Clinical Trial Protocol

	Document Number: **c27981303-05**
BI Trial No.	1368-0043
BI Investigational Medicinal Product	BI 655130 (Spesolimab)
Title	An open-label phase I trial to assess pharmacokinetics and safety of single subcutaneous doses and single intravenous doses of BI 655130 in healthy Chinese male and female subjects (single doses, open-label study in parallel-group design).
Lay Title	A trial in healthy Chinese volunteers to test how different doses of BI 655130 are taken up in the body.
Clinical Phase	I
Trial Clinical Leader	[redacted] Phone: [redacted] Fax: [redacted]
Principal Investigator	[redacted] Phone: [redacted] Fax: [redacted]
Status	Final Protocol (Revised Protocol (based on global amendment 04))
Version and Date	Version: 5.0 / Date: 26 Feb 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim (BI)
Protocol date	29 Jul 2019
Revision date	26 Feb 2021
BI trial number	1368-0043
Title of trial	An open-label phase I trial to assess pharmacokinetics and safety of single subcutaneous doses and single intravenous doses of BI 655130 in healthy Chinese male and female subjects (single doses, open-label study in parallel-group design).
Principal Investigator	[redacted]
Trial site	[redacted] Phone: [redacted] Fax: [redacted] Email: [redacted]
Clinical phase	I
Trial rationale	To investigate the PK and safety of spesolimab in Chinese healthy subjects
Trial objectives	To investigate PK, including dose proportionality, following single SC and IV doses of spesolimab in healthy Chinese subjects
Trial endpoints	Primary endpoint $AUC_{0-\infty}$ and C_{max} of spesolimab Secondary endpoints: The occurrence of treatment-emergent adverse events (AEs) The occurrence of drug-related AEs
Trial design	Open-label without placebo, parallel-group design

Number of subjects **total entered** **each treatment**	Up to 60 subjects including up to 10 subjects for replacement of early discontinuation 10 per dose group
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male or female subjects (at least three subjects for each gender within each dose group) Age of 18 to 45 years (inclusive) Body weight ≥50 kg for male and ≥45 kg for female Body mass index (BMI) ≥19 and <26 kg/m^2 for male and female at visit 1
Test product 1 **dose** **mode of admin** **Test product 2** **dose** **mode of admin**	BI 655130 (60 mg/mL) solution for infusion Single dose of 450 mg, 900 mg and 1200 mg IV as 90 min infusion BI 655130 (150 mg/mL) solution for injection Single dose of 300 mg and 600 mg SC injection
Comparator product **dose** **mode of admin**	Not applicable Not applicable Not applicable
Duration of treatment	One day (single dose) for each treatment
Statistical methods	Descriptive statistics will be calculated for all endpoints. Dose proportionality of Spesolimab will be explored using a regression model for $AUC_{0-\infty}$ and C_{max} for IV doses. A 90% confidence interval (CI) for the slope will be computed.

FLOW CHART S.C.

Single dose group for SC
Single dose of Spesolimab as 300 mg and 600 mg SC (subjects will receive only one dose)

Visit	Day	Time relative to first drug administration (planned time) [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{blood} [4]	Plasma ADA[8]	Laboratory[3]	Body weight	12-lead ECG	Vital signs (BP, PR, RR, body temperature)[10]	Query on AEs, concomitant therapies[11]
1	-28 to -3			screening[1]			X[14]	X	X	X	
	-2	-48:00	8:00	ambulatory visit			X[13]				X[13]
2	-1	-12:00	20:00	admission to trial site			X[9]				X
	1	-2:00	6:30		X[2]	X[2]	X[2,14]		X[2]	X[2]	X[2,5]
		0:00	8:00	drug administration							
		0:10	8:10							X	
		0:30	8:30		X				X	X	X[5]
		1:00	9:00							X	
		1:30	9:30						X	X	
		2:00	10:00	light breakfast[6]	X				X	X	
		3:00	11:00		X					X	
		4:00	12:00	lunch[6]	X					X	X[5]
		6:00	14:00						X	X	
		8:00	16:00		X					X	
		10:00	18:00	dinner[6]							
		12:00	20:00		X				X	X	X[5]
	2	24:00	8:00	breakfast[6]	X				X	X	X[5]
		28:00	12:00	lunch[6]							
		32:00	16:00							X	
		34:00	18:00	dinner[6]							X[5]
	3	48:00	8:00	breakfast[6] discharge from trial site (confirmation of fitness[7])	X				X	X	X[5]
	4	72:00	8:00	ambulatory visit	X		X				X[5]
	5	96:00	8:00	ambulatory visit	X						X[5]
	6	120:00	8:00	ambulatory visit	X						X[5]
	7	144:00	8:00	ambulatory visit	X						X[5]
	8	168:00	8:00	ambulatory visit	X		X		X	X	X[5]
	15	336:00	8:00	ambulatory visit	X	X					X[5]
	22	504:00	8:00	ambulatory visit	X		X		X	X	X
	29	672:00	8:00	ambulatory visit	X	X	X		X	X	X[5]
	36	840:00	8:00	ambulatory visit	X						X
	43	1008:00	8:00	ambulatory visit	X	X					X
	57	1344:00	8:00	ambulatory visit	X	X					X[5]
	71	1680:00	8:00	ambulatory visit	X	X					X
	92 ±2	2184:00	8:00	ambulatory visit	X	X	X[14]				X
	120 ±3	2856:00	8:00	ambulatory visit	X	X					X
	148 ±3	3528:00	8:00	ambulatory visit	X	X					X
3	176 ±3	4200:00	8:00	EoTrial [12]	X	X	X[14]	X	X	X	X[5]

1. Screening with subject information, informed consent as the first measure, includes physical examination, check of vital signs including temperature, respiratory rate (RR), systolic and diastolic blood pressure (BP) and pulse rate (PR), 12-lead electrocardiogram (ECG), safety laboratory parameters (under fasting conditions), pregnancy test, drug screening, alcohol breath test, demographics (including determination of body height and weight, smoking and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; procedures are to be performed and completed within three hours prior to drug administration. Within three hours prior to the planned dosing, planned time -2:00 will be used.
3. Safety laboratory parameters include clinical chemistry, haematology, coagulation and urinalysis; in addition at screening: serology (hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV], tuberculosis (QuantiFERON TB test), Follicle-stimulating hormone (FSH) and estradiol evaluation in questionable cases for determining postmenopausal status), and drug screening.
4. PK sampling times may be adapted based on information obtained during trial conduct.
5. Standardised assessment of local tolerability using the criteria swelling, induration, heat, redness, pain or other findings.
6. If several actions are indicated at the same time point, the intake of meals will be the last action.
7. Confirmation of fitness includes physical examination.
8. ADAs will be taken at baseline, Day 15, Day 29, Day 43, Day 57, Day 71, Day 92, Day 120, Day 148 and Day 176.
9. Only drug screening and alcohol breath test.
10. Evaluate vital signs at baseline, 10 minutes after and 1 hour post infusion/injection and in case of suspicion of hypersensitivity reaction including anaphylactic reaction.
11. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
12. EoTrial (end of trial) examination includes physical examination, body weight, vital signs, 12-lead ECG, safety laboratory parameters, recording of AEs and concomitant therapies. EoTrial to be performed not before last PK and ADA sampling.
13. Safety laboratory parameters are to be taken within two days prior to trial medication administration under fasting conditions and can be omitted if the screening examination is performed between Day -5 and Day -3. Also the AEs and concomitant therapies will be queried on Day -1.
14. At these time points, a urine pregnancy test will be done for female subjects.

FLOW CHART I.V.

Single dose group for IV
Single dose of Spesolimab as 450 mg, 900 mg and 1200 mg IV. (Subjects will receive only one dose)

Visit	Day	Time relative to first drug administration (planned time) [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{blood} [4]	Plasma ADA[8]	Laboratory[3]	Body weight	12-lead ECG	Vital signs (BP, PR, RR, body temperature)[11]	Query on AEs, concomitant therapies[12]
1	-28 to -3			screening[1]			X[15]	X	X	X	
	-2	-48:00	8:00	ambulatory visit			X[14]				X[14]
2	-1	-12:00	20:00	admission to trial site			X[10]				X
	1	-2:00	6:30		X[2]	X[2]	X[2,15]		X[2]	X[2]	X[2,5]
		0:00	8:00	drug administration start of infusion							
		0:10	8:10							X	
		0:30	8:30						X	X	X[5]
		1:00	9:00							X	
		1:30	9:30	▼ end of infusion[9]	X				X	X	
		2:00	10:00	light breakfast[6]	X				X	X	
		3:00	11:00		X					X	
		4:00	12:00	lunch[6]	X					X	X[5]
		6:00	14:00						X	X	
		8:00	16:00		X					X	
		10:00	18:00	dinner[6]							
		12:00	20:00		X				X	X	X[5]
	2	24:00	8:00	breakfast[6]	X				X	X	X[5]
		28:00	12:00	lunch[6]							
		32:00	16:00							X	
		34:00	18:00	dinner[6]							X[5]
	3	48:00	8:00	breakfast[6]discharge from trial site (confirmation of fitness[7])	X				X	X	X[5]
	4	72:00	8:00	ambulatory visit	X		X				X[5]
	5	96:00	8:00	ambulatory visit	X						X[5]
	6	120:00	8:00	ambulatory visit	X						X[5]
	7	144:00	8:00	ambulatory visit	X						X[5]
	8	168:00	8:00	ambulatory visit	X		X		X	X	X[5]
	15	336:00	8:00	ambulatory visit	X	X					X[5]
	22	504:00	8:00	ambulatory visit	X		X		X	X	X
	29	672:00	8:00	ambulatory visit	X	X	X		X	X	X[5]
	36	840:00	8:00	ambulatory visit	X						X
	43	1008:00	8:00	ambulatory visit	X	X					X
	57	1344:00	8:00	ambulatory visit	X	X					X[5]
	71	1680:00	8:00	ambulatory visit	X	X					X
	92 ±2	2184:00	8:00	ambulatory visit	X	X	X[15]				X
	120 ±3	2856:00	8:00	ambulatory visit	X	X					X
	148 ±3	3528:00	8:00	ambulatory visit	X	X					X
3	176 ±3	4200:00	8:00	EoTrial [13]	X	X	X[15]	X	X	X	X[5]

1. Screening with subject information, informed consent as the first measure, includes physical examination, check of vital signs including temperature, RR, systolic and diastolic BP and PR, 12-lead ECG, safety laboratory parameters (under fasting conditions), pregnancy test, drug screening, demographics (including determination of body height and weight, smoking and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; procedures are to be performed and completed within three hours prior to drug administration. Within three hours prior to the planned dosing, planned time -2:00 will be used.
3. Laboratory tests (safety laboratory parameters) include clinical chemistry, haematology, coagulation and urinalysis; in addition at screening: serology (HBV, HCV, HIV, QuantiFERON TB test, FSH and estradiol evaluation in questionable cases for determining postmenopausal status), and drug screening.
4. PK sampling times may be adapted based on information obtained during trial conduct.
5. Standardised assessment of local tolerability using the criteria swelling, induration, heat, redness, pain or other findings.
6. If several actions are indicated at the same time point, the intake of meals will be the last action.
7. Confirmation of fitness includes physical examination.
8. ADA samples will be taken at baseline, Day 15, Day 29, Day 43, Day 57, Day 71, Day 92, Day 120, Day 148 and Day 176 (EoTrial).
9. First measure after completion of infusion collection of PK sample.
10. Only drug screening and alcohol breath test.
11. Evaluate vital signs at baseline, 10 minutes after and 1hour post infusion/injection and in case of suspicion of hypersensitivity reaction including anaphylactic reaction.
12. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
13. EoTrial includes physical examination, body weight, vital signs, 12-lead ECG, safety laboratory parameters, recording of AEs and concomitant therapies. EoTrial to be performed not before last PK and ADA sampling.
14. Safety laboratory parameters are to be taken within two days prior to trial medication administration under fasting conditions and can be omitted if the screening examination is performed between Day −5 and Day − 3. Also the AEs and concomitant therapies will be queried on Day -1.
15. At these time points, a urine pregnancy test will be done for female subjects.

TABLE OF CONTENTS

ABBREVIATION

ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
AST	Aspartate transaminase
AtD	Atopic dermatitis
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$\%AUC_{tz-\infty}$	The percentage of $AUC_{0-\infty}$ obtained by extrapolation
BI	Boehringer Ingelheim
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CD	Crohn's Disease
CDC	Complement-dependent cytotoxicity
CRA	Clinical Research Associate
CRF	Case report form
CRP	C-Reactive Protein
CL	Total clearance of the analyte in plasma after intravenous administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CTL	Clinical trial leader
CTM	Clinical trial manager
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug-induced liver impairment
ECG	Electrocardiogram
EDC	Electronic Data Capture
EoTrial	End of trial
FIH	First-in-Human
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice

GPP	Generalised pustular psoriasis
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HS	Hidradenitis suppurativa
IB	Investigator's brochure
IBD	Inflammatory bowel disease
ICF	Informed consent form
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IL36R	Interleukin 36 receptor
IQRM	Integrated Quality and Risk Management
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
ITE	Indirect target engagement
IV	Intravenous
λ_z	Terminal rate constant in plasma
mAb	Monoclonal antibody
MRT	Mean residence time of the analyte in the body after intravenous bolus administration
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic parameter analysis set
PPP	Palmoplantar pustulosis
ppPASI	Palmoplantar Pustular Psoriasis Area and Severity Index
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
REP	Residual Effect Period
RR	Respiratory Rate
SAE	Serious adverse event(s)
SC	Subcutaneous
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma

TS	Treated set
UC	Ulcerative colitis
V_{ss}	Volume of distribution at steady state after single intravenous administration
V_z	Volume of distribution during the terminal phase after intravascular administration
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Spesolimab is a humanised antagonistic monoclonal IgG1 antibody that blocks human interleukin 36 receptor (IL36R) signaling. Binding of Spesolimab to IL36R is anticipated to prevent the subsequent activation of IL36R by cognate ligands (IL36α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways in inflammatory skin and bowel diseases such as generalised pustular psoriasis (GPP), palmoplantar pustulosis (PPP), atopic dermatitis (AtD), hidradenitis suppurativa (HS) and inflammatory bowel disease (IBD).Genetic human studies have established a strong link between IL36R signaling and skin inflammation, as demonstrated by the occurrence of GPP in patients with a loss-of-function mutation in IL36Rα, the gene encoding the endogenous inhibitor of IL36R, which resulted in uncontrolled IL36R signaling [R14-5158, R15-1421]. Mutations in other genes linked to the IL36 pathway such as CARD14 also lead to GPP [R16-0929]. IL36R signaling drives skin inflammation in several animal models, further supporting the strong link between IL36R biology and skin disorders based on human genetics [R14-5158].

IL36R is identified as a target for psoriasis based on (i) the abundant expression of all three stimulating ligands in human psoriatic lesional skin [R14-4037], (ii) IL36α overexpression in murine keratinocytes inducing a psoriatic-like phenotype [R15-1432], (iii) IL36R KO mice protecting against Imiquimod-induced skin inflammation [R15-1447], and (iv) IL36R blockade ameliorating skin inflammation in a transplanted psoriatic skin model [R15-1399].The link between IL36R-driven inflammation and epithelial inflammation has led to the hypothesis that IL36R signaling may play an important role in IBD. This hypothesis was tested using a suite of *in vitro* and *in vivo* assays. Immunostaining studies demonstrated that both IL36R and its ligands are expressed in intestinal biopsies taken from Crohn's disease (CD) patients. Human IL36 ligands enhance intestinal barrier permeability, a hallmark of IBD pathogenesis, using primary human intestinal epithelial cells co-cultured with intestinal myofibroblasts. The link between IL36R signaling and IBD was further strengthen by demonstrating that antagonist anti-mouse IL36R antibodies ameliorated intestinal inflammation in both acute chemically-induced and chronic T cell driven murine colitis models.

In addition, the therapeutic rational for an IL36R antagonist in IBD is based on the correlation of a set of IL36-induced genes upregulated in primary human intestinal myofibroblast, a disease relevant cell type, with gene signatures observed in ulcerative colitis (UC) and CD patients. Finally IL36R signaling in disease relevant cells such as intestinal myofibroblasts and macrophages induce both pro-inflammatory and tissue remodeling-related mediators (e.g. TGF-β, MMPs).

Altogether, these findings support a prominent role for IL36R in driving skin and intestinal inflammation and support anti-human IL36R antibody Spesolimab as a therapeutic agent for epithelial-mediated inflammatory diseases such as GPP, PPP, and IBD.

GPP is characterised by systemic inflammation of the skin and internal organs [R15-1421; R16-0933]. Acute GPP is difficult to treat and no approved or standard of care therapy is available in the US or EU. Current treatment options aiming to control acute GPP and maintain

response are cyclosporine, acitretin, and methotrexate [R16-0933]. Secukinumab, infliximab, brodalumab, and ixekizumab have been approved for GPP exclusively in Japan based on small local uncontrolled studies. To date, treatment is commonly not effective in suppressing acute flares during induction and recurrences emerge frequently.

PPP is a form of chronic PP characterised by sterile pustules limited to palms and soles [R16-0927]. Current, no approved or effective treatment is available.

Both UC and CD are characterised by abdominal pain, fever, bloody diarrhoea, and inflammatory lesions in the gastrointestinal mucosa. Current treatment options include aminosalicylates, glucocorticoid therapy, azathioprine, 6-mercaptopurine, and biologics (blocking TNF or integrin α4β7). Treatment of CD and UC is associated with a significant number of patients with primary and secondary non-response. In addition, treatment may be limited due to safety and tolerability issues. Therefore, despite progress, there remains a significant unmet medical need for new treatment options with an improved safety and efficacy profile compared with the current therapeutic standard.

1.2 DRUG PROFILE

1.2.1 Nonclinical Pharmacology

Spesolimab is a humanised monoclonal antibody (mAb) of the IgG1 isotype that is directed against human IL36R. It is derived from mouse antibody 81B4 (BI 674308) cloned into a human IgG1 Kappa backbone. Spesolimab binds to human IL36R with a binding avidity of less than 1 pM. Spesolimab inhibits IL36 ligand-stimulated NF-$_k$B activation in transformed epithelial cells and in primary human keratinocytes, dermal fibroblasts and intestinal myofibroblasts with IC90 values in a consistent range of 0.7 to 3.7 nM. Spesolimab also inhibits IL8 release in dermal fibroblasts and keratinocytes and IFNγ secretion in human peripheral blood mononuclear cell) stimulated with IL36α, IL36β, or IL36γ combined with IL12.

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

1.2.2 Toxicology

Spesolimab does not bind to IL36R from common toxicology species. Therefore, meaningful toxicity studies cannot be performed in any animal species with Spesolimab. Hazard identification studies were performed in mice using a mouse specific anti-IL36R mAb (BI 674304), a mouse IgG2a mAb with rat variable regions. In a 13-week intravenous (IV) toxicity study of BI 674304 in mice, no adverse effects of IL36R 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 [n00243876]. 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 IV injection via the caudal vein [n00257882]. 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 [n00240832, n00239291]. There were no signs of local irritation after single, 1 mL injections of the subcutaneous (SC) formulation in rabbits [n00248748]. These preclinical data suggest Spesolimab may be safely administered to humans.

1.2.3 Nonclinical pharmacokinetics

Spesolimab has a very weak binding affinity to cynomolgus monkeys. Its pharmacokinetics (PK) characteristics in cynomolgus monkeys therefore addresses only the overall catabolic stability and FcRn recycling properties of the molecule, rather than full PK evaluation including possible specific target-mediated drug disposition. The PK of Spesolimab in cynomolgus monkeys were approximately dose linear following the IV administration of 0.3, 1.5, and 10 mg/kg of Spesolimab. The clearance, steady-state volume of distribution, and terminal half-life ($t_{1/2}$) for the three dose groups were similar ranging from 0.168-0.219 mL/h/kg, 65.2-83 mL/kg, and 284-349 h, respectively. The SC bioavailability was 62.6% [n00243168]. Anti-drug antibodies (ADA) were observed in both the 10 mg/kg IV and 1.5 mg/kg SC. dose groups, whereas the 0.3 and 1.5 mg/kg IV monkeys tested negative for ADA. In the two-week GLP toxicology study in CD-1 mice with Spesolimab, exposure increased proportionally from 10 to 50 mg/kg, and there was no apparent difference in Spesolimab serum exposure between male and female mice [n00255537].

1.2.4 Prediction of human pharmacokinetics

PK data suggest TMDD kinetics for Spesolimab [c09985235]. The saturation of the non-linear elimination pathway is likely to occur after 0.3 mg/kg and Spesolimab exhibits linear kinetics from the next dose-level onwards up to 10 mg/kg. Based on the PK results in GPP patients, the elimination $t_{1/2}$ of Spesolimab was observed to be approximately three weeks in patients who are ADA-negative and approximately one week in patients who tested ADA-positive [c17444370]. Steady state was not attained after four weekly doses in the multiple dosing groups and the accumulation ratios were similar for the various dose groups. Preliminary PK data suggest the exposure of a 300 mg SC dose of Spesolimab is similar when administered as a single 2 mL injection or two separate 1 mL injections, which potentially provides flexibility to dose 300 mg with either 1 mL or 2 mL pre-filled syringes in future trials.

Pharmacodynamic (PD) effects in this first-in-human (FIH) single-rising-dose trial [c03361085] were assessed by indirect target engagement (ITE) of IL36R by Spesolimab using an ex vivo whole blood stimulation assay. Preliminary analyses indicate that >99% peripheral IL36R receptor occupancy is achieved with doses ≥1 mg/kg from 30 minutes post infusion to ten week.

1.2.5 Clinical experience in humans

As of Sep 2020, six phase I trials and four phase II trials have been completed for Spesolimab, five phase I trials were conducted in healthy subjects, one phase I trial in GPP patients and four phase II trials in PPP, UC, AD patients.

The trial 1368-0001 was a single-rising-dose trial that assessed safety, tolerability, PK and PD of Spesolimab in healthy subjects [c09985235]. A total of 59 subjects received Spesolimab IV infusions from 0.001 mg/kg to 10 mg/kg while 19 subjects received placebo administration. Safety and tolerability of all tested IV doses were good. The most frequent treatment-emergent adverse events (AEs) were nasopharyngitis (Spesolimab: 20.7%; placebo: 15.0%), headache (Spesolimab: 8.6%; placebo: 15.0%), influenza-like illness (Spesolimab: 6.9%; placebo: 10.0%), and diarrhoea (Spesolimab: 3.4%; placebo: 10.0%). There were two AEs of moderate intensity (injection site haematoma, headache), all remaining AEs were of mild intensity. There were no serious adverse events (SAEs), no AEs that led to discontinuation of trial medication, no protocol-specified AEs of special interest and no other significant AEs. Furthermore, no relevant changes were observed in safety laboratory parameters, vital signs, and 12-lead ECGs. Importantly, there were no relevant differences in frequencies of subjects with treatment emergent AEs between the treatment groups, and no dose dependency was observed.

In the multiple-rising-dose trial 1368-0002, a total of 40 healthy male subjects were enrolled in five sequential groups comprising eight subjects per group. The trial consisted of four dose groups receiving rising multiple doses of 3 mg/kg, 6 mg/kg, 10 mg/kg or 20 mg/kg. In addition, one dose group received one single dose (20 mg/kg) only. Within each of the five dose groups, six subjects have been randomised to receive the active drug and two received placebo. In trial 1368.2, no dose dependency was observed for all AEs. The incidences of drug related AEs were balanced across treatment groups up to 10 mg/kg bw dose, while higher incidences were reported in the 20 mg/kg bw dose group. However, all AEs were of mild or moderate intensity.

Overall, multiple IV doses of 3 mg/kg, 6 mg/kg, and 10 mg/kg, as well as single and multiple doses of 20 mg/kg Spesolimab were found to be safe and well tolerated by the subjects in this trial. The incidences of drug-related AEs were balanced across treatment groups up to 10 mg/kg dose, while higher incidences were reported in the 20 mg/kg dose group. All AEs were of mild or moderate intensity. No dose-dependent AEs or other clinically relevant changes in safety laboratory parameters, vital signs, or 12-lead ECG were observed.

The relative bioavailability trial 1368-0003 explores PK as well as safety and tolerability of an SC formulation of Spesolimab at two different dose strengths of 150 mg (1 mL) and 300 mg (2 mL) in an open-label, sequential group design. In addition, the trial determines the relative bioavailability of the 300 mg SC dose (test group) compared to one single 300 mg IV dose of Spesolimab (reference group). The trial has been conducted in 36 healthy male and female subjects with 12 subjects per dose group. Local tolerability of the SC formulation was as well tolerated. Following an SC injection of 150 mg of Spesolimab, there were two cases of redness and one case of swelling at the injection site in 12 subjects. For the 300 mg SC dose there was one further report of redness in 12 subjects dosed. All local events were of mild intensity, occurred within 30 minutes after injection and completely resolved within 4 hours. There were no reports of injection site pain. The type, intensity and duration of systemic AEs were similar

to what has been observed in the preceding single-rising dose / multiple rising dose studies 1368-0001 and 1368-0002. Most of the AEs were of mild intensity, there were no AEs considered to be dose limiting, and no SAEs.

In the single-rising-dosing trial in Japanese healthy subjects 1368-0009, 32 healthy Japanese male subjects were enrolled in four dose groups each comparing eight subjects per group. The trial consisted of three dose groups receiving single rising IV infusion doses of Spesolimab (300 mg, 600 mg, and 1200 mg) and one dose group receiving single SC doses of Spesolimab (300 mg). In each dose group, 6 subjects received Spesolimab and two subjects' placebo. A total of three of 18 subjects (16.7%) on IV doses of Spesolimab (one subject per IV dose level) were reported with an AE compared with two of eight subjects (25%) on placebo. No subject was reported with an AE following subcutaneous administration of spesolimab. AEs by preferred term reported on placebo were vomiting, chest comfort, and allergic rhinitis, while AEs reported on Spesolimab were upper respiratory infection (300 mg IV), contusion (600 mg IV), gastroenteritis (1200 mg IV), and temporomandibular joint syndrome (1200 mg IV). None of the observed AEs were judged by the investigator as related to the trial medication. SAEs, deaths, AEs of special interest (AESI) or other significant AEs (according to project definition) were not observed and no subject discontinued the trial due to an AE. The overall AE frequency following administration of single doses of 300 to 1200 mg IV or 300 mg SC. Spesolimab was comparable with placebo.

In 1368-0001 and 1368-0002 trials, TMDD-related PK profile was observed. The exposure showed dose-proportional profile from 0.05 mg/kg to 20 mg/kg in single IV infusion group. In 1368-0009 trial, the exposure was also dose proportional within the evaluated dose range (300 mg to 1200 mg). No severe AE was observed in the each trials.

The relative bioavailability trial 1368-0029 explored PK as well as safety and tolerability of an SC formulation of Spesolimab in four treatment groups [periumbilical injection of 300 mg SC given at one (x 2 mL) or two (2 x 1 mL) injection sites, periumbilical injection of 600 mg SC (2 x 2 mL) and 300 mg SC (1 x 2mL) given to the thigh]. A total of 48 subjects entered the trial and completed the planned observation time according to the clinical trial protocol. To sum up, Spesolimab was safe and well tolerated by the healthy subjects and no safety signal was identified in trial 1368-0029.

1.2.6 Residual Effect Period

The residual effect period (REP) of Spesolimab is 16 weeks. This is the period after the last dose with measurable drug levels and/or PD effects still likely to be present.

1.2.7 Drug product

For a more detailed description of the Spesolimab profile, please refer to the current investigator's Brochure (IB) [c03320877].

1.3 RATIONALE FOR PERFORMING THE TRIAL

A recently completed Japanese Phase I trial (1368-0009) explored safety, tolerability, and PK of Spesolimab following IV administration of single-rising- doses (300, 600, 1200 mg) and single SC dose (300 mg) in healthy Japanese male subjects. In this trial, the Spesolimab exposure after IV administration increased with increasing dose in a dose-proportional manner across the tested dose range from 300 mg to 1200 mg. The relative bioavailability of Spesolimab after 300 mg SC administration was 73.5%. The dose-normalised exposure maximum measured concentration of the analyte in plasma (C_{max}) and Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity ($AUC_{0-\infty}$) after single IV administration of Spesolimab were comparable and no large differences were observed between Japanese healthy subjects (trial 1368-0009) and non-Japanese healthy subjects (trial 1368-0001 and trial 1368-0002). The similar Spesolimab exposures was observed between Japanese healthy subjects and non-Japanese healthy subjects after single SC dose (300 mg; trial 1368-0009 and trial 1368-0003). The evaluation of the relative bioavailability between 300 mg SC and 600 mg SC was completed with Caucasian healthy volunteers (1368-0029).

The current trial will investigate the PK and safety of Spesolimab in healthy Chinese subjects. At the consultation meeting with NMPA held on Dec 2018, therapeutic dose was required to evaluate in this trial. The dose amount was set to cover the therapeutic dose of all indications.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this trial is without any (therapeutic) benefit to healthy subjects. Their participation in the trial, however, is of major importance to the development of a new therapy The subjects are exposed to the risks of the trial procedures and the risks related to the exposure to the trial medication.

Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling, may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to vein puncture for blood sampling. Other risks of related to trial-specific procedures include IV infusion or SC administration of study medication, which can cause local bruising, inflammation, nerve damage and pain.

The total volume of blood withdrawn during the entire trial per subject will not exceed the volume of a normal blood donation (400 mL). No health-related risk to healthy subjects is expected from this blood withdrawal.

Drug-related risks and safety measures

The toxicology package conducted in mice with a mouse-specific antibody (BI 674304) includes 4-, 13- and 26-week toxicity studies and reproductive/developmental toxicity studies without any findings which would preclude clinical studies in humans (see IB [c03320877]). There have been no dose or exposure-related abnormalities in safety laboratory parameters and no safety or tolerability concerns that would preclude further clinical development of Spesolimab.

Spesolimab has been tested and found safe and tolerable in humans in single- and multiple-rising-dose trials 1368-0001, 1368-0002, 1368-0003, 1368-0009 and 1368.29 in healthy male and female subjects and in trial and in several completed trials in patients

No clinically relevant abnormalities on treatment with Spesolimab with respect to safety laboratory parameters and vital signs were observed (see IB [c03320877]).
Based on studies in healthy subjects and patients, no specific drug-related risks are anticipated. Nevertheless, the following safety measures are/will be applied in this trial in order to minimise the risk for the healthy subjects:

- Careful dose selection based on data of the completed studies. In the first dose group of 300 mg SC, the exposure is projected to be similar to the Japanese healthy subjects who were enrolled in trial 1368-0009 and received the same SC dose.
- For the IV dose groups, the administration as 90 minutes infusion allows immediate discontinuation of drug administration should any safety concern arise.
- For both IV and SC dose groups, a time interval of at least two weeks will be maintained between first administration of trial medication in the actual dose level and first administration in the next dose level, which is expected to cover the period of highest risk/peak effect. The next dose will only be given if no safety concerns arise in the previous dose group and if none of the pre-specified trial-specific stopping criteria are met within each IV and SC dose groups.
- Extensive monitoring of 12-lead ECG and vital signs is incorporated, with 12-lead ECG to cover the anticipated period of highest drug exposure. As an additional measure, repeated single 12-lead ECGs are scheduled in the further course of the trial. The rationale for the intensified 12-lead ECG monitoring is not due to expected increased risk of Spesolimab mediated effects on cardiac repolarization, rather, it is been implemented to collect 12-lead ECG data at an early point in clinical development to perform 12-lead ECG interval assessment under drug. In general, for biologics, Time between start of the Q-wave and the end of the T-wave in an electrocardiogram (QT) prolongation is not usually an issue unless there are mechanistic effects with the mAb which can lead indirectly to the 12-lead ECG changes [R09-2768] but this is not expected to be the case for Spesolimab.
- Extensive safety laboratory testing will be performed.

- After each dosing, the subjects will stay at the site for at least 48 hours following drug administration.
- During in-house-confinement the subjects will be under close medical observation and thoroughly monitored for both expected and unexpected AEs.
- Close monitoring of subjects' signs and symptoms for hypersensitivity reactions during and after trial drug administration. Hypersensitivity reactions should be treated according to local medical standards [R11-4890].

Currently there are no data available to suggest interactions of Spesolimab [c03320877].

Although rare, potential for drug-induced liver injury (DILI) will be under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure subjects' safety; see also section 5.2.6.1.4, AEs of special interest.

As an antagonist of IL36R, Spesolimab affects one target of the immune system which is ubiquitously expressed. Due to the antagonistic effect, it is considered remote that Spesolimab may lead to an amplification of an effect that might not be sufficiently controlled by a physiologic feedback mechanism. In addition, preclinical investigations and BI's clinical programme have demonstrated no cases of cytokine release syndrome induced by Spesolimab to date.

Due to the lack of mechanism- or compound-related safety signals and the antagonistic mode of action of Spesolimab, it is considered that healthy subjects will not be exposed to undue risks in relation to the information expected from this trial. Considering the medical need for the development of an effective and well-tolerated drug for the therapy of
the expected benefit of this trial is considered to outweigh the potential risks and justifies the exposure of healthy subjects.

Benefit-Risk Assessment in context of COVID-19 pandemic for subjects participating in clinical trials investigating Spesolimab:

A thorough assessment has been conducted to evaluate whether spesolimab may pose a higher risk associated with COVID-19 infection. The key aspects of the assessment are summarized below.

Spesolimab is an immune-modulating humanized monoclonal antibody that blocks the human IL-36 receptor and thereby the pro-inflammatory IL-36 pathway. Available non-clinical and clinical data in 604 subjects (see c03320877) have not shown an increased risk of infections with spesolimab. However, similar to other immune modulating biological treatments, spesolimab may hypothetically increase the risk of infections. Therefore, risk mitigation measures, such as close monitoring of adverse events, as well as guidance on handling of acute infections occurring during the trial have been included within this clinical trial protocol.

The investigator may choose to perform COVID-19 testing as per his/her discretion if useful based on individual medical consideration and in the case of suspected COVID-19 infection.

As any other acute infection, a suspected or diagnosed COVID-19 infection should be treated according to the standard of care.

The investigators will take the totality of information related to each single subject 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 subject's (continued) participation in the planned trials. BI as the sponsor, where required, will support the investigator in their decision finding. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing, and/or is in the best interest of the patient.

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

The benefit-risk assessment of spesolimab remains favourable in the context of the COVID-19 pandemic.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this trial is to investigate PK, including dose proportionality, following single IV and SC doses of spesolimab in healthy Chinese subjects.

2.1.2 Primary endpoint

$AUC_{0-\infty}$ and C_{max} of spesolimab.

2.1.3 Secondary endpoint

The occurrence of treatment-emergent AEs.
The occurrence of drug-related AEs.

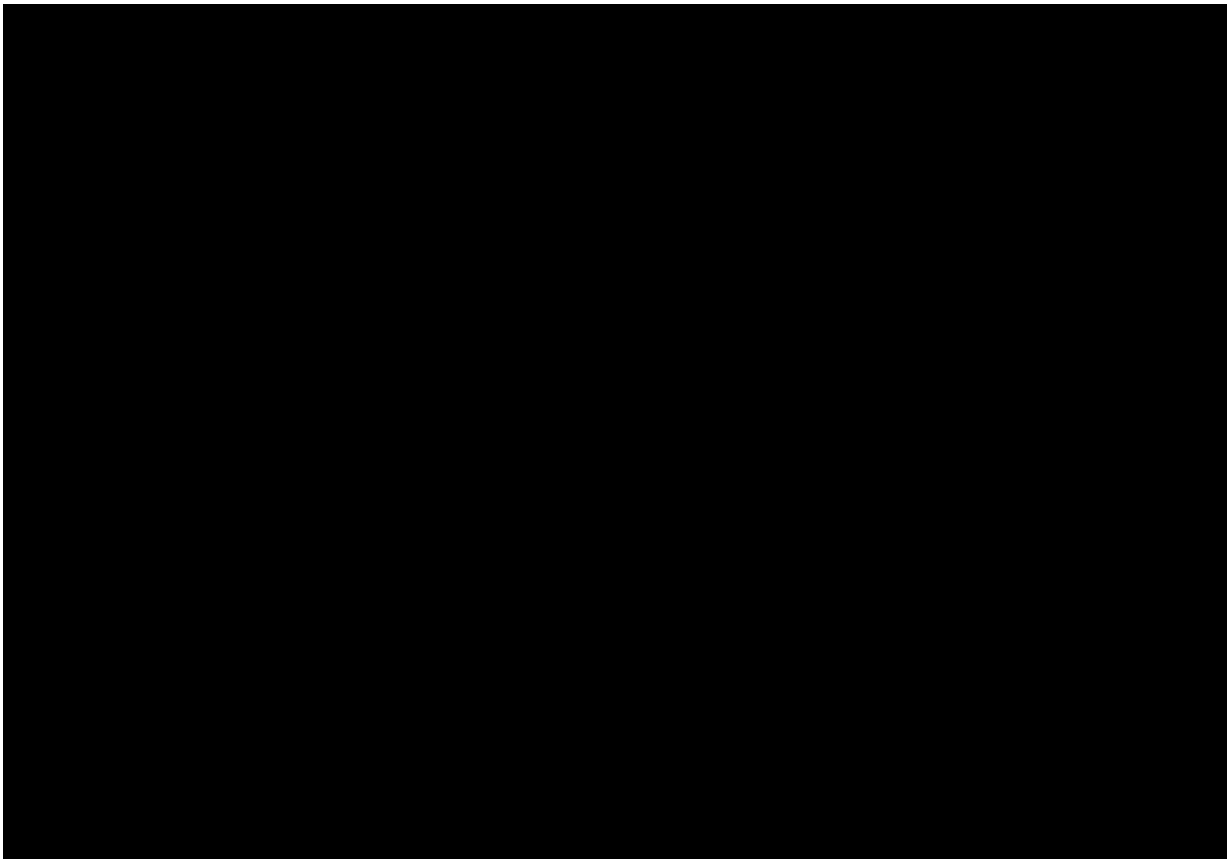
[redacted]

2.2.2.1 Safety and tolerability

Safety and tolerability of Spesolimab will be assessed based on:

- Safety laboratory parameters
- 12-lead ECG
- Vital signs (blood pressure [BP], pulse rate [PR], respiratory rate [RR], body temperature)
- Immunogenicity (ADA)

[redacted]



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This single-doses and parallel-group design for IV and SC administration trial is designed as open label, within dose groups.

It is planned to include up to 60 healthy male and female subjects in the trial. The subjects will be assigned to 5 groups each consisting of 10 subjects with at least 3 subjects for each gender within each dose group; In case of subjects not completed the trial, up to 10 replacement will be recruited for whole study. The cohorts within each SC and IV dose groups will be dosed sequentially (see Table 3.1: 1).

Only one dose is tested within each dose group. The dose groups to be evaluated are outlined in Table 3.1: 1.

Table 3.1: 1 Dose groups

Dose group	**1**	**2**	**3**	**4**	**5**
Dose	**IV**			**SC**	
	450 mg	900mg	1200 mg	300 mg	600 mg
No. of subjects entered	10	10	10	10	10
No. of subjects receiving active	10	10	10	10	10

The investigator is allowed to interrupt further dose escalation in the event the safety evaluation leads to concerns until alignment with sponsor is achieved.

The cohorts will be dosed consecutively in ascending order within IV and SC dose groups, and a time interval of at least two weeks will be maintained between the first drug administration to subjects in the previous dose group and the first drug administration to subjects in the subsequent dose group. The decision to treat the next dose cohort will be based upon safety.

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

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

The trial will be conducted in an open-label fashion. Blinding is not possible because the treatments are distinguishable. The open-label treatment is not expected to cause bias results, since the pharmacokinetic endpoints are derived from measurement of plasma concentrations of the analyte.

For safety reasons, a time interval of at least two weeks (taking into consideration that the $t_{1/2}$ of Spesolimab is four weeks) will be maintained between the first drug administration in the previous dose group and the first drug administration of the subsequent dose group within each SC and IV dose groups.

3.3 SELECTION OF TRIAL POPULATION

It is planned that up to 60 including 10 replaced healthy male and female subjects (at least three of each sex within each dose group) will enter the trial. Subjects will be recruited from the subjects' pool of the trial site.
A log of all subjects enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF irrespective of whether they have been treated with investigational drug or not.

3.3.1 Main diagnosis for trial entry

The trial will be performed in healthy subjects.

3.3.2 Inclusion criteria

Subjects will only be included in the trial if they meet the following criteria:

1. Healthy male or female subjects (at least three subjects for each gender within each dose group) according to the assessment of the investigator, as based on a complete medical history including a physical examination, vital signs (BP, PR, RR, body temperature), 12-lead ECG, and clinical laboratory tests.
2. Chinese ethnicity, according to the following criteria:
   Ethnic Chinese, born in China and have 4 ethnic grandparents who were all born in China.
3. Age of 18 to 45 years (inclusive).
4. Body weight ≥50 kg for male and ≥45 kg for female with body mass index (BMI) range ≥19 and <26 kg/m^2 at visit 1.
5. Signed and dated written informed consent prior to admission to the trial, in accordance with GCP and local legislation.
6. Female subjects who meet any of the following criteria from at least 30 days before the first administration of trial medication until 16 weeks after trial completion [c03320877]:
   - Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the subject information
   - A vasectomised sexual partner (vasectomy at least one year prior to enrolment)
   - Surgically sterilised (including hysterectomy)
   - Postmenopausal, defined as at least one year of spontaneous amenorrhoea (in questionable cases a blood sample with simultaneous levels of FSH above 40 U/L and estradiol below 30 mg/L is confirmatory).

3.3.3 Exclusion criteria

Subjects will be excluded in the trial if they meet the following criteria:

1. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to treatment or planned within 12 months after screening, e.g. hip replacement.
2. Any finding in the medical examination (including BP, PR, RR, Body temperature or 12-lead ECG) deviating from normal and assessed as clinically relevant by the investigator.
3. Repeated measurement of systolic BP outside the range of 90 to 140 mmHg, diastolic BP outside the range of 50 to 90 mmHg, or PR outside the range of 50 to 90 bpm.
4. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance.
5. Any evidence of a concomitant disease assessed as clinically relevant by the investigator.
6. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders.
7. History of relevant orthostatic hypotension, fainting spells, or blackouts.
8. Chronic or relevant acute infections including active and latent tuberculosis, human immunodeficiency virus (HIV) or viral hepatitis; QuantiFERON TB test will be performed at screening.
9. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.
10. Use of any Chinese traditional medicines and drugs (including prescription drug or over the counter) within 30 days of planned administration of trial medication.
11. Subject has been treated with any investigational drug of chemical or biologic nature within a minimum of 60 days or five $t_{1/2}$ (whichever is longer) of the drug prior to the Baseline (Week 0) Visit, or concurrent participation in another clinical trial in which investigational drug is administered.
12. Administered live vaccine within six weeks prior to treatment or have plans for administration of live vaccines during the trial period.
13. Smoker (more than ten cigarettes or three cigars or three pipes/day).
14. Inability to refrain from smoking on specified trial days.
15. Alcohol abuse (consumption of more than 20 g/day for females and 30 g/day for males).
16. Drug abuse or positive drug screening.
17. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended blood donation during the trial.
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial.
19. Inability to comply with the dietary regimen of the trial site.
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in male or repeatedly greater than 470 ms in females) or any other relevant 12-lead ECG finding at screening.
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome).
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with trial requirements, or has a condition that would not allow safe participation in the trial.

23. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
24. Female subjects will be excluded in the trial if they meet the following criteria:

    - Positive pregnancy test, pregnancy or plans to become pregnant up to 16 weeks of trial drug administration

    - Lactation

For trial restrictions, refer to section 4.2.2.

3.3.4 Withdrawal of subjects from treatment or assessments

Subjects 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.

If a subject is removed from or withdraws from the trial prior to the first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after the first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR.

At the time of discontinuation, a complete EoTrial examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see section 1.2.6), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

If it is known that a subject becomes pregnant during the trial, administration of the trial medication is to be stopped immediately, and the subject is to be removed from the trial. The subject is to be followed until she has given birth or until the end of the pregnancy. The subject's data are to be collected until the end of the trial (last visit of last subject) and reported in the CTR. For the reporting of pregnancy and associated events, refer to section 5.2.6.2.4.

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment

4. The subject can no longer receive trial treatment for medical reasons (such as pregnancy, surgery, AEs, or diseases)
5. An AE or clinically significant laboratory change or abnormality occurs that the investigator assesses as warranting discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg), clinically relevant changes in 12-lead ECG requiring intervention, or unexplained hepatic enzyme elevations at any time during the trial
6. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

In addition to these criteria, the investigator may discontinue subjects at any time based on his or her clinical judgment.

Even if the trial treatment is discontinued, the subject remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continuous follow up after trial treatment discontinuation, please see section 3.3.4.1.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim (BI) reserves the right to discontinue the trial at any time for any of the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New toxicological findings, SAEs, or any safety information invalidating the earlier positive benefit-risk assessment. Dose escalation will be terminated if more than 50% of the subjects at one dose level show drug-related and clinically-relevant AEs of moderate or severe intensity, or if at least one drug-related SAEs is reported.
3. Violation of GCP or the clinical trial protocol (CTP) or the contract with BI impairing the appropriate conduct of the trial.
4. The sponsor decides to discontinue the further development of the investigational product.
5. Dose escalation will be stopped if at least two subjects at one dose level have relevant individual QT prolongations, i.e. a QTc increase of greater than 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, as confirmed by a repeated ECG recording. The investigator/trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item three applies).

3.3.5 Replacement of subjects

If some subjects do not complete the trial, the Clinical Trial Leader (CTL) together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he or she replaces. Up to 10 subjects will be replaced for whole study. Data from replaced subjects will be available in the database.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product is manufactured by BI Pharma GmbH & Co. KG, Biberach, Germany. The spesolimab molecule is a heterodimer with a molecular weight of approximately 146 kDa.

4.1.1 Identity of the Investigational Medicinal Products

For subcutaneous administration

The characteristics of the test product are given below:

Substance:	BI 655130
Pharmaceutical formulation:	Solution for injection
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	150 mg/mL
Posology:	1-0-0
Route of administration:	SC injection (abdominal region)
Duration of use:	Single dose (300 mg, 600 mg)

For intravenous administration

The characteristics of the test product are given below:

Substance:	BI 655130
Pharmaceutical formulation:	Solution for infusion
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	60 mg/mL, 7.5 mL (per 10R glass vial)
Posology:	1-0-0
Route of administration:	IV infusion
Duration of use:	Single dose (450 mg, 900 mg, 1200 mg)

At the time of use, the IV solution for dosing will be prepared as detailed in the instruction given in ISF.

4.1.2 Selection of doses in the trial

Dose strengths will be investigated for both SC administration and IV administration in this trial. Doses for SC and IV will each cover potential therapeutic dose ranges and provide a safety margin for future development. Dose proportionality of exposure will be evaluated for IV group.
This trial is designed to evaluate the PK and safety of Spesolimab in Chinese healthy subjects.

4.1.3 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted and informed about the planned visit dates. The subjects who are willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects have been allocated to one of the 5 dose groups, the following subject will be allocated to one of the other dose groups. Therefore, the allocation of subjects to dose groups is not influenced by trial personnel, but only by the subjects' temporal availability. If more available subjects than target number for a cohort, the subjects will be enrolled according to the subsequence of signed ICF by subjects and gender ratio required by study. As the trial includes healthy subjects of only Chinese ethnicity, relevant imbalances between the dose groups are not expected.

The randomisation list of subject and medication numbers will be provided to the trial site in advance. The allocation of subject to trial subject number will be performed prior to the first administration of trial medication. Once a subject number has been assigned, it cannot be reassigned to any other subject.

It is an open-label trial without randomisation.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1. Each subject will receive one single dose of trial medication. For further details concerning timing see Flow Chart. Detailed instructions for the preparation are provided in ISF.

Table 4.1.4: 1 Final dose of BI 655130 in solution containing active drug

Dose group	Final dose of BI 655130 [mg]
1	450 mg (IV infusion)
2	900 mg (IV infusion)
3	1200 mg (IV infusion)
4	300 mg (SC injection)
5	600 mg (SC injection)

For intravenous administration

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. The detailed instructions for the dilution of the trial medication, the preparation of the infusion solution and the volume to be administered is provided in ISF. In all subjects, the infusion solution will be intravenously administered over 90 minutes approximately between 8:00 and 10:00 of the respective trial day. Start and end time of the infusion will be recorded.

In case of safety concerns, e.g. due to infusion reactions, the investigator or his/her designee should stop of the infusion. Based on his medical judgment, he/she will provide medications such as steroids, etc. as needed.

For administration of the infusion, an IV indwelling catheter is placed into an arm vein of the subject for saline infusion. A second indwelling catheter used for collection of blood samples will be placed on the contralateral arm.

The administration of the trial medication on all trial days will be done under supervision of the investigating physician or a designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

Water is allowed except for one hour before start of infusion and 1.5 hours after end of infusion.

For subcutaneous administration

Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. Trial medication will be injected subcutaneously in the abdominal region. The skin is sanitised before injection. Needle is placed subcutaneously and solution with trial medication is injected within 60 seconds. Detailed handling instructions will be provided in the ISF.

For all dose groups, standardised meals will be served as outlined in the Flow Chart. Subjects will be kept under close medical surveillance until 48 hours following drug administration. Thereafter subjects will be discharged and further assessments will be conducted in an ambulatory fashion. For restrictions with regard to diet see also section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The trial will be conducted in an open-label fashion.

This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias is low and does not outweigh practical considerations. Emergency envelopes will not be provided, since the treatments of all subjects are known in this open-label trial.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by [redacted]. They will be packaged and labelled in accordance with local law and the principles of Good Manufacturing Practice.

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

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the subject information form. Examples of the labels will be available in the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure storage area with limited access according to the recommended (labelled) storage conditions. Where necessary, a temperature log must be maintained to ensure that the drug supplies are stored at the correct temperature. If the storage conditions are found to be outside the specified range, the clinical trial manager (CTM) (as provided in the list of contacts) is to be immediately contacted.

4.1.8 Drug accountability

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

- Approval of the trial protocol by the IRB/ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre
- 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 CTP or immediately imminent signing of the CTP

Only authorised personnel as documented in the form ‘Trial Staff List’ may dispense trial medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused trial medication must be returned to the sponsor. All used medication will be disposed locally by the trial site. Receipt, usage, return and disposal must be documented on the respective forms in ISF. Account must be given for any discrepancies.

The investigator/pharmacist/investigational drug storage manager must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposal of unused or partially used products.

These records will include dates, quantities, batch/serial numbers, expiry (‘use-by’) dates, and the unique code numbers assigned to the investigational products and trial subjects. The investigator/pharmacist/investigational drug storage manager will maintain records that document adequately that the subjects were provided the doses specified by the CTP, and that reconcile all investigational products received from the sponsor. At the time of disposal or

return to the sponsor, the investigator/pharmacist/investigational drug storage manager must verify 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

There are no specific rescue drugs foreseen for the treatment of AEs. No special emergency procedures are to be followed. No additional treatment is planned. However, in case of AEs in need of treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

In principle, no concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on trial days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site, the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. On Day 1 for all subjects, no food is allowed for at least 10 hours before and 1.5 hours after administration of the trial medication (= end of infusion for IV dose group).

On all days of drug administration, starting from one hour before drug administration until 1.5 hours after the completion of administration liquid intake is not allowed. At 24 hours post-dose water intake will be within 1000 to 3000 mL. Total fluid intake on all 24 hours inhouse days is recommended to be at least 1500 mL and should not exceed 3500 mL.

Smoking is not allowed during in-house confinement at the trial site. On the ambulatory days it is restricted to not more than ten cigarettes or three cigars or three pipes/day.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed during inhouse confinement. Alcoholic beverages are not permitted starting 7 days before the first administration of trial medication until Day 28. From Day 29 onwards, alcohol consumption is restricted to 20 g alcohol/day corresponding to 500 mL beer or 200 mL of white wine/day.

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the first administration of trial medication until the EoTrial examination.

If female subjects of child-bearing potential are included in the trial, adequate contraception is to be maintained throughout the course of the trial (see section 3.3.2 for the definition of adequate measures).

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the trial centre under supervision of the investigating physician or a designee. The measured plasma concentrations will provide additional confirmation of compliance.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable. No efficacy endpoints will be evaluated in this trial.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

At the screening visit, the medical examination will include documentation of subject information, informed consent, demographics including height, body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR, RR and body temperature), 12-lead ECG, laboratory tests (including drug screen and pregnancy test), as well as physical examination. At the EoTrial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination including determination of weight.

5.2.2 Vital signs

Systolic and diastolic BP, body temperature, respiratory rate (RR) as well as PR or heart rate (heart rate is considered to be equal to PR in healthy subjects) will be measured by a BP monitor at the time points indicated in the Flow Chart, after subjects have rested for at least 5minutes in a supine position. All recordings should be made using the same type of BP recording instrument on the same arm if possible.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h. Overnight fasting is not required at the discretion of the investigator or designate for retests.

The parameters that to be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2. Reference ranges will be provided in the ISF.

Urine sediment examinations will only be performed if there is a clinically relevant abnormality in the urinalysis, and it is deemed clinically necessary by the investigator.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) Reticulocyte count White blood cell count (WBC) Platelet count
Automatic WBC differential (relative and absolute cell count)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin time (Quick's test and INR) Fibrinogen
Enzymes	Aspartate transaminase (AST/GOT) Alanine transaminase (ALT/GPT) Alkaline phosphatase (ALP)) Gamma-glutamyl transferase (GGT) Creatine kinase (CK) CK-MB, only if CK is elevated Lactate dehydrogenase (LDH) Serum Immunoglobulin E (IgE) [1]
Hormones [2]	Thyroid stimulating hormone (TSH) fT3, fT4
Substrates	Serum glucose Creatinine Total bilirubin Direct bilirubin Total protein Protein electrophoresis (Protein EP) [3] Albumin Globulin CRP Uric acid Total cholesterol Triglycerides
Electrolytes	Sodium Potassium Chloride Calcium Inorganic phosphate (IP)

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	Test name
Urinalysis (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine erythrocytes Urine leukocytes Urine pH
Urine sediment [4]	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)

1. In case of a potential systemic allergic reaction blood samples for determination of serum IgE will be collected 0.5 h, 2 h, 6 h and 24 h after onset of the event.
2. Only at screening
3. Only test at screening if total protein is abnormal and it is deemed clinically necessary by the investigator
4. Only if erythrocytes, leukocytes, nitrite or protein are abnormal in urinalysis and it is deemed clinically necessary by the investigator

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Except for pregnancy test, it is planned to perform these tests during screening only. Drug screening will be performed at screening. Pregnancy testing in women will be performed at screening, prior to treatment on Day 92, and as part of the EoTrial examination.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Benzodiazepine Cannabis Cocaine Opiates
Infectious screening (blood) [1]	Hepatitis B surface antigen (HBsAg, qualitative) Hepatitis B core antibody (Anti-HBs, qualitative) Hepatitis C antibodies (Anti-HCV, qualitative) HIV antibody (Anti-HIV, qualitative) QuantiFERON (qualitative)
Pregnancy test (Urine)	Beta human chorionic gonadotropin (beta-HCG)
Determining Postmenopausal status(blood)	FSH test (quantitative) Estradiol test (quantitative)

1. Only at screening

To encourage compliance with alcoholic restrictions, a breath alcohol test will be performed at screening, and may be repeated at any time during the trial at the discretion of an investigator or designate. The results will not be included in the CTR.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed by the local laboratory of the trial site or/and at a clinical research organization designated by the sponsor.

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Chart.

In order to achieve a stable heart rate at rest and to assure high quality recordings at comparable resting phases, all ECGs will be recorded for a 10-sec duration after the subjects have rested for at least 5minutes in a supine position. The site personnel will be instructed to assure a relaxed and quiet environment so that all subjects are at complete rest during the recordings. ECG assessment will always precede all other trial procedures of the same time point (except blood drawing from an IV cannula which is already in place) to avoid impact of sampling on the ECG quality. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

At all time points single ECGs will be recorded. All locally printed ECGs will be evaluated by the investigator or a designee. ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation). Additional (unscheduled) ECGs may be collected by the investigator for safety reasons. These ECGs are assigned to the prior scheduled time point. Unscheduled ECGs will not be included into the statistical analysis of interval lengths.

For the inclusion or exclusion (see section 3.3) of a subject and for the assessment of cardiac safety during the trial, the QT and QTcF values generated by the ECG machines or their manual corrections by the investigators will be used.

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.4.2 Continuous ECG monitoring

Not applicable.

5.2.5 Other safety parameters

5.2.5.1 Local tolerability

Local tolerability will be assessed by the investigator on the basis of 'swelling', 'induration', 'heat', 'redness', 'pain', or 'other findings'.

5.2.5.2 Suicidality assessment

Not applicable.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation patient 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, 12-lead ECG, physical examination, and laboratory test results, if they are judged clinically relevant by the investigator

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

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- Requires inpatient hospitalisation
- Requires 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 upon appropriate medical judgment 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'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in section 5.2.6.2.1, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

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

The latest list of 'Always Serious AEs' can be found in the EDC system, a remote data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

5.2.6.1.4 Adverse events of special interest

The term AEs of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.

The following are considered as AESIs in this trial:

- Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:
  - an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
  - ALT, and/or AST elevations ≥10-fold ULN

  These lab findings constitute a hepatic injury alert and the subjects 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 discussed in the statement paper from Sampson HA (Appendix 10.1.3, R11-4890).
- 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), hepatitis B virus [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), hepatitis C virus [HCV] progression (R17-2617).

5.2.6.1.5 Intensity (severity) of AEs

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

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

5.2.6.1.6 Causal relationship of AEs

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

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

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class
- A plausible time to onset of the event relative to the time of drug exposure
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome)
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is 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 $t_{1/2}$). 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 medication treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

Upon enrolment into a trial, the subjects baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Subjects will be required to report spontaneously any AEs as well as the time of onset, end time, and intensity of these events. In addition, each subject will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, subjects will be questioned for AEs (and concomitant therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as 'How do you feel?' Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A careful written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, and intensity of the event as well as any treatment or action required for the event and its outcome.

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

- From signing the informed consent onwards until an individual subject's EoTrial:
    - All AEs (serious and non-serious) and all AESIs.
    - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy subjects, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.

- After the individual subject's EoTrial:
    - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form 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.

5.2.6.2.3 Information required

All (S)AEs, including those persisting after the individual subject's EoTrial, must be followed up until they have resolved, have been assessed as 'chronic' or 'stable', or no further information can be obtained.

5.2.6.2.4 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a subject 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 Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part 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 Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Date and clock times of drug administration and PK sampling will be recorded in the CRFs. The actual sampling times will be used for determination of PK parameters.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. as a result of preliminary PK data), including addition of samples and visits, as long as the total blood volume taken per subject does not exceed 400 mL. Such changes would be implemented via non-substantial CTP Amendments.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

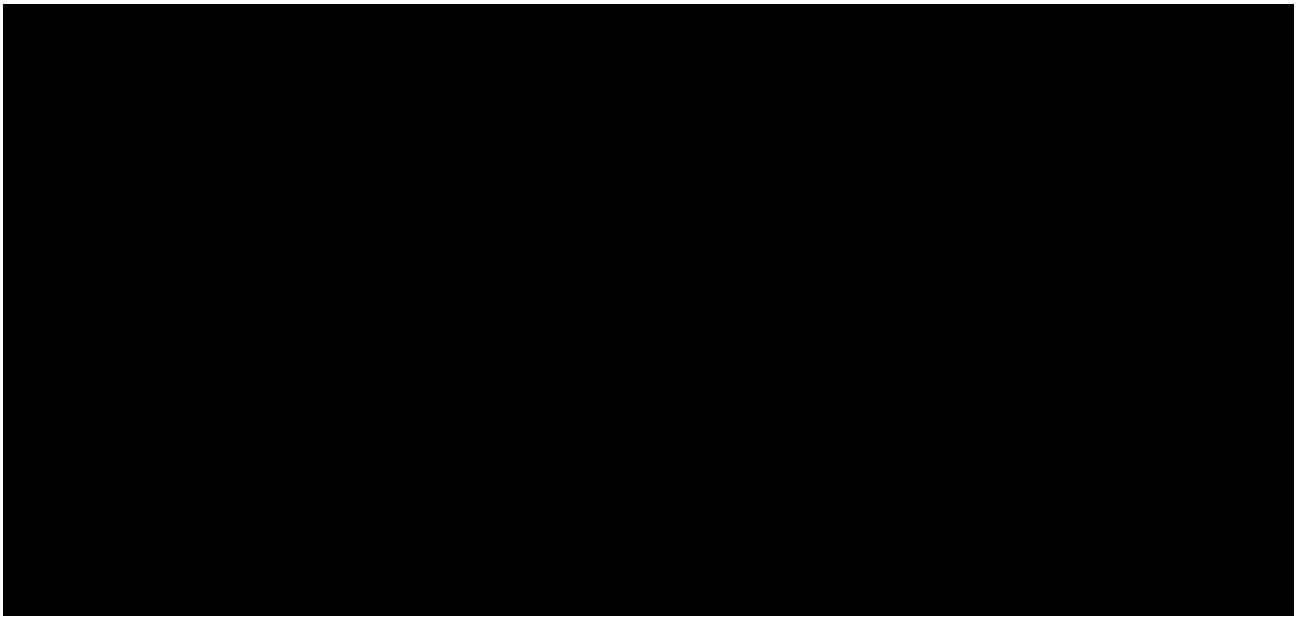
For quantification of Spesolimab plasma concentrations, approximately 3.0 mL of blood will be taken from a forearm vein (administrated arm is prohibited to use for blood sampling in IV dose groups up to 48 hours after the administration) into a K_2EDTA (ethylendiaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the Flow Chart under plasma PK. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. Two aliquots of plasma will need to be processed from the blood volume collected at each planned time point. The detailed procedure for sample processing and handling can be found in the Lab Manual.

After completion of the trial the plasma samples may be used for further methodological investigations**,** e.g. for stability testing. However, only data related to the analyte will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the final trial report is archived.

5.3.2.2 Blood sampling for anti-drug antibody (ADA) analysis

For ADA assessment, approximately 3.0 mL of blood for each sample will be taken from a forearm vein into a K2EDTA anticoagulant blood-drawing tube at the time points listed in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. Two aliquots of plasma for ADA will need to be processed from the blood volume collected at each planned time point. The detailed procedure for sample processing and handling can be found in the Lab Manual.

After completion of the trial the samples may be used for further methodological investigations, e.g. for stability testing. However, only data related to the anti-drug antibodies will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the final trial report has been archived.



5.4 BIOBANKING

Not applicable.

5.5 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine PK parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and 12-lead ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability, and are widely used in clinical trials. The PK parameters and measurements outlined in section 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening, observation visit, and EoTrial examination are given in the Flow Chart.

Trial measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 2 hour-period prior to the trial medication administration (including blank values for PK).

The acceptable deviation from the scheduled time for vital signs and 12-lead ECG will be:

- ±15 minutes up to including 12 hours
- ±30 minutes from 12 hours up to including 48 hours
- ±60 minutes from 48 hours up to Day 8
- ±24 hours from Day 15 up to Day 71
- ±48 hours on Day 92
- ±72 hours from Day 120 up to the last measurements

The tolerance for PK/ADA /laboratory parameters starting from the investigational administration will be:

- ±1 minutes up to including 1 hour
- ±5 minutes up to including 12 hours
- ±15 minutes up to including 48 hours
- ±60 minutes from 48 hours up to Day 8
- ±24 hours from Day 15 up to Day 71
- ±48 hours on Day 92
- ±72 hours from Day 120 up to the last measurements

If scheduled in the Flow Chart at the same time as a meal, blood sampling, vital signs and 12-lead ECG recordings have to be done first. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

For planned individual plasma concentration sampling times refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of PK parameter.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

After having been informed about the trial, all subjects will give their written informed consent in accordance with GCP and local legislation prior to enrolment in the trial.

For information regarding laboratory tests (including drug and virus screening), 12-lead ECG, vital signs, and physical examination, refer to sections 5.2.3 to 5.2.5.

6.2.2 Treatment period

Each subject will receive one dose of trial medication (Spesolimab) at Visit 2.

Trial participants will be admitted to the trial site in the evening of Day-1 and kept under close medical surveillance for at least 48 hours following drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or his designee. On all other trial days, the trial will be performed in an ambulatory fashion.

Trial medication will be administered as IV infusion or SC injection according to each dose group by the investigating physician or his designee. Details on treatments and procedures of administration are described in section 4.1.4.

For details on time points and procedures for collection of plasma analysis, refer to Flow Chart and section 5.3.2.

The safety measurements performed during the treatment period are specified in section 5.2 of this protocol and in the Flow Chart. For details on time points for all other trial procedures, refer to the Flow Chart. AEs and concomitant therapy will be assessed continuously from screening until the EoTrial examination.

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of 12-lead ECG and vital signs, and physical examination during the follow-up period, see sections 5.2.2 to 5.2.5.
Subjects who discontinue treatment before the end of the planned treatment period should undergo the EoTrial Visit.

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's EoTrial Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

The end of the trial as a whole is defined by the 'last regular visit completed by last subject' or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The primary objective of this trial is the evaluation and comparison of several PK parameters between all tested treatments, including an evaluation of dose proportionality for those in the IV dose groups. Endpoints as specified in section 2.1.2 will be assessed using descriptive statistics. $AUC_{0-\infty}$ and C_{max} for IV doses will be subjected to analysis of dose proportionality by use of the power model.

The secondary objective of this trial is the evaluation of safety and will be evaluated by descriptive statistics.

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in this trial.

Any confidence intervals computed are to be interpreted in the perspective of the exploratory character of the trial; i.e., confidence intervals are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were treated with at least one dose of trial drug. The treatment assignment will be determined based on the (first) treatment the subjects received. The treated set will be used for safety analyses.
- PK parameter analysis set (PKS): This set includes all subjects in the TS who provide at least one primary PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Descriptive and model based analyses of PK parameters will be based on the PKS. It is expected that PK data from replaced subjects is not evaluable and thus replaced subjects are not expected to be part of the PKS.

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be assessed by the trial team. Important protocol deviation (IPD) categories will be specified in the Integrated Quality and Risk Management (IQRM) Plan. IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

Pharmacokinetics

The PK parameters listed in section 2.1 for drug spesolimab will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

Plasma concentration data and parameters of a subject will be included in the statistical PK analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a subject's data will be documented in the CTR.

Relevant protocol deviations may be

- Incorrect trial medication taken, i.e. the subject received at least one dose of trial medication the subject was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- Missing samples/concentration data at important phases of PK disposition curve.

Plasma concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of PK parameters. Concentrations used in the PK calculations will be in the same format as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

7.3.1 Primary endpoint analyses

The primary endpoint as specified in section 2.1.2 will be derived according to BI standards (001-MCS-36-472). The analysis will be based on the PKS and will be descriptive in nature.

For IV doses the dose proportionality of $AUC_{0-\infty}$ and C_{max} will be analysed.

Assessment of dose proportionality

Dose proportionality will be explored via graphical checks and if applicable via the power model stated below. The analysis will be performed for the PK endpoints AUC/C_{max} specified in section 2.1.2.

The power model describes the functional relationship between the dose level and PK endpoint on the log scale via

$$y_{km} = \log(x_{km}) = \mu + b \cdot \log(D_k) + e_{km},$$

where

y_{km} logarithm of response (PK parameter) measured on subject m^{th} receiving dose k,
μ the overall mean,
β slope parameter of linear regression line,
D_k level of dose k, k=1, 2, 3,
e_{km} the random error associated with the m^{th} subject who was administered dose k ($e_{km} \sim N(0, \sigma^2)$ iid).

This equation can be fit as a linear regression model.

The slope parameter β together with its two-sided 90% confidence interval will be estimated. Perfect dose proportionality would correspond to a slope of 1. Additionally, the r-fold change $r^{\beta-1}$ together with its 90% CI will be derived.

7.3.2 Secondary endpoint analyses

Analysis of safety and tolerability is described in section 7.3.4.

[redacted]

7.3.4 Safety analyses

Safety will be assessed for the endpoints listed in section 2.1.2 and 2.2.2 based on the TS. Safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned. Treatments will be compared in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as vital signs, or laboratory parameters) or AEs will be assigned to treatments (see section 4.1) based on the concept of treatment emergent AEs. Therefore,

measurements planned or AEs recorded prior to intake of trial medication will be assigned to 'screening', those between trial medication intake and end of REP will be assigned to the treatment period. Events occurring after the REP but prior to trial termination date will be assigned to ‘follow-up’. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, intensity and causal relationship of AEs will be tabulated by treatment, primary system organ class and preferred term. SAEs, AESIs (see section 5.2.6.1.4) and other significant AEs (according to ICH E3) will be listed separately.

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

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

7.3.5 Pharmacokinetic-pharmacodynamic analyses

No analysis of the relationship between PK and PD parameters is planned for this trial.

7.4 INTERIM ANALYSES

If required for early interaction with regulatory agency, a first interim analysis may be conducted once all IV subjects have completed the study. In case this interim analysis will be done, an interim database lock will be conducted (for safety and PK data collected for IV subjects) and an interim report for the IV analysis will be written. Details of the analysis to be performed will be described in the TSAP.

A CTR including entire trial data (IV and SC subjects) will be prepared at the end of the trial.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

It is not planned to impute missing values for safety parameters.

7.5.2 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (001-MCS-36-472).

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analysed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

7.6 RANDOMISATION

It is an open-label trial without randomisation.

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to include up to 60 subjects in this trial in order to have in total 50 PK evaluable subjects, 10 subjects per dose group. Up to 10 subjects might be replaced due to early termination. The planned sample size is not based on a power calculation. The size of 10 subjects per dose group is commonly used in single dose studies of the present type and in general considered as sufficient for the exploratory evaluation of single dose safety and PK.

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

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the subject's treating physician.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The BI 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 general rule, no trial results should be published prior to finalisation of the CTR.

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

8.1 TRIAL APPROVAL, SUBJECTS 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 a patient's participation in the trial, written informed consent must be obtained from each subject (or the subject'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 subject information form are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

The subject must be informed that his/her personal trial-related data will be used by BI in accordance with the local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his or her medical records may be examined by authorised monitors (CTM / Clinical Research Associate [CRA]) or Clinical Quality Assurance auditors appointed by BI, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or his 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 IQRM 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 subjects will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the trial.

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial subject that include all

observations and other data pertinent to the investigation. Source data as well as reported data should follow the ‘‘ALCOA-C principles’ and be attributable, legible, contemporaneous, original, accurate and complete. Changes to the data should be traceable (audit trail).

Before providing any copy of subjects’ source documents to the sponsor, the investigator must ensure that all subject identifiers (e.g., subject’s name, initials, address, phone number, and identification card) have properly been removed or redacted to ensure subject confidentiality.

If the subject is not compliant with the protocol, any corrective action (e.g. re-training) must be documented in the subject file.

For the CRF, data must be derived from source documents, for example:

- Subject identification: sex, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject’s visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (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)
- 12-lead ECG results (original or copies of printouts)
- Completion of subject’s participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a subject 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 subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor’s clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The CRA/on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the 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:
The trial site must retain the source and essential documents (including ISF) for 15 years based on the site's Trial Close-Out Visit date.

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

Individual subject medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Subject confidentiality will be ensured by using subject identification code numbers.

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

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

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

- Sample and data usage has to be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to informed consent form (ICF) is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage

- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

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

The **end of the trial** is defined as the 'date of the last visit of the last subject in whole trial' ('Last Subject Completed') or 'end date of the last open AE' or 'date of the last follow-up test' or 'date of an AE has been decided as sufficiently followed-up', whichever is latest.

Early termination of the trial is defined as the premature termination of the trial for any reason before the end of the trial as specified in this protocol.

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by BI.

The trial will be conducted at site, under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.
BI has appointed a CTL, responsible for coordinating all required trial 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 CTM, CRAs, and investigators of participating trial sites

The trial medication will be provided by the [redacted].

Safety laboratory tests will be performed by the local laboratory of the trial site and [redacted].

Analyses of Spesolimab concentrations and ADA in plasma will be performed at [redacted] in [redacted]

On-site monitoring will be performed by BI.

Data management and statistical evaluation will be done by BI or a contract research organisation appointed by BI.

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.

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10. APPENDICES

10.1 CLINICAL EVALUATION OF LIVER INJURY

10.1.1 Introduction

Alterations of liver laboratory parameters, as described in section 5.2.6.1.4 (Protocol-specified AESIs), are to be further evaluated using the following procedures:

10.1.2 Procedures

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 h. If it is confirmed that ALT and/or AST values ≥3-fold ULN occur in conjunction with an elevation of total bilirubin of ≥2-fold ULN, the laboratory parameters listed below (clinical chemistry, serology, hormones, haematology) must be determined and made available to the investigator and to BI as soon as possible.
In addition,

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the 'DILI checklist' provided in the ISF
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the 'DILI checklist' provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the 'DILI checklist' provided in the ISF; and report these via the CRF.

Clinical chemistry
Alkaline phosphatase, albumin, PT or INR, CK, CK-MB, coeruloplasmin, α-1 antitrypsin, transferin, amylase, lipase, fasting glucose, cholesterol, triglycerides

Serology
Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody
Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)

Hormones, tumormarker
TSH

Haematology
Thrombocytes, eosinophils

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm.

- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (total and direct) at least weekly until the laboratory ALT and/or AST abnormalities stabilise or return to normal, then monitor further as specified in the CTP. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and GCP.

10.1.3 Diagnosis of Anaphylaxis

Clinical criteria for diagnosing anaphylaxis (R11-4890).

Anaphylaxis is highly likely when any one of the following three criteria are fulfilled
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongueuvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF,hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse],syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin-mucosal tissue (eg, generalised 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.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		18 Sep 2019
EudraCT number **EU number**		Not applicable
BI Trial number		1368-0043
BI Investigational Medicinal Product(s)		BI 655130 (Spesolimab)
Title of protocol		An open-label phase I trial to assess pharmacokinetics and safety of single subcutaneous doses and single intravenous doses of BI 655130 in healthy Chinese male and female subjects (single doses, open-label study in parallel-group design).
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Title Page
Description of change		Phone: [redacted]
Rationale for change		Update the contact information of Principal Investigator
Section to be changed		Flow Chart
Description of change		Annotation 8: ADAs/Nab samples will be taken at baseline, Day 15, Day 29, Day 43, Day 57, Day 71, Day 92, Day 120, Day 148 and Day 176 ~~after BI 655130 administration.~~
Rationale for change		The information has been corrected.
Section to be changed		Table 5.2.3:1 Routine laboratory tests
Description of change		Protein electrophoresis (Protein EP)[2] [3] ~~(only at screening examination)~~

		Updated the annotation 3: ~~Only if erythrocytes, leukocytes, nitrite or protein are abnormal in urinalysis and it is deemed clinically necessary by the investigator~~ Only test at screening if total protein is abnormal and it is deemed clinically necessary by the investigator. Urine sediment ~~3~~ 4 The annotation has been sequenced to 4.
Rationale for change		It is not mandatory to conduct protein electrophoresis at screening to assure healthy volunteers' safety after more information obtained for BI 655130. Therefore, the specific annotation has been created.
Section to be changed		Table 5.2.3:2 Exclusionary laboratory tests
Description of change		FSH test ~~(qualitative)~~ (quantitative) Estradiol test ~~(qualitative)~~ (quantitative)
Rationale for change		Correction: FSH test and Estradiol test should be quantitative

11.2 GLOBAL AMENDMENT 2

Date of amendment		07 May 2020
EudraCT number **EU number**		Not applicable
BI Trial number		1368-0043
BI Investigational Medicinal Product(s)		BI 655130 (Spesolimab)
Title of protocol		An open-label phase I trial to assess pharmacokinetics and safety of single subcutaneous doses and single intravenous doses of BI 655130 in healthy Chinese male and female subjects (single doses, open-label study in parallel-group design).
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		**Product name**
Description of change		BI 655130 to spesolimab
Rationale for change		Globalize change
Section to be changed		**Clinical Trial Protocol Synopsis**
Description of change		Total entered was changed from 50 up to 60 subjects including up to 10 subjects for replacement of early discontinuation
Rationale for change		Account up to 10 replaced subject number into total entered
Section to be changed		**Flow Chart S.C.**
Description of change		• Vital Signs added 10 mins • Add description in annotation 13: Also the AEs and concomitant therapies will be queried on Day -1 • AEs and concomitant therapies will be queried on Day 148. • Add wording to ‘urine’ in annotation 14.
Rationale for change		To provide clarification regarding to the activities
Section to be changed		**Flow Chart I.V.**
Description of change		• Vital Signs added 10 mins

		• Add description in annotation 14: Also the AEs and concomitant therapies will be queried on Day -1. • AEs and concomitant therapies will be queried on Day 148. • Add wording to 'urine' in annotation 15.
Rationale for change		To provide clarification regarding to the activities
Section to be changed		**1.2.5 Clinical experience in human**
Description of change		Added 1368-0029 study result in protocol
Rationale for change		Updated it according to IB version 7.0
Section to be changed		**3.1 Overall trial design and plan**
Description of change		• 'up to 60 healthy male and female subjects in the trial.' replaced 'a total of 50'. • Added' In case of subjects not completed the trial, up to 10 replacement will be recruited for whole study'
Rationale for change		Account up to 10 replaced subject number into total entered
Section to be changed		**Table 3.1:1 Dose Group**
Description of change		Re-order the IV and SC group. IV: group 1: 450 mg group 2: 900 mg group 3: 1200mg SC: group 4: 300mg group 5: 600mg
Rationale for change		Make the consistence in section 4.1.4
Section to be changed		**3.3 Selection of trial population**
Description of change		'up to 60 including 10 replaced' replaced '50'
Rationale for change		Account up to 10 replaced subject number into total entered
Section to be changed		**3.3.5 Replacement of subjects**
Description of change		Added: Up to 10 subjects will be replaced for whole study. Data from replaced subjects will be available in the database.
Rationale for change		Clarified total number of replaced subjects in the protocol
Section to be changed		**4.2.2.2 Restriction on diet and life-style**

Description of change		Deleted' Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire trial.'
Rationale for change		Not required according to available data
Section to be changed		**Table 5.2.3:1 Routine laboratory tests**
Description of change		Delete 'Manual Differential WBC' test and its annotation
Rationale for change		No manual WBC test will be done
Section to be changed		**Table 5.2.3:2 Exclusionary laboratory tests**
Description of change		Changed HBc to HCV
Rationale for change		It is typo to be corrected.
Section to be changed		**6.1 Visit Schedule**
Description of change		Clarified the tolerance for PK/ADA/Nab/laboratory parameters starting from the investigational administration
Rationale for change		Clarify the time window requirement
Section to be changed		**7.3 Planned analysis**
Description of change		Clarified the replaced subjects will not be part of PKS
Rationale for change		Clarified how to deal with the replaced subjects
Section to be changed		**7.4 Interim Analysis**
Description of change		An interim analysis is not planned. If the results of this PK trial is ~~requested during an~~ needed for interaction with regulatory agency, a preliminary analysis of available safety tolerability and/or PK data may be performed in order to provide the preliminary results.
Rationale for change		Update the wording.
Section to be changed		**7.7 Determination of sample size**
Description of change		Added 10 replaced subject into total subject number to ensure total 50 PK evaluable subjects
Rationale for change		Account up to 10 replaced subject number into total entered

11.3 GLOBAL AMENDMENT 3

Date of amendment		01 Jul 2020
EudraCT number **EU number**		Not applicable
BI Trial number		1368-0043
BI Investigational Medicinal Product(s)		BI 655130 (Spesolimab)
Title of protocol		An open-label phase I trial to assess pharmacokinetics and safety of single subcutaneous doses and single intravenous doses of BI 655130 in healthy Chinese male and female subjects (single doses, open-label study in parallel-group design).
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		**4.1.3 Method of assigning subjects to treatment groups**
Description of change		Deleted the regulation of contact in writing. Added 'If more available subjects than target number for a cohort, the subjects will be enrolled according to the subsequence of signed ICF by subjects and gender ratio required by study.'
Rationale for change		Clarified the method of assigning subjects qualified more than a cohort available
Section to be changed		**4.1.4 Drug assignment and administration of doses for each subject**
Description of change		**For intravenous administration** Deleted the sentence 'For the purpose of drug accountability, the infusion set will be weighed before and after drug administration.'
Rationale for change		It was not applicable for this trial
Section to be changed		**5.2.3 Safety laboratory parameters**
Description of change		Deleted manual differential white blood cell count
Rationale for change		It was not required any more
Section to be changed		**Table 5.2.3: 2 Exclusionary laboratory tests**

Description of change		Barbiturates test was deleted
Rationale for change		No availability of the test kit due to COVID-19 logistics reasons and no requirement to conduct this test in all subjects to verify the exclusion criteria.

11.4 GLOBAL AMENDMENT 4

Date of amendment		26 Feb 2021
EudraCT number **EU number**		Not applicable
BI Trial number		1368-0043
BI Investigational Medicinal Product(s)		BI 655130 (Spesolimab)
Title of protocol		An open-label phase I trial to assess pharmacokinetics and safety of single subcutaneous doses and single intravenous doses of BI 655130 in healthy Chinese male and female subjects (single doses, open-label study in parallel-group design).

To be implemented only after approval of the IRB / IEC / Competent Authorities	☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		FLOW CHART ABBREVIATION 2.2.2.1 Safety and tolerability 5.3.2.2 Blood sampling for anti-drug antibody (ADA) analysis 5.3.3.3 Analytical determination of ADA VISIT SCHEDULE 8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL
Description of change		Removed Nab (neutralizing antibody) test from trial
Rationale for change		Study team decided not to test Nab in this trial due to inappropriate Nab drug tolerance for analysis method and low necessity
Section to be changed		ABBREVIATION

Description of change		Added 'Hidradenitis suppurativa'
Rationale for change		Updated according to IB 8.0
Section to be changed		1.2.5 CLINICAL EXPERIENCE IN HUMANS
Description of change		Updated trial information
Rationale for change		Updated study information according to IB 8.0
Section to be changed		BENEFIT - RISK ASSESSMENT
Description of change		Updated trial information and added Covid-19 assessments
Rationale for change		Updated trial information and summarized the key benefit-Risk Assessment in context of COVID-19 pandemic for subjects participating in clinical trials investigating Spesolimab according to IB 8.0
Section to be changed		7.4 Interim analyses
Description of change		If required for early interaction with regulatory agency a first interim analysis may be conducted once all IV patients have completed the study
Rationale for change		The interim analysis result may be used for new drug application of Spesolimab.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

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Approval-Team Member Medicine		08 Mar 2021 17:37 CET
Approval-[redacted] Medicine		14 Mar 2021 19:32 CET
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Meaning of Signature	Signed by	Date Signed