patient may remain in the trial and follow the visit schedule and perform end of study (EoS) visit as planned. Ref. to Section 6.2.2 for more information about ileo-colonoscopy assessment in case patients discontinue early. After the early EoT visit patients should undergo only Visit 9 for early completion of the trial (not EoS visit).

S Body temperature will only be assessed until Visit 9 (i.e. V 1 – V 9).

T "Fasted" is defined as patients are not allowed to take any food for at least 6 hours prior to the visit procedures and until the blood samples are taken. At visits where fasting is not specifically required, it is acceptable for patients to be administered trial medication either fasted or non-fasted (*as preferred by the patient*). Fasting is not required for post-dose PK sampling.

U If a rescreening will be performed the ileocolonoscopy has only to be repeated if the time between the original screening ileocolonoscopy and randomisation is >6 weeks (time intervals slightly longer than 6 weeks have to be discussed with the Sponsor and can be approved if medically appropriate). If the reason for the screen failure was an enteric infection (including SARS-CoV-2 infections, only if GI symptoms were present due to the SARS-CoV-2 infection) the ileo-colonoscopy must be repeated. Depending on the reason, rescreening is allowed up to two times.
If at screening, PCR test for SARS-CoV-2 is positive and patient is asymptomatic, re-test SARS-COV-2 PCR test is allowed (up to 4 times) to confirm patient's eligibility before ileocolonoscopy and/or visit 2. If re-test SARS-COV-2 PCR test is negative, patient must meet all other eligibility criteria according to the CTP before patient is randomized at Visit 2. Already performed screening assessment do not need to be repeated.

V An additional ECG assessment has to be performed:
- for Visit 2: before the 3-hours PK blood sample is taken (i.e. two assessments – pre-dose and before the 3-hours PK sample).
- for Visit 6 and Visit 8: before the 6-hours PK blood sample is taken (i.e. two assessments – pre-dose and before the 6-hours PK sample).

W Further CD treatment has to be defined by the investigator. End of treatment with ustekinumab in the trial is V12.

X After the (early) 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 of and only via the BI`s SAE form, please see Section.5.2.6.2.1.

Y Patients are not allowed to get any biologic treatment with a TNF-alpha antagonist (adalimumab, infliximab, golimumab, certolizumab) or vedolizumab (or a biosimilar of these drugs) within 4 weeks prior to randomisation. If drug level testing for previously used biologic treatment confirms no detectable drug level before randomisation, patient can be enrolled despite not having completed 4 week from last treatment.

Z Patients tested positive for SARS-CoV-2 during the trial and who are asymptomatic can continue with the clinical trial as described in the CTP, based on Investigator's judgment. If subject develops any symptoms of SARS-CoV-2 infection, the discontinuation rules apply according to Section 3.3.4.1.

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ABBREVIATIONS

6-TG	6-thioguanine
ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AP	Abdominal Pain
ASA	Aminosalicylic Acid
AST	Aspartate Aminotransferase
AUC	Area under the Curve
AxMP	Auxiliary Medicinal Products
AZA	Azathioprine
BA	Bioavailability
BCG	Bacillus Calmette-Guerin
BI	Boehringer Ingelheim
CD	Crohn`s Disease
CDAI	Crohn’s Disease Activity Index
CDEIS	Crohn’s Disease Endoscopic Index of Severity
COVID-19	Coronavirus of 2019
C_{max}	Maximum Plasma Concentration
$C_{max,ss}$	Maximum Plasma Concentration at Steady State
C_{min}	Minimum Plasma Concentration
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP3A	Cytochrome P450 3A

DDI	Drug-Drug Interactions
DILI	Drug Induced Liver Injury
DMETTM	Drug Metabolism Enzymes and Transporters
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
eGFR	Estimated Glomerular Filtration Rate
EoS	End of Study (corresponds with End of Trial)
EoT	End of Treatment
ePRO	Electronic Patient Reported Outcome
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FCP	Faecal Calprotectin
FDA	Food and Drug Administration
FE	Food Effect
GCP	Good Clinical Practice
GHAs	Global Histologic Disease Activity Score
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
gRT	global Randomisation Team
HIV	Human Immunodeficiency Virus
IB	Investigator’s Brochure
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IGRA	Interferon Gamma Release Assay
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational Medicinal Product
IRB	Institutional Review Board

IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	intention-to-treat
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
i.v.	Intravenous
JAK	Janos Kinase
LPLT	Last patient last treatment
LOCF	Last observation carried forward
MAPK	Mitogen-Activated Protein Kinase
MDP	Muramyl Dipeptide
MedDRA	Medical Dictionary for Drug Regulatory Activities
MP	Mercaptopurine
MRD	Multiple Rising Dose
MTX	Methotrexate
NCF	Non-completers considered failure
nf	Not fasted
NIMP	Non-Investigational Medicinal Product
NOAEL	No-Observed-Adverse-Effect Level
NOD	Nucleotide Oligomerization Domain
NRI	Non Response Imputation
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamics
P-gP	P-glycoprotein
PK	Pharmacokinetics
p.o.	per os (oral)
PPD	Purified Protein Derivative
PROs	Patient Reported Outcomes
PRR	Pattern Recognition Receptors
q.d.	quaque die (once a day)
QT/QTc	Measurement representing the total time from ventricular depolarization to complete repolarization (uncorrected and corrected)
REP	Residual effect period

REML	Restricted maximum likelihood
RHI	Robarts histopathology index
RIPK2	Receptor-Interacting Protein Kinase-2
RNA	Ribonucleic Acid
RS	Randomised set
S1P	Sphingosine-1-phosphate receptor modulator
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus Type 2
s.c.	Subcutaneous
SES-CD	Simple Endoscopic Score for Crohn's disease
SF	Stool Frequency
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRD	Single Rising Dose
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Half life time
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
t_{max}	Timepoint of maximum plasma concentration
TMF	Trial Master File
TNFi	Tumor Necrosis Factor Inhibitor
TRUC	T-bet−/−RAG2−/−ulcerative colitis
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TST	Tuberculin Skin Test
ULN	Upper limit of normal
US PI	US Package Insert
WBC	White blood cell count
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

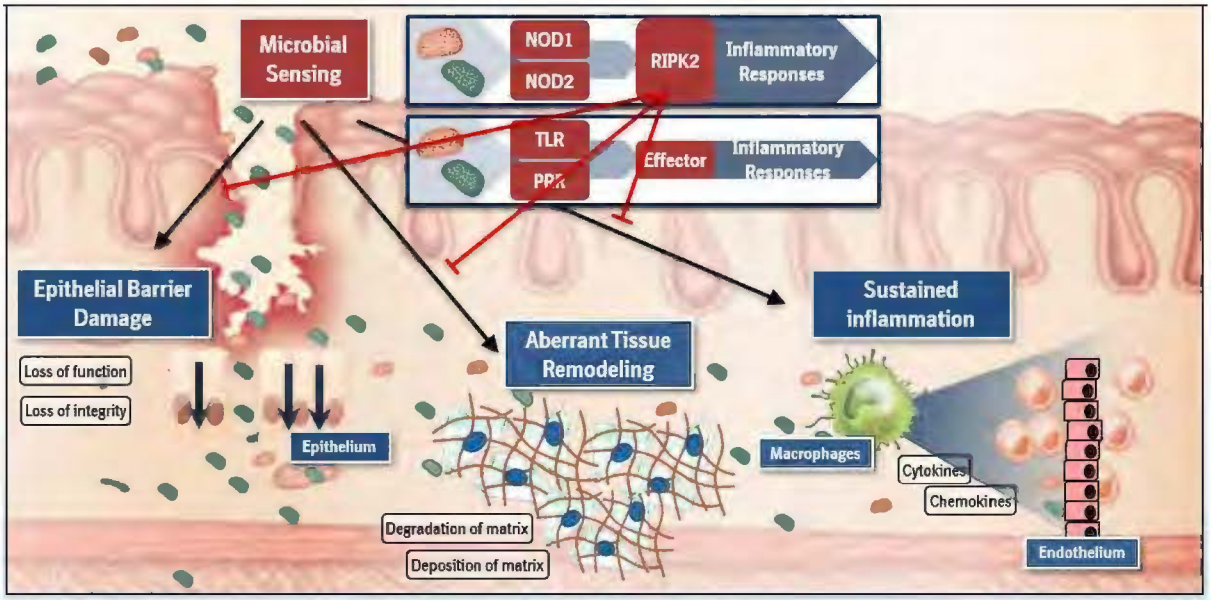
1.1 MEDICAL BACKGROUND

Crohn's disease (CD) is characterized by transmural inflammation with ulcerative lesions affecting any site within the gastrointestinal tract, with most frequent involvement of the terminal ileum, often combined with inflammation in the colon. CD incidence and prevalence have been rising in all ethnic groups; the recent incidence and prevalence have been reported to range from 7.9 to 20.2 and from 161 to 319 per 100,000, respectively [R13-2231]. CD typically follows a relapsing and remitting course, and causes substantial acute and long-term morbidity and increased mortality. Patients often develop local complications (for example (e.g.) fistulas, abscesses, strictures, or perforations), extra-intestinal manifestations (e.g. uveitis, arthritis, primary sclerosing cholangitis), or side effects of treatment, and may require major surgery. A recent review highlights the substantial direct and indirect costs associated with CD to patients and wider society [R18-2865]. Roughly a third of patients fall into each of the categories of mild, moderate, and severe disease.

Unmet need in CD is highest in patients with moderate to severe disease. Patients not responding to conventional therapy of glucocorticoids and immunomodulator agents (azathioprine (AZA) or mercaptopurine (MP) or methotrexate (MTX)), are treated with biologic tumor necrosis factor (TNF) α inhibitors (TNFi). However, treatment with a TNFi results in clinical remission in less than half of patients. Another 30-40% of patients receiving TNFi have only a limited response, or lose their response over time. Increasingly it has also been recognized that clinical response and more objective markers of inflammation are not always well-correlated in CD, and thus improvement in inflammation as documented by endoscopy is an emerging treatment goal. Real world evidence suggests that only about 25% of patients treated with TNFi have long term endoscopic remission. Additionally, there remain concerns over infection, lymphoma risks and melanoma with these agents. Additional biologic options (vedolizumab [an integrin antagonist] and ustekinumab [IL-12/23p19 inhibitor]) offer alternative treatment options for patients, but response rates to these agents do not exceed those associated with TNFi treatment. Furthermore, most trials suggest a lower efficacy of any compound in patients who previously failed TNFi treatment compared to patients who are TNFi naïve, probably reflecting that patients in this sub-population are more refractory. Medical treatment options for fistulizing and fibrotic disease remain limited. Thus, a substantial unmet need remains for agents with greater efficacy than current therapies, either as a stand-alone therapy or when added to existing therapies.

In CD, mucosal inflammation is driven by a disruption of the intestinal barrier in the context of a dysbiosis of the microbial flora, which leads to bacterial translocation into the bowel wall mucosa and submucosa followed by aberrant stimulation of immune and non-immune cells in the gut. Microbial stimulation of somatic cells is partially mediated by Nucleotide Oligomerization Domain (NOD) pattern recognition receptors through Receptor-Interacting Protein Kinase-2 (RIPK2) at the earliest stage in the development of the immuno-inflammatory cascade. RIPK2 inhibition is postulated to blunt the dominant NOD1/2-driven inflammatory response to the microbiome in the gut, while sparing other microbial sensing pathways to prevent broad immunosuppression.

NOD sensing and RIPK2 signaling amplifies pattern recognition receptors (PRR) induced NFkB/MAPK signalling and the NOD/RIPK2 pathway becomes the dominant PRR during chronic bacterial challenge.



NFκB, nuclear factor κB; **NOD**, nucleotide-binding oligomerisation domain-containing protein; **RIPK2**, receptor interacting serine/threonine-protein kinase 2; **PRR**, pattern recognition receptor; **TLR** toll-like receptor

Figure 1.1: 1 Therapeutic concept of BI 706321

RIPK2 inhibition will result in reduced levels of inflammatory cells and inflammatory mediators in intestinal tissue, in particular of the innate immune system, and improved epithelial barrier function, which is expected to lead to clinical and endoscopic response in CD. Oral medicines with a novel mode of action that include regulation of the complex interaction between microbiome and intestinal tissue, and have additional effects on epithelial barrier function would be particularly attractive for the current unmet need in CD, especially if they can be combined with current standard of care. Therefore, Boehringer Ingelheim (BI) is developing a RIPK2 inhibitor candidate, BI 706321.

1.2 DRUG PROFILE

1.2.1 BI 706321

Mode of action
BI 706321 is a potent and specific inhibitor of the human RIPK2 kinase.

Data from non-clinical studies
Relevant non-clinical pharmacology, Pharmacokinetics (PK), and toxicology study results are summarized below.

In vitro and ex vivo studies with BI 706321 have shown that it is effective at normalizing the induction of inflammation or inflammatory processes in several different types of disease relevant human primary cells and complex intestinal cellular systems. In vivo, RIPK2

inhibition was also demonstrated to significantly improve signs and symptoms of intestinal inflammation in the spontaneous *T-bet/Rag2* knockout (TRUC) mouse model of Inflammatory Bowel Disease (IBD).

The toxicity profile of BI 706321 has been assessed in safety pharmacology, genetic toxicity, embryo-fetal development, and repeat dose toxicity studies of up to 13-weeks in rat and monkey, respectively. RIPK2 is highly conserved across rat and cynomolgus monkey where sequences within the kinase domains are 95% and 97% identical to human, respectively.

The no-observed-adverse-effect level (NOAEL) in the 13-week monkey study was 8 mg/kg/day, corresponding to a steady state mean exposure of 988 nM maximum plasma concentration (C_{max}) and 6,060 nM•h AUC_{0-24h} (combined genders). These exposures are 28X (C_{max}) or 12X (AUC_{0-24h}) the exposure at the 8 mg daily dose in this trial.

The NOAEL in the 13-week rat study was 4 mg/kg/day in males and 1 mg/kg/day in females. The 4 mg/kg/day dose to male rats corresponded to a steady state mean exposure of 289 nM C_{max} and 2,250 nM•h AUC_{0-24h}, providing exposures 8X (C_{max}) or 4X (AUC_{0-24h}) the exposure at the 8 mg daily dose. The 1 mg/kg/day NOAEL in female rats corresponded to a steady state mean exposure of 47.5 nM C_{max} and 505 nM•h AUC_{0-24h}, providing 1.4X (C_{max}) or 1X (AUC_{0-24h}) the exposure at the 8 mg daily dose.

The NOAEL in the most sensitive species, rat, was defined by reversible ovarian finding of degeneration of the corpora lutea. Therefore, at clinically relevant BI 706321 exposures in women of child bearing potential, there is potential for effects to the ovary that may affect fertility. However, this finding is not clinically relevant in females who are not seeking to become pregnant. Considering that women of childbearing potential are required to use a highly effective method of contraception (see below) in BI 706321 clinical trials, the male NOAEL applies to both males and females using highly effective contraception. A human dose of 8 mg daily is 8X and 4X below current male rat NOAEL exposures for C_{max} and Area under the Curve (AUC), respectively.

There is risk for adverse effects to embryo-fetal development (embryolethality and fetotoxicity) at human exposures exceeding exposures at the NOAEL in rats, the most sensitive species (5 mg/kg/day to rats, corresponding to C_{max} of 184 nM and AUC_{0-24h} of 2,060 nM•h), which provide 5X and 4X human steady state exposure Cmax and AUC for an 8 mg dose once daily. Therefore, pregnant women should be excluded from clinical trials and a highly effective method of birth control should be utilized for women of childbearing potential.

BI 706321 is considered non-genotoxic. BI 706321 is not likely to be phototoxic at clinically relevant doses.

In summary, non-clinical BI 706321 safety data demonstrated an acceptable profile to support clinical trials in males and non-pregnant females of child bearing potential who are using highly effective methods of birth control.

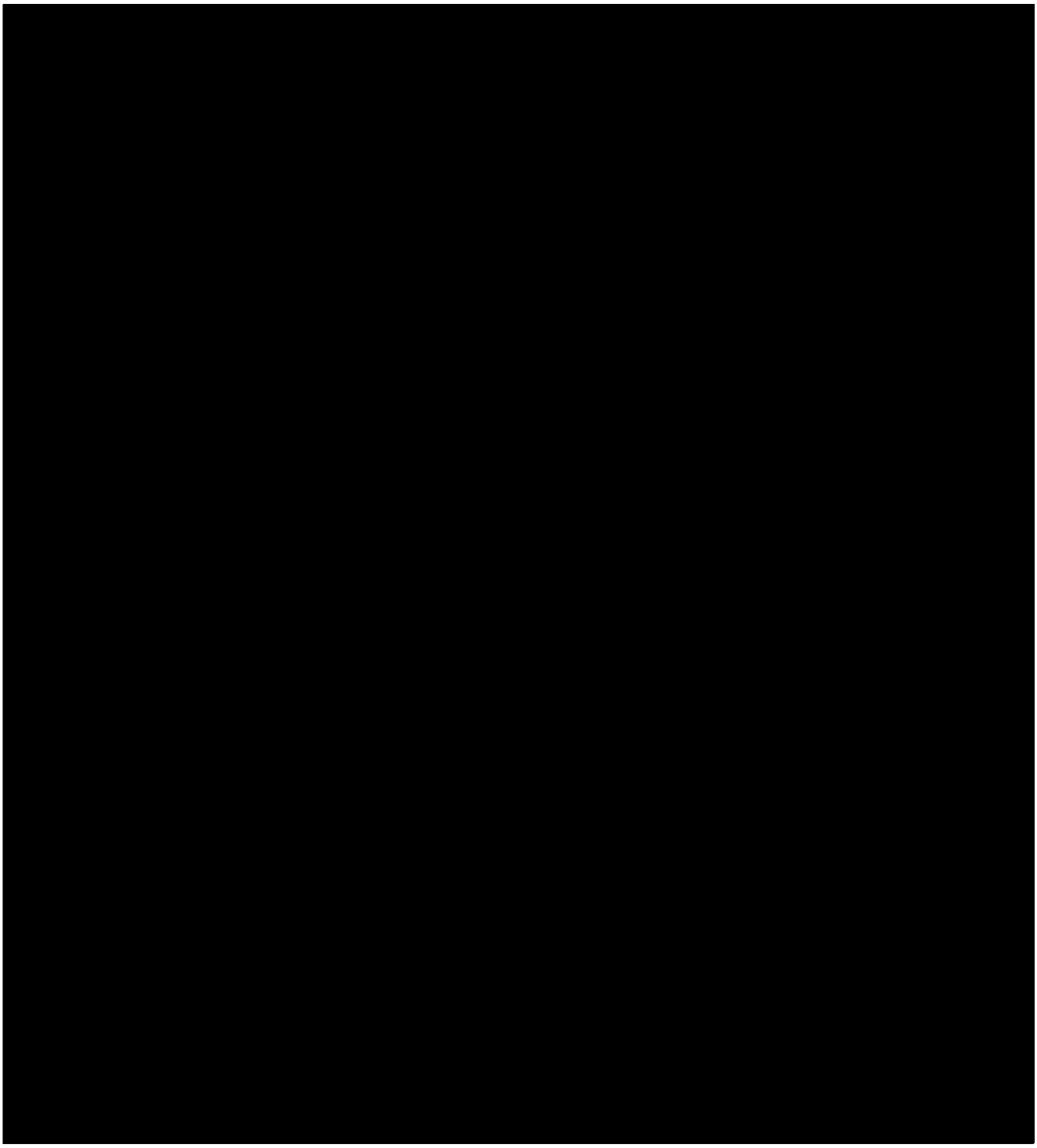
For full details on the nonclinical pharmacology, pharmacokinetics in animals and specific toxicology results refer to the current IB [c26475781], and Section 1.4.2.

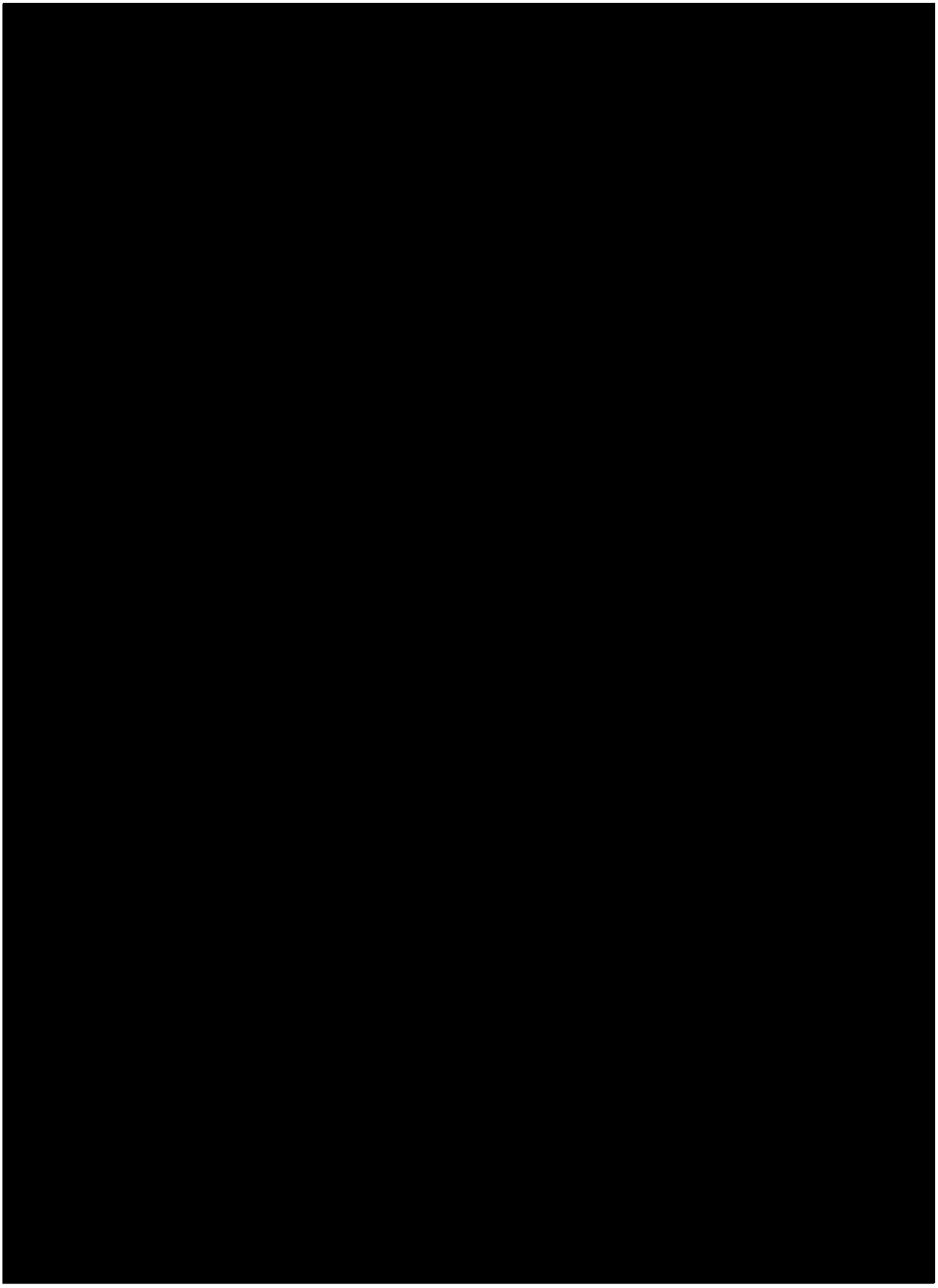
Data from clinical studies

As of April 2021, two clinical trials, a first in human Single Rising Dose (SRD) study 1425-0001 and an Multiple Rising Dose (MRD) study 1425-0002, are clinically complete.

The SRD study consisted of two parts: an SRD part (part I), and a relative bioavailability (BA) and food effect (FE) (part II) that compared tablet and capsule formulations, and assessed the effect of food on the tablet formulation. The SRD part consisted of 8 dose groups of 8 healthy male subjects each (6 active, 2 placebo) with dose levels of 0.3 mg, 0.6 mg, 1.2 mg BI 706321 administered as oral solution, and 2 mg, 4 mg, 8 mg, 15 mg and 25 mg of BI 706321 administered as a capsule. The relative bioavailability (BA) had a three-way crossover design with 12 healthy male subjects receiving the capsule fasted and a tablet given fasted and after a standardized high-fat meal.

In the MRD study, healthy male and female subjects of non-child bearing potential were given a single dose of BI 706321; then, following a five-day washout, these subjects were administered BI 706321 daily for 14 days. There were four dose levels of BI 706321 capsules: 2 mg q.d., 5 mg q.d., 8 mg q.d., and 10 mg q.d. There were 10 subjects (8 active, 2 placebo) in each dose group.





Clinical Safety

The first in human studies 1425-0001 (SRD) and 1425-0002 (MRD) are clinically complete. In the SRD part I, single doses of 0.3-25 mg of BI 706321 were well tolerated by healthy male subjects (n = 46). Based on preliminary analysis, the frequency of subjects with at least one treatment-emergent Adverse Event (AE) ranged from 0/6 (0%) to 3/5 (60%) of subjects in active treatment dose groups as compared to 6/15 (40%) of subjects on placebo. AEs reported in >1 subject on active treatment were coded as diarrhea (n=2, loose stool (8 mg) and watery stool (25 mg)) and nasopharyngitis (n=2, 0.6 and 15 mg). No such events were reported for subjects on placebo. Five drug related AEs were observed: dry lips (0.3 mg), dizziness (15 mg), generalized sensation of cold (25 mg), loose stool (8 mg) and watery stool (25 mg).

In the SRD part II (BA and FE), 4 mg tablets and capsules were administered to an additional 12 healthy male subjects under both fed and fasted conditions and were well-tolerated. Based on preliminary analysis, the total number of subjects with at least one treatment-emergent AE was 4/12 (33.3%) of subjects while on active treatment. Three subjects experienced drug related AEs: headache, loose stools, and decreased snoring.

In the MRD, multiple doses of 2-10 mg BI 706321 (n = 32) were well tolerated by healthy subjects for up to 14 days of dosing. Based on preliminary analysis, the frequency of subjects with at least one treatment-emergent AE ranged from 3/8 (37.5%) to 6/8 (75%) subjects on BI 706321 dose groups as compared to 1/7 subjects (14.3%) on placebo. AEs reported in >1

subject on active treatment were coded as influenza like illness (reported as ”flu like symptoms” n=5; 5 mg [1], 8 mg [2], 10 mg [2]), abdominal discomfort (n= 4; 5 mg [3] and 10 mg [1]), diarrhea (n=4; 5 mg [1], 8 mg [1], 10 mg [2]), headache (n=4; 5 mg [2], 8 mg [1], 10 mg [1]), constipation (n=2, 2 mg and 5 mg), and contusion (n=2; 5 mg and 10 mg). No such events were reported for subjects on placebo. One subject (2.6%) had on-treatment AEs which were considered drug related by the investigator (dry mouth and somnolence, 2 mg).

”Flu like symptoms” were considered mild-moderate in severity and were characterized by intermittent low-grade temperature elevations (maximum temperature 38.1°C), over a duration of 1-3 days. Concomitant headache and dysuria were experienced by one subject each. Minor, transient, elevations of C-reactive protein (CRP) were noted with these symptoms. All symptoms resolved spontaneously while on continuous BI 706321 treatment. Based on the brief and self-limited nature of the symptoms, they were considered to be of minor clinical significance.

Events coded as diarrhea were all mild in intensity and of short duration (< 1-3 days). Events coded as constipation and abdominal discomfort were all mild in intensity.

In both the SRD and MRD trials there were no AEs that led to discontinuation of the study drug; neither serious adverse event (SAE) nor severe AE were observed. Vital sign evaluation and safety laboratory testing did not reveal clinically relevant findings. No clinically relevant changes in any cardiac intervals as measured by centralized electrocardiogram (ECG) were observed in any subject exposed to BI 706321.

Overall, single dose administration of BI 706321 at doses of up to 25 mg and multiple-dose administration of BI 706321 at doses of up to 10 mg for up to 14 days, was generally well tolerated by healthy volunteers.

For a more detailed description of the BI 706321 profile, please refer to the current Investigator’s Brochure (IB) [c26475781].

1.2.2 Ustekinumab (Stelara)

Ustekinumab is a fully human monoclonal IgG1 antibody directed against the p40 subunit of interleukin (IL)-12 and IL-23, approved since 2016 for the treatment of moderate or severe CD.

For a more detailed description of ustekinumab, please refer to the current version of Summary of Product Characteristics (SmPC) or US Package Insert (US PI) for ustekinumab.

1.3 RATIONALE FOR PERFORMING THE TRIAL

As outlined in Section 1.1, despite therapeutic progress and three licensed biologic drug classes with different mechanisms of action, modest primary effect sizes and the phenomenon of secondary loss of response to these current available therapies sustain a significant unmet medical need in CD. The modest efficacy of the current drugs which address different components of the dysregulated inflammatory response in patients with CD suggests that

multiple pathologic pathways need to be targeted in tandem, to make major progress in treatment of this often severe and disabling disease. Combination treatments of established anti-inflammatory drugs with new medicines with a novel and differentiated mode of action might offer greater efficacy, in particular if such a combination partner would be orally available, safe and tolerable. BI 706321 may be such a candidate drug.

Pre-clinical evidence suggests that BI 706321 will not only inhibit the dysregulated innate immune response, but also normalize the expression of genes related to inflammation and intestinal barrier function (ref. to current version of the IB [c26475781]). Thus, its MoA targets two major aspects of CD pathogenesis, which are well differentiated from the MoA of ustekinumab (Stelara®), which via IL-12/23 inhibition primarily targets the dysregulated adaptive T cell response. Through these complementary effects of combination therapy, a substantial improvement in clinical and endoscopic outcomes may be achievable. At the same time, ustekinumab offers a well characterized and favorable safety profile and thus represents a well-suited combination partner for BI 706321. Combination therapy at the time of induction is proposed as this will provide the best opportunity to observe potential additive efficacy in participating patients. Additionally, the long-term effects of combination induction on endoscopic and clinical remission endpoints can be assessed. BI 706321 efficacy and safety data obtained by this trial will support its further development in the indication of CD.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (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

All patients enrolled in this study will have experienced and failed or developed intolerance to one or two TNFi previously, and thus are candidates to receive ustekinumab treatment as standard of care. Ustekinumab has been approved for treatment of various indications since 2009, and was specifically approved for the indication of Crohn's disease since 2016; the safety profile has been well-characterized and is considered mild. Within this trial, all patients will receive the approved dose of ustekinumab treatment for 48 weeks (ref. to Section 3.1). In addition, patients will receive during the induction period a 12-week randomised combination treatment with BI 706321 or placebo. BI 706321 has not yet been administered to any patients and its efficacy cannot be assumed. Therefore, participation in this clinical trial may not provide an additional individual benefit for patients with CD, as compared to them receiving standard ustekinumab treatment outside this clinical study.

However, based on the pre-clinical data summarized in Section 1.2, BI 706321 is hypothesized to have therapeutic efficacy in patients with moderate to severely active CD by blunting the chronic immune cell stimulation by the microbiome via reduced signal

transduction from the NOD1/2 pattern recognition receptors and normalizing genes related to intestinal barrier function. Furthermore, exploratory target engagement assessed pre- and post-treatment in the SRD trial of healthy volunteers suggests that BI 706321 will have biological activity at the doses given to patients in this trial.

Participation in this study may generate future benefit for the CD patient population as a whole if BI 706321 proves to show additional efficacy.

1.4.2 Risks

Subjects are exposed to risks related to the exposure to BI 706321 and ustekinumab, as well as the risks of study procedures.

1.4.2.1 Trial medication-related risks

Trial medication related safety risks may be assumed from the current knowledge (or the lack thereof) regarding the following:
Specific RIPK2 inhibition is a novel mechanism of action for which there is no precedent clinical data for multiple dose administration in patients. No other RIPK2 inhibitors are currently approved that could provide information on identified risks in molecules of this class. BI 706321 in single doses of 0.3 – 25 mg and multiple doses of 2 – 10 mg for 14 days were generally well tolerated by healthy subjects in the SRD and MRD trials. Below are the theoretical risk considerations based on literature, pre-clinical studies, and preliminary clinical studies, as well as general safety considerations of immunomodulatory drugs.

Impaired host defense
Based on the role of RIPK2 in the innate arm of the immune system, impaired host defense is a theoretical target-related pharmacologic effect of selective RIPK2 inhibition (see IB Section 7.6.1 [c26475781]). However, the translatability between preclinical models of infection or genetic loss of function mutations and usually incomplete pharmacologic inhibition of RIPK2 kinase activity in humans is unknown. It is important to note that RIPK2 inhibition will selectively block the NOD-RIPK2 pathway, but leave the remaining innate pattern recognition receptor signaling pathways (e.g. Toll-like receptor signaling) intact.

There is no clear signal of infectious risk identified in the nonclinical general toxicity studies with BI 706321. The AE of “nasopharyngitis” was experienced by two subjects in the 1425-0001 trial on active treatment as compared with none on placebo. Five subjects in the 1425-0002 MRD trial on active treatment with BI 706321 experienced “flu like symptoms” as compared with none on placebo. ”Flu like symptoms” were considered mild-moderate in severity and were characterized by intermittent low-grade temperature elevations (maximum temperature 38.1^{o}C), over a duration of 1-3 days. Concomitant headache and dysuria were experienced in one subject each. Minor, transient, elevations of CRP were noted with these symptoms. All symptoms spontaneously resolved without change in BI 706321 treatment. Based on the brief and self-limited nature of the symptoms, they were considered to be of minor clinical significance.

In the SRD trial 1425-0001, one subject in the 25 mg dose group reported a brief generalized sensation of cold approximately 10 hours after dosing with associated mild transient increase in temperature (37.4°C) and CRP (35.4 mg/L). In the MRD trial 1425-0002, minor transient elevations in CRP, up to a maximum value of 19.7 mg/L, were observed in a subset of subjects beginning after approximately 3-6 days of multiple dosing. CRP levels subsequently normalized within 48-96 hours while dosing was ongoing. Some of these subjects experienced symptoms reported as "flu like symptoms" described above, while other subjects had no such symptoms associated with these changes in CRP values. No clinically significant changes from baseline in ferritin, haptoglobin, or fibrinogen were observed. Given the minor and transient nature of these observed changes in CRP, in the absence of clinical symptoms, they were not considered clinically relevant.

Similar to other treatments that modulate the immune system, there is a lack of data with respect to vaccine safety and effectiveness in populations on such therapies. Live vaccines are not permitted 4 weeks prior to screening and throughout the study. It is not known whether non-live vaccinations (including, but not limited to currently available COVID-19 vaccines) received while in this trial will elicit an immune response sufficient to prevent disease. It is, however, unlikely that there will be any specific risks due to interactions between these non-live vaccines and BI 706321.

Risk mitigation: Patients with clinically relevant infections are excluded (ref. to Section 3.3.3.2) "Infectious Disease Exclusion Criteria"). All patients will closely be monitored by the investigators and trial team for the emergence of clinical Adverse Events (AE) related to infection and systemic inflammation. Severe and/or serious infections are also reflected in the individual patient treatment stopping rules. CRP levels in patients in this trial will be measured at every study visit, (including at Visit 3) after start of treatment.
Body temperature in this trial will be measured at every study visit, (including at Visit 3) after start of treatment and until Visit 9. Serum amyloid A, haptoglobin, ferritin and fibrinogen as markers of the acute phase response will also be monitored. For advice on COVID-19 vaccination, please refer to Section 4.2.2.1.

Cardiovascular system
In rats, repeat dosing up to 13 weeks resulted in increased incidence/severity of mononuclear infiltrates. Infiltrates were associated with an increased incidence of myocardial degeneration at higher exposure levels (97X/66X the estimated human steady state for C_{max} and AUC_{0-24} respectively for the 8 mg once daily dose). The finding in rats may be a species specific exacerbation of a common spontaneous background finding in rats. There were no histopathologic changes to the heart of monkeys at the highest dose levels in the 4- and 13-week studies that achieved 78X and 11X human exposure with a 8 mg dose once daily, respectively.

There is low risk for relevant cardiovascular effects at the exposures expected in this trial.

Studies in monkeys showed potential for prolongation of QT/QTc intervals. In the MRD trial, an exploratory analysis of central ECG data was conducted to characterise the effects of BI 706321 on QT/QTc. Based on preliminary analysis using random coefficient modelling,

the predicted mean differences between BI 706321 and placebo in QTcF change from baseline at gMean of $C_{max,ss}$ were below 10 msec at all dose levels; however, they slightly exceeded 5 msec in the 8 and 10 mg dose groups. No clinically relevant individual QTcF changes have been observed in any subject exposed to BI 706321; no relevant blood pressure and heart rate changes were noted.

Risk mitigation: A marked baseline prolongation of QT/QTc interval (such as QTcF intervals that are greater than 450 ms for men, 470 ms for female) or any other relevant ECG finding at screening or clinically relevant abnormal findings on physical examination of the cardiovascular system in the judgement of the investigator are excluded. ECG monitoring will be done, and concomitant medications with a known risk of increasing exposures of BI 706321 or known risk of QTc prolongation are to be used with caution. Troponin levels will be regularly monitored with safety labs.

Gastrointestinal system
A single dose resulted in an increased rate of gastric emptying and intestinal transit, and liquid accumulation to intestinal contents in rats. Repeat dosing resulted in soft, loose, wet, or liquid stool in rats and monkeys. Clinical events coded as diarrhea in the Phase I program were all mild in intensity and of short duration (< 1-3 days).
Risk mitigation: AEs consistent with alterations in stool consistency will be monitored.

Hepatobiliary system
In rats, there were increases in the incidence/severity of mononuclear cell infiltrates to the liver (occasionally associated with hepatocellular necrosis) at all dose levels, and increases in serum AST and ALT that did not consistently correlate with the liver infiltrates. In monkeys, there was hypertrophy of sinusoidal (Kupffer) cells that also was not associated with increases to AST or ALT. Because of the nature of the findings, these tissue changes are not considered a relevant risk in humans. No clinically significant changes in liver transaminases have been observed in completed or ongoing clinical studies with BI 706321.

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

Risk mitigation: Liver function tests will be monitored.

Genotoxicity, reproductive and developmental toxicity
In vitro and in vivo genetic toxicology studies indicated that BI 706321 is free of any genotoxic potential.

Reproductive findings were only seen in the rat studies. In female rats, reversible adverse effects to the ovaries (corpora lutea degeneration) were observed in females at 11X/7X the estimated human steady state for C_{max} and AUC_{0-24} respectively for a dose of 8 mg once daily. In male rats, there were reversible decreases in testes weights/size and seminiferous tubular degeneration/atrophy with epididymal oligospermia at very high exposures (97X/66X

the estimated human steady state for C_{max} and AUC_{0-24} respectively for a dose of 8 mg once daily).

Potential effects on embryo-fetal development were evaluated in pregnant rats and rabbits. In rats, there was embryolethality (increased post-implantation loss) and evidence of fetotoxicity (adverse effects on fetal growth) at 10 mg/kg/day, and no effects to embryo fetal development at ≤ 5 mg/kg/day. In rabbits, there were no effects to embryo-fetal development at ≤ 7 mg/kg/day. Therefore, there is potential risk for adverse effects to development at human exposures exceeding the embryo-fetal NOAEL in the rat (C_{max} of 184 nM and AUC_{0-24h} of 2,060 nM•h), which provided 5X and 4X estimated human steady state exposure C_{max} and AUC for a dose of 8 mg once daily.

As BI 706321 is not genotoxic nor suspected of human teratogenicity or fetotoxicity at subtherapeutic systemic exposure levels, the potential risk to embryo-fetal development as a result of vaginal or placental transfer from a male clinical trial participant to a female partner is considered negligible.

There is low risk for relevant reproductive effects at the exposures expected in this trial in males, and females who are not considering pregnancy. For safety margins between maximum exposures and GLP reproductive findings in rats, refer to Section 1.2.1.

Risk mitigation: Women of childbearing potential (WOCBP) who participate in the trial have to use highly effective methods of birth control as described in the eligibility criteria. Periodic pregnancy tests will be performed in WOCBP. Monitoring of male sex hormones as a measure of testicular function in males will be done every four weeks for the duration of BI 706321 therapy.

Hematopoietic toxicity
Reversible hematopoietic effects were seen in both rats and cynomolgus monkeys, as detailed in the current version of the IB. In trials 1425-0001 and 1425-0002, no clinically significant changes in blood counts were observed in healthy volunteers.

Risk mitigation: Subjects with significantly abnormal baseline peripheral blood counts will be excluded from participation (see Section 3.3.3). Complete blood counts with differential will be monitored.

Drug-drug interactions (DDI)
Based on in vitro studies, clinically relevant DDIs with BI 706321 are possible. For pre-clinical and clinical DDI potential and concomitant medications restrictions, see Section 4.2.2.1.

1.4.2.2 Risks related to ustekinumab administration

Ustekinumab is proven to be safe and tolerable in CD patients and thus represents a well-suited combination partner for BI 706321. Patients in this study will be exposed to the

standard risks associated with ustekinumab administration (ref. to current version of SmPC/US PI). Some of them are:

- Infections: Serious infections have occurred. Do not start ustekinumab during any clinically important active infection. If a serious infection or clinically significant infection develops, consider discontinuing ustekinumab until the infection resolves.
- Theoretical Risk for Particular Infections: Serious infections from mycobacteria, salmonella and Bacillus Calmette-Guerin (BCG) vaccinations have been reported in patients genetically deficient in IL12/IL-23. Diagnostic tests for these infections should be considered as dictated by clinical circumstances.
- Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with ustekinumab.
- Malignancies: ustekinumab may increase risk of malignancy. The safety of ustekinumab in patients with a history of or a known malignancy has not been evaluated.
- Hypersensitivity Reactions: Anaphylaxis or other clinically significant hypersensitivity reactions may occur.

1.4.2.3 Procedure-related risks

Risks of participating in this study include risks related to the trial specific procedures blood sampling, endoscopy with biopsy:

Blood sampling / Total blood volume
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.

The total volume of blood withdrawn during the entire study per patient will not exceed the volume of a normal blood donation (approximately 500 mL). No health-related risk is expected from this blood withdrawal.

Ileo-colonoscopy with biopsy
Ileo-colonoscopy with biopsy, although generally well tolerated, can be associated with diarrhoea, abdominal pain, perforation, bleeding, effects from anaesthetic medications, and infection. Patients scheduled for ileo-colonoscopy need to undergo bowel cleansing.

Patients who are unable and unwilling to undergo the procedure are excluded from the trial.

The potential risks which are described above will be minimized by close monitoring and selection of experienced trial sites. These risks are considered manageable and outweighed by the potential benefits at this stage of clinical development. For further details see current version of the IB [c26475781].

1.4.2.4 COVID-19

BI 706321
The available pharmacological, non-clinical and clinical data do not indicate an increased risk of contracting SARS-CoV-2 or severe clinical courses due to the treatment with BI 706321. However, similar to standard practice with other immune-modulating treatments, given the theoretical increased risk of infections, risk mitigation measures such as exclusion of subjects with underlying immunological disorders, monitoring for infectious adverse events, laboratory monitoring, and adherence to appropriate exposure safety margins have been implemented as outlined in the clinical trial protocols and patient informed consent forms.

Risk mitigation: Even though the risks associated with BI 706321 treatment are considered low, patients with active or recent SARS CoV-2 infection will not be included in the trial (see Section 3.3.3). A suspected SARS CoV-2 infection while in the trial will result in an immediate test. If positive, trial treatment will be discontinued or interrupted (see Section 3.3.4.1). Investigator and sponsor will closely align on the appropriate measures for monitoring, treatment and quarantine. Trial treatment may be resumed following recovery if clinical benefit is expected

Trial procedures
Trial conduct and protocol-defined procedures do not specifically impose more risk to trial participants. To address potential risks associated with operational aspects related to the participation in clinical trials in the context of the COVID-19 pandemic, different risk mitigation measures are considered, based on local requirements and development of the pandemic.

Other risks
Travelling to the site or being at the site for trial visits may potentially increase the risk of contracting a SARS CoV-2 infection.

Risk mitigation: The number of site visits is limited to the minimum required for the successful conduct of the trial. Measures are in place to ensure continued patient treatment, monitoring, and safety even if site visits are not possible (see Sections 4.1 and 6.2).

1.4.3 Discussion

BI 706321 is entering Phase II development, and clinical efficacy has not yet been proven. Crohn's disease patients participating in this clinical trial cannot be assumed to have an individual (therapeutic) benefit, however this early phase trial will use a BI 706321 dose that is anticipated to be in the therapeutically effective dose range and may contribute to alleviation of the signs and symptoms of CD when administered with ustekinumab; CD patient participation in studies is of major importance for the overall development of BI 706321, which represents a novel approach for the treatment of patients with CD.

Participation in this study may generate future benefit for other CD patients if BI 706321 is proven to show additional efficacy. The current clinical safety data in healthy volunteers as well as the results from toxicity and safety pharmacology studies demonstrate an acceptable

profile for this trial. The potential risks which are described in Section 1.4.2 will be minimized by careful patient and site selection as well as close monitoring.

In conclusion, in the context of the unmet medical need in CD, safety profile of BI 706321 and the study design, the benefit-risk evaluation of BI 706321 in this study is considered favourable for this stage of clinical development.

2. TRIAL OBJECTIVES AND ENDPOINTS

This is a Phase IIa trial evaluating proof of clinical principle based on the efficacy, tolerability, and safety of one dose regimen of BI 706321 compared to placebo in patients with moderate to severely active CD receiving ustekinumab induction treatment.

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objectives of this trial are to investigate a first signal of efficacy, safety and tolerability of BI 706321 in combination with ustekinumab treatment compared to placebo with ustekinumab treatment in patients with moderately to severely active CD at 12 weeks.

The primary objective is to estimate the difference in change from baseline in Simple Endoscopic Score for Crohn's disease (SES-CD) after 12 weeks. The primary treatment comparison will be between treatment groups while on treatment during the 12 week induction period.

In addition, the long-term effects of combination induction compared to monotherapy ustekinumab induction on endoscopic and clinical endpoints during maintenance therapy will be assessed.

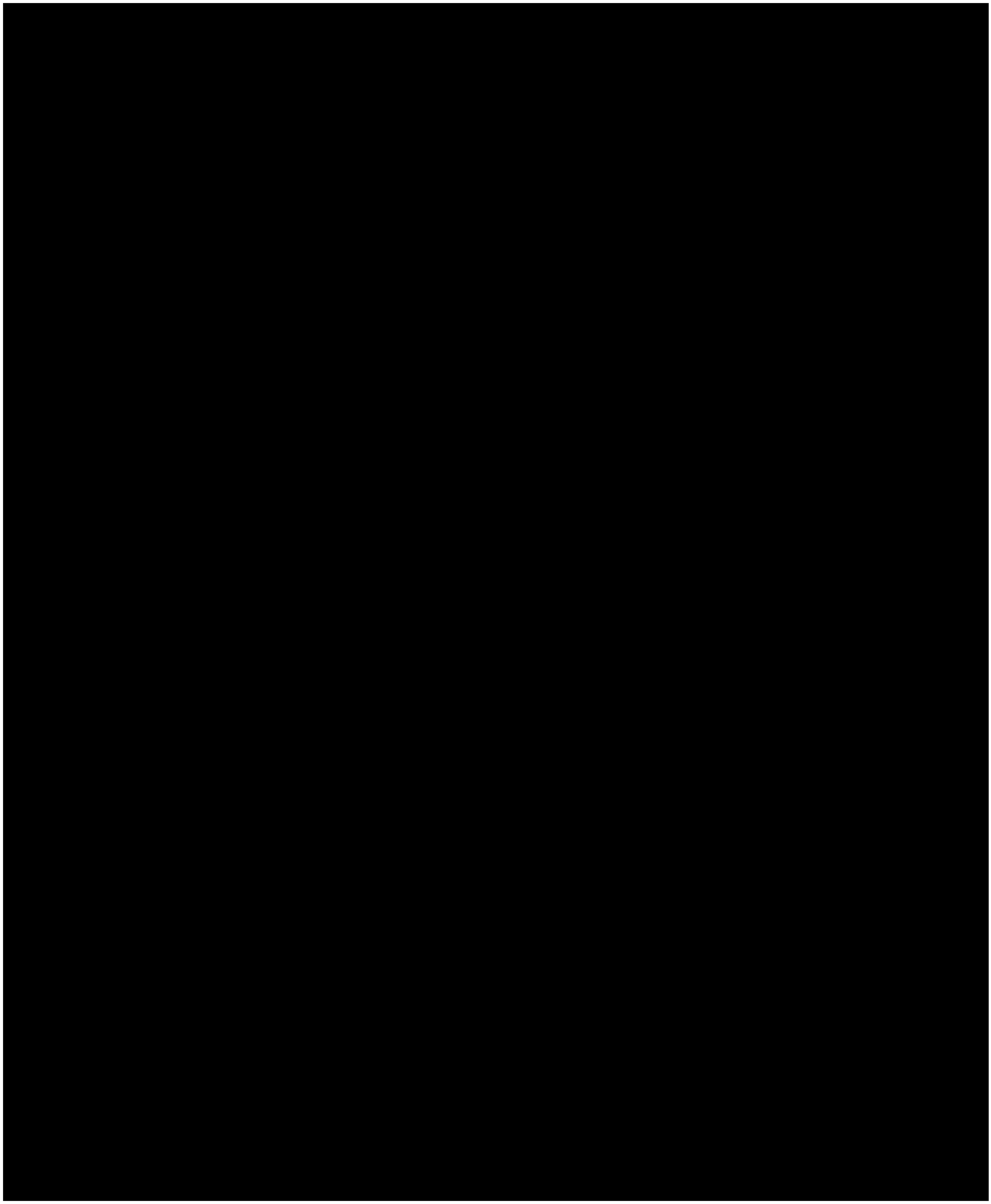
2.1.2 Primary endpoint

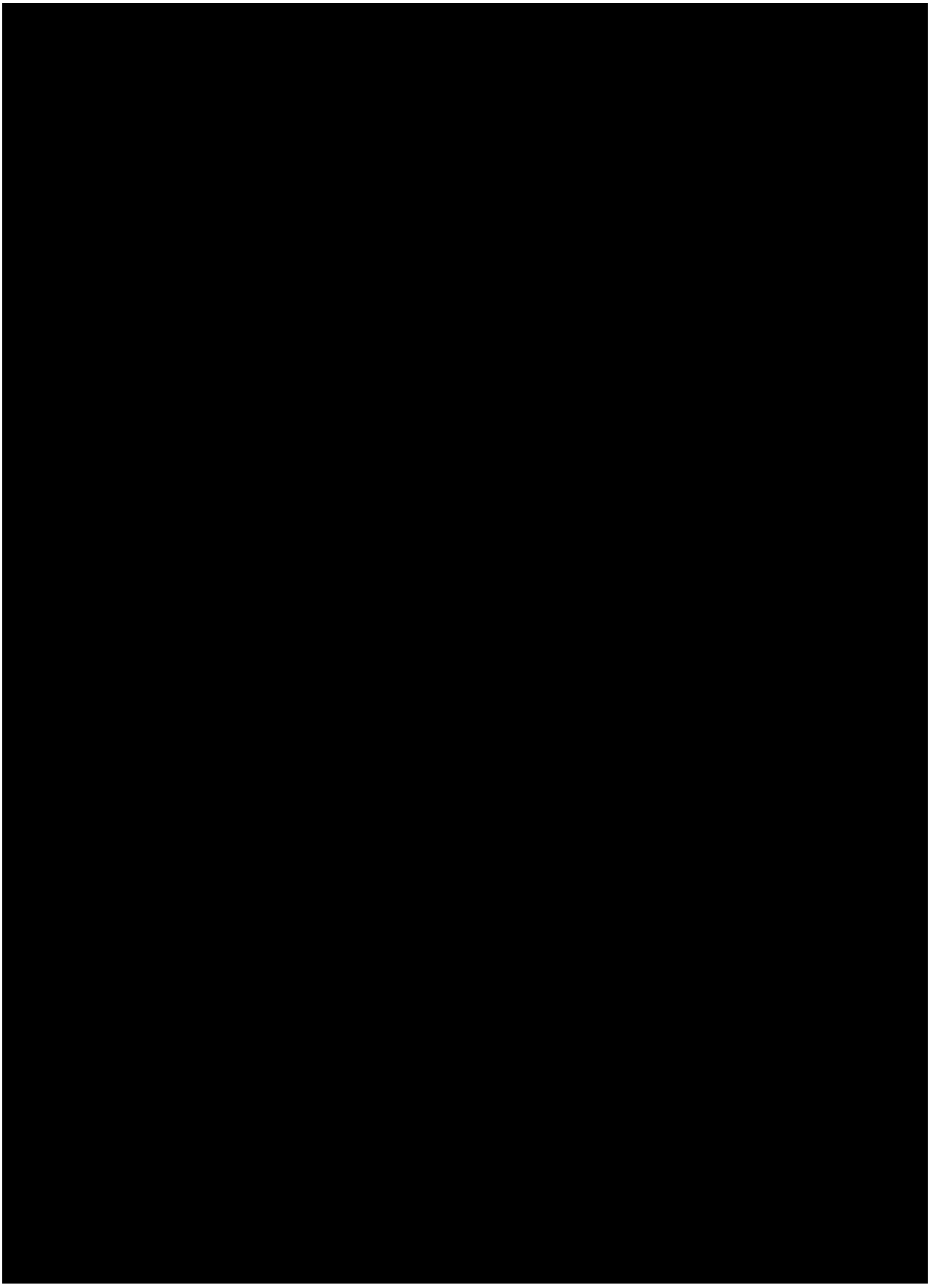
Absolute change from baseline in Simple Endoscopic Score for Crohn's disease (SES-CD) at week 12.

2.1.3 Secondary endpoints

- Percent change in SES-CD from baseline at Week 12
- Endoscopic response (defined as >50% SES-CD reduction from baseline, or for aninduction baseline SES-CD of 4, at least a 2 point reduction from induction baseline) at Week 12
- Endoscopic response (defined as >50% SES-CD reduction from baseline, or for an induction baseline SES-CD of 4, at least a 2 point reduction from induction baseline) at Week 48
- Endoscopic remission (defined as SES-CD score of ≤2) at week 12
- Endoscopic remission (defined as SES-CD score of ≤2) at week 48.
- Biological remission, defined as CRP < 5 mg/L and faecal calprotectin (FCP) < 250 ug/g at week 12
- Biological remission, defined as CRP < 5 mg/L and faecal calprotectin (FCP) < 250 ug/g at week 48
- Clinical remission at week 12, defined as a Crohn's Disease Activity Index (CDAI) score of <150
- Clinical remission at week 48, defined as a CDAI score of <150

- Clinical response at week 12, defined by a CDAI reduction from baseline of at least 100 points, or a CDAI score of <150
- Number of patients with treatment-emergent adverse event (TEAE) through end of treatment (EoT) and the REP period (i.e. through Visit 9)





3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a Phase IIa, randomised, double-blind, placebo-controlled evaluation of approximately 50 male and female patients with CD, using BI 706321 therapy in combination with a backbone ustekinumab induction regimen.

Patients will be randomised (1:1) to one of two arms as following:
Group 1: BI 706321 8 mg p.o. QD for 12 weeks in conjunction with standard induction dosing of ustekinumab*, followed by ustekinumab maintenance dosing for an additional 36 weeks.
Group 2: Placebo p.o. QD for 12 weeks in conjunction with standard induction dosing of ustekinumab*, followed by ustekinumab maintenance dosing for an additional 36 weeks.

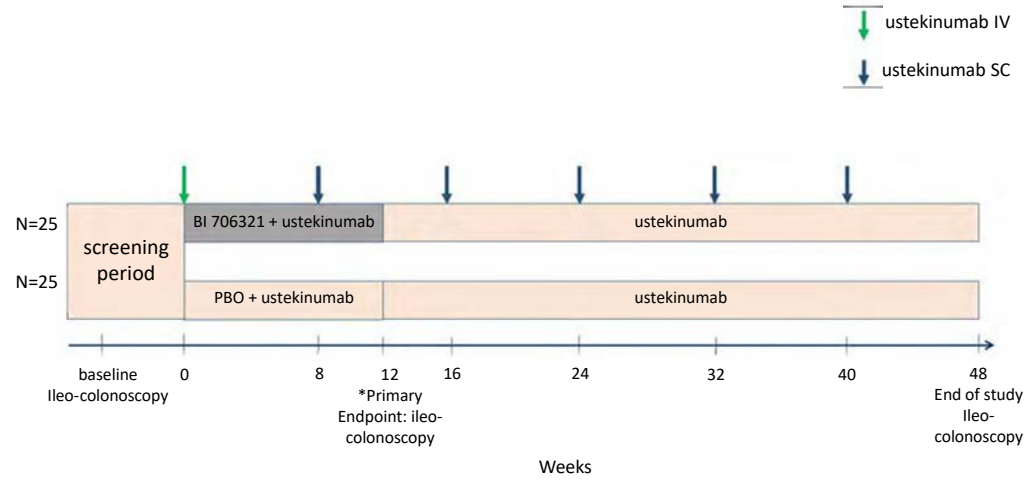


Figure 3.1: 1 Overview of study design and dosing

* Single IV infusion of 260 mg ustekinumab (body weight ≤55 kg), 390 mg ustekinumab (body weight 55-85 kg), or 520 mg ustekinumab (body weight >85 kg), followed by s.c. injection of 90 mg ustekinumab every 8 weeks

After the 12-week induction treatment period, patients will be treated with an additional 36 weeks of follow-on ustekinumab open label maintenance monotherapy. Ustekinumab therapy in both induction and maintenance will be administered in an open-label fashion. Both safety and efficacy data will be collected during the follow-up period.

The primary analysis will be performed soon after the last patient completes Week 12 visit procedures, including ileo-colonoscopy. However, treatment assignments during the initial 12-week induction phase will remain blinded to sites/investigators for the duration of the maintenance phase, in order to mitigate bias in the later assessments.

Patients will be permitted to continue during the induction phase the following therapies if dose levels have been stable for the designated time frames before randomisation (see Section 3.3.2 for details): oral corticosteroids (prednisone ≤20 mg/day or equivalent; budesonide ≤9 mg), antibiotics, 5-aminosalicylic acid (5-ASA), AZA, MP, 6-thioguanine (6-TG), or MTX.

However, the use of biological therapies other than ustekinumab (e.g., TNFα-antagonists, integrin inhibitors) will be prohibited during the trial.

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

The treatment duration with BI 706321 of 12 weeks is driven by the maximum treatment duration covered by current preclinical toxicology data.

The double-blind concept was chosen to reduce investigator and patient expectation bias with regard to the treatment dependent effects as much as possible.

The use of a combination study design in the development of BI 706321 is justified by its complementary and differentiated effects as compared to ustekinumab. Ustekinumab is a current treatment standard for our study population of patients who have tried and failed or lost response to TNFi. However, ustekinumab treatment leads to only 38% and 21% clinical response Crohn's Disease Activity Index (CDAI 100 point) and clinical remission at Week 8 respectively, in CD patients who had failed or were intolerant to prior treatment with a TNFi (ref. to current version of SmPC/US PI). Though clinical response and remission rates in a subsequent study of ustekinumab therapy are higher (> 50%) by 16 weeks of treatment, rates of endoscopic response and remission at that time remain quite low (37.8% and 11.1% respectively, in patients who have been exposed to at least one biologic) [R21-1348].

BI 706321 blunts inflammatory signaling from innate microbial sensing by epithelial, myeloid, and endothelial cells, and has effects on epithelial barrier function, whereas ustekinumab targets the p40 subunit common to IL-12 and IL-23 and primarily exerts its anti-inflammatory effects by modulation of T lymphocytes and Natural killer cells (NK cells). Therefore, all patients in the placebo and active treatment groups will benefit from receiving ustekinumab, which represents current standard of care for patients failing one or more TNFa inhibitors. This design also reduces the risk to the patient of worsening of disease if treated with placebo therapy alone.

It is postulated that combination induction therapy will offer better overall efficacy due to the complementary and differentiated immune-modulating effects of the two agents, as well as the additional effects of BI 706321 on epithelial barrier function.

The overall trial duration with ustekinumab of 48 weeks followed by a final ileo-colonoscopy will allow assessment of the long-term effect of the initial 12 week period of BI 706321 combination induction treatment on the endoscopic endpoints at the end of monotherapy maintenance. This is with the understanding that early effects on endoscopic scores may be observed in a subset of patients by 12 weeks, however maximal endoscopic improvement and

separation from the ustekinumab+placebo arm may not be reached in the majority of patients until 6-12 months after initiation of therapy - particularly in patients who are TNFi-experienced. Therefore, patients will be followed for up to 36 weeks on maintenance monotherapy to monitor further structural improvement using fecal, and blood biomarkers (at 16, 24, 32, 40, and 48 weeks), as well as a repeat ileo-colonoscopy with tissue sampling at week 48. Treatment assignments during the initial 12-week induction phase will remain blinded to sites/investigators for the duration of the maintenance phase, in order to mitigate bias in the later assessments.

There may be patients who fail to have an adequate response to therapy or lose response to therapy during the follow-on ustekinumab treatment. If ustekinumab dose escalation or treatment cessation is deemed necessary by the investigator, these patients will exit the study and be managed according to best local medical practice. Clinical and endoscopic data will be obtained prior or soon after such early treatment discontinuation.

The group size (approximately 25 patients per treatment group) is sufficient for assessing first therapeutic effects and safety, tolerability, PK and Pharmacodynamics (PD) of BI 706321 in combination with ustekinumab. For information can be found in Section 7.5.

3.3 SELECTION OF TRIAL POPULATION

Approximately 50 male and female adult patients suffering from moderately to severely active CD will be included in several countries in approximately 50 sites. The number of sites might be increased in case the recruitment is slower than initially expected. Sufficient subjects will be screened to ensure that 50 eligible subjects are randomised.

An interim assessment of baseline biomarkers will be performed after approximately 20 patients are entered (refer to Section 7.2.7). Based on this assessment *and if no individual stopping rules are met,* the Sponsor may recruit additional patients to improve the sensitivity of exploring the relationship between RIPK2 pathway-specific biomarkers and endoscopic responses among the treatment groups after 12 weeks, however the total number of randomised patients will not exceed 76 (i.e. 13 additional patients per treatment arm, so as to limit total additional enrolment to no greater than ~50% of the originally proposed sample size).

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the Sponsor should be contacted immediately to whether the subject may proceed with the study or should be discontinued.

3.3.1 Main diagnosis for trial entry

Male and female patients with documented history of ileal, colonic, or ileocolonic CD diagnosed by local standards and current presence of mucosal ulcers in at least one segment of the ileum or colon and a SES-CD score ≥7 (for patients with isolated ileitis ≥4), as assessed by ileo-colonoscopy and confirmed by central independent reviewer(s) before start of study treatment, and are clinical candidates for treatment with ustekinumab as judged by the investigator and according to local reimbursement guidelines (*where applicable*).

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

3.3.2 Inclusion criteria

1. Male or female patients.
2. ≥18 – ≤75 years, at date of signing informed consent.
3. Diagnosis of CD for at least 3 months prior to Visit 1, as confirmed at any time in the past by endoscopy and/OR radiology, and supported by histology.[1]
4. Elevated CRP (≥5 mg/L) OR elevated fecal calprotectin (≥250 µg/g)
5. Symptomatic CD defined as CDAI ≥150.
6. Presence of mucosal ulcers in at least one segment of the ileum or colon and a SES-CD score ≥7 (for patients with isolated ileitis ≥4), as assessed by ileo-colonoscopy and confirmed by central independent reviewer(s) before start of study treatment.
7. Patients who are experienced to at least 1 TNF antagonist at a dose approved for CD. Patients may have stopped TNF antagonist treatment due to primary or secondary non-responsiveness, intolerance (see definitions in Appendix 10.7), or for other reasons.
8. May be receiving a therapeutic dose of the following:
    - Oral 5-ASA compounds must have been at a stable dose for at least 4 weeks prior to randomisation and must continue on this dose until week 12 and/or
    - Oral corticosteroids if indicated for treatment of CD must be at a prednisone equivalent dose of ≤ 20 mg/day, or ≤ 9 mg/day of budesonide, and have been at a stable dose for at least 2 weeks immediately prior to randomisation and must continue on this dose until week 12. [Allowed steroid treatments: Locally administered steroids as e.g. intra-articular, nasal inhalation or intra-ocular administration are allowed.] and/or
    - AZA, MP, 6-TG, or MTX, provided that dose has been stable for the 8 weeks immediately prior to randomisation and must continue on this dose until week 12.

[1] That means, the imaging part can be confirmed at any time in the past (which is more than 3 months prior Visit 1) by endoscopy and/or radiology. Radiology however, is not necessarily required. In addition, the histology result should be available also and it should support the diagnosis of CD.

9. Women of childbearing potential (WOCBP)[2] must be ready and able to use highly effective methods of birth control per International Councila on Harmonisation (ICH) M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information or in Section 4.2.2.3.
10. Signed and dated written informed consent in accordance with ICH- Good Clinical Practice (GCP) and local legislation prior to admission to the trial.

3.3.3 Exclusion criteria

3.3.3.1 Gastrointestinal Exclusion Criteria

1. Have any current or prior abscesses, unless they have been drained and treated at least 6 weeks prior to randomisation and are not anticipated to require surgery. Patients with active fistulas may be included if there is no anticipation of a need for surgery and there are currently no abscesses present based on investigator`s judgement.
2. Have complications of CD such as strictures, stenosis, short bowel syndrome, or any other manifestation that might require surgery, or could preclude the use of SES-CD/CDAI to assess response to therapy, or would possibly confound the evaluation of benefit from treatment with BI 706321 (based on investigator's judgement).
3. Patient with an inflammatory bowel disease (IBD) diagnosis other than CD.
4. Have had any kind of bowel resection or diversion within 4 months or any other intra-abdominal surgery within 3 months prior to Visit 1. Patients with current ileostomy, colostomy, or ileorectal anastomosis are excluded.
5. Treatment with:
    - any non-biologic medication for IBD (e.g. tacrolimus or mycophenolate mofetil, systemic corticosteroids), other than those allowed per inclusion criteria, within 30 days prior to randomisation
    - any biologic treatment with a TNF-alpha antagonist (adalimumab, infliximab, golimumab, certolizumab pegol) or vedolizumab (or a biosimilar of these drugs) within 4 weeks prior to randomisation. (If drug level testing for previously used biologic treatment confirms no detectable drug level before randomisation, patient can be enrolled despite not having completed 4 week from last treatment.)
    - any previous treatment with ustekinumab (or a biosimilar of this drug)
    - any previous treatment with an investigational (or subsequently approved) non-biologic/biologic drug for CD (including but not limited to JAK inhibitors [e.g. upadacitinib], S1P modulators, IL-23 inhibitors [e.g. risankizumab], anti-integrins).
    - any investigational drug for an indication other than CD during the course of the actual study and within 30 days or 5 half-lives (whichever is longer) prior to randomisation.
    - any prior exposure to rituximab within 1 year prior to randomisation.

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

6. Positive stool examination for C difficile (toxin A/B and GDH antigen – test positive) or other intestinal pathogens <30 days prior to randomisation. Re screening can be undertaken following documented successful treatment, no sooner than 1 week after last intake of antimicrobial therapy. If stool examination for C. Diff is indeterminate (toxin A/B positive and GDH antigen negative or toxin A/B negative and GDH antigen positive), a reflex PCR test must be done to assess eligibility. A positive PCR test will lead to exclusion.
7. Evidence of colonic moderate/severe mucosal dysplasia or colonic adenomas, unless properly removed.
8. Fecal transplant ≤ 30 days prior to randomisation.

3.3.3.2 Infectious Disease Exclusion Criteria

9. Increased risk of infectious complications (e.g. recent pyogenic infection, any congenital or acquired immunodeficiency (e.g. Human immunodeficiency virus (HIV)), past organ or stem cell transplantation (with exception of a corneal transplant > 12 weeks prior to screening) or have ever received stem cell therapy (e.g., Prochymal). Prior treatment with a somatic cell therapy product (e.g., Alofisel) is not excluded, provided it was administered >8 weeks prior to randomisation.
10. Live or attenuated vaccination within 4 weeks prior to randomisation.
11. Have received BCG vaccines ≤1 year prior to randomisation.
12. Active or latent TB:
    - Patients with active tuberculosis are excluded.
    - Patients will be screened with Interferon Gamma Release Assay (IGRA) such as QuantiFERON or T spot, the patient may also be evaluated for the presence of TB with any additional test required by local practice. Patients with positive test results are excluded unless patient is known to have had a previous diagnosis of active or latent TB and has completed appropriate treatment per local practice/guidelines within the last 3 years and at least 6 months before first administration of trial medication under this protocol (patients may be rescreened once to meet this specific criterion)
    - Patients with indeterminate QuantiFERON or invalid/borderline T spot may be re-tested with IGRA (once), and if again inconclusive, should have a Purified Protein Derivative (PPD) skin test.
    - If IGRA is not available or result remains indeterminate after repeat testing, tuberculin skin test (TST) should be performed: A tuberculin skin test positive reaction ≥10mm (≥5mm if receiving ≥15mg/d prednisone or its equivalent) is considered positive. Patients with a positive TST are excluded unless they have completed treatment as above.
13. Presence of clinically significant acute or chronic infections not otherwise listed, including viral hepatitis, COVID-19, or others based on investigator's judgement. A patient can be rescreened (up to two times) if the patient was treated and is cured from the acute infection. If at screening, PCR test for SARS-CoV-2 is positive and patient is asymptomatic, re-test SARS-COV-2 PCR test is allowed (up to 4 times) to confirm patient's eligibility before ileo-colonoscopy and/or Visit 2. If re-test SARS-COV-2 PCR test is negative, patient must meet all other eligibility criteria according to the

CTP before patient is randomized at Visit 2. Already performed screening assessment do not need to be repeated.

3.3.3.3 General Exclusion Criteria

14. Have any documented active or suspected malignancy or history of malignancy within 5 years prior to screening except appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin, or history of in situ carcinoma of uterine cervix (treated >3 years); patients with a remote history of malignancy (≥ 5 years prior to screening) may be considered and have to be discussed with sponsor on a case-by-case basis.
15. Major surgery (major according to the investigator's assessment) performed within 16 weeks prior to randomisation or planned within 4 months after screening, e.g. hip replacement.
16. Pathological safety lab parameters (*one retesting is allowed*):
    - Haemoglobin <8.5 g/dL
    - White blood cell (WBCs) <3,500 cells/mm^3
    - Neutrophils <1,500 cells/mm^3
    - Platelets <100,000 /mm^3
    - Estimated glomerular filtration rate (eGFR) ≤60 ml/(min*1,73 m^2)
    - Aspartate aminotransferase (AST) OR Alanine aminotransferase (ALT) >2 times the Upper Level of Normal (ULN). Total bilirubin >2x ULN with ratio of direct/indirect >1 (patients with Gilbert's syndrome are not excluded),
    - Troponin: >ULN
17. Currently enrolled in another investigational device or drug study (for investigational studies, except any patient who has completed investigational drug treatment including residual effect period) or receiving other investigational treatment(s).
18. Women who are pregnant, nursing, or planning pregnancy (both men and women) while enrolled in the study.
19. 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.
20. Evidence of a current or previously disease, medical condition (including chronic alcohol or drug abuse, or chronic liver disease with hepatic impairment) other than CD, surgical procedure, medical examination finding (including vital signs and ECG), or laboratory value at the screening visit outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or complete the trial, compromise the safety of the patient, or compromise the quality of the data.
21. A marked baseline prolongation of QT/QTc interval (such as QTcF intervals that are greater than 450 ms for men, 470 ms for female) or any other relevant ECG finding at screening. Both have to be confirmed by repeated ECG recording.
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. History of allergy/hypersensitivity to trial medication excipients.

24. Have previously undergone allergy immunotherapy for prevention of anaphylactic reactions
25. Are unable or unwilling to undergo multiple venepunctures, ileo-colonoscopies (with biopsies) or preparation for ileo-colonoscopies.
26. Previous enrolment in this trial, except if meets re-screening criteria.

3.3.4 Withdrawal 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; please see Section 3.3.4.1 and Section 3.3.4.2 below.

Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect important trial follow up 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 Adverse Event collection reporting (please see Section 5.2.6.2.1 and Section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment (including ustekinumab open-label maintenance treatment after week 12) if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment. Please refer to Sections 4.2.1 and 4.2.2
- The patient can no longer receive trial treatment and/or ustekinumab treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy), e.g. (but not limited to):
  - Symptomatic SARS-CoV-2 infection, confirmed by lab testing
  - if, in the investigator's opinion, the patient requires alternative biologic therapy or an increased dose of ustekinumab for their CD due to persistently high disease activity or worsening based on CDAI score (>450, or an increase by 100 points from baseline), the study treatment may be stopped and patients may receive medical treatment for active disease as per investigator's judgement.
  - Diagnosis with a malignant neoplasm, severe infection, serious infection, and opportunistic or tuberculosis infection.
  - At week 24 (Visit 10):

- Absence of at least CDAI-70 clinical response as defined by a reduction from baseline in the CDAI score of ≥70 points, or a CDAI score of <150.

In case of a temporary treatment discontinuation for a medical reason of up to 14 days (*i.e. once per patient in the trial*), trial treatment may be restarted if medically justified by the investigator.

If the trial treatment (BI 706321/placebo and/or ustekinumab) is discontinued before completing 10 weeks of treatment in the induction treatment period, the patients should undergo the procedures of the early EoT visit and Visit 9 as the last visit in the trial as outlined in the Flow Chart and in Section 6.2.2. If a patient has to stop BI 706321/placebo trial treatment after completing 10 weeks of treatment in the induction treatment period and if it is medically appropriate to continue treatment with ustekinumab, the patient may remain in the trial and follow the visit schedule as planned. If in the opinion of the investigator it is not medically appropriate to continue treatment with ustekinumab, the patient should perform an early EoT visit and Visit 9 as the last visit in the trial. Further CD treatment has to be defined by the investigator.

If new efficacy/safety information becomes available, Boehringer Ingelheim 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.

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

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

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see Section 3.3.4.1.
   - Including, but not limited to, the following scenario, further enrolment, randomisation into the trial, and treatment of already randomised patients will be interrupted by the sponsor if:
     - 2 patients on active treatment with serious adverse reactions representing the same MedDRA preferred term (and not reflecting exacerbations of the underlying CD) and

- Which, after evaluation by the Sponsor, are considered to have a reasonable causal relationship to BI 706321, and are not typically observed with ustekinumab therapy

After the trial has been interrupted, it will only be restarted after an appropriate safety evaluation has been conducted and concluded that the benefit-risk of the overall trial is still favourable, and appropriate risk-mitigation measures have been implemented if needed. If a re-start is appropriate, additional patients may be enrolled to replace the patients who were discontinued early due to the trial interruption.

3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.
4. Termination of drug development either overall or in this indication

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 Investigational Medicinal Products BI 706321will be provided by BI.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Description of test product BI 706321

Substance:	BI 706321
Pharmaceutical formulation:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	1 mg, 2 mg and 5 mg
Posology:	once per day, 8 mg per day in total (3 tablets per day in total)
Method and route of administration:	Oral

Table 4.1.1: 2 Description of test product placebo matching BI 706321

Substance:	Placebo matching BI 706321
Pharmaceutical formulation:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	not applicable
Posology:	once per day (3 tablets per day in total)
Method and route of administration:	Oral

4.1.2 Selection of doses in the trial and dose modifications

BI 706321 dose selection for this trial is based on data obtained in the first-in-human SRD (1425-0001) and MRD (1425-0002) trials. In these trials single dose levels up to 25 mg and multiple dose levels up to 10 mg were safe and well tolerated.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised to treatment groups according to a randomisation plan in a 1:1 ratio with corticosteroid use (yes or no) as a stratification factor. Randomisation will be performed at Visit 2 using a central randomisation center and Interactive Response Technology (IRT) system to allocate patients to treatment groups. Note that the medication number is different from the patient number (the latter is generated during screening via the IRT system).

4.1.4 Drug assignment and administration of doses for each patient

Trial medication will be dispensed in a double-blinded manner to patients. That means, investigators and patients will not know if a patient is assigned to BI 706321 or placebo.

All patients will be dispensed the trial medication consisting in total 17 trial medication kits (i.e. dispensing will be done during the trial stepwise via the IRT system at Visit 2, Visit 4, Visit 5, Visit 6 and Visit 7.

Further information can be found in the ISF.

The trial medication can be taken with or without food.

At Visit 2, patients will be instructed by a qualified site staff member to take their trial medication once daily in the morning. This should be done every day approximately at the same time. Patients will be requested to document the time points of intake in their patient diary.

On visit days (i.e. Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, and Visit 8), the trial medication has to be taken in the morning at the trial site.

No double doses should be taken, and dose reductions are not permitted.

If a scheduled dose is missed by:

- Less than 12 hours after the scheduled dose time, the patient must take the missed dose and take all remaining doses at scheduled time. The error must be documented in the patient diary and reported to the study doctor at the next study visit.
- 12 hours or more after the scheduled dose time, the patient must skip the missed dose and take the next scheduled dose; subsequent doses must be taken at the scheduled time. The error must be documented in the patient diary and reported to the study doctor at the next study visit.

The date and time of study drug administration at the trial visits (i.e. at the site, Visit 3, Visit 4, Visit 5, Visit 6, Visit 7 and Visit 8) will be captured in the eCRF.

In case of a temporary treatment discontinuation for a medical reason of up to 14 days (i.e. once per patient in the trial), trial treatment may be restarted if medically justified by the investigator, please see Section 3.3.4.1.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, please see Section 6), physical patient visits to the sites may not be feasible or may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue trial treatment. Where permitted by local law and regulations, the trial site team may arrange a transfer of the trial medication to the patient's home (e.g. site staff delivers the trial medication to the patient after assignment by the IRT system). In agreement with the sponsor, a home visit service or telemedicine may assist the patient with medication administration.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Table 4.1.5.1: 1 summarizes the masking/blinding level of individual functions involved in the trial.

Table 4.1.5.1: 1 Overview about blinding status of trial role and functions

Role/function	Timing of Unblinding/receiving access to the treatment information (including rationale)
Patients	Blinded until data ready for final analysis.
Investigators/site staff	Blinded until data ready for final analysis.
Sponsor (incl. clinical trial/project team)	Unblinded descriptive analyses will be performed at different time points during the trial conduct (see Section 7.2.7). The release of treatment codes at the individual time points will be documented accordingly.

Independent centralised assessments of endoscopic scores will be performed in a blinded fashion as described in Section 3.2.

The randomisation codes will be provided to bioanalytics prior to last patient completed to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo/comparator patients. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded

During the time a role/function is blinded, the treatment information are kept restricted by the global Randomisation Team (gRT) per Sponsor Standard Operating Procedure (SOP).

Ustekinumab treatment is open-label for the Sponsor, patients and investigator/site staff.

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 randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance 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 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 the 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 list of contacts) 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 clinical trial protocol by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC)
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator (*if applicable*),
- Availability of FDA Form 1572 (*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. Patients should be instructed to return unused investigational drug.

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 Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor.

At the time of return to the sponsor or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Ustekinumab is classified as an Auxiliary Medicinal Products (AxMP) / Non-Investigational Medicinal Product (NIMP) (i.e. used as described in the current version of SmPC/US PI) and will be paid for by BI. However if mandated by local requirements ustekinumab can be regarded as Investigational Medicinal Product (IMP).

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation (see Section 3.3) may be permissible. Other concomitant therapies should be limited to those essential for the non-CD related care of the patient and should be carefully evaluated by the Investigator and the Sponsor should be contacted when there are questions regarding concomitant medications. All concomitant medications and the reason(s) for use will be documented throughout the course of the study.

If the patient requires additional CD therapy or dose increase of concomitant CD medication(s) to treat the underlying CD due to disease worsening (see Section 3.3.4.1 and Section 4.2.2), the study drug must be discontinued and patients treatment should be managed according to local standard of care. Such patients should complete early EoT and Visit 9 or early EoS visit as described in Sections 6.2.2 and 6.2.3.

Management of Adverse Events:
In case of AEs in need of treatment, symptomatic therapy according to investigator judgement will be permitted. All concomitant therapies will be recorded on the appropriate pages of the eCRF.

Systemic hypersensitivity including infusion reaction and anaphylactic reaction

Any hypersensitivity reactions should be treated according to medical standards. To be able to prospectively define and assess any potential cases of anaphylaxis, the clinical criteria for diagnosis of anaphylaxis defined in Section 10.6 are to be considered [R11-4890]

In case of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA [R11-4890] suspected to be caused by ustekinumab, the investigator should discontinue treatment with ustekinumab and study drug. Follow instructions for preparation and handling of ustekinumab as per current version of SmPC/US PI.

Severe infections, serious infections, opportunistic or tuberculosis infections.

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

Malignancies

- In case of new occurrence of malignant neoplasm, the investigator should discontinue treatment with study drug. Diagnostics and treatment have to be initiated according to local standard of care.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The medications (or classes of medications) listed in Tables 4.2.2.1:1 and 4.2.2.1:2 must not be taken for the time periods as specified.

If patients receive optional concomitant CD treatment, these need to be on stable doses prior to randomisation until Visit 8/week 12, as specified in eligibility criteria (see Section 3.3.2 and Section 3.3.3).

Patients are encouraged to receive COVID-19 vaccination according to local public health advice and vaccine availability. If possible, vaccination should be completed 4 weeks prior to study screening. The patient may receive (non-live) COVID-19 vaccine(s) during the study, however there is no specific data available with regard to vaccine efficacy while receiving BI 706321 treatment.

Table 4.2.2.1: 1 Restrictions regarding previous and concomitant treatment

Medication or class of medications	Restriction
Investigational products not otherwise described below	Within 30 days or 5 half-lives (whichever is longer) prior to randomisation and until the end of the trial
Any biologic approved for CD[1] (except ustekinumab): adalimumab, infliximab, certolizumab pegol, vedolizumab, natalizumab (or a biosimilar of these drugs)	Not allowed from 4 weeks prior to randomisation or from time when no detectable drug level was confirmed until end of the trial For use as a CD treatment medication, refer to Section 4.2.1
5-ASA compounds	• Rectal 5-ASA compounds are not permitted during the study and must have been discontinued at least 4 weeks prior to Visit 2. • Oral 5-ASA compounds must have been at a stable dose for at least 4 weeks prior to Visit 2, and remain stable at this dose until week 12. • If oral 5-ASA compounds were recently discontinued, they must have been discontinued at least 4 weeks prior to Visit 2.
Immunomodulators	• Patients receiving chronic treatment with AZA, MP, 6-TG, or MTX prior to Visit 2 must have been on a stable dose for at least 8 weeks prior to Visit 2 and must continue on this same dose during the study. • Patients who have discontinued therapy with AZA, MP, 6-TG, or MTX must have stopped the medication at least 8 weeks prior to Visit 2 to be considered eligible for randomisation. • Patients must not have received therapy with other known immunomodulators (e.g., cyclosporine, tacrolimus, sirolimus, pentoxifylline, or mycophenolate mofetil) within 8 weeks or 5 half-lives of agent from Visit 2, whichever is longer, and until the end of the trial.

Footnotes are provided on the next page

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

Medication or class of medications	Restriction
Systemic corticosteroids (e.g., prednisone, budesonide)	• Parenteral (SC, IM, or IV) or rectal corticosteroids are not permitted during the study and must not have been used within a 4-week period prior to Visit 2, and until the end of the trial. • Oral corticosteroids must be at a prednisone equivalent dose of ≤20 mg/day, or ≤9 mg/day of budesonide, and have been at a stable dose for at least 2 weeks prior to Visit 2, and must remain stable until week 12. • If oral corticosteroids were recently discontinued, discontinuation must have been completed at least 2 weeks prior to Visit 2.
CD specific antibiotics	• If using a CD-specific antibiotic for treatment of CD, patients must have been using the antibiotic for at least 4 weeks before Visit 2 at a stable dose and should continue this at the same dose until week 12. • If not currently using a CD specific antibiotic, the stop date must have been at least 4 weeks prior to Visit 2.
Opioids	• Patients with regular daily opioid or cannabis use for more than 3 months prior to Visit 2 are excluded due to the interference of such medications with key efficacy endpoints (CDAI)
Any investigational (or subsequently approved) or non-approved non-biologic/biologic for CD (including but not limited to IL-23 inhibitors [e.g. risankizumab], anti-integrins, JAK inhibitors [e.g. upadacitinib], S1P modulators)	Prior to the study and for the trial duration up to EOS visit • For use as a CD treatment medication, refer to Section 4.2.1

1 As of the date of the initial clinical trial protocol (i.e. 26 Apr 2021)

Tapering of corticosteroids
The tapering of systemic corticosteroids is requested for patients achieving clinical remission at or after week 12 (Visit 8) of the study. In such patients steroids must be tapered at a maximum rate of prednisone 2.5 mg per week (or equivalent – see Appendix 10.5) to a dosage of 0. If a patient experiences a loss of clinical response (increase in CDAI of at least 100 points from baseline on 2 consecutive visits) during steroid tapering, the dosage of prednisone may be increased back to the dosage used at study entry.

Drugs with potential to prolong the QT/QTc interval
Caution is advised with concomitant use of drugs that may increase the exposure of BI 706321 (e.g. strong CYP3A inhibitors) or have high risk of prolonging the QTc interval (e.g. Tricyclic anti-depressants, erythromycin) during the period from 1 week prior to randomisation until Visit 9/week 16. If such concomitant use is planned, close ECG monitoring by the investigator is advised. A list to support the identification of drugs that may increase the exposure of BI 706321 (e.g. strong CYP3A inhibitors) or have a high risk for prolonging the QT can be found in the ISF.

Drug-drug interactions (DDI)
Based on in vitro studies, clinically relevant drug-drug interactions (DDI) with BI 706321 are possible. Particularly, based on in vitro data, BI 706321 is metabolized via CYP3A and is also a substrate of P-glycoprotein (P-gp). A clinical DDI study to evaluate the effect of itraconazole (dual inhibitor of CYP3A and Pgp) on the PK of BI 706321 has been completed [c35839633]. For details, refer to Section 1.2.1 Drug Interactions.

At the 8 mg dose selected for this trial, in vitro data suggests that DDI potential due to the inhibition of P-gp by BI 706321 is possible. Clinically relevant DDIs due to inhibition of all other investigated transporters are considered unlikely.

Concomitant medications which are moderate and strong CYP3A inducers and P-gp substrates for which an increase in exposure could present a potential patient risk should not be co-administered together with BI 706321.

DDI potential of other co-administered CD treatments
The metabolism of 5-ASA compounds, AZA, MP, 6-TG, and MTX is primarily based on processes that do not involve cytochrome P450 (CYP) enzymes. None of these compounds are known to be P-gp substrates (MP is a substrate of ENT2 and MTX is a substrate of BCRP and MRP2). Given that there is no clear clinical evidence showing the modulation of CYP3A or P-gp by these compounds, clinically relevant DDIs between these compounds and BI 706321 are not expected.

The overall DDI risk with co-administration of corticosteroids is acceptable. Prednisone, methylprednisolone, and dexamethasone are weak CYP3A inducers, thus the exposure of BI 706321 might be slightly reduced when co-administered. In vitro studies report 21-desacetyl deflazacort, deflazacort, budesonide, methylprednisolone, and prednisone are P-gp substrates. As they are also CYP3A4 substrates, most clinical DDI findings regarding these corticosteroids resulted from CYP3A induction or inhibition, although inhibition and

induction of P-gp may also have contributed. When corticosteroids are co-administered together with BI 706321, the exposure of these corticosteroids might be slightly increased due to the inhibition of P-gp by BI 706321, however given the dosage limitations specified in the trial inclusion criteria (prednisone equivalent dose of ≤ 20 mg/day or ≤ 9 mg/day of budesonide, see Section 3.3.2), and the potential degree of increase (approximately <1.5X AUC), this range of interaction is considered acceptable.

Table 4.2.2.1: 2 Restricted concomitant medication and foods[1] – from 1 week prior to randomisation until Visit 9/week 16 (list of medications is in ISF).

Medications or class of medications	Specified restriction time
Drugs or foods that are strong or moderate CYP3A inducers (e.g. phenytoin, carbamazepine, phenobarbital, rifampin)	1 week prior to randomisation until Visit 9 / week 16
Drugs that are P-gp substrates for which an increase in exposure could present a potential patient risk (e.g., dabigatran, digoxin, fexofenadine)	

1 Patients should avoid foods that are known strong or moderate inducers of CYP3A e.g., St. John's Wort

A list to support the identification of drugs that may have potential DDI interactions with BI 706321 can be found in the ISF. The list does not contain medications which are used for CD therapy (see Table 4.2.2.1:1). The list is not comprehensive. For example, drugs that are solely indicated for disease that are excluded in this trial, such as cancer drugs, may not be listed. For further guidance investigators are referred to the current IB [c26475781] and/or may contact the Sponsor. All other concomitant medications will be recorded in the eCRF up to the EoS visit.

4.2.2.2 Restrictions on diet and life style

Blood samples for safety should be taken after patient has fasted for at least 6 hours as indicated in the Flow Chart (only Visit 2, 6, 7, 8 and 9). Please also see Section 4.1.4. After randomisation, participants should avoid foods that are known strong or moderate inducers of CYP3A such as St. John's Wort.

4.2.2.3 Contraception requirements

WOCBP (for the definition please refer to Section 3.3.3) must use one medically approved method of birth control from screening through Visit 8, and for a period of at least 28 days (*i.e. until Visit 9*) after last trial drug intake.

WOCBP (trial participant) must use a highly effective (non-barrier) method of birth control per ICH M3 (R2) that results in a failure rate of less than 1% per year when used consistently and correctly if their sexual partner is a man able to father a child.

- 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 (IUS).
- Bilateral tubal occlusion.
- 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.

After Visit 9 the current version of SmPC/US PI for ustekinumab has to be followed.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on tablet counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of actually taken} \times 100}{\text{Number of tablets which should have been taken as directed by the investigator}}$$

If the number of doses taken is not between 80-120% site staff will explain to the patient the importance of treatment compliance.

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 endoscopy (ileocolonoscopy) examination provides information on the inflammatory 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 be used for histopathologic examination and exploration of disease and RIPK2 pathway specific biomarkers.

Clinician's assessment portion of CDAI assesses the CD disease activity.

PROs include the IBDQ, and the diary portion of the CDAI. The Patient reported outcome-2 (PRO-2) includes only the two CDAI items stool frequency and abdominal pain and will be analyzed retrospectively based on those recorded elements of the CDAI score.

5.1.1 Ileocolonoscopy-related assessments (SES-CD and CDEIS)

The endoscopy (ileocolonoscopy) examination provides information on the inflammatory status of the terminal ileum and colon. The endoscopic CD activity will be assessed using the Simple Endoscopic Score for Crohn's Disease (SES-CD). 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 calculation details are provided in Appendix 10.3.

The Crohn's Disease Endoscopic Index of Severity (CDEIS) is a scoring system in which 6 endoscopic variables (presence of ulcers, superficial ulcers, nonulcerated stenosis, ulcerated stenosis, proportion of ulcerated surface, proportion of surface affected by disease) are assessed in each of the 5 ileocolonic segments: rectum, sigmoid and left colon, transverse colon, right colon, and ileum. CDEIS scores range from 0 to 44 with higher scores indicating more severe disease [R97-2645].

The SES-CD and CDEIS will be measured at the timepoints noted in the Flow Chart.

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.

Central review will be assessed based on both the SES-CD and CDEIS.

Further information can be found in the Vendor Manual.

The patient has to undergo bowel preparation before each ileocolonoscopy, following the local standards.

5.1.2 Crohn's Disease Activity Index (CDAI)

The clinical changes in 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 a Diary daily. The CDAI will be assessed at the timepoints noted in the Flow Chart and it is provided in Appendix 10.5.

5.1.3 Inflammatory Bowel Disease Questionnaire (IBDQ)

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

The IBDQ will be measured at the timepoints noted in the Flow Chart.

The IBDQ has a 2-week recall period.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete and symptomatic physical examination will be performed at the time points specified in the Flow Chart.

A complete physical examination (indicated in the Flow Chart as "full") includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities and skin.

A symptomatic physical examination will be performed at the timepoints specified in the Flow Chart. It includes an examination which is driven by signs and symptoms reported by the patients or identified by the investigator.

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

Measurement of height and body weight (including determination of the ideal body weight) will be performed at the time points specified in the Flow Chart.

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 (*only at Visit 1 until Visit 9*), systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

Body weight and height will be evaluated at the time points specified in the Flow Chart, both should be done with shoes and clothes and in the same way throughout the trial.

5.2.3 Safety laboratory parameters

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

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.

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 hepatic injury are fulfilled, a number of additional measures will be performed (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, excluding Ustekinumab drug levels and anti-drug antibody levels (for all visits) and for the screening visit: Enteric pathogens, Previously used biologic treatment, Infection testing .

Table 5.2.3: 1 Laboratory tests

Functional lab group	Test name	Only Screening	V 2, V4 – V 9*	Only V3	V10 - V13
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) White blood cell count (WBC) Platelet count/Thrombocytes (quant)	X	X		X
	Reticulocytes (relative and absolute)	X	X		
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes	X	X		X
Manual differential WBC (if Automatic differential WBC is abnormal and clinically relevant in the opinion of the investigator), relative and absolute	Polymorphonuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes	X	X		X
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin time (INR) Fibrinogen	X	X		
Enzymes	AST (GOT), SGOT ALT (GPT), SGPT Alkaline phosphatase (AP)	X	X		X
	Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Lipase Amylase	X	X		

Table 5.2.3: 1 Laboratory tests (cont`d)

Functional lab group	Test name	Only Screening	V 2, V4 – V 9*	Only V3	V10 - V13
Substrates	Glucose BUN (blood urea nitrogen) Creatinine Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Protein, total Serum albumin	X	X		X
	Uric acid Haptoglobin Ferritin Troponin	X	X		
	Cholesterol, total HDL cholesterol LDL cholesterol Triglycerides		Only V2, V6, V7, V8, V9		
	eGFR (estimated by CKD-EPI formula)	X			
	C-Reactive Protein (CRP, high sensitivity)	X	X	X	X
Substrates	Serum Amyloid A (SAA)	X	X	X	
Electrolytes	Sodium Potassium Calcium Chloride Bicarbonate	X	X		X
Hormone panel (males only);	Testicular function panel: FSH (follicle stimulating hormone), LH (luteinizing hormone), total testosterone, free testosterone	X	Only V6, V7, V8		
Urine Macro and Micro Panel	Color & Clarity Specific Gravity pH Protein Glucose Ketones Bilirubin Urobilinogen Blood Nitrite Leukocyte Esterase	X	X		

Table 5.2.3: 1 Laboratory tests (cont`d)

Functional lab group	Test name	Only Screening	V 2, V4 – V 9*	Only V3	V10 - V13
Urine Pregnancy test (only for WOCBP)	Human Chorionic Gonadotropin in the urine	X	X		
Serum Pregnancy test (only for WOCBP) at screening or if urine pregnancy test is positive	Human Serum Chorionic Gonadotropin	X	X		
Fecal studies	Enteric pathogens: Salmonella Shigella Yersinia Campylobacter Vibrio E. coli O157/H7 Clostridia difficile toxin (toxin A/B and GDH antigen), if results indeterminate, a reflex PCR test will be done; Enteric parasites and their ova (including Cryptosporidia)	X			
	As part of the "Faecal sampling for Biomarkers" • Fecal calprotectin • Fecal lactoferrin	X	Only V2, V6, V7, V8 and V9		X
Ustekinumab drug levels and anti-drug antibody levels (only as per flowsheet)	Serum ustekinumab concentration Antibodies to ustekinumab		Only V2, V6, V7 and V8		Only V10 and V13
Previously used biologic treatment	adalimumab, infliximab, golimumab, certolizumab pegol, vedolizumab (*only if patients previously treated with and < 4 weeks since last dose*)	X			
Hormones	Thyroid stimulating hormone (TSH) (free T3 and T4, reflex in case of abnormal TSH)	X			

Table 5.2.3: 1 Laboratory tests (cont`d)

Functional lab group	Test name	Only Screening	V 2, V4 – V 9*	Only V3	V10 - V13
Infection testing	Hepatitis B Surface antigen (qualitative) Hepatitis B Core antibody (qualitative) Hepatitis B-DNA (reflex in case of positive HBV Core Antibody and negative HBV Surface Antigen) Hepatitis C antibody (qualitative) Hepatitis C Virus RNA PCR (reflex in case of positive HCV antibody and treated HCV infection) HIV-1 and HIV-2 antibody (qualitative) QuantiFERON®-TB* COVID-19 (*can be repeated during the trial in the case of a suspected SARS-COV2 infection*) **There is the trial site option to perform a TST (PPD skin test). If the first Quantiferon®-TB-Gold Plus test result is indeterminate, a re-test should be performed. If the Quantiferon®-TB-Gold Plus re-test is indeterminate, a PPD skin test should be performed.*	X				

* Not Visit 8A, 8B, 8C

5.2.4 Electrocardiogram

Twelve-lead resting triplicate ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Chart. Precise electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). ECGs may be repeated for quality reasons and the repeated recording used for analysis.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment so that all patients are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in one position.

ECG recording will always precede all other study procedures scheduled for the same time to avoid compromising ECG quality. At Visit 2 an additional assessment after the intake of the trial medication should be done before the 3-hours PK blood sample is taken (i.e. 3 hours PK postdose sample). At Visit 6 and Visit 8 an additional assessment after the

intake of the trial medication should be done before the 6-hours PK blood sample is taken (i.e. 6 hours PK postdose sample).

If necessary, additional ECGs may be recorded for safety reasons. These unscheduled ECGs will also be centrally read and assigned to "UNSCHED/Unscheduled"-time point in the Sponsor's database. UNSCHED locally read ECGs will not be captured in the eCRF, only as AE, if any.

The digital ECG recordings will be transmitted to a vendor for central evaluation. The evaluation will be performed during the study and/or after the study but will not influence the treatment of the patient. All ECGs will be stored electronically in the system of the vendor. In case of repeat ECGs due to quality reasons, only the repeated ECG recordings will be transferred to the central ECG lab, whereas the initially recorded ECGs will be discarded. UNSCHED ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths. Data transfer from the central ECG lab to the sponsor is described in a document that is filed in the Trial Master File (TMF). Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the Food and Drug Administration (FDA) requirements for annotated digital ECGs [R09-4830].

In addition, all ECGs will be evaluated by the investigator or a designee. Clinically relevant abnormal findings (the investigator is instructed to give special attention to the QT values) will be reported either as baseline condition (*if identified at the Visit 1A*) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

5.2.5.1 Patient Diary

The diary will be given to the patient at Visit 1. Patients are asked to complete the diary on a daily basis which will cover the trial medication intake (time and with/without food, i.e. from Visit 2 to Visit 8) and the CDAI score.

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 conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

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

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation 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.

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:

Potential Severe DILI
A potential severe Drug Induced Liver Injury (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.

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 (severity) of the AE should be judged based on the following:

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

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 aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).

- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is 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 End of Study (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 (see Section 5.2.6.2.2), but not on the CRF.

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 CRO'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 Contract Research Organisation (CRO) or 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.

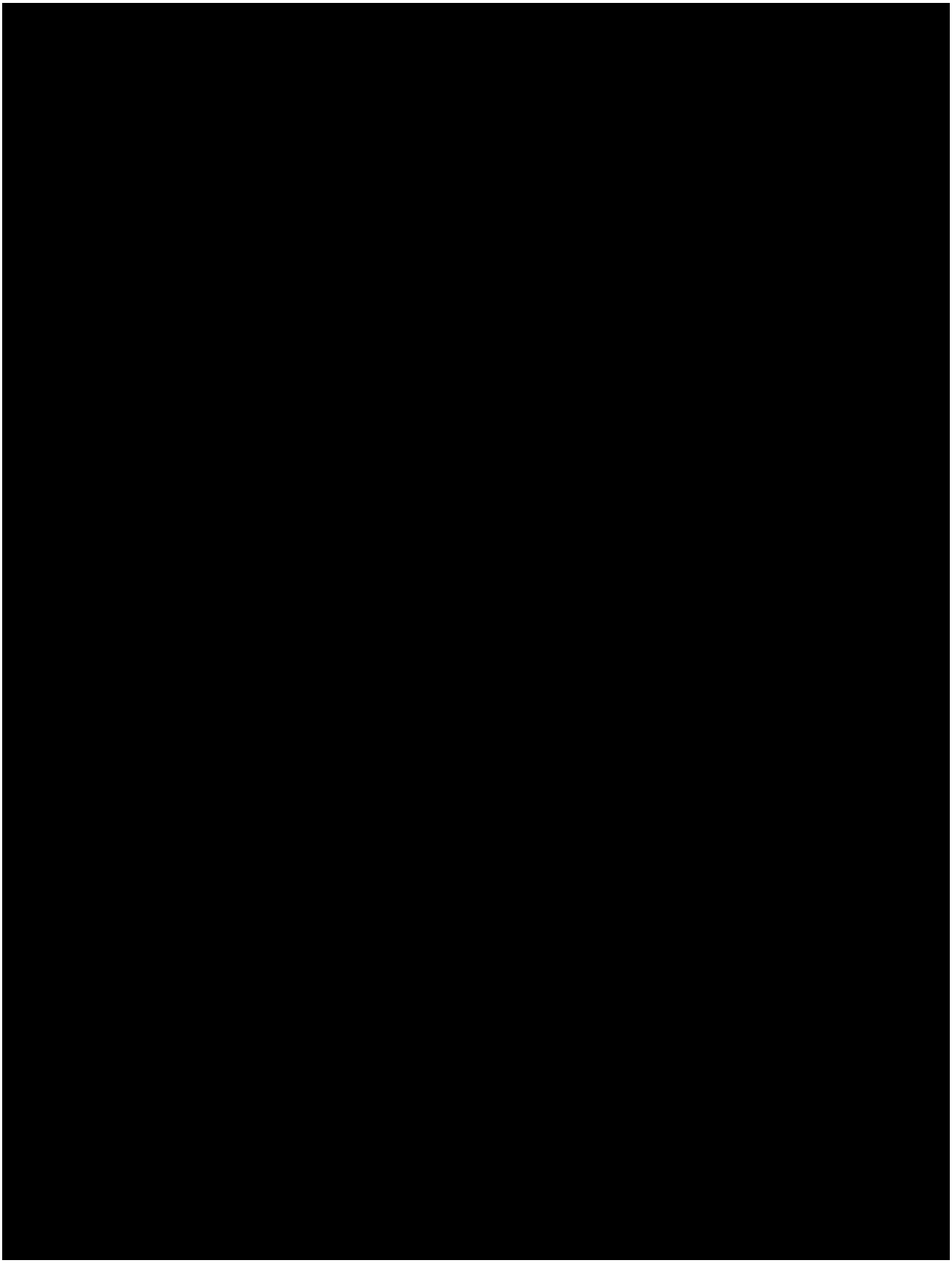
5.2.6.2.3 Pregnancy

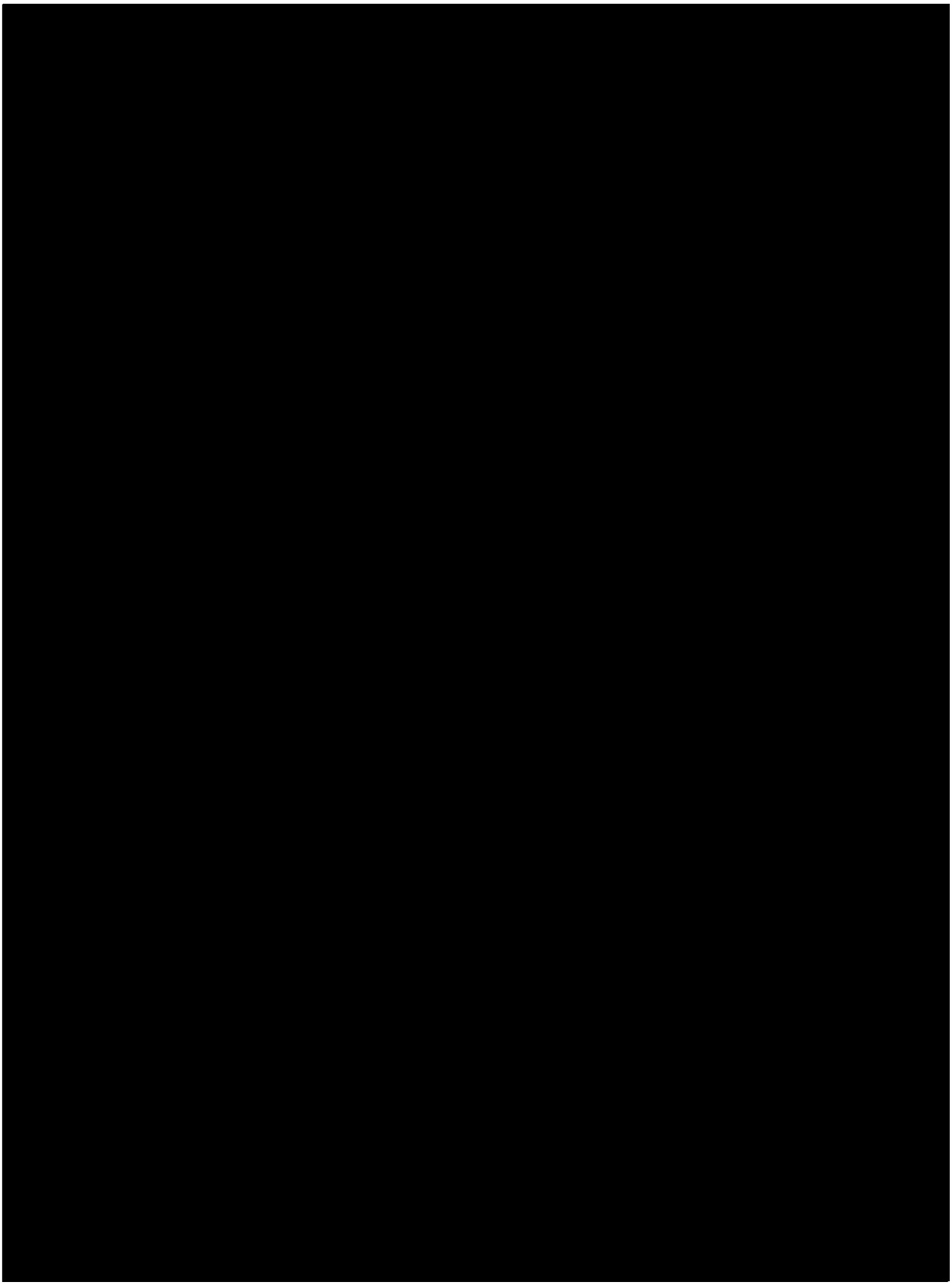
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring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

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the CRO'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.





5.5 BIOBANKING

Blood samples (10 ml) and stool samples (1-5 g) will be collected at timepoints indicated in the Flow Chart for the analysis of biomarkers.

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.

5.6 OTHER ASSESSMENTS

N/A

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements conducted for primary and secondary endpoints are using standard methods. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug, and are widely used in clinical trials. The

pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure. The biomarkers and pharmacodynamic parameters and measurements outlined in Section 5.4 are of exploratory nature.

6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this clinical trial protocol 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, and home healthcare nurse visits. Such alternative measures will be mentioned in the patient information.

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) is to be counted from Day 1 (i.e. Visit 2, the randomisation visit). If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Unscheduled visits may be included as deemed necessary by the investigator.

Patients will get a patient diary for documentation of trial medication intake and documentation of parameter for the CDAI scoring.

If a patient misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

Depending on the reason, rescreening is allowed up to two times (ref. to Flow Chart and Section 3.3 for more information). If a rescreening will be performed the ileo-colonoscopy will need to be repeated if the time between the original screening ileocolonoscopy and randomisation is > 6 weeks. If the reason for the screen failure was an enteric infection (including SARS-CoV-2 infections, only if GI symptoms were present due to the SARS-CoV-2 infection) the ileo-colonoscopy must be repeated.

If at screening, PCR test for SARS-CoV-2 is positive and patient is asymptomatic, re-test SARS-COV-2 PCR test is allowed (up to 4 times) to confirm patient's eligibility before ileo-colonoscopy and/or Visit 2. If re-test SARS-COV-2 PCR test is negative, patient must meet all other eligibility criteria according to the CTP before patient is randomized at Visit 2. Already performed screening assessment do not need to be repeated.
On visit days (i.e. Visit 3, Visit 4, Visit 5, Visit 6, Visit 7, and Visit 8), the trial medication has to be taken in the morning at the trial site.

In situations where an individual patient is unable to attend a clinic visit (because e.g. of force majeure or other disrupting circumstances such as pandemic, war) the investigator must assess the risk-benefit for the individual patient and may decide to perform a visit remotely or home visit if this is in the best interest of the patient and if agreed with the Sponsor. The visits when the ileocolonoscopy is performed can only be done at the clinical site.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Screening Period
All patients must sign an Informed Consent consistent with ICH GCP guidelines prior to any study specific procedures; this includes the option that the patient signs the Informed Consent during an extra contact to the study site prior to the actual screening visit. The patient should be recorded on the enrolment log as a screened patient when Visit 1 is performed.
Screening period could be extenended for additional 21 days, if this is required due to logistical reasons (e.g. delay in lab assessment) and approved by sponsor.

Run-in Period
N/A.

Baseline Conditions
Any pre-existing medical conditions considered as relevant by the investigator, excluding the indication of the trial, are to be recorded into the eCRF in the appropriate page. Any abnormal clinically significant findings observed at Visit 1 need to be documented as Baseline Conditions.

Medical History:
All relevant medical history according to the investigator judgment will be captured in the eCRF.

6.2.2 Treatment period(s)

On Visit 2 the first intake of the trial medication will be done under direct supervision of the investigator or [redacted]designee. Induction treatment period includes visits until Visit 8, when the last intake of BI 706321 or placebo occurs.

Details on administration of study treatment are described in Section 4.1.4. The treatment with ustekinumab will start together with trial medication treatment.

If a patient permanently discontinues BI 706321/placebo and/or ustekinumab treatment before completing 10 weeks of treatment in the induction treatment period, an early EoT visit is required within 14 days after the last BI 706321/placebo dose. This early EoT visit will include the same procedures as a normal EoT visit (i.e. Visit 8), except there will be no endoscopic assessment if <6 weeks of trial treatment is received. Assessment of CDAI does not need to be repeated if early EoT is done within 7 days after a previous visit. For early completion of the trial after the early EoT visit, patients should undergo only Visit 9 (and not EoS visit).

If a patient discontinues BI 706321/placebo trial treatment after completing 10 weeks of treatment of the induction treatment period (early EoT visit has to be performed) and if it is medically appropriate to continue treatment with ustekinumab, the patient may remain in the trial and follow the visit schedule and perform EoS visit as planned. If patients discontinue

after completing 10 weeks of treatment, the endoscopic assessment should be performed at 12 weeks after randomisation.

Assessments have to be performed as per the Flow Chart.

6.2.3 Follow-up period and trial completion

- In this trial the follow-up period starts with Visit 8A. Throughout the follow-up period the patient will receive ustekinumab. The last administration of ustekinumab in the trial is V12.
- If the decision is made for a patient to permanently discontinue ustekinumab treatment early but between Visit 8 and Visit 9, Visit 9 should be performed as the last trial visit at least 16 days after the last BI 706321/placebo dose.
- If a patient permanently discontinues ustekinumab treatment early during the follow-up period but after Visit 9, an early EoS visit is required within 14 days after the decision had been made to discontinue ustekinumab treatment. If early discontinuation occurs after week 24 or beyond, the ileo-colonoscopy assessment of the EoS visit should be performed.
- For all patients the reason for withdrawal from trial treatment (e.g. AEs) must be recorded in the eCRF. These data will be included in the trial database and reported.
- At visit EoS the investigator will decide on the further treatment of CD, which is not in the scope of this clinical trial.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

This is a Phase IIa, randomised, double-blind, placebo-controlled study to investigate a first signal of efficacy, safety and tolerability of BI 706321 in combination with ustekinumab treatment in patients with moderately to severely active CD. This is an exploratory trial. No confirmatory testing is performed and hence no null and alternative hypotheses are defined. A justification of the sample size is provided in Section 7.5.

7.2 PLANNED ANALYSES

The primary analyses will be conducted after the last patient completes the (e)EOT visit and will be based on the intent-to-treat (ITT) principle, comprising all participants who were randomised and received at least one dose of assigned therapy during the trial.

Safety analyses will be based on actual treatment received.

7.2.1 General considerations

Patient analysis sets:

- Randomised set (RS): all randomised patients, treated or not.
- Treated set (TS): all patients who received at least one dose of trial medication. Treatment assignment will be as treated.
- Full analysis set (FAS): all patients in the RS who received at least 1 dose of trial medication and have analysable post-baseline data (observed or imputed) in at least one efficacy parameter. Treatment assignment will be as randomised.

The FAS will be used for all efficacy endpoints. The TS will be used in all safety evaluations. The efficacy analyses will follow the ITT principle in assigning patients to treatment groups, therefore, efficacy analyses will be analysed as randomised using the FAS. Safety analysis will be performed on randomised patients who received at least one dose of trial medication and will be based on the actual treatment received. The FAS and other patient analysis sets will be fully specified in the TSAP. Additional patient analyses sets not listed above may be defined with details also included in the TSAP.

Handling of Intercurrent Events
The intercurrent events that defined in this trial are discontinuation of BI 706321 during the first 12 weeks.

Strategies for handling of intercurrent events may include:

- Treatment Policy: Intercurrent events are not considered relevant. This strategy is in line with an ITT approach.
- Composite: Individuals who experience an intercurrent event will be considered as treatment failure.

All intercurrent events involving early treatment discontinuation as well as other additional unexpected events will be reviewed during the conduct of the trial. Handling of these as well as other potential strategies will be documented in the TSAP.

7.2.2 Primary endpoint analyses

The FAS will be used for the analysis of the primary endpoint. The primary analysis is a restricted maximum likelihood (REML) based analysis of covariance (ANCOVA) comparing the absolute change from baseline in SES-CD scores at Week 12. Baseline will be the based on screening endoscopic assessment (See Flow Chart). For the ANCOVA model, absolute change in SES-CD score will be the dependent variable, treatment group and baseline corticosteroid use (yes/no) will be fixed effects and baseline SES-CD score will be continuous covariate. The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom and adjust standard errors. Adjusted means for each group and mean difference between treatment groups will be presented along with confidence intervals (95%).

In line with the treatment policy approach all patients with post-baseline endoscopic assessments will be included in the analysis regardless of the occurrence of intercurrent events. Since there is only one planned post baseline endoscopic assessment at Week 12, patients without a post baseline assessment will be excluded from the primary analysis.

To assess the homogeneity of the treatment effect on the primary endpoint across the levels of baseline corticosteroid use, the same ANCOVA model will be fitted, but also including the treatment by baseline corticosteroid use interaction. A descriptive p-value of treatment effect homogeneity will be calculated. No overall treatment effect will be estimated from this model as it is not interpretable.

Sensitivity analyses

Depending on the timing of intercurrent events and consequences they may have on the timing of the post-baseline endoscopic assessment, specific rules for handling of missing data or data collected prior to Week 12 may be implemented for additional analysis of changes in SES-CD.

Descriptive tabulations and figures for SES-CD scores and changes at each visit (baseline, Week 12, Week 48) with the change from baseline will be produced.

Additional details of these analyses will be included in the TSAP.

7.2.3 Secondary endpoint analyses

Percent change from baseline to Week 12 in SES-CD score will be analysed in the same manner as the primary endpoint.

Unadjusted absolute rate difference between treatment groups will be calculated simply as the difference in the observed proportion of patients who achieve binary response and remission

endpoints. The influence of stratification factors (baseline corticosteroid use or other potential prognostic factors) and/or baseline SES-CD will also be explored. These analyses will be specified in the TSAP.

Consistent with a composite strategy for handling of interrcurrent events and potential missing data, Non Response Imputation (NRI) will be applied to clinical and endoscopic response and remission endpoints, that is imputing as failure to achieve a response.

Further details will be given in the TSAP.

7.2.5 Safety analyses

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All AEs with an onset between start of BI 706321/placebo + ustekinumab and end of the REP, a period of 16 days after the last dose of trial medication (BI 706321/placebo), will be assigned to the Induction period for evaluation. Additionally, AEs with an onset between start of BI 706321/placebo + ustekinumab and (e)EOS will be assigned to the Induction + Follow-up period. AEs with onset before the first intake of any trial medication will be assigned to the Screening period.

All treated patients (i.e. the TS) will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring only during the Induction period or the Induction+Follow-up period as defined above will be considered ‘treatment-emergent’ during the respective period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

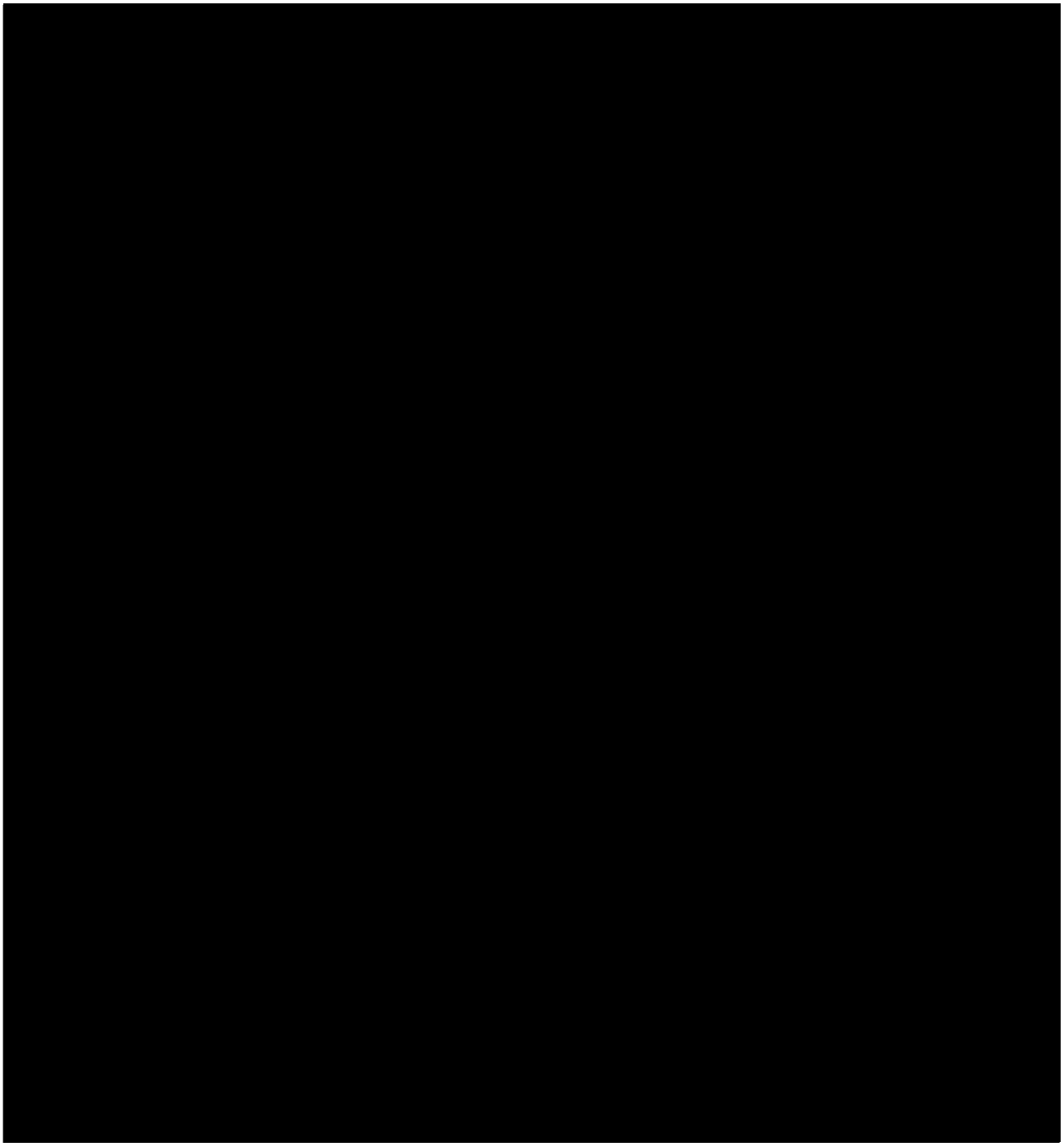
Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at database lock. Summaries will be presented by treatment for all AEs and the defined AESIs.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the

reference range as well as values defined as clinically relevant will be summarised. 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 examination findings, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Summaries of EEG data will be specified in the TSAP.



7.2.7 Interim Analyses

- An interim analysis is planned after approximately 20 patients have been randomised into the study to assess baseline biomarkers associated with the RIPK2 pathway. This assessment of the RIPK2 pathway-specific biomarkers may lead to an increase in the final sample size to improve the sensitivity of exploring the relationship between RIPK2 pathway-specific biomarkers and endoscopic responses among the treatment groups following 12 weeks of treatment. This potential sample size increase may be up to 26 additional patients.
- Additional unblinded assessments (i.e. unblinded descriptive analyses) of secondary and further endpoints as data are collected may also be performed in order to assess the RIPK2 efficacy and enable the review of safety data. Further details and time points for analysis will be specified in a separate operational plan.

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 for the induction period.

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

Details on deriving the CDAI total score and its components in case of missing data will be included in the TSAP

Depending on the nature and timing of intercurrent events and the collection of the post-baseline endoscopic assessment during the first 12 weeks, rules for handling of these SES-CD

assessments as they relate to the change from baseline at week 12 may be considered for sensitivity analyses. Additional details will be documented in the TSAP.

Generally, with regards to handling of missing data on the binary secondary endpoints the NRI will be applied, that is imputing as a failure to achieve a response after 12 Weeks.

For binary endpoints that are collected at multiple visits, 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 failure.

Other imputation approaches may be considered for the primary and secondary endpoints. These approaches along with rules for handling of missing data for further endpoints will be specified in the TSAP.

The handling of missing data for the population PK analysis will be described in a separate Population PK Analysis Plan.

7.4 RANDOMISATION

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

An IRT system will be used for the assignment of patients to treatment groups. Patients will be randomised (1:1) to the either BI 706320 + ustekinumab or Placebo + ustekinumab for 12 weeks.

Randomisation will be stratified based on baseline corticosteroid use (yes/no).

7.5 DETERMINATION OF SAMPLE SIZE

This is an exploratory trial and is planned to include 50 patients to investigate efficacy and tolerability and safety of BI 706321 in combination with ustekinumab treatment in patients with moderately to severely active CD. The sample size is chosen with the objective to primarily have low error probabilities to:

- observe a positive outcome given that ustekinumab + BI 706321 is not more effective compared to ustekinumab + placebo
- observe a negative outcome given that ustekinumab + BI 706321 is more effective than ustekinumab + placebo

Table 7.5:1 below show the criteria considered for treatment effects and observed outcomes that would be considered positive and negative.

Probabilities were calculated from simulations under the assumptions that changes in SES-CD scores are normally distributed with a common standard deviation of 7.0 for each group. Under these assumptions and conditions, the probability of observing an improvement of ≥ 2 points in SES-CD given ustekinumab+BI 706321 is not more effective compared to ustekinumab+placebo is 16.0% and the probability of observing an insufficient level of improvement in SES-CD of <0.5 given that ustekinumab+BI 706321 is more effective in SES-CD by 2.5 points than ustekinumab+placebo is 15.3%.

Table 7.5: 1 Criteria considered for treatment effect, positive/negative outcome and error probabilities for N=25 per group

Assumed true treatment effect	**Observed outcome**	**Error probability***
Combination treatment is **insufficiently effective** (no difference between groups)	**Positive:** Observe an improvement of ≥ 2 points in SES-CD score between groups under the **assumption that the combination treatment effect is insufficient**.	Observe a positive outcome with an ineffective treatment(i.e. false positive) **16.0%**
Combination treatment is **sufficiently effective** (combination therapy is better with an improvement of 2.5 points in SES-CD score)	**Negative:** Observe insufficient improvement (Δ<0.5) in SES-CD between groups under the **assumption that the combination treatment effect is sufficient**	Observe a negative outcome with an effective treatment (i.e. false negative) **15.3%**

*Calculated from 10,000 simulations for two groups with N=25/group and assuming a normal distribution for change in SES-CD score and standard deviation of 7.0 in each group. SAS version 9.4 was used for simulations.

Using the same assumptions of true insufficient and sufficient effect, the probability for observing a negative outcome (difference < 0.5) if combination treatment is ineffective is 59.7% and the probability of observing positive outcome (difference of ≥ 2) if combination treatment is effective is 60.3%. This leaves about 24% uncertainty where the observed outcome is neither positive nor negative (i.e. between 0.5 and 2.0) under each assumed true effect. In this case, the evaluation of expression in RIPK2 pathway genes will be needed to assess whether the combination treatment may be effective or not.

Assessing the proportion of patients with elevated expression in RIPK2 pathway genes at the interim analysis will inform on the potential need to increase the sample size up to a maximum of 76.

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 Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation - 536/2014 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 as 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 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 Clinical Trial Report.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority 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 [applies to all countries except Germany]) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be given sufficient time to consider participation in the trial. The investigator 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 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 (ECG, endoscopy) will be provided to vendor (central reading, imaging). Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

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

8.3.2 Direct access to source data and documents

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

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, please see Section 6), site access may be restricted thus limiting the ability to perform standard site monitoring activities on site such as on-site source data review and source data verification. Therefore, some of these activities may be performed remotely, based on a documented risk assessment and in alignment with local regulations.

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 medication 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 request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

The investigators will have access to a CRO`s web portal 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 Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by a CRO with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

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

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service, a central images service, an electronic Patient Reported Outcome (ePRO) service and an IRT vendor will be used in this trial. Details will be provided in the respective Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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R07-4722 Guidance for industry: E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) 2005.

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R18-2865 Gater A, Kitchen H, Heron L, et al. Development of a conceptual model evaluating the humanistic and economic burden of Crohn's disease: implications for patient-reported outcomes measurement and economic evaluation. Expert Rev. Pharmacoeconomics Outcomes Res. 2015;15(4):643-656.

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R21-1348 Danese S, Vermeire S, D'Haens G, et al. Clinical and endoscopic response to ustekinumab in Crohn's disease: week 16 interim analysis of the STARDUST trial. J Crohns Colitis 2020;14:49-52.

9.2 UNPUBLISHED REFERENCES

c26475781 BI 706321 Investigator's Brochure. Current version.

c34844753 TMCP List of Analyses for BI 706321

c35839633 BI 706321 Clinical Trial Report 1425-0010

10. APPENDICES

10.1 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

Table 10.1: 1 Time schedule for PK blood sampling

Visit	Week	Day	Timepoint	Planned Time*	PK Sample	Sampling Window
2	0	1	Predose	-1:00	X	60 to 5 minutes before start of dosing
			1 hour postdose	1:00	X	0:30 h – 1:30 h postdose
			3 hours postdose***	3:00	X	2:30 h – 3:30 h postdose
			6 hours postdose**	6:00	X	5:00 h – 7:00 h postdose or at next day in the morning
3	1	4	Predose	71:00	X	60 to 5 minutes before start of dosing
4	1	8	Predose	167:00	X	60 to 5 minutes before start of dosing
5	2	15	Predose	335:00	X	60 to 5 minutes before start of dosing
6	4	29	Predose	671:00	X	60 to 5 minutes before start of dosing
			1 hour postdose	673:00	X	0:30 h – 1:30 h postdose
			3 hours postdose	675:00	X	2:30 h – 3:30 h postdose
			6 hours postdose***	678:00	X	5:00 h – 7:00 h postdose
7	8	57	Predose	1343:00	X	60 to 5 minutes before start of dosing

Table 10.1: 1 Time schedule for PK blood sampling (cont`d)

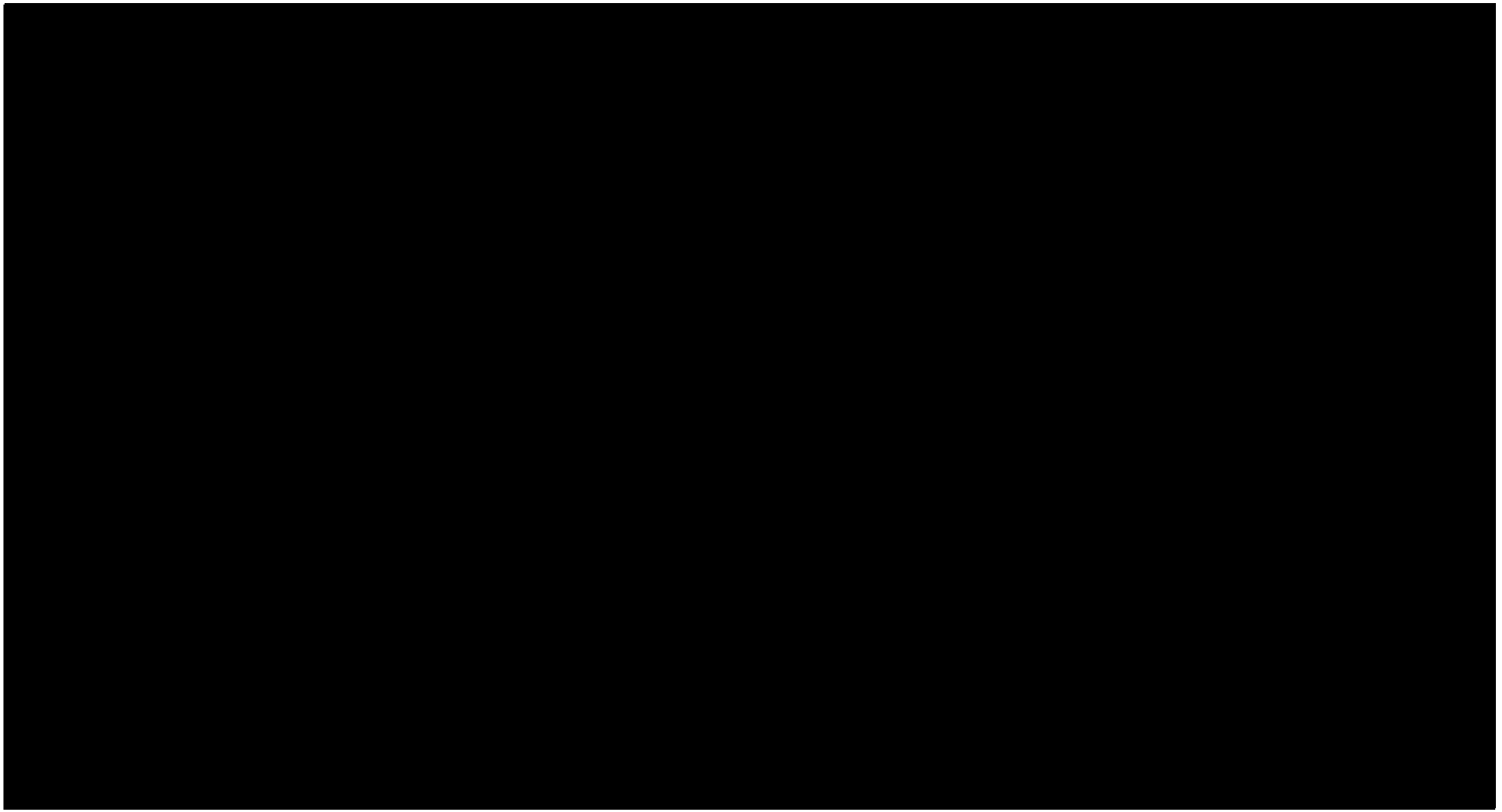
Visit	Week	Day	Timepoint	Planned Time*	PK Sample	Sampling Window
8 (EOT†)	12	85	Predose	2015:00	X	60 to 5 minutes before start of dosing
			1 hour postdose	2017:00	X	0:30 h – 1:30 h postdose
			3 hours postdose	2019:00	X	2:30 h – 3:30 h postdose
			6 hours postdose***	2022:00	X	5:00 h – 7:00 h postdose
8A	12	86	24 hours postdose	2040:00	X	24:00 h – 48:00 h postdose
8B	12	89	96 hours postdose	2112:00	X	96:00 – 120:00 h postdose
8C	12	91	144 hours postdose	2160:00	X	144:00 h – 156:00 h postdose

*The PK analysis for this study will use a population PK approach. Therefore, samples do not have to be taken precisely at the Planned Time. Instead they must be taken at any time during the Sampling Window that corresponds to the Planned Time in this table. However, i**t is essential that the exact sample date and time, as well as the date and time of the dose before the PK sample is taken are recorded.**

**This sample can also be taken as late as approximately 24 h after first dosing at the next day to allow flexibility. Such a visit has to be captured as UNSCHED visit.

***an ECG assessment has to be performed before blood sample is taken.

† If a patient terminates the study before Visit 8, the early EoT visit needs to be scheduled within 14 days after the last dose. If the early EoT visit is scheduled within 3 days after the last dose, 4 PK samples will be collected at timepoints relative to the regular dosing time during the early EoT visit. If the early EoT visit is scheduled more than 3 days after the last dose, 1 PK sample will be collected at regular dosing time during the early EoT visit. It is essential that the **exact sample date and time**, as well as the **date and time of the last IMP intake** are recorded.



10.3 SIMPLE ENDOSCOPIC SCORE FOR CROHN'S DISEASE (SES-CD)

Table 10.3: 1 SES-CD Score

	SES CD score			
Variable	0	1	2	3
Size of ulcers	None	Aphthous ulcers (W0.1-≤0.5 cm)	Large ulcers (W>0.5- ≤2 cm)	Very large ulcers (>W2 cm)
Extent of ulcerated surface	None	<10%	10-30%	>30%
Extent of affected surface	Unaffected segment	<50%	50-75%	>75%
Presence and type of narrowings	None	Single, can be passed	Multiple, can be passed	Cannot be passed

Score 0 - 3

	Ileum	Right colon	Transverse colon	Left colon	Rectum	SUM
Size of ulcers						+
Extent of ulcerated surface						+
Extent of affected surface						+
Presence and type of narrowings						=
						Sum of all variables Total

10.4 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 10.4: 1 Activity score for Crohn's Disease

Variable	Weighting Factor
Sum of daily number of liquid or very soft stools in the last 7 days	x 2
Abdominal pain: Sum of daily rating in the last 7 days (0=none, 1=mild, 2=moderate, 3=severe)	x 5
General well-being: Sum of 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 gangrenosum, aphthous stomatitis - Anal fissure, fistula, or abscess - Other bowel-related fistulae - Fever over 37.8°C (100°F) during past 7 days	x 20
Taking medication 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

10.5 EQUIVALENT DOSES OF CORTICOSTEROIDS

Table 10.5: 1 Equivalent doses of Corticosteroids

Drug	Equivalent dose (mg)	Conversion factor
Prednisone	5.00	X 1.00
Prednisolone	5.00	X 1.00
Triamcinolone	4.00	X 1.25
6-Methylprednisolone	4.00	X 1.25
Dexamethasone	1.00	X 5.00
Betamethasone	0.75	X 6.70
16-Methylprednisolone	6.00	X 0.80
Fluocortalon	5.00	X 1.00
Cloprednol	3.75 – 5.00	X 1.00 – 1.50
Deflazacort	6.00	X 0.80
Cortisol (hydrocortisone)	20.0	X 0.25
Cortisone	25.0	X 0.20

10.6 CLINICAL CRITERIA FOR 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-tongueuvula)

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 lipstongue-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.

10.7 DEFINITION OF PRIMARY, SECONDARY NONRESPONSE OR INTOLERANCE TO ANTI-TNF THERAPY

The criteria for primary non-response (inadequate initial response), secondary non response (response followed by loss of response), or intolerance to TNF antagonists are described below.

10.7.1 Primary non-response (inadequate initial response) to TNF antagonists

Eligible patients must satisfy criteria A, B, and C.

A. Have received induction doses of:
- Infliximab (2 or 3 doses of ≥ 5 mg/kg) or
- Adalimumab (at a dose of 160 mg followed by a dose ≥ 80 mg or at a dose of 80 mg followed by a dose ≥ 40 mg or
- Certolizumab pegol (2 or 3 doses of ≥ 400 mg)

AND

B. Did not initially respond to these induction doses of infliximab, adalimumab, or certolizumab pegol as evidenced by the presence of at least 1 of the following signs or symptoms related to persistence of Crohn's Disease, as assessed by a treating physician:
- Lack of improvement or worsening in stool frequency.
- Lack of improvement or worsening in daily abdominal pain.
- Occurrence, lack of improvement, or worsening of fever thought to be related to Crohn's Disease.

- Recurring drainage from a previously nondraining fistula or development of a new draining fistula.
- Lack of improvement or worsening in rectal bleeding.
- Initiation or increase in antidiarrheal medication.

These signs and symptoms of Crohn's Disease must have occurred ≥ 2 weeks after receiving the last induction dose of infliximab, adalimumab or certolizumab pegol and are offered only as a benchmark of the minimally acceptable criteria required to designate a patient as having had an inadequate initial response to infliximab, adalimumab or certolizumab pegol therapy. This benchmark acknowledges that the CDAI is not routinely recorded in clinical practice.

AND

C. Have documentation available to the investigator that meets the following 2 requirements:

- Provide the dates and doses of the failed infliximab, adalimumab or certolizumab pegol induction therapy.
- Documents that the patient had persistence of disease activity following infliximab, adalimumab, or certolizumab pegol therapy.
- Examples of acceptable documents include: medical records, letter provided by a referring physician, or other "reason for referral" documents (e.g., insurance authorization form).

10.7.2 Secondary non response (response followed by loss of response) to TNF antagonists

Eligible patients must satisfy criteria A, B, C, and D.

A. Initially responded to induction therapy

AND

B. Have received at least 2 maintenance doses of:

- Infliximab (at a dose of ≥ 5 mg/kg) or
- Adalimumab (at a dose of ≥ 40 mg) or
- Certolizumab pegol (at a dose of ≥ 400 mg)

AND

C. Have or had at least 1 of the following signs or symptoms related to recurrence of Crohn's Disease, as assessed by a treating physician:

- Worsening in stool frequency.
- Worsening in daily abdominal pain.
- Occurrence or worsening in fever thought to be related to Crohn's Disease.
- Recurring drainage from a previously nondraining fistula or development of a new draining fistula.

- Worsening in rectal bleeding.
- Initiation or increase in antidiarrheal medication.

These signs and symptoms of Crohn's Disease must have occurred ≥ 2 weeks after receiving the last maintenance dose of infliximab, adalimumab, or certolizumab pegol and are offered only as a benchmark of the minimally acceptable criteria required to designate a patient as having lost response to infliximab, adalimumab, or certolizumab pegol therapy. This benchmark acknowledges that the CDAI is not routinely recorded in clinical practice.

AND

D. Have documentation available to the investigator that meets the following 2 requirements:

- Provide the dates and doses of the failed infliximab, adalimumab, or certolizumab pegol maintenance therapy.
- Documents that the patient had recurrence of disease activity despite infliximab, adalimumab, or certolizumab pegol therapy.

Examples of acceptable documents include: medical records, letter provided by a referring physician, or other "reason for referral" documents (e.g., insurance authorization form).

10.7.3 Intolerance to TNF antagonists

Eligible patients must satisfy criteria A and B.

A. Have had an adverse reaction that meets 1 of the following 3 criteria:

1. Significant acute infusion/administration reaction;
2. Significant delayed infusion/administration reaction (for example, delayed hypersensitivity or serum-sickness like reaction);
3. Significant injection site reaction.

Definitions of these 3 criteria are provided below. Adverse reactions also must have followed ≥ 1 dose of infliximab, adalimumab, or certolizumab pegol and, in the treating physician's opinion, precluded continued use of the therapy.

A significant acute infusion/administration reaction is defined as an adverse reaction that was:

- Manifested through ≥ 1 of the following symptoms.
  - i. Fever greater than 100°F (37.8°C).
  - ii. Chills or rigors.
  - iii. Itching.
  - iv. Rash.
  - v. Flushing.
  - vi. Urticaria or angioedema.
  - vii. Breathing difficulties (dyspnea, chest paint or tightness, shortness of breath, wheezing, stridor).
  - viii. Clinical hypotension (pallor, diaphoresis, faintness, syncope), blood pressure less than 90 mm Hg systolic and 60 mm Hg diastolic, or a systemic or orthostatic drop in systolic blood pressure of greater than 20 mm Hg.

AND

- Was considered related to the infusion/administration of infliximab, adalimumab, or certolizumab pegol.

A significant delayed infusion/administration reaction is defined as an adverse reaction that:

- Was manifested through 1 or more of the following symptoms:
  - i. Myalgias
  - ii. Arthralgias
  - iii. Fever greater than 100°F (37.8°C).
  - iv. Malaise
  - v. Rash.

AND

- Occurred > 24 hours and < 15 days after infusion/administration of infliximab, adalimumab, or certolizumab pegol

AND

- Was considered related to the infusion/administration of infliximab, adalimumab, or certolizumab pegol.

A significant injection site reaction is defined as an adverse reaction that:

- Was manifested through 1 or more of the following symptoms:
  - i. Significant bruising.
  - ii. Erythema.
  - iii. Hemorrhage.
  - iv. Irritation.
  - v. Pain.
  - vi. Pruritus.
  - vii. “Injection site reaction.

AND

- Occurred within 24 hours of an SC injection of adalimumab or certolizumab pegol.

AND

- Was considered related to the injection.

B. Have documentation available to the investigator that meets the following 2 requirements:

- Provides the date of discontinuation of infliximab, adalimumab, or certolizumab pegol.
- Documents that the patient had intolerance to infliximab, adalimumab, certolizumab pegol therapy.

Examples of acceptable documents include: medical records, letter provided by a referring physician, or other “reason for referral” documents (e.g., insurance authorization form).

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		01 Jul 2021
EudraCT number **EU number**		2020-004527-16
BI Trial number		1425-0003
BI Investigational Medicinal Product(s)		BI 706321
Title of protocol		A Phase IIa, randomised, double-blind, placebo-controlled trial to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BI 706321 orally administered for 12 weeks in patients with Crohn`s Disease (CD) receiving ustekinumab induction treatment
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS
Description of change		The title was corrected from: "A Phase IIa, randomised, double-blind, placebo-controlled trial to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BI 706321 orally administered for 12 weeks in patients with Crohn's Disease (CD)" To: "A Phase IIa, randomised, double-blind, placebo-controlled trial to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BI 706321 orally administered for 12 weeks in patients with Crohn's Disease (CD) **receiving ustekinumab induction treatment**"
Rationale for change		Correction of reflect the full and correct title in the synopsis (*no content-wise change*)
Section to be changed		Flowchart
Description of change		• Dispense Patient Diary: "X" at Visit 2, Visit 4, Visit 5, Visit 6 and Visit 7 were deleted as the patient will get a diary at Visit 1 for the entire section. • Collect & Review Patient Diary: "X" were added to Visit 3, Visit 8A, Visit 8B, Visit

		8C, Visit 9, Visit 10, Visit 11, Visit 12, Visit 13 • Footnote "X": "CRO`s SAE form" was changed to "**BI**`s SAE form".
Rationale for change		Corrections to reflect the content of the respective sections, *no content-wise change*.
Section to be changed		1.2.1 (Data from non-clinical studies)
Description of change		The sentence were corrected from: "In vivo, RIPK2 inhibition was also demonstrated to significantly improve signs and symptoms of intestinal inflammation in the spontaneous *T-bet/Rag2* knockout (TRUC) mouse model of Inflammatory Bowl Disease (IBD)." To: "In vivo, RIPK2 inhibition was also demonstrated to significantly improve signs and symptoms of intestinal inflammation in the spontaneous *T-bet/Rag2* knockout (TRUC) mouse model of Inflammatory Bow**e**l Disease (IBD)."
Rationale for change		Correction of the typo (bowel), *no content-wise change*.
Section to be changed		3.3.2
Description of change		Inclusion criteria 9 and 10 were merged (i.e. no content change). The inclusion criterion # 11 of version 1.0 of the CTP is now inclusion criterion # 10.
Rationale for change		Correction, inclusion criterion was splitted incorrectly during the formatting process. *No content-wise change*.
Section to be changed		3.3.41
Description of change		"An individual patient will discontinue trial treatment and/or ustekinumab treatment after week 12 if:…" were changed to "An individual patient will discontinue trial treatment **(including ustekinumab open-label maintenance treatment after week 12)** if:"
Rationale for change		FDA request during initial submission
Section to be changed		3.3.4.1
Description of change		The sublisting of the last bullet point were corrected and for the very last sublisting bullet

		point the wording "o **At week 24 (visit 10):**" were visualised.
Rationale for change		Correction of listing formatting and formatting mistake (i.e. hidden text).
Section to be changed		3.3.4.3
Description of change		The second discontinuation criterion was amended with " • Including, but not limited to, the following scenario, further enrolment, r randomisation into the trial, and treatment of already randomised patients will be interrupted by the sponsor if: o 2 patients on active treatment with serious adverse reactions representing the same MedDRA preferred term (and not reflecting exacerbations of the underlying CD) and o Which, after evaluation by the Sponsor, are considered to have a reasonable causal relationship to BI 706321, and are not typically observed with ustekinumab therapy After the trial has been interrupted, it will only be restarted after an appropriate safety evaluation has been conducted and concluded that the benefit risk of the overall trial is still favourable, and appropriate risk-mitigation measures have been implemented if needed. If a re-start is appropriate, additional patients may be enrolled to replace the patients who were discontinued early due to the trial interruption."
Rationale for change		FDA request during initial submission

11.2 GLOBAL AMENDMENT 2

Global Amendment 2 was created to fulfil the requirements of the French Ethics committee and Health Authority. Due to non-participation of France, Global Amendment 2 was never effective and never implemented.

11.3 GLOBAL AMENDMENT 3

Date of amendment		16 May 2022
EudraCT number **EU number**		2020-004527-16
BI Trial number		1425-0003
BI Investigational Medicinal Product(s)		BI 706321
Title of protocol		A Phase IIa, randomised, double-blind, placebo-controlled trial to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BI 706321 orally administered for 12 weeks in patients with Crohn`s Disease (CD) receiving ustekinumab induction treatment
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Updated ≥50% SES-CD to >50% SES-CD
Rationale for change		Alignment with more recent consensus definitions.
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Re-wording of inclusion criterion No. 3
Rationale for change		Clarification of inclusion criterion.
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Update of inclusion criterion No. 5
Rationale for change		Based on sponsor internal assessment and investigators' feedback.
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Update of inclusion criterion No. 7
Rationale for change		Based on sponsor internal assessment and investigators' feedback.
Section to be changed		Clinical Trial Protocol Synopsis
Description of change		Update of exclusion criterion No. 7 (Pathological safety lab parameters)
Rationale for change		Correction of typo.
Section to be changed		Flowchart
Description of change		Update of days at week 16 to 113

Rationale for change		Correction of typo.
Section to be changed		Flowchart
Description of change		Addition of screening period extension.
Rationale for change		Due to logistical reasons screening period could be extended, if approved by sponsor.
Section to be changed		Flowchart
Description of change		Update of test kits for Ustekinumb serum level.
Rationale for change		Updated according central laboratory procedure.
Section to be changed		Flowchart
Description of change		Footnote U updated to allow re-test for SARS-CoV-2 infected patients who are asymptomatic.
Rationale for change		Updated to reflect changing knowledge regarding COVID-19 pandemic.
Section to be changed		Flowchart
Description of change		Footnote Z added to give guidance in case a patient tests positive during the trial.
Rationale for change		Updated to reflect changing knowledge regarding COVID-19 pandemic.
Section to be changed		1.2.1
Description of change		Based on *in vitro* studies, clinically relevant drug-drug interactions (DDI) with BI 706321 are possible. Based on *in vitro* data, BI 706321 is mainly metabolized via CYP3A and is also a substrate of P-glycoprotein (P-gp). A clinical DDI study **(study 1425-0010)** to evaluate the effect of itraconazole (dual **strong** inhibitor of CYP3A and P-gp) on the PK of BI 706321 **~~is ongoing~~ has been completed. A 2 week administration of itraconazole resulted in only ~2.2 fold increase in AUC of BI 706321.** **Physiologically-based pharmacokinetic (PBPK) modelling of BI 706321 was conducted using data from 1425-0001, 1425-0002, and 1425-0010 in order to assess CYP3A DDI liabilities. Simulations based on the PBPK model were congruent with the results seen in 1425-0010 and additionally showed that no relevant DDI is expected following administration of weak CYP3A perpetrators, and at most a minor increase in exposure is**

		expected following moderate CYP3A inhibitors [c34844753]. Furthermore, based on the only ~2.2-fold increase in AUC of BI 706321 following 2-week administration with itraconazole, as seen in study 1425-0010, even in the presence of strong CYP3A inhibitors, exposures are not expected to exceed any safety thresholds. **Based on the high permeability of BI 706321, inhibition of P-gp is not expected to have a clinically relevant effect; this is supported by PBPK modelling, whereby the complete removal of P-gp transport (equivalent to 100% inhibition of P-gp) resulted in no noticeable change in exposure.** Concomitant medications which are moderate and strong CYP3A inducers ~~**or inhibitors**~~ and ~~**P-gp inhibitors or**~~ P-gp substrates are discussed in Section 4.2.2.1
Rationale for change		Drug interactions information updated with data from completed clinical study and modelling.
Section to be changed		1.4.2
Description of change		Addition of caution for attention to QTc to be taken in the event of use of concomitant medications with a known risk of increasing exposures of BI 706321.
Rationale for change		Removal of some drug-drug interaction restrictions due to new clinical and modelling data, which may result in circumstances where limited increases in BI 706321 exposures may occur.
Section to be changed		2.1.3
Description of change		Updated ≥50% SES-CD to >50% SES-CD
Rationale for change		Alignment with more recent consensus definitions.
Section to be changed		3.3.2 Inclusion criteria
Description of change		Re-wording of inclusion criterion No. 3
Rationale for change		Clarification of inclusion criterion.
Section to be changed		3.3.2 Inclusion criteria
Description of change		Update of inclusion criterion No. 5

Rationale for change		Based on sponsor internal assessment and investigators' feedback.
Section to be changed		3.3.2 Inclusion criteria
Description of change		Update of inclusion criterion No. 7
Rationale for change		Based on sponsor internal assessment and investigators' feedback.
Section to be changed		3.3.3 Exclusion criteria
Description of change		Update of exclusion criterion No. 6 Confirmatory PCR test added if C difficile toxin A/B and antigen test is indeterminate.
Rationale for change		Clarification of C diff testing instructions in case of indeterminate first result.
Section to be changed		3.3.3 Exclusion Criteria
Description of change		Addition of text to exclusion criterion No. 13: **If at screening, PCR test for SARS-CoV-2 is positive and patient is asymptomatic, re-test SARS-COV-2 PCR test is allowed (up to 4 times) to confirm patient's eligibility before ileo-colonoscopy and/or visit 2. If re-test SARS-COV-2 PCR test is negative, patient must meet all other eligibility criteria according to the CTP before patient is randomized at visit 2. Already performed screening assessment do not need to be repeated.**
Rationale for change		Updated to reflect changing knowledge regarding COVID-19 pandemic
Section to be changed		3.3.3 Exclusion Criteria
Description of change		Update of exclusion criterion No. 16: Aspartate aminotransferase (AST) ~~**and**~~ **OR** Alanine aminotransferase (ALT) > 2 times the Upper Level of Normal (ULN). Total bilirubin > 2 x ULN with ratio of direct/indirect >1 (patients with Gilbert's syndrome are not excluded),
Rationale for change		Correction of typo.
Section to be changed		3.3.4.1
Description of change		Absence of **at least** CDAI-70 clinical response as defined by a reduction from baseline **in the CDAI score of ≥ 70 points, or a CDAI score of <150.**
Rationale for change		Wording added for clarification.

Section to be changed		4.2.2
Description of change		Removal of restrictions to concomitant use of moderate and strong CYP3A inhibitors. Removal of restrictions to concomitant use of Pgp-inhibitors. Addition of caution for attention to QTc to be taken in the event of use of concomitant medications with a known risk of limited increases in exposures of BI 706321 (e.g. strong CYP3A inhibitors)
Rationale for change		Data from clinical DDI study 1425-0010 and modelling now available which shows no clinical effect on exposures of BI 706321 due to Pg-p inhibition, minor increase in exposures of BI 706321 due to moderate CYP3A inhibitors, and limited effects on increase in exposures of BI 706321 in the presence of strong CYP3A inhibitors which are not expected to exceed safety thresholds.
Section to be changed		5.2.3
Description of change		Data transfer from Central Laboratory to BI deleted.
Rationale for change		Specific data analyzed by the central laboratory will not be transferred to BI, according to specification with central laboratory.
Section to be changed		5.3.2.1
Description of change		Blood volume deleted.
Rationale for change		Blood volume is stated in central laboratory specifications.
Section to be changed		5.4.1
Description of change		Stool samples will be collected to assess changes in the levels of inflammatory markers such as but not limited to fecal calprotectin, lactoferin, haptoglobin, hemoglobin, ~~**MMP12,**~~ MPO, proteinase 3, resistin, serpin A4, PGRPS, properdin, chitinase 3L like 1, lipocalin 2, ~~**HMGB1**~~ and neopterin pre- and (at various time points) post-treatment in both treatment groups.
Rationale for change		Adaption based on current development approach.

Section to be changed		6.1
Description of change		Addition of text: **If at screening, PCR test for SARS-CoV-2 is positive and patient is asymptomatic, re-test SARS-COV-2 PCR test is allowed (up to 4 times) to confirm patient's eligibility before ileo-colonoscopy and/or visit 2. If re-test SARS-COV-2 PCR test is negative, patient must meet all other eligibility criteria according to the CTP before patient is randomized at visit 2. Already performed screening assessment do not need to be repeated.**
Rationale for change		Updated to reflect changing knowledge regarding COVID-19 pandemic
Section to be changed		6.2.1
Description of change		The patient should be recorded on the enrolment log as a screened patient when Visit 1~~A~~ is performed.
Rationale for change		Correction of typo.
Section to be changed		6.2.1
Description of change		Addition of screening period extension.
Rationale for change		Due to logistical reasons screening period could be extended, if approved by sponsor.
Section to be changed		7.2.1
Description of change		Full analysis set (FAS): all patients in the RS who received at least 1 dose of trial medication **and have analysable data (observed or imputed) in at least one efficacy parameter.**
Rationale for change		Added for clarification
Section to be changed		7.2.2
Description of change		The FAS will be used for the analysis of the primary endpoint. The primary analysis is a restricted maximum likelihood (REML) based analysis of covariance (ANCOVA) ~~**analysis of covariance**~~ comparing the absolute change from baseline in SES-CD scores at Week 12.
Rationale for change		Correction of typo.
Section to be changed		7.2.6
Description of change		Note that not all analyses of biomarker data will be reported in the main CTR and some (e.g.

		transcriptomic analyses) ~~**will**~~ may be reported separately
Rationale for change		Correction of typo.
Section to be changed		10.2: 1
Description of change		Update of days at week 16 to 113
Rationale for change		Correction of typo.
Section to be changed		10.3
Description of change		Specification of scores and wording Updated.
Rationale for change		To be consistent with central reading center.
Section to be changed		10.4.1
Description of change		Average changed to sum.
Rationale for change		Correction of typo.

11.4 GLOBAL AMENDMENT 4

Date of amendment		04 Aug 2023
EudraCT number **EU number**		2020-004527-16
BI Trial number		1425-0003
BI Investigational Medicinal Product(s)		BI 706321
Title of protocol		A Phase IIa, randomised, double-blind, placebo-controlled trial to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BI 706321 orally administered for 12 weeks in patients with Crohn`s Disease (CD) receiving ustekinumab induction treatment
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Title page
Description of change		Update of Clinical Trial Leader name and contact data
Rationale for change		New Clinical Trial Leader assigned

Section to be changed		Clinical Trial Protocol Synopsis, Flow Chart Footnote Y, and Section 3.3.3.1
Description of change		Exclusion criterion No. 5: "Treatment with: (…) o any biologic treatment with a TNF-alpha antagonist (adalimumab, infliximab, golimumab, certolizumab pegol) or vedolizumab **(or a biosimilar of these drugs)** within 4 weeks prior to randomisation (…)"
Rationale for change		Biosimilars added for clarity
Section to be changed		Clinical Trial Protocol Synopsis and Section 3.3.3.1
Description of change		Exclusion criterion No. 5: "Treatment with: (…) o any previous treatment with ustekinumab **(or a biosimilar of this drug)** (…)"
Rationale for change		Biosimilars added for clarity
Section to be changed		Clinical Trial Protocol Synopsis and Section 3.3.3.1
Description of change		Exclusion criterion No. 5: "Treatment with: (…) o any previous treatment with an investigational **(or subsequently approved)** non-biologic/~~-or~~ biologic drug for CD (including but not limited to JAK inhibitors **[e.g. upadacitinib]**, S1P modulators, IL-23 inhibitors **[e.g. risankizumab]**, anti-integrins) (…)"
Rationale for change		Exclusion criteria clarified to reflect the change of marketing status of risankizumab and upadacitinib for CD from investigational to approved
Section to be changed		Clinical Trial Protocol Synopsis, Sections 3.1, 3.3.2, and 4.2.2.1 (Table 4.2.2.1: 1)
Description of change		6-TG added as an allowed concomitant medication and removed from the list of restricted medications
Rationale for change		To accommodate 6-TG usage in the trial as a standard of care for CD in some countries
Section to be changed		Flow Chart
Description of change		CDEIS scoring system added for the evaluation of ileocolonoscopy results
Rationale for change		For consistency with Sections 2.2.2 and 5.1.1

Section to be changed		Flow Chart Footnote O
Description of change		"Trial drug (BI 706321 or Placebo) and ustekinumab ~~will~~ **are recommended to** be given simultaneously."
Rationale for change		To add more flexibility for investigators
Section to be changed		Flow Chart Footnote T
Description of change		It was specified that fasting is not required for post-dose PK sampling.
Rationale for change		For clarity
Section to be changed		Flow Chart Footnote U
Description of change		"If a rescreening will be performed the ileo-colonoscopy has only to be repeated ~~if the rescreening is done later than 6 weeks after the initial screening~~ **if the time between the original screening ileocolonoscopy and randomisation is >6 weeks (time intervals slightly longer than 6 weeks have to be discussed with the Sponsor and can be approved if medically appropriate)** (…)"
Rationale for change		For consistency with Section 6.1
Section to be changed		Flow Chart Footnote W
Description of change		Added: "**End of treatment with ustekinumab in the trial is V12."**
Rationale for change		Added for clarity
Section to be changed		Flow Chart, Sections 3.3.4.1, 4.2.1, 6.2.2, and 6.2.3
Description of change		Procedures for early termination of trial drug clarified
Rationale for change		Additional details provided to cover all possible scenarios for patients who early terminate trial treatment
Section to be changed		Flow Chart and Section 6.2.1
Description of change		Screening period extended to 21 days
Rationale for change		Due to logistical reasons screening period could be extended if approved by the sponsor
Section to be changed		Abbreviations
Description of change		List of abbrevations updated
Rationale for change		To reflect changes in the document

Section to be changed		1.4.2.2
Description of change		"Tuberculosis (TB): Evaluate patients for TB prior to initiating treatment with ustekinumab~~. Initiate treatment of latent TB before administering ustekinumab.~~"
Rationale for change		Sentence deteted for consistency with Section 3.3.3.2, Excl. 12
Section to be changed		4.2.1, 4.2.2.1 (Table 4.2.2.1: 1)
Description of change		'Rescue therapies/medication' language updated
Rationale for change		No rescue therapy defined for the trial
Section to be changed		4.2.2.1
Description of change		Table 4.2.2.1: 1 (restrictions regarding previous and concomitant treatment): Any biologics approved for CD class of medication clarified by adding a footnote and biosimilars
Rationale for change		For clarity
Section to be changed		4.2.2.1
Description of change		Table 4.2.2.1: 1 (restrictions regarding previous and concomitant treatment) updated to add restrictions on the use of JAK inhibitors (including upadacitinib), S1P modulators, and IL-23 inhibitors (including risankizumab) approved for CD
Rationale for change		Updated to reflect the change of marketing status of risankizumab and upadacitinib for CD from investigational to approved
Section to be changed		4.2.2.1
Description of change		Table 4.2.2.1: 1 "(…) Patients with regular daily opioid or cannabis use ~~over the past~~ **for more than** 3 months prior to Visit 2 are excluded due to the interference of such medications with key efficacy endpoints (CDAI) (…)"
Rationale for change		Reworded for clarity
Section to be changed		5.1.1
Description of change		Description of CDEIS assessment added
Rationale for change		To provide details on the CDEIS assessment

Section to be changed		5.4.3
Description of change		Minor change in the description of biopsy sample collection
Rationale for change		For consistency with the lab manual
Section to be changed		6.2.3
Description of change		"(…) Throughout the follow-up period the patient will receive ustekinumab. **The last administration of ustekinumab in the trial is V12**~~. , until the EoS visit is reached (Visit 13).~~ (…)"
Rationale for change		For consistency with the Flow Chart
Section to be changed		8.1
Description of change		Exception on legal representatives added for Germany
Rationale for change		To meet local regulatory requirements
Section to be changed		9.1
Description of change		List of references updated
Rationale for change		To reflect changes in the document
Section to be changed		10.1
Description of change		A footnote added to Table 10.1: 1 to describe PK sampling in case of early termination of trial treatment before Visit 8
Rationale for change		To clarify the process of PK samling in case a patient terminates the study before Visit 8
Section to be changed		10.4
Description of change		Minor rewordings
Rationale for change		For consistency with the eCRF
Section to be changed		Throughout the Clinical Trial Protocol
Description of change		Minor changes made throughout the document
Rationale for change		Correction of minor grammatical or typographical errors

APPROVAL / SIGNATURE PAGE

Document Number: c33919902 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-version-05

Title: A Phase IIa, randomised, double-blind, placebo-controlled trial to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BI 706321 orally administered for 12 weeks in patients with Crohn`s Disease (CD) receiving ustekinumab induction treatment

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Program [redacted]	[redacted]	07 Aug 2023 15:15 CEST
Author-Trial Statistician		07 Aug 2023 16:38 CEST
Approval-Clinical Trial Leader		08 Aug 2023 08:05 CEST
Verification-Paper Signature Completion		08 Aug 2023 08:11 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed

CO-ORDINATING INVESTIGATOR SIGNATURE

Trial Title: **A Phase IIa, randomised, double-blind, placebo-controlled trial to evaluate the safety, efficacy, pharmacokinetics and pharmacodynamics of BI 706321 orally administered for 12 weeks in patients with Crohn`s Disease (CD) receiving ustekinumab induction treatment**

Trial Number: **1425-0003**

Protocol Version: **5.0**

I herewith certify that I agree to adhere to the trial protocol and to all documents referenced in the trial protocol.

Date: 07-aug-2023

Name: [redacted] Signature: [redacted]

DocuSigned by:
[redacted]
Naam ondertekenaar: [redacted]
Reden voor ondertekening: Ik keur dit document goed
Ondertekentijd: [redacted] | 5:52:58 AM CDT
[redacted]

Affiliation: [redacted]

Signed signature page is located in BIRDS

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Abschlusszertifikat

Umschlag-ID: 8836B43DD0D0407EABB19BA98715536C

Status: Abgeschlossen

Betreff: Complete with DocuSign: clinical-trial-portocol-version-05-signature-page-ci-[redacted].docx

Quellumschlag:

Dokumentenseiten: 1

Signaturen: 1

Zertifikatsseiten: 4

Initialen: 0

Signatur mit Anleitung: Aktiviert

Umschlag-ID-Stempel: Aktiviert

Zeitzone: (UTC+01:00) Amsterdam, Berlin, Bern, Rom, Stockholm, Wien

Umschlagersteller:
[redacted]

IP-Adresse: [redacted]

Eintragsverfolgung

Status: Original
07.08.2023 12:24:53

Inhaber [redacted]

Standort: DocuSign

Unterzeichnerereignisse	Signatur	Zeitstempel
[redacted] Full [redacted] of Medicine Sicherheitsstufe: E-Mail, Kontoauthentifizierung (erforderlich)	DocuSigned by: [redacted] Naam ondertekenaar: [redacted] Reden voor ondertekening: Ik keur dit document goed Ondertekentijd: [redacted] | 5:52:58 AM CDT [redacted] Signaturübernahme: [redacted] Signatur-ID: [redacted] Mit IP-Adresse: [redacted] Mit Signaturauthentifizierung über DocuSign-Passwort Mit Signiergrund (auf jeder Registerkarte): Ik keur dit document goed	Gesendet: 07.08.2023 12:27:00 Eingesehen: 07.08.2023 12:52:40 Signiert: 07.08.2023 12:53:03

Vereinbarung bezüglich elektronischer Unterlagen und Signaturen:
Akzeptiert: 07.08.2023 12:52:40
ID: 3785170a-68c2-4089-bf5f-78d6b8786138

Vor-Ort-Unterzeichner – Ereignisse	Signatur	Zeitstempel

Bearbeiterversandereignisse	Status	Zeitstempel

Beauftragtenzustellereignisse	Status	Zeitstempel

Vermittlerversandereignisse	Status	Zeitstempel

Zertifizierter Versand - Ereignisse	Status	Zeitstempel

Kopienereignisse	Status	Zeitstempel

Zeugen-Ereignisse	Signatur	Zeitstempel

Notarereignisse	Signatur	Zeitstempel

Umschlagereignisse – Überblick	Status	Zeitstempel
Umschlag gesendet	Hash-codiert/verschlüsselt	07.08.2023 12:27:00
Zertifiziert zugestellt	Sicherheitsprüfung ausgeführt	07.08.2023 12:52:40
Signiervorgang abgeschlossen	Sicherheitsprüfung ausgeführt	07.08.2023 12:53:03

Umschlagereignisse – Überblick	**Status**	**Zeitstempel**
Abgeschlossen	Sicherheitsprüfung ausgeführt	07.08.2023 12:53:03

Zahlungen	**Status**	**Zeitstempel**

Vereinbarung bezüglich elektronischer Unterlagen und Signaturen

Boehringer Ingelheim
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