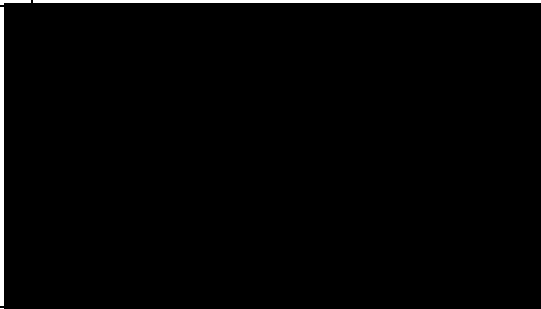


**Clinical Trial Protocol**

<b>Document Number:</b>		<b>c15932366-04</b>
<b>EudraCT No.:</b> <b>EU Trial No.:</b>	2017-004230-28	
<b>BI Trial No.:</b>	1368-0005	
<b>BI Investigational Product(s):</b>	BI655130 (SPESOLIMAB)	
<b>Title:</b>	A Phase II/III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of BI655130 (SPESOLIMAB) Induction Therapy in patients with moderate-to-severely active ulcerative colitis who have failed previous biologics therapy	
<b>Lay Title:</b>	BI655130 (SPESOLIMAB) induction treatment in patients with moderate-to-severe ulcerative colitis	
<b>Clinical Phase:</b>	II/III	
<b>Trial Clinical Monitor:</b>	[REDACTED]	
	Phone: [REDACTED] Fax: [REDACTED]	
<b>Coordinating Investigators</b>	[REDACTED]	
<b>Status:</b>	Final Protocol (Revised protocol (based on Global Amendment 3))	
<b>Version and Date:</b>	<b>Version: 4.0</b>	<b>Date: 09 October 2019</b>
<b>Page 1 of 152</b>		
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## CLINICAL TRIAL PROTOCOL SYNOPSIS

<b>Company name</b>	Boehringer Ingelheim
<b>Finished product name</b>	Not applicable
<b>Active ingredient name:</b>	BI655130 (SPESOLIMAB)
<b>Protocol date</b>	02 November 2017
<b>Revision date</b>	09 October 2019
<b>Trial number</b>	1368-0005
<b>Title of trial:</b>	A Phase II/III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of BI655130 (SPESOLIMAB) Induction Therapy in patients with moderate-to-severely active ulcerative colitis who have failed previous biologics therapy
<b>Coordinating Investigators:</b>	
<b>Trial site(s):</b>	Multi-centre study
<b>Clinical phase:</b>	II/III
<b>Objective(s):</b>	<ul style="list-style-type: none"><li>to prove the concept of clinical activity of BI655130 (SPESOLIMAB) in patients with moderate-to-severely active ulcerative colitis who have failed previous biologic treatments and to identify efficacious and safe dose regimens in Part 1 (Phase II)</li><li>to confirm efficacy and safety of BI655130 (SPESOLIMAB) in patients with moderate-to-severely active ulcerative colitis who have failed previous biologic treatments in Part 2 (Phase III)</li><li>To provide, along with induction study 1368-0018 and the run-in cohort of 1368-0020, the target population to be evaluated in the randomised withdrawal study 1368-0020.</li></ul>
<b>Methodology:</b>	Randomised, parallel-design, multiple-doses, placebo-controlled, double-blind (Part 1: three active dose groups and a placebo group; Part 2: two active dose groups and a placebo group)
<b>Number of patients entered:</b>	160 (part1) 390 (part2)
<b>Number of patients on</b>	40 Patients per treatment arm (part1)

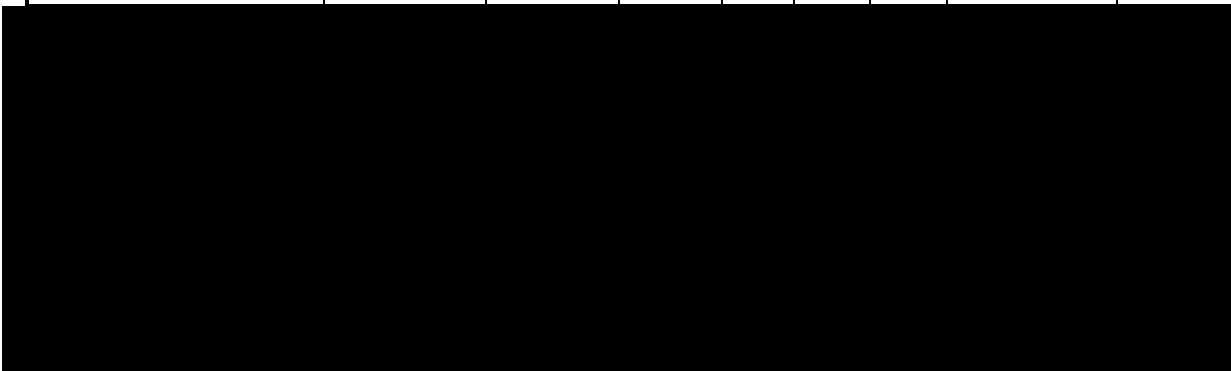
<b>each treatment:</b>	130 patients per treatment arm (part2)
<b>Diagnosis :</b>	Patients with moderate-to-severely active ulcerative colitis who have failed previous biologic treatments.
<b>Main in- and exclusion criteria</b>	<p><i>Main criteria for inclusion:</i></p> <ul style="list-style-type: none"> <li>• Male or female patients, aged 18 to 75 years at date of signing informed consent</li> <li>• Diagnosis of ulcerative colitis <math>\geq 3</math> months prior to screening by clinical and endoscopic evidence corroborated by a histopathology report</li> <li>• Moderate to severe activity (total MCS (Mayo Clinical Score) 6 to 12 with a RBS (rectal bleeding score) <math>\geq 1</math> AND a SFS (stool frequency score) <math>\geq 1</math> AND mESS (modified Endoscopic Subscore) <math>\geq 2</math> within 7-28 days prior to first dose)</li> <li>• Well documented failure or intolerance with approved doses of TNF<math>\alpha</math> antagonists and/or vedolizumab in the past</li> </ul> <p><i>Main criteria for exclusion:</i></p> <ul style="list-style-type: none"> <li>• Evidence of abdominal abscess, fulminant colitis or toxic megacolon</li> <li>• Ileostomy, colostomy, or symptomatic stenosis of the intestine</li> <li>• Treatment with forbidden medication without appropriate wash-out</li> <li>• Clinically significant intestinal or extra-intestinal infection</li> </ul>
<b>Test product(s):</b>	BI655130 (SPESOLIMAB)
<b>dose:</b>	<p>Part 1: 300 mg single dose (SD) at week 0; 450 mg or 1200 mg every 4 weeks (q4w, at Weeks 0, 4 and 8)</p> <p>Part 2: 300 mg SD, 450 mg q4w, 750 mg q4w or 1200 mg q4w (at Weeks 0, 4 and 8); Two of the above doses will be selected dependent on part 1 results</p>
<b>mode of administration:</b>	Intravenous (i.v.)
<b>Comparator products:</b>	Placebo
<b>dose:</b>	0 mg (placebo) at Week 0, 4 and 8
<b>mode of administration:</b>	Intravenous (i.v.)
<b>Duration of treatment</b>	12 weeks
<b>Endpoints</b>	<p><b>Primary endpoint:</b></p> <p>Proportion of patients with Clinical Remission at week 12        (defined as mMCS SFS=0 or 1, if drop <math>\geq 1</math> from BL; and RBS=0; and mESS<math>\leq 1</math>)</p> <p><b>Key Secondary endpoint(s) (Part 2 only):</b></p> <p>Proportion of patients with Mucosal Healing at week 12        (defined as modified endoscopic Subscore (mESS) <math>\leq 1</math>).</p> <p>Proportion of patients with Clinical response at week 12        (defined as total MCS reduction <math>\geq 3</math> pts. and <math>\geq 30\%</math> from BL; AND RBS drop from baseline by <math>\geq 1</math>pt., or absolute RBS <math>\leq 1</math> pt.)</p>

	<p><b>Secondary endpoint (incl. in statistical testing strategy; Part 2 only)</b></p> <p>Change in IBDQ score from baseline at week 12</p> <p>Proportion of patients with combined Mucosal healing and histologic remission at week 12</p> <p>(defined as mESS <math>\leq</math> 1 and Robarts Histology Index <math>\leq</math> 6)</p>
<p><b>Safety criteria:</b></p>	<p>Physical examination, vital signs, 12-lead Electrocardiogram (ECG), laboratory tests, adverse events, serious adverse events and tolerability. The intensity grading of AEs and abnormal laboratory values will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0.</p>
<p><b>Statistical methods:</b></p>	<p>The trial consists of 2 parts which, for the purpose of statistical analyses, will be treated as two independent parts whereby the false positive rate is separately controlled within each trial part:</p> <p><u>Part 1:</u> Demonstrate proof of concept of clinical activity as an induction therapy with respect to achieving a non-flat dose response curve on the primary endpoint, and subsequently to identify suitable dose regimens for BI655130 (SPESOLIMAB) regarding efficacy and safety for further pivotal testing in part 2 of this trial. For this purpose, a multiple comparison procedure with modelling techniques (MCPMod) approach is considered. Randomized set will be used.</p> <p><u>Part 2:</u> Confirm the efficacy and safety of two different doses of BI655130 (SPESOLIMAB) versus placebo as an induction therapy.      Formal statistical hypothesis testing will be performed at an overall 1-sided alpha level of 0.025.</p> <p>Each trial part will be analyzed independently of the remaining trial part, i.e.</p> <ul style="list-style-type: none"> <li>• Only patients randomized into part 1 will be included in the analyses of part 1,</li> <li>• Only patients randomized into part 2 will be included in the confirmatory analyses of part 2</li> </ul> <p>For trial part 2, the primary analysis of the clinical remission for each dose of BI655130 (SPESOLIMAB) versus placebo will be tested using the stratified Cochran-Mantel-Haenszel test at a nominal 1-sided 0.025 significance level stratified by the randomization stratification factors (prior biologic use and concomitant corticosteroid therapy at visit2) and based on the RS. The key secondary endpoints will be analysed using the same approach as for the primary analysis. Overall, the testing strategy will follow a closed testing principle defining two families of endpoints/comparisons. The first family consists of the primary endpoint comparisons for each dose of BI655130 (SPESOLIMAB) separately vs placebo, whereas the second family is defined by the pre-specified secondary endpoint comparisons for each dose of BI655130 (SPESOLIMAB) separately vs placebo. For the first family, type I error control is ensured by using the truncated Hochberg approach. For the second family, a graphical approach is applied. For publication purposes, the 2-sided p-values will also be reported. Note that a stratification for Japan versus non-Japan will also be done in order to assure that sufficient patients per treatment group are recruited specifically to support individual country submission in Japan; this strata will be treated as an operational strata and will not be included into the analyses of the primary endpoint in Part 2 of the trial.</p>

**FLOW CHART: PART 1/PROOF OF CONCEPT**

Trial periods	Screening		Blinded intravenous therapy					Fup
	V1a (Screening)	V1b (Pre-baseline)	V2 <sup>11</sup>	V3	V4	V5	V6 <sup>14</sup> /EOT	EOS <sup>14</sup>
Week	-5 to -2	-4 to -1	0	2	4	8	12	24
Day	-35 to -14	- 28 to -7	0	14	28	56	84	168
Visit window (days)	N.A.	N.A.	0	±4	±4	±4	±4	+7
Informed consent	X							
In-/exclusion criteria	X		X					
Demographics	X							
eDiary dispensing and instructions <sup>10</sup>	X							
eDiary Upload and review		X	X	X	X	X	X	X
Medical history	X							
Prior therapies	X							
Ulcerative colitis history	X							
Colonoscopy + biopsy <sup>1,2</sup>		X						
Sigmoidoscopy + biopsy, mESS recording <sup>2,3</sup>		X					X	
PGA		X	X	X	X	X	X	X
Physical exam (incl. vital signs) <sup>4</sup>	X <sup>C</sup>	X <sup>T</sup>	X <sup>T</sup>	X <sup>T</sup>	X <sup>T</sup>	X <sup>C</sup>	X <sup>C</sup>	X <sup>T</sup>
Weight	X		X		X	X	X	X
Height	X							
12-lead ECG	X		X		X	X		X
Pregnancy test <sup>5</sup>	X		X		X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Safety laboratory tests <sup>7</sup>	X		X	X	X	X	X	X

Trial periods	Screening		Blinded intravenous therapy					Fup
	V1a (Screening)	V1b (Pre-baseline)	V2 <sup>11</sup>	V3	V4	V5	V6 <sup>14</sup> /EOT	EOS <sup>14</sup>
Week	-5 to -2	-4 to -1	0	2	4	8	12	24
Day	-35 to -14	-28 to -7	0	14	28	56	84	168
Visit window (days)	N.A.	N.A.	0	±4	±4	±4	±4	+7
Infections screening (Hep B, Hep C, HIV)	X							
QuantiFERON-TB test	X							X
Optional blood sampling for assessment of drug levels for previous biologics	X							
Blood sampling for PK			X <sup>8</sup>	X	X <sup>8</sup>	X <sup>8</sup>	X	X
Blood sampling for ADAs			X <sup>8</sup>		X <sup>8</sup>	X <sup>8</sup>	X	X



Stool sampling for enteric pathogens <sup>6</sup>	X							
IBDQ <sup>9</sup>			X	X	X	X	X	X
EQ-5D(-5L) <sup>9</sup>			X			X	X	X
Contact IRT	X		X		X	X	X	
Randomization			X					
Study drug administration			X <sup>11,12</sup>		X <sup>12</sup>	X <sup>12</sup>		
Study completion							X	X
Roll-over into 1368-0017 <sup>13</sup>							X	



respective visits. These patients do have the option to do EOS visit earlier than week 24, 16 weeks after last study drug administration. Until then they should follow the [Flow Chart](#).

13. All patients completing week 12 of the study will be offered to enter open label trial 1368-0017. These patients are not requested to complete follow up period and will have their End of study visit at visit V6, co-inciding with the BL visit and start of study drug administration in 1368-0017.
14. EoS visit will be at week 12 (V6) for patients rolling-over into open label trial 1368-0017; and at week 24 for patients who will not enter open label trial 1368-0017.



## FLOW CHART: PART 2 / CONFIRMATORY EFFICACY/ SAFETY EVALUATION

Trial periods	Screening		Blinded intravenous therapy					Fup
	V1a (Screening)	V1b (Pre- baseline)	V2 <sup>11</sup>	V3	V4	V5	V6 <sup>14</sup> / EOT	EOS <sup>14</sup>
Week	-5 to -2	-4 to -1	0	2	4	8	12	24
Day	-35 to -14	- 28 to - 7	0	14	28	56	84	168
Visit window (days)	N.A.	N.A.	0	±4	±4	±4	±4	+7
Informed consent	X							
In-/exclusion criteria	X		X					
Demographics	X							
eDiary Dispensing and instructions <sup>10</sup>	X							
eDiary Upload and Review		X	X	X	X	X	X	X
Medical history	X							
Prior therapies	X							
Ulcerative colitis history	X							
Colonoscopy + biopsy <sup>1,2</sup>		X						
Sigmoidoscopy + biopsy, mESS recording <sup>2,3</sup>		X					X	
PGA		X	X	X	X	X	X	X
Physical exam (incl. vital signs) <sup>4</sup>	X <sup>C</sup>	X <sup>T</sup>	X <sup>T</sup>	X <sup>T</sup>	X <sup>T</sup>	X <sup>C</sup>	X <sup>C</sup>	X <sup>T</sup>
Weight	X		X		X	X	X	X
Height	X							
12-lead ECG	X		X		X	X		X
Pregnancy test <sup>5</sup>	X		X		X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Safety laboratory tests <sup>7</sup>	X		X	X	X	X	X	X

Trial periods	Screening		Blinded intravenous therapy					Fup
	V1a (Screening)	V1b (Pre- baseline)	V2 <sup>11</sup>	V3	V4	V5	V6 <sup>14</sup> / EOT	EOS <sup>14</sup>
Week	-5 to -2	-4 to -1	0	2	4	8	12	24
Day	-35 to -14	- 28 to - 7	0	14	28	56	84	168
Visit window (days)	N.A.	N.A.	0	±4	±4	±4	±4	+7
Infections screening (Hep B, Hep C, HIV)	X							
QuantiFERON-TB test	X							X
Optional blood sampling for assessment of drug levels for previous biologics	X							
Blood sampling for PK			X <sup>8</sup>	X	X <sup>8</sup>	X <sup>8</sup>	X	X
Blood sampling for ADAs			X <sup>8</sup>		X <sup>8</sup>	X <sup>8</sup>	X	X
Stool sampling for enteric pathogens <sup>6</sup>	X							
IBDQ			X	X	X	X	X	X
SF-36, FACIT-Fatigue <sup>9</sup>			X			X	X	X
EQ-5D(-5L) , WPAI- UC <sup>9</sup>			X			X	X	X
HCRU <sup>15</sup> assessments			X	X	X	X	X	X
Contact IRT	X		X		X	X	X	
Randomization			X					
Study drug administration			X <sup>11,12</sup>		X <sup>12</sup>	X <sup>12</sup>		
Study completion							X	X
Roll-over into 1368-							X	

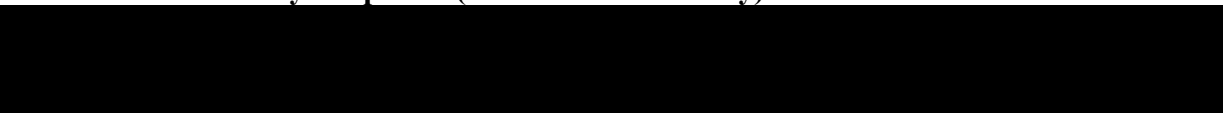
Trial periods	Screening		Blinded intravenous therapy					Fup
Visit	V1a (Screening)	V1b (Pre-baseline)	V2 <sup>11</sup>	V3	V4	V5	V6 <sup>14</sup> / EOT	EOS <sup>14</sup>
Week	-5 to -2	-4 to -1	0	2	4	8	12	24
Day	-35 to -14	- 28 to - 7	0	14	28	56	84	168
Visit window (days)	N.A.	N.A.	0	±4	±4	±4	±4	+7
0020 <sup>13</sup>								

**Footnotes:**

1. If disease extent has not been performed within past 12 months from screening, a full colonoscopy will be performed during screening period, instead of the screening and baseline sigmoidoscopy, to determine the extent of disease.
2. [REDACTED] At visits with study drug administration this should to be done prior to the study drug infusion. Colonoscopy and sigmoidoscopy images will be scored using the modified Mayo Endoscopy Score (mESS) recorded by the site investigator and centrally read by an external independent assessor(s); management of images will be performed by an external vendor.
3. Sigmoidoscopies will be performed at visit V1b if no colonoscopy is done.
4. Physical examination: C=complete, T=targeted. Refer to [Section 5.2.1](#). In addition, at Visits 2, 4 and 5 vital signs will be assessed at approximately 5 and 60 minutes after the end of study drug administration. Monitor for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the first dose administered at Visit 2 and 1 hour following all other doses of study drug (at Visits 4 and 5).
5. Only applicable for women of childbearing potential. A serum pregnancy test will be performed at screening. Urine pregnancy tests will be performed at all other visits indicated in the [Flow chart](#). In case of a positive urine pregnancy test, a serum pregnancy test will be done. Urine pregnancy testing should be done prior to administration of study drug in case there is dosing at study visits. Study drug should only be administered in case of a negative test result. More frequent testing should be done if required by the local regulation and / or authority or per investigator judgment.
6. If collection is not possible at Visit 1a, stool sample has to be collected at (or prior to) Visit 1b or at an unscheduled visit.
7. Includes clinical chemistry, haematology, coagulation and urinalysis assessments. Patient must be fasting for at least 8 hours prior to blood collection (except screening visit). If not fasted mark on laboratory requisition form. At visits with study drug administration this should be done prior to the study drug infusion.
8. At study visits with study drug administration, pre-dose PK/ADA [REDACTED] samples will be obtained approximately within 1 hour prior to start of i.v. infusion.

9. The IBDQ, FACIT-Fatigue, SF-36, EQ-5D(-5L), and WPAI-UC, patient-reported outcome tools, must be completed by the patient on his/her own in the pre-specified order in a quiet area/room before any other visit assessments or treatments and, as much as possible, before any interaction with the investigator or other members of the study team. Refer to [Section 6.2.1](#).
10. A diary will be used by the patient for the daily reporting of bowel movement frequency and rectal bleeding (blood in stool). This information will be used for the calculation of Mayo score at the visits. Please make sure that time window between visits V1a and visit V1b is minimum 7 days. This will ensure that enough eDiary data (SFS and RBS) are collected before visit V1b in order to calculate the baseline Mayo score. PGA (Physician Global Assessment) should be completed at all visits except visit 1a. Refer to [Section 6.2.1](#).
11. First study drug administration will be administered at V2.
12. Patients who terminate study drug early should be encouraged to follow all study procedures per the [Flow Chart](#) until week 12, but not receive any more study drug at the respective visits. These patients do have the option to do EOS visit earlier than week 24, i.e. 16 weeks after last study drug administration. Until then they should follow the [Flow Chart](#).
13. All patients completing week 12 of the study will be offered to enter maintenance trial 1368-0020. These patients are not requested to complete follow up period and will have their End of study visit at visit V6, co-inciding with the BL visit, randomisation and start of study drug administration in 1368-0020.
14. EOS visit will be at week 12 (V6) for patients rolling-over into maintenance trial 1368-0020; and at week 24 for patients who will not enter maintenance trial 1368-0020.
15. Healthcare resource utilisation (HCRU) data will be captured at every study visit.

## TABLE OF CONTENTS

TITLE PAGE .....	1
CLINICAL TRIAL PROTOCOL SYNOPSIS .....	2
FLOW CHART: PART 1/PROOF OF CONCEPT .....	5
FLOW CHART: PART 2 / CONFIRMATORY EFFICACY/ SAFETY EVALUATION .....	9
TABLE OF CONTENTS .....	13
ABBREVIATIONS .....	17
<b>1. INTRODUCTION.....</b>	<b>20</b>
1.1 DRUG PROFILE .....	20
1.2 MEDICAL BACKGROUND .....	22
1.3 RATIONALE FOR PERFORMING THE TRIAL .....	22
1.4 BENEFIT - RISK ASSESSMENT.....	23
<b>2. TRIAL OBJECTIVES AND ENDPOINTS.....</b>	<b>28</b>
2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS.....	28
2.1.1 Main objectives.....	28
2.1.2 Primary endpoint (Part 1 and Part 2).....	28
2.1.3 Key Secondary endpoints (Part 2 / Phase III only).....	28
2.1.4 Secondary endpoint (Part 1 and Part 2) .....	28
2.1.5 Secondary endpoints (Part 1 / Phase II only) .....	29
	
<b>3. DESCRIPTION OF DESIGN AND TRIAL POPULATION.....</b>	<b>32</b>
3.1 OVERALL TRIAL DESIGN AND PLAN .....	32
3.1.1 Part 1 / Proof of Concept.....	33
3.1.2 Transition from Part 1 to Part 2.....	34
3.1.3 Part 2 / Confirmatory Efficacy/Safety Evaluation.....	37
3.1.4 Follow-up period:.....	38
3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S) .....	38
3.3 SELECTION OF TRIAL POPULATION .....	39
3.3.1 Main diagnosis for trial entry .....	40
3.3.2 Inclusion criteria .....	40
3.3.3 Exclusion criteria .....	41
3.3.3.1 Gastrointestinal Exclusion Criteria .....	41
3.3.3.2 Infectious Disease Exclusion Criteria .....	42
3.3.3.3 General Exclusion Criteria.....	42
3.3.4 Withdrawal of patients from therapy or assessments .....	43
3.3.4.1 Withdrawal from trial treatment .....	43

3.3.4.2	Withdrawal of consent for trial participation .....	44
3.3.4.3	Discontinuation of the trial by the sponsor .....	44
<b>4.</b>	<b>TREATMENTS.....</b>	<b>45</b>
<b>4.1</b>	<b>INVESTIGATIONAL TREATMENTS .....</b>	<b>45</b>
<b>4.1.1</b>	<b>Identity of the Investigational Medicinal Products.....</b>	<b>45</b>
<b>4.1.2</b>	<b>Selection of doses in the trial.....</b>	<b>46</b>
<b>4.1.3</b>	<b>Method of assigning patients to treatment groups.....</b>	<b>47</b>
<b>4.1.4</b>	<b>Drug assignment and administration of doses for each patient.....</b>	<b>47</b>
<b>4.1.5</b>	<b>Blinding and procedures for unblinding.....</b>	<b>48</b>
4.1.5.1	Blinding.....	48
4.1.5.2	Unblinding and breaking the code .....	49
<b>4.1.6</b>	<b>Packaging, labelling, and re-supply.....</b>	<b>50</b>
<b>4.1.7</b>	<b>Storage conditions .....</b>	<b>50</b>
<b>4.1.8</b>	<b>Drug accountability.....</b>	<b>50</b>
<b>4.2</b>	<b>OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS .....</b>	<b>51</b>
<b>4.2.1</b>	<b>Other treatments and emergency procedures .....</b>	<b>51</b>
<b>4.2.2</b>	<b>Restrictions .....</b>	<b>53</b>
4.2.2.1	Restrictions regarding previous and concomitant treatment are summarized in Table 4.2.2.1: 1 .....	53
4.2.2.2	Restrictions regarding women of childbearing potential .....	55
<b>4.3</b>	<b>TREATMENT COMPLIANCE .....</b>	<b>55</b>
<b>5.</b>	<b>ASSESSMENTS .....</b>	<b>56</b>
<b>5.1</b>	<b>ASSESSMENT OF EFFICACY .....</b>	<b>56</b>
<b>5.2</b>	<b>ASSESSMENT OF SAFETY .....</b>	<b>56</b>
<b>5.2.1</b>	<b>Physical examination .....</b>	<b>56</b>
<b>5.2.2</b>	<b>Vital signs.....</b>	<b>57</b>
<b>5.2.3</b>	<b>Safety laboratory parameters .....</b>	<b>57</b>
<b>5.2.4</b>	<b>Electrocardiogram .....</b>	<b>60</b>
<b>5.2.5</b>	<b>Other safety parameters.....</b>	<b>61</b>
<b>5.2.6</b>	<b>Assessment of adverse events.....</b>	<b>61</b>
5.2.6.1	Definitions of AEs .....	61
5.2.6.2	Adverse event collection and reporting .....	64
<b>5.3</b>	<b>DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS .....</b>	<b>66</b>
<b>5.3.1</b>	<b>Assessment of pharmacokinetics .....</b>	<b>66</b>
<b>5.3.2</b>	<b>Methods of sample collection .....</b>	<b>66</b>
5.3.2.1	Plasma sampling for PK analysis.....	67
5.3.2.2	Plasma sampling for ADA assessment .....	67
<b>5.3.4</b>	<b>Pharmacokinetic – pharmacodynamic relationship .....</b>	<b>67</b>

<b>5.5</b>	<b>OTHER ASSESSMENTS.....</b>	<b>70</b>
<b>5.6</b>	<b>APPROPRIATENESS OF MEASUREMENTS .....</b>	<b>73</b>
<b>6.</b>	<b>INVESTIGATIONAL PLAN.....</b>	<b>74</b>
<b>6.1</b>	<b>VISIT SCHEDULE.....</b>	<b>74</b>
<b>6.2</b>	<b>DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS .....</b>	<b>74</b>
<b>6.2.1</b>	<b>Screening and run-in period(s) .....</b>	<b>74</b>
<b>6.2.2</b>	<b>Treatment period(s) .....</b>	<b>76</b>
<b>6.2.3</b>	<b>Follow up period and trial completion .....</b>	<b>77</b>
<b>7.</b>	<b>STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE .....</b>	<b>79</b>
<b>7.1</b>	<b>STATISTICAL DESIGN – MODEL .....</b>	<b>79</b>
<b>7.2</b>	<b>NULL AND ALTERNATIVE HYPOTHESES .....</b>	<b>80</b>
<b>7.3</b>	<b>PLANNED ANALYSES .....</b>	<b>87</b>
<b>7.3.1</b>	<b>Primary endpoint analyses .....</b>	<b>88</b>
<b>7.3.2</b>	<b>Key Secondary endpoint analyses .....</b>	<b>92</b>
<b>7.3.3</b>	<b>Secondary endpoint analyses .....</b>	<b>92</b>
<b>7.3.5</b>	<b>Safety analyses.....</b>	<b>93</b>
<b>7.3.6</b>	<b>Pharmacokinetic and pharmacodynamic analyses.....</b>	<b>94</b>
<b>7.4</b>	<b>INTERIM ANALYSES .....</b>	<b>95</b>
<b>7.5</b>	<b>HANDLING OF MISSING DATA .....</b>	<b>96</b>
<b>7.6</b>	<b>RANDOMISATION .....</b>	<b>97</b>
<b>7.7</b>	<b>DETERMINATION OF SAMPLE SIZE .....</b>	<b>98</b>
<b>7.7.1</b>	<b>Sample size determination for Part 1 .....</b>	<b>98</b>
<b>7.7.2</b>	<b>Sample size determination for Part 2.....</b>	<b>100</b>
<b>8.</b>	<b>INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE .....</b>	<b>103</b>
<b>8.1</b>	<b>TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT .....</b>	<b>103</b>
<b>8.2</b>	<b>DATA QUALITY ASSURANCE .....</b>	<b>104</b>
<b>8.3</b>	<b>RECORDS .....</b>	<b>104</b>
<b>8.3.1</b>	<b>Source documents .....</b>	<b>104</b>
<b>8.3.2</b>	<b>Direct access to source data and documents.....</b>	<b>105</b>
<b>8.3.3</b>	<b>Storage period of records .....</b>	<b>106</b>
<b>8.4</b>	<b>STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY .....</b>	<b>106</b>
<b>8.4.1</b>	<b>Collection, storage and future use of biological samples and corresponding data .....</b>	<b>106</b>
<b>8.5</b>	<b>TRIAL MILESTONES.....</b>	<b>107</b>
<b>8.6</b>	<b>ADMINISTRATIVE STRUCTURE OF THE TRIAL .....</b>	<b>107</b>
<b>9.</b>	<b>REFERENCES.....</b>	<b>109</b>

9.1	PUBLISHED REFERENCES.....	109
9.2	UNPUBLISHED REFERENCES.....	115
10.	APPENDICES .....	116
10.1	MAYO SCORING SYSTEM FOR THE ASSESSMENT OF ULCERATIVE COLITIS ACTIVITY .....	116
10.2	HISTOLOGIC ACTIVITY SCORE .....	118
10.3	EQUIVALENT DOSES OF CORTICOSTEROIDS.....	119
10.4	PATIENT REPORTED OUTCOMES .....	119
10.4.1	Inflammatory Bowel Disease Questionnaire (IBDQ) .....	119
10.4.2	EQ-5D-5L.....	119
10.6	DEFINITION OF PRIMARY, SECONDARY NONRESPONSE OR INTOLERANCE TO ANTI-INTEGRIN OR ANTI-TNF THERAPY .....	121
10.7	DIAGNOSIS OF ANAPHYLAXIS .....	126
10.8.	SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA (OMERACT) .....	127
11.	DESCRIPTION OF GLOBAL AMENDMENT(S) .....	129
11.1	GLOBAL AMENDMENT 1 .....	129
11.2	GLOBAL AMENDMENT 2 .....	135
11.3	GLOBAL AMENDMENT 3 .....	145



## ABBREVIATIONS

ADA	Anti-drug antibodies
ADCC	antibody-dependent cellular cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area under the Curve
b.i.d.	bis in die (twice daily dosing)
BL	Base Line
CCDS	Company Core Data Sheet
BIO	Biologics
CD	Crohn's disease
CDC	complement-dependent cytotoxicity
CI	Confidence Interval
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CTCAE	Common Terminology Criteria for Adverse Events
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CT	Concomitant Therapy
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOT	End of Treatment
EOS	End of Study
ePRO	Electronic Patient Reported Outcome
EQ-5D(-5L)	Questionnaire developed by EuroQoL Group
ESS	Mayo Endoscopy Score
EudraCT	European Clinical Trials Database
FACIT	Functional Assessment of Chronic Illness Therapy
FAS	Full Analysis Set
FC	Flow Chart
FcR	Fc receptor - a protein found on the surface of certain cells
FIH	First in human
GCP	Good Clinical Practice
GPP	generalized pustular psoriasis
HPC	Human Pharmacology Centre
HCRU	Healthcare resource utilisation
HT29	a human colorectal adenocarcinoma cell line with epithelial morphology
IB	Investigator's Brochure
IBD	inflammatory bowel disease
IBDQ	Inflammatory Bowel Disease Questionnaire
IC90	Inhibitory concentration of 90 (mg/mL)

IEC	Independent Ethics Committee
IFN $\gamma$	Interferon gamma
IgG1	Immunglobulin G1
IHC	Immunohistochemistry
IL36R	Interleukin 36R
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITE	indirect target engagement
i.v.	intravenous
LoEE	List of Essential Element
MCS	Mayo Clinical Score
mMCS	modified Mayo Clinical Score
MedDRA	Medical Dictionary for Drug Regulatory Activities
mESS	modified Endoscopic Subscore
MST	Medical Sub Team
NF- $\kappa$ B	Nuclear factor 'kappa-light-chain-enhancer' of activated B-cells
NOAEL	No-observed-adverse-effect level
OPU	Operative Unit
PBO	Placebo
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamics
PK	Pharmacokinetics
pMCS	partial Mayo Clinical Score
p.o.	per os (oral)
PoC	proof of concept
PPP	palmoplantar pustulosis
q.d.	quaque die (once a day)
q.w.	quaterly week (every 4 <sup>th</sup> week)
eDC	electronic Data Capturing
RBS	Rectal Bleeding Score
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
RS	Randomized Set
SAE	Serious Adverse Event
s.c.	subcutaneous
SF-36	36 question instrument to measure health-related quality of life
SFS	Stool Frequency Score
SMC	Safety Monitoring Committee
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMDD	target-mediated drug disposition
TB test	blood test that aids in the detection of <i>Mycobacterium tuberculosis</i> , the bacteria which causes tuberculosis (TB)
TCM	Trial Clinical Monitor
TDMAP	Trial Data Management and Analysis Plan

TGF- $\beta$	tissue growth factor
t.i.d.	ter in die (3 times a day)
TMF	Trial Master File
TNF	Tumor necrosis factor
TNFi	TNF $\alpha$ inhibitor
TSAP	Trial Statistical Analysis Plan
UC	Ulcerative Colitis
WHO	World Health Organization
WOCBP	Woman of childbearing potential
WPAI-UC	Work Productivity and Activity Impairment Questionnaire, Ulcerative Colitis -specific version

## 1. INTRODUCTION

### 1.1 DRUG PROFILE

BI655130 (SPESOLIMAB) is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signaling. Binding of BI655130 (SPESOLIMAB) to IL36R is anticipated to prevent the subsequent activation of IL36R by cognate ligands (IL36  $\alpha$ ,  $\beta$  and  $\gamma$ ) and downstream activation of pro-inflammatory and pro-fibrotic pathways with the aim to reduce epithelial cell/ fibroblast/ immune cell-mediated inflammation and interrupt the inflammatory response that drives pathogenic cytokine production in inflammatory diseases including generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP) and inflammatory bowel disease (IBD).

#### *Preclinical studies*

BI655130 (SPESOLIMAB) binds to human IL36R with a binding avidity of less than 1 pM. BI655130 (SPESOLIMAB) inhibits IL36 ligand-stimulated NF- $\kappa$ B activation in HT29 and transformed epithelial cells and in primary human dermal fibroblasts or intestinal myofibroblasts with IC90 values in a consistent range of 0.7 to 3.7 nM. BI655130 (SPESOLIMAB) also inhibits IL8 release in primary human intestinal myofibroblasts and IFN $\gamma$  secretion in human PBMC stimulated with IL36 $\alpha$ , IL36 $\beta$ , or IL36 $\gamma$  combined with IL12.

Mutations of two key residues (L234 and L235) to alanine were made to BI655130 (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 BI655130 (SPESOLIMAB) will be a non-depleting therapy in vivo.

#### *Toxicology studies*

BI655130 (SPESOLIMAB) does not bind to IL-36R from common toxicology species. Therefore, meaningful toxicity studies of the molecule cannot be performed in any animal species with BI655130 (SPESOLIMAB). However, hazard identification studies of the mode-of-action (MoA) of IL-36R inhibition were performed in mice using a mouse specific anti-IL-36R monoclonal antibody (BI 674304), which is a mouse IgG2a monoclonal antibody with rat variable regions. In a 13-week intravenous toxicity study of BI 674304 in mice, no adverse effects of IL-36R antagonism were seen at a dose (50 mg/kg, twice weekly) that was 5 fold higher than the dose that was protective in an experimental mouse colonic inflammation model. In the 26-week toxicity study, male and female mice (20-30/sex/group at 0, 10 and 50 mg/kg/day) were administered BI 674304 twice weekly for 26 weeks by intravenous injection via the caudal vein. There were no BI 674304-related changes in clinical observations, body weights, food consumption, ophthalmology, clinical pathology parameters (hematology, clinical chemistry), organ weights, macroscopic or microscopic examinations. The no-observed-adverse-effect level (NOAEL) was considered to be 50 mg/kg/day.

The in vitro cytokine release and tissue cross-reactivity assays demonstrate that the risk of transient cytokine release in humans is low and that, as expected, BI655130 (SPESOLIMAB) stains epithelium in a variety of tissues. There were no signs of local irritation after single, 1 mL injections of the subcutaneous formulation in rabbits.

These preclinical toxicology data support chronic BI655130 (SPESOLIMAB) dosing in humans.

#### Clinical PK/PD studies

BI655130 (SPESOLIMAB) or placebo (PBO) was administered to 78 healthy volunteers at single ascending i.v. doses from 0.001 mg/kg to 10 mg/kg body weight. Safety and tolerability of all tested i.v. doses was good. There were no drug-related SAEs. AEs categorized as related to treatment were observed in 3/19 (15.8%) subjects in the placebo group and in 7/59 (11.9%) subjects treated with BI655130 (SPESOLIMAB). The most frequent treatment-emergent AEs were nasopharyngitis (BI655130 (SPESOLIMAB): 21%; PBO: 15%), headache (BI655130 (SPESOLIMAB): 9%; PBO: 15%), influenza like illness (BI655130 (SPESOLIMAB): 7%; PBO: 10%), and diarrhoea (BI655130 (SPESOLIMAB): 3%; PBO: 10%). There were two AEs of moderate intensity (injection site haematoma, headache), all remaining AEs were of mild intensity. There was no apparent relationship between the frequency of AEs and the dose. There were no relevant changes compared to placebo for laboratory safety, including clinical chemistry, haematology, coagulation parameters, and urinalysis. No clinically relevant changes were observed in 12 lead ECGs, vital signs, and cardio-monitoring.

PK analysis showed that exposure ( $AUC_{0-tz}$  and  $C_{max}$ ) to BI655130 (SPESOLIMAB) increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg. The effective half-life of BI655130 (SPESOLIMAB) is approximately 4 weeks in the linear dose range. Overall, PK data so far suggests target-mediated drug disposition (TMDD) kinetics for BI655130 (SPESOLIMAB). Anti-drug antibodies (ADA) were detected in 8 patients, 3 of those had pre-existing levels. Pharmacodynamic effects in this FIH Single Rising Dose trial [[c03361085-07](#)] were assessed by indirect target engagement (ITE) of IL36R by BI655130 (SPESOLIMAB) using an ex-vivo whole blood stimulation assay. All doses higher than 0.001 mg/kg were biologically active, corresponding to the minimum anticipated biological effect level, MABEL.

In a multiple rising dose trial, BI655130 (SPESOLIMAB) or placebo have been administered to healthy volunteers at multiple ascending i.v. doses of 3, 6, 10 and 20 mg/kg given qw for 4 weeks (i.e. 4 administrations) or a single dose of 20mg/kg (8 subjects each, 3:1 on active or PBO). Overall, BI655130 (SPESOLIMAB) was well tolerated. There were no dose dependent AEs, AEs considered to be dose limiting and no SAEs. In all cases the AEs were of mild or moderate intensity. Furthermore, there were no clinically relevant abnormalities on treatment with BI655130 (SPESOLIMAB) with respect to safety laboratory, vital signs, or ECGs as assessed by a central reader. Importantly, based on the preliminary analysis of the ITE studies, more than 90% of peripheral IL36R was engaged for at least 22 weeks after the last application of four weekly doses. For further details and most recent results refer to the current Investigator's Brochure [[c03320877-07](#)].

### Summary

BI655130 (SPESOLIMAB) is an anti IL36R antibody with a high clinical activity to block IL36R signaling, as demonstrated in patients with Generalized Pustular Psoriasis, a severe inflammatory skin disease driven by uncontrolled IL36 activity. IL36R inhibition shows a favorable nonclinical safety profile. Importantly, BI655130 (SPESOLIMAB) has been tested in healthy volunteers with single or multiple dosing up to four weeks of 20 mg/kg i.v. q.w., which were all safe and well tolerated. Therefore, BI655130 (SPESOLIMAB) might be a promising drug to treat patients suffering from ulcerative colitis.

For further details and most recent results refer to the current Investigator's Brochure (IB) [[c03320877-07](#)].

## 1.2 MEDICAL BACKGROUND

Ulcerative Colitis (UC) is a chronic inflammatory bowel disease characterized by the key symptoms of chronic diarrhea, bloody stools and abdominal pain. It has an estimated incidence of 24.3 and 19.2 cases per 100,000 persons per year in Europe and the USA, respectively, resulting in a continuously rising prevalence [[R15-0886](#)]. UC is characterized clinically by abdominal pain, fever, and blood or mucosa-containing diarrhea, and pathologically by inflammatory lesions in the gastrointestinal mucosa. Inflammatory lesions characteristically occur distal to the terminal ileum, and by confinement of lesions to the mucosa and submucosa without transmural inflammation. UC typically follows a relapsing and remitting course, and is associated with substantial acute and long-term morbidity and increased mortality. The mainstays of drug therapy for UC are: orally administered aminosalicylates, glucocorticoids, oral immunosuppressive agents azathioprine and 6-mercaptopurine, and TNF antagonists. In patients with mild UC, 5-ASAs are safe and effective for induction and maintenance treatment. Glucocorticoids, immunosuppressives, TNF antagonists, and more recently vedolizumab, are reserved for patients with moderate to severe disease, in whom the primary goals of drug therapy are to induce and subsequently to maintain remission from signs and symptoms of active disease.

Biologic treatment of moderate/severe UC is associated with approximately one third of patients each failing with primary or secondary non-response. In addition, treatment may be limited due to safety and tolerability issues. Therefore, despite of therapeutic progress, there remains a significant unmet medical need for new treatment options with an improved safety and efficacy profile compared to the current therapeutic standard.

## 1.3 RATIONALE FOR PERFORMING THE TRIAL

BI655130 (SPESOLIMAB) is currently under development for the treatment of ulcerative colitis (UC). Its unique dual mode of action targets pro-inflammatory cytokines as well as tissue remodeling effects and thus may provide a clear advantage over current drugs and investigational compounds, which target inflammation only. The potential BI655130 (SPESOLIMAB) effects on remodeling may directly increase mucosal healing, induce deeper

tissue healing (histologic remission) and reduce stricturing and fistulizing complications of IBD.

The link between IL36R driven inflammation and epithelial inflammation has led to the hypothesis that IL36R signalling may play an important role in inflammatory bowel diseases such as UC. This hypothesis was tested using a suite of in vitro and in vivo assays. Immunostaining studies demonstrated that both IL-36R and its ligands are expressed in intestinal biopsies from patients with chronic IBD. Human IL36 ligands enhanced epithelial intestinal barrier permeability, a hallmark of IBD pathogenesis, based on a study using primary human intestinal epithelial cells co-cultured with intestinal myofibroblasts. The link between IL36R signalling and IBD was further strengthened by demonstrating that antagonist anti-mouse IL36R antibodies ameliorated intestinal inflammation in both acute chemically induced and chronic T cell driven murine colitis models. The therapeutic rationale for an IL36R antagonist in IBD is further based on the correlation of a set of IL36-induced genes upregulated in primary human intestinal myofibroblasts, a disease relevant cell type, with gene signatures observed in ulcerative colitis and Crohn's disease (CD) patients. Finally, IL36R signalling in disease relevant cells such as intestinal myofibroblasts and macrophages induce not only pro-inflammatory but also tissue remodelling related mediators (e.g., tissue growth factor TGF- $\beta$ , matrix metalloproteinase), which differentiates this mechanism from TNF alpha, integrin and IL23 targeting pathways. Altogether these findings indicate that IL36 is a key regulatory cytokine upstream of various pro-inflammatory and tissue-remodelling cytokines including TGF- $\beta$ , TNF $\alpha$  and IL23, and support a prominent role of IL36R in driving intestinal inflammation and fibrosis.

In addition, data on pharmacokinetics of 12 weeks of BI655130 (SPESOLIMAB) treatment in UC patients will be collected and correlated with the pharmacodynamic (PD) treatment response. These data will help understand the PK characteristics of BI655130 (SPESOLIMAB) in UC, which may differ from those in healthy volunteers and patients with other diseases due to the expected intestinal protein loss subsequent to mucosal inflammation and ulceration in the colon. A robust understanding of the PK/PD response correlation will be obtained using a modelling approach and will support dose selection for adult phase III testing and the pediatric development program.

The most recent and more detailed information is available in the current IB [c03320877-07].

#### 1.4 BENEFIT - RISK ASSESSMENT

Preclinical profiles of BI655130 (SPESOLIMAB) and clinical data from healthy volunteer trials suggest that BI655130 (SPESOLIMAB) is safe, tolerable and may address an unmet medical need in UC patients by a dual anti-inflammatory and anti-fibrotic mechanism of action, cf. [Section 1.2](#) and the IB [c03320877-07]. Results of the PoC trial 1368-0011 in acute GPP demonstrate that BI655130 (SPESOLIMAB) treatment rapidly clears pustules, the primary lesions in GPP, a disease closely linked to loss-of-function mutations in the natural IL36R antagonist. A different pustular inflammatory epithelial disease is PPP, which does not show the clear genetic association to the IL36 signalling pathway as GPP. Although the small

pilot study of BI655130 (SPESOLIMAB) in 59 patients with this disease (1368.15) failed to achieve the primary endpoint, a subgroup analysis has shown a strong dose dependent effect on pustule severity, the primary and most burdensome lesion of this disease. These data indicate that BI655130 (SPESOLIMAB) indeed inhibits IL36 in human disease and thus has the potential to also treat other neutrophil granulocyte related inflammatory epithelial diseases such as IBD. The most recent and more detailed information is available in section 6 of the current IB [[c03320877-07](#)].

No relevant animal species is available for toxicology testing of the highly human specific antibody BI655130 (SPESOLIMAB). However, preclinical toxicology studies with a mouse surrogate antibody have demonstrated the safety of IL-36R inhibition in mice (IB [c03320877-07](#), Section 5.1.2).

A total of more than 212 subjects have been exposed to single or multiple i.v. doses of BI 655130 as of September 2018 (see IB). BI 655130 was safe and well tolerated in four healthy volunteers trials evaluating the i.v. and s.c. formulation (for details cf. Section 1.2 and IB [c03320877-07](#)).

Moreover, two trials exploring efficacy and safety of single (1368-0011) or multiple (1368-0015) doses of BI655130 (SPESOLIMAB) in patients with Generalized Pustular Psoriasis (GPP, n=7) or Palmoplantar Pustulosis (PPP; n=59) demonstrated the favourable safety profile of BI655130 (SPESOLIMAB) in these severe inflammatory skin diseases. Finally, two (1368 - 0004, 1368-0010) clinical trials exploring efficacy and safety of BI655130 (SPESOLIMAB) in patients with Ulcerative Colitis (UC; target n=10 and 30) are currently ongoing and have not yet indicated a BI655130 (SPESOLIMAB) related safety concern.

Although no direct benefit for individual patients can be assumed, based on the PoC achieved in GPP and the strong preclinical rationale, there is a reasonable chance that BI655130 (SPESOLIMAB) may not only alleviate signs and symptoms of active ulcerative colitis but even directly promote mucosal and histological healing, which is associated with improved clinical outcomes (reductions in immunosuppressive treatments, hospitalizations, colectomy and colorectal cancer [[R16-0572](#)]). Participation in this study may thus help to generate future benefit for larger groups of patients with UC, if BI655130 (SPESOLIMAB) proves to be successful in treating this disease.

There are no identified or potential risks for-BI655130 (SPESOLIMAB), based on the toxicology programme or any clinical trials conducted for this product to date (see also [Section 1.2](#)). No other IL-36 receptor antagonist is currently approved, providing information on identified risks in molecules of this class.

The risks shown in the table below are hypothetical in nature; these are derived from general safety considerations of immunomodulatory drugs.



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

Hypothetical risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
<b>Investigational Medicinal Product</b>		
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety. See also <a href="#">Section 5.2.6</a> , adverse events of special interest
	After administration of any biologic agent or protein, there is a possibility of occurrence of adverse immune reactions which can be local (e.g. redness, pruritus, and or swelling at the injection site) or systemic (e.g. anaphylactic reactions).	Patients with a history of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients are excluded from the trial.  In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to interrupt and treat the condition. Systemic hypersensitivity reaction is defined as AESI. It is subject to close monitoring and investigators are requested assess these conditions using the criteria discussed in the statement paper from Sampson HA[ <a href="#">R11-4890</a> ].
Infections	Inhibition of the immune response with an immune-modulating biologic may increase the risk of infections.  A recent characterization of individuals with homozygous IL36R KO	Screening procedures for infections are established for this trial. Patients with any relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis or tuberculosis are excluded from the trial. Treatment of infections should be initiated promptly

	<p>mutations revealed that normal immune function was broadly preserved suggesting that IL36 signaling pathway inhibition does not compromise host defences [R11-4890].</p>	<p>according to standards of care. Severe infections and opportunistic infections are considered AESI for this trial. These conditions and serious infections are subject to close monitoring.</p>
Malignancies	<p>Inhibition of the immune response with an immune-modulating biologic may increase the risk of a decreased immune defense against malignancies</p> <p>A recent characterization of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signaling pathway inhibition does not compromise host defences <a href="#">R17-3632</a></p>	<p>Patients with a recent history of malignancy will be excluded from participation in this trial.</p> <p>In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with BI655130 (SPESOLIMAB).</p> <p>Diagnostics and treatment have to be initiated according to local standard of care.</p> <p>Malignancies represent always serious adverse events and are subject to close monitoring</p>
<b>Trial procedures</b>		
Blood Sampling	<p>As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain.</p> <p>Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood</p>	<p>These risks will be addressed by careful safety monitoring and risk mitigation measures such as</p> <ul style="list-style-type: none"> <li>(a) close clinical monitoring for AEs;</li> <li>(b) selection of experienced sites and site staff;</li> <li>(c) training.</li> </ul>

	transfusions.	
Colonoscopy or sigmoidoscopy with biopsy	Can be associated with diarrhea, abdominal pain, perforation, bleeding, effects from anaesthetic medications, and infection	These risks will be addressed by careful monitoring and risk mitigation measures such as (a) close clinical monitoring for AEs; (b) selection of sites with experienced site staff; (c) colonoscopy/sigmoidoscopy will be done according to the standard local care procedure including local clinic/hospital consent authorizing this procedure (d) training
<b>Other risks</b>		
Administration of Placebo	If the patient is randomized to receive a placebo, the patient's condition could get worse during the course of the trial.	If the patient, including placebo treatment patient, requires additional medical therapy to treat the underlying ulcerative colitis due to disease worsening the study drug must be discontinued and patients may receive conventional treatment for active disease.

Based on the findings in the nonclinical studies conducted to date and in accordance with international regulatory guidelines, the inclusion of Women of Child Bearing Potential (WOCBP) in this study is justified. To minimize the risk of unintentional exposure of an embryo or fetus to the investigational drug, WOCBP must agree to the requirements for the pregnancy testing and contraceptive methods described in [Section 4.2.2.2](#)

### **Summary of benefit-risk assessment**

Due to the lack of mechanism- or compound-related safety signals and the antagonistic mode of action of BI655130 (SPESOLIMAB) it is considered unlikely that UC patients be exposed to any undue risks in this trial. Considering the medical need of the development of an effective and well tolerated drug specifically and directly treating the structural aspects of UC, the benefit of this trial is considered to outweigh the potential risks for individual UC patients participating in this trial.

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

## 2. TRIAL OBJECTIVES AND ENDPOINTS

### 2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

#### 2.1.1 Main objectives

This trial has two sequentially enrolling parts with different objectives. The primary objectives of this trial are

- to prove the concept of clinical activity of BI655130 (SPESOLIMAB) in patients with moderate-to-severely active ulcerative colitis who have failed previous biologic treatments and to identify efficacious and safe dose regimens in Part 1 (Phase II)
- to confirm efficacy and safety of BI655130 (SPESOLIMAB) in patients with moderate-to-severely active ulcerative colitis who have failed previous biologic treatments in Part 2 (Phase III)
- To provide, along with induction study 1368-0018 and the run-in cohort of 1368-0020, the target population to be evaluated in the randomised withdrawal study 1368-0020.

Both parts of the trial share the same endpoints and definitions, though primary, key secondary and secondary endpoints will only be included in the statistical testing strategy in part 2 (Phase III).

#### 2.1.2 Primary endpoint (Part 1 and Part 2)

- **Proportion of patients with Clinical Remission at week 12**  
(defined as mMCS SFS=0 or 1, if drop  $\geq 1$  from BL; and RBS=0; and mESS $\leq 1$ )

#### 2.1.3 Key Secondary endpoints (Part 2 / Phase III only)

- **Proportion of patients with Mucosal Healing at week 12**  
(defined as mESS  $\leq 1$ )
- **Proportion of patients with Clinical response at week 12**  
(defined as total MCS reduction  $\geq 3$  pts. and  $\geq 30\%$  from BL; AND RBS drop from baseline by  $\geq 1$ pt., or absolute RBS  $\leq 1$  pt)

*Note that for part 2 / Phase III only, the above-defined key secondary endpoints are included into the statistical testing strategy in a hierarchical manner subsequent to performance of the test on the primary endpoint. For further details, refer to [Section 7.2](#)*

#### 2.1.4 Secondary endpoint (Part 1 and Part 2)

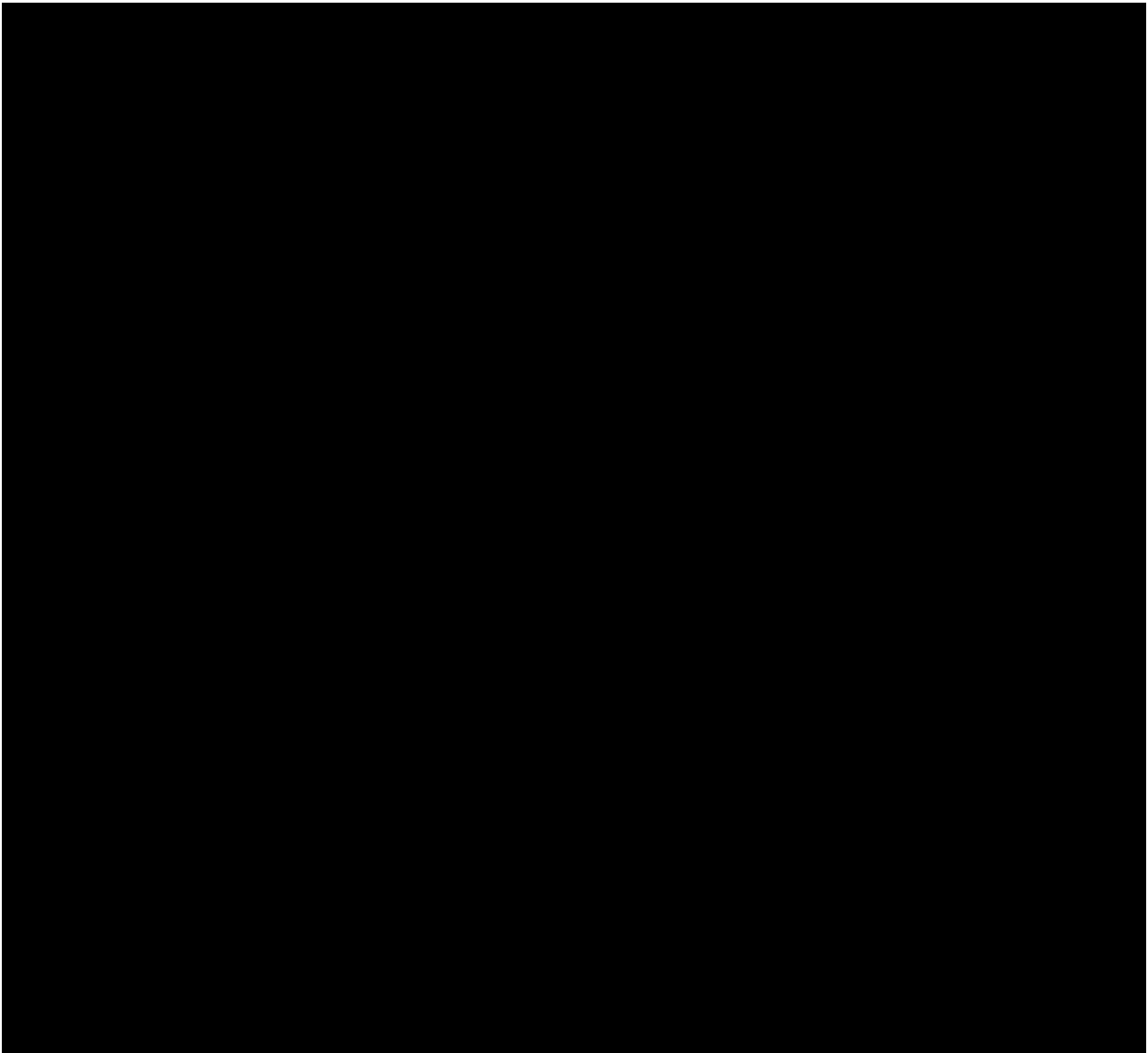
- **Change in IBDQ score from baseline at week 12**

- **Proportion of patients with combined Mucosal healing and histologic remission at week 12**  
(defined as mESS  $\leq$  1 and Robarts Histology Index  $\leq$  6)

*Note that for part 2 / Phase III only, the above-defined secondary endpoints are included into the statistical testing strategy in a hierarchical manner subsequent to performance of the tests on the key secondary endpoints. For further details, refer to [Section 7.2](#)*

#### **2.1.5 Secondary endpoints (Part 1 / Phase II only)**

- **Proportion of patients with Mucosal Healing at week 12**
- **Proportion of patients with Clinical response at week 12**



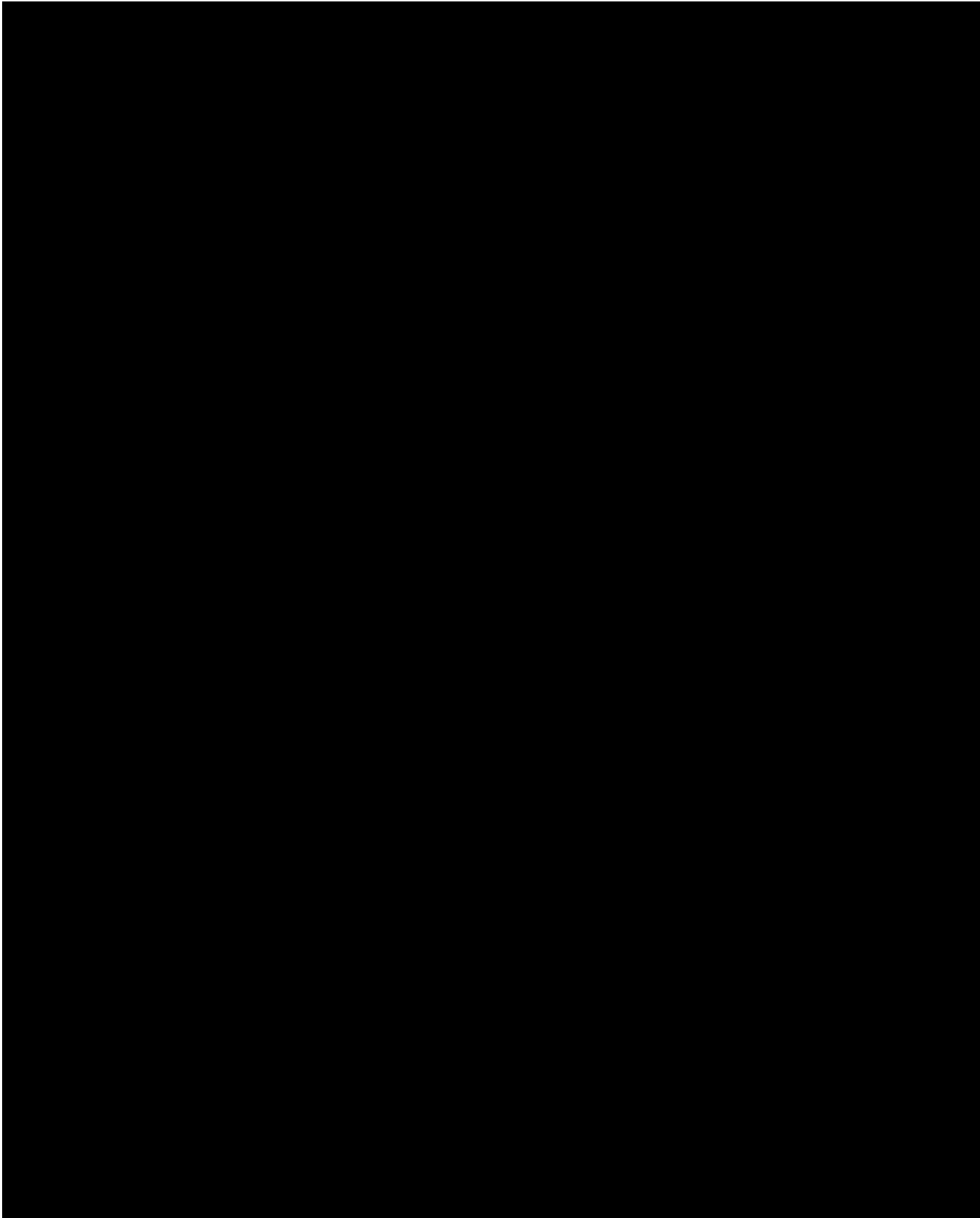


Table 2.2.2:1 Definition of Clinical Outcomes

Type of Response	MCS subscore				Total MCS	Modified MCS
	RBS	mESS	SFS	PGA		
<b>Clinical remission (CR)</b>	0	≤1	0 or 1, and drop ≥1 from baseline			≤2
<b>Total Clinical remission (tCR)</b>	≤1	≤1	≤1	≤1	≤2	
<b>Clinical response</b>	≤1 or Reduction from BL ≥1	not missing	not missing	not missing	Reduction from BL ≥3 and ≥30%	
<b>Symptomatic remission</b>	0	≤1	0	≤1	≤2	

- Abbreviations: RBS – rectal bleeding score; mESS – modified endoscopic subscore; SFS – stool frequency score; PGA – physician’s global assessment;
- If greyed out, the corresponding criterion (in column) is not relevant to evaluate the corresponding type of response(in row)
- Total MCS is calculated as the sum of RBS, mESS, SFS and PGA
- Modified MCS is calculated as the sum of RBS, mESS and SFS
- Partial MCS is calculated as the sum of RBS, SFS and PGA

### 3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

#### 3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multi-national, randomised, parallel-group, double-blind, phase II/III trial of BI655130 (SPESOLIMAB) in moderate to severe ulcerative colitis. This trial will investigate and confirm the efficacy and safety of 12 weeks of induction treatment with different dose regimens of BI655130 (SPESOLIMAB) in patients with moderate-to-severe ulcerative colitis who have failed previous biologic treatments in the past.

The trial comprises two distinct parts with different objectives, but with identical study populations, study endpoints and visit schedules. Two of the three BI655130 (SPESOLIMAB) regimens tested in Part 1 or a dose of 750mg q4w will be selected based on pre-defined decision criteria for confirmatory testing in part 2, but will not exceed the highest dose tested in part 1. The advantage of the operationally seamless design for the trial sites is the longer recruitment window, which will allow to enrol more patients, and to gain experience with the protocol measures. The anticipated shortened duration between end of the first trial part and start of the next will reduce the risk of measurement errors and protocol violations within Part 2, the confirmatory part of the trial. The overall expectation is therefore an increase in both site efficiency as well as the quality of the study. In addition, the increased experience with protocol measures is expected to lead to a reduction in the variability associated with efficacy measurements thereby increasing the precision of treatment estimates particularly in the confirmatory part, Part 2, of the trial. Finally, the accelerated recruitment compared to two separate trials may reduce time to availability of a new drug potentially filling a high unmet medical need in this population of patients.

A schematic overview of trial design is shown in Figure 3.1:1.

Figure 3.1:1 Trial Design

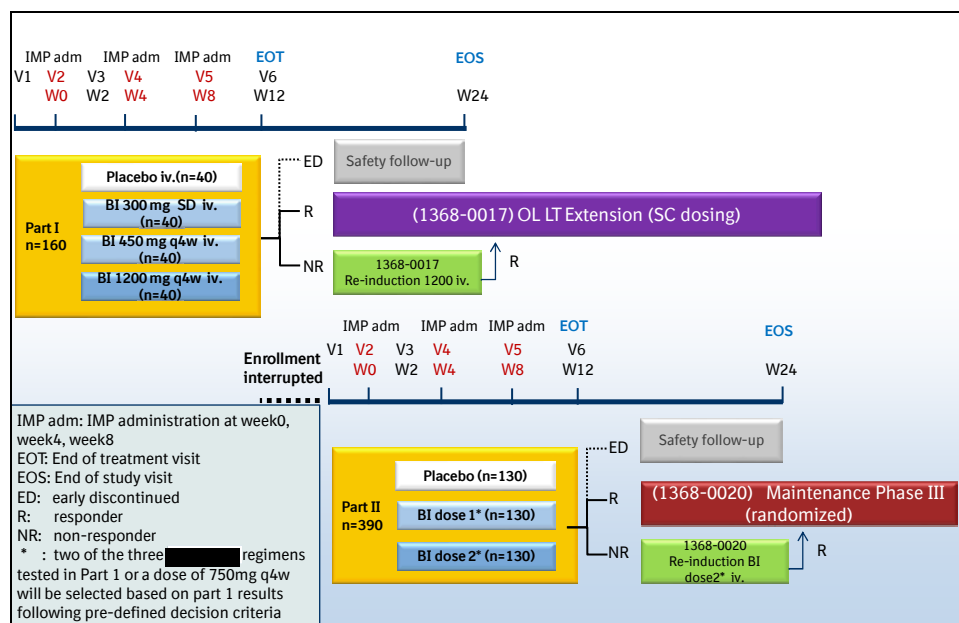




Table 3.1:1 Study definitions

Rescue Treatment	New or increase in dose of any medication, or a surgical procedure, applied to treat new or worsening symptoms related to ulcerative colitis
Disease worsening	Worsening of clinical status or symptoms of ulcerative colitis requiring administration of rescue medication in the investigator's opinion – in patients without a clinical response
Disease flare	Increase in partial MCS score by $\geq 2$ points from baseline (in 2 subsequent visits) and increase in rectal bleeding score by $\geq 1$ point from baseline (in 2 subsequent visits), confirmed by increase of modified endoscopic subscore by $\geq 1$ point from baseline with modified endoscopic subscore abs. increase by $\geq 2$ points in absence of enteric pathogens in stool
Treatment Failure	Disease worsening, need for rescue medications or surgical intervention for treatment of UC; or a study drug-related adverse event, leading to discontinuation from treatment with study drug.

For clinical endpoint definitions cf. [table 2.2.2:1](#)

The distinct trial parts are defined as follows:

### 3.1.1 Part 1 / Proof of Concept

Part 1 of the trial will consist of a screening period of up to a maximum of 5 weeks and a 12 week, parallel group, placebo-controlled, double-blind intravenous induction therapy period, and a 12 week safety follow-up period for patients not rolling-over into maintenance trial 1368-0017.

Approximately 160 eligible patients with moderate to severe ulcerative colitis who have failed previous biologic treatments in the past will be randomised in a 1:1:1:1 ratio to one of the 4 following treatment groups:

- Group 1: Placebo i.v., q4w (n=40)
- Group 2: BI655130 (SPESOLIMAB) 300 mg i.v., single dose (SD) (n=40)
- Group 3: BI655130 (SPESOLIMAB) 450 mg i.v., q4w (n=40)
- Group 4: BI655130 (SPESOLIMAB) 1200 mg i.v., q4w (n=40)

Enrolment will be competitive. Randomization will be stratified by previous BIO treatment failure and concomitant corticosteroid therapy at visit 2/randomization. In addition, a stratification for Japan versus non-Japan will be done in order to assure that sufficient patients per treatment group are recruited specifically to support individual country submission in Japan; this strata will be treated as an operational strata and will not be included into the analyses of the primary endpoint. Screening of patients who have

failed TNF $\alpha$  antagonists-AND-Vedolizumab will be closed once 48 patients have been randomized into this stratum (cf. [Section 4.1.3](#)).

Part 1 will explore the efficacy (proof of concept of clinical activity) and safety of three different dose regimens of BI655130 (SPESOLIMAB) compared to placebo as induction treatment in ulcerative colitis; the PK/PD relationship in ulcerative colitis will also be established and help select the two dose regimens for part 2. A total of 160 patients will be randomized (1:1:1:1) to receive 12 weeks of treatment with BI655130 (SPESOLIMAB) 300 mg i.v. SD, BI655130 (SPESOLIMAB) 450 mg i.v. q4w; BI655130 (SPESOLIMAB) 1200 mg i.v. q4w, or matching placebo. At week 12, patients will be evaluated for the primary endpoint of clinical remission.

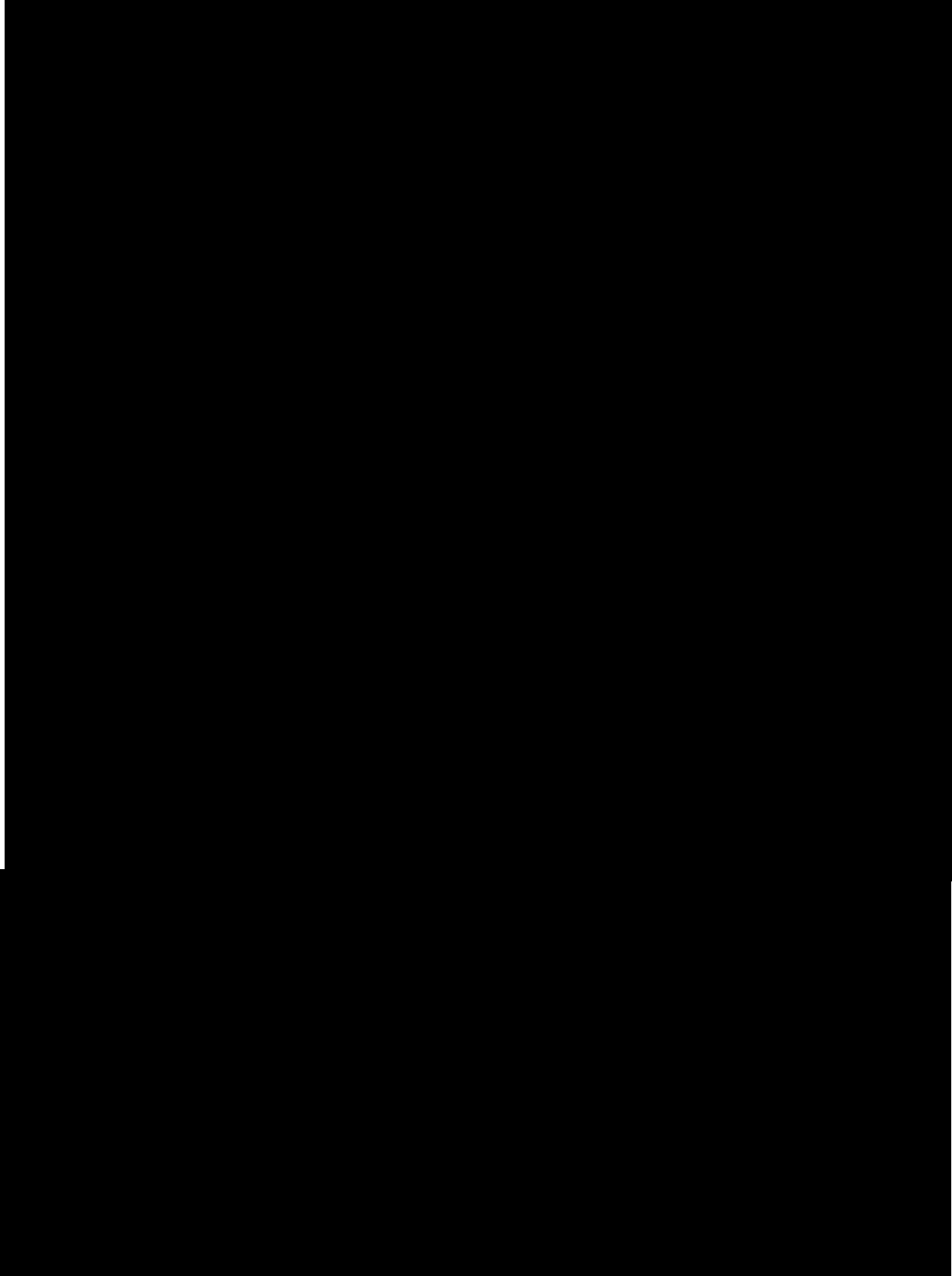
Patients who terminate study drug early will continue safety follow up in this study until 16 weeks after last study drug administration, while patients who complete the 12-week primary endpoint assessment in part 1 of this study will enter the maintenance trial 1368-0017, which offers open label active treatment with BI655130 (SPESOLIMAB) guided by the outcome of Part 1 of the induction trial:

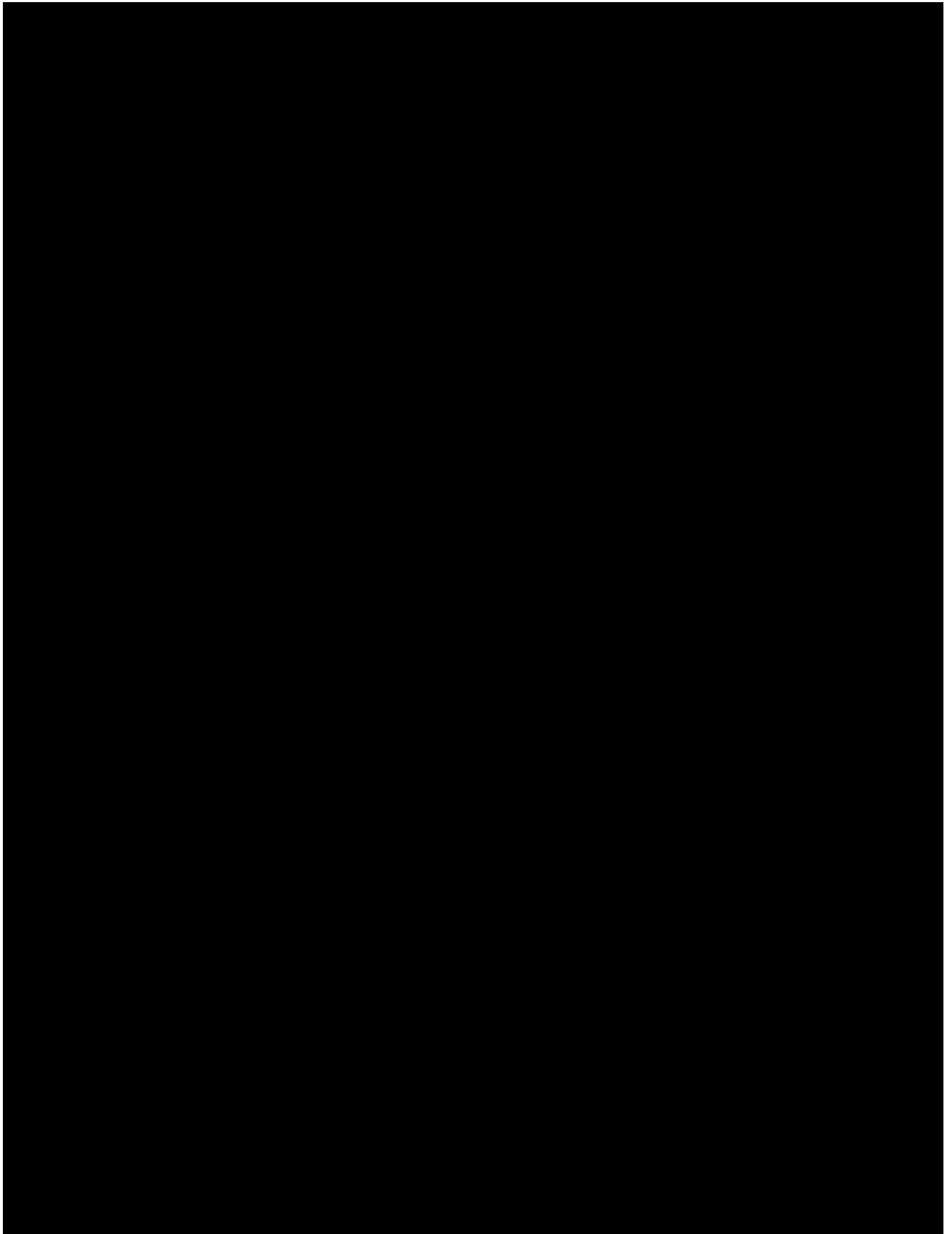
- patients meeting the clinical response endpoint (cf. [Section 5.1](#)) at week 12 will receive long-term maintenance treatment with SC maintenance dosing of BI655130 (SPESOLIMAB) for up to 7 years.
- patients not achieving the clinical response (whether on active drug or placebo) at week 12 of Part 1 of the trial will undergo a further 12 weeks open label re-induction with a high dose i.v. regimen of BI655130 (SPESOLIMAB) in trial 1368-0017, after which eligibility will be re-assessed. If the patient subsequently meets the clinical response definition, then patients will be entered into the s.c. maintenance part, while non-responders will be discontinued from the trial 1368-0017.

### 3.1.2 Transition from Part 1 to Part 2

1368-005/Part 1 will be the first part to commence. After the last patient has been enrolled into part 1, enrollment will be interrupted until the initiation of screening into part 2 has been released by the sponsor based on a thorough review of the clinical efficacy and safety as well as pharmacokinetic results of part 1 both by the independent DMC and a part 1 review committee which includes sponsor representatives, the DMC chair and the co-ordinating investigators.

The following doses are available for testing in Part 2 of the trial: 300 mg SD (approx. 100 mg q4w), 450 mg q4w, 750 mg q4w, and 1200 mg q4w. No other dose is foreseen to be selected for Part 2. Criteria have therefore been defined to guide the part 1 review committee decision on the initiation of Part 2 and on which of the pre-specified BI655130 (SPESOLIMAB) doses will continue into Part 2; the part 1 review committee may however select different regimens from the available doses than those pre-defined in this section following their review of the data.





### 3.1.3 Part 2 / Confirmatory Efficacy/Safety Evaluation

Part 2 of the trial will consist of a screening period of up to a maximum of 5 weeks, a 12 week, parallel group, placebo-controlled, double-blind intravenous induction therapy period, and a 12 week safety follow-up period for patients not rolling-over into subsequent maintenance study 1368-0020.

Approximately 390 eligible patients with moderate to severe UC who have failed previous biologic treatments in the past will be randomised in a 1:1:1 ratio to one of the 3 following treatment groups:

Group 1: Placebo i.v. q4w	(n= 130)
Group 2: BI655130 (SPESOLIMAB) selected low dose i.v. q4w	(n= 130)
Group 3: BI655130 (SPESOLIMAB) selected high dose i.v. q4w	(n= 130)

For the dose selection process for part 2 cf. [Section 3.1.2](#).

Randomization will be stratified by previous BIO treatment failure and concomitant corticosteroid therapy at visit 2/randomization. In addition, a stratification for Japan versus non-Japan will be done in order to assure that sufficient patients per treatment group are recruited specifically to support individual country submission in Japan; this strata will be treated as an operational strata and will not be included into the analyses of the primary endpoint. Screening of patients who have failed TNF $\alpha$  antagonists-AND-Vedolizumab will be closed once 117 patients have been randomized into this stratum (cf. [Section 4.1.3](#)).

Part 2 will be one of two independent trials to confirm the efficacy and safety of induction treatment with BI655130 (SPESOLIMAB) in a randomized, double-blind, placebo controlled design. This part is assumed to have an identical population to that of Part 1 and will initiate, once review of the completed Part 1 data has been performed and

decision on part 2 doses has been taken. This scenario is fully dependent upon the pre-defined decision criteria for Part 1 having been successfully met (see [Section 3.1.2](#)).

Patients who discontinue study drug early will be followed up in this study until 16 weeks after last study drug administration, while patients who complete the 12-week primary endpoint assessment in part 2 of this study will enter the pivotal maintenance trial 1368-0020, which offers a randomized maintenance treatment guided by the outcome of Part 2 of the induction trial:

- patients on BI655130 (SPESOLIMAB) treatment who meet the clinical response endpoint (cf. [Section 5.1](#)) at week 12 will be entered into the double-blind, placebo controlled randomised withdrawal study (1368-0020) and randomized to receive subcutaneous treatment with BI655130 (SPESOLIMAB) or placebo until week 52.
- patients on placebo treatment who meet the clinical response endpoint (cf. [Section 5.1](#)) at week 12 will be entered into the double-blind, placebo controlled randomised withdrawal study (1368-0020) and mock-randomized to receive subcutaneous treatment with placebo until week 52.
- patients not achieving a clinical response (whether on active drug or placebo) will undergo a further 12 weeks open label i.v. re-induction with BI655130 (SPESOLIMAB) in study 1368-0020, after which eligibility will be re-assessed. Patients who subsequently meet the clinical response definition, will be randomized into the randomized withdrawal part of study 1368-0020, while non-responders will be discontinued from the trial 1368-0020.

#### 3.1.4 Follow-up period:

After completion of treatment period, those patients not rolling over into one of the maintenance trials (1368-0017 or 1368-0020) will continue safety follow-up for an additional 12 weeks after the Visit 6. This observation period covers 16 weeks after the last dose of BI655130 (SPESOLIMAB) which represents around 4-5 half lives of BI655130 (SPESOLIMAB).

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

This operationally seamless trial design, with separate proof-of-concept (Part 1, phase II) and confirmation of efficacy and safety parts (Part 2, phase III), will include pre-defined decision criteria for continuing BI655130 (SPESOLIMAB) doses from Part 1 into Part 2 (see [Section 3.1.2](#)), with the intent of ensuring that a positive proof-of-concept will quickly be followed by the confirmation of efficacy and safety of this new compound with its unique dual mode-of-action in patients with ulcerative colitis. Should Part 1 results, however, indicate the need for design modifications in Part 2 beyond those pre-specified in the protocol (i.e. pre-specified dose selection), then initiation of Part 2 may be postponed until the required modifications have been implemented via a global CTP amendment (e.g. other dose regimens or endpoints).

A parallel group, randomized, double-blind and placebo controlled trial was considered most appropriate to demonstrate PoC, while a PK/PD modelling approach will be employed to select two doses for subsequent confirmation of the efficacy and safety of BI655130 (SPESOLIMAB). The placebo control group in Parts 1 and 2 is thus required to compare both efficacy and safety of BI655130 (SPESOLIMAB) in patients with moderate-to-severely active ulcerative colitis who failed previous biologic treatments. However, all placebo patients failing induction treatment will be offered open label active re-induction treatment as part of the subsequent maintenance trials.

The selection of target patients with moderate-to-severely active ulcerative colitis who failed at least one previous biologic treatment (defined as an inadequate response or loss of response to TNF antagonists and/or vedolizumab) is based on the high unmet medical need in such patients, where persistent mucosal inflammation is associated with an increased risk of disease progression, colon cancer and other complications.

The treatment duration of 12 weeks with BI655130 (SPESOLIMAB) was selected for both parts to exceed the 4-8 weeks duration of induction treatment reflected in the labels of biologics currently approved for IBD [[R15-4915](#), [R17-1974](#)]. This duration has been extended with the aim to maximize treatment efficacy and inform on the optimal induction duration with this new mode of action.

The three active induction dose regimens in part 1 of 300mg i.v. SD, 450mg i.v. q4w and 1200mg i.v. q4w have been selected to represent one partially effective (300mg SD) and two effective dose schedules, based on receptor occupancy rates, ITE and PK/PD results from phase I studies (cf. [Section 4.1.2](#)). Part 1 will allow to establish proof-of-concept and dose/exposure-response relationship, and thus to select the optimal dose regimens for Part 2 of this trial. Part 2 will investigate the two most efficacious, tolerable and safe doses from the Part 1 regimens, unless an unexpected safety or efficacy finding requires dose modification beyond the pre-specified transition scenarios in [Section 3.1.2](#) per CTP amendment.

Thus, this trial design is considered adequate to achieve the objectives outlined above.

### 3.3 SELECTION OF TRIAL POPULATION

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

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

### 3.3.1 Main diagnosis for trial entry

Patients with moderate-to-severely active ulcerative colitis who have failed previous biologic treatments.

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

### 3.3.2 Inclusion criteria

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

1. 18 - 75 years, at date of signing informed consent, males or females
2. Diagnosis of ulcerative colitis  $\geq 3$  months prior to screening by clinical and endoscopic evidence corroborated by a histopathology report
3. Moderate to severe activity (total MCS 6 to 12 with a RBS  $\geq 1$  AND an SFS  $\geq 1$  AND mESS  $\geq 2$  within 7-28 days prior to first dose)
4. Endoscopic activity extending proximal to the rectum ( $\geq 15$  cm from anal verge)
5. Well-documented demonstration of inadequate response or loss of response or have had unacceptable side effects with approved doses of TNF $\alpha$  antagonists (infliximab, adalimumab, golimumab) and/or vedolizumab in the past as per definition in the CTP [Appendix 10.6](#) (screening of both TNF $\alpha$  antagonists-AND-Vedolizumab failure patients will be capped once 48 randomized patients in Part 1 and 117 randomized patients in Part 2 meet this criterion; patients who have already been screened at the time of the cap will continue to be randomized into the study)
6. May be receiving a therapeutic dose of the following:
  - Oral 5-ASA compounds, provided that dose has been stable for at least the 4 weeks immediately prior to randomisation, and/or
  - Oral corticosteroids ( $\leq 20$  mg per day of prednisone or equivalent), provided that dose has been stable for the 2 weeks immediately prior to randomisation, and/or
  - Oral budesonide ( $\leq 9$  mg per day) or beclomethasone dipropionate ( $\leq 5$  mg per day), provided that dose has been stable for the 2 weeks immediately prior to randomisation, and/or
  - Azathioprine, 6-MP or methotrexate, provided that dose has been stable for the 8 weeks immediately prior to randomisation.
  - Probiotics (e.g. *S. boulardii*) provided that dose has been stable for the 4 weeks immediately prior to randomisation.
7. Patients with extensive colitis or pancolitis of  $>10$  years duration or family history of colorectal cancer or personal history of increased colorectal cancer risk must have had a negative colorectal cancer screening within  $<1$  year prior to enrolment (otherwise to be done during screening colonoscopy).
8. Women of childbearing potential (WOCBP) must be ready to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods



meeting these criteria is provided in [Section 4.2.2.2](#) Restrictions regarding women of childbearing potential *Note: A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tuba ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.*

9. Signed and dated written informed consent for 1368.5, in accordance with GCP and local legislation prior to admission into the trial

### 3.3.3 Exclusion criteria

#### 3.3.3.1 Gastrointestinal Exclusion Criteria

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

1. Evidence of abdominal abscess at screening
2. Evidence of fulminant colitis or toxic megacolon at screening
3. Ileostomy, colostomy, or known fixed symptomatic stenosis of the intestine
4. Treatment with:
  - any non-biologic medication (e.g. cyclosporine, tacrolimus or mycophenolate mofetil, intravenous corticosteroids, tofacitinib), other than those allowed per inclusion criteria, which is listed in [Section 4.2.2](#) within 30 days prior to randomisation
  - any biologic treatment with a TNF $\alpha$  antagonist (adalimumab, infliximab, golimumab, certolizumab) or vedolizumab within 8 weeks prior to randomisation. (If drug level testing for previously used biologic treatment confirms no detectable drug level before randomization, patient can be enrolled despite not having completed 8 weeks from last treatment.)
  - any previous treatment with an approved dose of ustekinumab where locally approved and available.
  - rectal 5-ASA, parenteral or rectal corticosteroids (incl. budesonide) within 2 weeks prior to screening
  - any *investigational* non-biologic drug for UC (including but not limited to JAK inhibitors, S1P modulators) within 30 days prior to randomisation
  - any *investigational* biologic for UC (including IL-12 and IL-23 inhibitors; etrolizumab) within 8 weeks. (If drug level testing for previously used biologic treatment confirms no detectable drug level before randomization, patient can be enrolled despite not having completed 8 weeks from last treatment.)
  - any prior exposure to BI655130 (SPESOLIMAB), natalizumab or rituximab
5. Positive stool examinations for *C. difficile* (toxin A/B – test positive) or other intestinal pathogens < 30 days prior to screening
6. Have had previous surgery or are anticipated to require surgical intervention for UC

7. Evidence of colonic moderate/severe mucosal dysplasia or colonic adenomas, unless properly removed
8. Primary sclerosing cholangitis
9. Faecal transplant  $\leq$  30 days prior to randomisation

### 3.3.3.2 Infectious Disease Exclusion Criteria

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

### 3.3.3.3 General Exclusion Criteria

14. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin, or history of cervical cancer in situ (treated  $>$ 3years); patients with remote history of malignancy ( $\geq$ 5 years prior) may be considered and have to be discussed with sponsor case-by-case
15. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomization or planned during study conduct, e.g. hip replacement.
16. Pathological safety lab parameters: haemoglobin  $<$  9 g/dL, total white blood count (WBC)  $<$  3000 cells/ $\mu$ l, neutrophils  $<$  1000 cells/ $\mu$ l, thrombocytes  $<$  100.000/ $\mu$ l, creatinine  $\geq$  2 mg/dL, total bilirubin  $>$  2 x ULN with ratio of direct/indirect  $>$ 1 (patients with Gilbert's syndrome are not excluded), Alkaline Phosphatase  $>$ 3 x ULN. – measured and confirmed by Central laboratory at screening visit.

17. Currently enrolled in another investigational device or drug study (for investigational studies except any patient who have completed investigational drug treatment including residual effect period)
18. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
19. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than ulcerative colitis, surgical procedure, medical examination finding (including vital signs and electrocardiogram (ECG)), or laboratory value at the screening visit outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data
20. Any psychiatric or social problems possibly interfering with ability to comply with all study visits/procedures
21. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.

### 3.3.4 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole (“withdrawal of consent”) with very different implications, please see [Sections 3.3.4.1](#) and [3.3.4.2](#) below.

Every effort should be made to keep the randomised patients in the trial: if possible on treatment, or at least to collect important trial data.

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomization, as well as the explanation of the consequences of withdrawal.

The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and CRF.

#### 3.3.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication. Please refer to [Section 4.2.2](#) for restricted medication during this trial. The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- If a hepatic injury alert (as defined in [Section 5.2.6.1](#)) is detected without identification of an alternative cause in the work-up according to the “DILI checklist”, discontinuation of treatment with study drug should be considered.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing

or able to stick to the trial requirements in the future. For individual stopping rules related to specific adverse events, please see [Section 4.2.1](#) Other treatments and emergency procedures.

Patients who terminate study drug early should be encouraged to follow all study procedures per the [Flow Chart](#) until week 12, but not receive any more study drug at the respective visits. Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the [Flow Chart](#) (FC) and [Section 6.2.3](#). For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the CRF. These data will be included in the trial database and reported.

#### 3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision.

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see [Section 3.3.4.1](#) above.

#### 3.3.4.3 Discontinuation of the trial by the sponsor

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

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

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

## 4. TREATMENTS

### 4.1 INVESTIGATIONAL TREATMENTS

#### 4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Description of test product, BI655130 (SPESOLIMAB)

Substance:	BI 655130 (BI655130 (SPESOLIMAB))
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Anti-human IL-36 Receptor mAb
Molecular weight:	146 kDa
Unit strength:	150mg/vial (20mg/mL), 7.5mL fill volume
Route of administration:	Intravenous infusions
Posology:	300 mg single dose at Week 0; or 450 mg, 750 mg or 1200 mg at Week 0, 4 and 8
Duration of use:	12 weeks

Table 4.1.1: 2 Description of test product placebo to BI655130 (SPESOLIMAB)

Substance:	Placebo to BI 655130 (BI655130 (SPESOLIMAB)); 7.5mL fill volume
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Not applicable
Molecular weight:	Not applicable
Unit strength:	Not applicable
Route of administration:	Intravenous infusions
Posology:	Weeks 0, 4 , and 8
Duration of use:	12 weeks

Table 4.1.1: 3 Description of test product BI655130 (SPESOLIMAB)

Substance:	BI 655130 (BI655130 (SPESOLIMAB))
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Anti-human IL-36 Receptor mAb
Molecular weight:	146 kDa
Unit strength:	BI655130 (SPESOLIMAB) 300 mg/vial (60mg/mL), 5 mL fill volume
Route of administration:	Intravenous infusions
Posology:	300 mg single dose at Week 0; or 450 mg, 750 mg or 1200 mg at Week 0, 4 and 8
Duration of use:	12 weeks

Table 4.1.1: 4 Description of test product placebo to BI655130 (SPESOLIMAB)

Substance:	Placebo to BI 655130 (BI655130 (SPESOLIMAB)), 5mL fill volume
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Not applicable
Molecular weight:	Not applicable
Unit strength:	Not applicable
Route of administration:	Intravenous infusions
Posology:	Weeks 0, 4 , and 8
Duration of use:	12 weeks

#### 4.1.2 Selection of doses in the trial

The aim of part 1 of the study is to achieve proof-of-clinical-concept and select dose regimens for confirmatory testing in part 2. The BI655130 (SPESOLIMAB) dose regimens have been selected to represent a potential suboptimal dose (300mg SD) and two effective doses, one near (450mg, q4w) and one at (1200mg, q4w) the plateau of the dose response curve, based on receptor occupancy rates, ITE and PK/PD results obtained in phase I studies, indicating that doses  $\geq 3$  mg/kg achieved high target engagement in peripheral blood of

healthy volunteers, which has been sustained for at least 22 weeks after last dose, which represents the latest follow-up time point (IB [c03320877-07](#)). Thus, under consideration of the half life of ~4-5 weeks and the extended target engagement in healthy volunteers peripheral blood, the 300mg SD regimen, which correspond to  $\geq 3$ mg/kg body weight for the vast majority of UC patients in a typical UC trial (assuming an average weight of approximately  $75 \pm 15$ kg; [R15-1340](#)), this dose could represent a biologically active dose. However, multiple fold higher doses are likely to be required to achieve larger effects in the gut tissue of patients with UC, due to their expected higher clearance rate, target expression and the need to penetrate into the tissue. To accommodate for these effects, 4.5-fold (450mg q4w) and 12-fold (1200mg q4w) higher doses will also be tested in part 1 of this trial and are likely to be near or at the plateau of the dose response curve. In summary it is anticipated that the proposed doses of 300 mg SD, 450 mg q4w and 1200 mg q4w over the 12-week period will support a robust characterization of the dose-response and exposure-response relationship.

The doses for part 2 will be selected based on the results from part 1 as discussed above (cf. [Section 3.1](#)) and are expected to provide sufficiently differentiated PK exposures to translate into differential efficacy/safety and to allow appropriate exposure/ response analyses after completion of part 2. The criteria for dose selection in part 2 are specified in [Section 3.1.2](#).

#### 4.1.3 Method of assigning patients to treatment groups

During visit 2, eligible patients in both study parts will be randomised to receive 12 weeks of treatment (i.e. three administrations) with Placebo or either of the two (part 2) or three (part 1) active dose regimens at equal distribution and stratified according to previous BIO experience (TNF-AND-Vedo versus TNF-OR-Vedo), and concomitant corticosteroid therapy at visit 2/randomization (yes/no). In addition, a stratification for Japan versus non-Japan will be done in order to assure that sufficient patients per treatment group are recruited specifically to support individual country submission in Japan; this strata will be treated as an operational strata and will not be included into the analyses of the primary endpoint. In order to limit the proportion of last-line-treatment patients, screening of both TNF-AND-Vedo failure patients will be capped once 48 randomized patients in Part 1 and 117 randomized patients in Part 2 meet this criterion; the patients who have been already screened at time of implementation of the cap will continue screening procedures in preparation for randomization into the study. The assignment and capping of enrolment into the TNF-AND-Vedo stratum will be done via Interactive Response Technology (IRT).

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

#### 4.1.4 Drug assignment and administration of doses for each patient

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

In case of safety concerns, e.g., due to infusion reactions, it is in the discretion of the investigator or his/her designee to adapt the infusion scheme, including but not limited to slowing down the infusion rate, interrupting the infusion and - provided no further safety concern exist - restarting at a slower rate. Further, based on his medical judgment he/she will

provide medications such as steroids, etc., as needed (cf. [Section 4.2.1](#) for handling of infusion reactions). Detailed instructions for handling of infusion reactions are also provided in the ISF.

For administration of the infusion, an intravenous indwelling catheter is placed into an arm vein of the subject.

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

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

#### **4.1.5 Blinding and procedures for unblinding**

##### **4.1.5.1 Blinding**

For Part 1 of the study, patients, investigators, as well as sponsor personnel involved in the trial conduct or analysis, will remain blinded with regard to the randomised treatment assignments until after the database lock for the final week 12 analysis on Part 1 has been performed. At this time, all dosing visits will have been completed, although some patients who did not roll-over directly into the maintenance trial (1368-0017) will continue the safety follow-up. Since the final analysis of part 1 of the trial in terms of both efficacy and safety will be complete, and because no further patient dosing visits are planned in this trial part, the randomization codes for part 1 will be formally unblinded subsequent to the week 12 database lock, and the part 1 trial results will be published to support enrolment into part 2 of the study.

For Part 2 of the study, patients, investigators, as well as sponsor personnel involved in the trial conduct or analysis, will remain blinded with regard to the randomised treatment assignments until after the database lock for the final analysis on part 2 of the current trial has been performed. Once the database lock has been performed, the sponsor will be officially unblinded to the randomization details for this trial part and the part 2 trial results will be published to support enrolment into subsequent studies. Patients and investigators will continue to remain blinded to the individual treatment allocations in part 2 of the current trial through the end of the subsequent maintenance trial, 1368-0020. A logistics plan will be developed describing the mechanisms to be put in place to assure that the patients and investigators remain blinded to individual patient data, and which is to be finalized prior to the treatment unblind for the final analysis on Part 2.



For each study part, the randomisation codes will be provided to bio-analytics prior to last patient out (or prior to last patient out for the week 12 analysis on Part 1) to allow for the exclusion from the analyses of PK samples taken from placebo patients. Bio-analytics will not disclose the randomisation code or the results of individual measurements for each trial part until the applicable trial part has been officially un-blinded to the sponsor. Serum drug levels and demographic data together with treatment assignments and dosing information may be made available to individuals outside of the trial team for the purpose of PK dataset generation and analysis in accordance with sponsor's standard procedures.

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

#### 4.1.5.2 Unblinding and breaking the code

An emergency code break (envelope) will be available to the investigator / pharmacist / investigational drug storage manager (for Japan: only to the investigator). This code break may only be opened in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. If the code break for a patient is opened, the sponsor must be informed immediately. The reason for opening the code break must be documented on the envelope and/or appropriate CRF page along with the date and the initials of the person who broke the code.

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

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

Treatment unblinding will be performed prior to each DMC meeting as a prerequisite for generation of the applicable DMC summaries required, subsequent to database lock for the 12-week final analysis on Part 1 of the study, as well as subsequent to the final trial database lock at which time analyses on Part 2 of the study will be done. Treatment unblind for study Part 1 will be officially released once database lock for the week 12 final analysis on part 1 has been performed. Treatment unblind for study Part 2 will be officially released to the sponsor once database lock for the final analysis of part 2 of the current trial has been performed; mechanisms to protect the blind of patients and investigators for this trial part will be implemented through the end of the subsequent maintenance trial, 1368-0020 and will be described in a separate logistic plan (see [Section 4.1.5.1](#)).

#### 4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

#### 4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately. Refer to ISF. Trial medication must be securely stored, e.g. in a locked refrigerator or at a pharmacy. The medication may only be dispensed to trial patients according to the Clinical Trial Protocol (CTP) by authorized personnel as documented in the trial staff list. IMP will only be prepared for infusion just prior to infusion.

#### 4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB / ethics committee ,
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (if applicable).

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

The investigator/pharmacist/ investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

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

manager must verify that all unused drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

## 4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

### 4.2.1 Other treatments and emergency procedures

If the patient requires additional medical therapy or dose increase of baseline ulcerative colitis medication to treat the underlying ulcerative colitis due to disease worsening (cf. [Table 3.1.1](#) Study Definitions), the study drug must be discontinued and patients may receive conventional treatment for active disease. Such patients should stay in the trial but will be considered as treatment failures in the intent-to-treat (ITT) analysis.

If infusion or anaphylactic reaction had already occurred in the very same patient in the past, pre-treatment with steroids before next IMP administration is permitted as secondary prophylaxis.

Systemic steroids dosed intravenously or orally for less than 24 hours as treatment of infusion or anaphylactic reactions are permitted and do not lead to treatment discontinuation nor to assignment as treatment failures in the ITT analysis.

Management of Adverse Events:

#### Systemic hypersensitivity including infusion reaction and anaphylactic reaction

In case of systemic hypersensitivity including infusion reactions and anaphylactic reaction emerging during or after infusion of study drug, the investigator should consider in accordance with severity of the reaction and local standard of care to

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

Also draw a plasma sample for IgE and ADA as detailed in the Lab Manual (Section 10 of the ISF). Consider also the evaluation of histamine, serum tryptase, and complement components.

In case of systemic hypersensitivity including infusion reaction and anaphylactic reaction, based on patient's clinical course and medical judgment, the infusion may be re-initiated in case of mild or moderate infusion reactions (according to RCTC grading of "allergic reaction / hypersensitivity" in ISF) at lower speed with gradual increase to complete the infusion as detailed in the Instructions for Preparation and Handling of BI655130 (SPESOLIMAB)/Placebo in the Investigator Site File.

In case of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA ([Appendix 10.7 R11-4890](#)) suspected to be caused by the trial medication, the investigator should discontinue treatment with study drug

When a non-acute hypersensitivity reaction related to immune complexes (i.e., serum sickness) is suspected, please draw a sample for the laboratory assessment for circulating immune complexes.

Severe infections (according to RCTC grading in [Appendix 10.8](#)), serious infections, opportunistic or mycobacterium tuberculosis infection

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

#### Malignancies

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

## 4.2.2 Restrictions

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

Table 4.2.2.1: 1 Restrictions regarding previous and concomitant treatment

Medication or class of medications	Restriction
any biologic <i>approved</i> for UC adalimumab, infliximab, golimumab, vedolizumab	Not allowed from 8 weeks prior to randomisation or from time when no detectable drug level was confirmed until end of the trial For use as rescue medication, refer to <a href="#">Section 4.2.1</a>
any <i>investigational or non-approved</i> biologic for UC (incl. ustekinumab, other IL-23 inhibitors, etrolizumab, certolizumab)	not allowed from 8 weeks prior to randomisation or when negative drug level is detected before randomization until end of the trial For use as rescue medication, refer to <a href="#">Section 4.2.1</a> .
Any prior treatment with a dose of Ustekinumab approved for UC only applicable where locally approved and available	Any prior exposure is prohibited
Any <i>non-biologic</i> immunomodulator, other than those allowed per inclusion criteria #6 (incl. cyclosporine, tofacitinib and other JAK inhibitors, tacrolimus, sirolimus, mycophenolate mofetile)	Not allowed from 30 days prior to randomisation until end of the trial For use as rescue medication, refer to <a href="#">Section 4.2.1</a> .
Any immunomodulator allowed per inclusion criteria #6 (Azathioprine, 6-mercaptopurine or methotrexate)	Only allowed during the trial, if dose is stable for at least 8 weeks prior to randomisation until end of the trial For use as rescue medication, refer to <a href="#">Section 4.2.1</a> .
Any biologic for treatment for any other indication ( e.g. Dupilumab for the treatment of atopic dermatitis)	Not allowed from 8 weeks prior to randomisation until end of the trial
Fecal microbiota transplantation (FMT)	Not allowed from 30 days prior to randomisation until end of the trial
BI655130 (SPESOLIMAB), natalizumab or rituximab	Any prior exposure is prohibited
5-ASA	<u>Oral administration:</u> Only allowed during the trial, if dose is stable for at least 4 weeks prior to randomisation until end of the trial <u>Rectal route of administration (5-ASA):</u> Not allowed from 2 weeks prior to screening up to end of the trial For use as rescue medication, refer to <a href="#">Section 4.2.1</a> .

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

Medication or class of medications	Restriction
Corticosteroids (incl. budesonide)	<p><u>Oral administration:</u></p> <p>Oral steroids are only allowed if indicated for treatment of UC and at a dose of <math>\leq 20</math>mg per day of prednisone or equivalent and with stable dose for at least 2 weeks prior to randomisation and throughout the trial.</p> <p>Short (&lt;7 days) decrease of dose for treatment of AEs <u>with subsequent increase back to initial baseline dose level is allowed</u></p> <p>Oral budesonide (<math>\leq 9</math> mg per day), provided that dose has been stable for the 2 weeks immediately prior to randomisation</p> <p>Oral beclomethasone dipropionate (<math>\leq 5</math> mg per day), provided that dose has been stable for the 2 weeks immediately prior to randomisation</p> <p><u>Parenteral administration:</u></p> <p>Not allowed from 2 weeks prior to screening up to end of the trial.</p> <p>Note: parenteral steroids dosed for less than 24hours as treatment of infusion or anaphylactic reactions are permitted.</p> <p><u>Rectal administration:</u></p> <p>Not allowed from 2 weeks prior to screening up to end of the trial</p> <p>Note: steroids will be tapered (or discontinued for budesonide) in subsequent maintenance trial.</p> <p>For use of steroids as rescue medication, refer to <a href="#">Section 4.2.1</a>.</p> <p>Allowed steroid treatments:</p> <p>Short-term use (&lt;7 days) of systemic (oral or parenteral) corticosteroids is allowed for treatment of AE not related to the underlying UC from 4 weeks prior to randomisation until end of the trial.</p> <p>Locally administered steroids as e.g. intra-articular, nasal inhalation or intra-ocular administration are allowed.</p>
NSAID	<p>Chronic use (i.e. <i>daily</i> use for &gt;2 weeks) not allowed from 2 weeks prior to screening up to end of the trial</p> <p>(Note: occasional use of NSAIDs and acetaminophen for headache, arthritis, myalgias, menstrual cramps, etc., and daily use of baby or low dose (81-162.5mg) aspirin for cardiovascular prophylaxis are permitted.)</p>
Probiotics	<p>Only allowed during the trial, if dose is stable for at least 4 weeks prior to randomisation until end of the trial</p>
Live ofattenuated vaccines	<p>Not allowed from 6 weeks prior to screening up to end of the trial</p>
Antibiotics for IBD	<p>Not allowed from 4 weeks prior to screening up to end of the trial</p>

#### 4.2.2.2 Restrictions regarding women of childbearing potential

Women of childbearing potential must use the contraception methods described below. This information is provided to the patients in the patient information.

Highly effective methods of birth control for female participants.

- Combined (estrogen and progestogen containing) hormonal birth control associated with inhibition of ovulation.
- Progestogen-only hormonal birth control associated with inhibition of ovulation.
- Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS).
- Tubal occlusion (blocking of the fallopian tubes).
- Vasectomy of sexual partner (proven effective by absence of sperm on the ejaculation).
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception.

### 4.3 TREATMENT COMPLIANCE

Study medication will be administered in accordance with the protocol, under supervision of the investigating physician or a designee at the site. Any missed dose has to be documented and reported to the CT Manager.

## 5. ASSESSMENTS

### 5.1 ASSESSMENT OF EFFICACY

The changes in UC activity during the trial will be assessed at visits including endoscopies using the modified Mayo score (disease activity score, not including the PGA (physician global assessment) item, but including the modified ESS (any degree of friability defines a score of at least 2), and the Roberts histopathology index (RHI). In addition, the total Mayo score (including PGA in addition to modified Mayo Score) will be explored as secondary endpoint to facilitate indirect comparisons against currently approved or investigational drugs. At all visits, the partial MCS (pMCS; all subscores except mESS) will be recorded to assess clinical disease activity.

Mucosal healing will be assessed by endoscopy using a blinded central reader and will be defined as a mESS  $\leq$  1. Local reading will be recorded for exploratory reasons, and to be used for endpoint assessment if central reading is not available for technical reasons.

Please refer to [Appendix 10.1](#) (Mayo Score/modified Mayo score) and to [Appendix 10.2](#) (Roberts histopathology index) for further details.

### 5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

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

#### 5.2.1 Physical examination

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

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



### 5.2.2 Vital signs

Vital signs evaluations will be performed at visits as shown in the [Flow Chart](#). This includes temperature, pulse rate, systolic/diastolic blood pressure and respiratory rate. Respiratory rate, pulse rate, and blood pressure will be measured after patients have been sitting comfortably for at least five minutes. Measurement of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements. At dosing visits (Visits 2, 4 and 5) vital signs evaluations will be performed pre-dose and additional evaluations will be taken approximately at 5 minutes post-dose and 60 minutes post-dose.

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

### 5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in [Table 5.2.3:1](#). For the sampling time points please see the flowchart.

All analyses will be performed by a central laboratory, the respective reference ranges will be provided in the ISF. A local laboratory may be used for selected tests in exceptional cases. Patients should be fasting for at least 8 hours prior to the blood sample being taken (except screening visit).

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to [Section 5.2.6](#)). Laboratory results (i.e. all safety laboratory and clinical laboratory data relevant for current clinical practice) of the patients will be available in real time to the respective investigator (via laboratory reports) and to the sponsor (via the central laboratory website) and selected abnormal laboratory alerts will be flagged to the site and sent to sponsor in real time.

Clinically relevant abnormal findings will be reported as baseline conditions or AEs. A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed using an unscheduled visit laboratory kit and should be repeated until normalization or stabilization or until an alternative explanation has been found. Abnormal laboratory values will be also graded for intensity by using RCTC Version 2.0 criteria [[R13-3515](#)].

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

Table 5.2.3: 1 Exclusionary testing<sup>1</sup>

<b>Category</b>	<b>Test name</b>
Infections screening (only at screening)	Hepatitis B Surface Antigen (qualitative) Hepatitis B core Antibody HBV-DNA (quantitative, PCR) <sup>2</sup> Hepatitis C Antibodies (qualitative) HIV-1, and HIV-2 Antibody (qualitative)
TB screening	QuantiFERON®-TB <sup>3,4</sup>
Serum Pregnancy test (only for female patients of childbearing potential)	Human Serum Chorionic Gonadotropin
Stool studies to evaluate for enteric pathogens	Salmonella Shigella Yersinia Campylobacter Vibrio E. coli O157/H7 Clostridia difficile toxin Enteric parasites and their ova (including Cryptosporidia)

<sup>1</sup> At screening only (visit 1)

<sup>2</sup> A HBV-DNA should be conducted if Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative (definition of occult HBV infection: B core Antibody is positive, Hepatitis B Surface Antigen is negative; HBV DNA detectable).

<sup>3</sup> There is the trial site option to perform a PPD skin test

<sup>4</sup> If the 1st QuantiFERON®-TB test result is undetermined, a re-test should be performed. If the retest QuantiFERON-TB test result is undetermined, a PPD skin test should be performed. This applies for QuantiFERON®-TB test at screening as well as at EOS visit.

Table 5.2.3: 2 Laboratory tests

<b>Category</b>	<b>Test name</b>
Haematology	Hematocrit (Hct) Hemoglobin (Hb) Glycosylated Hbc (HbA1c) (only at screening) Red Blood Cell Count/ Erythrocytes Reticulocyte Count White Blood Cells / Leukocytes Platelet Count/ Thrombocytes
Diff. Automatic	Neutrophils (relative and absolute count) Eosinophils (relative and absolute count) Basophils (relative and absolute count) Monocytes (relative and absolute count) Lymphocytes (relative and absolute count)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin time (INR) Fibrinogen
Enzymes	AST (GOT) ALT (GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Amylase Lipase
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Substrates	Glucose BUN (blood urea nitrogen) Uric acid Creatinine eGFR (estimated by CKD-EPI formula) (only at screening) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Troponin (Reflex, in case of elevated CK) Protein, Total Albumin C-Reactive Protein (CRP) (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol

Table 5.2.3: 2 Laboratory tests (cont.)

<b>Category</b>	<b>Test name</b>
Specific gamma-globulin quantification	IgE <sup>1</sup> , IgG
Urine Pregnancy test (only for female patients of childbearing potential)	Human Chorionic Gonadotropin in urine
Serum Pregnancy test (only for female patients of childbearing potential if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Hormones (only at screening)	TSH (free T3 and free T4 in case of abnormal TSH result)
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leukocytes Urine pH
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes
Urine (only at screening)	Albumin (quantitative)
Faecal sample	Calprotectin Lactoferrin
Infections screening	HBV-DNA (quantitative) EOT Visit <sup>2</sup>
QuantiFERON-TB test	QuantiFERON®-TB <sup>3,4,5</sup>

<sup>1</sup> Only in case of allergic reaction

<sup>2</sup> HBV-DNA in case of occult HBV infection (for definition see [Table 5.2.3: 1](#) footnote 2)

<sup>3</sup> There is the trial site option to perform a PPD skin test instead, if Quantiferon testing is not feasible

<sup>4</sup> If the 1st QuantiFERON®-TB test result is undetermined, a re-test should be performed. If the retest QuantiFERON-TB test result is undetermined, a PPD skin test should be performed. This applies for QuantiFERON®-TB test at screening as well as at EOS visit.

<sup>5</sup> The test will only be done at the end of study (EOS) visit in patients not continuing treatment in the subsequent maintenance study.

## 5.2.4 Electrocardiogram

The 12-lead ECGs will be recorded as scheduled in the flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis.

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

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

### 5.2.5 Other safety parameters

In case of an infusion reaction monitor the patient per standard of care, grade the intensity of the reaction according to RCTC grading (cf. ISF) and proceed as described in [Section 4.2.2.1](#). Also draw plasma sample for IgE and ADA (anti-drug antibodies), as detailed in the CTP [Section 5.2.3](#) and the lab manual.

All cases of malignancies that are detected during the trial will be reported as SAEs. Patients with a history of malignancy (except for specific cancers) will be excluded from this trial per the exclusion criteria ([Section 3.3.3](#)).

### 5.2.6 Assessment of adverse events

#### 5.2.6.1 Definitions of AEs

##### **Adverse event**

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

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

##### **Serious adverse event**

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
- or
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

For Japan only: the following events will be handled as “deemed serious for any other reason”. AEs which possibly lead to disability will be reported as SAEs.

#### **AEs considered “Always Serious”**

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in [Section 5.2.6.2](#), subsections “AE Collection” and **AE reporting to sponsor and timelines**”

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

The latest list of “Always Serious AEs” can be found in the eDC system. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events should always be reported as SAEs as described above.

#### **Adverse events of special interest (AESIs)**

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

The following are considered as AESIs:

- Systemic hypersensitivity including infusion reaction and anaphylactic reaction
  - Any suspicion of severe infusion reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA ([Appendix 10.7 R11-4890](#)).
- Severe infections (according to RCTC grading in [Appendix 10.8](#))
- Opportunistic and mycobacterium tuberculosis infections
  - These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, post-transplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous

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

### Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- a. ALT or AST >5x ULN
- b. ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- c. AST and/or ALT  $\geq$ 3 fold ULN combined with an elevation of total bilirubin  $\geq$ 2 fold ULN measured in the same blood draw sample

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed. If an alternative cause for the hepatic injury cannot be identified in the follow-up assessments specified in the "DILI checklist", discontinuation of treatment with study drug should be considered.

### Intensity (severity) of AEs

The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by OMERACT [[R13-3515](#)]. Refer to the ISF for intensity/severity classification. Intensity options are:

Grade 1	mild
Grade 2	moderate
Grade 3	severe
Grade 4	life-threatening

### Causal relationship of AEs

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

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 diminished).

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
- Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

#### 5.2.6.2 Adverse event collection and reporting

##### **AE Collection**

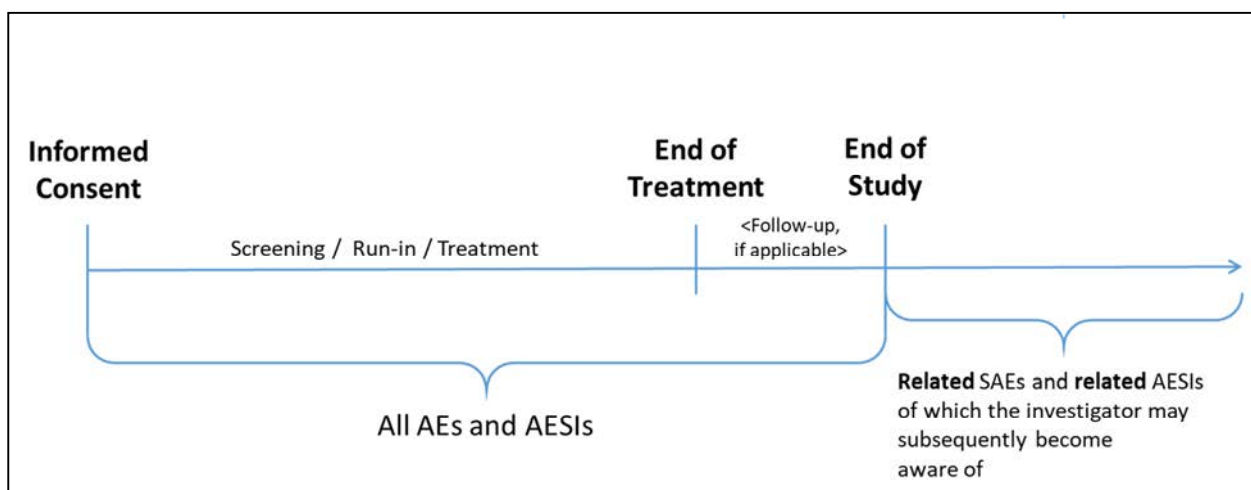
The investigator shall maintain and keep detailed records of all AEs in the patient files. The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the first dose of trial medication in the extension trial:
    - all AEs (non-serious and serious) and all AESIs.
  - For patients not rolling over into subsequent open label extension studies:
    - from signing the informed consent onwards until the individual patient's end of trial( including 16 weeks follow-up visit after last treatment dose) :
    - all AEs ( non-serious and serious) and all AESIs.
- After the individual patient's end of the trial:  
the Investigator does not need to actively monitor the patient for AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment



related AESIs of which the Investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form, but not on the CRF.

Figure 5.2.6.2: 1 Adverse event collection and reporting



### AE reporting to sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process 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 send the BI SAE form.

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

### Information required

For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable.

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

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

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those

persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

### **Pregnancy**

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

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

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

## **5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS**

### **5.3.1 Assessment of pharmacokinetics**

BI655130 (SPESOLIMAB) concentrations will be reported descriptively. No PK parameters will be calculated. PK data will be incorporated into a larger pharmacometric analysis with other trials of the BI655130 (SPESOLIMAB) project. Also, ADAs will be measured and their impact on PK will be assessed. The relationship between PK and selected efficacy endpoints, biomarkers and AEs may be assessed. PK and demographic data together with treatment assignments and dosing information may be made available to individuals outside of the trial team for the purpose of PK dataset generation in accordance with sponsor's standard procedures.

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

### **5.3.2 Methods of sample collection**

Optional use of plasma aliquots: Plasma samples may be used for further methodological investigations (ex: for future stability testing). However, only data for measuring the analyte and antibody responses to the analyte will be generated by these investigations. The PK study samples will be discarded after completion of the investigations but not later than 5 years after the final study report has been signed. Following the finalization of the ADA

bioanalytical report, ADA aliquots will be transferred to long term storage for possible/optional ADA characterization in the future.

#### 5.3.2.1 Plasma sampling for PK analysis

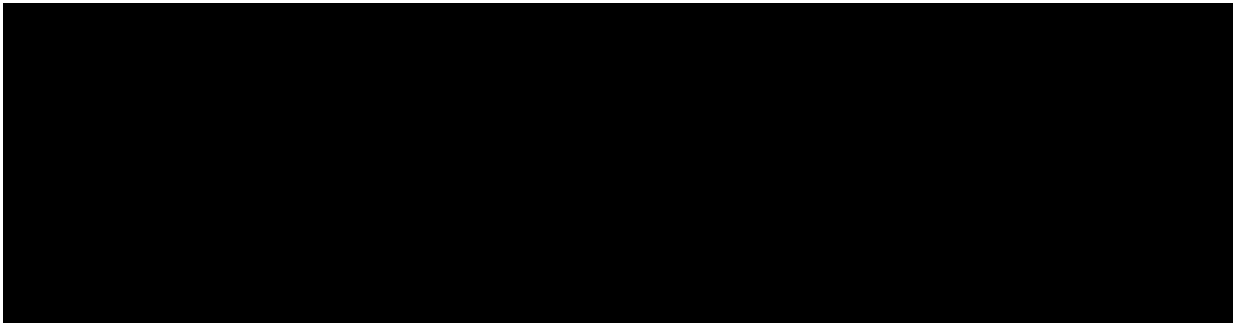
For quantification of BI655130 (SPESOLIMAB) plasma concentrations, blood will be taken from a forearm vein into a K2EDTA (ethylenediaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the [Flow Chart](#) under plasma PK. Handling procedures can be found in the lab manual (Section 10 of the ISF).

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 study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

#### 5.3.2.2 Plasma sampling for ADA assessment

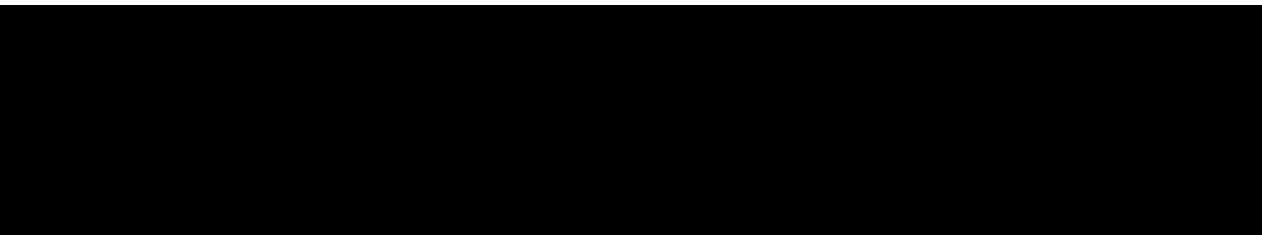
For ADA assessment, blood will be taken from a forearm vein into a K2EDTA anticoagulant blood-drawing tube at the time points listed in the [Flow Chart](#) under plasma ADA. Handling procedures can be found in the Laboratory manual (Section 10 of the ISF).

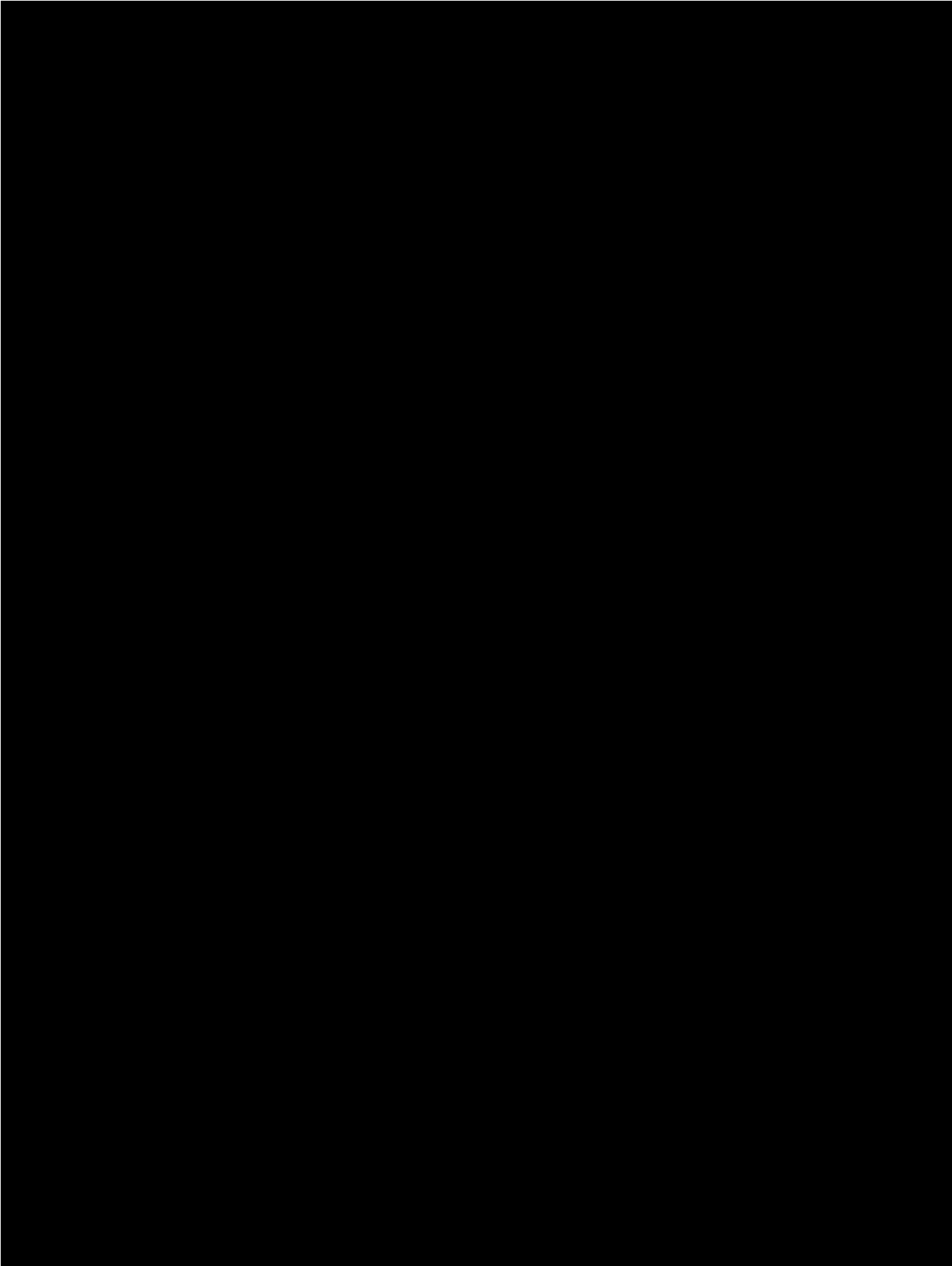
After completion of the trial, the plasma samples may be used for further methodological investigations, e.g. for stability testing. However, only data related to the ADAs will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations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

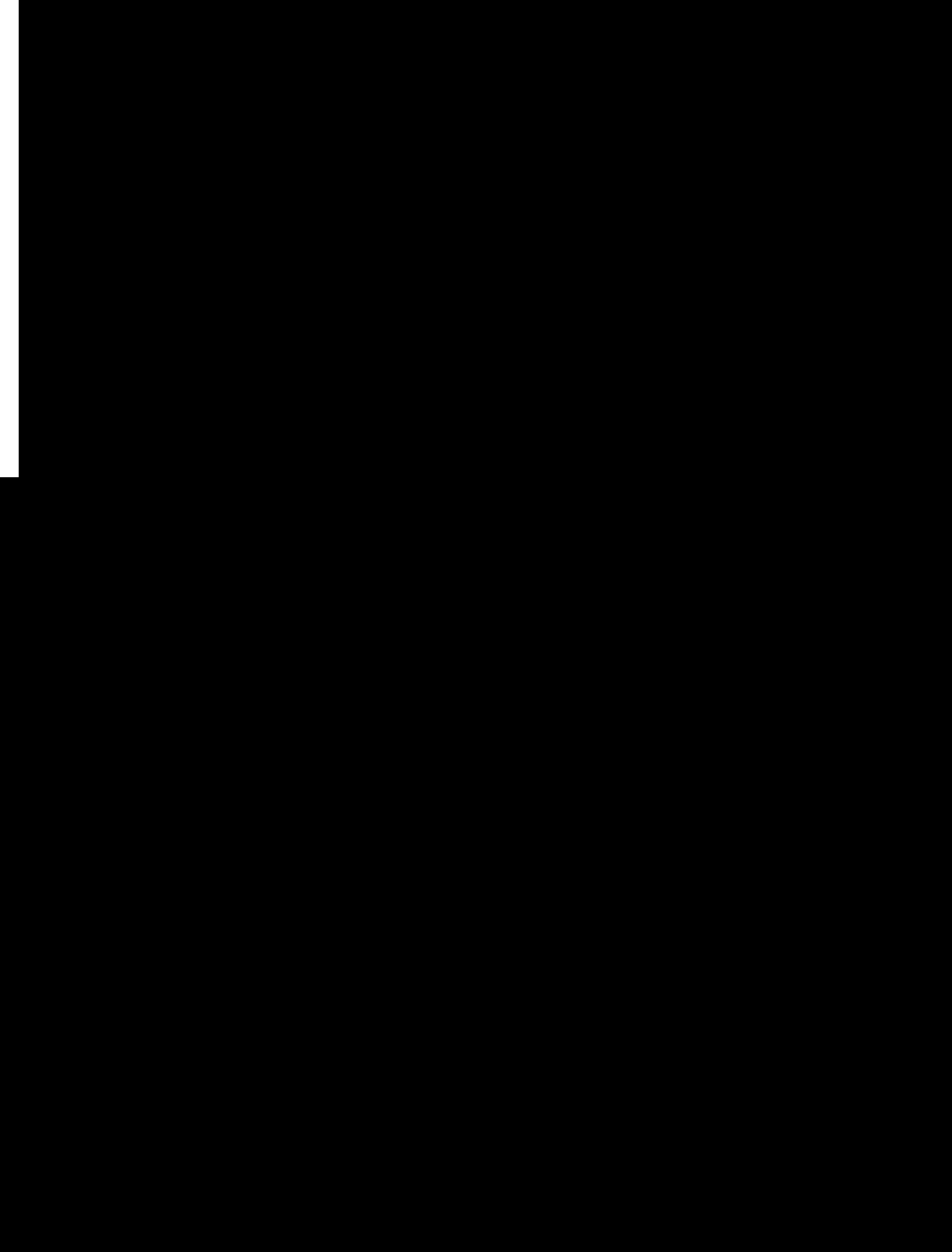


#### 5.3.4 Pharmacokinetic – pharmacodynamic relationship

The PK and PD data from this study will be used for investigation of the PK/PD relationship of BI655130 (SPESOLIMAB).







## 5.5 OTHER ASSESSMENTS

### Colonoscopy, Sigmoidoscopy

Colonoscopy and sigmoidoscopy will be performed according to standard of care. Local and central reading will be performed according to information in ISF. Histopathology will be performed at a central laboratory.

### **Biopsy Collection Instructions**

**With proper consent, two sets of three biopsies (a total of 6 biopsies) will be obtained during each endoscopy procedure in the following order: Three (3) [REDACTED] for Histology and Immunohistochemistry (IHC) analysis**

All biopsies taken at a visit should be taken in close proximity to each other (within 3 cm). In patients where involved area extends to  $\geq 20$  cm proximal the anal verge the biopsies should be taken between 15 and 20 cm.

In patients where involved area extends to  $< 20$  cm proximal the anal verge the biopsies should be taken at the most proximal boundary of the involved site (at least 1 cm inside the boundary).

The distance of each biopsy sampling from anus must be noted down in the CRF for each subject.

All subsequent post-treatment biopsies for a subject should be taken approximately at the same distance from the anus, not more than 3 cm distal to the original site of baseline biopsies. These biopsies are taken irrespective of the location of the boundary of the involved site.

Biopsies from the bed of the ulcers are not permitted.

Optional assessment of drug level in blood of biologics used for the treatment of UC before screening for this study will be performed prior to randomization. Analysis will be done using a central laboratory vendor. This assessment will allow to randomize respective patients within a period shorter than 8 weeks when negative drug level of previous biologics is detected.

### Patient-reported outcomes (PROs)

The following PROs will be used in trial 1368-0005:

### **IBDQ (Inflammatory Bowel Disease Questionnaire)**

The IBDQ is the most frequently used disease-specific PRO instrument for the measurement of health-related quality of life in clinical trials with patients with IBD. It contains 32 questions on bowel and systemic symptoms as well as emotional and social functioning. The aim of including the IBDQ is to offer a patient-reported perspective on a range of symptoms

and impacts that have been shown to be relevant to patients with UC. Its psychometric properties in patients with IBD, including UC, are well-documented [[R97-3596](#), [R16-0240](#), [R97-3472](#)], and it has been used in several UC clinical trials [[R17-2222](#), [R15-1340](#), [R17-2223](#), [R17-2217](#), [R17-2221](#)]. In a recent systematic literature review of disease-specific health-related quality of life questionnaires in IBD, it emerged as the measure with the best overall psychometric properties [[R16-0031](#)].

The response options describe the magnitude or frequency of impairment from 1 (most severe) to 7 (no impairment), and the sum score (range: 32-224 points) is reported. A score change of 16 is reported to reflect the minimal clinically important difference (MCID) [[R16-0240](#)]. The recall period is 2 weeks.

### **SF-36 (36-Question Short Form) (part 2 only)**

The SF-36 is a widely used instrument to measure health-related quality of life among healthy subjects and patients with acute and chronic conditions. It consists of 36 questions [[R97-1093](#)]. SF-36 scores can be compared across different populations of patients and healthy subjects. The purpose of the SF-36 in this study is to assess general health related quality of life of patients with UC. The SF-36 has been frequently used in UC and is judged to have good psychometric properties [[R15-5976](#), [R17-2222](#), [R17-2221](#)].

Response options vary but are mostly a 5- or 3-item Likert scale. Subscales (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health) are reported individually and summarised as Physical Component Summary (PCS) and Mental Component Summary (MCS) scores (range: 0-100, with a score of 50±10 considered to reflect the US norm [[R16-0032](#)]). A 4 point difference is recommended as an MCID threshold for between-groups comparisons of the PCS and MCS [[R16-0033](#), [R15-5876](#)]. Given the nature of UC, the acute version of the SF-36 with a 1-week recall period will be used.

### **FACIT-Fatigue (Functional Assessment of Chronic Illness Therapy – Fatigue) (part 2 only)**

The FACIT-Fatigue is a 13-item questionnaire [[R10-6433](#), [R07-4311](#)] that assesses self-reported fatigue and its impact upon daily activities and function.

The purpose of the FACIT-Fatigue in this study is to assess the impact of fatigue on subjects with UC. It has been reported to have good reliability, validity and responsiveness for patients with UC [[R15-5869](#), [R15-5866](#), [R15-5867](#)].

Answers are based on a 5-point Likert scale. Responses of “not at all,” “a little,” “somewhat,” “quite a bit,” and “very much” are available for each question, and correspond to scores of 0, 1, 2, 3, and 4, respectively (total score range: 0-52). An MCID of 3-4 points in change score has been reported [[R16-0029](#)]. The recall period for items is 7 days.

### **WPAI-UC (Work Productivity and Activity Impairment Questionnaire, UC-specific version) (part 2 only)**

The WPAI-UC is the UC-specific version of a frequently used questionnaire with 6 questions assessing social functioning, in particular regarding absenteeism, presenteeism and daily activity impairment.

Since UC predominantly affects adults of working age, the WPAI-UC is included in order to obtain patient-reported information on productivity loss due to UC and thus to estimate its societal impact. Validity, reliability and responsiveness in UC are supported by published data [[R17-2219](#), [R17-2216](#), [R17-2218](#)].

Response options include the number of hours worked and missed (due to UC and due to unrelated reasons) and a numeric rating scale (0-10) assessing the impairment of work and daily activities due to UC. Work impairment is calculated as the sum of presenteeism and absenteeism, with a 7% change in impairment estimated to be clinically meaningful [[R15-5875](#)]. The recall period is 7 days.

### **EQ-5D-5L (EuroQol 5-level, 5-dimensional health-related quality of life measure)**

The EQ-5D self-report questionnaire was developed by the European Quality of Life Group (EuroQol Group) and is a standardised instrument for use as a measure of health outcome [[R96-2382](#)]. It contains 5 questions on different dimensions of health (e.g. mobility, self-care) and one visual analogue scale on current health.

The EQ-5D is included primarily to derive utilities for different health states in UC for the purpose of cost-effectiveness modelling. In addition, published data also support the validity, reliability and responsiveness of its visual analogue scale as a measure of general health-related quality of life in UC [[R15-5871](#), [R15-5868](#), [R17-2219](#), [R17-2221](#)].

Response options include a five-level ordinal scale reporting on the five dimensions of health and a visual analogue scale reporting the patient's self-rated health status as number between 0 and 100. MCIDs for the five-dimensional part and the visual analogue scale have been estimated as 0.074 and 7 points, respectively [[R10-0936](#), [R16-0030](#)]. All questions refer to the current health status ("today").

### **Healthcare resource utilisation (HCRU), part 2 only**

For the purpose of a separate health economic analysis (such as cost-utility analysis), health care resource utilisation (HCRU) data will be collected throughout the study.

Resource use data collected for calculating direct costs will include unscheduled hospitalisations, healthcare provider visits, and emergency room/ICU use.



## **5.6 APPROPRIATENESS OF MEASUREMENTS**

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

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

## 6. INVESTIGATIONAL PLAN

### 6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the [Flow Chart](#). Each visit data (with its window) up to EOS is to be counted from Day 0 (Visit 2). If any of these visits has to be rescheduled, the date of subsequent visits should be calculated from Day 0 (Visit 2). There should be at least 14 days between two consecutive study drug administrations. Follow-up visits (after EOT) refer to the last dose administration of BI655130 (SPESOLIMAB) at visit V5 (Week 8). Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

### 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

PROs should be completed by the patient on his/her own in the pre-specified order in a quiet area/room before any other visit assessments or treatments (including the first administration of study medication at V2), and, as much as possible, before any interaction with the investigator or other members of the study team.

The order of completion for PROs is as follows, as applicable for each PRO at relevant visits according to the [Flow Chart](#):

1. IBDQ
2. FACIT-Fatigue (part 2 only)
3. SF-36 (part 2 only)
4. EQ-5D-5L
5. WPAI-UC (part 2 only)

Measurement of vital signs should precede blood sampling and be assessed pre-dose at all dosing visits.

#### 6.2.1 Screening and run-in period(s)

After patients have been informed about the trial, written informed consent in accordance with GCP and the local legislation must be obtained prior to performing any study related procedures.

Once they have consented, the patient is considered to be enrolled in the trial. The patient should be recorded on the subject enrolment log. Patient will be assigned a patient number and enrolment must be recorded in the eCRF pages.

### **Screening visit (Visit 1a):**

The Screening visit (Visit 1a) should normally take place no more than 35 days before Visit 2 and be complete no less than 14 days prior to Visit 2. At this visit, information will be collected for evaluation of trial eligibility as indicated in the [Flow Chart](#).

### Baseline Conditions

Chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, ECG, safety labs, and any condition requiring therapy (excluding UC) will be reported on the baseline condition eCRF page.

Patients who have a laboratory test value outside the range specified by the inclusion criteria may have the test repeated to determine eligibility. The result must be available prior to Visit 2 (Day 0).

### Demography

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

### Medical and Surgical History

Information on clinically significant previous and concomitant illnesses, other than UC, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the screening visits will be recorded as medical and surgical history at screening. For planned procedures/hospitalisations during the trial, documentation should be completed at the time of the screening. Regarding the UC, a detailed history of the disease, including date of diagnosis, disease extent and severity, hospitalizations, and extraintestinal manifestations will be collected. Also, previous and concomitant treatment for UC will be recorded.

### Blood sampling

Blood samples will be taken for safety lab, infection screening (HIV, HBV, HCV, TBC). For women of childbearing potential, a serum pregnancy test will be performed. Optionally blood samples will be taken for drug level analysis of biologics previously used for UC.

### Stool sampling

A stool sample will be collected to exclude existence of enteric pathogens. If collection is not possible at Visit 1a, stool sample has to be collected at (or prior to) Visit 1b or at an unscheduled visit. For further details, please refer to the lab manual (Section 10 of the ISF).

### Patient diary

Patients who are eligible at Visit 1a will receive a patient diary to be used for daily reporting of stool frequency and rectal bleeding (blood in stool) during the week prior to visits which include assessment of Mayo score

Patients will be instructed on the use of the diary during screening and treatment phase. The diary will be returned at EOS visit.

#### **Visit 1b:**

The Visit 1b should take place no more than 28 days and no less than 7 days prior to Visit 2.

A full colonoscopy will be performed at this visit to assess disease extent and exclude malignancy (per local standard of care, e.g. by serial mucosal biopsies, chromoendoscopy, magnification endoscopy or other sensitive measures) if no fully documented procedure is available  $\leq$  12 months prior to screening. If a full colonoscopy is available from the past 12 months prior to Visit 1, a sigmoidoscopy incl. biopsy will be performed instead. Images will be centrally read by an external independent assessor.

Based on the results from sigmoidoscopy (or colonoscopy, if applicable) and clinical symptoms of the patient, a baseline Mayo score will be determined. Results from the mucosal biopsies will be used as first baseline value for endpoint parameters. Refer to Section 15 of the ISF for details.

For a detailed description of the trial procedures at Visits 1a and 1b, please refer to the [Flow Chart](#).

The time window for Visit 1a and 1b other than is specified in the [Flow Chart](#) should be agreed at the discretion of the PI, in alignment with the trial monitor on a case by case basis.

Re-screening will be allowed once in part 1 and in part 2 respectively.

#### **6.2.2 Treatment period(s)**

The treatment period is from Visit 2 to End of Treatment (EoT) Visit.

Study related procedures will be performed as specified in the [Flow Chart](#).

#### Pregnancy testing

Urine pregnancy testing for all women of child-bearing potential will be conducted on-site approximately every four weeks and must be negative to continue treatment. The pregnancy testing should be done **prior to** study drug administration. A positive urine test must be confirmed with a serum pregnancy test.

#### Blood sampling

Blood sampling (e.g., for safety lab, BMs) should be done **prior to** study drug administration and **prior to** sigmoidoscopy, if applicable. Patients should come in a fasted condition. If a patient comes in a non-fasted condition, where a fasting condition is required, the visit should be performed, the non-fasted condition documented on the laboratory requisition, and the patient reminded about the expected conditions.

### Sigmoidoscopies

Sigmoidoscopies will be done after blood sampling and **prior to** study drug administration. During sigmoidoscopies, biopsies will be taken for endpoint evaluation at time points as indicated in the [Flow Chart](#). Please refer to Section 5 of the ISF for further information on the collection and the processing of biopsies.

### PK and ADA sampling

At visits with study drug administration, blood sampling for PK assessments should be done approximately within one hour **prior to** study drug administration.

### Clinical monitoring after study drug administration:

The patient will be monitored for infusion reactions at the site for approximately 2 hours after after the end of first study drug infusion and 1 hour following all other doses of study drug. At all visits with study drug administration, vital signs will be assessed pre-dose, and at approximately 5 and 60 minutes after end of infusion.

### Unscheduled visits

The patient may be called in for additional unscheduled visits due to safety reason at the discretion of the investigator or the sponsor, unless the patient has withdrawn his/her consent. The patient may also contact the site due to safety reason for an unscheduled visit. The unscheduled visit may include additional collection of blood samples for safety reasons. The unscheduled visit may also include additional assessments deemed necessary by the investigator such as laboratory samples, ECGs, or other procedures which were missed at a previous visit. All unscheduled visits should be described (including the reason for the visit) and documented in the medical/source record, and in the eCRF.

### Concomitant medication review

Data concerning concomitant medications and procedures will be collected throughout the trial, as specified in the [Flow Chart](#). These data will be obtained at scheduled or unscheduled trial visits provided spontaneously by the patient or as a result of questioning the patient.

## **6.2.3 Follow up period and trial completion**

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

For patients completing the safety FU period, the EOS visit is scheduled at 16 weeks after the last dose of study drug, ie at week 24 for those discontinuing after completing 12 weeks of treatment.

All patients completing the study will be offered to enter open label trial 1368-0017 or 1368-0020 respectively, where responders will receive SC maintenance treatment, while non-responders undergo i.v. re-induction. These patients are not requested to complete follow up period and will have their EOS visit at visit V6, co-inciding with the BL visit and start of study drug administration in 1368-0017 or 1368-0020 respectively.

Early treatment discontinuation

Patients who terminate study drug early should be encouraged to follow all study procedures per the [Flow Chart](#) until week 12, but not receive any more study drug at the respective visits. Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the [Flow Chart](#) (FC) and [Section 6.2.3](#).

Further treatment after the end of the trial

At the end of the trial, patients will be treated for their UC at the discretion of the investigator, according to local UC guidelines (e.g. ECCO guideline [R17-0243](#)).

Trial completion:

Trial completion is defined as a patient having reached the EOS visit. EOS visit will be at week 12 (V6) for patients rolling-over into subsequent maintenance trial; and at week 24 for patients who will not enter subsequent maintenance trial.

Regarding instructions for drug administration at missed or delayed visits, please refer to [Section 4.1.4](#).

## 7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

### 7.1 STATISTICAL DESIGN – MODEL

This trial is designed as a randomised, parallel-group, and double-blind, and placebo-controlled trial with 3 active doses of BI655130 (SPESOLIMAB) in Part 1 of the trial and 2 active doses of BI655130 (SPESOLIMAB) in Part 2 of the trial in patients with moderate to severe ulcerative colitis who have failed previous biologic treatments in the past.

The trial consists of 2 parts (cf. [Section 3.1](#)) which, for the purpose of statistical analyses, will be treated as two independent parts whereby the false positive rate is separately controlled within each trial part:

Part 1: To demonstrate proof of concept of clinical activity as an induction therapy on the primary endpoint of clinical remission at week 12 with respect to achieving a non-flat dose response curve, and subsequently to define suitable dose regimens for BI655130 (SPESOLIMAB) regarding efficacy and safety for further pivotal testing in part 2 of this trial. For this purpose, a multiple comparison procedure with modelling techniques (MCPMod) approach is considered.

Part 2: to confirm the efficacy and safety of two different doses of BI655130 (SPESOLIMAB) versus placebo as an induction therapy. Formal statistical hypothesis testing will be performed at an overall 1-sided alpha level of 0.025.

Each trial part will be analyzed independently of the remaining trial part, i.e.

- Only patients randomized into part 1 will be included in the analyses of part 1,
- Only patients randomized into part 2 will be included in the confirmatory analyses of part 2

In order to describe the full efficacy, safety and tolerability profile of BI655130 (SPESOLIMAB) in the population of patients with moderate to severe ulcerative colitis who have failed previous biologic treatments in the past, a pooled efficacy and safety analysis by dose group will also be generated, if at least one of the BI655130 (SPESOLIMAB) doses is identical in both study parts.

Note that statistical testing will be performed based on one-sided hypotheses and p-values. For publication purposes also two sided p-values will be derived; details of this will be specified in the TSAP.

Decision criteria for determining the achievement of proof of concept and subsequent dose selection criteria for the two doses of BI655130 (SPESOLIMAB) that will be studied in Part 2 of the trial are described in [Section 3.1.2](#).

Randomization for parts 1 and 2 will be stratified based on

- previous BIO treatment failure ( (TNF $\alpha$  antagonists-**OR**-Vedolizumab) versus (TNF $\alpha$  antagonists-**AND**-Vedolizumab) ) and
- concomitant corticosteroid therapy at visit 2/randomization (yes/no)
- Japan versus non-Japan  
To assure that sufficient patients per treatment group are recruited specifically to support individual country submission in Japan; this strata will be treated as an operational strata and will not be included into the analyses of the primary endpoint.

In addition, due to the low number of patients to be recruited into part 1 of this trial, the primary analysis of this part will be performed without consideration of stratification.

The proportion of patients who achieve clinical remission at Week 12 is the primary efficacy endpoint for each part of this trial. Clinical remission is defined as achieving an RBS = 0, an SFS = 0 or = 1 if there is a corresponding decrease  $\geq 1$  from baseline, as well as a modified ESS  $\leq 1$ , each of these components being measured as a part of the modified Mayo Clinical Score (mMCS). Colonoscopy and sigmoidoscopy images will be centrally read by an external independent assessor(s); images will also be read locally. The primary analysis will be performed using the centrally-read endoscopy scores; only if centrally-read data are missing will the local endoscopy score be used instead.

Considering the binary nature of the primary endpoint, this trial is designed to show an increase in the proportion of patients who demonstrate clinical remission for BI655130 (SPESOLIMAB) relative to Placebo. The primary analysis method for the confirmatory part of this trial (Part 2) will be the Cochran-Mantel-Haenszel risk difference estimation stratified by the randomization factors of previous BIO treatment failure and concomitant corticosteroid therapy at visit 2/randomization.

## 7.2 NULL AND ALTERNATIVE HYPOTHESES

The null and alternative hypotheses are described below separately for each trial part.

### Part 1

The null hypothesis is that there is a flat dose response curve comparing the placebo and the BI655130 (SPESOLIMAB) dose groups. The alternative hypothesis is that there is a non-flat dose response curve indicating a benefit of BI655130 (SPESOLIMAB) over Placebo.

The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of Type I error (one sided  $\alpha$  of 20%). The pre-specified models and their parameters used for this test are outlined in [Section 7.3.1](#) and [Section 7.7](#).

### Part 2

Two doses of BI655130 (SPESOLIMAB) are planned to be investigated in this trial part; a low dose and a high dose. The exact doses to be included are dependent upon the outcome of



trial analysis on part 1 and the subsequent application of decision criteria as described in [Section 3.1.2](#).

This part of the trial is designed to confirm that at least one of two selected doses of BI655130 (SPESOLIMAB) is superior to placebo in achieving clinical remission at Week 12 in patients with moderate to severe ulcerative colitis who have failed previous biologic treatments in the past.

The null and alternative hypotheses for each of these two tests on the primary endpoint are described as follows:

(1) BI655130 (SPESOLIMAB) low dose vs. Placebo

$H_{0,11}$ : Effect of BI655130 (SPESOLIMAB) low dose on clinical remission at week 12  $\leq$  Placebo;  
versus  
 $H_{A,11}$ : Effect of BI655130 (SPESOLIMAB) low dose on clinical remission at week 12  $>$  Placebo.

(2) BI655130 (SPESOLIMAB) high dose vs. Placebo

$H_{0,12}$ : Effect of BI655130 (SPESOLIMAB) high dose on clinical remission at week 12  $\leq$  Placebo;  
versus  
 $H_{A,12}$ : Effect of BI655130 (SPESOLIMAB) high dose on clinical remission at week 12  $>$  Placebo.

Further hypotheses will be tested on the family of secondary endpoints in a hierarchical manner. The overall testing strategy used to control the type I error for each of the endpoints and for each of the treatments is described below. The null and alternative hypotheses for each of the two tests on each of the secondary endpoints are described as follows.

For Mucosal Healing at week 12

(3) BI655130 (SPESOLIMAB) low dose vs. Placebo

$H_{0,21}$ : Effect of BI655130 (SPESOLIMAB) low dose on mucosal healing at week 12  $\leq$  Placebo;  
versus  
 $H_{A,21}$ : Effect of BI655130 (SPESOLIMAB) low dose on mucosal healing at week 12  $>$  Placebo.

(4) BI655130 (SPESOLIMAB) high dose vs. Placebo

$H_{0,22}$ : Effect of BI655130 (SPESOLIMAB) high dose on mucosal healing at week 12  $\leq$  Placebo;  
versus  
 $H_{A,22}$ : Effect of BI655130 (SPESOLIMAB) high dose on mucosal healing at week 12  $>$  Placebo.

For the Clinical Response at week 12

(5) BI655130 (SPESOLIMAB) low dose vs. Placebo

$H_{0,31}$ : Effect of BI655130 (SPESOLIMAB) low dose on clinical response at week 12  $\leq$  Placebo;

versus

$H_{A,31}$ : Effect of BI655130 (SPESOLIMAB) low dose on clinical response at week 12  $>$  Placebo.

(6) BI655130 (SPESOLIMAB) high dose vs. Placebo

$H_{0,32}$ : Effect of BI655130 (SPESOLIMAB) high dose on clinical response at week 12  $\leq$  Placebo;

versus

$H_{A,32}$ : Effect of BI655130 (SPESOLIMAB) high dose on clinical response at week 12  $>$  Placebo.

For the change from baseline in IBDQ at week 12

(7) BI655130 (SPESOLIMAB) low dose vs. Placebo

$H_{0,41}$ : Effect of BI655130 (SPESOLIMAB) low dose on change from baseline in IBDQ at week 12  $\leq$  Placebo;

versus

$H_{A,41}$ : Effect of BI655130 (SPESOLIMAB) low dose on change from baseline in IBDQ at week 12  $>$  Placebo.

(8) BI655130 (SPESOLIMAB) high dose vs. Placebo

$H_{0,42}$ : Effect of BI655130 (SPESOLIMAB) high dose on change from baseline in IBDQ at week 12  $\leq$  Placebo;

versus

$H_{A,42}$ : Effect of BI655130 (SPESOLIMAB) high dose on change from baseline in IBDQ at week 12  $>$  Placebo.

For the combined Mucosal Healing and Histologic Remission at week 12

(9) BI655130 (SPESOLIMAB) low dose vs. Placebo

$H_{0,51}$ : Effect of BI655130 (SPESOLIMAB) low dose on combined Mucosal Healing and Histologic Remission at week 12  $\leq$  Placebo;

versus

$H_{A,51}$ : Effect of BI655130 (SPESOLIMAB) low dose on combined Mucosal Healing and Histologic Remission at week 12  $>$  Placebo.

(10) BI655130 (SPESOLIMAB) high dose vs. Placebo

$H_{0,52}$ : Effect of BI655130 (SPESOLIMAB) high dose on combined Mucosal Healing and Histologic Remission at week 12  $\leq$  Placebo;

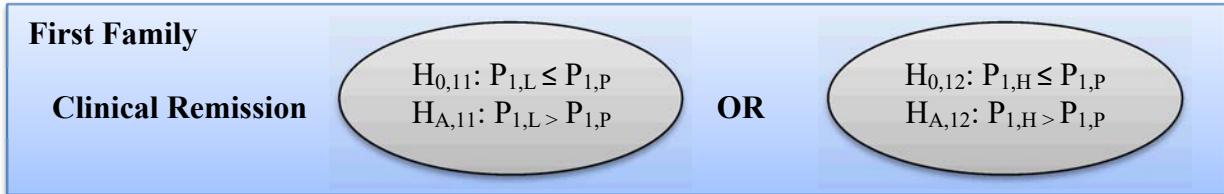
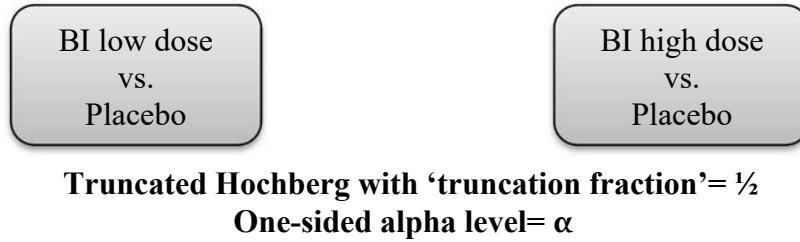
versus

$H_{A,52}$ : Effect of BI655130 (SPESOLIMAB) high dose on combined Mucosal Healing and Histologic Remission at week 12  $>$  Placebo.

Overall the testing strategy will follow a closed testing principle defining two families of endpoints/comparisons. The first family consists of the primary endpoint comparison for both doses of BI655130 (SPESOLIMAB) vs placebo, whereas the second family is defined by the key-secondary (mucosal healing and clinical response) and secondary endpoints (change from baseline in IBDQ, and combined Mucosal Healing and Histologic Remission) comparisons for both doses of BI655130 (SPESOLIMAB) vs placebo.

Regarding the first family, to control the overall type I error rate at a 1-sided 0.025 alpha significance level for both of these two treatment comparisons on the primary endpoint at week 12, the (truncated) Hochberg method will be applied. The weight of the truncated Hochberg method is chosen as 0.5. Therefore, if both primary endpoint p-values are  $\leq 0.01875$  (one-sided), then both comparisons involving the two BI655130 (SPESOLIMAB) dose regimens will be declared statistically significant. If the maximum of the p-values for the two dose comparisons is  $> 0.01875$  (one-sided), then the other p-value will be tested at the 0.0125 one-sided level and declared to be statistically significant only if that p-value is  $\leq 0.0125$  (one-sided). The remaining alpha,  $\alpha'$ , to be used in the second family will be 0.025 (one-sided) if both primary endpoints show significance. If only one comparison is significant then  $\alpha'$  will be  $0.025/4=0.00625$  according to the truncated Hochberg procedure with weight of 0.5. If neither dose is declared to be statistically significant for the primary endpoint, then no further testing can be conducted.

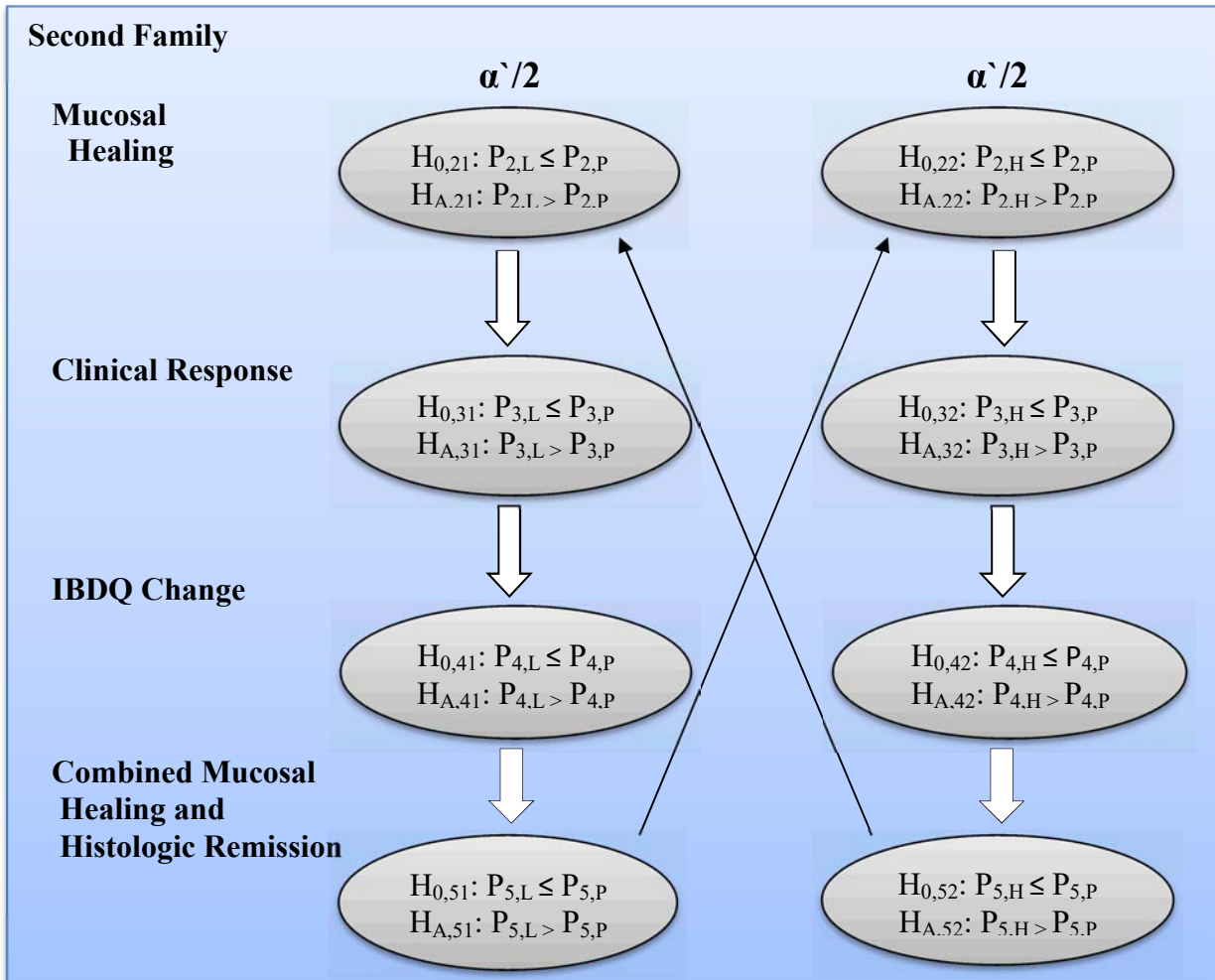
If both doses of BI655130 (SPESOLIMAB) on the primary endpoint are declared to be statistically significant, then the following graphical procedure will be used to attribute the remaining  $\alpha'$  to the testing of each of the (hierarchically-ordered) key-secondary and secondary endpoints as follows:



If both doses are Significant on primary



One-sided alpha=  $\alpha' = \alpha = 0.025$



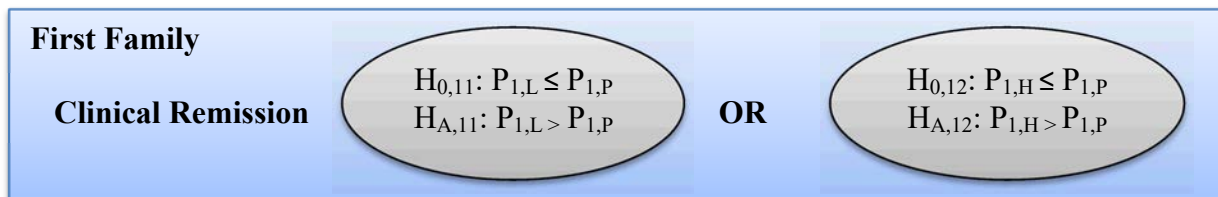
Note: H=High dose of BI655130 (SPESOLIMAB); L=Low dose of BI655130 (SPESOLIMAB); P=Placebo

If both doses of BI655130 (SPESOLIMAB) show significance in the first family, then the remaining alpha ( $\alpha'=0.025$ , one-sided) to be used in the secondary family will be equally split between the two doses of BI655130 (SPESOLIMAB) leading to an initial  $\alpha$  of 0.0125 per comparison. The test of a subsequent secondary endpoint in the hierarchical sequence, for a particular dose of BI655130 (SPESOLIMAB), is only performed if the test of the previous secondary endpoint on that same dose was successful. If, for one of the doses of BI655130 (SPESOLIMAB), the test on each of the endpoints (primary, key secondary, and secondary) is successful, then the remaining alpha may be passed to the secondary endpoint comparisons regarding the other dose leading to an initial level of 0.025 (one-sided).

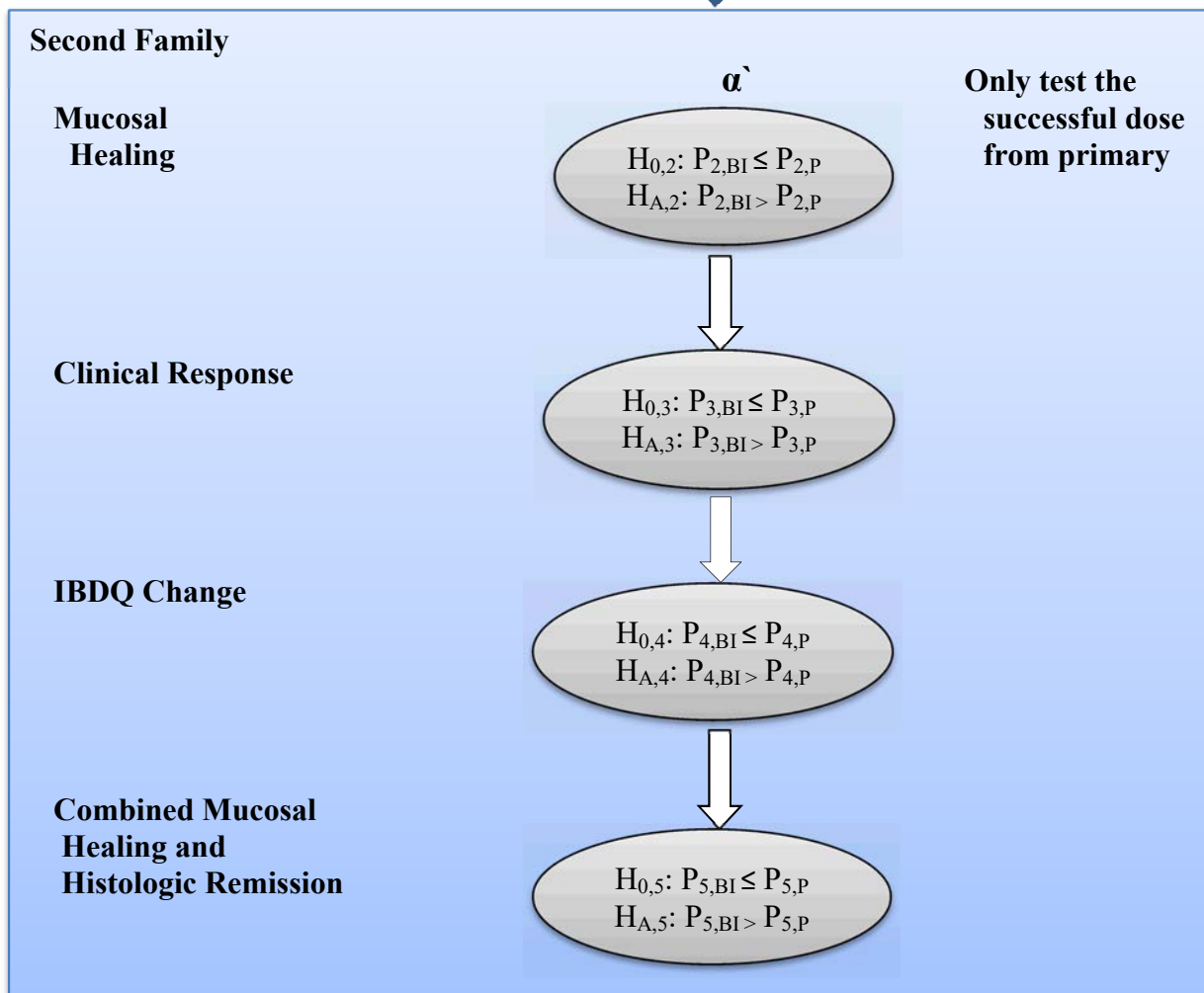
If only one of the doses of BI655130 (SPESOLIMAB) on the primary endpoint is declared to be statistically significant, then the following graphical procedure will be used to attribute the remaining  $\alpha'$  to the testing of each of the (hierarchically-ordered) key-secondary and secondary endpoints as follows:



Truncated Hochberg with 'truncation fraction' = 1/2  
 One-sided alpha level =  $\alpha$



If only one dose is Significant on primary  $\downarrow$  One-sided alpha =  $\alpha' = \alpha/4 = 0.00625$



Note: H=High dose of BI655130 (SPESOLIMAB); L=Low dose of BI655130 (SPESOLIMAB); P=Placebo; BI= the single dose of BI655130 (SPESOLIMAB) that was successful on the test of the primary endpoint (low or high dose)

If only one dose of BI655130 (SPESOLIMAB) shows statistical significance in the first family, then the tests for the secondary family will only be performed with respect to the comparisons involving the same dose of BI655130 (SPESOLIMAB) for which the primary endpoint was successful, utilizing the remaining alpha ( $\alpha'=0.00625$ , one-sided) transferred from the primary family. In this case, there will be no alpha passing to the other dose even if all tests on the secondary endpoints are successful.

(Simulation-based) power calculations with respect to the planned sample size and the chosen testing strategy for the primary analysis can be found in [Sections 7.7.1](#) and [7.3.1](#) respectively.

### 7.3 PLANNED ANALYSES

There will be 4 main patient populations in this trial for analyses: the randomized set (RS), the safety analysis set (SAF), the modified RS (m-RS), and the per-protocol set (PPS). Each of these populations will be derived separately for each of the 2 trial parts.

#### Randomized Set (RS)

This patient set includes all randomized patients. Treatment assignment will be as randomized. This is the main analysis set for presentation of efficacy on binary endpoints.

#### Safety Analysis Set (SAF)

This patient set includes all patients who were randomized and received at least one dose of study drug. It will be the main analysis set for presentation of safety. Patients will be analyzed according to the actual treatment.

#### Modified Randomized Set (m-RS)

This patient set includes all patients in the RS who had a baseline and at least one post-baseline measurement for the endpoint under consideration. Treatment assignment will be as randomized. This is the main analysis set for presentation of efficacy on continuous data, e.g. IBDQ.

#### Per-Protocol Set (PPS)

This patient set includes all patients in the RS who adhered to the CTP without any IPVs (potentially affecting the study outcome) which lead to exclusion from the PPS. This set will be used for sensitivity analysis on the primary efficacy endpoint.

Further analysis sets, e.g. for the BM assessments, will be defined in the TSAP.

Important violations of the protocol will include violations of the key inclusion and exclusion criteria, incorrect medications taken, concomitant use of restricted medications, and any other violations of the protocol deemed important by the study team. All decisions concerning important protocol violations will be made prior to un-blinding of the database for the respective trial part.

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

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

#### Part 1 – Week 12 Final Analysis

The analysis will be performed once all randomised patients have completed the first 12 weeks of Part 1 of the trial, and a database lock will be done. At this time, the final analysis of the efficacy and safety data through Week 12 on Part 1 will be performed and the Part 1 data will be officially unblinded (see also [Section 4.1.5.1](#)). Details of the analysis to be performed will be described in the Part 1 TSAP which is planned to be finalized prior to achieving database lock for the Week 12 analysis on Part 1.

The results on Part 1 will be reviewed by the DMC and by a part 1 review committee which includes sponsor representatives, the DMC chair and the co-ordinating investigators. The decision to amend or to initiate part 2 without modifications (taking into account the decision criteria described in [Section 3.1.2](#)) will be made by the sponsor based upon the recommendations of the independent DMC and the part 1 review committee.

#### Part 2 – Confirmatory Part 2 Analysis

The final analysis will be performed once all randomised patients have completed Part 2 of the trial. At this time, the final analysis of the efficacy and safety data on Part 2 will be performed. This analysis actually reflects the final analysis of the trial, and the complete analysis of trial Part 2 hence there is no need to adjust the alpha level for this particular trial part. Details of the analysis to be performed will be described in the Part 2 TSAP which is planned to be finalized prior to achieving database lock for Part 2. For details on the nature of the unblind at this time, refer to [Section 4.1.5.1](#).

Pooled efficacy and safety analyses of the entire trial, including both Parts 1 and 2, will be done, if applicable, as previously described. The follow-up data collected after week 12 for patients who continued in the safety follow-up of Part 1 will also be presented.

A Clinical Trial Report will be prepared which will describe the separate analyses performed on each of the trial parts, and also the pooled analyses of the entire trial.

### **7.3.1 Primary endpoint analyses**

The evaluation of clinical remission at Week 12 is the primary objective for efficacy in each part of this trial and is described using the proportion of patients who achieve clinical remission at this time-point based on endoscopy results obtained from central reading. Only if the centrally read endoscopy result is missing at a time-point will the locally read result be used instead.

For the stool frequency and rectal bleeding items reported in the patient diary, an average of the last 3 non-missing daily assessments collected within the last 7 days prior to the applicable visit will be used for the determination of clinical remission. If the patient undergoes bowel preparation for endoscopy on any of the days before a visit, the stool frequency and rectal bleeding subscores on that day(s) should be considered to be missing. In addition, the stool frequency and rectal bleeding subscore will be considered to be missing both on the day of and the day after the endoscopy.



## Part 1 – proof of clinical concept

### *Primary analysis*

The primary endpoint is the proportion of patients with clinical remission after 12 weeks of treatment.

The analyses for PoC and dose-finding will be performed using MCPMod techniques [[R10-1424](#), [R15-1961](#)] for binary data whereby several possible dose response models (patterns) will be evaluated (while keeping full control of the type I error at 20%, one-sided) to identify the best-fitting model. The doses which are included in Part 1 are placebo, and BI655130 (SPESOLIMAB) 300 mg SD, 450 mg q4w, and 1200 mg q4w; for modelling purposes, 300 mg SD will be approximated by a dose of 100 mg q4w in order to align doses on a single unit.

For the PoC testing and for the sample size calculation the following model assumptions and resulting graphs ([Figure 7.3.1:1](#)) have been selected to cover both the plausible and a diverse range of potential dose response patterns:

#### Linear

E<sub>max</sub>: assumes 90% of the maximum effect is achieved at 300 mg SD dose

Exponential: assumes 1% of the maximum effect is achieved at 300 mg SD dose

Logistic: assumes 30% of the maximum effect is achieved at 300 mg SD dose and 85% of the maximum effect is achieved at 450 mg q4w dose

Sigmoid E<sub>max</sub>: assumes 30% of the maximum effect is achieved at 300 mg SD dose and 75% of the maximum effect is achieved at 450 mg q4w dose

Note that the actual shapes are applied on the parameter scale (logit for binary data) according to Pinheiro et al. [[R15-4293](#)] and that the q4w dose is used as model parameter.

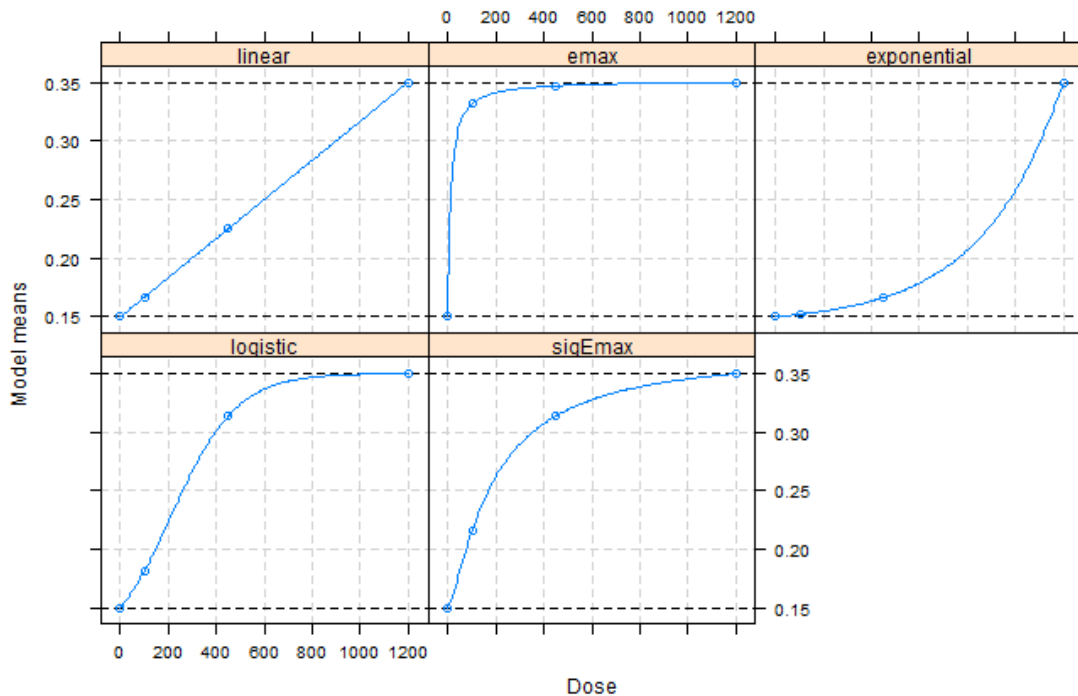


Figure 7.3.1: 1: Shape of the considered dose response patterns for the MCPMod analysis

PoC is established if at least one dose response pattern is statistically significant, rejecting the null hypothesis of a flat dose response relationship on clinical remission at week 12 jointly for each of the candidate dose response models, with a contrast test controlled for the family-wise type I error rate at a one sided  $\alpha = 20\%$ .

If PoC is established, the statistically significant model(s) from the above candidate set are refitted to the data to generate new estimates for all model parameters.

The statistically significant model with the lowest Akaike Information Criterion (AIC) value will be determined as the best fitting model and will be used for characterization of the dose-response curve.

The choice of two target doses to be investigated in Part 2 of the trial – the confirmatory trial part – is described in [Section 3.1.2](#). The maximum effective dose, as well as the selection of the two pre-specified doses for testing in Part 2, will be based on the modelled efficacy estimates. Only doses within the dose range investigated (0 mg - 1200 mg q4w) will be considered.

If considered necessary and for the purpose of further model refinement, MCPMod might be repeated on the primary endpoint but with an extended set of shapes including the original candidates. Additionally a sensitivity analysis based on model averaging across the statistically significant models may be conducted in order to assess the robustness of the chosen primary approach. Furthermore, covariates may be taken into account in further

sensitivity analyses, i.e. inclusion of stratification parameters. Details of these analyses will be described in the TSAP.

#### Further analyses

Unadjusted absolute risk differences of the clinical remission at week 12 between the BI655130 (SPESOLIMAB) arms and the placebo group will be provided. In addition 95% confidence intervals will be displayed. More details on the above analyses as well as potential additional sensitivity analyses will be described in the TSAP.

As a further analysis, a logistic regression model on the proportion of patients achieving clinical remission at week 12 with fixed factors for treatment, previous BIO and corticosteroid use as strata will also be applied for the RS. In case the model does not converge, an exact method may be employed. Otherwise, analyses will be performed adjusting for each of the strata (prior biologic use and concomitant corticosteroid therapy at visit 2/randomization) individually.

The likelihood-ratio test will be used to test for differences between treatments. Adjusted odds ratios together with 95% confidence intervals will be used to quantify the effect of treatment, comparing all treatments to placebo; details will be provided in the TSAP.

#### Part 2 – formal, confirmatory statistical testing part

The primary analysis of the clinical remission for each dose of BI655130 (SPESOLIMAB) versus placebo will be tested using the stratified Cochran-Mantel-Haenszel (CMH) test at a nominal 1-sided 0.025 significance level stratified by the randomization factors (prior biologic use and concomitant corticosteroid therapy at visit 2/randomization) and based on the RS. The difference in the proportion of responders, and the associated confidence intervals will be presented for each active group versus the placebo group using the Mantel-Haenszel type weighted average of differences using weights as proposed by Greenland & Robins [R09-1299]. The approach to control the Type I error for multiple comparisons between the two BI655130 (SPESOLIMAB) doses and placebo is described in [Section 7.2](#).

Secondary analysis of the primary endpoint will include:

- A logistic regression model on the proportion of patients achieving clinical remission at week 12 with fixed factors for treatment, previous BIO, and concomitant corticosteroid use at visit 2/randomization as strata will be applied for the RS. In case the model does not converge, analyses will be performed adjusting for each of the strata (previous BIO and concomitant corticosteroid use at visit 2 /randomization) individually. The estimates from the logistic regression are on the logit scale, and the difference in proportions will be calculated as the difference between the predicted probabilities in the treatment groups on the original scale, with the confidence interval calculated using the cumulative distribution function method of Reeve [R16-4414]; further details will be provided in the TSAP.
- Sensitivity analysis utilizing the PPS
- Sensitivity analyses which utilize alternative methods for the handling of missing data as described in [Section 7.5](#).

### Exploratory Pooled Analyses of Parts 1 and 2

In order to describe the full efficacy profile of BI655130 (SPESOLIMAB) in the population of patients with moderate to severe ulcerative colitis who have failed previous biologic treatments in the past, an integrated analysis of the clinical remission data, by dose group, will be generated for the RS, if at least one of the BI655130 (SPESOLIMAB) doses is identical in both study parts. Data from Parts 1 and 2 of the trial will be pooled together. The objectives of this pooled analysis are:

- Increase precision on treatment estimates (and differences to Placebo) in this patient population;
- Investigate effect of subgroups on the treatment effect, i.e.
  - Race
  - Gender
  - Region
  - Previous BIO use
  - Previous corticosteroid use
  - Other

An exploratory assessment of the pooled data from Parts 1 and 2 will be performed by repeating the primary analysis (stratified CMH test) as well as the sensitivity analysis using the [Part 2 specified] logistic regression model (including additionally a fixed effect for study part); only those treatments which are common to both parts will be included. All p-values presented will be considered nominal in nature and no adjustment for multiplicity will be made. Subgroups will be assessed descriptively.

### **7.3.2 Key Secondary endpoint analyses**

For Part 1 of the study, there are no key secondary endpoints defined.

For Part 2 of the study, the treatment effects on the key secondary endpoints of mucosal healing at week 12, and clinical response at week 12 will be tested in a hierarchical manner as a part of the pre-specified testing strategy, subsequent to the test of the primary endpoint, which is defined in [Section 7.2](#). The analysis of both endpoints will be performed using the same approach as that defined for the primary analysis in part 2 of the study based on the RS.

### **7.3.3 Secondary endpoint analyses**

For both trial parts, the change from baseline of IBDQ scores at Week 12 will be analyzed based on the m-RS. It will be analyzed using a restricted maximum likelihood (REML) based repeated measures approach. The model will include fixed, categorical effects of treatment, visit and treatment by visit interaction, and stratification factors (prior biologic use and concomitant corticosteroid therapy at visit 2/randomization), as well as the continuous, fixed covariates of baseline and baseline by visit interaction. An unstructured covariance structure will be used to model the within-patient measurements. The Kenward- Roger approximation will be used to estimate denominator degrees of freedom. The primary treatment comparison will be the contrast between treatments after 12 weeks of treatments. For Part 1 of the trial, if model convergence issues occur due to inclusion of strata in the model, these terms may be dropped and separately evaluated.

#### Part 1 – proof of clinical concept

If considered appropriate, a MCPMod approach may also be applied to selected secondary endpoints on Part 1 of the trial.

For each secondary binary endpoint, unadjusted absolute risk differences at week 12 between the BI655130 (SPESOLIMAB) arms and the placebo group will be provided along with the corresponding 95% confidence intervals. A logistic regression model may also be performed on the RS using the approach as described above for the further analyses on the primary endpoint of Part 1 of the trial.

#### Part 2 – formal, confirmatory statistical testing part

For Part 2 of the study, the treatment effects on the secondary endpoints of change from baseline in IBDQ at week 12 and combined mucosal healing and histologic remission at week 12 will be tested in a hierarchical manner as a part of the pre-specified testing strategy, subsequent to the tests of the key secondary endpoints, which is defined in [Section 7.2](#).

For all secondary endpoints which are binary in nature, the analysis will be performed using the same approach as that defined for the primary analysis based on the RS.

### **7.3.5 Safety analyses**

Adverse events will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced.

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

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered ‘treatment-emergent’. The residual effect

period (REP) is defined as 16 weeks after the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. The primary set of safety outputs will be done including data through the first 12 weeks of treatment (consistent with the timing of the primary efficacy analysis); further outputs will be also produced which include all safety data through the REP.

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

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

Immunogenicity data will be analysed in a descriptive way.

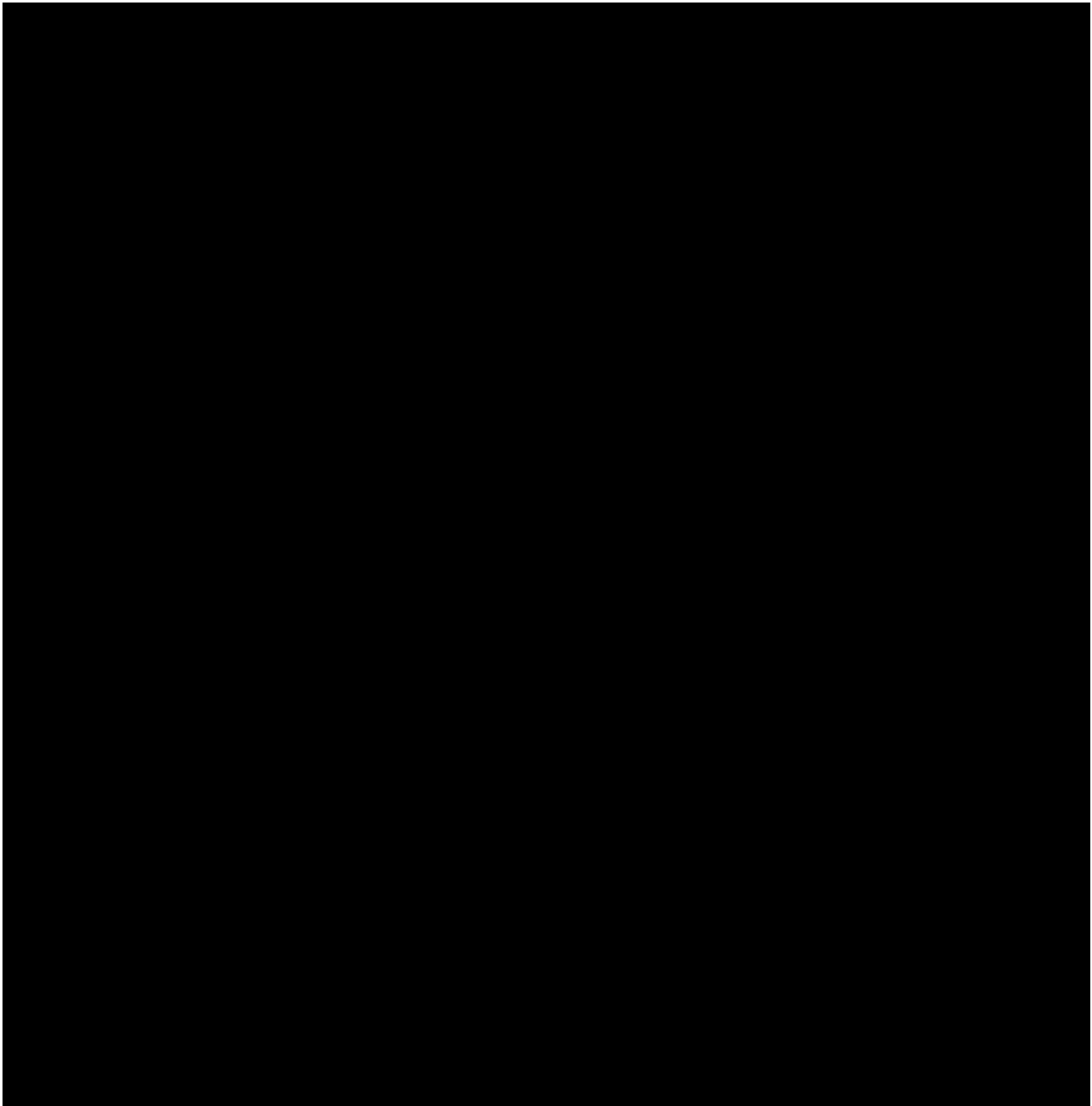
#### Pooled Analyses of Parts 1 and 2

In order to describe the full safety and tolerability profile of BI655130 (SPESOLIMAB) in the population of patients with moderate to severe ulcerative colitis who have failed previous biologic treatments in the past, an integrated analysis of the safety data, by dose group, will be generated, if at least one of the BI655130 (SPESOLIMAB) doses is identical in both study parts. Data from Parts 1 and 2 of the trial will be pooled together. The objectives of this pooled analysis are:

- Investigate safety and tolerability of subgroups in this patient population using descriptive methods, i.e.
  - Race
  - Gender
  - Region
  - Previous BIO use
  - Previous corticosteroid use
  - Other

#### **7.3.6 Pharmacokinetic and pharmacodynamic analyses**

BI655130 (SPESOLIMAB) concentrations will be reported descriptively. No PK parameters will be calculated.



#### 7.4 INTERIM ANALYSES

In order to ensure the patient's safety during the trial, a fully external DMC (same DMC for both parts 1 and 2), independent of the trial and project teams, will be set-up to review all available un-blinded safety data as well as selected efficacy data at regular intervals following first-patient-in. A DMC SAP which describes the analyses required for assessment by the DMC will be produced and finalized prior to first patient randomised into the trial. Further details will be provided in a DMC charter.

No interim analyses of the primary endpoint(s) are planned for part 1 or for part 2 of the trial.

The primary analysis of Part 1 of the trial will be performed once all treated patients have completed the 12-week treatment period in this trial part; an interim data base snapshot will be done.

The primary analysis of Part 2 of the trial will be performed once all treated patients have completed this trial part.

## **7.5 HANDLING OF MISSING DATA**

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

If one or more subscores on the primary efficacy endpoint, calculated using the Mayo Clinic score, are missing at a visit then the overall outcome at that visit is also considered to be missing.

With regards to the handling of missing data on the primary efficacy endpoint, Non Response Imputation (NRI) will be applied, that is imputing as a failure to achieve a response.

If a patient takes rescue medication for the treatment of ulcerative colitis prior to observing the primary endpoint, then all data subsequent to the intake of such rescue will be considered to represent a failure to achieve a response (NRI). Further details with regard to what constitutes a rescue intake with potential impact on the primary efficacy endpoint will be described in the TSAP.

Sensitivity analyses will be performed on the primary (and key secondary) efficacy endpoint(s) using a multiple imputation approach for missing data. The method will include all post-baseline time-points up to and through week 12. The technical details regarding the implementation of the multiple imputation will be specified in the TSAP. Note that only on-treatment data is used for imputation since even if a patient discontinues following the first dose of BI655130 (SPESOLIMAB) on Day 0, the REP of 16 weeks means that no off-treatment data can be available at the time of the primary (or key secondary) endpoint analysis (at week 12):

- Utilize all available data regardless of rescue intake, then multiply impute any missing data up to and including week 12;
- Efficacy data after censoring (i.e. any observation collected after the first intake of rescue medication) will be set to missing, then multiply impute all missing data up to and including week 12.

Further sensitivity analyses to assess the robustness of the results on the primary efficacy endpoint may be performed and will be described in the TSAP.

For secondary and further endpoints, rules for handling of missing data will be specified in the TSAP if necessary. With respect to safety evaluations, it is not planned to impute missing values.



## 7.6 RANDOMISATION

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

After screening, eligible patients will be stratified according to previous BIO treatment failure (TNF $\alpha$  antagonists-**OR**-Vedolizumab versus TNF $\alpha$  antagonists-**AND**-Vedolizumab) and concomitant corticosteroid therapy (yes/no) at visit 2/randomization. There will be four strata for analysis purposes:

Stratum 1: TNF $\alpha$  antagonists-**OR**-Vedolizumab failure and concomitant corticosteroid therapy at visit 2/randomization;

Stratum 2: TNF $\alpha$  antagonists-**OR**-Vedolizumab failure and NO concomitant corticosteroid therapy at visit 2/randomization;

Stratum 3: TNF $\alpha$  antagonists-**AND**-Vedolizumab failure and concomitant corticosteroid therapy at visit 2/randomization;

Stratum 4: TNF $\alpha$  antagonists-**AND**-Vedolizumab failure and NO concomitant corticosteroid therapy at visit 2/randomization;

In addition, a stratification for Japan versus non-Japan will be done in order to assure that sufficient patients per treatment group are recruited specifically to support individual country submission in Japan; this strata will be treated as an operational strata and will not be included into the analyses of the primary endpoint.

The randomization system will include a cap for the stratum of patients with double MoA failure (strata 3 and 4). Screening of both TNF $\alpha$  antagonists-**AND**-Vedolizumab failure patients will be capped for part 1 once 48 randomized patients in Part 1 and capped for Part II once 117 randomized patients in Part 2 meet this criterion, This capping will apply to new patients for screening, while the patients who have been already screened at time of implementation of the cap will continue screening procedures in preparation for potential randomization into the study.

Within each stratum, patients will be randomized in a 1:1:1:1 randomization ratio (1:1:1 for Part 2) to receive either placebo or one of three (two for Part 2) BI655130 (SPESOLIMAB) dose regimens (low dose, intermediate dose, or high dose). The randomization will be done in blocks to achieve balanced allocation. The block size of the randomization will be documented in the CTR.

The process of randomization is done via an IRT. Practical aspects of the treatment allocation process are detailed in [Section 4.1.3](#).

## 7.7 DETERMINATION OF SAMPLE SIZE

The study is intended to show a benefit of BI655130 (SPESOLIMAB) over placebo in terms of the difference in proportion of patients achieving clinical remission at Week 12 in both Parts 1 and 2.

### 7.7.1 Sample size determination for Part 1

The aims of Part 1 are two-fold. A first aim is to show a significant non-flat dose-response across the different doses of BI655130 (SPESOLIMAB) and placebo assuming a higher rate of remission on BI655130 (SPESOLIMAB) versus Placebo of 0.20. Subsequently, at least one modelled dose within the (total) dose range considered [0 mg, 1200 mg q4w] should show a benefit of at least 0.16 (see rationale below) in the proportion of patients achieving clinical remission at week 12 compared to placebo for demonstration of PoC (and subsequent Go decision). In cases where the benefit compared to placebo is less than 0.16 but at least 0.11 then a more detailed analysis of the part 1 results (e.g. subgroup analyses, PK/PD analyses, biomarker analyses) will be done in order to define the optimal path forward. Assumptions for the efficacy of the selected doses are provided in the table below.

For placebo, the proportion of patients who achieve clinical remission when a centrally-read endoscopy is used is typically very low [[R17-2467](#)]; therefore, for Placebo, a fixed rate of 15% of patients achieving clinical remission at week 12 will be considered for sample size planning in this trial.

Based on these assumptions and the planned sample size of 160 (= 40:40:40:40) the success probability (achieved when the proportion of patients achieving clinical remission at week 12 on a dose of BI655130 (SPESOLIMAB) exceeds the placebo effect by 0.16) is approximately 66% for the base case where a maximum difference to placebo of 0.20 is assumed (0.35, 0.30, 0.25 vs 0.15 for clinical remission rates at week 12 of BI655130 (SPESOLIMAB) high to low doses and placebo respectively). In the case that there is no treatment benefit, the false positive probability is limited by the  $\alpha$ -level for the significance testing of the non-flat dose-response curve of 20% (one-sided).

The following [Table 7.7.1:1](#) provides success probabilities under different scenarios, whereby success is defined as 1) Significant non-flat dose-response achieved AND 2) Treatment benefit of at least 'delta' compared to placebo for at least one modelled dose within the considered dose range.

Table 7.7.1:1 Probability of achieving the threshold difference in treatments given expected treatment response rates and a total sample size of 160 patients (based on MCPMod alpha-level of 20% [one-sided]) in Part 1

Scenario	Population Response Rate				Expected max. Response Difference	Delta	Success probability*	N per treatment group (1:1:1:1)
	Low dose BI	Middle dose BI	High dose BI	Placebo				
+	0.25	0.30	0.35	0.15	0.20	0.16	0.672	40
+M+	0.25	0.35	0.35	0.15	0.20	0.16	0.746	40
+L-	0.20	0.30	0.35	0.15	0.20	0.16	0.704	40
Sub-optimal	0.20	0.25	0.30	0.15	0.15	0.16	0.460	40
Minimal	0.15	0.20	0.25	0.15	0.10	0.16	0.268	40
No Effect	0.15	0.15	0.15	0.15	0.00	0.16	0.020	40
++	0.25	0.40	0.40	0.15	0.25	0.16	0.896	40
+	0.25	0.30	0.35	0.15	0.20	0.11	0.836	40
+M+	0.25	0.35	0.35	0.15	0.20	0.11	0.870	40
+L-	0.20	0.30	0.35	0.15	0.20	0.11	0.855	40
Sub-optimal	0.20	0.25	0.30	0.15	0.15	0.11	0.675	40
Minimal	0.15	0.20	0.25	0.15	0.10	0.11	0.496	40
No Effect	0.15	0.15	0.15	0.15	0.00	0.11	0.088	40
++	0.25	0.40	0.40	0.15	0.25	0.11	0.952	40

Success probabilities have been calculated using R Version 3.2.2 based on simulations (10000 simulations per scenario). Thereby the calculations for the PoC step have been performed using DoseFinding R-package 0.9-15 [[R15-2001](#)].

A: Expected + case: Main scenario reflecting assumptions for efficacy of 0.15 (placebo), 0.25 (low dose), 0.30 (medium dose), and 0.35 (high dose).

B: Expected +M+ case: Same scenario as A but assuming a higher response rate for the medium dose of 0.35.

C: Expected +L- case: Same scenario as A but assuming a lower response rate for the low dose of 0.20.

D: Suboptimal: Scenario reflecting a suboptimal maximum response rate. The response rates are assumed to be 0.15 (placebo), 0.20 (low dose), 0.25 (medium dose), 0.30 (high dose).

E: Minimal: Scenario with a low treatment benefit of 0.10 maximum compared to placebo. Represents a ‘worse-case’ scenario for treatment benefit.

F: No effect: Scenario reflecting no treatment benefit.

G: Plus Plus: Scenario reflecting large efficacy compared to placebo: 0.15 (placebo), 0.25 (low dose), 0.40 (medium dose), 0.40 (high dose).

### 7.7.2 Sample size determination for Part 2

Sample size calculation for part 2 of the trial has been performed with the statistical software R, Version 3.3.2.

As noted with the sample size calculation for Part 1, the proportion of patients who achieve clinical remission on Placebo when a centrally-read endoscopy is used is typically very low [[R17-2467](#)]; therefore, for this trial, a fixed rate of 15% of patients achieving clinical remission on Placebo at week 12 will be considered for further sample size planning.

Based on an application of the defined testing strategy (see [Section 7.2](#)) regarding the different endpoints, a simulation based power calculation has been performed for sample size assessment on both the primary and key secondary endpoints. For this purpose a correlation of 0.5 has been assumed between the different endpoints.

[Table 7.7.2: 2](#) presents scenarios for the planning of this trial whereby a difference versus Placebo of 0.20 is assumed for the proportion of patients who achieve clinical remission at week 12 (the primary endpoint). Calculations were performed using a 1-sided overall alpha level of 0.025 with a truncated Hochberg correction (‘truncation fraction’ = 1/2) applied to correct for multiplicity as a result of performing 2 treatment comparisons versus Placebo.

In line with the expected treatment benefit on the primary endpoint of clinical remission, it is also required that the magnitude of the BI655130 (SPESOLIMAB) response on key secondary endpoints, i.e., both the proportion of patients with mucosal healing and the proportion of patients with clinical response be at least 0.20 larger than the corresponding effect on placebo. Assuming therefore, an overall type 1 error= 0.025 (1-sided), a difference of 0.20 for each BI655130 (SPESOLIMAB) dose relative to Placebo in mucosal healing (rate assumed for each dose of BI655130 (SPESOLIMAB): 0.35, and placebo: 0.15), and a difference of 0.25 in clinical response (rate assumed for each dose of BI655130 (SPESOLIMAB): 0.60, and placebo: 0.35), and given the total of 390 patients (130 per treatment arm), the overall power that both/at least one dose(s) of BI655130 (SPESOLIMAB) would achieve statistical significance versus placebo for the primary and both key secondary endpoints will be approximately 81%/96% respectively (with a graphical approach used to attribute the remaining  $\alpha'$  from the test on the primary endpoint in order to correct for multiplicity because of multiple endpoints as well as two doses of BI655130 (SPESOLIMAB)). Note that alpha passing, for the case when both doses of BI655130

(SPESOLIMAB) are statistically significant on the primary endpoint and one dose is subsequently statistically significant on all endpoints in the secondary family (key secondary and secondary), is not considered in the sample size evaluation.

Table 7.7.2: 1 Power to achieve statistical significance for the primary endpoint (clinical remission) and both key secondary endpoints (mucosal healing and clinical response) on both doses of BI655130 (SPESOLIMAB) under various scenarios

Scenario	Population Response Rate			Overall power to achieve all 3 endpoints	
	Clinical remission (H/L/P)	Mucosal Healing (H/L/P)	Clinical Response (H/L/P)	Power for both doses of BI655130 (SPESOLIMAB) to be stat. sig.	Power for at least one dose of BI655130 (SPESOLIMAB) to be stat. sig.
+	0.35/0.35/0.15	0.35/0.35/0.15	0.60/0.60/0.35	81.4%	95.6%
Sub-optimal	0.30/0.30/0.15	0.30/0.30/0.15	0.60/0.60/0.35	49.1%	77.2%
Minimal	0.25/0.25/0.15	0.25/0.25/0.15	0.60/0.60/0.35	13.5%	36.0%
++	0.40/0.40/0.15	0.40/0.40/0.15	0.60/0.60/0.35	92.3%	98.9%
↓ Placebo +	0.30/0.30/0.10	0.30/0.30/0.10	0.60/0.60/0.35	88.2%	97.9%
↓ low dose BI	0.35/0.30/0.15	0.35/0.30/0.15	0.60/0.55/0.35	57.8%	89.8%

Table 7.7.2:2 Power to achieve statistical significance for the primary endpoint (clinical remission) on both doses of BI655130 (SPESOLIMAB) under various scenarios

Scenario	Population Response Rate			Expected Response Difference	N per treatment group (1:1:1)	Power for both doses of BI655130 (SPESOLIMAB) to be stat. sig.	Power for at least one dose of BI655130 (SPESOLIMAB) to be stat. sig.
	High dose BI	Low dose BI	Placebo				
+	0.35	0.35	0.15	0.20	130	92.5%	98.6%
Sub-optimal	0.30	0.30	0.15	0.15	130	69.2%	88.9%
Minimal	0.25	0.25	0.15	0.10	130	31.3%	58.1%
++	0.40	0.40	0.15	0.25	130	99.0%	99.9%
↓ Placebo +	0.30	0.30	0.10	0.20	130	96.6%	99.6%
↓ low dose BI	0.35	0.30	0.15	0.20/0.15	130	78.7%	96.5%

To be noted that the sample size for Part 2 of the study may be adapted based on results from Part 1 in which case a protocol amendment will be required.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

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

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following webpage: [trials.boehringer-ingelheim.com](http://trials.boehringer-ingelheim.com). The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report. The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

### **8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT**

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

The investigator or a designee must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

The patient must be given sufficient time to consider participation in the trial. The investigator or a designee obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or a designee must sign (or place a seal on) and date the informed consent form.

If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

## 8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

## 8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See [Section 4.1.5.2](#) for rules about emergency code breaks. For drug accountability, refer to [Section 4.1.8](#).

### 8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see [Section 8.3.2](#)). The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

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

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

- Patient identification: gender, year of birth (in accordance with local laws and regulations)



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

### 8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

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

An adaptive approach to clinical trial monitoring will be utilised. The sponsor will perform a risk assessment of the trial to determine the extent and nature of monitoring required in order to ensure the reliability and robustness of the results. Regular review of risk reports will provide sponsor oversight during trial conduct and direct monitoring activities to the areas of greatest risk which have the most potential impact to patient safety and data quality.

The investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results. The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in [Section 8.3.1](#).

The sponsor will also monitor compliance with the protocol and ICH GCP.

An adaptive approach to clinical trial monitoring will be utilised. This is initiated by an assessment of the risk associated with the trial combined with identification of critical data

and processes. An Integrated Quality and Risk Management Plan documents the strategies involved with the implementation of onsite, offsite and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to patient safety and data quality. Trial oversight is achieved by regular review of a report of risk which then influences any monitoring adaptations.

The investigator /institution will allow on-site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results. The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in [Section 8.3.1](#). The sponsor will also monitor compliance with the protocol and ICH GCP.

### 8.3.3 Storage period of records

#### Trial site(s):

The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

#### Sponsor:

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

## EXPEDITED REPORTING OF ADVERSE EVENTS

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

## 8.4 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.

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

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

### 8.4.1 Collection, storage and future use of biological samples and corresponding data

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

- Sample and data usage has to be in accordance with the separate biobanking informed consent

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

## 8.5 TRIAL MILESTONES

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

The **end of the trial** is defined as the date of the last visit of the last patient in the whole trial (“Last Patient Out”). The “**Last Patient Drug Discontinuation**” (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

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

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

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

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

## 8.6 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

A project-independent, fully-external data-monitoring committee (DMC), will be established to assess the progress of the clinical trial, including an unblinded safety and efficacy assessment at specified intervals on each study Part, and to recommend to the sponsor whether to continue, modify, or stop either a single BI655130 (SPESOLIMAB) dose or the

trial due to safety or ethical concerns. Measures will be put in place to ensure blinding of the project team and all other trial participants (see [Section 7.4](#) for further details). The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

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

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Manager (CT Manager), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

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

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

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

## 9. REFERENCES

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## 10. APPENDICES

### 10.1 MAYO SCORING SYSTEM FOR THE ASSESSMENT OF ULCERATIVE COLITIS ACTIVITY

The Mayo score (Schroeder et al., N Engl J Med, 1987) is a composite disease activity score consisting of four items or subscores: stool frequency (relative to normal), rectal bleeding, physician's global assessment, and endoscopic appearance. As proposed by FDA draft guidance [R17-0038], the endoscopic subscore is modified so that a value of 1 does not include friability. The overall range of the Mayo score is 0-12 (higher scores being worse) and each subscore has a range of 0-3 (Table 10.1: 1). At visits without sigmoidoscopy, a partial Mayo score without endoscopy subscore will be assessed. The overall range of this partial Mayo score is 0-9.

In addition, based on FDA's recommendation [R17-0038], a modified Mayo score will be assessed, which excludes physician's assessment. The overall range of the modified Mayo score is 0-9.

The scores for stool frequency and rectal bleeding will be calculated as an average based on the last 3 non-missing scores from the 7 days prior to each applicable visit, as collected from the patient diary. If the patient undergoes bowel preparation for colonoscopy on any of the days before a visit, the stool frequency and rectal bleeding subscore for that day(s) should be considered missing. In addition, the stool frequency and rectal bleeding subscore will be considered to be missing both for the day of and the day after the endoscopy.

The endoscopic appearance score will be assessed by both, the investigational site and a central reader, who is independent from the investigator.

Table 10.1: 1 Mayo score (adopted from Schroeder et al, 1987)

Components	Subscore	Severity	Score
		Normal number of stools for patient	0
	Stool Frequency <sup>a</sup> (daily)	1 to 2 stools more than normal	1
		3 to 4 stools more than normal	2
		≥5 stools more than normal	3
		No blood seen	0
<b>CLINICAL RESPONSE</b>  (Patient's Symptoms)	Rectal Bleeding <sup>b</sup> (daily)	Streaks of blood with stool	1
		Obvious blood with stool	2
		Blood alone passes	3
		Normal	0
	Physician's Global Assessment <sup>d</sup>	Mild disease	1
		Moderate disease	2
		Severe disease	3
<b>MODIFIED ENDOSCOPIC RESPONSE</b>  (Objective Evidence of Inflammation)	Endoscopic Appearance <sup>c</sup>	Normal	0
		Mild disease	1
		Moderate disease	2
		Severe disease	3

- a) Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.  
 b) The daily bleeding score represents the most severe bleeding of the day.  
 c) Modified endoscopic appearance: 0 (normal), Mild (erythema, decreased vascular pattern, granularity), Moderate (marked erythema, loss of vascular pattern, any friability, erosions), Severe (spontaneous bleeding, ulceration).  
 d) The physician's assessment acknowledged the three other criteria, the patient's daily record of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Schroeder KW, Tremaine WJ, Ilstrup DM

Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis: a randomized study.

N Engl J Med 317 (26), 1625 - 1629 (1987)

## 10.2 HISTOLOGIC ACTIVITY SCORE

The Robarts histopathology index is a histologic activity score (Mosli et al, Gut2015). The total score ranges from 0 (no disease activity) to 33 (severe disease activity).

Table 10.2: 1 Robarts Histopathology Index (RHI) by components

Component	
Intercept	
Chronic inflammatory infiltrate	0=No Increase 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase
Lamina propria neutrophils	0=None 1=Mild but unequivocal increase 2=Moderate increase 3=Marked increase
Neutrophils in epithelium	0=None 1=<5% crypts involved 2=<50% crypts involved 3=>50% crypts involved
Erosion or ulceration	0=No erosion, ulceration, or granulation tissue 1=Recovering epithelium + adjacent inflammation 1=Probably erosion-focally stripped 2=Unequivocal erosion 3=Ulcer or granulation tissue

Mosli MH, Feagan BG, Zou G, et al. Development and validation of a histological index for UC. Gut 2015.

Based on this, the RHI will be calculated as follows:

$RHI = 1 \times \text{chronic inflammatory infiltrate level (4 levels)} + 2 \times \text{lamina propria neutrophils (4 levels)} + 3 \times \text{neutrophils in epithelium (4 levels)} + 5 \times \text{erosion or ulceration (4 levels after combining Geboes 5.1 and 5.2)}$

### 10.3 EQUIVALENT DOSES OF CORTICOSTEROIDS

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

### 10.4 PATIENT REPORTED OUTCOMES

#### 10.4.1 Inflammatory Bowel Disease Questionnaire (IBDQ)

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

#### 10.4.2 EQ-5D-5L

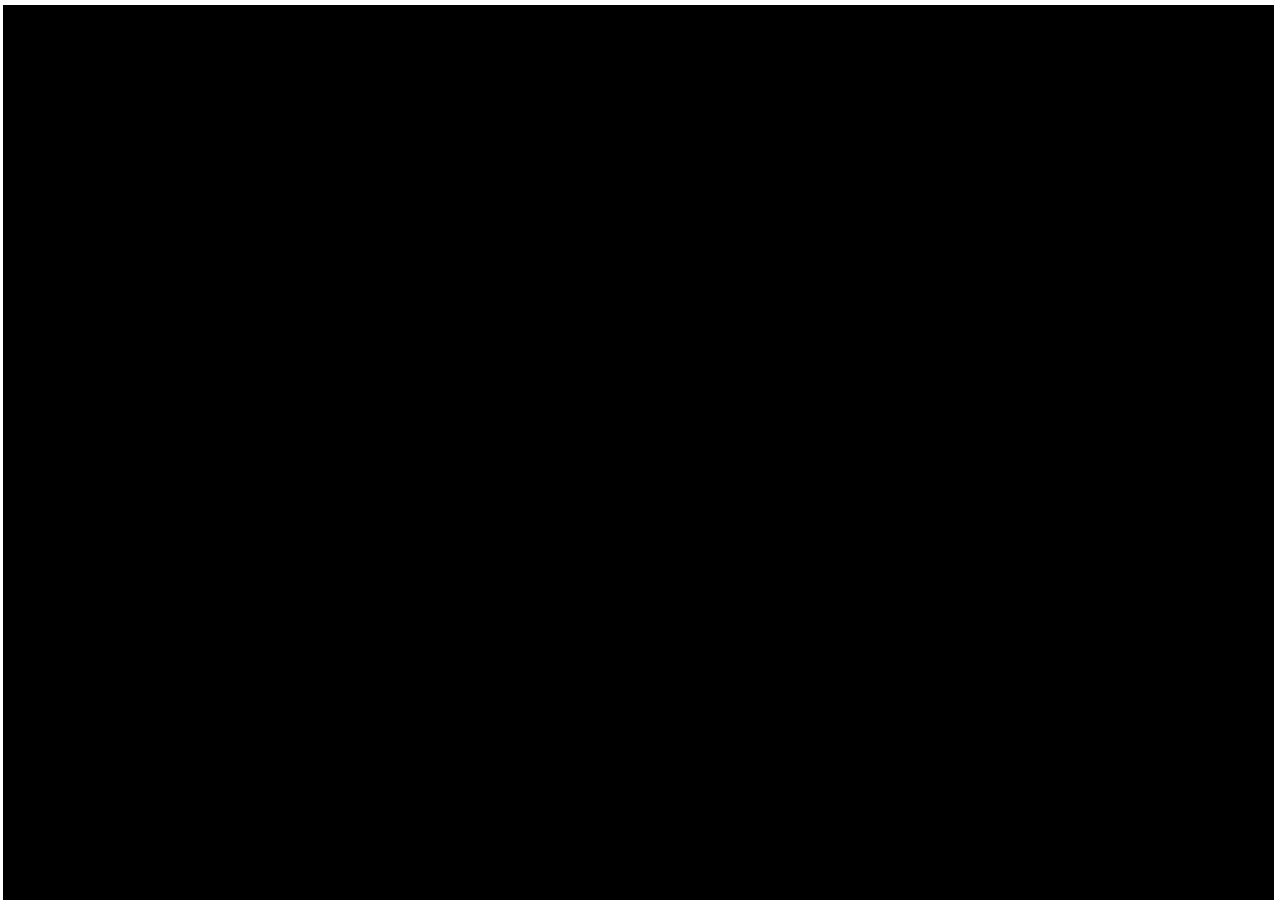
The EQ-5D(-5L) is a standardized instrument developed by the EuroQoL Group for use as a generic, preference-based measure of health outcome. The EQ-5D(-5L) questionnaire captures two basic types of information, an overall health rating using a visual analog scale and a descriptive “profile,” or “health state”. The health state is converted to a single weighted index score by applying coefficients from a validated value set. The index score is used in both clinical and economic evaluations of health care. These two basic types of information cannot be combined and will be reported separately.

The health state index measures five health dimensions. The health states for each respondent are converted into a single index number using a specified set of country-specific weights. A

higher score indicates a more preferred health status with 1.0 representing perfect health and 0 representing death. A missing answer on any one question leads to a missing overall score.

For purposes of the analyses for this study, all patients' EQ-5D(-5L) index scores will be calculated using the UK weights.

The VAS asks respondents to rate their present health status on a 0 - 100 visual analog scale, with 0 labelled as "Worst imaginable health state" and 100 labelled as "Best imaginable health state." The VAS score is determined by observing the point at which the subject's hand drawn line intersects the scale.





## 10.6 DEFINITION OF PRIMARY, SECONDARY NONRESPONSE OR INTOLERANCE TO ANTI-INTEGRIN OR ANTI-TNF THERAPY

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

### I. Primary nonresponse to current or prior therapy with vedolizumab, infliximab, adalimumab, or golimumab (inadequate initial response)

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

#### A. Have received induction doses of:

- Vedolizumab (2 or 3 doses of  $\geq 300$  mg) or
- Infliximab (2 or 3 doses of  $\geq 5$  mg/kg) or
- Adalimumab (at a dose of 160 mg followed by a dose  $\geq 80$  mg **or** at a dose of 80 mg followed by a dose  $\geq 40$  mg or

- Golimumab (2 or 3 doses of 50 or 100 mg (per locally approved label))

AND

**B. Did not initially respond to these induction doses of vedolizumab, infliximab, adalimumab, or golimumab as evidenced by the presence of at least 1 of the following signs or symptoms related to persistence of Ulcerative Colitis, as assessed by a treating physician:**

- Lack of improvement, or worsening in stool frequency.
- Lack of improvement, or worsening in daily abdominal pain.
- Occurrence, lack of improvement, or worsening of fever thought to be related to Ulcerative Colitis.
- Lack of improvement or worsening in rectal bleeding.
- Initiation or increase in antidiarrheal medication.

These signs and symptoms of Ulcerative Colitis must have occurred  $\leq$  2 weeks after receiving the last induction dose of vedolizumab, infliximab, adalimumab, or golimumab, and are offered only as a benchmark of the minimally acceptable criteria required to designate a patient as having had an inadequate initial response.

AND

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

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

**II. Secondary nonresponse to current or prior therapy with vedolizumab, infliximab, adalimumab or golimumab (response followed by loss of response)**

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

**A. Initially responded to induction therapy**

AND

**B. Have received at least 2 maintenance doses of:**

- Vedolizumab (at a dose of  $\geq 300$  mg) or
- Infliximab (at a dose of  $\geq 5$  mg/kg) or
- Adalimumab (at a dose of  $\geq 40$  mg) or
- Golimumab (at a dose of  $\geq 50$  or 100 mg (per locally approved label))

**AND**

**D. Have or had at least 1 of the following signs or symptoms related to recurrence of Ulcerative Colitis, as assessed by a treating physician:**

- Lack of improvement, or worsening in stool frequency.
- Lack of improvement, or worsening in daily abdominal pain.
- Occurrence, lack of improvement, or worsening of fever thought to be related to Ulcerative Colitis.
- Lack of improvement or worsening in rectal bleeding.
- Initiation or increase in antidiarrheal medication.

These signs and symptoms of Ulcerative Colitis must have occurred  $\leq 2$  weeks after receiving the last maintenance dose of vedolizumab, infliximab, adalimumab or golimumab and are offered only as a benchmark of the minimally acceptable criteria required to designate a patient as having lost response.

**AND**

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

- Provide the dates and doses of the failed maintenance therapy.
- Documents that the patient had recurrence of disease activity despite the failed maintenance therapy.

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

**III. Current or prior intolerance to therapy with vedolizumab, infliximab, adalimumab, or golimumab**

Eligible patients must satisfy criteria A and B.

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

**1. Significant acute infusion/administration reaction;**

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

**Definitions of these 3 criteria are provided below. Adverse reactions also must have followed  $\geq 1$  dose of vedolizumab, infliximab, adalimumab, or golimumab and, in the treating physician's opinion, precluded continued use of the therapy.**

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

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

**AND**

- Was considered related to the infusion/administration of vedolizumab, infliximab, adalimumab, or golimumab.

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

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

AND

- Occurred > 24 hours and < 15 days after infusion/administration of vedolizumab, infliximab, adalimumab, or golimumab.

AND

- Was considered related to the infusion/administration of vedolizumab, infliximab, adalimumab, or golimumab.

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

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

AND

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

AND

- Was considered related to the injection.

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

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

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

## 10.7 DIAGNOSIS OF ANAPHYLAXIS

### Clinical Criteria for diagnosing anaphylaxis [[R11-4890](#)]

<b>Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled</b>
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
<i>AND AT LEAST ONE OF THE FOLLOWING</i>
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to <u>known</u> allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.

\*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg +[2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

**10.8. SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY  
 COMMON TOXICITY CRITERIA (OMERACT)**

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
	Asymptomatic, or transient  Short duration (< 1 week)  No change in life style  No medication or OTC	Symptomatic  Duration (1–2 weeks)  Alter lifestyle occasionally  Meds relieve. (may be prescription),  Study drug continued	Prolonged symptoms, reversible, major functional impairment  Prescription meds/partial relief  May be hospitalized <24h  Temporary study drug discontinuation, or/and dose reduced	At risk of death  Substantial disability, especially if permanent.  Multiple meds  Hospitalised >24h  Study drug discontinued
<b>A.ALLERGIC/IMMUNOLOGIC</b>				
A1. Allergic reaction/hyper-sensitivity (including drug fever)	Transient rash; drug fever < 38° C, transient asymptomatic bronchospasm	Generalized urticaria responsive to meds; or drug fever > 38° C, or reversible bronchospasm	Symptomatic bronchospasm, requiring meds; symptomatic urticaria persisting with meds, allergy related oedema/angioedema	Anaphylaxis, laryngeal/pharyngeal edema, requiring resuscitation
A2. Autoimmune reaction	Serologic or other evidence of autoimmune reaction but patient asymptomatic: all organ function normal and no treatment is required (e.g.,	Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immune-	Reversible autoimmune reaction involving function of a major organ or toxicity requiring short term immune-suppressive treatment (e.g., transient colitis or	Causes major organ dysfunction, or progressive, not reversible, or requires long term administration of high dose immune-suppressive

	vitiligo)	suppressive drugs (e.g., hypo-thyroidism)	anemia)	therapy
A3. Rhinitis (includes sneezing, nasal stuffiness, post nasal discharge)	Transient, non-prescription meds relieve	Prescription med required, slow	Corticosteroids or other prescription med. with persistent disabling symptoms such as impaired exercise tolerance	NA



## 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

### 11.1 GLOBAL AMENDMENT 1

<b>Date of amendment</b>		18 December 2017
<b>EudraCT number</b> <b>EU number</b>		2017-004230-28
<b>BI Trial number</b>		1368-0005
<b>BI Investigational Product(s)</b>		BI 655130
<b>Title of protocol</b>		A Phase II/III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of BI 655130 Induction Therapy in patients with moderate-to-severely active ulcerative colitis who have failed previous biologics therapy
<b>To be implemented only after approval of the IRB / IEC / Competent Authorities</b>		x
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		
<b>Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only</b>		
<b>Section to be changed</b>		5.2.6.1 Definitions of AEs
<b>Description of change 1</b>		<p>Hepatic injury</p> <p>A hepatic injury is defined by the following alterations of hepatic laboratory parameters:          an elevation of AST and/or ALT &gt;3 fold ULN combined with an elevation of total bilirubin &gt;2 fold ULN measured in the same blood draw sample, and/or          aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN</p> <p>These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the “DILI checklist” provided in the ISF.</p> <p>In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal</p>

	<p>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.</p> <p><i>changed to:</i></p> <p>Hepatic injury</p> <p>A hepatic injury is defined by the following alterations of hepatic laboratory parameters:</p> <ol style="list-style-type: none"> <li>a. ALT or AST &gt;5x ULN</li> <li>b. ALT or AST &gt;3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (&gt; 5%)</li> <li>c. AST and/or ALT &gt;3 fold ULN combined with an elevation of total bilirubin &gt;2 fold ULN measured in the same blood draw sample</li> </ol> <p>These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the “DILI checklist” provided in the ISF.</p> <p>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.</p> <p>If an alternative cause for the hepatic injury cannot be identified in the follow-up assessments specified in the “DILI checklist”, discontinuation of treatment with study drug should be considered.</p>
<p><b>Rationale for change</b></p>	<p>FDA request for change the definition of hepatic injury to be consistent with the FDA Guidance for Industry</p>
<p><b>Section to be changed</b></p>	<p>3.3.3.3 General Exclusion Criteria</p>
<p><b>Description of change 2</b></p>	<p>Pathological safety lab parameters: haemoglobin &lt; 8 g/dL,</p> <p><i>changed to:</i></p>

		Pathological safety lab parameters: haemoglobin < 9 g/dL,
<b>Rationale for change</b>		FDA recommendation for excluding patients with a hemoglobin less than 9g/dL (instead of <8g/dL) to allow for patients to have fluctuations or a small drop in hemoglobin without causing them to discontinue the trial.
<b>Section to be changed</b>		Title page
<b>Description of change 3</b>		Update on CIs addresses
<b>Rationale for change</b>		Administrative change
<b>Section to be changed</b>		Flowchart ½, footnote #5
<b>Description of change 4</b>		<i>Statement added:</i> More frequent testing should be done if required by the local regulation and / or authority or per investigator judgment
<b>Rationale for change</b>		To allow Countries to be compliant with local standards
<b>Section to be changed</b>		Flow charts part1 /2, footnote #10
<b>Description of change 5</b>		A diary will be used by the patient for the “daily reporting of bowel movement frequency and rectal bleeding (blood in stool). This information will be used for the calculation of Mayo score at the visits. In addition, background medication will be recorded by patients in diary provided and assessed by study staff” changed to:  10. “A diary will be used by the patient for the daily reporting of bowel movement frequency and rectal bleeding (blood in stool). This information will be used for the calculation of Mayo score at the visits.”
<b>Rationale for change</b>		To reflect study operational set up
<b>Section to be changed</b>		6.2.1. Screening and run-in period(s)
<b>Description of change 6</b>		Patient diary Patients who are eligible at Visit 1a will receive a patient diary to be used for 1) daily reporting of stool frequency and rectal bleeding (blood in stool) during the week prior to visits which include assessment of Mayo score, as well as 2) daily intake of concomitant UC medication over the whole treatment period.

		<p><i>changed to:</i>          Patient diary          Patients who are eligible at Visit 1a will receive a patient diary to be used for daily reporting of stool frequency and rectal bleeding (blood in stool) during the week prior to visits which include assessment of Mayo score</p>
<b>Rationale for change</b>		To reflect study operational set up
<b>Section to be changed</b>		Flow charts part1 /2, footnote #4
<b>Description of change 7</b>		<p>Monitor for signs and symptoms of hypersensitivity reactions for approximately 3 hours after the first dose administered at Visit 2</p> <p><i>Changed to:</i>          Monitor for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the first dose administered at Visit 2</p>
<b>Rationale for change</b>		Typo correction
<b>Section to be changed</b>		Withdrawal from trial treatment
<b>Description of change 8</b>		Added: If a hepatic injury alert (as defined in section 5.2.6: 1) is detected without identification of an alternative cause in the work-up according to the “DILI checklist”, discontinuation of treatment with study drug should be considered
<b>Rationale for change</b>		Additional stopping rule added
<b>Section to be changed</b>		4.3 Treatment compliance
<b>Description of change 9</b>		<p>Study medication will be administered in accordance with the protocol by authorised study personnel (e.g. study nurse).</p> <p><i>Changed to:</i>          Study medication will be administered in accordance with the protocol, under supervision of the investigating physician or a designee at the site</p>
<b>Rationale for change</b>		To express the requirement that physician should be present at administration of study medication
<b>Section to be changed</b>		5.2.6.2 Adverse event collection and reporting

Description of change 10		<i>Sentence deleted:</i> Exemptions to SAE reporting Protocol specified outcome events should be collected on the appropriate CRF page only.
Rationale for change		Protocol doesn't define exemptions to SAE reporting
Section to be changed		5.3.2 Methods of sample collection
Description of change 11		The PK study samples will be discarded after completion of the investigations but not later than 3 years after the final study report has been signed. <i>Changed to:</i> The PK study samples will be discarded after completion of the investigations but not later than 5 years after the final study report has been signed.
Rationale for change		Typo correction
Section to be changed		6.2.1 Screening and run-in period(s)



Rationale for change		Administrative change – incorrect sentence deletion
Section to be changed		8.1 Trial approval, Patient information, Informed consent
Description of change 13		The investigator must give a full explanation to trial patients ..... The investigator obtains written consent of the patient's ... The investigator must sign (or place a seal on) and date the informed consent form. <i>Changed to:</i> The investigator or a designee must give a full explanation to trial patients ... The investigator or a designee obtains written consent of the patient's ... The investigator or a designee must sign (or place a seal on) and date the informed consent form.
Rationale for change		Clarification on informed consent process
Section to be changed		5.2.6.2 Adverse event collection and reporting
Description of change 14		<i>Following sentence deleted:</i> Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires a

		written consent of the pregnant partner.
Rationale for change		No genotoxicity or demonstrated or suspected human teratogenicity/fetotoxicity of BI 655130 at subtherapeutic systemic exposure levels

## 11.2 GLOBAL AMENDMENT 2

<b>Date of amendment</b>		05 October 2018
<b>EudraCT number</b>		2017-004230-28
<b>EU number</b>		
<b>BI Trial number</b>		1368-0005
<b>BI Investigational Product(s)</b>		SPESOLIMAB
<b>Title of protocol</b>		A Phase II/III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of SPESOLIMAB Induction Therapy in patients with moderate-to-severely active ulcerative colitis who have failed previous biologics therapy
<b>To be implemented only after approval of the IRB / IEC / Competent Authorities</b>		<b>x</b>
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		
<b>Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only</b>		
<b>Section to be changed</b>		Flow chart 1, 2
<b>Description of change 1</b>		Correction in calculation of trial periods
<b>Rationale for change</b>		Administrative
<b>Section to be changed</b>		Footnote #4 of Flow Chart, part 1 and part 2
<b>Description of change 2</b>		In addition, at Visits 2, 4 and 5 vital signs will be assessed at approximately 5 and 60 minutes after study drug administration. <i>Changed to:</i> In addition, at Visits 2, 4 and 5 vital signs will be assessed at approximately 5 and 60 minutes after the end of study drug administration.
<b>Rationale for change</b>		To clarify visit procedures
<b>Section to be changed</b>		Footnote #8 of Flow Chart, part 1 and part 2
<b>Description of change 3</b>		At study visits with study drug administration, pre-dose PK/ADA/flow cytometry ██████████ samples <i>changed to:</i> At study visits with study drug administration, pre-dose PK/ADA ██████████ samples
<b>Rationale for change</b>		Correction of statement on planned analysis
<b>Section to be changed</b>		Footnote #10 of Flow Chart, part 1 and part 2
<b>Description of change 4</b>		This information will be used for the calculation of Mayo score at the visits. This information will be used for the calculation of Mayo score at the visits.

		<p><i>changed to:</i>          Please make sure that time window between visits V1a and visit V1b is minimum 7 days. This will ensure that enough eDiary data (SFS and RBS) are collected before visit V1b in order to calculate the baseline Mayo score. PGA (Physician Global Assessment) should be completed at all visits.</p>
<b>Rationale for change</b>		To clarify study procedure requirement
<b>Section to be changed</b>		[REDACTED]
<b>Description of change 5</b>		
<b>Rationale for change</b>		
<b>Section to be changed</b>		Table 3.1:1 Study definitions
<b>Description of change 6</b>		<p>Rescue Medication  <i>changed to:</i>          Rescue Treatment          New or increase in dose of any medication applied to treat new or persisting symptoms related to ulcerative colitis  <i>changed to:</i>          New or increase in dose of any medication, or a surgical procedure, applied to treat new or persisting symptoms related to ulcerative colitis</p> <p>Disease flare:          Increase in partial MCS score by <math>\geq 2</math> points from nadir, confirmed at a subsequent visit, AND by endoscopy showing an increase by <math>\geq 1</math> point from nadir in the modified Endoscopic Subscore (mESS)  <i>changed to:</i>          Disease flare:          Increase in partial MCS score by <math>\geq 2</math> points from nadir observed during a regular or unscheduled study visit, confirmed subsequently by sigmoidoscopy with the modified Endoscopic Subscore (mESS) <math>\geq 2</math> AND a second partial Mayo score measurement confirming the increase from nadir by <math>\geq 2</math>, in absence of enteric pathogens in stool</p>
<b>Rationale for change</b>		To provide more detailed specification



<b>Section to be changed</b>		3.1.2 Transition from Part 1 to Part 2 7.3 Planned Analyses
<b>Description of change 7</b>		The title ‘steering committee’ applied to the personnel involved in the review of the completed part 1 data has been changed to the ‘part 1 review committee’.
<b>Rationale for change</b>		Administrative change – the decision for the doses to be continued into Part 2 of the trial involves a data review on the completed Part 1 of the trial only by identified personnel; there is no consideration on data of other trials external to this trial in this decision. Hence, there is no involvement of a project-wide steering committee. More accurately, therefore, a Part 1 review committee has instead been defined to reflect that data review is solely confined to the completed trial part 1 data only.
<b>Section to be changed</b>		3.3.2 Inclusion criteria #3
<b>Description of change 8</b>		Moderate to severe activity (total MCS 6 to 12 AND mESS $\geq$ 2 within 7-28 days prior to first dose) <i>changed to:</i> Moderate to severe activity (total MCS 6 to 12 with a RBS $\geq$ 1 AND an SFS $\geq$ 1 AND mESS $\geq$ 2 within 7-28 days prior to first dose)
<b>Rationale for change</b>		<u>For SFS<math>\geq</math>1:</u> this is to adapt per FDA’s modified definition of clinical remission endpoint, in which SFS drop from baseline $\geq$ 1 is required. The adaption in SFS $\geq$ 1 at baseline ensure that all patients enrolled in this study have chance to achieve remission after treatment of SPESOLIMAB. <u>For RBS<math>\geq</math>1:</u> To reflect inclusion criteria in Tofa CTP.
<b>Section to be changed</b>		3.3.2 Inclusion criteria #5
<b>Description of change 9</b>		Demonstrated in the past inadequate response or loss of response or have had unacceptable side effects with approved doses of TNF $\alpha$ antagonists (infliximab, adalimumab, golimumab) and / or vedolizumab <i>changed to:</i> Well-documented demonstration of inadequate response or loss of response or have had unacceptable side effects with approved doses of TNF $\alpha$ antagonists (infliximab, adalimumab,

		golimumab) and/or vedolizumab in the past as per definition in the CTP Appendix 10.6
<b>Rationale for change</b>		To add requirement on documentation
<b>Section to be changed</b>		3.3.2 Inclusion criteria #6
<b>Description of change 10</b>		Oral budesonide ( $\leq 9$ mg per day ), provided that dose has been stable for the 2 weeks immediately prior to randomisation <i>changed to:</i> Oral budesonide ( $\leq 9$ mg per day) or beclomethasone dipropionate ( $\leq 5$ mg per day), provided that dose has been stable for the 2 weeks immediately prior to randomisation
<b>Rationale for change</b>		To allow previous beclomethasone dipropionate treatment
<b>Section to be changed</b>		3.3.2 Inclusion criteria #8
<b>Description of change 11</b>		Women of childbearing potential (WOCBP) and men able to father a child must be ready to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in <a href="#">Section 4.2.2.2</a> Restrictions regarding women of childbearing potential, in <a href="#">Section 4.2.2.3</a> Restriction for male participants and in the patient information. <i>changed to:</i> Women of childbearing potential (WOCBP) must be ready to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in <a href="#">Section 4.2.2.2</a> Restrictions regarding women of childbearing potential
<b>Rationale for change</b>		To align with updated contraception requirements in Investigator Brochure, version 5
<b>Section to be changed</b>		3.3.3.1. Exclusion criteria #9
<b>Description of change 12</b>		Faecal transplant $\leq 6$ months before screening <i>changed to:</i> Faecal transplant $\leq 30$ days prior to randomisation
<b>Rationale for change</b>		Update on restricted period
<b>Section to be changed</b>		3.3.3.2 Exclusion criteria #12
<b>Description of change 13</b>		Active or latent TB: Patients with a positive

		<p>TB test within one month of screening are excluded:</p> <ul style="list-style-type: none"> <li>• A positive QuantiFERON TB (Patients with suspected false positive or indeterminate QuantiFERON TB result may be re-tested once)</li> <li>• If Quantiferon not available or providing indeterminate results after repeat testing : A tuberculin skin test reaction <math>\geq 10\text{mm}</math> (<math>\geq 5\text{mm}</math> if receiving <math>\geq 15\text{mg/d}</math> prednisone or its equivalent)</li> </ul> <p><i>changed to:</i>          Active or latent TB: Patients with a positive TB test during screening are excluded, unless:</p> <ul style="list-style-type: none"> <li>• Patient had previous diagnosis of active or latent TB and has completed appropriate treatment per local practice/guidelines within the last 3 years and at least 6 months before first administration of trial medication under this protocol (patients may be re-screened once to meet this criterion)</li> <li>• A positive QuantiFERON TB (Patients with suspected false positive or indeterminate QuantiFERON TB result may be re-tested once)</li> <li>• If Quantiferon not available or providing indeterminate results after repeat testing, tuberculin skin test should be performed : A tuberculin skin test positive reaction <math>\geq 10\text{mm}</math> (<math>\geq 5\text{mm}</math> if receiving <math>\geq 15\text{mg/d}</math> prednisone or its equivalent)</li> </ul>
<p><b>Rationale for change</b></p>		<p>Alignment with project specific definition on TB exclusion</p>
<p><b>Section to be changed</b></p>		<p>3.3.3.2 Exclusion criteria #12</p>
<p><b>Description of change 14</b></p>		<p>Relevant chronic or acute infections including human immunodeficiency virus (HIV) or viral hepatitis. A patient can be re-screened if the patient was treated and is cured from the acute infection.</p> <p><i>changed to:</i>          Relevant chronic or acute infections including active tuberculosis, human immunodeficiency virus (HIV) infection or viral hepatitis. A patient can be re-screened if the patient was treated and is cured from the acute infection.</p>

<b>Rationale for change</b>		To specify an active tuberculosis as an exclusion criterium
<b>Section to be changed</b>		4.2.1 Other treatments and emergency procedures
<b>Description of change 15</b>		Statement added: If infusion or anaphylactic reaction had already occurred in the very same patient in the past, pre-treatment with steroids before next IMP administration is permitted as secondary prophylaxis.
<b>Rationale for change</b>		Clarification on prophylaxis
<b>Section to be changed</b>		4.2.1 Other treatments and emergency procedures 5.2.6.1. Adverse events of special interest
<b>Description of change 16</b>		<p>Following statements deleted:  <u>Cytokine release syndrome (CRS)</u>          This syndrome manifests when a large number of immune cells becomes activated and releases inflammatory cytokines.          Potentially life-threatening complications of a cytokine release syndrome include cardiac dysfunction, respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation. In case of suspicion of a cytokine release syndrome, it is recommended to measure IL-6 levels in the local laboratory if the assay is available.          The investigator should discontinue treatment with study drug. Aggressive supportive care is essential for patients experiencing CRS, with early intervention for hypotension and treatment of concurrent infections. IL-6 receptor blockade with tocilizumab should be considered. Corticosteroids should be reserved for neurologic toxicities and CRS not responsive to tocilizumab [R16-5751].</p> <ul style="list-style-type: none"> <li>• <u>Cytokine release syndrome</u> <ul style="list-style-type: none"> <li>○ May manifest when a large number of immune cells becomes activated and releases inflammatory cytokines.              Potentially life-threatening complications include cardiac dysfunction, respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation.</li> </ul> </li> </ul>
<b>Rationale for change</b>		According to Investigator Brochure, version 5, Cytokine release syndrome is not considered as

		AESI anymore.
<b>Section to be changed</b>		4.2.2 Restriction
<b>Description of change 17</b>		<p>Added:          Fecal microbiota transplantation (FMT) – not allowed from 30 days prior to randomisation until end of the trial  <u>Oral administration:</u>          Oral budesonide (<math>\leq 9</math> mg per day), provided that dose has been stable for the 2 weeks immediately prior to randomisation  <i>changed to:</i>  <u>Oral administration:</u>          Oral steroids are only allowed if indicated for treatment of UC and at a dose of <math>\leq 20</math>mg per day of prednisone or equivalent and with stable dose for at least 2 weeks prior to randomisation and throughout the trial.          Oral budesonide (<math>\leq 9</math> mg per day), provided that dose has been stable for the 2 weeks immediately prior to randomisation          Oral beclomethasone dipropionate (<math>\leq 5</math> mg per day), provided that dose has been stable for the 2 weeks immediately prior to randomisation</p> <p>Added:          Allowed steroid treatments:          Short-term use (&lt;7 days) of systemic (oral or parenteral) corticosteroids is allowed for treatment of AE not related to the underlying UC from 4 weeks prior to randomisation until end of the trial. Locally administered steroids as e.g. intra-articular, nasal inhalation or intra-ocular administration are allowed.</p> <p>NSAID: Chronic use not allowed from 2 weeks prior to screening up to end of the trial</p> <p><i>changed to:</i></p> <p>NSAID: Chronic use (i.e. <i>daily</i> use for &gt;2 weeks) not allowed from 2 weeks prior to screening up to end of the trial</p> <p>Deleted:          Antidiarrheals: Only allowed during the trial, if dose is stable for at least 2 weeks prior to</p>

		randomization and throughout the trial.
<b>Rationale for change</b>		Update on restriction
<b>Section to be changed</b>		4.2.2.2 Restrictions regarding women of childbearing potential
<b>Description of change 18</b>		Highly effective methods of birth control for female and female partner(s) of male participants who are able to become pregnant include: <i>changed to:</i> Highly effective methods of birth control for female participants.
<b>Rationale for change</b>		Consistency with changes in Investigator Brochure, version 5
<b>Section to be changed</b>		4.2.2.3 Restrictions for male participants
<b>Description of change 19</b>		Deleted: 4.2.2.3 Restrictions for male participants Men should avoid sperm donation for the entire duration of the trial.
<b>Rationale for change</b>		Consistency with changes in Investigator Brochure, version 5
<b>Section to be changed</b>		6.2.1 Screening and run- in period (s)
<b>Description of change 20</b>		The Screening visit (Visit 1a) should normally take place no more than 35 days before Visit 2 and be complete no less than 7 days prior to Visit 2. <i>changed to:</i> The Screening visit (Visit 1a) should normally take place no more than 35 days before Visit 2 and be complete no less than 14 days prior to Visit 2.  <b>Visit 1b:</b> The Visit 1b should take place no more than 8 days and no less than 6 day prior to Visit 2. <i>changed to:</i> <b>Visit 1b:</b> The Visit 1b should take place no more than 28 days and no less than 7 day prior to Visit 2.
<b>Rationale for change</b>		Typo correction
<b>Section to be changed</b>		6.2.2 Treatment periods
<b>Description of change 21</b>		<u>Concomitant medication review</u> Data concerning concomitant medications and procedures will be collected throughout the trial, as specified in the <a href="#">Flow Chart</a> . These data will be obtained at scheduled or unscheduled trial visits

		<p>based on information provided in the patient diaries, provided spontaneously by the patient or as a result of questioning the patient.</p> <p><i>changed to:</i></p> <p><u>Concomitant medication review</u></p> <p>Data concerning concomitant medications and procedures will be collected throughout the trial, as specified in the <a href="#">Flow Chart</a>. These data will be obtained at scheduled or unscheduled trial visits provided spontaneously by the patient or as a result of questioning the patient.</p>
<b>Rationale for change</b>		To reflect the fact that ConMed is not recorded in patient diaries.
<b>Section to be changed</b>		7.3 Planned analysis
<b>Description of change 22</b>		<p>The results on Part 1 will be reviewed by the DMC and by a steering committee which includes sponsor representatives, the DMC chair and the coordinating investigators. The decision to amend or to initiate part 2 without modifications (taking into account the decision criteria described in <a href="#">Section 3.1.2</a>) will be made by the sponsor based upon the recommendations of the independent DMC and the steering committee.</p> <p><i>changed to</i></p> <p>The results on Part 1 will be reviewed by the DMC and by a part 1 review committee which includes sponsor representatives, the DMC chair and the coordinating investigators. The decision to amend or to initiate part 2 without modifications (taking into account the decision criteria described in <a href="#">Section 3.1.2</a>) will be made by the sponsor based upon the recommendations of the independent DMC and the part 1 review committee.</p>
<b>Rationale for change</b>		Adapted for steering committee definition
<b>Section to be changed</b>		7.3 Planned analysis
<b>Description of change 23</b>		<p>There will be 4 main patient populations in this trial for analyses: the randomized set (RS), the treated set (TS), the modified RS (m-RS), and the per-protocol set (PPS). Each of these populations will be derived separately for each of the 2 trial parts.</p> <p><i>changed to:</i></p> <p>There will be 4 main patient populations in this trial for analyses: the randomized set (RS), the <u>safety analysis set (SAF)</u>, the modified RS (m-RS),</p>

		and the per-protocol set (PPS). Each of these populations will be derived separately for each of the 2 trial parts.  <u>Treated Set (TS)</u> <i>changed to:</i> <u>Safety Analysis Set (SAF)</u>
<b>Rationale for change</b>		Changes in analysis groups definition
<b>Section to be changed</b>		8.5. Trial milestones
<b>Description of change 24</b>		The <b>start of the trial</b> is defined as the date when the first patient in the whole trial signs informed insent. <i>changed to:</i> The <b>start of the trial</b> is defined as the date when the first patient in the whole trial signs informed consent.
<b>Rationale for change</b>		Typo correction



### 11.3 GLOBAL AMENDMENT 3

<b>Date of amendment</b>		09 October 2019
<b>EudraCT number</b>		2017-004230-28
<b>EU number</b>		
<b>BI Trial number</b>		1368-0005
<b>BI Investigational Product(s)</b>		BI655130 (SPESOLIMAB)
<b>Title of protocol</b>		A Phase II/III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of BI655130 (SPESOLIMAB) Induction Therapy in patients with moderate-to-severely active ulcerative colitis who have failed previous biologics therapy
<b>Global Amendment due to urgent safety reasons</b>		
<b>Global Amendment</b>		<b>X</b>

<b>Section to be changed</b>		All sections
<b>Description of change 1</b>		BI 655130 <i>changed to:</i> BI 655130 ( SPESOLIMAB)
<b>Rationale for change</b>		Brand name added

<b>Section to be changed</b>		All sections
<b>Description of change 2</b>		Corticosteroid use <i>changed to:</i> Concomitant corticosteroid therapy at V2
<b>Rationale for change</b>		More precise clarification of corticosteroids stratification

<b>Section to be changed</b>		Flowchart 1 and 2
<b>Description of change 3</b>		Possibility to measure drug level of previous biologics was added
<b>Rationale for change</b>		Possibility to measure drug level of previous biologics was added to give possibility to shorten washout period from currently defined 8 weeks per Protocol based on results of drug level of previous biologics treatment level.

<b>Section to be changed</b>		Flowchart 1 and 2
<b>Description of change 4</b>		Requirement to contact IRT at EOS visit removed
<b>Rationale for change</b>		Typo in previous version

<b>Section to be changed</b>		Flowchart 1 and 2
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<b>Description of change 5</b>		PGA assessmet added in separate line; Footnote 10 – PGA collection requirement clarified
<b>Rationale for change</b>		To ensure protocol compliance

<b>Section to be changed</b>		1.4 BENEFIT-RISK ASSESSMENT
<b>Description of change 6</b>		Benefit-Risk assessment section was re-phrased
<b>Rationale for change</b>		To reflect latest IB wording and BI project standard wording

<b>Section to be changed</b>		
<b>Description of change 7</b>		
<b>Rationale for change</b>		

<b>Section to be changed</b>		Tab. 3.1:1 Rescue treatment
<b>Description of change</b>		New or increase in dose of any medication, or a surgical procedure, applied to treat new or persisting symptoms related to ulcerative colitis <i>Changed to:</i> New or increase in dose of any medication, or a surgical procedure, applied to treat new or worsening symptoms related to ulcerative colitis
<b>Rationale for change</b>		More precise definition

<b>Section to be changed</b>		Tab. 3.1:1 Disease flare
<b>Description of change</b>		Increase in partial MCS score by $\geq 2$ points from nadir observed during a regular or unscheduled study visit, confirmed subsequently by sigmoidoscopy with the modified Endoscopic Subscore (mESS) $\geq 2$ AND a second partial Mayo score measurement confirming the increase from nadir by $\geq 2$ , in absence of enteric pathogens in stool - after achievement of a clinical response (as defined in <a href="#">table 2.2.2:1</a> ) <i>Changed to:</i> Increase in partial MCS score by $\geq 2$ points from baseline (in 2 subsequent visits) and increase in rectal bleeding score by $\geq 1$ point from baseline (in

		2 subsequent visits), confirmed by increase of modified endoscopic subscore by $\geq 1$ point from baseline with modified endoscopic subscore abs. increase by $\geq 2$ points in absence of enteric pathogens in stool (as defined in table 2.2.2:1)
<b>Rationale for change</b>		alignment with expert experiences with other UC programs

<b>Section to be changed</b>		All Sections
<b>Description of change</b>		Stratification for Japan versus rest of world <i>Changed to:</i> Stratification for Japan versus non-Japan
<b>Rationale for change</b>		More precise wording

<b>Section to be changed</b>		3.3.2 Inclusion criteria #5
<b>Description of change</b>		Agonists <i>Changed to:</i> Antagonists
<b>Rationale for change</b>		typo

<b>Section to be changed</b>		3.3.3.1 Exclusion criteria #4
<b>Description of change</b>		any biologic treatment with a TNF $\alpha$ antagonist (adalimumab, infliximab, golimumab) or vedolizumab within 8 weeks prior to randomisation <i>Changed to:</i> any biologic treatment with a TNF $\alpha$ antagonist (adalimumab, infliximab, golimumab, certolizumab) or vedolizumab within 8 weeks prior to randomisation. (If drug level testing for previously used biologic treatment confirms no detectable drug level before randomization, patient can be enrolled despite not having completed 8 weeks from last treatment.)
<b>Rationale for change</b>		Possibility to measure drug level of previous biologics was added to give possibility to shorten washout period from currently defined 8 weeks per Protocol based on results of drug level of previous biologics treatment level. Adaptation to current status of biologics treatment

<b>Section to be changed</b>		3.3.3.1 Exclusion criteria #4
<b>Description of change</b>		any <i>investigational</i> biologic for UC (including but not limited to ustekinumab and other IL-23 inhibitors) within 12 weeks prior to randomisation (except etrolizumab: within 8 weeks prior to

		randomisation) <i>Changed to:</i> any <i>investigational</i> biologic for UC (including IL-12 and IL-23 inhibitors; etrolizumab) within 8 weeks. (If drug level testing for previously used biologic treatment confirms no detectable drug level before randomization, patient can be enrolled despite not having completed 8 weeks from last treatment.)
<b>Rationale for change</b>		Possibility to measure drug level of previous biologics was added to give possibility to shorten washout period per Protocol based on results of drug level of previous biologics treatment level and to align with current standard Reflecting current status of biologics treatment

<b>Section to be changed</b>		3.3.3.1 Exclusion criteria #5
<b>Description of change</b>		Positive stool examination for C.difficile or other intestinal pathogens <i>Changed to:</i> Positive stool examinations for C. difficile (toxin A/B – test positive)
<b>Rationale for change</b>		Reflecting requirements for C.difficile positivity also included in central lab flagging

<b>Section to be changed</b>		3.3.3.2 Exclusion criteria#14
<b>Description of change</b>		patients with remote history of malignancy (< 10 years prior) <i>Changed to:</i> patients with remote history of malignancy (≥5 years prior)
<b>Rationale for change</b>		Project standard

<b>Section to be changed</b>		Section 4.1.1 Identity of the Investigational Medicinal Products
<b>Description of change</b>		Added description of test product and placebo for CMC12K material
<b>Rationale for change</b>		Required for additional countries to be added later in 2020

<b>Section to be changed</b>		Section 4.2.1 Management of AEs
<b>Description of change</b>		Infusion reactions including anaphylactic reactions <i>Changed to:</i> <u>Systemic hypersensitivity including infusion reaction and anaphylactic reaction</u>

<b>Rationale for change</b>	Project standard wording
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<b>Section to be changed</b>	Tab. 4.2.2.1 Restrictions regarding previous and concomitant treatment
<b>Description of change</b>	<p><i>Added :</i>          any biologic <i>approved</i> for UC adalimumab, infliximab, golimumab, vedolizumab Not allowed from 8 weeks prior to randomisation or from time when no detectable drug level was confirmed until end of the trial</p> <p>any <i>investigational or non-approved</i> biologic for UC (incl. ustekinumab, other IL-23 inhibitors, etrolizumab, certolizumab) Not allowed from 8 weeks prior to randomisation or from time when no detectable drug level was confirmed until end of the trial</p> <p>Any prior dose of Ustekinumab approved for UC is prohibited          Any biologic for treatment for any other indication ( e.g. Dupilumab for the treatment of atopic dermatitis - Not allowed from 8 weeks prior to randomisation until end of the trial          Oral corticosteroids: Short (&lt;7 days) decrease of dose for treatment of AEs <u>with subsequent increase back to initial baseline dose level is allowed</u></p>
<b>Rationale for change</b>	Reflecting current status of biologics treatment for UC and additional restrictions re-evaluated

<b>Section to be changed</b>	Tab. 5.2.3. Laboratory tests footnotes
<b>Description of change</b>	<p>If the 1st QuantiFERON®-TB test result is undetermined, a re-test should be performed. If the retest QuantiFERON-TB test result is undetermined, a PPD skin test should be performed</p> <p><i>Added:</i>          This applies for QuantiFERON®-TB test at screening as well as at EOS visit.</p>
<b>Rationale for change</b>	More precise wording

<b>Section to be changed</b>	5.2.6.1 Adverse events of special interest ( AESIs)
<b>Description of change</b>	Infusions reactions and anaphylactic reaction

		<i>Changed to:</i> <u>Systemic hypersensitivity including infusion reaction and anaphylactic reaction</u>
<b>Rationale for change</b>		Project standard

<b>Section to be changed</b>		5.2.6.2 AE Collection section
<b>Description of change</b>		<p><b><u>AE Collection</u></b></p> <p>The investigator shall maintain and keep detailed records of all AEs in the patient files.          The following must be collected and documented on the appropriate CRF(s) by the investigator:</p> <ul style="list-style-type: none"> <li>• From signing the informed consent onwards until either roll over into subsequent study 1368-0017 or 1368-0020 or until the end of residual effect period, REP): (for patients not enrolling into the subsequent studies):             <ul style="list-style-type: none"> <li>- all AEs (non-serious and serious) and all AESIs.</li> </ul> </li> <li>• For patients not rolling over into subsequent studies:              until the individual patient's end of trial:              - all related SAEs and all related AESIs. After the individual patient's end of the trial:              the Investigator does not need to actively monitor the patient for AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related relevant SAEs and relevant AESIs of which the Investigator may become aware of</li> </ul> <p><i>Changed to:</i></p> <p>The investigator shall maintain and keep detailed records of all AEs in the patient files.          The following must be collected and documented on the appropriate CRF(s) by the investigator:</p> <ul style="list-style-type: none"> <li>• From signing the informed consent onwards until the first dose of trial medication in the extension trial:              - all AEs (non-serious and serious) and all AESIs.</li> <li>• For patients not rolling over into subsequent open label extension studies:              from signing the informed consent onwards until the individual patient's end of trial (including 16 weeks follow-up visit after last treatment dose):</li> </ul>

		- all AEs ( non-serious and serious) and all AESIs. the Investigator does not need to actively monitor the patient for AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the Investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form, but not on the CRF.
<b>Rationale for change</b>		Project standard
<b>Section to be changed</b>		5.2.6.2 AE reporting to sponsor and timelines
<b>Description of change</b>		Fax reporting requirement removed
<b>Rationale for change</b>		Administrative requirement
<b>Section to be changed</b>		5.4.5 DNA banking
<b>Description of change</b>		Storage of the paxgene Blood DNA tubes changed from ambient to frozen
<b>Rationale for change</b>		Correction to align with lab manual
<b>Section to be changed</b>		5.5. Other Assessments
<b>Description of change</b>		<i>Added:</i> Optional assessment of drug level in blood of biologics used for the treatment of UC before screening for this study will be performed prior to randomization. Analysis will be done using a central laboratory vendor. This assessment will allow to randomize respective patients within a period shorter than 8 weeks when negative drug level of previous biologics is detected.
<b>Rationale for change</b>		Additional blood analysis added
<b>Section to be changed</b>		6.1 Visit Schedule
<b>Description of change</b>		If any of these visits has to be rescheduled, the date of subsequent visits should be calculated from date of previous visit. <i>Changed to:</i> If any of these visits has to be rescheduled, the date of subsequent visits should be calculated from day 0 (visit 2). There should be at least 14 days between two consecutive study drug administrations.

<b>Rationale for change</b>		Correction of mistake in previous version
<b>Section to be changed</b>		Section 10.1
<b>Description of change</b>		<i>Added:</i> In addition, the stool frequency and rectal bleeding subscore will be considered to be missing both for the day of and the day after the endoscopy.
<b>Rationale for change</b>		FDA guidance

<b>Section to be changed</b>		10.6 Definition of primary, secondary nonresponse or intolerance to anti-integrin or anti-TNF therapy
<b>Description of change</b>		Golimumab (2 or 3 doses of $\geq 100$ mg) <i>Changed to:</i> Golimumab (2 or 3 doses of 50 or 100 mg (per locally approved label ) Where applicable
<b>Rationale for change</b>		typo



<b>Section to be changed</b>		10.6 Definition of primary, secondary nonresponse or intolerance to anti-integrin or anti-TNF therapy
<b>Description of change</b>		These signs and symptoms of Ulcerative Colitis must have occurred $\geq 2$ weeks <i>Changed to:</i> These signs and symptoms of Ulcerative Colitis must have occurred $\leq 2$ weeks
<b>Rationale for change</b>		typo



**APPROVAL / SIGNATURE PAGE**
**Document Number: c15932366**
**Technical Version Number:4.0**
**Document Name: clinical-trial-protocol-version-04**

**Title:** A Phase II/III Randomized, Double-blind, Placebo-controlled, Multicenter Study to Evaluate the Safety and Efficacy of BI 655130 (SPESOLIMAB) Induction Therapy in patients with moderate-to-severely active ulcerative colitis who have failed previous biologics therapy

**Signatures (obtained electronically)**

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Drug Safety		10 Oct 2019 13:46 CEST
Approval-Therapeutic Area 		10 Oct 2019 13:49 CEST
Author-Clinical Trial Leader		10 Oct 2019 13:53 CEST
Approval-Team Member Medicine		10 Oct 2019 17:33 CEST
Approval-Biostatistics		11 Oct 2019 07:20 CEST
Verification-Paper Signature Completion		11 Oct 2019 08:59 CEST

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