Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c27319443-05**
EudraCT No. **EU Trial No.**	2019-001673-93	
BI Trial No.	1368-0007	
BI Investigational Medicinal Product(s)	Spesolimab, (BI 655130)	
Title	An open label, long term safety trial of spesolimab treatment in patients with fistulising Crohn's disease who have completed previous spesolimab trials	
Lay Title	A study to test long-term treatment with spesolimab in patients with fistulising Crohn's disease who took part in previous trials.	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Principal Investigator < or > Coordinating Investigator	[redacted]	
Status:	Final Protocol (Revised Protocol (based on global amendment No. 2))	
Version and Date	**Version: 3.0**	**Date: 21 Jan 2021**

Proprietary confidential information.
© 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies. All rights reserved.
This document may not - in full or in part - be passed on, reproduced, published or otherwise used without prior written permission.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	28 November 2019
Revision date	21 January 2021
BI trial number	1368-0007
Title of trial	An open label, long term safety trial of spesolimab treatment in patients with fistulising Crohn's disease who have completed previous spesolimab trials
Coordinating Investigator	[redacted]
Trial site(s)	Multi-centre trial
Clinical phase	II
Trial rationale	Provide to patients with fistulising Crohn's disease extended acces to a potentially beneficial treatment and evaluate long term tolerability, safety, and efficacy.
Trial objective(s)	1. To evaluate the long-term safety of spesolimab in patients with fistulising Crohn's disease who have completed treatment in previous trials. 2. To evaluate the long-term efficacy of spesolimab in patients with fistulising Crohn's disease who have completed treatment in previous trials.
Trial endpoints	Primary Endpoint • Exposure adjusted rate of patients with treatment emergent adverse event (AEs) up to week 336 Secondary Endpoints • Proportion of patients with perianal fistula remission at weeks 48, 96, 144, 192, 240, 288, and 336 • Proportion of patients with perianal fistula response at weeks 48, 96, 144, 192, 240, 288, and 336
Trial design	Open label (OL), 7 year, single group, long-term extension study
Total number of treated patients	Up to 20
Number of patients on each treatment	All patients will receive spesolimab.
Diagnosis	Patients with fistulising Crohn's disease
Main in- and exclusion criteria	Inclusion Criteria • Patient older than 18 years

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

	• Has completed all treatments as assigned and the EOT visit in the previous induction trial in fistulising CD and is willing and able to continue treatment in 1368-0007 • Has obtained an individual health benefit, per investigator judgement (such as fistula response or remission or other clinical improvement), from treatment in the parent trial. • Signed and dated written informed consent for 1368-0007 in accordance with GCP and local legislation prior to admission into the trial • Women of childbearing potential (WOCBP) must be ready to use highly effective methods of birth control per ICH M3 (R2) Exclusion criteria • Have experienced study treatment-limiting adverse events during induction treatment with study drug • Have developed any condition which meets the exclusion criteria from the original induction study • Any condition which in the opinion of the investigator affects the safety or ability to participate in this trial
Test product(s)	Spesolimab, BI 655130
dose	300 mg s.c./4 weeks 1200 mg i.v. followed by 600 mg s.c./4 weeks in case of fistula relapse
mode of administration	Subcutaneous (s.c.) Intravenous (IV) in case of fistula relapse
Comparator product(s)	Not applicable
dose	Not applicable
mode of administration	Not applicable
Duration of treatment	Approximately 7 years
Statistical methods	Descriptive statistics only.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

FLOW CHART 1

FLOWCHART 1A: V1, M1-M13

Visit	V1[1]	M1	M2	M3	M4	M5	M6	M7
Week	-2 to M1	1	4	8	12	16	20	24
Day	-14 to -7	1	29	57	85	113	141	169
Visit Window (days)	N.A	0	±7	±7	±7	±7	±7	±7
Visit type[20]	A	B	C	C	D	C	C	E
Informed Consent	X							
Eligibility criteria	X	X						
Demographics	X							
Medical/Surgical history	X							
eDiary [redacted]	[redacted]	[redacted]			[redacted]			[redacted]
Rectoscopy or proctoscopy [redacted]	[redacted]							
Physical exam (including vital signs),weight[3]	X[C]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]
12 lead-ECG	X	X						
Pregnancy test[4]	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X
Adverse events[17]	X	X	X	X	X	X	X	X
Pelvic MRI [redacted]	[redacted]							
Safety laboratory test[6]	X	X			X			X
QuantiFERON-TB test	X							
Blood infection testing	X							
[redacted]	[redacted]	[redacted]						[redacted]
[redacted]	[redacted]	[redacted]						[redacted]
[redacted]	[redacted]	[redacted]						[redacted]
Stool sampling for enteric pathogens[15]	X							
Urine sampling for albumin	X							
[redacted]	[redacted]	[redacted]						[redacted]
[redacted]	[redacted]	[redacted]			[redacted]			[redacted]
Contact IRT	X	X	X	X	X	X	X	X
Study drug administration[11]		X	X	X	X	X	X	X
Local tolerability assessment		X	X	X	X	X	X	X

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Visit	M8	M9	M10	M11	M12	M13	Continue with M14 to M84 according visit type and then to end of treatment and end of study visits.
Week	**28**	**32**	**36**	**40**	**44**	**48**	
Day	**197**	**225**	**253**	**281**	**309**	**337**	
Visit Window (days)	±7	±7	±7	±7	±7	±7	
Visit type[20]	**C**	**C**	**D**	**C**	**C**	**F**	
Informed Consent							
Eligibility criteria							
Demographics							
Medical/Surgical history							
eDiary [redacted]			[redacted]			[redacted]	
Rectoscopy or proctoscopy [redacted]						[redacted]	
Physical exam (including vital signs),weight[3]	X[I]	X[I]	X[I]	X[I]	X[I]	X[C]	
12 lead-ECG						X	
Pregnancy test[4]	X	X	X	X	X	X	
Concomitant therapy	X	X	X	X	X	X	
Adverse events[17]	X	X	X	X	X	X	
[redacted]						[redacted]	
Safety laboratory test[6]			X			X	
QuantiFERON-TB test						X	
[redacted]						[redacted]	
[redacted]						[redacted]	
[redacted]						[redacted]	
[redacted]						[redacted]	
[redacted]			[redacted]			[redacted]	
Contact IRT	X	X	X	X	X	X	
Study drug administration	X	X	X	X	X	X	
Local tolerability assessment	X	X	X	X	X	X	

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

FLOWCHART 1B: M14-M84

See flow chart 1A for procedures to be done depending on visit type. The same visit schedule repeats yearly until the end of seven years as follows.
These treatment visits will follow the same ±7 day visit window.

M14-M25												
Visit	M14	M15	M16	M17	M18	M19	M20	M21	M22	M23	M24	M25
Week	52	56	60	64	68	72	76	80	84	88	92	96
Day	365	393	421	449	477	505	533	561	589	617	645	673
Visit type	C	C	D	C	C	E	C	C	D	C	C	F[#]
M26-M37												
Visit	M26	M27	M28	M29	M30	M31	M32	M33	M34	M35	M36	M37
Week	100	104	108	112	116	120	124	128	132	136	140	144
Day	701	729	757	785	813	841	869	897	925	953	981	1009
Visit type	C	C	D	C	C	E	C	C	D	C	C	F*
M38-M49												
Visit	M38	M39	M40	M41	M42	M43	M44	M45	M46	M47	M48	M49
Week	148	152	156	160	164	168	172	176	180	184	188	192
Day	1037	1065	1093	1121	1149	1177	1205	1233	1261	1289	1317	1345
Visit type	C	C	D	C	C	E	C	C	D	C	C	F*
M50-M61												
Visit	M50	M51	M52	M53	M54	M55	M56	M57	M58	M59	M60	M61
Week	196	200	204	208	212	216	220	224	228	232	236	240
Day	1373	1401	1429	1457	1485	1513	1541	1569	1597	1625	1653	1681
Visit type	C	C	D	C	C	E	C	C	D	C	C	F*
M62-M73												
Visit	M62	M63	M64	M65	M66	M67	M68	M69	M70	M71	M72	M73
Week	244	248	252	256	260	264	268	272	276	280	284	288
Day	1709	1737	1765	1793	1821	1849	1877	1905	1933	1961	1989	2017
Visit type	C	C	D	C	C	E	C	C	D	C	C	F*
M74-M84												
Visit	M74	M75	M76	M77	M78	M79	M80	M81	M82	M83	M84	
Week	292	296	300	304	308	312	316	320	324	328	332	
Day	2045	2073	2101	2129	2157	2185	2213	2241	2269	2297	2325	
Visit type	C	C	D	C	C	E	C	C	D	C	C	

*Visit type F after visit M25: no blood and stool sampling for biomarkers

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

FLOWCHART 1C: END OF TREATMENT AND END OF STUDY VISITS

Trial Periods		
Visit	**M85/EOT**	**EOS[12]**
Week	**336**	**352**
Day	**2353**	**2466**
Visit Window (days)	±7	+7
eDiary [redacted]	[redacted]	[redacted]
Rectoscopy or proctoscopy [redacted]	[redacted]	
Physical exam (including vital signs),weight[3]	X[C]	X[C]
12 lead-ECG	X	X
Pregnancy test[4]	X	X
Concomitant therapy	X	X
Adverse events[17, 19]	X	X
[redacted]	[redacted]	
Safety laboratory test[6]	X	X
QuantiFERON-TB test	X	X
Blood infection testing[21]	X	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Study drug administration[12]	X	
Contact IRT	X	
Local tolerability assessment	X	
Study completion		X

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

FLOW CHART 2A: PATIENTS WITH INFLAMMATORY FLARE WITH NO FISTULA RELAPSE

These visits will be done when the patient presents with a flare but no fistula relapse starting with flare confirmation visit, followed with visits F1 to F6, re-start at F1 and repeat visits type F1 to F6 until EOT or a new flare or fistula relapse occurs.

Naming convention will be i.e.: FL02V04F5: second flare, flare visit number 4, visit type 5
Flare Confirmation number: FLn (luminal flare and fistula relapse will count as consecutive numbers)

Visit number: Vn (consecutive number of visits at each flare/relapse)
Visit type: from F1 to F6

Trial periods	**Flare confir-mation**	**Flare maintenance treatments**					
Visit	**FLn**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Week (always count after last dose of of maintenance treatment)[22]	**N.A.**	**4**	**8**	**12**	**16**	**20**	**24**
Day[22]	**N.A.**	**29**	**57**	**85**	**113**	**141**	**169**
Visit Window (days)	**N.A.**	±7	±7	±7	±7	±7	±7
eDiary [redacted]	[redacted]	[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ileocolonoscopy+ [redacted]	X			X			
		rectoscopy or proctoscopy after 12 weeks, at visit F3, and at every 48 weeks from FLn					
[redacted]	[redacted]						
Physical exam (with vital signs), weight[3]	X^T	X^T	X^T	X^T	X^T	X^T	X^T
12-lead ECG	X			X			X
Pregnancy test[4]		X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X
Adverse events[17]	X	X	X	X	X	X	X
Safety laboratory tests[6]	X	X		X		X	
[redacted]	[redacted]						[redacted]
[redacted]	[redacted]			[redacted]			[redacted]
[redacted]	[redacted]			[redacted]			[redacted]
Stool sampling for enteric pathogens[15]	X						
[redacted]	[redacted]						[redacted]
Contact IRT	X	X	X	X	X	X	X
Study drug administration[22]		X	X	X	X	X	X
Local tolerability assessment		X	X	X	X	X	X

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

FLOW CHART 2B: FISTULA RELAPSE (WITH OR WITHOUT A LUMINAL FLARE)

These visits will be done when the patient presents with a fistula relapse, with or without luminal flare, starting with fistula relapse confirmation visit, followed by an IV reinduction visit and then visits F1 to F6, re-start at F1 and repeat visits type F1 to F6 until EOT or a new fistula relapse occurs.

Naming convention will be i.e.: FL02V04F5: second fistula, fistula visit number 4, visit type 5
Fistula relapse confirmation number: FLn (luminal flare and fistula relapse will count as consecutive numbers)
Visit number: Vn (consecutive number of visits at each flare/fistula relapse)
Visit type: from F1 to F6

Trial periods	**Fistula confir-mation**	**i.v. re-indu ction**	**Flare/Fistula relapse maintenance treatments**					
Visit	**FLn**	**Rn**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Week	**0**	**0**	**4**	**8**	**12**	**16**	**20**	**24**
Day	**-5 to -3**	**0**	**29**	**57**	**85**	**113**	**141**	**169**
Visit Window (days)	**N.A.**	**±2**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
eDiary [redacted]	[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Seton placement if needed (should be retired after 4wk)	X							
Eligibility criteria		X						
Physical exam (with vital signs), weight[3]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]
[redacted]	[redacted]				[redacted]			
Rectoscopy, proctoscopy[2]	Every 48 weeks, done with MRI							
12-lead ECG		X			X			X
Pregnancy test[4]		X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X
Adverse events[17]	X	X	X	X	X	X	X	X
Safety laboratory tests[6]	X		X		X		X	
[redacted]	[redacted]	[redacted]						[redacted]
[redacted]		[redacted]			[redacted]			[redacted]
[redacted]		[redacted]			[redacted]			[redacted]
[redacted]		[redacted]						[redacted]
Contact IRT		X	X	X	X	X	X	X
Study drug administration[14]		X	X	X	X	X	X	X
Local tolerability assessment			X	X	X	X	X	X

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

FLOW CHART 2C: PATIENTS WITH FLARE/FISTULA RELAPSE –EOT/EOS VISIT

Trial periods	Follow-up		
Visit	...	EOT	EOS[12]
Week		336 wk from initial M1	16 wk after EOT
Day		2353 days after initial M1	113 days after EOT
Visit Window (days)		±7	+7
eDiary [redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
Ileocolonoscopy, rectoscopy, proctoscopy		X[13]	
Physical exam (with vital signs), weight[3]		x[c]	x[c]
[redacted]		[redacted]	
12-lead ECG		X	X
Pregnancy test[4]		X	X
Concomitant therapy		X	X
Adverse events[17,19]		X	X
Safety laboratory tests[6]		X	X
[redacted]		[redacted]	[redacted]
Blood Infection testing[21]		X	
[redacted]		[redacted]	[redacted]
Contact IRT		X	
Study drug administration[12]		X	
QuantiFERON-TB test [18]		X	X
Local tolerability assessment		X	
Study completion			X

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Footnotes

1. Visit V1 of this long-term extension study should be performed preferably during the last visit (EOT) of the preceding trial. This is strongly recommended. In case it is not possible at EOT visit, maximum days allowed between trials from EOT parent trial to V1 of this trial will be 28 days. Procedures of V1 will not need to be repeated if patient do not have any clinical significant change.
2. Rectoscopy or proctoscopy have to be performed every 48 weeks during maintenance treatment period. Additional it hasto be done: a) at screening (EOT of parent trial); full Ileocolonoscopy/colonoscopy/sigmoidoscopy, instead of proctoscopy or rectoscopy could be performed if clinically indicated as per investigator judgement b) In case of inflammatory flare, an unscheduled confirmatory ileocolonoscopy has to be performed. An ileocolonoscopy after 12 weeks to check response to flare treatment is not mandatory but could be performed if eclinically indicated as per investigator judgement
3. Physical examination: C=complete, T=targeted. Refer to Section 5.2.1 and 5.2.2. Measurement of vital signs should precede blood sampling and be assessed pre-dose at all dosing visits and at screening for visit F1 in case of inflammatory fistula relapse, with i.v. study drug administration, vital signs will be assessed at approximately 5 and 60 minutes after study drug administration. Monitor for signs and symptoms of hypersensitivity reactions for 1h following i.v. study drug administration. At s.c. dosing visits, vital signs will be assessed at approximately 10 minutes after study drug administration. Also at Visit M1 and Visit M2 (s.c. dosing visits) additional vital signs assessments will be performed approximately 60 minutes post-dose (i.e. 60 min. after last injection).
4. For women of childbearing potential. Urine pregnancy tests will be performed at all visits indicated in the Flow Chart. In case of a positive urine pregnancy test, a serum pregnancy test will be done. Urine pregnancy testing should be done at screening and later prior to administration of study drug. Study drug should only be administered in case of a negative test result. More frequent testing should be done if required by the local regulation or per investigator judgment.
5. [redacted]
6. Includes clinical chemistry, hematology, coagulation and urinalysis assessments. Patient is not required to be fasting prior to blood collection. If fasted mark it on laboratory requisition form. At visits with study drug administration scheduled blood sampling should be done prior to the study drug administration. TSH and Glycosylated Hbc (HbA1c) tests have to be done at screening and then every 48 weeks at visit type F. See section 5.2.3 safety laboratory parameters for complete list of testing required.
7. [redacted]
9. [redacted]
10. [redacted]
11. First study drug will be administered at M1.
12. For patients who discontinue study medication before scheduled end of treatment, an early EOT visit has to be scheduled. No treatment administration will be done at this visit. EOS visit will be 16 weeks after last dose of study medication.
13. For patients with inflammatory flares only, endoscopy (rectoscopy, proctoscopy, sigmoidoscopy, colonoscopy or full ileocolonoscopy) does not need to be repeated if done within 6 weeks prior to EOT visit.
14. Patients who develop a fistula relapse will receive a single infusion of 1200mg spesolimab i.v. followed 4 weeks later by intensified maintenance treatment with 600mg spesolimab s.c. q4W until the originally scheduled EOT visit (i.e. at week 336 after start of first sc. maintenance treatment)
15. Stool sampling for enteric patogens only need at visit 1 and in case of inflammatory flare, according routine medical practice. If collection is not possible at visit 1, stool sample has to be collected at visit M1.
16. [redacted]
17. Please see Section 5.2.6.2.1 for important instructions regarding AE collection in parent and extension trial further below
18. Quantiferon in all patients, either in maintenance flowchart or in case of flare/fistula relapse), will be tested every 48 weeks (aprox 1 year) from day 1 (visit M1), and at EOT and EOS.
19. After the EOS visit (individual patient's end of the trial) the investigator should report only any cancers of new histology and exacerbations of existing cancer (if applicable), trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of and only via the BI SAE form for this extension trial , please see section 5.2.6.2.1.
20. Visit types include all procedures that should be done at every type of visit from week 48(M13), see flow chart 1B.
21. Infection testing for HBV (not HCV and HIV) to be repeated at EOT
22. Patients who present a luminal inflammatory flare (but NO fistula relapse) might receive standard of care treatment for flare as per investigator judgement, while continuing with their spesolimab maintenance dose of 300mg s.c. visit F1 will be done 4 weeks after last visit dosed, but not after flare confirmation visit.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

TABLE OF CONTENTS

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

[redacted]

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

ABBREVIATIONS

[redacted]	[redacted]
ADCC	Antibody-dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AP	Abdominal Pain
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
CA	Competent Authority
CD	Crohn's disease
[redacted]	[redacted]
CDC	Complement-dependent Cytotoxicity
[redacted]	[redacted]
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CRO	Contract Research Organisation
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
EC	Enterocutaneous
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPP	Generalized Pustular Psoriasis
HA	Health Authority
HIV	Human Immunodeficiency Virus
i.v.	intravenous
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
[redacted]	[redacted]
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LPLT	Last Patient Last Treatment
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Drug Regulatory Activities
MoA	Mode-of-action
MRI	Magnetic Resonance Image
[redacted]	[redacted]
NAB	Neutralizing Antibodies
OL	Open Label
OPU	Operative Unit
PBO	Placebo
[redacted]	[redacted]
[redacted]	[redacted]
PoCC	Proof of Clinical Concept
[redacted]	[redacted]
[redacted]	[redacted]

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

RCT	Randomized Controlled Trial
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
s.c.	subcutaneous
SAE	Serious Adverse Event
SF	Stool Frequency
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment Emergent Adverse Event
TSAP	Trial Statistical Analysis Plan
UC	Ulcerative Colitis
ULN	Upper Level of Normal
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Crohn's Disease (CD) is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract clinically characterized by abdominal pain, fever, and bloody or mucus-containing diarrhoea (R13-2231). The disease affects the gastrointestinal tract discontinuously from mouth to anus, but most commonly the ileum and colon (40%), followed by the small bowel only (30%), and the colon only (25%) (R13-2233). The mean age at CD diagnosis is approximately 30 years with a slight predominance of women (R16-1923).

Repeated episodes of acute gut inflammation and epithelial damage in these patients lead to abnormal tissue remodeling responses, with aberrant epithelial to mesenchymal transition (EMT) repairing process. Altered EMT is one of the key drivers of fistula formation in patients with IBD. [R20-2041, R20-2042].

The incidence of CD seems to be increasing with more recent estimates varying from 7.9 to 20.2 cases/100,000 per year, and a prevalence of 161 to 319 cases/100,000 in populations of North America and Europe (R13-2231). Mucosal lesions may be complicated not only by stricture formation, but also by perforation and fistula formation, which may require hospitalization for medical or surgical management.

Fistulas represent one of the most important complications in patients with CD and have a deep impact on patients's wellbeing. At time of CD diagnosis, two third of patients present with inflammatory disease and up to one-third of the patients already reveal stricturing or penetrating complications of their inflammatory bowel disease. One third of CD patients will develop fistulas at least once during the course of the disease. Perianal fistulas are the most common and their presence has been shown to be a risk factor for pourer outcomes in these patients (R19-2044, R19-2046). Surgery, though often required to treat perianal fistulas, often does not provide a definitive cure (R17-3555).

There is a paucity of randomized controlled trials (RCTs) for the treatment of fistulizing CD. Established treatment, however, includes treatment of associated luminal disease, particularly rectal disease, which it has been shown to influence fistula outcomes. Current standard medical treatments used for treatment of related draining perianal fistulas include antibiotics, which are useful to treat infection but do not appear to have long-term effects on the fistula itself, immunosuppressives, and anti-TNF agents. Most of the evidence on routinely used medical treatment is derived from subgroup analyses or secondary outcome measures, while there is limited evidence from clinical trials with perianal fistula healing as a main outcome. Amongst anti-TNF agents, infliximab has been approved for treatment of perianal fistulising active Crohn`s disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy). This comes from one positive RCT with infliximab on the patient group. However, only approximately half of infliximab treated patients achieved

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

closure of all fistulas (R00-0812) and after 1 year only a third of fistulas remain closed (R04-0551). Two recent meta-analyses did not show any effect of anti-TNF therapy for fistulising CD (R15-4344, R19-2045). Recently a large RCT has shown the efficacy of the injection of allogenic mesenchymal stem cells (Alofisel®) to induce remission of complex fistulas. The remission rate delta was only 16% compared to placebo; however, patients who received active treatment had significantly lower relapse rates at one year of follow up (R18-2555). Alofisel® is approved in the EU to induce remission of complex fistulas. The loss of clinical response to these agents is a substantial clinical problem. Other biologics are used off-label for treating fistulas such as adalimumab, certolizumab, ustekinumab and vedolizumab. The majority of patients with CD with perianal fistulas will require some surgical procedure (abcess drainage, seton placement, fistulotomy, fistulectomy or, in some instances, bowel resection) on top of the medical treatment. Surgical interventions aim to achieve fistula closure while preserving the anal sphincter function. However, they have shown limited efficacy and sphincter function cannot always be preserved.

Currently, it is believed that combined medical and surgical therapy might be more effective than one treatment modality alone (R17-3555).

1.2 DRUG PROFILE

Mode of action
Spesolimab is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL-36R signaling. Binding of spesolimab to IL-36R is anticipated to prevent the subsequent activation of IL-36R by cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways with the aim to reduce epithelial cell/ fibroblast/ immune cell-mediated inflammation and interrupt the inflammatory response that drives pathogenic cytokine production in inflammatory diseases including generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP) and inflammatory bowel disease (IBD).

Preclinical studies
Spesolimab binds to human IL-36R with a binding avidity of less than 1 pM and inhibits IL36 ligand-stimulated NF-κB activation in HT29 and transformed epithelial cells and in primary human dermal fibroblasts or intestinal myofibroblasts with IC90 values in a consistent range of 0.7 to 3.7 nM. Spesolimab also inhibits IL8 release in primary human intestinal myofibroblasts and IFNγ secretion in human PBMC stimulated with IL36α, IL36β, or IL36γ combined with IL12. Thus, spesolimab inhibition of both inflammatory and fibrotic pathways might hold promise to treat inflammatory bowel disease, especially Crohn's disease. This condition manifests with increased gut wall inflammation and fibrosis, which lead to altered tissue remodelling, tissue penetration and, hence, to strictures and fistulas manifestations. (P19-05294, R19-2047).

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

abrogate both ADCC and CDC effector functions and indicate that spesolimab will be a non-depleting therapy in vivo.

Toxicology studies
Spesolimab does not bind to IL-36R from common toxicology species. Therefore, meaningful toxicity studies of the molecule cannot be performed in any animal species with spesolimab. However, hazard identification studies of the mode-of-action (MoA) of IL-36R inhibition were performed in mice using a mouse specific anti-IL-36R monoclonal antibody (BI 674304), which is a mouse IgG2a monoclonal antibody with rat variable regions. In a 13-week intravenous toxicity study of BI 674304 in mice, no adverse effects of IL-36R antagonism were seen at a dose (50 mg/kg, twice weekly) that was 5 fold higher than the dose that was protective in an experimental mouse colonic inflammation model. In the 26-week toxicity study, male and female mice (20-30/sex/group at 0, 10 and 50 mg/kg/day) were administered BI 674304 twice weekly for 26 weeks by intravenous injection via the caudal vein. There were no BI 674304-related changes in clinical observations, body weights, food consumption, ophthalmology, clinical pathology parameters (hematology, clinical chemistry), organ weights, macroscopic, or microscopic examinations. The no-observed-adverse-effect level (NOAEL) was considered to be 50 mg/kg/day.

The in vitro cytokine release and tissue cross-reactivity assays demonstrate that the risk of transient cytokine release in humans is low and that, as expected, spesolimab stains epithelium in a variety of tissues. There were no signs of local irritation after single, 1 mL injections of the subcutaneous formulation in rabbits.

These preclinical toxicology data support chronic spesolimab dosing in humans.

Data from clinical studies
Spesolimab or placebo (PBO) was administered to 78 healthy volunteers at single ascending i.v. doses from 0.001 mg/kg to 10 mg/kg body weight. Safety and tolerability of all tested i.v. doses was good. There were no drug-related SAEs.

PK analysis showed that exposure ($AUC_{0\text{-}tz\ and\ Cmax}$) to spesolimab increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg. The effective half-life of spesolimab is approximately 4 weeks in the linear dose range. Overall, PK data so far suggests target-mediated drug disposition (TMDD) kinetics for spesolimab.

Pharmacodynamic effects in this FIH Single Rising Dose trial (c03361085) were assessed by indirect target engagement (ITE) of IL-36R by spesolimab using an ex-vivo whole blood stimulation assay. Preliminary analyses indicate that ≥94% peripheral IL-36R receptor occupancy is achieved with doses ≥0.05mg/kg from 30 minutes post infusion to 10 weeks.

In a multiple rising dose trial, spesolimab or placebo have been administered to healthy volunteers at multiple ascending i.v. doses of 3, 6, 10, and 20 mg/kg given qw for 4 weeks (thus, for an individual of 75Kg, a maximum dose of 1500mg iv was given every week for 4 weeks) or a single dose of 20 mg/kg (8 patients each, 3:1 on active or PBO). Overall, spesolimab was well tolerated. There were no dose dependent AEs, AEs considered to be

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

dose limiting and no SAEs. In all cases the AEs were of mild or moderate intensity. Furthermore, there were no clinically relevant abnormalities on treatment with spesolimab with respect to safety laboratory, vital signs, or ECGs as assessed by a central reader. For further details and most recent results refer to the current Investigator`s Brochure (IB) (c03320877-08).

Studies in Patients
Efficacy data are available from a proof of concept study in patients with generalized pustular psoriasis (GPP). In this trial (1368.11) seven patients received a single intravenous dose of 10 mg/kg BI 655130, and were monitored for 20 weeks. At week 1 after dosing, Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of clear or almost clear (0 or 1) was achieved in five patients, and by Week 4 in all seven patients. Within 48 hours postdose, pustules were completely cleared in three patients, by week 1 in five patients and by week 2 in six of seven patients. A major improvement in (GPPASI) was observed in all patients with a mean (SD) percent change from baseline of 73.2% (16.2) at week 2; by week 4, this was further reduced to 82.0% and was maintained to week 20 (83.6%).

In the PoCC trial in PPP 1368.15 were a total of 59 patients were randomized, two patients experienced severe AEs in each of the three trial arms (300 mg, 900 mg BI 655130 and Placebo). One SAE was reported in the 300 mg spesolimab arm and one in the placebo arm. Four AEs (10.5%) in patients treated with BI 655130 and three AEs (14.3%) in patients treated with placebo led to discontinuation of trial medication. Three patients in the 900 mg spesolimab arm and two in the placebo arm experienced a significant AE (according to project definition). No AESI were reported. No clinically relevant abnormalities on treatment with spesolimab with respect to safety laboratory and vital signs were observed. Overall, BI 655130 was well tolerated and no safety signal was identified in trial 1368.15. See table 6.3.1.2:4 from IB (c03320877-08)

Summary
Spesolimab is an anti IL-36R antibody with a high clinical activity to block IL-36R signaling, as demonstrated in patients with Generalized Pustular Psoriasis (GPP) and Palmoplantar Pustulosis (PPP), both severe inflammatory skin diseases driven by uncontrolled IL36 activity. IL-36R inhibition shows a favourable nonclinical safety profile. In addition, spesolimab has been tested in more than 180 healthy volunteers and 45 PPP or GPP patients for up to 16 weeks. All tested dose groups up to 20 mg/kg i.v. q.w. were safe and well tolerated and did not demonstrate any particular safety signal clearly related to spesolimab. Therefore, spesolimab might be a promising drug to treat patients suffering from IBD.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Spesolimab unique dual mode of action targets pro-inflammatory cytokines as well as tissue remodeling defects seen in CD patients that lead to fistulas and stricture formation. Thus, spesolimab may provide a clear advantage over current drugs and investigational compounds, which target inflammation only.The potential spesolimab effects on IBD related defective tissue remodeling may directly increase mucosal healing, induce deeper tissue healing

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

(histologic remission) and reduce the worst complications of CD, stricturing and fistulising, which are known to be risk factors for worst outcomes in these patients.

This study will provide patients who derived an individual health benefit from treatment in the preceding trial with a long-term treatment option and potentially improve quality of life. In parallel, this study will help to characterize the long-term safety and efficacy profile of spesolimab in CD.

[redacted]

1.4 BENEFIT - RISK ASSESSMENT

BI 655130 represents an investigational drug which has largely completed phase I and is currently undergoing phase II evaluation in various indications (GPP, PPP, AtD and IBD). In line with this stage of development, clinical evidence for efficacy of spesolimab in patients is limited. However, preclinical profiles of spesolimab and clinical data from healthy volunteers' trials suggest that the compound is safe, tolerable and may address an unmet medical need in CD patients by a dual anti-inflammatory and anti-fibrotic mechanism of action, cf. the IB (c03320877-08).

There are no identified or potential risks for spesolimab, based on the toxicology programme or any clinical trials conducted for this product to date (see also Section 1.2).

Preclinical toxicology studies with a mouse surrogate antibody have demonstrated the safety of chronic IL-36Rinhibition in mice (IB Section 5.1.2 c03320877-08,). A recent publication has assessed the clinical phenotype and immune function in 12 healthy individuals harboring an IL-36R knock-out polymorphism (R17-3632). This study demonstrated the absence of any specific diseases or conditions, in particular of recurrent, severe or opportunistic infections or malignancies, in the medical records of these patients. Also, serological and in-vitro studies indicated normal levels of non-, tetanus- or varicella-specific immune globulins, and normal immune functions as compared to matched controls, indicating that IL36 blockade is likely to represent a safe and well tolerated therapeutic concept.

More than 180 healthy volunteers have been exposed in phase I SRD and MRD studies to single or multiple doses of spesolimab up to dose levels of 20mg/kg given once weekly (qw) for 4 weeks. spesolimab was safe and well tolerated in healthy volunteers trials at all dose groups up to the highest tested dose of 20 mg/kg body weight given once a week for up to 4 weeks (for details IB c03320877-08).

Results from the PoCC trial 1368-0011 in acute GPP, a disease closely linked to loss-of-function mutations in the natural IL-36R antagonist, demonstrate that spesolimab treatment

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

rapidly clears pustules, the primary lesions in GPP. In this trial, no clinically relevant abnormalities on treatment with spesolimab with respect to safety laboratory and vital signs was observed. None of the reported AEs was severe, serious or led to discontinuation. No AEs were reported as significant.

A different pustular inflammatory epithelial disease is PPP, which does not show the clear genetic association to the IL36 signalling pathway as GPP. A small pilot study of spesolimab in 59 patients with this disease (1368.15) has failed the primary endpoint (REF latest version of IB or Data on File). However. a subgroup analysis has shown a strong dose dependent effect on pustule severity, the primary and most burdensome lesion of this disease. In this PPP trial 1368.15, spesolimab was well tolerated and no safety signal was identified in trial 1368.15 (see more detailed information in IB) These data indicate that spesolimab indeed inhibits IL36 in human disease and thus has the potential to also treat other neutrophil granulocyte related inflammatory epithelial diseases such as IBD. The most recent and more detailed information is available in section 6 of the current IB (c03320877-08).

A PoCC-Phase IIa trial in 51 patients with AtD (1368.32) has also failed the primary endpoint. However, results suggest a meaningful treatment effect after 8 weeks of treatment with Spesolimab compared to placebo (c03320877-08). Spesolimab was well tolerated, and no safety signal was identified in trial 1368.32.

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

No other IL-36 receptor antagonist is currently approved or in advanced phases of clinical development. Thus, there is no information available on identified risks for other molecules of this class.

Based on the strong rationale (section 1.3), there is a reasonable chance that spesolimab may promote healing in fistulising CD. Moreover only patients deriving an individual health benefit from spesolimab in the parent study (e.g. by achieving a fistula response or remission or other clinical improvement), will be offered to roll-over into this study and directly receive open label active spesolimab maintenance treatment (300mg s.c. q4w) for up to 7 years. Patients experiencing a fistula relapse in this long-term study will be offered to receive high dose treatment (1200mg IV single dose) followed by an intensified spesolimab maintenance treatment (600mg s.c. q4W). Patients who present a luminal inflammatory flare without fistula relapse might receive antiinflammatory therapy as per SOC to treat luminal flare based on clinician judgement while continuing the same spesolimab maintenance dose (300 or 600 mg s.c. q4w).

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Patients who present a fistula relapse with negative spesolimab drug level (with or without ADA) or who experience fistula relapse more than twice within a 12 month time period will be discontinued and switched to available SOC at the investigator`s discretion. This will allow patients to receive an initial high dose spesolimab re-treatment, whilst limiting the duration of spesolimab exposure in patients no longer benefitting from treatment.

Therefore, based on the eligibility criteria and the safety profile as currently known (see section 1.2), all patients participating in this trial are expected to receive clinical benefit with acceptable risks. Participation in this study may thus help to maintain individual benefit ant to generate future benefit for larger groups of patients with CD if spesolimab proves to be successful in treating this disease.

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

Table 1.4:1 Further IMP or trial related risks and mitigation measures

Hypothetical risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Investigational Medicinal Product		
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators	Timely detection, evaluation and follow up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety. See also Section 5.2.6, adverse events of special interest
Systemic hypersensitivity reaction	Reactions to i.v. administered biologic agents represent the manifestations of systemic hypersensitivity reactions and include anaphylaxis, pruritus, hypotension and respiratory distress.	Definition of Systemic hypersensitivity including infusion reaction and anaphylactic reaction as adverse events of special interest (AESI) Selection of sites experienced in treatment of IBD patients with biologics Implementation of a fully independent data-monitoring committee (DMC) Close monitoring of patient after infusion at the site according Instructions for preparation and Handling of spesolimab. The short-term use of parenteral systemic steroids is allowed in this study. Systemic hypersensitivity reactions are readily detectable, transient in nature, and usually manageable with standard medical treatment.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 1.4:1 (cont) Further IMP or trial related risks and mitigation measures

Hypothetical risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Infections	Inhibition of the immune response with an immune-modulating biologic may increase the risk of infections. A recent characterization of individuals with homozygous IL-36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signaling pathway inhibition does not compromise host defences (R17-3632).	Screening procedures for infections will be established for this trial. Patients with any relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis or tuberculosis are excluded from the trial. Treatment of infections should be initiated promptly according to standards of care. Severe infections and opportunistic infections are considered AESIs for this trial. These conditions and serious infections are subject to close monitoring.
Malignancies	Inhibition of the immune response with a immune-modulating biologic may increase the risk of a decreased immune defense against malignancies. A recent characterization of individuals with homozygous IL-36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signaling pathway inhibition does not compromise host defences (R17-3632).	In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with spesolimab. Diagnostics and treatment have to be initiated according to local standard of care. Malignancies represent always serious adverse events and are subject to close monitoring
Trial procedures		
Local hematoma, bruising, skin erythema.	Risk associated with infusion/subcutaneous injection	Use of experienced sites
Diarrhea, abdominal pain, perforation, bleeding effects of anaesthetic medications, infection	Risks associated with Colonoscopy and biopsy	Selection of sites experienced in taking care of IBD patients

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

1.4.1 Discussion

Patients entering this trial will already have received a benefit from treatment with spesolimab in a preceeding trial. This, in adition to the medical need for effective and well tolerated drug specifically and directly treating the structural aspects of CD makes it conceivable to anticipate that the benefits of receiving further treatment will outweigh the risks in these patients. Moreover, since there are no mechanism- or compound-related safety alarm signals from all above mentioned data from spesolimab, it is highly likely that eligible patients for the study, CD patients with perianal fistulising disease, will not be exposed to undue risks and adverse events.

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

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

BI 655130 is an immune-modulating humanized monoclonal antibody that blocks the human IL-36 receptor and thereby the pro-inflammatory IL-36 pathway. Available non-clinical and clinical data have not shown an increased risk of infections with BI 655130. However, similar to other immune modulating biological treatments, BI 655130 may hypothetically increase the risk of infections. Risk mitigation measures, such as exclusion of patients with increased risk of infections, close monitoring of adverse events, as well as guidance on treatment and handling of acute infections occurring during the trial are described in the clinical trial protocol. As any other acute infection, a suspected or diagnosed COVID-19 infection should be treated according to the standard of care and interruption of study medication should be considered.

Currently, information about the immune response in patients with COVID-19 is sparse and inconclusive. There are some reports suggesting high-levels of pro-inflammatory cytokines in the severe cases, with much of the morbidity associated with coronavirus infection, potentially related to immune activation and inflammation. To date, there is no reliable evidence suggesting a link between SARS-CoV-2 infections and the IL-36 pathway targeted by BI 655130. Considering the current knowledge of COVID-19 and the implemented risk mitigation measures addressing the potential risk of infections, patients studied in trials with BI 655130 are not believed to be at higher risk of COVID-19 due to their background or concomitant diseases. Protocol-defined procedures do not impose undue risk to study participants. The benefit-risk assessment of BI 655130 remains favourable in the context of the COVID-
19 pandemic.

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each patient's (continued) participation in the planned trials. BI as the sponsor, where required, will support the investigator in their decision finding.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

Table 2.1:1 Definitions of Study Outcomes

perianal fistula remission	closure of all external openings, no drainage / discharge despite gentle finger compression, that were open and draining at baseline (BL) of parent trial and closure of all external openings that were newly emerged during the parent trial or this trial
perianal fistula response	closure and no drainage /discharge despite gentle finger compression of at least 50% in number of external openings regardless of the onset time, compared with the number of open and drainage fistulas at baseline of parent trial

[redacted]

2.1.1 Main objectives

1. To evaluate the long-term **safety** of spesolimab in patients with perianal fistulising Crohn's disease who have completed treatment in parent trials
2. To evaluate the long-term **efficacy** of spesolimab in patients with perianal fistulising Crohn's disease, who have completed treatment in parent trials

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

2.1.2 Primary endpoint(s)

Exposure adjusted rate of patients reporting a treatment emergent adverse event (TEAE) up to week 336 of maintenance treatment

2.1.3 Secondary endpoint(s)

- Proportion of patients with perianal fistula remission at weeks 48, 96, 144, 192, 240, 288, and 336
- Proportion of patients with perianal fistula response at weeks 48, 96, 144, 192, 240, 288, and 336

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

[redacted]

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This open label (OL), single group, long-term extension study of approximately 7 year duration, investigates the long term safety and efficacy of spesolimab in patients with perianal fistulas due to Crohn's disease who have completed treatment in a parent spesolimab trial. It is expected that a maximum of 20 patients will roll-over from study 1368-0008. Patients from other trials of spesolimab who meet the eligibility criteria may also be included in this trial in future and this will increase the number of participants.

Patients rolling over will be monitored for induction outcome at the EOT visit of the original trial and perform V1 of 1368-0007 at the same time, and initiate treatment upon availability of the MRI and endoscopy results.

Maintenance Treatment

Patients rolling-over into 1368-0007 trial must complete the treatment period in the preceding trial with an individual benefit (as per investigator`s judgement).

The maintenance treatment in this study will be open-label and will evaluate one dose regimen (300mg s.c. q4w) of spesolimab. The trial will consist of a screening period lasting for a maximum of 14 days, followed by a 336 week maintenance treatment period and a 16 week safety follow-up period.

Proctoscopy or rectoscopy, as per routine clinical practice will be performed for all patients at EOT visit of the parent study and once every 48 weeks in this study to evaluate mucosal healing and to provide mucosal biopsy specimens for molecular pharmacodynamic assessments. Patients participating in the study will consent to undergo an ileocolonoscopy in case of a suspected flare. Full iIleocolonoscopy/ colonoscopy or sigmoidoscopy instead of proctoscopy or rectoscopy could be performed if clinically indicated as per investigator judgement.

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

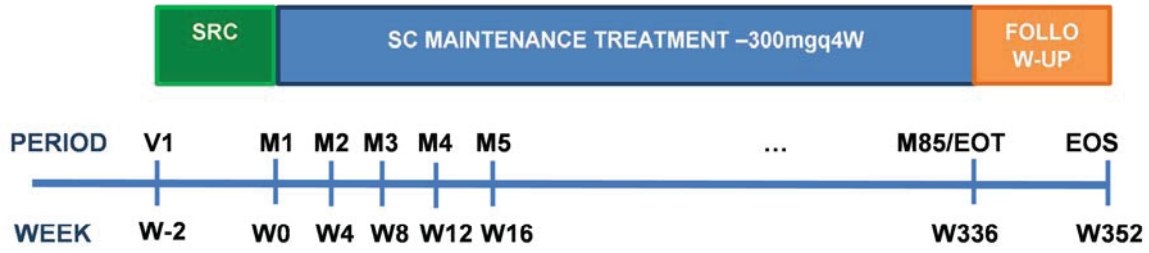


Figure 3.1:1 Trial design

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

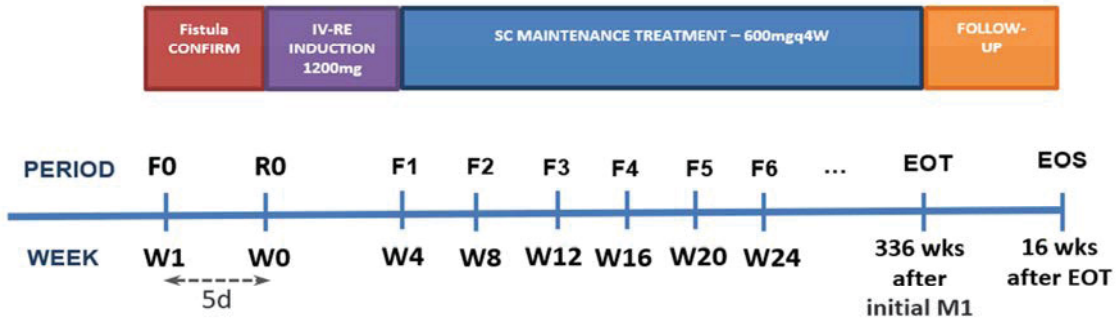
Fistula relapse or luminal inflammatory flare treatment:
During this 7-year study, patients may experience worsening of their Crohn`s disease either by experiencing a fistula relapse or a luminal inflammatory flare.

Fistula relapse is suspected if ≥1 external fistula orifice re-emerges, which was open at baseline or newly emerged during the preceding trial but was closed at completion of the parent study or at any time during the current trial; or which emerged newly. Fistula relapse is confirmed in a second independent visit (Flowchart 2B).

A patient with a confirmed fistula relapse will receive a single i.v. infusion of 1200mg spesolimab. At week 4 after the single i.v. infusion dose, patients will continue with an intensified subcutaneous spesolimab maintenance dosing of 600mg q4W, as seen in Figure 3.1:2. An additional visit has to be planned at week 12 after the single i.v. infusion to check the patient`s response status. For patients with fistula relapse, this week 12 assessment will include clinical assessment, [redacted] and MRI, which will guide investigator judgment of patient response status.

Luminal inflammatory flare, is defined as an increase in PRO-2 score [sum of 7-day weighted stool frequency (SF) and abdominal pain (AP) , components of the [redacted], using the original [redacted] multiplying factors of 2 for SF and 5 for AP] by >50 points from baseline of the current trial, plus an increase in [redacted] score by ≥100 points from baseline of the current trial with an absolute [redacted] >220 in a second independent confirmation visit, with an absolute [redacted], in absence of enteric pathogens in stool. In case of a suspected inflammatory flare, the site will ask the patient to immediately start entering his [redacted] symptom score data into the eDiary until the next scheduled or unscheduled visit at which a flare confirmation assessment will be performed, and then to continue entering the data as planned (i.e. for 10 days before each visit).

A patient with a luminal inflammatory flare (endoscopically confirmed) without fistula relapse might be treated as per SOC based on clinician judgement while continuing the same spesolimab maintenance dose according flow chart 2A After 12 weeks of flare confirmation (visit F3) a new rectoscopy/proctoscopy and [redacted] assessment will be performed to assess luminal flare response to SOC as per investigator judgement. For details of trial procedures, please follow the Flow chart 2A.



Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Figure 3.1:2 Trial design in case of fistula relapse

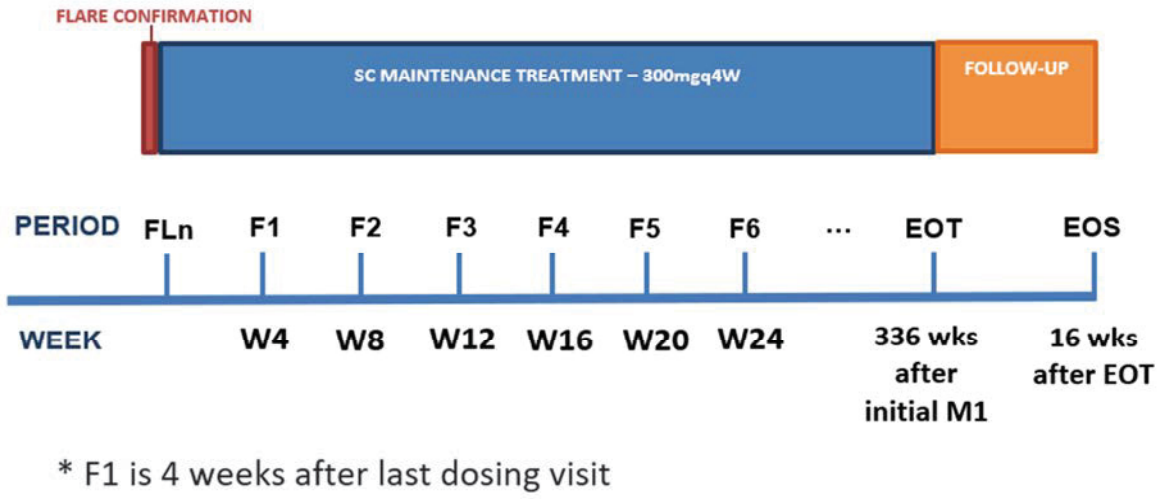


Figure 3.1:3 Trial design in case of luminal inflammatory flare

Patients who are no longer deriving a clinical benefit will be required to discontinue treatment. See Section 3.3.4.1 for details

Several interim analyses of PK, biomarker, and clinical data will be performed throughout the conduct phase of this study to support future trial applications, investigator brochures, regulatory documents, and scientific publications. The final analysis of the entire trial data will be performed once all patients have completed the last scheduled trial visit. The end of trial is defined as “last patient out”; i.e. last scheduled visit completed by last patient.

An independent Data Monitoring Committee is established to evaluate safety data of all ongoing spesolimab studies periodically, and to provide feedback on whether or not to continue the study with or without modifications.

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

Patients who complete treatment with spesolimab or placebo in parent trial and had individual health benefit from induction treatment will be offered to roll-over into this trial to receive long-term treatment with active drug.

This long-term study mainly aims to offer active maintenance treatment to patients who have benefited from induction treatment in a trial of spesolimab, and to characterize the safety and tolerability of spesolimab long-term treatment. It will also characterize the persistence of clinical outcome over a long period of spesolimab treatment and the efficacy of high dose rescue treatment for fistula relapses. Although a placebo control would improve this safety

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

and efficacy assessment, it would withhold patients in need from active treatment and is not justifiable for longer than the treatment period in the parent induction study. An active comparator is not suitable for this highly treatment-experienced and heterogeneous study population, where any approved treatment would have to be tailored towards the patient`s individual treatment history. Moreover, patients responding to spesolimab induction treatment are likely to maintain their response on continued treatment with spesolimab, but to fail maintenance treatment if switched to a drug with a different MoA, which they may have failed in the past. Therefore, neither an active comparator nor placebo can be justified for this trial.

It is acknowledged that the reporting of data for this open-label, single-arm trial will likely be biased due to, among others, selection and reporting bias. This is, however, deemed acceptable given that all patients who derived an individual health benefit from previous induction treatment and who continued into this extension trial will be able to receive an active maintenance treatment with spesolimab for their ongoing disease.

3.3 SELECTION OF TRIAL POPULATION

Patients in this long-term open label extension trial will be rolled-over after participating in a parent induction trial with spesolimab.

Patients must have tolerated treatment in the parent trial and have completed the treatment period. They must be willing to continue long term treatment with spesolimab for up to 7 years.

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

3.3.1 Main diagnosis for trial entry

Patients with fistulising Crohn’s disease who have completed treatment in the parent trial.

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

3.3.2 Inclusion criteria

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

1. Patient older than 18 years

2. Has completed all treatments (placebo or active treatment) and the EOT visit in the parent induction trial in fistulising CD and is willing and able to continue treatment in 1368-0007.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

3. Has obtained an individual health benefit, per investigator judgement (such as fistula response or remission or other clinical improvement), from treatment in the parent trial.

4. Signed and dated written informed consent for 1368-0007 in accordance with GCP and local legislation prior to admission into the trial.

5. Women of childbearing potential (WOCBP) must be ready to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

   Note: A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. 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.

3.3.3 Exclusion criteria

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

1. Have experienced treatment-limiting adverse events during induction treatment with study drug.

2. Have developed any condition which meets the exclusion criteria from the original induction study.

3. Any condition which in the opinion of the investigator affects the safety or ability to participate in this trial.

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 Sections 3.3.4.1 and 3.3.4.2 below.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Sections 5.2.6.2.1 and 5.2.6.2.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- 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 the investigator and/or sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- A patient treated for a luminal inflammatory flare or fistula relapse meets one of the criteria for discontinuation as described below.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment. Please refer to Section 4.2.1 and 4.2.2.
- The patient needs surgical interventions for CD including any fistula surgical procedures (except seton drainage, see Table 4.2.1.2:1)
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- The patient is required to stop treatment due to a specific adverse events as described in Section 4.2.1

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.

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

Treatment discontinuation

Patients with a fistula relapse will be discontinued from treatment if one of the following occurs:

- If patient has no clinical benefit after reinduction as per investigator judgement
- Fistula relapse with negative drug levels at the confirmation visit (with or without positive ADA).
- Ocurrence of >2 confirmed fistula relapses within a 12 month period.

Patients can discontinue trial treatment at any time they feel they are losing the benefit from continuing treatment with the study drug.

Patients who terminate the study drug in 1368-0007 prematurely should complete an early EOT visit instead of the next planned visit followed by a safety follow up (EOS) visit 16 weeks after the last study drug intake.

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.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

3.3.4.3 Discontinuation of the trial by the sponsor

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

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

Further follow up of patients affected will occur as described in Section 3.3.4.1.

The investigator/trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 Spesolimab solution for s.c. injection

Substance:	Spesolimab, BI 655130
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH¬ Co. KG
Unit strength:	Spesolimab 150mg/pre-filled syringes (150mg/mL)
Molecular weight	146 kDa
Unit strength	Spesolimab 150mg / syringe or vial (to be switched to 300mg when 2mL syringe or vials are available)
Posology:	300 mg at Week 0 and then every 4 weeks (2 injections every visit with 1mL syringes/ 1 injection when switching to 2ml device) 600 mg every 4 weeks as intensified treatment for patients with fistula relapse (4 injections every visit with 1mL syringes/ 1 injection when switching to 2ml device)
Mode of administration:	Subcutaneous injections

Table 4.1.1: 2 Spesolimab i.v. infusion

Substance:	Spesolimab, BI 655130
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	Spesolimab 300mg/vial (60mg/mL)
Posology:	1200 mg single dose in case of fistula relapse
Method and route of administration:	Intravenous infusion

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

4.1.2 Selection of doses in the trial and dose modifications

This trial, 1368-0007, aims to offer a maintenance treatment for patients with perianal CD who have failed available therapies and whom are considered to have benefited from previous induction therapy in the parent trial.

The spesolimab subcutaneous dose regimen chosen for 1368-0007 has thus been selected with the objective of achieving maintenance of induction therapy effect with the safest profile based on available data from Phase I and Phase II studies in HV and patients with PPP and UC, respectively.

Bioavailability of the s.c. relative to the i.v. formulation of spesolimab is approx. 50%-70 % (cf. section 6.2 of IB c03320877-08). A subcutaneous dose of 300mg would therefore correspond to ~210 mg as an i.v. dose and thus represents the lowest dose of 3 mg/kg which was found to be fully active in the indirect target engagement assays in studies 1368-0001 and 1368-0002.

The dosing interval of every 4 weeks (q4w) was selected based on the half-life of approximately 4-5 weeks in healthy volunteers and PPP patients, as determined in the PoCC trial 1368-0015 and phase I studies 1368-0001 and 1368-0002, respectively. Thus, after one half life (~4 weeks) patients` exposure would drop below the threshold required to maintain maximal target engagement.

In patients experiencing a fistula relapse, a single 1200mg i.v. high treatment dose will be administered, followed by a maintenance dose of 600mg q4w, as defined in Section 3.1 to double the exposure compared to the original failing maintenance regimen.

The loading i.v. dose of 1200mg is expected to be at the plateau of the dose/response curve and to provide maximal efficacy based on data indicating high and sustained target engagement at doses ⩾3mg/kg and a half-life as long as 4-5 weeks in healthy volunteers and PPP patients respectively (cf. sections 6.1 and 6.2 of the IB c03320877-08). This dosing regimen will achieve exposures below the highest dose regimen that was found safe in phase I studies. It therefore is also being tested in ongoing studies in IBD trials. These doses may be adapted later (via protocol amendment) based on emerging data from other trials with spesolimab.

4.1.3 Method of assigning patients to treatment groups

Not applicable, as all patients in this trial will receive the same treatment.

4.1.4 Drug assignment and administration of doses for each patient

During visit M1, eligibility criteria will be assessed and eligible patients will be allocated to receive open-label active treatment. The assignment of treatment will be done via Interactive Response Technology (IRT). The appropriate medication number will be assigned and documented in the CRF.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Injection site should not be close to a vein and it should avoid sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses.

Detailed instructions for Handling and Use of s.c. injection are provided in the ISF.

Patients must be closely monitored for local or systemic hypersensitivity reactions for 1 hour following s.c. study drug administration. Subcutaneous administration of biologic agents involves the risk of local (injection site) or systemic hypersensitivity reactions. Study personnel should observe the injection site for signs of redness, swelling or hardness. They should also ask patients about itching, dizziness, or shortness of breath. Patients should be advised that if they experience redness, swelling, or other changes at the injection site, they should notify site personnel. They should further be advised that if they experience itching all over, or a feeling of being swollen, dizzy, or short of breath, they should seek emergency medical attention immediately and notify site personnel.

A single dose of 1200 mg spesolimab i.v. will be used as fistula relapse treatment. Intravenous infusion including observational time for possible infusion reactions will last approximately 2.5 hours.

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

During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may discuss with BI to continue the trial treatment and trial medication may be shipped to the patient's home if acceptable according to local law and regulations.
In case of safety concerns, e.g. due to infusion reactions, it is in the discretion of the investigator or his/her designee to adapt the infusion scheme (cf. Section 4.2.1 for handling of infusion reactions). Detailed instructions for handling of infusion reactions are also provided in the ISF.

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

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

4.1.5 Blinding and procedures for unblinding

This is an open label, single arm trial; therefore, no blinding will be necessary. In this open-label trial, treatment allocation will not be concealed throughout the trial.

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 an IRT system, which will also monitor expiry dates of supplies available at the sites.
For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Research Associate (CRA), as provided in the 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 IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the Principal Investigator
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the Principal Investigator
- Availability of FDA Form 1572 (if applicable)

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

sponsor <and/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

4.2.1.1 Allowed concomitant therapies

CD-Related Treatments

Patients in this trial may be on conventional immunosuppressants or anti-TNFα biologic treatment for CD. These may consist of one or more of the following drugs (cf. Section 4.2.1.2
for restrictions), which are therefore permitted concomitant medications:

- Oral 5-ASA compounds, provided that dose has been stable prior to randomisation in parent trial and during current trial, and/or
- Oral corticosteroids (≤ 20 mg per day of prednisone or equivalent), provided that dose has been stable prior to randomisation in parent trial and during current trial, and/or
- Oral budesonide (≤ 9 mg per day), provided that dose has been stable in parent trial and during current trial, and/or
- Azathioprine, 6-MP, 6-TG or methotrexate, provided that dose has been stable in parent trial and during current trial,
- Approved anti-TNFα (e.g. infliximab, adalimumab, certolizumab pegol; or respective biosimilars) provided that dose has been stable in parent trial and during current trial
- Probiotics (e.g. S. boulardii) provided that dose has been stable for > 4 weeks prior to randomisation
- Regular use of anti-diarrheals

Dose has to be stable before rolling over and throughout the trial. The only exceptions are anti-diarrheals, which may be adjusted to current symptoms, and steroid reduction.

Patients who present a luminal flare (but no fistula relapse) might receive standard of care treatment for moderate-to-severe CD, while continuing with their spesolimab maintenance dose. Thus, on top of the concomitant therapies listed above, patients with luminal flare (but no fistula relapse) are also allowed to receive concomitant approved doses for treatment of moderate to severe CD including (but not limited to) the following therapies:

- anti-TNFα (this might be associated to Azathioprine / 6-MP/ MTX)
- Integrin receptor antagonists
- IL12/ 23 antagonists

Steroids

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Systemic steroids dosed intravenously or orally for less than 24 hours as treatment of infusion or anaphylactic reactions are permitted and do not lead to treatment discontinuation (see Table 4.2.1.2:1).
If mild-to-moderate infusion or anaphylactic reaction had already occurred in the same patient in the parent trial or occurs in this trial, the patient may be pre-treated with steroids as secondary prophylaxis before future IMP administrations.

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

Peri-OP antibiotics
Peri-OP antibiotics are allowed if required according to standard of care.

Other treatments
Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation are permissible. All concomitant medications should be carefully evaluated by the investigator and the sponsor representative should be contacted when there are questions regarding concomitant medications.

Management of Adverse Events:

"*Systemic hypersensitivity including infusion reaction and anaphylactic reaction*"

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

- Immediately interrupt the infusion / Stop further injections
- Treat with systemic anti-histamines, i.v. steroids, and in case of a severe allergic reaction (eg, anaphylactic reaction) epinephrine
- Draw a plasma sample for IgE and ADA as detailed in the Lab Manual (ISF)
- Consider the evaluation of histamine, serum tryptase, and complement components

In case of infusion reaction /systemic hypersensitivity, based on patient's clinical course and medical judgment, the infusion may be re-initiated / the injection(s) may be continued in case of mild or moderate infusion reactions / systemic hypersensitivity (according to RCTC grading in ISF) at lower speed with gradual increase to complete the infusion / injections as detailed in the Instructions for Preparation and Handling of spesolimab in the Investigator Site File. In any case, the total duration of infusion should not exceed 90 minutes (1.5 hours) provided that the maximum time between the start of preparation and completion of administration of the solution to the patient does not exceed 150 minutes (2.5 hours).

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

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

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

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

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

Malignancies

In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with study drug. Diagnostics and treatment have to be initiated according to local standard of care.

4.2.1.2 Restricted medications

Restrictions regarding previous and concomitant treatment are summarized in the following

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 4.2.1.2:1 Restrictions regarding concomitant treatment

Medication or class of medications	Restriction
Any biologic or non-biologic drug approved for CD other than the anti TNFα listed in section 4.2.1.1	Not allowed until end of the trial * Approved doses for treatment of moderate-to-severe CD are allowed for rescue medication ONLY in patients who present with luminal inflammatory flare BUT NO FISTULA RELAPSE.
Any investigational or non-approved biologic or non-biologic for CD	Not allowed until end of the trial
Autologous or allogeneic haematopoietic (HSC) or mesenchymal stem cell (MSC) therapy	Not allowed until end of the trial
5-ASA	Oral administration: Only allowed during the trial, if dose is stable prior to treatment initiation until end of the trial Rectal route of administration: Not allowed from screening up to end of the trial For use as rescue medication, refer to Section 4.2.1.1
Corticosteroids (incl. budesonide)	Oral administration: Oral systemic corticosteroids only allowed at a dose of ≤ 20mg per day of prednisone or equivalent and with stable dose prior to treatment initiation in this study. Oral budesonide (≤9 mg per day), provided that dose has been stable prior to treatment initiation in this study. Allowed steroid treatments: Short-term use (<7 days) of systemic (oral or parenteral) corticosteroids is allowed for treatment of AE not related to the underlying CD. Parenteral corticosteroids dosed for less than 24 hours as treatment of infusion or anaphylactic reactions are permitted. Locally administered steroids as e.g. intra-articular, nasal inhalation or intra-ocular administration are allowed.
NSAID	Chronic use not allowed from screening to end of the trial (Note: occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc., and daily use of baby or low dose (81-162.5mg) aspirin for cardiovascular prophylaxis are permitted.)
Probiotics	Only allowed during the trial provided that dose has been stable prior to treatment initiation and up to end of the trial
Antidiarrheals	Allowed during the trial as needed
Live-attenuated vaccines	Not allowed from screening up to end of the trial
Antibiotics for IBD	Not allowed from screening up to end of the trial (antibiotics given for other indications are allowed if taken for no longer than 3 weeks)

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

4.2.1.3 Restricted fistula interventions

Surgical interventions for CD are not allowed during the trial.
Any surgical intervention or procedure for perianal and enterocutaneous fistulas (except seton drainage) are also not allowed (patient shall be discontinued) since they would interfere with the clinical endpoints of the trial. Some examples are summarized in table 4.2.1.3:1 (not an exhaustive list).

Table 4.2.1.3:1 Examples of restricted procedures for perianal and enterocutaneous fistulas

Procedure for perianal and enterocutaneous fistulas	**Restriction**
- Cutting of fistulas - Shortening of fistulas - Splitting of fistulas - Fibrin glue	Not allowed from start of until end of the trial

4.2.2 Other restrictions

4.2.2.1 Restrictions on diet and life style

No restrictions on diet or lifestyle of the patients are required.

4.2.2.2 Contraception requirements

Women of childbearing potential must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly during the trial, and for a period of at least 16 weeks after the last study drug administration. A double barrier method of contraception is not required. A list of contraception methods meeting these criteria is provided in the patient information.
Female Patients

Acceptable methods of birth control for this trial are:

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

Or

Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation,

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.
Male Patients:
Contraception of male trial participants and female partners of male trial participants are not required.

4.3 TREATMENT COMPLIANCE

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

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

[redacted]

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

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

5.2.1 Physical examination

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

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

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

5.2.2 Vital signs

Vital signs evaluations will be performed at visits as shown in the Flow Chart. This includes body temperature, pulse rate, systolic/diastolic blood pressure and respiratory rate. Respiratory rate, pulse rate, and blood pressure will be measured after patients have been sitting comfortably for at least five minutes. Measurement of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital sign measurements. At dosing visits, vital sign evaluations will be performed pre-dose for both visits with i.v. and s.c. administration of study drug. At s.c. dosing visits, vital signs will be assessed at approximately 10 minutes after study drug administration. Also, at visit M1 and visit M2 (s.c. dosing visits) additional vital signs assessments will be performed approximately 60 minutes post-dose (i.e. 60 min. after last injection). At visits with i.v. dose administration, vital sign evaluations will be performed pre-dose and additional evaluations will be taken at 5 and 60 minutes post-dose

5.2.3 Safety laboratory parameters

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

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

Patients do not have to be fasted for the blood sampling for the safety laboratory.

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 (see Section 5.2.6).

The central laboratory will transfer the results of the analysis to the sponsor.

Clinically relevant abnormal laboratory test results must be confirmed using an unscheduled visit laboratory kit and should be repeated until normalization or stabilization or until an alternative explanation has been found. Abnormal laboratory values will be also graded for intensity by using RCTC Version 2.0 criteria (R13-3515).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (see Section 5.2.6.1) and the DILI Checklist provided in the ISF EDC system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 5.2.3: 1 Laboratory tests

Category	**Test name**
Haematology	Hematocrit (Hct)
	Hemoglobin (Hb)
	Glycosylated Hbc (HbA1c) (required to be tested at screening and every 48 weeks)
	Red Blood Cell Count/ Erythrocytes
	Reticulocyte Count
	White Blood Cells / Leukocytes
	Platelet Count/ Thrombocytes
Diff. Automatic	Neutrophils (relative and absolute count)
	Eosinophils (relative and absolute count)
	Basophils (relative and absolute count)
	Monocytes (relative and absolute count)
	Lymphocytes (relative and absolute count)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs)
	Neutrophils, polymorphonuclear (PMN)
	Eosinophils
	Basophils
	Monocytes
	Lymphocytes
Coagulation	Activated Partial Thromboplastin Time (aPTT)
	Prothrombin time (INR)
	Fibrinogen
Enzymes	AST (GOT)
	ALT (GPT)
	Alkaline Phosphatase (AP)
	Creatine Kinase (CK)
	CK-MB, only if CK is elevated
	Gamma-Glutamyl Transferase (GGT/γ-GT)
	Lactic Dehydrogenase (LDH)
	Amylase
	Lipase
Electrolytes	Calcium
	Sodium
	Potassium
	Chloride

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Table 5.2.3: 1 (cont) Laboratory tests

Category	**Test name**
Substrates	Glucose
	BUN (blood urea nitrogen)
	Uric acid
	Creatinine
	eGFR (estimated by CKD-EPI formula) (only at screening)
	Bilirubin Total
	Bilirubin Direct (if total is elevated)
	Bilirubin Indirect (if total is elevated)
	Troponin (Reflex, in case of elevated CK)
	Protein, Total
	Albumin
	C-Reactive Protein (CRP)
	Cholesterol, total
	Triglycerides
	LDL-Cholesterol
	HDL-Cholesterol
Specific gamma-globulin quantification	IgE[1], IgG
Infections testing	Hepatitis C Antibodies (qualitative)[4]
	HIV-1, and HIV-2 Antibody (qualitative)[4]
	Hepatitis B Surface Antigen (qualitative)[5]
	Hepatitis B core Antibody[5]
	AntibodyHBV-DNA (quantitative PCR)[2,5]
TB screening	QuantiFERON®-TB[3,6]
Urine Pregnancy test (only female patients of childbearing potential)	Human Chorionic Gonadotropin in urine
Serum Pregnancy test (only female patients of childbearing potential if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Hormones (required to be tested at screening and every 48 weeks)	TSH (free T3 and free T4 in case of abnormal TSH result)
Urinalysis (dipstick)	Urine Nitrite
	Urine Protein
	Urine Glucose
	Urine Ketone
	Urobilinogen
	Urine Bilirubin
	Urine RBC/ Erythrocytes
	Urine WBC/ Leukocytes
	Urine pH
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria
	Urine Cast in Sediment
	Urine Squamous Epithelial Cells
	Urine Sed. Crys., Unspecified
	Urine Sediment RBC/ Erythrocytes
	Urine Sediment WBC/ Leucocytes
Urine (only at screening)	Albumin (quantitative)
Faecal sample	Calprotectin

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

[1]Only in case of allergic reaction

[2] A HBV-DNA should be conducted if Hepatitis B core Antibody is positive and Hepatitis B surface Antigen is negative.

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

[4]HCV and HIV at screening only.
[5]HBV at screening and EOT.
[6]In patients with a previously (i.e. in ongoing extension trial) negative QuantiFERON®-TB test, the test should be repeated every 48 weeks, as long as the results are negative.

Table 5.2.3: 2 Additional testing

Category	Test name
Stool studies to evaluate for enteric pathogens (Faecal assessment for enteric pathogens has to be done V 1 and at suspicion of an disease flare to exclude enteric infection)	Salmonella Shigella Yersinia Campylobacter E. coli Clostridia difficile toxin Enteric parasites and their ova (including Cryptosporidia)

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis.

Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.

Clinically relevant abnormal findings will be reported as adverse events and will be followed up and/or treated as medically appropriate.

5.2.5 Other safety parameters

Local tolerability at the administration site of the subcutaneous injection will be assessed by the investigator at the specified visits as noted in the Flow Chart.

Local tolerability at the administration site of spesolimab will be assessed by the investigator during the study drug administration visit and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reactions like "swelling", "induration", "heat", "redness", "pain", or any other findings should be reported as an adverse event in the eCRF.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 or not considered related to the medicinal product.

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. However, if these abnormalities are AEs of the parent trial and still ongoing after first dose in extension trial, they should not be recorded as baseline conditions. In such situations section 5.2.6.2 should be followed.

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

considered to be "serious" even though they may not have met the criteria of an SAE as defined above.
The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described 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 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 (see Section 5.2.6.2.2).

The following are considered as AESIs:

Hepatic injury
A hepatic injury 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 draw sample, and/or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

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

Systemic hypersensitivity including infusion reaction and anaphylactic reaction
Any suspicion of severe infusion reaction systemic / hypersensitivity reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria in Appendix 10.8 (R11-4890). All confirmed and suspected cases of systemic hypersensitivity, including infusion reaction and anaphylactic reaction, will be reported as AESIs.
Any observed local tolerability reactions like "swelling", "induration", "heat", "redness", "pain", or any other findings should be reported as an adverse event in the eCRF.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

In case of an infusion reaction monitor the patient per standard of care, grade the intensity of the reaction according to RCTC grading (see ISF) and proceed as described in Section 4.2.1 Also draw plasma sample for IgE and ADA (anti-drug antibodies), as detailed in the CTP section 5.2.3 and the lab manual.

Severe infections (according to RCTC grading in ISF)

Opportunistic and mycobacterium tuberculosis infections
These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, post-transplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only), paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression (R17-2617)

5.2.6.1.5 Intensity (severity) of AEs

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

Grade 1 mild

Grade 2 moderate

Grade 3 severe

Grade 4 life-threatening

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.
Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

- 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 drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

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 (special notes on SAE form reporting where needed):

- From the time of first dose of trial drug administration in the extension trial until the individual patient's end of trial:
  all AEs (serious and non-serious) and all AESIs.
- All AEs that started in the parent trial (onset date in parent trial) and are still ongoing after 1st IMP administration in the extension trial:

  - Re-record the AE in the extension trial eCRF with the same information as it was recorded in the parent trial.
  - Should the AE end during the course of the extension trial,
    ⇨ update both - the extension trial eCRF and the parent trial eCRF. If the parent trial is already locked, update only the extension trial eCRF. In this case the

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

update for the parent trial will be handled outside of the eCRF of the parent trial.

- However, concerning reporting on the SAE form (if applicable), the follow-up report will still be sent on the parent trial SAE form, no new SAE form is to be completed for the extension trial.
- If the intensity of an ongoing AE changes after 1st IMP administration in the extension trial:

  ⇨ update both - the extension trial eCRF and the parent trial eCRF- with the end date for the initial/previous intensity. If the parent trial is already locked, update only the extension trial eCRF. In this case the update for the parent trial will be handled outside of the eCRF of the parent trial.

  ⇨ The AE with the new intensity will be handled as new event; this means it is only recorded in the extension trial eCRF.
  - Example: If the intensity increased then the new AE name/term should contain "Worsening of…" or "Exacerbation of…"

  Considerations for reporting on the SAE form, when intensity change qualifies as worsening/exacerbation of an event that had already been reported on the SAE form:
  - corresponding follow up report to be sent on the parent trial SAE form with date of worsening as event end date.
  - extension trial SAE form to be sent as initial report for the extension trial for new event "Worsening/Exacerbation of…." with date of worsening as onset date.

  Considerations for reporting on the SAE form, when intensity change qualifies as worsening/exacerbation of an event and requires for the first time reporting on the SAE form (meeting for the first time seriousness/AESI criteria):
  - only extension trial SAE form to be sent - as initial report for the extension trial for new event "worsening/exacerbation of…." with date of worsening as onset date.

- All AEs with an end date **before** the 1st IMP administration in the extension trial, even if Informed Consent of the extension trial was already signed:

  - Record only in the eCRF of the parent trial.
  - In case of an AE reportable on the SAE form, send the update only on the SAE form of the parent trial.
  - Do not re-record in the extension trial eCRF, do not complete a new SAE form for the extension trial.

- After the EoS visit in the extension trial:

The investigator does not need to actively monitor the patient for new AEs but should

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

only report any occurrence of cancer (cancer of new histology, exacerbations of existing cancer, if applicable) and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2) for the extension trial, but not on the CRF (neither on CRF for extension nor for partent trial).

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

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

For further details specific to the AE reporting of this extension trial see Section 5.2.6.2.1.

5.2.6.2.3 Pregnancy

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

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

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

[redacted]

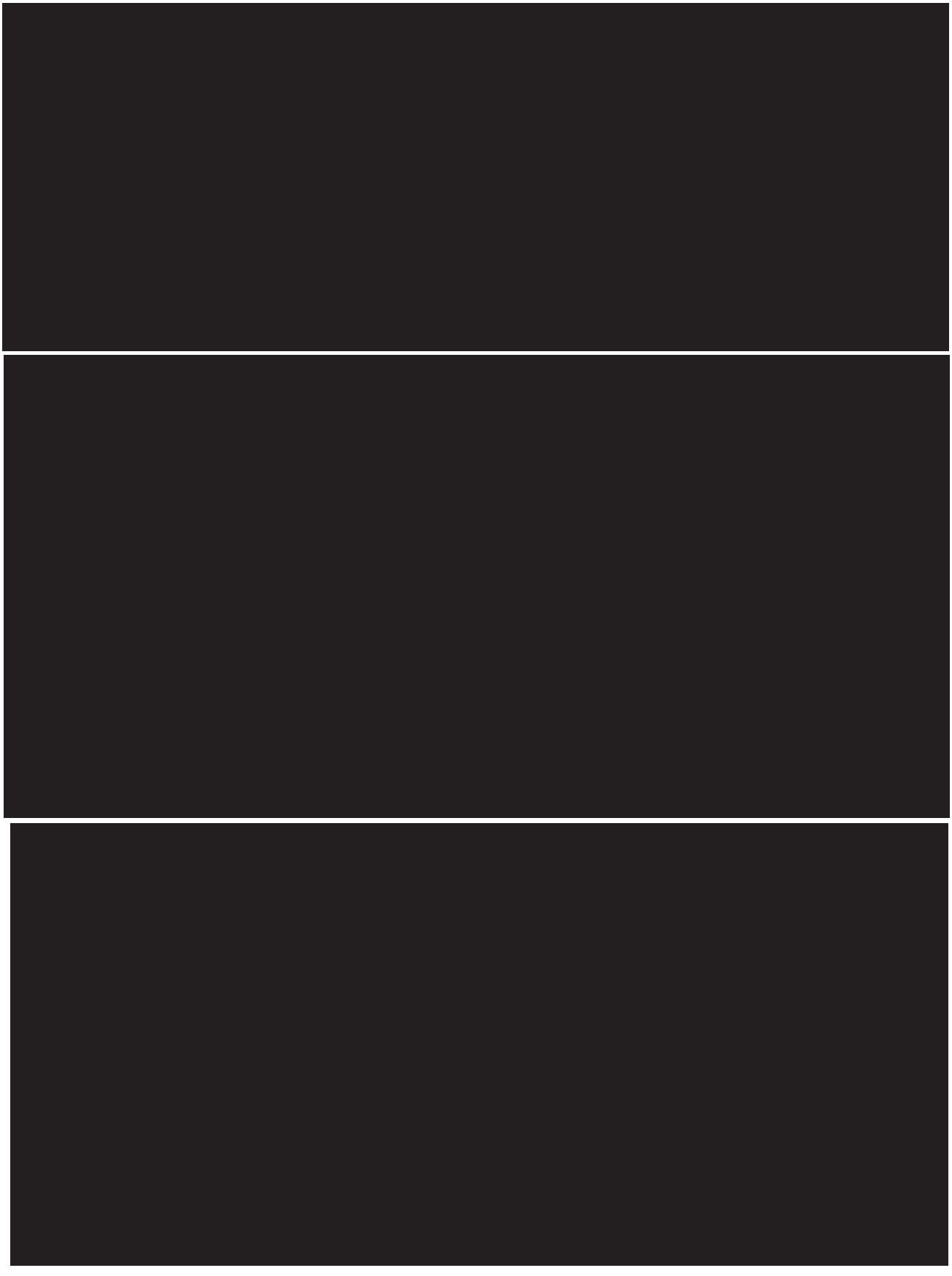
Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

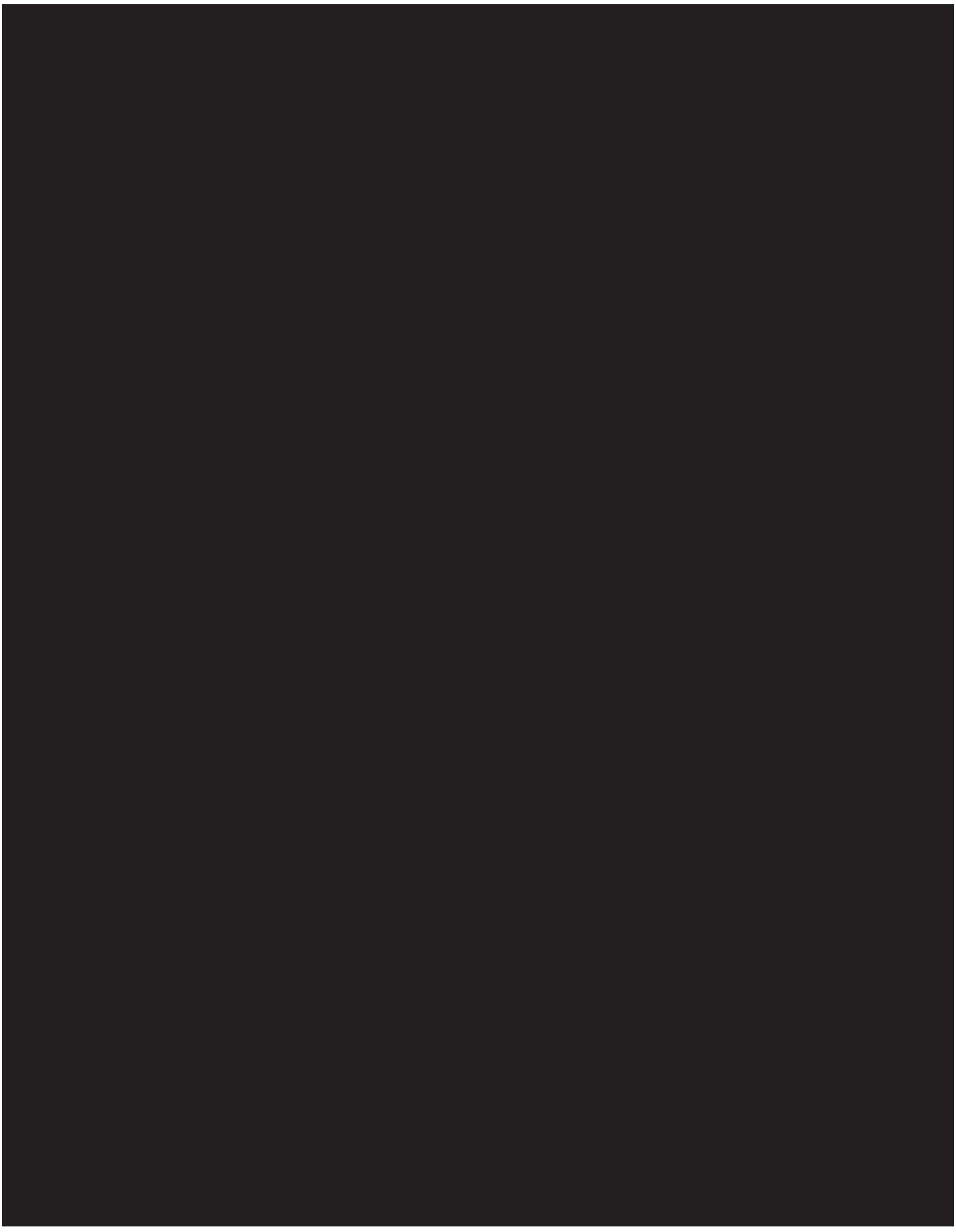
[redacted]

[redacted]

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies



Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies



Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

5.6 APPROPRIATENESS OF MEASUREMENTS

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

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Charts. Each visit date (with its window) up to EOT is to be counted from Day 1. If any of these visits has to be rescheduled, the date of subsequent visit should be calculated from Day 1. EOT refers to the last dose administration of spesolimab at week 336. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

[redacted]

6.2.1 Screening and run-in period(s)

Screening Period

After patients have been informed about the trial, written informed consent in accordance with GCP and the local legislation must be obtained prior to performing any study related procedures. Once they have consented, the patient is considered to be enrolled in the trial. The patient should be recorded on the patient enrolment log. Patient will be assigned a patient number and enrolment must be recorded in the eCRF pages.

Screening Visit (Visit 1):
Visit 1 should be performed in one visit, in combination with EOT visit of the preceding trial. Procedures performed at EOT visit of previous trial should not be repeated at V1 of 1368-0007. Visit 1 could be performed up to 28 days after EOT of preceding trial in excepcional cases. Procedures of V1 will not need to be repeated if investigator considers that patient do not have any clinical significant change.

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

Baseline Conditions
These are ongoing conditions with onset date prior trial inclusion. However, if these conditions are AEs of the parent trial and still ongoing after first dose in extension trial, they should not be recorded as baseline conditions. In such situations section 5.2.6.2 should be followed.

Patients who have a laboratory test value outside the range specified by the elegibility criteria may have the test repeated to determine eligibility. The result must be available prior to Visit M1 (Day 1).

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

Medical and Surgical History
Information on clinically significant previous and concomitant diseases, other than CD, should be registered in baseline conditions as follow up from the parent induction studies.

[redacted]

Blood sampling
Blood samples will be drawn for safety lab, infection screening, [redacted]. Safety labs will be done at local lab only at this visit.There will be specific Central lab kits for parameters not checked at EOT of parent trial, as infection screening, HbA1C, THS, urine protein. From this visit, all labs will be done through the Central Lab Details will be provided in the laboratory manual and the ISF.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Pregnancy testing
For women of childbearing potential, a urine pregnancy test will be performed.

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

Quantiferon TB testing
Patients with suspected false positive or indeterminate QuantiFERON TB result may have the test repeated once. If after repeat testing the QuantiFERON TB result is "indeterminate" a PPD skin test may be performed locally. A tuberculin skin test reaction ≥10mm (≥ 5mm if receiving ≥15mg/d prednisone or its equivalent) is considered positive.

Patients who now test positive for QuantiFERON TB test may continue and receive treatment in this study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis.

If presence of latent tuberculosis is established, patients can receive anti-tuberculosis treatment (according to local practice/guidelines) and continue receiving study medication.

[redacted]

6.2.2 Treatment period(s)

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

Study related procedures during treatment period will be performed as specified in the Flow chart 1 and Flowcharts 2, in case patients develop an inflammatory flare or fistula relapse.

Pregnancy testing
Urine pregnancy testing for all women of child-bearing potential will be conducted on-site every 4 weeks at visits with study drug administration and must be negative to continue

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

treatment. More frequent testing should be done if required by the local regulation and / or authority or per investigator judgment.

The pregnancy testing should be done **prior to** study drug administration. A positive urine test must be confirmed with a serum pregnancy test.

Blood sampling
Blood sampling (e.g., for safety lab, [redacted]) should be done, if applicable, **prior to** study drug administration and **prior to** rectoscopy/proctoscopy. It is not required that patient is fasted prior to collection of the safety laboratory testing as indicated in Flowcharts, but patient has to be asked and information will be collected on lab requisition form if patient was fasting or not 8 hours prior to blood sampling.

Endoscopy (Proctoscopy/rectoscopy/sigmoidoscopy/ colonoscopy or full ileocolonoscopy). It will be performed once per year during treatment period. Additionally, ileocolonoscopies have to be done in case of disease flare as indicated in Flowchart 2.

Ileocolonoscopy can be performed instead of proctoscopy or rectoscopy if required per local guidelines (i.e. colon cancer screening or others) or routine clinical practice.

[redacted]

Stool sampling
A stool sample will be collected for faecal biomarkers.

Clinical monitoring after study drug administration:

Local tolerability at the administration site of the subcutaneous injection will be assessed by the investigator at the specified visits as noted in the Flow Chart.

At all dosing visits vital signs will be assessed pre- and post-dose, please see section 5.2.2 for further details.

Unscheduled visits
The patient may be asked for additional unscheduled visits due to safety reason at the discretion of the investigator or the sponsor, unless the patient has withdrawn his/her consent. The patient may also contact the site due to safety reason for an unscheduled visit. The unscheduled visit may include additional collection of blood samples for safety reasons and

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

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

6.2.3 Follow-up period and trial completion

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

For patients completing the safety FU period, the EOS visit is scheduled at 16 weeks after the last dose of study drug. For more details please follow Flow Charts.

6.2.3.1 Early treatment discontinuation

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

6.2.3.2 Trial completion

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

6.2.3.3 Further treatment after the end of the trial

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

This trial is designed as a single arm, open-label trial in patients with fistulising Crohn's disease who have completed the planned treatment period in the parent induction trial.

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

7.1 NULL AND ALTERNATIVE HYPOTHESES

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

7.2 PLANNED ANALYSES

7.2.1 General considerations

There will be only one patient population in this trial for analyses – the Treated Set (TS). The TS includes all patients who received at least one dose of study drug. It will be the main analysis set for presentation of both safety and efficacy.

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

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

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

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

7.2.2 Primary endpoint analyses

Refer to Section 2.1.2 for the description of the primary endpoint. The primary analyses will be descriptive in nature. All treated patients will be included in the primary analyses. No hypothesis testing is planned.

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment of this trial and end of the residual effect period

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

(REP), a period of 16 weeks after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. For all patients who, due to a fistula relapse received the intensified treatment with spesolimab, safety assessments including adverse events, laboratories, vital signs, etc., which occurred subsequent to such intake will be excluded from presentations according to the planned treatment; these data will, however, be included in summaries where all data after any use of spesolimab are displayed.

Exposure-adjusted adverse event incidence rates will be calculated using the following approach:

The incidence rate (per 100 patient years) of a selected adverse event (also known as the incidence density rate or person-time incidence rate) is defined as the number of patients experiencing the adverse event during the time at risk divided by the total time of patients at risk to contribute an event to the analysis multiplied by 100, where:

> Time at risk (in subject years) = ((date of onset of AE – study drug start date) + 1) / 365.25

The study drug start date refers to the start date of this trial. If, for a patient, no treatment emergent adverse event occurred, then the time at risk will be censored at the minimum of: date of death; drug stop date + 112 days; start date of CD inflammatory flare or fistula relapse treatment with spesolimab; last contact date; or, date of database snapshot if an interim analysis was performed.

For each AE, the incidence rate will therefore be calculated as:

> Incidence rate = 100 * number of patients with TEAE / Total TEAE-specific time at risk.

Exact 95% confidence intervals around the observed AE incidence rate will also be provided.

7.2.3 Secondary endpoint analyses

Refer to Section 2.1.3 and Table 2.1:1 for a description of the secondary endpoints. All secondary endpoints will be assessed descriptively. Details will be provided in the TSAP.

[redacted]

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

7.2.5 Safety analyses

Refer to Section 7.2.2 for a description of the analyses of the primary endpoint, which for the present trial is a safety endpoint.

For the additional safety analyses described below, all treated patients will be included. In general, these additional safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment in this trial and the end of the REP. Refer to Section 7.2.2 for the complete description of a treatment-emergent adverse event.

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

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

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

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

[redacted]

7.2.7 Interim Analyses

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

Since patients will be enrolled into this study over a time period of several years and in line with the exploratory nature and open label design of the study, such analyses will be performed on demand and are not feasible to be pre-defined.

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

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

For the efficacy outcomes derived from [redacted], no missing data imputations are planned to be performed.

If a patient experiences an inflammatory flare or fistula relapse during the maintenance period prior to observing the efficacy outcome at a specific visit, then all data subsequent to the intake of such rescue medication will be set to missing. Additional summaries of all data observed, including data gathered following rescue medication intake, will also be provided. Further details with regard to what constitutes a rescue intake with potential impact on the efficacy data will be described in the TSAP.

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

7.4 RANDOMISATION

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

7.5 DETERMINATION OF SAMPLE SIZE

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

Up to 20 patients who meet the entry criteria are planned for inclusion into this trial, rolling over from the parent trial. The parent trial's study cohort has a size of 20.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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 the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations 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 (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."
The investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.
The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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. 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 documents will be provided to the Sponsor. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name,

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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.

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.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

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

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed"). The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.
Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

A project-independent, fully-external data-monitoring committee (DMC), will be established to assess the progress of the clinical trial, including an unblinded safety and efficacy assessment at specified intervals, and to recommend to the sponsor whether to continue, modify, or stop either a single spes olimab dose or the trial due to safety or ethical concerns.

The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

BI has appointed a 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 the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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, and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

9. REFERENCES

9.1 PUBLISHED REFERENCES

R00-0812 Present DH, Rutgeerts P, Targan S, Hanauer SB, Mayer L, Hogezand RA van, et.al Deventer SJH van.Infliximab for the treatment of fistulas in patients with Crohn's disease. N Engl J Med. 1999. 340 (18): 1398 – 1405.

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

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

R11-4890 Sampson HA, et al Second symposium on the definition and management of anaphylaxis: summary report - second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. 2nd Symp of the National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis (FAA) Network on the Definition and Management of Anaphylaxis, Jul 2005, J Allergy Clin Immunol 117 (2), 391 - 397 (2006)

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

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

R13-3515 Woodworth T, Furst DE, Alten R, Bingham C, Yocum D, Sloan V, et.al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. J Rheumatol. 2007. 34 (6): 1401 - 1414

R15-4344 Ford AC, Sandborn WJ, Khan KJ, et al. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011.106:644–659, quiz 660

R15-5253 Khanna R, Zou G, D'Haens G, Feagan BG, Sandborn WJ, Vandervoort MK, et.al. A retrospective analysis: the development of patient reported outcome measures for the assessment of Crohn's disease activity. Aliment Pharmacol Ther. 2015. 41:77-86.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

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

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

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

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

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

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

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

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

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

R17-2222 Feagan BG, Reinisch W, Rutgeerts P, Sandborn WJ, Yan S, Eisenberg D, et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients.Am J Gastroenterol 102, 794 - 802 (2007)

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

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

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

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

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

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

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

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

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

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

P19-05294 Rieder F, Fiocchi C, Rogler G. Mechanisms, management, and treatment of fibrosis in patients with inflammatory bowel diseases. Gastroenterology 2017. 152: 340-350 e6

R19-2044 Loly C, Belaiche J, Louis E. Predictors of severe Crohn's disease. Scand J Gastroenterol. 2008. 43: 948-954

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

R19-2045 De Groof EJ, Sahami S, Lucas C, et al. Treatment of perianal fistula in Crohn's disease: a systematic review and meta-analysis comparing seton drainage and anti-tumour necrosis factor treatment. Colorectal Dis. 2016. 18: 667-675

R19-2046 Beaugerie L, Sokol H. Clinical, serological and genetic predictors of inflammatory bowel disease course. World J Gastroenterol. 2012. 18: 3806-3813

R19-2047 Gordon IO, Agrawal N, Willis E, et al. Fibrosis in ulcerative colitis is directly linked to severity and chronicity ofmucosal inflammation. Aliment Pharmacol Ther. 2018. 47: 922-939

R20-2041 Rieder F, Fiocchi C. Intestinal fibrosis in IBD - a dynamic, multifactorial process. Nat Rev Gastroenterol Hepatol. 2009. 6: 228-235.

R20-2042 Rieder F, Fiocchi C. Mechanisms of tissue remodeling in inflammatory bowel disease. Dig Dis. 2013. 31: 186-193.

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

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

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

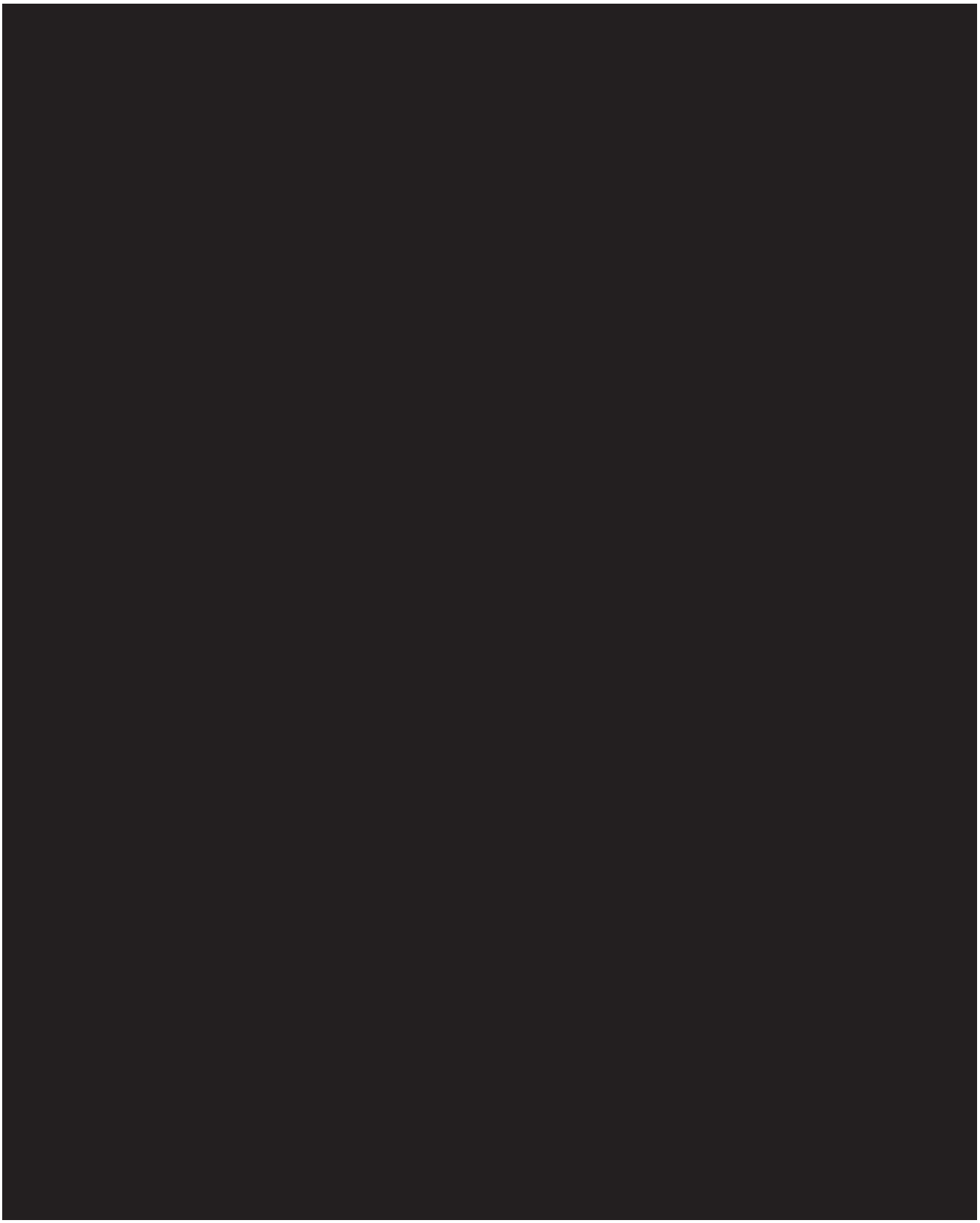
9.2 UNPUBLISHED REFERENCES

c03320877-08 Investigator's Brochure, BI 655130 current version

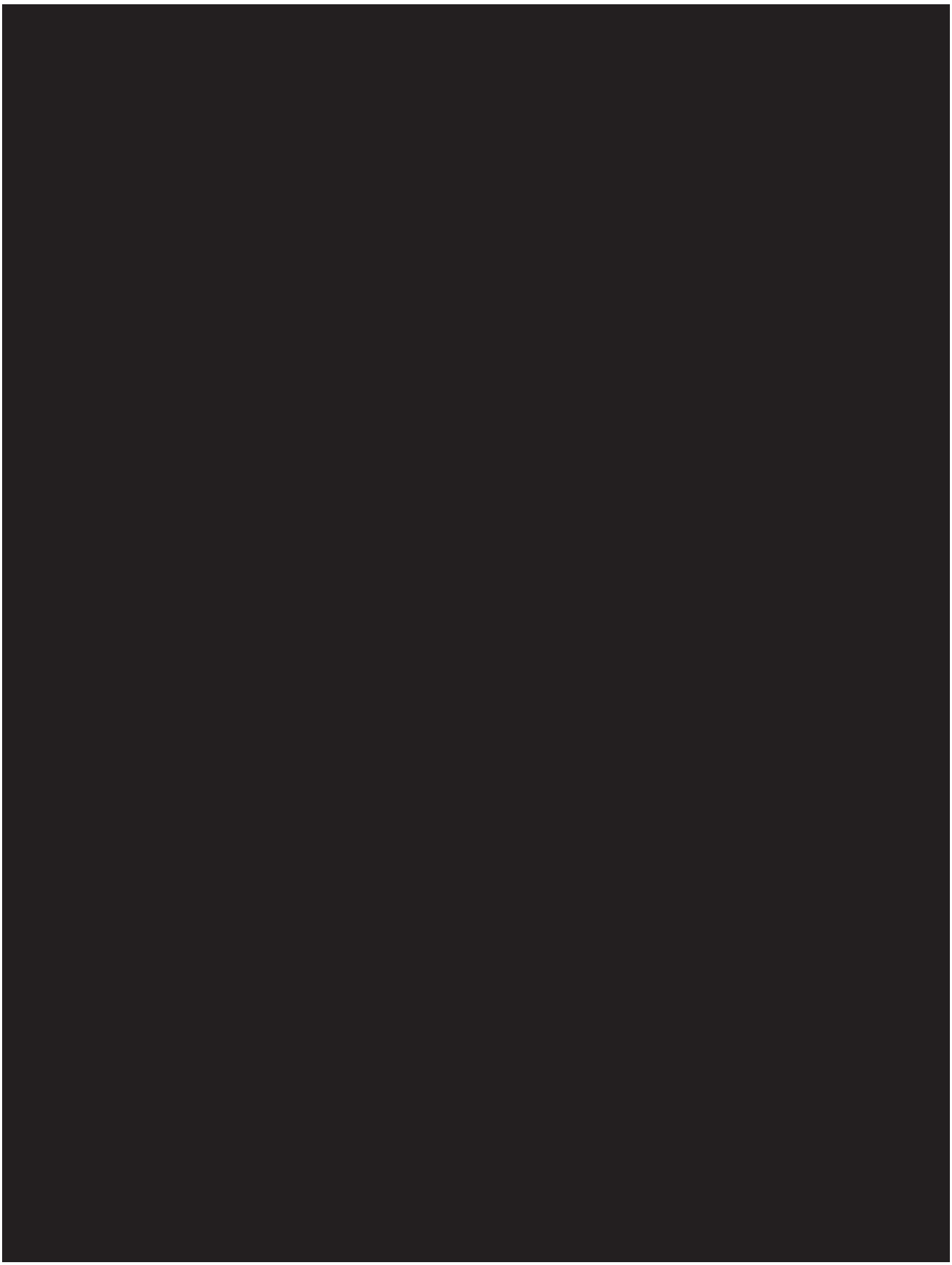
c03361085 [redacted] Clinical Trial Protocol: Single-blind, partially randomised, placebo-controlled Phase I study to investigate safety, tolerability,pharmacokinetics and pharmacodynamics of single rising intravenous doses of BI 655130 in healthy male volunteers. 1368.1. Version 6. 27 Jan 2016.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

10 APPENDICES

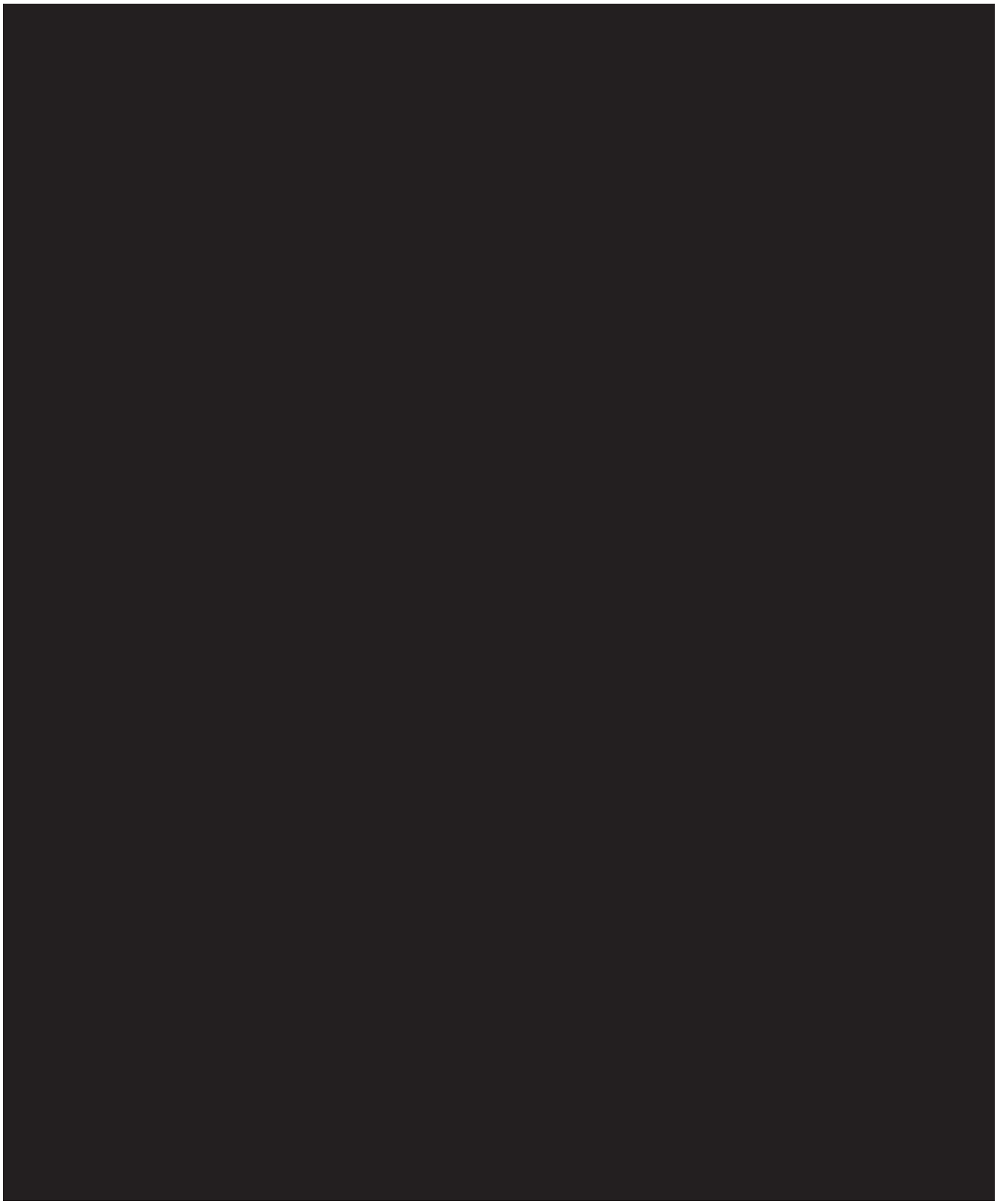


Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

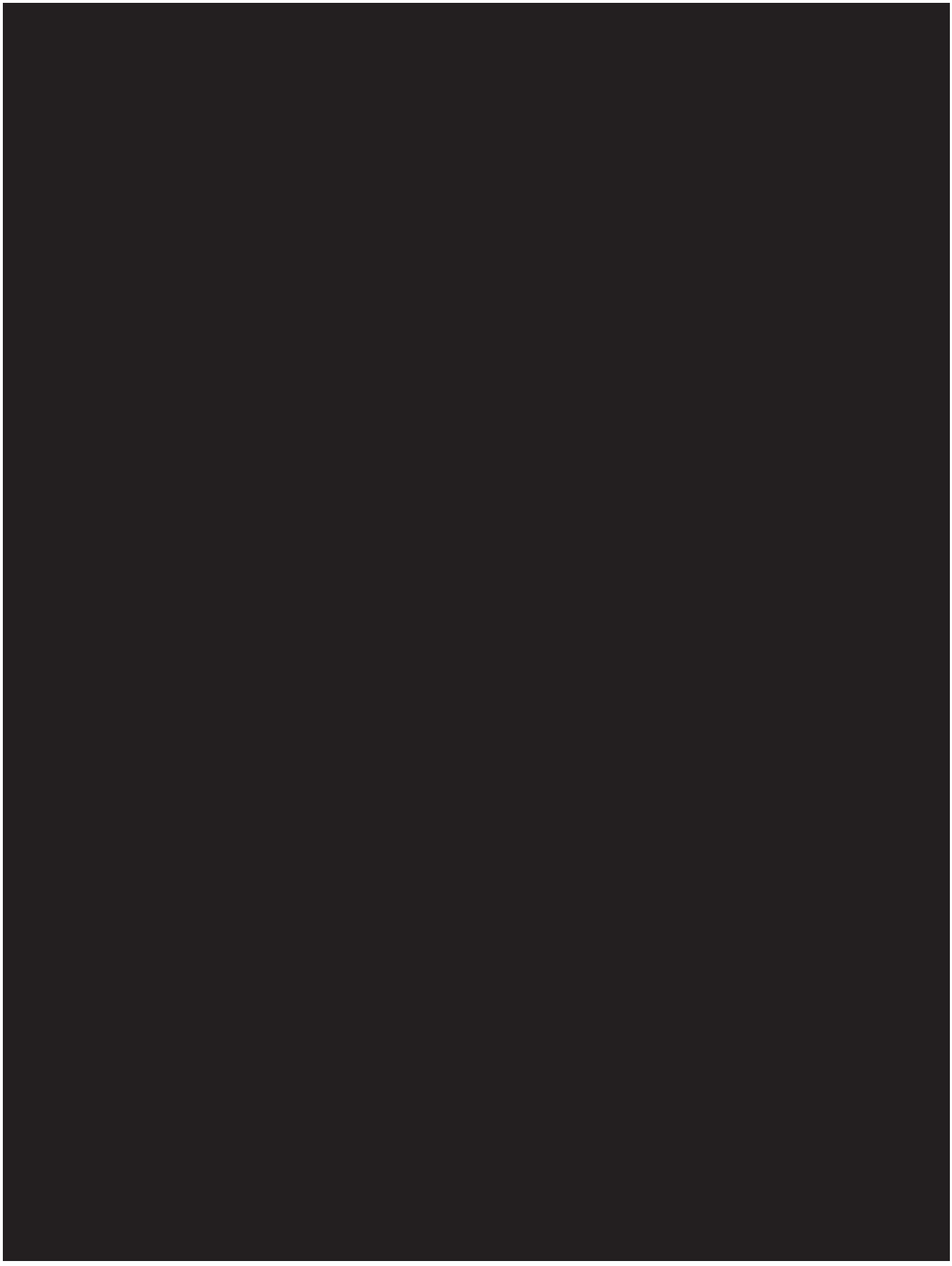


Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

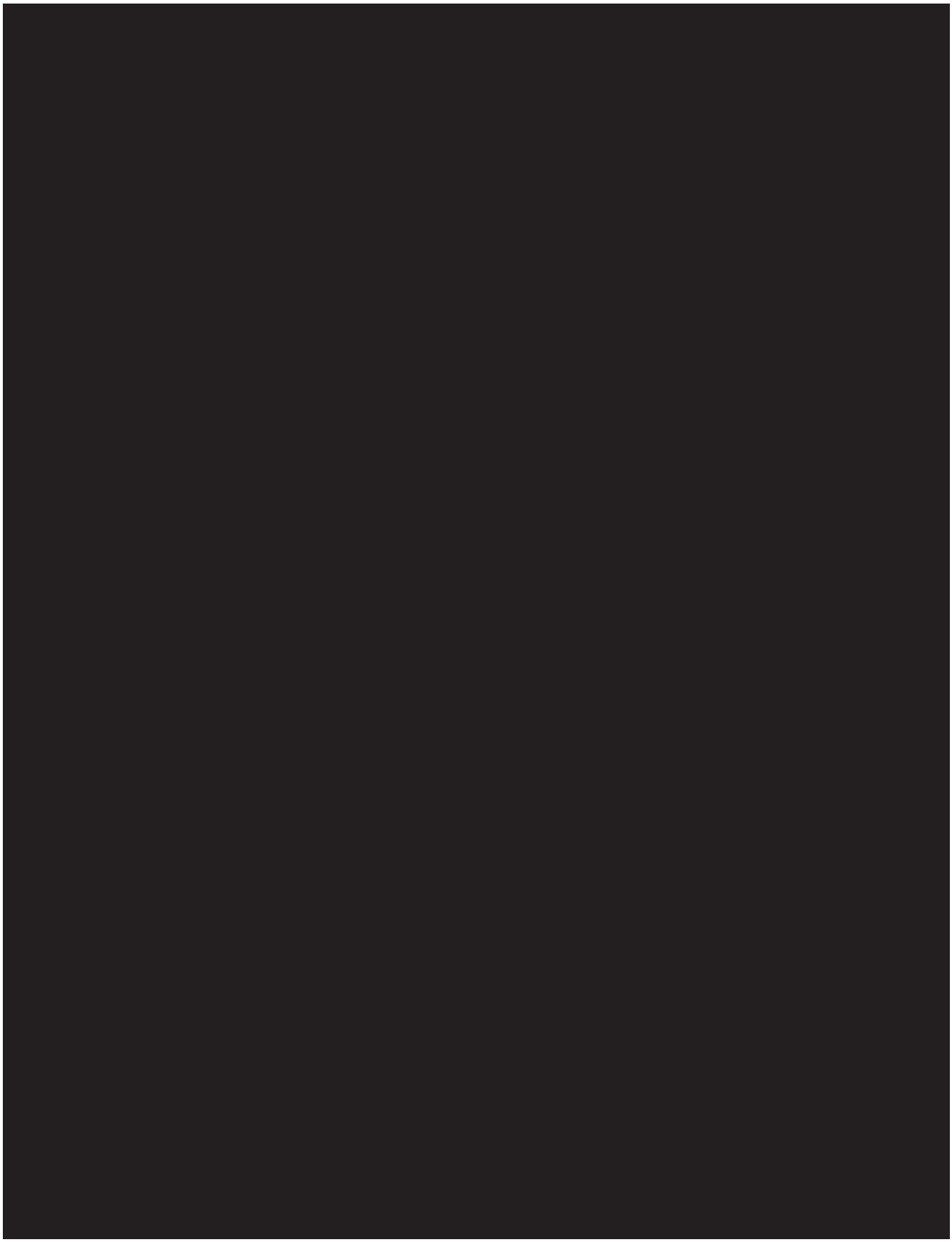
Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies



Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies



Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies



Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

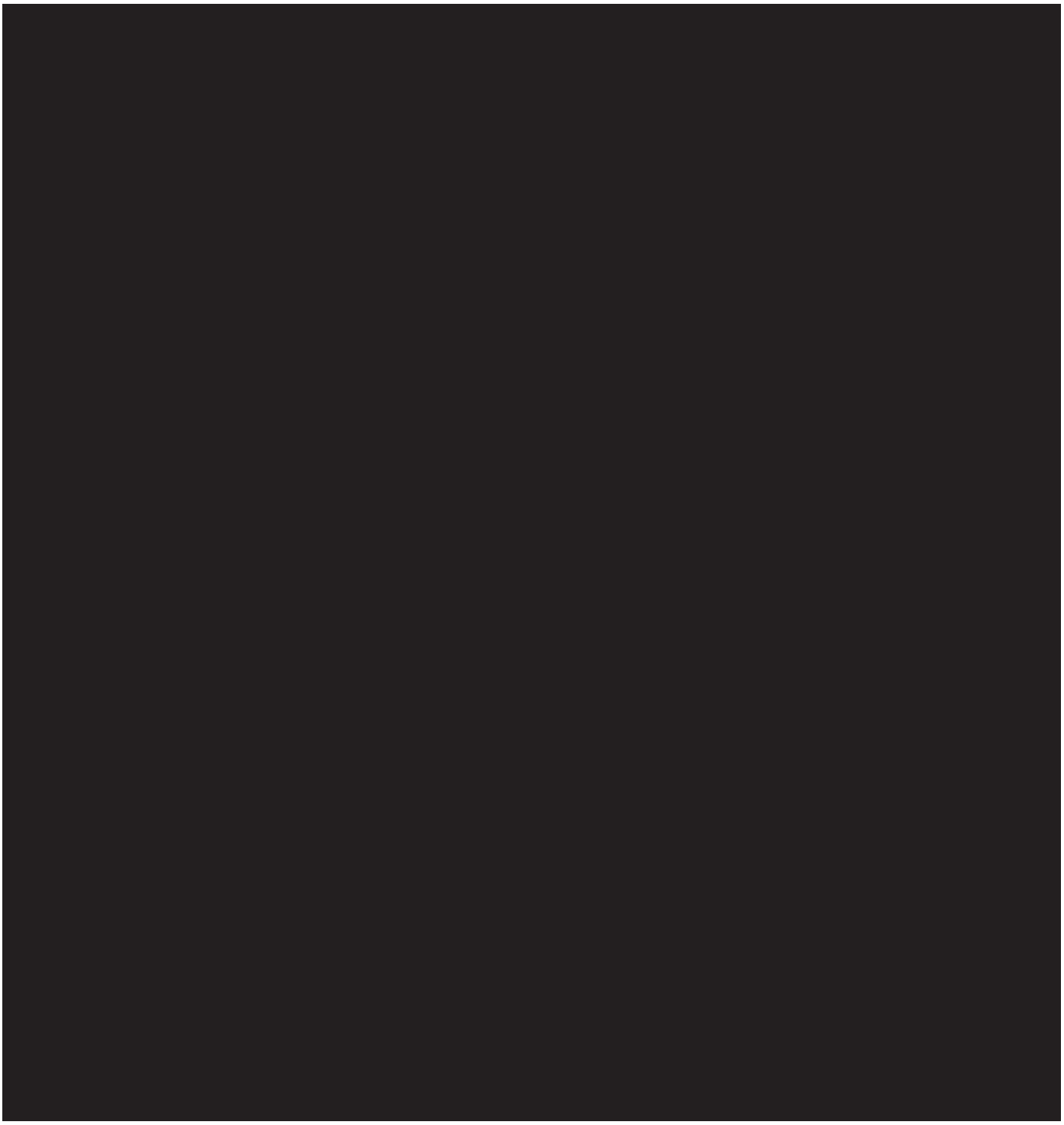
10.6 EQUIVALENT DOSES OF CORTICOSTEROIDS

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

In order to obtain the equivalent dose of prednisone, please multiply the dose taken by the patient by the value in the column ‘Conversion Factor’. See Table 4.2.1.2:1.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies



Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

10.8 DIAGNOSIS OF ANAPHYLAXIS

Clinical Criteria for diagnosing anaphylaxis

(R11-4890**)**

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

AND AT LEAST ONE OF THE FOLLOWING

a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia (collapse), syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (eg, hypotonia (collapse), syncope, incontinence)

d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

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

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		20 March 2020
EudraCT number EU number		2019-001673-93
BI Trial number		1368-0007
BI Investigational Medicinal Product(s)		Spesolimab (BI 655130)
Title of protocol		An open label, long term safety trial of spesolimab treatment in patients with fistulising Crohn's disease who have completed previous spesolimab trials
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Clinical Trial Synopsis, Section 2.1
Description of change		Endpoints for endoscopic remission and response removed.
Rationale for change		No ileocolonoscopies will be performed. See below
Section to be changed		Flow Chart 1A, 1C
Description of change		Ileocolonoscopy will not be mandatory. Instead recto-or proctoscopy requested for screening and yearly afterwards [redacted] segment rectum. Removal of the need to have central reading ileocolonoscopy.
Rationale for change		Ileocolonoscopy is not needed for eligibility purposes and neither for assessment of perianal activity. This patient population (perianal CD) is expected to have low inflammation scores as per eligibility criteria. Thus, the chance for this small sample size study to reliable evaluate spesolimab effect on endoscopic inflammation beyond the rectum is very low. Hence, this clinical outcome will be explored but there is no justification for a full ileocolonoscopy to be mandatory.
Section to be changed		Flow Chart 2A and 2B
Description of change		Clarification of visit names for patients with flare or fistula relapse. Split flow chart in two parts.
Rationale for change		Make naming convention of flare/fistula visits more understandable for investigators.
Section to be changed		Footnote 2
Description of change		Timepoints were rectoscopy or proctoscopy should

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

		be performed and when ileocolonoscopy is mandatory or optional.
Rationale for change		See description above.
Section to be changed		Footnotes 5.19
Description of change		Include MRI at EOT visit, quantiferon tested every 48 weeks
Rationale for change		Clarifications and corrections.
Section to be changed		Section 2.1 and section 2.1.3
Description of change		Endoscopic and [redacted] removed from secondary to further endpoints
Rationale for change		Patient population is expected to have low endoscopic and [redacted] as per eligibility criteria (perianal disease and [redacted] < 250). Therefore, the chance for this small sample size study to reliable evaluate spesolimab effect on endoscopic inflammation beyond the rectum is very low. Hence, this clinical outcome will be explored but has been removed from main endpoints
Section to be changed		Section 2.1 and 3.1
Description of change		Definition of CD inflammatory flare.
Rationale for change		Changed [redacted] of flare to an absolute value instead of a change from baseline as there will not be ileocolonoscopy performed at screening.
Section to be changed		Section 3, Section 6.2.1, Section 6.2.2
Description of change		Ileocolonoscopy is not mandatory. Instead recto-or proctoscopy requested for screening and yearly afterwards [redacted] for segment rectum. Ileocolonoscopy only mandatory as a confirmation of flare. .
Rationale for change		Ileocolonoscopy is not needed for eligibility purposes and neither for assessment of perianal activity. This patient population (perianal CD) is expected to have low inflammation scores as per eligibility criteria. Thus, the chance for this small sample size study to reliable evaluate spesolimab effect on endoscopic inflammation beyond the rectum is very low. Hence, this clinical outcome will be explored but there is no justification for a full ileocolonoscopy to be mandatory.
Section to be changed		Section 3.3.4.1
Description of change		Change of criteria for treatment discontinuation in case of flare/fistula.
Rationale for change		Leave the decision to terminate treatment to the investigator judgement, allowing the investigator to

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

		decide if there is clinical benefit for the patient instead of restricting the chance to continue to those who meet restricted definition of clinical response as per as a more global approach to patient clinical improvement, since these patients might not have other available options.
Section to be changed		4.1.1 Identity of the Investigational Medicinal Products
Description of change		Inclusion of number of injection/vial per dosis
Rationale for change		Clarification of posology
Section to be changed		Table 4.2.1.2:1 Restrictions regarding concomitant treatment
Description of change		Restriction for autologous or allogeneic haematopoietic (HSC) or mesenchymal stem cell (MSC) therapy
Rationale for change		Inclusion on restriction of a therapy
Section to be changed		Section 5.1
Description of change		Endoscopic CD activity amended: assessment by recto-or proctoscopy using [redacted] for the segment rectum
Rationale for change		See above. Ileocolonoscopy
Section to be changed		Section 5.1.3
Description of change		Vibrio removed from infection testing CRP: high density analysis not required Type of E. coli removed (O157/H7)
Rationale for change		This test not needed for safety profile of Spesolimab
Section to be changed		5.2.6.2.1 and footnotes 17 and 19
Description of change		Procedure for reporting AEs and SAEs considering both parent and extension trial.
Rationale for change		Clarification of procedure for reporting AEs.
Section to be changed		Section 5.4.3 and 5.5
Description of change		Change on location of biopsies, only from rectum.
Rationale for change		Adapt to change in ileocolonoscopy/rectoscopy /proctoscopy and biopsies only taken from rectum

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

11.2 GLOBAL AMENDMENT 2

Date of amendment		21 January 2021
EudraCT number EU number		2019-001673-93
BI Trial number		1368-0007
BI Investigational Medicinal Product(s)		Spesolimab (BI 655130)
Title of protocol		An open label, long term safety trial of spesolimab treatment in patients with fistulising Crohn's disease who have completed previous spesolimab trials
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Flow chart 1A, 1C
Description of change 1		Inclusion of blood sampling for biomarkers, and removal of stool sampling for lactoferrin. Clarification on infection testing and urine albumin. Change time window for visit M1-V1.
Rationale for change		New biomarkers needed in aligment with parent trial and other clarifications to avoid discrepancies between local and central lab.
Section to be changed		Flow chart 2A and 2B, footnote 14 and 22, sections 1.4, 3.1, 4.2.1, Figure 3.1:3.
Description of change 2		Differentiate luminal inflammatory flare from fistula relapse treatment. New flow chart for patients with only inflammatory flare. For safety labs: change visit where labs are required to FLn, F1, F3, F5.
Rationale for change		Patients who maintain fistula response but present luminal inflammatory flare could be treated with SOC concomitantly with spesolimab. For safety labs, correction needed.
Section to be changed		Footnotes 3, 6,8 ,21
Description of change 3		3.Include additional vital signs assessments at visit M1 and M2. 6. Clarification on TSH and HbA1C 8. inclusion of blood biomarkers testing 21. clarification on infection testing at EOT visit.
Rationale for change		Align with protocol changes and avoid misunderstanding.
Section to be changed		Section 1.1, 1.2, 1.3
Description of change 4		Update on news on the disease, treatment and study data included. Update on spesolimab UC

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

		development status.
Rationale for change		Update investigators on latest status of spesolimab development in IBD and other indications.
Section to be changed		Section 1.4
Description of change 5		Rewording of section to include new spesolimab data and Covid-19 procedures.
Rationale for change		Update to reflect current drug profile. Inclusion of benefit-risk assessment in context of Covid-19 pandemia.
Section to be changed		Section 2.2.1 and Table 5.2.3:1
Description of change 6		Remove faecal lactoferrin
Rationale for change		Not relevant for this indication.
Section to be changed		Section 3.3.4.1 and table 4.2.2:2
Description of change 7		Clarification that **surgical procedures to treat fistulas** are not allowed after randomization and patient should be discontinued.
Rationale for change		Clarification to investigators that previously restricted surgical procedures include procedures to treat perianal and /or enterocutaeous fistulas since these would confound efficacy endpoints.
Section to be changed		Section 4.1.4
Description of change 8		During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may discuss with BI to continue the trial treatment and trial medication may be shipped to the patient's home if acceptable according to local law and regulations.
Rationale for change		Challenges due to covid-19 are acknowledged and the flexibility should be given to administer the trial medication at home taken the requirements described above into account.
Section to be changed		Section 4.2.1 and table 4.2.1.2:1
Description of change 9		Reorganisation of information on concomitant treatments. Inclusion of stable doses of anti-TNF as allowed concomitant treatment during the study. Clarifications on steroids and antibiotics treatment and allowed surgeries. Inclusion of approved medications to treat moderate-to-severe luminal inflammatory flares as concomitant therapy in patients with fistula response but who present luminal flare.
Rationale for change		Clarify use of concomitant treatments. To align with new eligibility criteria in parent trial 1368.8, which allows stable doses of anti-TNF therapy

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

		(SOC for luminal inflammatory activity control in CD patients). UC spesolimab phase II program data does not support use of spesolimab in luminal inflammatory flare. Thus, patients who present with luminal inflammatory flare while maintaining fistula response will be treated with SOC.
Section to be changed		Section 5.2.2.
Description of change 10		Inclusion of additional vital signs measurement at visit 1 at M1 post dose.
Rationale for change		Include safety measure after two first subcutaneous doses.
Section to be changed		Table 5.2.3: 1
Description of change 11		Include clarifications in some labs: HbA1c, TSH. Delete bicarbonate and fecal lactoferrin.
Rationale for change		Clarification of when to test some parameters and deletion of parameters that are not relevant for the disease.
Section to be changed		Section 5.4.1
Description of change 12		[redacted]
[redacted]		
Section to be changed		Section 5.4.2
Description of change 13		Include when the rectal biopsies should be done
Rationale for change		Clarification.
Section to be changed		Section 5.5 and 6.2.1
[redacted]		[redacted]
Section to be changed		Section 10.6
Description of change 15		Delete appendix.
Rationale for change		No needed for this indication.

Proprietary confidential information © 2021 Boehringer Ingelheim International GmbH or one or more of its affiliated companies

12. REFERENCES FOR CTP AUTHORS

NA

APPROVAL / SIGNATURE PAGE

Document Number: c27319443 **Technical Version Number:5.0**

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

Title: An open label, long term safety trial of spesolimab treatment in patients with fistulising Crohn's disease who have completed previous spesolimab trials

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	21 Jan 2021 09:24 CET
Approval-Team Member Medicine		21 Jan 2021 10:14 CET
Approval-Biostatistics		21 Jan 2021 10:38 CET
Approval-Therapeutic Area [redacted]		21 Jan 2021 11:23 CET
Approval-Biostatistics		28 Jan 2021 13:02 CET
Approval-Team Member Medicine		28 Jan 2021 13:03 CET
Author-Clinical Trial Leader		28 Jan 2021 13:05 CET
Approval-Therapeutic Area [redacted]		28 Jan 2021 15:08 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Verification-Paper Signature Completion	[redacted]	28 Jan 2021 15:15 CET