Clinical Trial Protocol

	Document Number:	**c21616656-06**
EudraCT No.	2019-000805-60	
BI Trial No.	1371-0008	
BI Investigational Medicinal Product(s)	BI 894416	
Title	Safety, tolerability, pharmacokinetics [redacted] of single rising oral doses and multiple rising oral doses of BI 894416 versus placebo in male patients with asthma (single-blind, randomised, placebo-controlled, parallel group design).	
Lay Title	Evaluation of safety and tolerability of BI 894416 in patients with mild asthma.	
Clinical Phase	Phase Ib	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Principal Investigator	[redacted] Phone [redacted]	
Status	Final Protocol (Revised Protocol (based on global amendment 5))	
Version and Date	Version: 6.0	Date: 14 Oct 2020

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	05 April 2019
Revision date	14 October 2020
BI trial number	1371-0008
Title of trial	Safety, tolerability, pharmacokinetics [redacted] of single rising oral doses and multiple rising oral doses of BI 894416 versus placebo in male patients with asthma (single-blind, randomised, placebo-controlled, parallel group design).
Principal Investigator	[redacted] Phone [redacted]
Trial site	[redacted]
Clinical phase	Phase Ib
Trial rationale	In this trial, safety and tolerability of BI 894416 will be assessed in patients with mild asthma using single rising oral doses and multiple rising oral doses [redacted]
Trial objectives	To investigate safety, tolerability, pharmacokinetics [redacted] following single and multiple rising doses of BI 894416
Trial endpoints	Primary endpoint to assess safety and tolerability of BI 894416 is the percentage of patients with drug-related adverse events Secondary endpoints: Efficacy Endpoints (for lung function and small airway assessment) from MRD part: Airway Resistance (Raw) after 7 days of treatment Single-rising dose (SRD) part: $AUC_{0-\infty}$ and C_{max} of BI 894416 Multiple-rising dose (MRD) part: • After the first dose: AUC_{0-8} and C_{max} of BI 894416 • After the last dose: $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 894416
Trial design	Single-blind, randomised within dose groups, placebo-controlled parallel-group design

Number of patients	
total entered	80*
each treatment	10 per dose group (8 on BI 894416 and 2 on placebo) for SRD and MRD part ** Additional patients may be entered to extend the number of patients within a dose group or to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose and exposure in the respective trial part will not be exceeded. Thus, the actual number of patients entered may exceed 80 (may exceed 40 per trial part) but is not to exceed 100 (is not to exceed 50 per trial part).*
Diagnosis	Patients with mild asthma
Main criteria for inclusion	Male patients with mild asthma, age of 18 to 55 years (inclusive), body mass index (BMI) of 18.5 to 32 kg/m^2 (inclusive)
Test product	BI 894416 as tablet formulation
dose	SRD part: 75 mg, 125 mg, 170 mg (interim dose, added based on preliminary PK data), 175 mg, 225 mg MRD part: 10 mg t.i.d., 25 mg t.i.d., 50 mg t.i.d., 60 mg (interim dose, added based on preliminary PK data), 70 mg t.i.d.
mode of admin.	Oral with 240 mL of water
Comparator product(s)	Matching placebo(s)
dose	Not applicable
mode of admin.	Oral with 240 mL of water
Duration of treatment	BI 894416 and placebo: Single rising dose (SRD) Part 1 day Multiple rising dose (MRD) and 9 days
Statistical methods	Descriptive statistics will be calculated for all endpoints.

FLOW CHARTS

SINGLE-RISING DOSE (SRD) PART – OVERVIEW

Trial Period	**Screening**	**Treatment**							**Follow Up**
Visit	**1**	**2**	**3**		**4**	**5**	**6**	**7**	**8**
Day	-28 to -3	-3 to -1	1	2	3	4	5	8	15 to 17
Visit type	**O**	**O**	**I**		**O**	**O**	**O**	**O**	**O**
Informed consent[1]	X								
Demographics[2,3]	X								
Review of in/exclusion criteria	X		X						
Medical History[3]	X								
Baseline Medications	X								
Reversibility Testing	X								
Physical Examination	X[20]		X					X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				[redacted]
Bodyplethysmography	X								X
[redacted]	[redacted]								[redacted]
Vital Signs[5]	X	X	X	X	X	X			X
Safety Laboratory test[6]	A	B[16, 21]	C,B	C	B			C	C
Drug Screening[7]	X		X						
Cotinine Test	X		X						
Stationary Admission			X						
Treatment Allocation[8]			X						
12-lead ECG[9]	X[15]	X[17]	X[18]	X[18]	X	X			X
Continuous ECG monitoring[10]			X						
Pharmacogenomic sampling[11]			X						
BI 894416 or placebo administration[8]			X[19]						
PK blood[9,12]			X	X	X	X	X		
PD [redacted]			[redacted]	[redacted]					
PK urine[13]			◄-	-	-►				
Adverse Events[14]		X	X	X	X	X	X	X	X
Concomitant Therapy[14]		X	X	X	X	X	X	X	X

O = Outpatient, I = Inhouse

1. Patient must be informed and written informed consent obtained prior to starting any screening procedures.
2. Including determination of body height and weight, smoking history and alcohol history.
3. Data are not needed to be entered in the electronic case report form (eCRF) again if already collected and entered in eCRF for a previous screening for this study within 30 days before current screening.
4. [redacted]
5. Vital signs must be completed prior to bodyplethysmography.
6. Letters A, B, and C describe different sets of safety laboratory examinations (see Section 5.2.4)
7. Drug screening will be performed at screening and prior to dosing on Day 1 of visit 3. A breath alcohol test will be performed prior to BI 894416 or placebo administration in Visit 3, and may be repeated at any time during the study at the discretion of an investigator or designee.
8. At Day 1 the following procedures must be completed prior to BI 894416 or placebo administration: Safety laboratory, neurological examination, Vital signs, ECG, [redacted] and PK samplings. The respective procedures are to be performed and completed within 3 h prior to BI 894416 or placebo administration. Allocation to treatment at Visit 3 could be performed at any time following enrolment but had to be completed prior to BI 894416 or placebo administration.
9. PK samplings and ECGs should be done in direct sequence for matching reasons. Please refer to Flow Chart "SRD part – Time schedule";

10. Continuous ECG monitoring to be done starting at least 15 minutes pre-dose of BI 894416 or placebo administration and for at least 4 hours following BI 894416 or placebo administration (3-lead ECG recording).
11. This sample is optional. In case a patient takes part in both a SRD and a MRD dose group only one pharmacogenomic sample is to be taken. The pharmacogenomics sample requires a separate consent.
12. PK samples for plasma level determination of BI 894416 [redacted] assay are to be taken at the time points as outlined in Flow Chart "SRD part – Time schedule" and in Section 5.3.2.2 Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK [redacted]) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per patient.
13. PK urine samplings for determination of BI 894416 amount eliminated in urine are to be taken at following time intervals: A blank urine sample is to be obtained within 3 hours prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals 0-4, 4-8, 8-12, 12-24 and 24-48 h (see Flow Chart "SRD part – Time schedule"; Section 5.3.2.3).
14. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked at time points indicated in the Flow Chart "SRD part – Time schedule" below.
15. 12-lead ECG and rhythm strip over at least 15 min.
16. Safety laboratory to be taken and to be medically evaluated within 3 days (within 76 hours) prior to administration of BI 894416; this ambulatory visit including safety laboratory, neurological exam, ECG and adverse event questioning can be omitted if the screening examination is performed on Day -3, Tables 5.2.4: 1 and 5.2.4: 2.
17. Three triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes (refer to Flow Chart "SRD part – Time schedule" and Section 5.2.5.1).
18. All ECGs at this day will be done as triplicate ECG (for details refer to SRD part – Time schedule and Section 5.2.5.1).
19. Oral with 240 mL of water after an overnight fast of at least 10 h. (please also refer to Section 4.2.2.2)
20. Physical examination includes an echocardiography (stress) test in the screening period in patients aged 45 and older.
21. SARS-CoV-2 PCR Test will be done at Visit 2 only. Result must be available prior to randomization. If Visit 2 is omitted (see footnote 16), the test must be performed on day -3 to -1.

SRD PART – TIME SCHEDULE

Visit	Day	Planned time (relative to BI 894416 or placebo administration [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[6]	PK $_{blood}$[8,9,10]	PD $_{blood}$ assay[8,9]	[redacted]	Physical Examination[9]	Neurological examination[9]	Vital signs (BP, PR)[9,12]	12-lead ECG[9,10]	Continuous ECG monitoring	Questioning for AEs and concomitant therapy[16]
1	-28 to -3			Screening (SCR)[1]	A[7]				X[17]	X	X	X		
2	-3 to -1	-72:00	08:00	Ambulatory visit[2]	B[2]					X		X[13]		X
3	1	-3:00	06:00	Admission, treatment allocation	C[7]	X	X		X	X	X	X[14]	X[15]	X
		0:00	**08:00**	**BI 894416 or placebo administration[3]**									▲	
		0:15	08:15			X							|	
		0:30	08:30			X					X	X[14]	|	X
		0:45	08:45			X					X		|	X
		1:00	09:00			X					X	X[14]	|	X
		1:30	09:30			X					X	X[14]	|	
		2:00	10:00	240 mL fluid intake		X	X				X	X[14]	|	X
		2:30	10:30			X					X	X[14]	|	
		3:00	11:00			X					X	X[14]	|	X
		4:00	12:00	240 mL fluid intake, thereafter lunch[4]	B	X	X			X	X	X[14]	▼	X
		6:00	14:00			X					X	X[14]		X
		8:00	16:00	Snack (voluntary)[4]		X	X				X	X[14]		X
		10:00	18:00			X								
		11:00	19:00	Dinner										
		12:00	20:00			X					X	X[14]		X
	2	24:00	08:00	Breakfast[4]	C	X	X			X	X	X[14]		X
3		28:00	12:00	Lunch[4]										X
3		32:00	16:00	Snack (voluntary)										
3		34:00	18:00	Discharge from trial site		X					X	X		X
4	3	48:00	08:00	Ambulatory visit	B	X				X	X	X		X
5	4	72:00	08:00	Ambulatory visit		X					X	X		X
6	5	96:00	08:00	Ambulatory visit		X								X
7	8	168:00	08:00	Ambulatory visit	C				X					X
8	15 to 17			Final Follow Up Visit[5]	C				X	X	X	X		X

1. Patient must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, reversibility testing (Appendix 10.3), neurological examination, bodyplethysmography, [redacted], check of vital signs, ECG (12-lead ECG and rhythm strip over at least 15 min), safety laboratory (including drug screening), demographics (including determination of body height and weight, smoking and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Demographic and medical history data are not needed to be entered in the electronic case report form (eCRF) again if

already collected and entered in eCRF for a previous screening for this study within 30 days before current screening. [redacted]

2. Safety laboratory to be taken and to be medically evaluated within 3 days (within 76 hours) prior to administration of BI 894416; this ambulatory visit including safety laboratory, neurological exam, ECG and adverse event questioning can be omitted if the screening examination is performed on Day -3.
3. Oral with 240 mL of water after an overnight fast of at least 10 h; (please also refer to Section 4.2.2.2)
4. If several actions are indicated at the same time point, the intake of meals will be the last action.
5. Final Follow up Visit includes physical examination, neurological examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
6. Letters A, B and C describe different sets of safety laboratory examinations (see Section 5.2.4).
7. Drug screening will be performed at screening and prior to dosing on Day 1 of visit 3. A breath alcohol test will be performed prior to BI 894416 or placebo administration at Visit 3, and may be repeated at any time during the study at the discretion of an investigator or designee. Pharmacogenomic samples will be collected if needed (This sample is optional. In case a patient takes part in both a SRD and a MRD dose group only one pharmacogenomic sample is to be taken.).
8. PK samples for plasma level determination of BI 894416 [redacted] are to be taken at the time points as outlined in Flow Chart "SRD part – Time schedule" and in Section 5.3.2.2 Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK [redacted] data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per patient.
9. For allowed deviation from the scheduled time please refer to Section 6.1.
10. PK samplings and ECGs should be done in direct sequence for matching reasons.
11. PK urine samplings for determination of BI 894416 amount eliminated in urine are to be taken at following time intervals: A blank urine sample is to be obtained within 3 hours prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals 0-4, 4-8, 8-12, 12-24 and 24-48 h (see Flow Chart "SRD part – Time schedule"; Section 5.3.2.3).
12. Vital signs must be completed prior to bodyplethysmography.
13. Three triplicate ECG are recorded within approximately one hour. The recordings should be separated by at least 15 minutes (refer to Flow Chart "SRD part – Time schedule" and to Section 5.2.5.1);
14. Triplicate ECG (refer to Flow Chart "SRD part – Time schedule" and to Section 5.2.5.1);
15. Continuous ECG monitoring to be done starting at least 15 minutes pre-dose of BI 894416 or placebo administration and for at least 4 hours following BI 894416 or placebo administration (3-lead ECG recording).
16. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart "SRD part -Time schedule".
17. Physical examination includes an echocardiography (stress) test in the screening period in patients aged 45 and older.

MULIPLE-RISING DOSE (MRD) PART – OVERVIEW

Trial Period	**Screening**		**Treatment**											**Follow Up**				
Visit	**1**	**2**	**3**											**4**	**5**	**6**	**7**	**8**
Day	-28 to -3	-3 to -1	-1	1	2	3	4	5	6	7	8	9 / EOT	10	11	12	13	16	23 to 30
Visit type	**O**	**O**	**I**											**O**	**O**	**O**	**O**	**O**
Informed consent[1]	X																	
Demographics[2,3]	X																	
Review of in/exclusion criteria	X			X														
Medical History[3]	X																	
Baseline Medication	X																	
Physical Examination	X[22]			X			X					X		X			X	X
Reversibility Testing[4]	X																	
Neurological examination	X		X	X	X	X	X	X	X	X	X	X	X		X		X	X
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Laboratory test[6]	A	B[17,23]		C	B	C		B			C			C		C	C	C
Drug Screening[7]	X			X														
Cotinine Test	X			X								X						
Stationary Admission			X															
Discharge from site													X					
[redacted]			[redacted]									[redacted]						
Body plethysmography	X		X									X						X
[redacted]	[redacted]		[redacted]									[redacted]						[redacted]
12-lead ECG[9]	X		X[18]	X[19]	X[19]	X	X	X	X	X	X	X[19]	X[19]	X	X	X	X	X
Pharmacogenomic sampling[10]				X														
Treatment Allocation[11]				X														
BI 894416 or placebo administration[11,12]				X[20]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[21]	X[20]						
PK blood[9,13,14]				X	X			X		X	X	X	X	X	X	X		
[redacted]				[redacted]	[redacted]							[redacted]	[redacted]					
PK urine[15]				◄-	-►							◄-	-►					
Adverse Events[16]		X[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy[16]		X[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

O = Outpatient, I = Inhouse, EOT = End of Treatment

1. Patients must be informed and written informed consent obtained prior to starting any screening procedures.
2. Including determination of body height and weight, smoking and alcohol history.
3. Data are not needed to be entered in the electronic case report form (eCRF) again if already collected and entered in eCRF for a previous screening for this study within 30 days before current screening.
4. Reversibility testing (Appendix 10.3) can be omitted if patient took part in one of the SRD groups before.
5. Vital signs must be completed prior to bodyplethysmography.
6. Letters A, B and C describe different sets of safety laboratory examinations (see Section 5.2.4).
7. Urine drug screening will be performed at screening and prior to dosing on Day 1 of visit 3. A breath alcohol test will be performed prior to BI 894416 or placebo administration in Visit 3, and may be repeated at any time during the study at the discretion of an investigator or designee.
8. [redacted]
9. PK samplings and ECGs should be done in in direct sequence for matching reasons. Please refer to Flow Chart "MRD part – Time schedule";
10. This sample is optional. A separate consent is required. In case a patient takes part in both a SRD and a MRD dose group only one pharmacogenomic sample is to be taken.
11. At Day 1 the following procedures must be completed prior to BI 894416 or placebo administration: Safety laboratory, neurological examination, Vital signs, ECG, PD and PK samplings. The respective procedures are to be performed and completed within 3 h prior to BI 894416 or placebo administration. Allocation to treatment at Visit 3 could be performed at any time following enrolment but had to be completed prior to BI 894416 or placebo administration.
12. BI 894416 or placebo administration at Day 1 and Day 9 once daily in the morning (qd) and at Day 2 to Day 8 three times daily at an interval of 8 hours (tid).
13. PK samples for plasma level determination of BI 894416 [redacted] are to be taken at the time points as outlined in Flow Chart "MRD part – Time schedule"; Section 5.3.2.2 and in Appendix 10.2. [redacted], Section 5.3.2.2 and in Appendix 10.2. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK [redacted] data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per patient.
14. [redacted]
15. PK urine samplings for determination of BI 894416 amount eliminated in urine are to be taken at following time intervals: A blank urine sample is to be obtained within 3 hours prior to administration of trial medication. [redacted] Other urine samples are to be collected over the stated post-dose intervals 0-4, 4-8, 8-12 and 12-24h after BI 894416 or placebo administration on Day 1 and Day 9 only.
16. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked at time points indicated in the Flow Chart "MRD part – Time schedule".
17. Safety laboratory to be taken and to be medically evaluated within 3 days (within 76 hours) prior to administration of BI 894416; this ambulatory visit for safety laboratory and questioning for AEs and concomitant therapies can be omitted if the screening examination is performed on Day -3 or if lab sample can be taken on Day -1 and the lab results can be medically evaluated before BI 894416 or placebo administration at Day 1, Tables 5.2.4: 1 and 5.2.4: 2.
18. Three triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes (refer to Flow Chart "MRD part – Time schedule" and to Section 5.2.5.1);
19. Triplicate ECG (refer to Flow Chart "MRD part – Time schedule" and to Section 5.2.5.1);
20. Oral with 240 mL of water after an overnight fast of at least 10 h; (please also refer to Section 4.2.2.2)
21. Oral with 240 mL of water

22. Physical examination includes an echocardiography (stress) test in the screening period in patients aged 45 and older. Assessment can be omitted if patient took part in one of the SRD groups before.
23. SARS-Cov-2 PCR Test will be done at Visit 2 only. Result must be available prior to randomization. Result must be available prior to randomization. If Visit 2 is omitted (see footnote 17), the test must be performed on day -3 to -1.

MRD PART / TIME SCHEDULE

Visit	Day	Planned time (relative to BI 894416 or placebo administration [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK blood[10, 11 12,13]	[redacted]	PK urine[11 14]	Physical Examination[11]	Neurological examination[11]	Bodyplethysmography and [redacted]	Vital signs (BP, PR)[11]	[redacted]	12-lead ECG[11,13]	Questioning for AEs and concomitant therapy[11,20]
1	-28 to -3			**Screening (SCR)[1]**	A[8]				X[21]	X	X	X		X	
2	-3 to -1				B[9]							X			X[9]
3	-1	-17:00	15:00	**Admission**						X	X[16]	X	X	X[18]	X
3	1	-1:00	07:00					X	X			X[17]		X[19]	X
3	1	-0:05	07:55		C[8]	X									
3	1	**0:00**	**08:00**	**BI 894416 or placebo administration[2]**				▲							
3	1	0:15	08:15			X		|						
3	1	0:30	08:30			X		|				X		X[19]	
3	1	0:45	08:45			X		|							
3	1	1:00	09:00	240 mL fluid intake		X		|				X		X[19]	
3	1	1:30	09:30			X		|						X[19]	
3	1	2:00	10:00			X		|				X		X[19]	X
3	1	2:30	10:30			X		|						X[19]	
3	1	3:00	11:00	240 mL fluid intake		X		|				X		X[19]	
3	1	4:00	12:00			X		+		X			X		X[19]	X
3	1	5:00	13:00	Lunch				|							
3	1	6:00	14:00			X		|				X		X[19]	
3	1	8:00	16:00			X		+					X		X[19]	X
3	1	9:00	17:00					|							
3	1	10:00	18:00			X		|							
3	1	11:00	19:00	Dinner				|							
3	1	12:00	20:00			X		+					X		X[19]	X
3	2	22:30	06:30					|		X			X			X
3	2	23:00	07:00					|								
3	2	23:55	07:55		B	X		|							
3	2	24:00	8:00	**BI 894416 or placebo administration[2]**				▼							X[19]	
3	2	25:00	09:00	Breakfast									X			
3	2	28:00	12:00							X						X
3	2	29:00	13:00	Lunch												
3	2	32:00	16:00	**BI 894416 or placebo administration[3,4]**									X			X
3	2	33:00	17:00													
3	2	34:00	18:00										X		X	X
3	2	35:00	19:00	Dinner												
3	2	40:00	24:00	**BI 894416 or placebo administration[3]**									X			
3	3	47:00	07:00							X			X		X	X
3	3	47:55	07:55		C											
3	3	48:00	8:00	**BI 894416 or placebo administration[2]**												
3	3	49:00	09:00	Breakfast									X			
3	3	52:00	12:00							X						X
3	3	53:00	13:00	Lunch												
3	3	56:00	16:00	**BI 894416 or placebo administration[3,4]**									X		X	X
3	3	57:00	17:00													

Visit	Day	Planned time (relative to BI 894416 or placebo administration [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK $_{blood}$ [10, 11 12,13]	PD $_{blood}$ assay[10, 11]	PK $_{urine}$ [11 14]	Physical Examination[11]	Neurological examination[11]	Bodyplethysmography and FeNO[11,15]	Vital signs (BP, PR)[11]	Nasal Brushing[11]	12-lead ECG [11,13]	Questioning for AEs and concomitant therapy[11,20]
3	3	58:00	18:00									X		X	X
3	3	59:00	19:00	Dinner											
3	3	64:00	24:00	**BI 894416 or placebo administration[3]**								X			
3	4	70:30	06:30						X			X		X	X
3	4	71:00	07:00							X					
3	4	72:00	8:00	**BI 894416 or placebo administration[2]**											
3	4	73:00	09:00	Breakfast								X			
3	4	76:00	12:00							X					X
3	4	77:00	13:00	Lunch											
3	4	80:00	16:00	**BI 894416 or placebo administration[3,4]**								X		X	X
3	4	81:00	17:00												
3	4	82:00	18:00												X
3	4	83:00	19:00	Dinner											
3	4	88:00	24:00	**BI 894416 or placebo administration[3]**								X			
3	5	95:00	07:00									X			X
3	5	95:55	07:55		B	X	X								
3	5	96:00	8:00	**BI 894416 or placebo administration[2]**											
3	5	97:00	09:00	Breakfast											
3	5	98:00	12:00							X					X
3	5	101:00	13:00	Lunch											
3	5	104:00	16:00	**BI 894416 or placebo administration[3,4]**								X		X	X
3	5	105:00	17:00												
3	5	106:00	18:00												X
3	5	107:00	19:00	Dinner											
3	5	112:00	24:00	**BI 894416 or placebo administration[3]**											
3	6	119:00	07:00									X			X
3	6	119:55	07:55												
3	6	120:00	8:00	**BI 894416 or placebo administration[2]**											
3	6	121:00	09:00	Breakfast											
3	6	124:00	12:00							X					
3	6	125:00	13:00	Lunch											
3	6	128:00	16:00	**BI 894416 or placebo administration[3,4]**								X		X	X
3	6	131:00	19:00	Dinner											
3	6	136:00	24:00	**BI 894416 or placebo administration[3]**											
3	7	143:00	07:00									X			X
3	7	143:55	07:55			X	X								
3	7	144:00	8:00	**BI 894416 or placebo administration[2]**											
3	7	145:00	09:00	Breakfast											
3	7	148:00	12:00							X					
3	7	149:00	13:00	Lunch											
3	7	151:55	15:55												
3	7	152:00	16:00	**BI 894416 or placebo administration[3,4]**								X		X	X

Visit	Day	Planned time (relative to BI 894416 or placebo administration [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[7]	PK $_{blood}$ [10, 11 12,13]	PD $_{blood}$ assay[10, 11]	PK $_{urine}$ [11 14]	Physical Examination[11]	Neurological examination[11]	Bodyplethysmography and FeNO[11,15]	Vital signs (BP, PR)[11]	Nasal Brushing[11]	12-lead ECG [11,13]	Questioning for AEs and concomitant therapy[11,20]
3	7	155:00	19:00	Dinner											
3	7	159:55	23:55												
3	7	160:00	24:00	**BI 894416 or placebo administration[3]**											
3	8	167:00	07:00									X			X
3	8	167:55	07:55		C	X	X								
3	8	168:00	8:00	**BI 894416 or placebo administration[2]**											
3	8	169:00	09:00	Breakfast											
3	8	172:00	12:00							X					
3	8	173:00	13:00	Lunch											
3	8	175:55	15:55			X	X								
3	8	176:00	16:00	**BI 894416 or placebo administration[3,4]**								X		X	X
3	8	179:00	19:00	Dinner											
3	8	183:55	23:55			X									
3	8	184:00	24:00	**BI 894416 or placebo administration[3]**											
3	9	190:30	06:30					X	X			X[17]			X
3	9	191:00	07:00								X[16]				
3	9	191:55	07:55			X	X							X[19]	
3	9	192:00	08:00	**BI 894416 or placebo administration[2,5]**				▲							
3	9	192:15	08:15			X									
3	9	192:30	08:30			X						X		X[19]	
3	9	192:45	08:45			X									
3	9	193:00	09:00	240 mL fluid intake		X						X		X[19]	
3	9	193:30	09:30			X								X[19]	
3	9	194:00	10:00			X	X					X		X[19]	
3	9	194:30	10:30			X								X[19]	
3	9	195:00	11:00	240 mL fluid intake		X						X		X[19]	
3	9	196:00	12:00			X	X	┼		X		X		X[19]	X
3	9	197:00	13:00	Lunch											
3	9	198:00	14:00			X						X		X[19]	
3	9	200:00	16:00			X	X	┼				X	X	X[19]	
3	9	202:00	18:00			X									
3	9	204:00	20:00			X		┼				X		X[19]	X
3	10	216:00	08:00	Discharge from site		X	X	▼		X		X		X[19]	X
4	11	240:00	08:00	Ambulatory Visit	C	X			X			X		X	X
5	12	264:00	08:00	Ambulatory Visit		X				X		X		X	X
6	13	288:00	08:00	Ambulatory Visit	C	X						X		X	X
7	16			Ambulatory Visit	C				X	X		X		X	X
8	23-30			Final Follow Up Visit[6]	C				X	X	X[16]	X[17]		X	X

1. Patient must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include physical examination, reversibility testing (Appendix 10.3; Reversibility testing can be omitted if patient took part in one of the SRD groups before), neurological examination, check of vital signs, ECG (12-lead ECG and rhythm strip over at least 15 min), safety laboratory (including drug screening), bodyplethysmography, [redacted] demographics (including determination of body height and weight, smoking and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Demographic and medical history data are not needed to be entered in the electronic case report form (eCRF) again if already collected and entered in eCRF for a previous screening for this study within 30 days before current screening.

2. Oral with 240 mL of water after an overnight fast of at least 10 h; (please also refer to Section 4.2.2.2)
3. Oral with 240 mL of water;
4. Patient must be fasted for 2 h prior to trial medication administration. Afterwards snack (voluntary) 1 h after BI 894416 or placebo administration (see Section 4.2.2.2);
5. To be done between 7-10 am
6. Final FU Visit includes physical examination as well.
7. Letters A, B and C describe different sets of safety laboratory examinations (see Section 5.2.4).
8. Urine drug screening will be performed at screening and prior to dosing on Day 1 of Visit 3. A breath alcohol test will be performed prior to BI 894416 or placebo administration in Visit 3, and may be repeated at any time during the study at the discretion of an investigator or designee. Pharmacogenomic samples will be collected if needed. (This sample is optional. In case a patient takes part in both a SRD and a MRD dose group only one Pharmacogenomics sample is to be taken.).
9. Safety laboratory to be taken and to be medically evaluated within 3 days (within 76 hours) prior to administration of BI 894416; this ambulatory visit for safety laboratory and questioning for Aes and concomitant therapies can be omitted if the screening examination is performed on Day -3 or if lab sample can be taken on Day -1 and the lab results can be medically evaluated before BI 894416 or placebo administration at Day 1.
10. PK samples for plasma level determination of BI 894416 and [redacted] are to be taken at the time points as outlined in Flow Chart "MRD part – Time schedule"; Section 5.3.2.2 and in Appendix 10.2. [redacted] Section 5.3.2.2 and in Appendix 10.2. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK or PD data) including addition of samples and visits as long as the total blood volume taken does not exceed 500 mL per patient
11. For allowed deviation from the scheduled time please refer to Section 6.1.
12. [redacted]
13. PK samplings and ECGs should be done in direct sequence for matching reasons.
14. During the days of urine collection, total fluid intake should be at least 1.5 litres and should not exceed 3.0 litres per day. A blank urine sample (x) is to be obtained within 3 hours prior to administration of trial medication. [redacted]. Other urine samples are to be collected over the stated post-dose intervals (◄— | — | —►) 0-4, 4-8, 8-12 and 12-24 h after BI 894416 or placebo administration on Day 1 and Day 9 only.
15. [redacted]
16. To be done between 7-10 am and at Day 9 and Visit 8 +/- 30 min of the time conducted at D-1;
17. Vital signs must be completed prior to bodyplethysmography.
18. Three triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes (refer to Flow Chart "MRD part – Time schedule" and to Section 5.2.5.1);
19. Triplicate ECG (refer to Flow Chart "MRD part – Time schedule" and to Section 5.2.5.1);
20. Aes and concomitant therapies will be recorded throughout the trial, but will be specifically asked at time points indicated in the "MRD part – Time schedule"
21. Physical examination includes an echocardiography (stress) test in the screening period in patients aged 45 and older. Assessment can be omitted if patient took part in one of the SRD groups before.

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[redacted]

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
[redacted]	[redacted]
ALCOA	attributable, legible, contemporaneous, original, accurate (dimension of integrity)
AMP	Auxiliary Medicinal Product
ANOVA	Analysis of variance
AUC	Area under the Curve
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
[redacted]	[redacted]
$AUC_{\tau,ss}$	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
$AUMC_{t1-t2}$	Area under the first moment curve of the analyte in plasma over the time interval t_1 to t_2
β	Slope parameter associated with the power model used to evaluate dose proportionality
BA	Bioavailability
b.i.d.	bis in die (twice daily dosing)
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BMS	Biomarker set
BP	Blood pressure
CA	Competent authority
CCDS	Company Core Data Sheet
[redacted]	[redacted]
CDISC	Clinical Data Interchange Standards Consortium

CI	Confidence interval
[redacted]	[redacted]
C_{max}	Maximum measured concentration of the analyte in plasma
$C_{max,ss}$	Maximum measured concentration of the analyte in plasma at steady state
[redacted]	[redacted]
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Clinical Trial Lead
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Arithmetic coefficient of variation
DDI	Drug Drug Interaction
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
eDC	electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EoT	End of Treatment
EoTrial	End of Trial
ePRO	electronic Patient Reported Outcome
EudraCT	European Clinical Trials Database
F	Absolute bioavailability factor

FAS	Full Analysis Set
FC	Flow Chart
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
FEV1	Forced Expiratory Volume (Pressure) in 1 second
[redacted]	[redacted]
FOB	Faecal occult blood
[redacted]	[redacted]
FVC	Forced (expiratory) Vital Capacity
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GI	Gastro-intestinal
GINA	Global Initiative for Asthma
gMean	Geometric mean
HPC	Human Pharmacology Centre
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometry
HR	Heart rate
IB	Investigator's Brochure
IEC	Independent Ethics Committee
iPD	Important protocol deviation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
[redacted]	[redacted]
[redacted]	[redacted]
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LLOQ	Lower limit of quantification
LoEE	List of Essential Element
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MRD	Multiple-rising dose
[redacted]	[redacted]

[redacted]

MST	Medical Sub Team
NOTEL	No toxic effect level
OPU	Operative Unit
[redacted]	[redacted]
PE	Polyethylene
PEF	Peak Expiratory Flow
PfOS	Powder for reconstitution of an oral solution
PFT	Pulmonary Function Test
PIB	Powder in the bottle
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
p.o.	per os (oral)
PP	Polypropylene
ppb	Parts per billion
PR	Pulse rate
PTF	Peak-Trough Fluctuation
PTS	Peak-trough swing
q.d.	quaque die (once a day)
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	Reference treatment
[redacted]	[redacted]
Raw	Airway Resistance
REP	Residual Effect Period
RR	Respiratory rate
RV	Residual Volume
SAE	Serious Adverse Event
s.c.	subcutaneous
SCR	Screening
SMC	Safety Monitoring Committee

SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRD	Single-rising dose
ss	(at) steady state
SUSAR	Suspected unexpected serious adverse reaction
[redacted]	[redacted]
SYK	Spleen Tyrosine Kinase
T	Test product or treatment
[redacted]	[redacted]
TDMAP	Trial Data Management and Analysis Plan
t.i.d.	ter in die (3 times a day)
TMF	Trial Master File
TS	Treated set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
US PI	US Package Insert
[redacted]	[redacted]
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

BI 894416 is an oral, selective non-receptor protein tyrosine kinase SYK (spleen tyrosine kinase) inhibitor under clinical development for the indication of uncontrolled severe persistent asthma.

This trial will be performed to investigate the safety, tolerability, pharmacokinetics a [redacted] of single rising oral doses and multiple rising oral doses of BI 894416 versus placebo in male patients with mild asthma.

1.1 MEDICAL BACKGROUND

Asthma is a heterogeneous disease characterized by a chronic inflammatory process of the airways and driven by both the innate and adaptive immune pathways [R14-4230, P08-01263]. In severe asthma, the T type 2 inflammation (T2) -high and T2-low, and the non-T2 pathways are involved associated with a mixed pattern of inflammation involving eosinophil, basophil, mast, neutrophil, innate lymphoid and dendritic cells [R15-5888, R16-0945].

SYK is a non-receptor cytoplasmic tyrosine kinase that is predominantly expressed in cells of hematopoietic lineage, including B cells, T cells, monocytes, NK cells, mast cells, basophils, and neutrophils [R15-5470]. SYK is a key component of the signal transduction associated with the T2-high and T2-low, and non-T2 asthma pathways that is activated through interaction with allergens and a number of innate and adaptive immune receptors including Fc receptors on basophils, mast, B- and T cells. SYK is essential for the FcεR1-mediated activation and degranulation of mast cells and basophils. SYK is also important in the signal propagation of the dectin family of innate receptors, present on macrophages, dendritic cells and neutrophils. Furthermore, SYK has important roles in B-cell and T-cell development, with partially redundant functions with Zeta-chain-associated protein kinase of 70 kDa (ZAP70) [R15-5470, R16-5298].

For more details on medical background see the current version of the Investigator's Brochure (IB) [c03536505].

1.2 DRUG PROFILE

1.2.1 BI 894416

BI 894416 is a potent and selective inhibitor of SYK. Based on pre-clinical in vitro and in vivo data, SYK inhibition is expected to have effect on the non-T2 and T2 inflammatory pathway components of severe asthma.

So far, BI 894416 was investigated in one clinical phase I first-in-man trial (BI study number 1371-0001) and one clinical phase I drug-drug interaction trial (BI study number 1371-0004) in both healthy male volunteers. In addition, the effect of a high-fat, high-calorie breakfast on

BI 894416 absorption is investigated in phase I trial 1371-0021 (study is ongoing at time of preparation of this protocol).

Trial 1371-0001 consisted of two trial parts, a single-rising dose (SRD) part and a relative bioavailability (rel BA) part. Single-dose treatment with up to 70 mg BI 894416 or placebo as oral solution in the SRD part of trial 1371-0001 as well as administration of three single doses (10, 10, and 40 mg BI 894416) as tablet or oral solution in the rel BA part was safe and well tolerated. For details on safety and tolerability as well as on pharmacokinetics and biomarker data of trial 1371-0001 refer to the IB [c03536505].

Trial 1371-0004 investigated the effect of strong inhibition of CYP3A and inhibition of P-glycoprotein on an oral single dose of BI 894416. In that trial 3 mg BI 894416 was given without (period 1) or together with 200 mg itraconazole q.d. (period 2; 3 days pre-treatment, a fourth dose of itraconazole 1 h before BI 894416, and a fifth dose of itraconazole 23 h following BI 894416 dosing). Preliminary PK data (based on planned time points) indicate that the ratios of C_{max}, AUC_{0-tz} and $AUC_{0-\infty}$ of BI 894416 in plasma when given together with itraconazole and when given alone resulted in a 1.13, 1.42 and 1.43 fold increase in gMean exposure, respectively. BI 894416, alone or together with itraconazole, was assessed as safe and well-tolerated in trial 1371-0004. For more details refer to the IB [c03536505].

For a more detailed description of the BI 894416 profile, please refer to the current Investigator's Brochure (IB) [c03536505].

1.2.2 Residual Effect Period

The Residual Effect Period (REP, i.e., the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present) of BI 894416 has not been defined yet. However, the elimination half-life of BI 894416 is short (gMean terminal half-life between 2.96 and 5.31 h in the SRD part of trial 1371-0001) and the mode of action is reversible. This suggests that the occurrence of any potential adverse effects would likely be limited to a short time period (i.e. few days).

Conservatively, a minimum observation period of 2 weeks after last administration with BI 894416 or placebo has been selected, i.e. the individual patient's end of trial is 14 days following last dosing with BI 894416 or placebo at the earliest.

All AEs reported between administration of BI 894416 and the individual patient's end of trial will be counted as on-treatment AEs.

1.3 RATIONALE FOR PERFORMING THE TRIAL

BI 894416 is an oral SYK (spleen tyrosine kinase) inhibitor that is being developed for patients with severe asthma.

The first single rising dose study was conducted in healthy volunteers (1371-0001). In trial 1371-0001 doses of BI 894416 up to 70 mg were given and assessed as safe and well-tolerated. In this trial, safety and tolerability of BI 894416 will be assessed in patients with

asthma using single rising oral doses and multiple rising oral doses. [redacted]

[redacted]

In this trial, up to 225 mg single dose and 70 mg three times a day (tid) are planned to be administered on the basis of calculations using the predicted systemic exposure and consideration of the human cap for exposure. The mean human cap for exposure (AUC_{0-24}) has been set 3-fold below exposure at the dog NOAEL and 7-fold below the lowest exposure in dogs where neurologic effects were observed. For details on exposures, please refer to Section 4.1.2.

Based on its half-life, its reversible mode of action, and results from preclinical studies, BI 894416 is not expected to have long-term effects following single dose and no expected carry-over effect for the minimum 21 day interval between single and multiple rising dosing. Therefore, for patients willing to participate in one of the MRD dose groups a previous participation in one dose group of the SRD part is allowed if BI 894416 has been administered in the SRD part more than 21 days prior to planned first administration of BI 894416 in the MRD part.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this study is without any therapeutic benefit for patients in the single rising dose (SRD) portion of the study. Patients enrolled in the study will receive some benefit from thorough investigation of their health status including pulmonary testing, review by physicians experienced in respiratory medicine, a review of current medications and the requirement for inhaled corticosteroid use. Patients may also have some short term clinical benefit in the multiple rising dose (MRD) portion of the study should there be an effect on lung function or airway resistance. For patients beyond 44 years of age at screening, there will also be an assessment of stress cardiac ultrasound, which could be beneficial for screened (and not enrolled) patients with relevant finding, for further general medical follow-up.

[redacted]

The patients are exposed to the risks of the study procedures and the risks related to the exposure to the trial medication as noted below.

1.4.1 Expected benefit for the target indication

Asthma is a heterogeneous disease that is driven by the innate and adaptive immune pathway. In severe asthma, both the T2-high and T2-low, and the non T2 inflammation pathways are involved, and associated with a mixed pattern of inflammation involving eosinophil, basophil, mast, neutrophil, innate lymphoid and dendritic cells. Up to 50% of severe asthma is driven by the non T2 and/or T2-low alone or in combination with the T2-high pathway. This non T2 / T2-low component represents an area of unmet medical need that does not respond as well to high dose inhaled corticosteroids or other current controller therapy, or current T2-high monoclonal antibodies targeted therapies. One subgroup of steroid-resistant asthma includes those patients with late-onset (post-puberty), obese patients with difficult to treat asthma symptoms. As such, inclusion criteria have been set to allow the potential for patients to be included up to 55 years of age and up to BMI of 32.

Spleen tyrosine kinase (SYK) is a key component of signal transduction associated with the T2-high and T2-low, and non-T2 asthma pathways that is activated through interaction with allergens and a number of innate and adaptive immune receptors including Fc receptors on basophils, mast, B and T cells. SYK is also important in the signal propagation of the dectin family of innate receptors, present on macrophages, dendritic cells and neutrophils.

Such a therapy would meet a substantial unmet need for patients with asthma, for those with a non T2 and/or T2-low component, whether early/late-onset or steroid resistant, and could become a safe and effective alternate or add on also in T2 asthma to high dose inhaled corticosteroids, oral systemic corticosteroids or T2-high biological monoclonal antibodies.

1.4.2 Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venipuncture for blood sampling.

ECG electrodes may cause local and typically transient skin reactions.

The total volume of blood (including volume needed for the Platelet Function Assay) withdrawn during the entire study per patient will not exceed the volume of a normal blood donation (500 mL). No health-related risk to patients is expected from this blood withdrawal.

Patients will be followed up until 14 days after the last treatment.

[redacted] ther study

procedures such as spirometry, bodyplethysmography, [redacted] and blood pressure measurement are not expected to cause any adverse events.

An echocardiography (stress) test will only be performed in patients over 45 years of age. Complications may include arrhythmias, hypotension, acute coronary syndrome, heart failure, light-headedness, exercise-related injury, body aches and fatigue. Acute coronary syndrome is rare. Complications are rare, especially with patients having no pre-existent reason for testing or cardiac history, both of which would have been excluded in any case.

1.4.3 Drug-related risks and safety measures

1.4.3.1 Risks related to BI 894416

No specific risk is expected in patients volunteering in this study from a point of view of age (specifically 45 to 55 years of age) or BMI above 29 (specifically 30 to 32) based on the mechanism of this drug.

Potential effects on immune cells

SYK is involved in the function of basophil, mast, neutrophil and dendritic cells. Moreover, SYK is implicated in the development and function of both T cells and B cells. For details refer to the IB [c03536505].

The risk due to effects of BI 894416 on immune cells to patients participating in this trial is expected to be low, for the following reasons:

- Inhibition of SYK is not expected to have a negative effect with regards to the immune response of innate immune cells to viral or bacterial infections due to redundancy in the infection immune response. The key neutrophil and dendritic cell functions most likely will be triggered by alternative pathways.
- Any potential changes in T cell populations in humans related to SYK inhibition are expected to be reversible and are likely of a lower magnitude than what was observed in the rat, as the maintenance of peripheral T cells in humans is controlled primarily through homeostatic mechanisms that control peripheral proliferation [R17-1830].
- Human ex vivo lymphocyte pharmacology BI 894416 data showed an offset (i.e. required higher exposure) for inhibition of B cell (B-cell receptor) compared to basophil (CD63) activation. In vitro studies showed that BI 894416 had no effect on B-cell proliferation or IgM expression at concentrations up to 10 µM. At higher concentrations, IgE production was decreased, and IgG production was increased.

Risk mitigation and monitoring: Patients with a history or diagnosis of relevant immunological disease will be excluded from trial participation (see Section 3.3.3). Adverse events will be monitored for an increase in infectious adverse events. Safety laboratory testing contains WBC, differential blood count, CRP, serum immunoglobulins and differentiation of lymphocytes (including T-cell subsets and B-cell numbers).

Tumour biology and carcinogenicity

The SYK pathway has been hypothesized to act as both a tumour suppressor and a tumour promoter in different types of human cancers [R16-4459]. An increased risk of carcinogenic/metastatic potential in epithelial cancers has been reported in the literature related to SYK knock-out, but not related to SYK inhibition. Allelic deletion of SYK has been associated with breast adenocarcinoma [R15-4770]. However, there is no evidence that pharmacologic inhibition of SYK will increase carcinogenicity or metastatic risk. Preclinical data with a potent and selective tool SYK inhibitor, BI 1002494, are in line with an absence of a carcinogenic effect due to inhibition of SYK enzymatic function [n00243171].

Risk mitigation and monitoring: Only male patients are included in this trial. In view of the extended time necessary to induce a carcinogenic effect, administration of BI 894416 for up to 9 days is not considered a relevant carcinogenic risk to patients participating in this study. Accordingly, no further risk mitigation is required in this study.

Platelet aggregation and bleeding risk

A role of SYK in platelet function has been demonstrated in literature [R15-5470]. Several platelet functions rely on SYK signalling (e.g. collagen receptor GPVI) but others are independent of SYK [R16-5240]. *In vitro* studies using human platelets demonstrated that at concentrations up to 100 µM, BI 894416 had no effect on extrinsic or intrinsic coagulation pathways. Also, BI 894416 did not inhibit ADP-induced platelet aggregation up to 100 µM. However, BI 894416 inhibited collagen- and arachidonic acid-induced platelet aggregation at 3 µM and 5 µM. However, platelet function as measured by bleeding time is not affected by a drug unless all the platelet pathways are inhibited due to redundancy within the system. Therefore, no risk for bleeding exists with regard to platelet inhibition unless a patient is also on another antiplatelet drug that blocks these other pathways.

Risk mitigation and monitoring: Use of any other concomitant drug that could reasonably inhibit platelet aggregation or coagulation (e.g. acetylsalicylic acid) will be prohibited (see Sections 3.3.3 and 4.2.2.1). Adverse events will be monitored for any signs of bleeding or bleeding-related adverse events.

Bone density

SYK is reported to be involved in osteoclast differentiation, development and function. For details see the IB [c03536505]. In this trial, patients are exposed to BI 894416 for only 9 days. Due to the extremely slow turnover of bone tissue, no relevant effect on bone is expected with this short-term administration, and no specific monitoring of bone density is necessary in this trial.

Mortality / morbidity in preclinical studies

Mortality / sacrifice due to morbidity occurred in CByB6F1 non-transgenic mice and in Wistar Han rats. Clinical signs preceding morbidity were similar in both rodent species and included respiratory changes (rapid, shallow, and/or labored breathing), decreased motor activity, ruffled fur, hunched or prostrate posture, eye changes (squinting, discharge) and/or

hypothermia. One humane sacrifice due to overt neurotoxicity was done in one dog in a 3-day escalation study as described in the next section. Details are listed in the IB [c03536505].

Risk mitigation and monitoring: Patients will be in-house at the trial site under close medical observation for 34 h after administration of BI 894416 or placebo in the SRD part and during the administration period until 24 h after the last administration of BI 894416 or placebo in the MRD part. Safety laboratory will be done at pre-defined time points during the trial. Vital signs and ECGs will be measured frequently during the trial, and patients will be instructed to report AEs spontaneously and will be asked at pre-defined time points for AEs. In case of AEs in need of treatment, the investigator can authorise symptomatic therapy. In those cases, patients will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

Neurotoxicity

In dog toxicology studies, acute adverse neurological effects with tremor and movement disorder assessed as dyskinesia (paresis / rigidity) were observed at high exposures (IB [c03536505]). One dog was euthanized due to overt neurotoxicity in 3-day escalation study at 90 mg/kg/day. In dose escalation study in dogs with assessment of neurotoxicity [n00245394], all clinical signs of neurotoxicity were reversible with cessation of dosing. No structural changes were observed on histopathology. Peripheral nerve conduction velocity and EEG were unchanged. No specific mechanism causing the neurological effects in dogs has been elucidated. Therefore, it has not been determined whether the neurological changes are species specific; however, external expert review considered this is most likely a channelopathy specific to dog and not likely to occur in man (see IB).

Risk mitigation and monitoring: Patients with relevant neurological disorder in the medical history are excluded from trial participation (see Section 3.3.3). Neurological examinations will be performed at screening, and patients with clinically relevant findings in the neurological examination will be excluded from study participation (see Section 3.3.3). At pre-defined time points during the trial, neurological examinations will be performed. If necessary (investigator decision), unscheduled neurological examinations may be added at any time during the trial. Relevant findings in the neurological examination during the trial will be reported as AEs. If necessary, patients may be sent for further, more specific evaluation and treatment to a neurologist.

Genotoxicity, reproductive and developmental toxicity

Genetic toxicology results by weight of evidence indicate that BI 894416 is not mutagenic or clastogenic. In the 2-week repeat dose range finding study in male rats [n00240179], degeneration of spermatids of the testes was observed at ≥400 mg/kg/day, which is considered a secondary effect, related to overt toxicity and morbidity.

Risk mitigation: Men able to father a child must ensure that two medically approved and highly effective methods of birth control throughout the trial, and for a period of at least 28 days after last trial drug intake is used. They must use one barrier method, i.e. condom or occlusive cap with spermicide, or vasectomized partner, and one highly effective non-barrier

method including oral, injected or implanted hormonal contraceptives, intrauterine device or system.

Female partner: WOCBP must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly during the study, and for a period of at least 28 days after the last dose of study drug.

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

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

Phototoxicity

Patients will be advised to avoid direct exposure to sun and UV light during the entire study (see Section 4.2.2.2). Further protective measures would not be necessary given the low phototoxic potential of BI 894416.

Potential effects on QT interval

Preclinical studies suggested no proarrhythmic potential or cardiovascular liability with BI 894416. However, statistical results of first-in-man trial 1371-0001 showed a slight and possibly dose- and concentration-dependent increase of QTcF interval. At gMean C_{max} of the 70 mg dose group, placebo- and baseline-corrected predicted mean QTcF increase was 5.9 ms (upper limit of the 90% CI was 10.5 ms).

Risk mitigation: Patients with cardiovascular disorders, patients who used drugs that cause QT/QTc prolongation, patients that show a marked baseline prolongation of QT/QTc interval or any other relevant ECG finding at screening, and patients with a history of additional risk factors for Torsade de Pointes arrhythmia are excluded from trial participation (see Section 3.3.3). Moreover, patients are in-house under close observation for 34 h following drug administration in the SRD part and following 24 h following last administration of BI 894416 or placebo in the MRD part, and ECGs are done pre- and post-dose at the time points given in the Flow Charts.

1.4.3.2 Drug-induced liver injury

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see also Section 5.2.6.1.4.

1.4.3.3 Summary of safety measures

The following precautionary measures will be taken in this study in order to minimise the risk for patients:

- Dose selection is based on safety, PK and [redacted] results of previous first-in-man trial 1371-0001, the mode of action, the expected pharmacologically active exposure, expected systemic exposures after single- and multiple-dose administration, and toxicity findings in preclinical studies. Escalation factor between dose steps decrease with increasing doses. For details see Sections 4.1.2.
- A maximum acceptable human exposure has been defined for single and multiple-dose based on toxicity findings (see Section 4.1.2). Dose escalation is guided by preliminary analysis of BI 894416 PK (C_{max} and AUC_{0-24} for single dose; $C_{max,ss}$ $AUC_{0-24,ss}$ for multiple dose). The exposure in the next higher single-dose group will be predicted based on preliminary data of the current and preceding single dose groups and the exposure in the next higher multiple-dose group will be predicted based on preliminary data of the current and preceding single-dose and multiple dose groups. The next higher dose level will only be administered if

1. predicted gMean value for AUC_{0-24} of the next dose group does not exceed the maximum acceptable human exposure of 36,150 nM*h (see Section 4.1.2),
2. the upper limit of the 95% prediction interval for AUC_{0-24} of individual patients in the next dose group does not exceed 63,000 nM*h and 3) predicted gMean value for C_{max} of the next dose group does not exceed 5,233 nM.

- SRD part only: For safety reasons, each dose group of 10 patients (8 on active and 2 on placebo) will be divided into two cohorts of 2 patients each (1st and 2nd cohort) and one cohort of 6 patients (3rd cohort). The first 2 cohorts will be dosed in a single blinded, fixed-sequence fashion (1st cohort: 'active – placebo'; 2nd cohort: 'active-active'). The 3rd cohort will consist of 5 patients on active and 1 patient on placebo (1st active, remaining 4 active plus 1 placebo randomised) in a single blind fashion. The first trial medication administration of cohort 1 and the first trial medication administration of cohort 2 will be separated by at least 22 hours. This time interval is expected to be sufficient to detect relevant first acute effects of BI 894416 prior to dosing the second patient with BI 894416 at one dose level. The first trial medication administration of cohort 2 and the first trial medication administration of cohort 3 will be separated by at least 46 hours (Section 3.1 and Appendix 10.1).
- MRD part only: For safety reasons, each dose group of 10 patients (8 on active and 2 on placebo) will be divided into two cohorts of 2 patients each (1st and 2nd cohort) and one cohort of 6 patients (3rd cohort). The first 2 cohorts will be dosed in a single blinded, fixed-sequence fashion (1st cohort: 'active – placebo'; 2nd cohort: 'active-active'). The 3rd cohort will consist of 5 patients on active and 1 patient on placebo

(1st active, remaining 4 active plus 1 placebo randomised) in a single blind fashion. The first trial medication administration of cohort 1 and the first trial medication administration of cohort 2 will be separated by at least 70 hours. The first trial medication administration of cohort 2 and the first trial medication administration of cohort 3 will be separated by at least 70 hours (Section 3.1 and Appendix 10.1).

- A documented Safety Review takes place prior to next dose level, both for the MRD and for the SRD part. The next dose level in either part is only permitted if there are no safety concerns precluding the next dose level in the SRD and MRD part and if none of the pre-specified stopping criteria are met. The minimum time interval between dosing of the first patient of an SRD dose group (dose group N) and dosing of the first patient of the subsequent SRD dose group (dose group N+1) is at least 12 days. The minimum time interval between first dosing of the first patient of an MRD dose group (dose group N) and first dosing of the first patient of the subsequent MRD dose group (dose group N+1) is at least 21 days. For details see Section 3.1 and Appendix 10.1.
- Patients with relevant neurological disorder in the medical history are excluded from trial participation (see Section 3.3.3). Neurological examinations will be performed at screening, baseline and pre-defined time points during treatment (see Flow Charts and Section 5.2.2). Additional neurological examinations may be performed as necessary upon investigator judgment. If necessary, patients may be sent for further evaluation and treatment to a local neurologist.
- Patients 45 years of age and older will be screened for potential cardiovascular issues at screening by an echocardiography and echocardiography stress test. These patients would be excluded from the trial. The procedure is implemented because of the early nature of this program and not because of any specific cardiac risk of this compound.
- Safety laboratory examinations will be performed at pre-defined time points before and for at least two weeks after the last trial medication administration. These examinations include extensive standard safety laboratory examinations. In addition, immune monitoring (including white blood cell count, differential blood count, lymphocyte differentiation and immunoglobulins) will be included as detailed in Flow Charts (time points) and Section 5.2.4 (test details).
- A thorough ECG and heart rate monitoring including continuous ECG monitoring for 4 h post dose (SRD part only) and in addition frequent 12-lead ECG and vital signs measurements at time points as described in the Flow Chart are planned.
- In the SRD part, patients will be confined for at least 34 h after study trial medication administration to the trial site. In the MRD part, patients will be confined to the trial site during the administrations of BI 894416 or placebo until 24 h after the last administration. During in-house confinement the patients are under medical observation and are monitored for both expected and unexpected adverse events.
- Patients with female partners of child-bearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information
- A documented Safety Review takes place prior to start of each dose group (see Section 3.1).

1.4.4 SARS-CoV-2 and COVID-19 related risks and safety measures

1.4.4.1 Backgound on SYK and viral infection

- SYK-coupled immune receptors are largely restricted to the CLEC family of innate receptors and the Fc family of immunoglobulin-signaling receptors. There is no evidence in the literature suggesting that coronavirus mediated innate signaling is associated with SYK-coupled receptors [R20-1374].
  Although some target cells (e.g. neutrophil and dendritic cells) also play a role in response to viral or bacterial infections, inhibition of the SYK is not expected to have a negative effect with regards to the immune response of innate immune cells to viral or bacterial infections, due to a high level of redundancy in the immune response.

- Pre-clinical studies conducted in B-cells and T-cells, BI 894416 had no effect on T-cell proliferation or activation, and only IL-2 secretion was significantly inhibited at concentrations relevant to estimated human efficacious exposures. BI 894416 had no effect on B-cell proliferation or IgM expression, but a mild effect on switching from IgE to IgG was observed. Preclinical safety data from a similar SYK inhibitor TAVALISSE (fostamatinib) did not show any effect of SYK inhibition on viral (influenza) clearance from the lungs of rats [R13-1374].

- Safety data from a similar SYK inhibitor TAVALISSE (fostamatinib) did not show an overall increase in infections in Ph III 52 week studies in patients with rheumatoid arthritis who have not improved with disease-modifying anti-rheumatic drugs (DMARDs). In a study of 923 patients, serious adverse events of infections or infestations occurred at frequency of < 1% in any active dose arm. Other non-serious adverse events did not show an increased rate of infections when compared to placebo.

1.4.4.2 Risk related to compound

To date, 186 number of patients have been treated with BI 894416 in single or multiple dose studies. In the SRD healthy volunteer trial 1371-0001, one subject was reported with a severe AE of respiratory tract infection, which was not considered drug-related. In this SRD/MRD study in asthma patients, one event of upper respiratory, two events of lower respiratory tract infection and one event of otitis externa in 3 patients was reported. None of these events were serious or related to drug administration.

Based on the mode of action and available clinical data, it is not expected, that use of BI 894416 would place healthy volunteers or asthma patients at increased risk of contracting or altering the response to any Coronavirus infection in general. The benefit risk of BI 894416 therefore remains unchanged in regards to the safety of the clinical trial participants.

1.4.4.3 Risk related to patients with underlying conditions contracting COVID-19

Patients with moderate to severe asthma maybe at higher risk of developing severe symptoms from infection with COVID-19, which can affect patients' respiratory tract, cause an asthma

exacerbation, and possibly lead to pneumonia and acute respiratory disease (https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/asthma.html). Treatment with BI 894416 is not known to increase this risk. Based on the mode of action and available clinical data, it is not expected that use of BI 894416 would place asthma patients at increased risk of contracting SARS-CoV-2 or would lead to a more severe disease. The benefit risk of BI 894416 therefore remains unchanged in regards to the safety of the clinical trial participants.

1.4.4.4 Procedure-related risks

For a defined period of the study, patients will be in-house at the trial site. During this phase, there is a potential risk for spreading the infection within a cohort or to the site staff, if an infected subject was enrolled into the trial. Also, there are trial procedures, e.g. collecting blood samples, recording of ECG, or assessing vital signs, that are impossible to perform from a distance of 1.5 to 2 meters, which is the generally recommended distance to keep between humans, in order to prevent the transmission of SARS-CoV-2.

Risk mitigation: A risk management plan has been set up at the site detailing specific cautionary measures, e.g. hygiene rules, wearing of face masks and physical distance which is filed in the ISF. In addition, a screening on SARS-CoV-2 has been implemented, to be performed as part of the safety assessments on Day -3 to -1. Patients positive for SARS-CoV-2 must not be randomized in accordance with exclusion criteria 4, 5, and 10. In case a COVID-19 infection is suspected in a patient during trial participation, SARS-CoV-2 testing is to be initiated without delay to enable patient exclusion or discontinuation (see withdrawal criteria).

1.4.5 Overall assessment

BI 894416 is a highly specific SYK inhibitor that has been adequately characterised in pre-clinical studies. The non-clinical safety package supports administration of BI 894416 for up to 4 weeks duration to men. At higher exposures, dose-limiting toxicities were identified in the mouse, rat, and dog. These toxicities are either monitorable, reversible, or safety margins have been defined (see Section 4.1.2) to the maximum acceptable exposure in this study.

Data from oral administration of three SYK inhibitors other than BI 894416 are available and provide additional information on safety and tolerability of this class of drug in man. Published data indicate acceptable safety and tolerability of these three other SYK inhibitors in healthy volunteers.

In previous first-in-man trial 1371-0001, single doses of up to 70 mg BI 894416 were given and were assessed as safe and well-tolerated.

Inhibition of SYK has the potential to address a substantial unmet need for patients with severe asthma, especially those with a non T2 and/or T2-low component, whether early/late-onset or steroid resistant, and could become a safe and effective alternate also in T2 asthma to high dose inhaled corticosteroids, oral systemic corticosteroids or T2-high biological monoclonal antibodies.

Transition from single dose regimen to multiple dose studies requires assessment of safety, tolerability and pharmacokinetics of BI 894416 in patients. [redacted]

Potential risks for the patients in relation to the COVID-19 pandemic situation have been evaluated together with the principle investigator. With regard to study treatment, no relevant impact is expected on the subject's health condition (like e.g. increased susceptibility to infections, immune suppression, or impaired lung function). In the unlikely case that despite all implemented measures a COVID-19 case occurs in a trial participant while in the study, the withdrawal criterion for patients experiencing an infection has been added to also cover study discontinuation in case of confirmed COVID-19 disease.
To minimize the risk that infected patients spread the infection to others during the trial, patients are only to be admitted to the site at Visit 3, if they fulfill the strict criteria as laid out by the Robert Koch Institute (RKI) for allowing medical staff to return to their workplace (Category III persons) after having been tested SARS-CoV-2 positive, see:
https://www.rki.de, particularly
https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Entlassmanagement.html.
This includes a symptom-free interval of 48 hours and a negative PCR test (see Section 5.2.4). As RKI recommendations may be subject to change, current recommendations will be re-assessed on a periodic basis and trial procedures adapted accordingly, if applicable.

Considering the medical need for an effective and safe treatment of severe asthma, the benefit of this trial is assessed to outweigh the potential risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The trial will be performed to compare several doses of BI 894416 with placebo in patients with mild asthma. In the first part, doses will be compared in an SRD format. In the second part, doses will be compared in an MRD format over 7 days.

In both parts, the primary comparisons of interest are between the percentage of patients with drug-related adverse events at each dose and placebo during single and multiple dosing regimens. Based on these, the primary trial objective is to assess safety and tolerability of BI 894416 at each dose.

Secondary measures of interest are the geometric means of BI 894416 plasma $AUC_{0-\infty}$ and C_{max} after single dose in SRD part and AUC_{0-8} and C_{max} after single dose as well as $AUC_{\tau,ss}$ and $C_{max,ss}$ after 7 days multiple dosing in MRD part. The objective is to assess the pharmacokinetics of BI 894416 following single and multiple administration.

Additional secondary measures of interest in the MRD portion of this trial are the mean Airway Resistance (Raw post dose) after 7 days of tid treatment at each dose and placebo of MRD part. The objective is to support identification of an efficacious dose in patients using "Raw", a measure for airway resistance, as an outcome.

[redacted]

All primary and secondary comparisons will be descriptive and made on an on-treatment basis.

2.1.2 Primary endpoint

Primary endpoint to assess safety and tolerability of BI 894416 is the percentage of patients with drug-related adverse events.

2.1.3 Secondary endpoints

Efficacy Endpoints: (for lung function and small airway assessment) from MRD part:

- Raw after 7 days of treatment

Pharmacokinetic Endpoints for BI 894416:

SRD part:

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)
- C_{max} (maximum measured concentration of the analyte in plasma)

MRD part:

After the first dose:
- AUC_{0-8} (area under the concentration-time curve of the analyte in plasma over the time interval 0 to 8h)
- C_{max} (maximum measured concentration of the analyte in plasma)

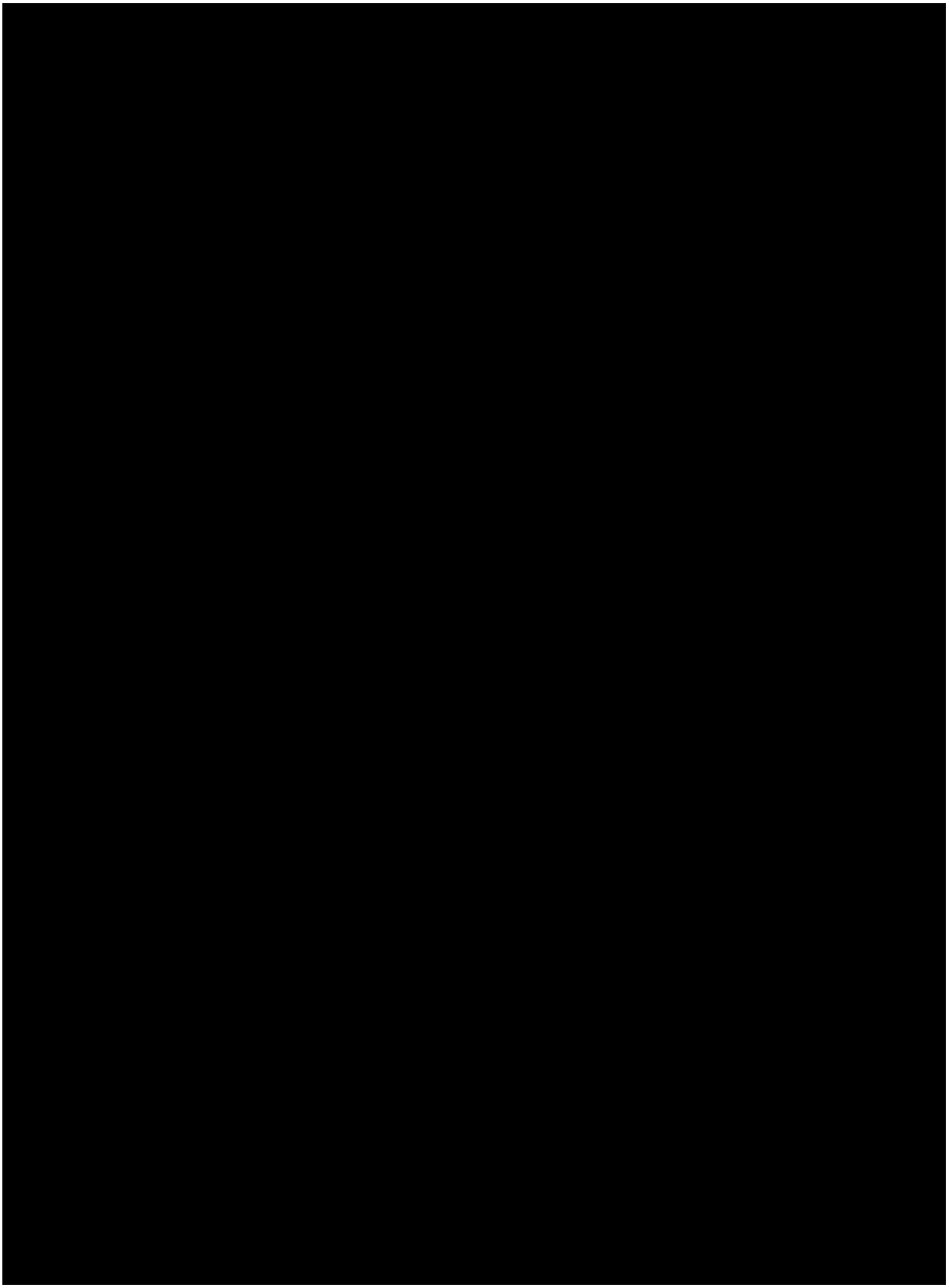
After the last dose:
- $AUC_{\tau,ss}$ (area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ)
- $C_{max,ss}$ (maximum measured concentration of the analyte in plasma at steady state)

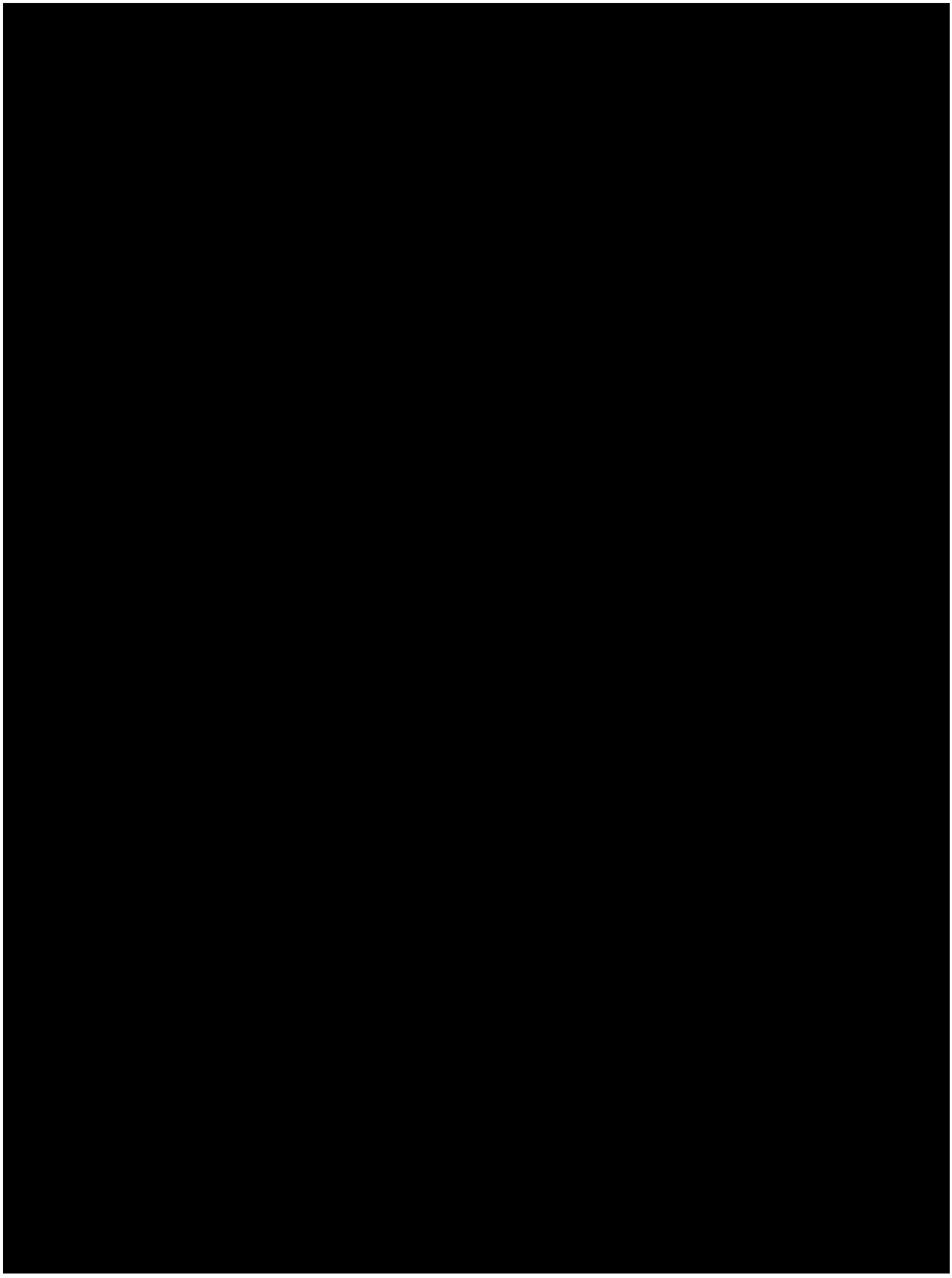
[redacted]

2.2.2.1 Safety and tolerability

Safety and tolerability of BI 894416 will be assessed based on:
- AEs (including clinically relevant findings from the physical examination and the neurological examination)
- Safety laboratory tests
- 12-lead ECG
- For the SRD part: Continuous ECG monitoring

[redacted]





3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The 1371-0008 study is a randomised, placebo-controlled, single-blind, parallel group study assessing safety and tolerability as well as PK [redacted] of single and multiple rising doses of BI 894416 versus placebo in patients with mild asthma. The study will be conducted at a single Phase I center in Germany.

A total of 32 patients will be treated with a single dose of BI 894416 in the SRD portion (Part 1) of the trial and a total of 32 patients will be treated up to 7 days with tid dosing and 2 days with qd dosing of BI 894416 in the MRD portion (Part 2) of the trial. Both part 1 and part 2 consist of 4 dose groups comprising 10 patients per group. However, the number of patients within a dose group may be extended or additional patients may be entered to part 1 and/or part 2 to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose will not be exceeded. Thus, the actual number of patients entered may exceed 80 (may exceed 40 per trial part) but is not to exceed 100 (is not to exceed 50 per trial part). Such changes may be implemented via non-substantial CTP Amendments under the presumption that exposures above the previously defined limits are not exceeded (as expected for a dose escalation criteria).

PK [redacted] measures will be used to characterize the dose-exposure-response relationship with regards to BI 894416 plasma concentrations a[redacted] Preliminary PK measure will be assessed prior to each dose escalation during the study to ensure that predicted gMean of C_{max} of patients does not exceed 5,233 nM, predicted gMean values for AUC_{0-24} do not exceed the maximum acceptable human exposure of 36,150 nM*h and that the upper limit of the 95% prediction interval for AUC_{0-24} of individual patients in the next dose group does not exceed 63,000 nM*h.

[redacted] airway resistance measures will also be taken to assess early efficacy signals in patients at therapeutically relevant doses.

Safety Monitoring Committee (SMC) members are selected from within the trial team to review individual and aggregated PK and safety data at the conclusion of dosing for each dose group, to determine the acceptability of safety and tolerability, and recommend next dose level/dose escalation. Details of the SMC responsibilities and procedures are described in the SMC Charter.

Part 1 (SRD Portion):
Part 1 is designed as single-blind, randomised, and placebo-controlled within parallel dose groups.

A total of 40 male patients is planned to participate in the SRD part, according to 4 sequential groups comprising 10 patients per group. However, additional patients may be entered to allow testing of additional doses or to extend the number of patients within a dose group on

the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose is not exceeded. Thus, the actual number of patients entered in the SRD part may exceed 40, but will not exceed 50 patients entered. In addition the dosage of the highest SRD dose group may be reduced, e.g. to ensure that predicted exposure is below the exposure limit (Section 4.1.2). Such changes may be implemented via non-substantial CTP Amendments.

In the event that a dose level needs to be given in this trial that is expected to exceed the exposure limits (Section 4.1.2), a thorough review of safety information obtained during the trial will be conducted and a substantial amendment will be submitted to CA and IEC for approval prior to dosing that dose level.

Within each dose group, 8 patients are planned to receive BI 894416 and 2 are planned to receive placebo. Only one dose is tested within each dose group. Each dose group will consist of 3 cohorts which will be treated subsequently for safety reasons (please also refer to Section 4.1.4 and Appendix 10.1).

The dose groups to be evaluated are outlined in Table 3.1: 1 below. Selection of doses, the maximal acceptable human systemic exposure limit and the exposure multiples are described in Section 4.1.2.

Table 3.1: 1 SRD Dose groups

Dose Group	1	2	5	3	4
Dose [mg]	75	125	170**	175	225*
Number of patients	10	10	10	10	10
Patients receiving placebo	2	2	2	2	2
Patients receiving active drug	8	8	8	8	8

* The dosage may be reduced to a dose >175 mg and <225 mg in case that preliminary PK analysis predict that a dose lower than 225 mg is needed to not exceed the limits of exposure (Section 4.1.2).

** With CTP version 3.0, an interim dose group (dose group 5) of 170 mg is inserted between dose group 2 and 3. 10 patients will be enrolled, 2 patients receiving placebo and 8 patients receiving active drug. Enrollment follows the cohort scheme as described below (see also Section 4.2.1).

On the first study day of each dose level, the 1st cohort (active-placebo) will be treated in the following order: First patient (active – sentinel patient) followed later by the second patient (placebo).

The 2nd cohort (active-active) will be treated not earlier than 22 hours later (minimum time interval between 1st patient of 1st cohort and 1st patient of 2nd cohort).

The 3rd cohort (1st active, remaining 4 active plus 1 placebo randomised) will be treated not earlier than 46 hours later (minimum time interval between 1st patient of 2nd cohort and 1st patient of 3rd cohort) to avoid an overlap.

The dose groups will normally be investigated consecutively in ascending order of doses, maintaining a time interval of at least 12 days between the first trial medication administration in the previous dose group (dose group N) and the first trial medication administration of the subsequent dose group (dose group N+1). The decision to proceed to the next dose group will be based upon the safety, tolerability, and pharmacokinetic data of the preceding dose groups and will only take place once sufficient information is available (see below). In case a lower dose level is chosen, a non-substantial amendment may be used in case the previously defined exposure limits are not expected to be exceeded.

Part 2 (MRD Portion):
Part 2 is designed as single-blind, randomised, and placebo-controlled within parallel dose groups.

A total of 40 male patients is planned to participate in the MRD part, according to 4 sequential groups comprising 10 patients per group. However, additional patients may be entered to allow testing of additional doses or to extend the number of patients within a dose group on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose is not exceeded. Thus, the actual number of patients entered in the MRD part may exceed 40, but will not exceed 50 patients entered. Such changes may be implemented via non-substantial CTP Amendments. In addition the dosage of the highest MRD dose group may be reduced, e.g. to ensure that predicted exposure is below the exposure limit (Section 4.1.2). The highest MRD dose might also be reduced to ensure that exposure covered during preceding SRD part (obtained exposure) will not be exceeded by predicted gMean exposure values $C_{max,ss}$ and $AUC_{0-24,ss}$ (Section 4.1.2).

In the event that the sponsor and SMC agree to investigate a dose level that is expected to exceed the exposure limits (Section 4.1.2), a thorough review of safety information will be conducted and a substantial amendment will be submitted to CA and IEC for approval prior to dosing that dose level.

Within each dose group, 8 patients are planned to receive BI 894416 and 2 are planned to receive placebo. Only one dose is tested within each dose group. Each dose group will consist of 3 cohorts which will be treated subsequently for safety reasons (please also refer to Section 4.1.4 and Appendix 10.1).

The dose groups to be evaluated are outlined in Table 3.1: 2 below. Selection of doses, the maximal acceptable human systemic exposure limit and the exposure multiples are described in Section 4.1.2.

Table 3.1: 2 MRD Dose groups

Dose Group	1	2	3	5	4
Dose [mg] tid	10	25	50	60**	70*
Number of patients	10	10	10	10	10
Patients receiving placebo	2	2	2	2	2
Patients receiving active drug	8	8	8	8	8

* The dosage may be reduced to a dose >50 and <70 mg tid in case that preliminary PK analysis predict that a dose lower than 70 mg tid is needed to not exceed the limits of exposure (Section 4.1.2) or to not exceed the exposure covered by the SRD part of the trial with predicted gMean $C_{max,ss}$ and $AUC_{0-24,ss}$ values.

** With CTP version 5.0, an interim dose group (dose group 5) of 60 mg tid is inserted between dose group 3 and 4. 10 patients will be enrolled, 2 patients receiving placebo and 8 patients receiving active drug. Enrollment follows the cohort scheme as described below (see also Section 4.2.1).

On the first study day of each dose level, the 1st cohort will be treated in the following order: First patient (active – sentinel patient) followed by the second patient (placebo).

The 2nd cohort (active-active) will be treated not earlier than 70 hours later (minimum time interval between 1st patient of 1st cohort and 1st patient of 2nd cohort).

The 3rd cohort (1st active, remaining 4 active plus 1 placebo randomised) will be treated not earlier than 70 hours later (minimum time interval between 1st patient of 2nd cohort and 1st patient of 3rd cohort).

The dose groups will be investigated consecutively in ascending order of doses, maintaining a time interval of at least 21 days between the first trial medication administration in the previous dose group (dose group N) and the first trial medication administration of the subsequent dose group (dose group N+1). The decision to proceed to the next dose group will be based upon the safety, tolerability, and pharmacokinetic data of the preceding MRD dose group and on the data from previous SRD group and will only take place once sufficient information is available (see below).

Safety Monitoring Committee (SMC) before dose escalation in SRD and MRD part
Progression from one SRD dose group to the next higher SRD group and from one MRD group to the next higher MRD group would only be allowed after a PK and safety analysis of the observed results from the preceding SRD and MRD dose groups, respectively. For this a documented Safety Review, performed by a Safety Monitoring Committee (SMC), must take place prior to each dose escalation. The dose escalation decision tree (Figure 3.1:1 and Appendix 10.1) shows when the SRD and MRD groups can be started dependent on the review of previous SRD and MRD data. The next dose level will only be given if, in the opinion of the Principal Investigator (or an authorised deputy) and SMC, no safety concerns arose in the preceding dose group(s) (i.e., no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to Section 3.3.4.3) (Discontinuation of the trial by the sponsor). Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator (or

an authorised deputy) or the Sponsor of the study, e.g. because of any unforeseen adverse events, etc.

Although no formal Safety Review will be done within a dose group (e.g., between cohorts of the same dose level), safety will be monitored closely and continuously by the investigator during this trial, and an individual will only be dosed in the absence of any safety concern.

At minimum, data from six patients on active drug (BI 894416) from every required dose group (see Figure 3.1:1 and Appendix 10.1) need to be available for escalation to a higher dose / start of the next higher MRD dose group. For minimum dataset with regards to preliminary PK data see Section 7.4 (Preliminary PK analyses). For each safety review meeting, all relevant available safety data of both SRD and MRD parts should be included in the review. The minimum data set for dose escalation in SRD or MRD part is described below.

For escalation to the next higher dose in the SRD part, the minimum data set for review consists of the following data:

- AEs in the preceding dose groups from SRD part *up to at least 7 days post BI 894416*, including clinically relevant findings from ancillary safety testing listed below. Note: AEs may be ongoing at the time of Safety Reviews and AE information may be patient to change prior to Database Lock.
- Results from 12-lead ECG and continuous ECG monitoring from SRD part in the preceding dose groups *up to at least 3 days post BI 894416 administration.*
- Vital signs in the preceding dose groups from SRD part *up to at least 3 days post BI 894416 administration.*
- Clinical laboratory tests in the preceding dose groups from SRD part *up to at least 7 days after dosing with BI 894416.*
- Preliminary PK data as per Section 7.4 (Preliminary PK analyses).
- Check of criteria for stopping patient treatment as per Section 3.3.4.3 (Discontinuation of the trial by the sponsor)

For escalation to the next higher dose in the MRD part, the minimum data set for review consists of the following data:

- AEs in the preceding dose groups from SRD and MRD part up to *at least 7 days post last BI 894416 dosing*, including clinically relevant findings from ancillary safety testing listed below. Note: AEs may be ongoing at the time of Safety Reviews and AE information may be patient to change prior to Database Lock.
- Results from 12-lead ECG (from SRD and MRD part) and continuous ECG monitoring (from SRD part, only) in the preceding dose groups *up to at least 4 days (MRD part) or up to at least 3 days (SRD part) post last BI 894416 administration.*
- Vital signs in the preceding dose groups from SRD and MRD parts *up to at least 4 days (MRD part) or up to at least 3 days (SRD part) post last BI 894416 administration.*
- Clinical laboratory tests in the preceding dose groups from SRD and MRD parts *up to at least 7 days after last dosing with BI 894416.*

- Preliminary PK data from previous SRD and MRD parts as per Section 7.4 (Preliminary PK analyses).
- Check of criteria for stopping patient treatment as per Section 3.3.4.3 (Discontinuation of the trial by the sponsor)

An overview of all relevant trial activities is provided in the Flow Charts. For visit schedules and details of trial procedures at selected visits, refer to Section 6 and to Flow Charts, respectively.

A dose-escalation decision tree for the trial is shown below in Figure 3.1:1 and Appendix 10.1.

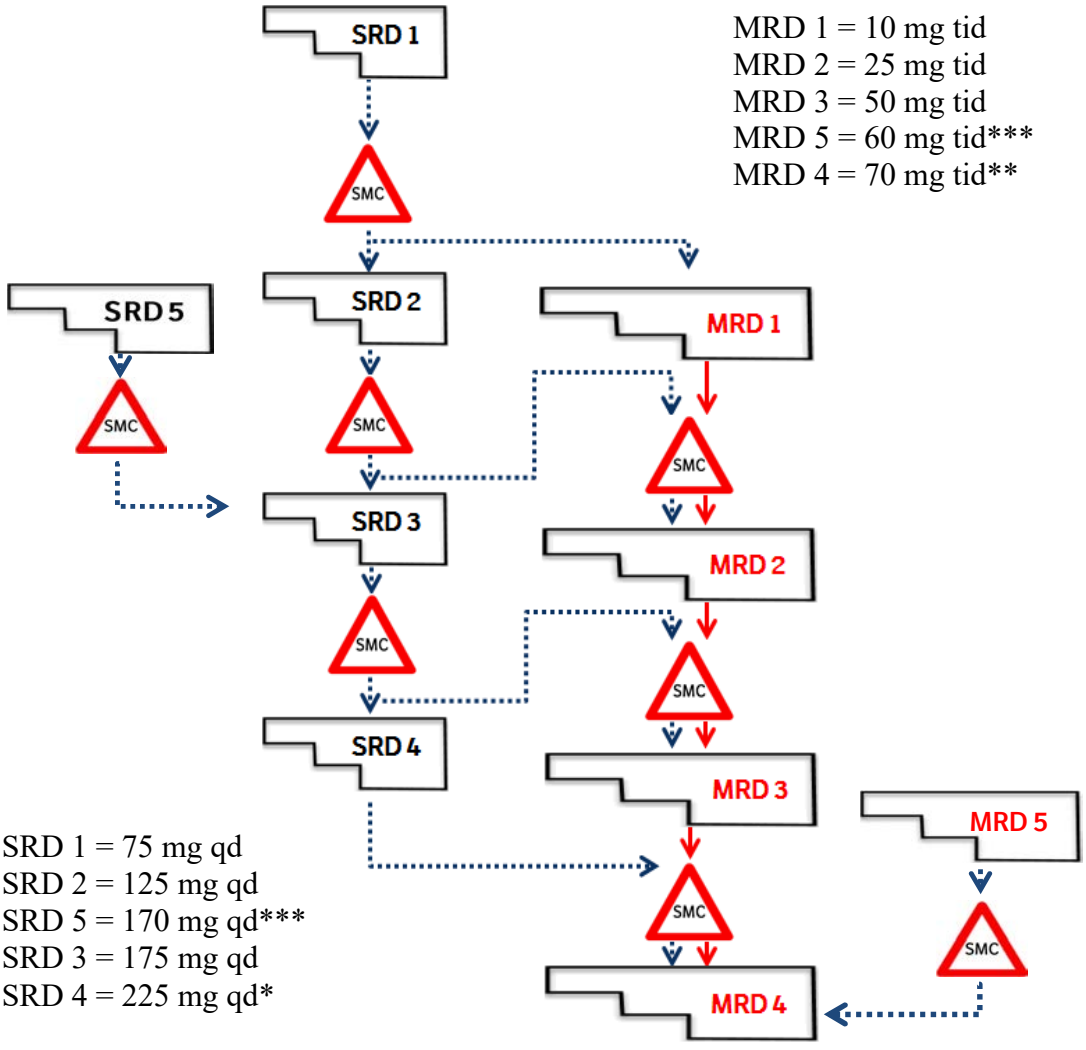


Figure 3.1:1 Dose group escalation overview

The figure shows the timepoints at which the SMC will assess available data from previous dose groups in order to conduct safety review meetings for escalation to a higher dose group in the SRD or MRD part. For more details see text in Section 3.1 and Appendix 10.1. For each safety review meeting, all relevant available safety data of both SRD and MRD parts should be included in the review.

* SRD, 225 mg dose: The highest dose might be reduced, in case preliminary PK analysis predict that expected exposure would exceed exposure limit (see Section 4.1.2).

** MRD 70 mg tid: The highest MRD dose might be reduced, in case preliminary PK analysis predict that expected exposure would exceed exposure limit (see Section 4.1.2) or to ensure that exposure covered during preceding SRD part will not be exceeded by the predicted gMean C_{max} and AUC_{0-24} values.

*** interim dose group added based on preliminary PK data (see also Section 4.2.1).

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

For single- and multiple-rising dose trials, the sequential rising dose design described in Section 3.1 is viewed favourably under the provision not to expose the patients involved to undue risks.

Single-blind conditions regarding the patient's treatment (active or placebo) are maintained within each dose group. However, patients and investigators will be aware of the dose of BI 894416 administered. The disadvantage of the trial design is a possible observer bias with regard to the dose-dependent effects; in addition, the sequential dosing of groups could potentially result in time-related effects. However, as such effects are expected to be small relative to the differences between the doses in the broad range investigated, unbiased comparisons between treatments can still be expected.

It is standard in single and multiple rising dose trials to include a placebo group to control for safety, tolerability, [redacted] of the trial medication. Each dose group consists of 10 patients, with 8 on active treatment, and 2 on placebo. For data analysis purposes, the placebo control group will include all patients of all dose groups treated with placebo. Eight patients per active treatment group are generally considered to be sufficient for the exploratory evaluation of pharmacokinetics.

3.3 SELECTION OF TRIAL POPULATION

Only male patients will be included in the trial because no data on reproductive toxicology are available at this time and because, until availability of the results of the 26-week Tg.rasH2 carcinogenicity study, study populations are restricted to male patients (see IB c03536505). It is planned that approximately 80 male patients in total will enter the study. The actual number of patients entered may exceed the total of 80 if additional intermediate or lower doses are tested or if number of patients of a dose group is extended (see Section 3.1).

[redacted] In addition, the target patient population may allow for an early clinical read-out of efficacy from the MRD portion e.g. changes in airway resistance (Raw), [redacted] Assessment of safety in a patient population is considered more relevant for subsequent studies in the development program.

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

3.3.1 Main diagnosis for trial entry

Outpatients with a history of asthma are eligible for inclusion if they meet all the inclusion criteria (Section 3.3.2) and none of the exclusion criteria (Section 3.3.3). Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

Patients may participate once in the SRD and once in the MRD portions of the study (for details see exclusion criterion #13).

3.3.2 Inclusion criteria

Patients will only be included into the trial, if they meet the following criteria:

1. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial. Medication washout and medication restrictions according to protocol are allowed only after informed consent is obtained.
2. Male patients aged at least 18 years but not more than 55 years at the time of informed consent.
3. Men able to father a child must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.
4. Pre-bronchodilator clinic measured FEV_1 of ≥ 70% of predicted normal at the screening visit (Visit 1). Calculations will be based on Global Lung Function Initiative (GLI) formula (R15-0845).
5. A diagnosis of asthma, diagnosed by a physician.
6. Patients should be non-smokers or ex-smokers who stopped smoking at least 12 weeks prior to screening and are expected to be able to not smoke for the duration of the study.
7. Patients must be able to perform all trial related procedures including pulmonary function tests, nasal brushings.
8. BMI of 18.5 to 32 kg/m^2 (incl.)
9. For MRD part: Patients are allowed to be on stable inhaled low dose corticosteroid (please refer to GINA guidelines) for at least 4 weeks prior to screening.

3.3.3 Exclusion criteria

Patients will not be allowed to participate if any of the following general criteria apply:

1. Any finding in the medical examination (including BP, PR, echocardiography and echocardiography stress test or ECG and including the neurological examination) is deviating from normal and judged as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 50 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance

4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular (stress), metabolic, immunological or hormonal disorders
6. Relevant abnormality on stress echocardiography for those 45 of age and older at screening.
7. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)
8. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
9. History of relevant orthostatic hypotension, fainting spells, or blackouts
10. Chronic or relevant acute infections
11. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
12. Use of drugs within 30 days prior to administration of trial medication that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
13. Participation in another trial where an investigational drug other than BI 894416 has been administered within 60 days or 5 half-lives (whichever is greater) prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug. In case of planned participation in the MRD part in this trial the previous participation in one dose group of the SRD part is allowed if BI 894416 has been administered more than 21 days prior to planned administration of BI 894416 in the MRD part. (Participation in an SRD dose group after the patient has participated in the MRD part is not allowed.)
14. Alcohol abuse (consumption of more than 24 g per day) (please refer to Appendix 10.5)
15. Drug abuse or positive drug screening
16. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
17. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
18. Inability to comply with dietary regimen of trial site
19. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms) or any other relevant ECG finding at screening
20. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
21. Patient unable or unwilling to comply with study requirements, or has a condition that would not allow safe participation in the study
22. History of relevant neurological disorder affecting the peripheral or central nervous system (this includes, but is not limited to: stroke, epilepsy, inflammatory or atrophic diseases affecting the nervous system, cluster headache or any cancer of the nervous system)*
23. History of immunological disease except allergy not relevant to the trial (such as mild hayfever or dust mite allergy) and except asthma in childhood or adolescence

24. History of cancer (other than successfully treated basal cell carcinoma)
25. Use of any drug that could reasonably inhibit platelet aggregation or coagulation (e.g. acetylsalicylic acid) within 10 days prior to administration of trial medication, or planned use during the trial or within 7 days after last dose of trial medication.

* Febrile seizures in childhood or adolescence, recovered carpal tunnel syndrome, recovered uncomplicated meningitis, recovered herpes zoster, tension headache, occasional benign tics (e.g. due to stress) or minor par- or dysesthesia (e.g. as a side effect of prior blood withdrawal) do not constitute a history of relevant neurological disorder.

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

If a patient is removed from or withdraws from the trial prior to the first administration of trial medication, at least the basic information of this patient will be entered in the case report form (eCRF). The minimum requirements to enter in eCRF will be listed in an ´eCRF instruction guide´.

At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the eCRF.

3.3.4.1 Discontinuation of trial treatment

An individual patient must discontinue trial treatment if:

1. The patient withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The patient is no longer able to participate for other medical reasons (such as surgery, adverse events (AEs), or diseases)
4. One adverse event of severe intensity or one SAE occurs.
5. The patient shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.
6. The patient experiences an infection with SARS-CoV-2 (as confirmed by PCR testing, see Section 5.2.4).

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

A patient can also be removed from the trial if eligibility criteria are being violated or if the patient fails to comply with the protocol (for instance, by non-adherence to dietary rules, or non-attendance at study assessments).

If a patient is removed from or withdraws from the trial prior to administration of trial medication, basic data of this patient will be entered in the case report form (eCRF) or trial database and will not be reported in the clinical trial report (CTR).

If a patient is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the eCRF. In this case, the data will be included in the eCRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the eCRFs. These discontinuations will be discussed in the CTR.

Even if the trial treatment is discontinued, the patient remains in the trial and, given his agreement, will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Charts and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

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

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk assessment. More specifically, the trial will be terminated if more than 50% of the actively dosed patients at one dose level show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported.
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP or the CTP by a trial site or investigator, disturbing the appropriate conduct of the trial

The sponsor decides to discontinue the further development of the investigational product.

3.3.4.4 Discontinuation of the trial –Stopping rules

1. Dose escalation will be stopped as soon as at least 2 patients at one dose level on active drug showed relevant individual QT prolongation, i.e. absolute QT or QTc greater than 500 ms or a QTc increase of greater 60 ms from baseline, which has been confirmed by a repeat ECG recording.
2. Dose escalation in the respective trial part will be stopped if the estimated systemic exposure of the next dose level is expected to exceed C_{max} of 5233 nM (group gMean values), AUC_{0-24} of 36,150 nM·h, (group gMean values) or 63,000 nM*h (for the 95th

percentile of any given patient in the next dose group). In this case, an interim dose level lower than the planned next dose level may be given, or the highest dose group of the SRD and/or MRD part may be reduced, or additional patients may be entered in the current dose group, as long as the expected systemic exposure is not expected to exceed the above mentioned levels. Alternatively, the next dose level may be given if the previous dose levels are deemed safe after thorough review and after a substantial amendment has been approved by both competent authority and IEC.

3. Dose escalation to the highest dose group (70 mg tid) in the MRD part will not be done if the estimated systemic exposure (gMean $C_{max,ss}$ or $AUC_{0-24,ss}$) is expected to exceed the plasma exposure levels observed in the SRD part of the trial. In this case, the dose of the highest MRD dose group may be reduced to a dose >50 mg and <70 mg tid as long as the expected systemic exposure (gMean $C_{max,ss}$ and $AUC_{0-24,ss}$) is covered by the (preliminary) values measured in the SRD part (Section 4.1.2).

3.3.4.5 Discontinuation of a study part (SRD, MRD)

Dose escalation from an interim dose to the next planned dose level might be stopped, if the next dose level is not considered to contribute significantly to the PK analysis and the safety data set (e.g. if the dose difference is small).

If the SRD is stopped temporarily because criteria are met, the MRD will continue in the meantime.

3.3.5 Replacement of patients

In case that one dose group in this trial is completed by less than 6 patients on active treatment (due to e.g. drop-outs or recruitment reasons), the clinical trial leader together with the trial pharmacokineticist and the trial statistician are to decide if and how many patients will be replaced. A maximum of 3 patients can be replaced in each dose group (SRD and MRD). Only those patients will be replaced, which have not withdrawn due to adverse drug reactions or adverse events based on study procedures. A replacement patient will be assigned a unique patient number, and will be assigned to the same treatment as the patient he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

BI 894416 and placebo tablets.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test products are given below:

Table 4.1.1: 1 Test products

Substance:	BI 894416
Pharmaceutical formulation:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	10 mg, 25 mg or 100 mg
Posology:	SRD part – single dose MRD part – tid dosing
Method and route of administration:	p.o.

The characteristics of the reference product (placebo) are given below:

Substance:	Placebo matching BI 894416 to match 10mg, 25mg and 100mg BI 894416 tablets
Pharmaceutical formulation:	Tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	0 mg
Posology:	SRD part- single dose MRD part – tid dosing
Method and route of administration:	p.o.

4.1.2 Selection of doses in the trial and dose modification

Maximum exposure (exposure cap)
The human exposure cap, which will be used to limit dosing, corresponds to a C_{max} gMean value of 5,233 nM and AUC_{0-24} gMean value of 36,150 nM·h, the latter corresponding to 3-fold below exposure at the dog NOAEL and 7-fold below the lowest exposure in dogs where neurologic effects were observed. In addition, predicted exposures above 63,000 nM·h will not be permitted for the 95th percentile of any given patient of the next dose group in this study. A neurological clinical examination assessment will be done in this trial at pre-defined time points (see Flow Charts). For more details on toxicology data supporting the selected human exposure cap, please see the current version of the Investigator's Brochure (IB) [c03536505].

Maximum dose
Maximum dose is described below, and this dose will not be exceeded in this trial. The doses selected for this trial cover the estimated therapeutic range and are expected to be necessary for successful development of BI 894416.

For the highest single dose in the SRD part, the C_{max} gMean value is predicted to slightly exceed the upper limit of exposure (see Table 4.1.2: 1 below). This dose will only be given if exposure (C_{max}) at high doses is lower than currently predicted, i.e. the dose escalation stopping criterion referring to plasma exposure prediction is not reached (see Section 3.3.4.4) after single dose administration of up to 175 mg. Note: Before this trial, highest dose given to humans was 70 mg, i.e. predictions for doses higher than 70 mg are based on extrapolation and actual exposures may differ from predictions.

In case that preliminary PK analysis during the trial predict that exposure limit (see above) is exceeded with the highest SRD dose, the dose may be reduced to a dose > 175 and <225 mg, as long as the predicted exposure at this reduced dose does not exceed the exposure limit.

In case the sponsor and SMC agree to test a dose level that is expected to exceed the maximal acceptable exposure defined above, this would only be done after approval of a substantial amendment by competent authority and IEC (according to Section 7.5 of EMA guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with IMPs [R18-1299]).

Preliminary PK analysis
Dose escalation will be guided by preliminary PK analysis to ensure that the expected AUC and C_{max} gMean values and the expected individual values (95th Percentile for AUC_{0-24}) for exposure at the next planned dose level do not exceed the maximum acceptable exposure.

Interim Dose Levels
With CTP version 3.0, an interim single dose group of 170 mg (SRD group 5) is added following dose group 2 (125 mg). Dose escalation to the next MRD dose group (dose group 3) may occur, as long as the expected systemic exposure (gMean $C_{max,ss}$ and $AUC_{0-24,ss}$) is covered by the (preliminary) values measured in the interim SRD 5 dose group. See also Section 3.1.
With CTP version 5.0, an interim multiple dose group of 60 mg tid (MRD group 5) is added following dose group 3 (50 mg tid). Dose escalation to the next MRD dose group (dose group 4) may occur, as long as the expected systemic exposure (gMean $C_{max,ss}$ and $AUC_{0-24,ss}$) is covered by the (preliminary) values measured in the highest SRD dose group. See also Section 3.1.

SRD part
Table 4.1.2: 1 shows predicted PK parameters for single dose administration. Exposure multiples are calculated as a ratio of the maximal acceptable human exposure divided by predicted systemic exposure after single dosing.

Table 4.1.2: 1 Predicted SRD PK parameters

Dosing Regimen [mg]	AUC_{0-24} [nM*h] (gMean)	Exposure multiple[1]	AUC_{0-24} [nM*h] (95th percentile)	Exposure multiple[2]	C_{max} [nM] (gMean)	Exposure multiple[3]
75 mg q.d.	12730	2.840	23262	2.708	1861	2.812
125 mg q.d.	21557	1.677	40152	1.569	3132	1.671
170 mg q.d.	29043	1.245	55171	1.142	4255	1.230
175 mg q.d.	29897	1.209	56794	1.109	4380	1.195
225 mg q.d.	38849	0.931	72987	0.863	5658	0.925

[1] in relation to AUC gMean exposure limit (36150 nM*h)
[2] in relation to 95th percentile exposure limit (63000 nM*h)
[3] in relation to C_{max} gMean exposure limit (5233 nM)

The new interim dose 170 mg was inserted based on modelling from previous SRD part PK data.
Predicted PK parameters have been adapted for doses ≥ 175 mg based on preliminary PK analysis including data from 75 mg and 125 mg dose groups.

Table 4.1.2: 2 SRD PK parameters obtained for doses up to 170 mg q.d.*

Dosing Regimen [mg]	gMean AUC_{0-24} [nM*h] (gCV [%])	gMean C_{max} [nM] (gCV [%])
75 mg q.d.	15200 (38.2)	2340 (29.7)
125 mg q.d.	25700 (29.9)	4128 (26.1)
170 mg q.d.	31700 (20.6)	5280 (24.3)

* Results from preliminary pharmacokinetic non-compartmental analysis

<u>MRD part</u>
Table 4.1.2: 2 shows predicted PK parameters for multiple dose administration. Exposure multiples are calculated as a ratio of the maximal acceptable human exposure divided by predicted systemic exposure after multiple dosing.

Table 4.1.2: 3 Predicted MRD PK parameters

Dosing Regimen [mg]	$AUC_{0-24,ss}$ [nM*h] (gMean)	Exposure multiple[1]	$AUC_{0-24,ss}$ [nM*h] (95th percentile)	Exposure multiple[2]	$C_{max,ss}$ [nM] (gMean)	Exposure multiple[3]
10 mg t.i.d.	3691	9.794	6931	9.090	261	20.021
25 mg t.i.d.	13695	2.640	27453	2.295	960	5.450
50 mg t.i.d.	27577	1.311	52616	1.197	1929	2.712
60 mg t.i.d.	31727	1.139	61596	1.023	2241	2.335
70 mg t.i.d.	37732	0.958	72492	0.869	2648	1.977

[1] in relation to AUC gMean exposure limit (36150 nM*h)
[2] in relation to 95th percentile exposure limit (63000 nM*h)
[3] in relation to C_{max} gMean exposure limit (5233 nM)

The new interim dose 60 mg tid was inserted based on modelling from previous MRD part PK data. Predicted PK parameters have been adapted for doses ≥ 60 mg tid based on preliminary PK analysis including data from 10 mg tid, 25 mg tid and 50 mg tid dose groups.

The predicted exposure for 60 mg tid ($AUC_{0-24,ss}$) is 31727nM*h. The predicted exposure is covered by the exposure (AUC_{0-24}) obtained after administration of 170 mg q.d. (31700 nM*h). The difference of 27 nM*h is considered neglectable, taking the PK variability into consideration. In addition, the predicted exposure does not exceed the 95th percentile exposure limit for $AUC_{0-24,ss}$ for 60 mg tid (61596 nM*h vs.63000 nM*h).

Table 4.1.2: 4 MRD PK parameters obtained for doses up to 50 mg t.i.d.*

Dosing Regimen [mg]	gMean AUC_{0-24} [nM*h] (gCV [%])	gMean C_{max} [nM] (gCV [%])
10 mg t.i.d.	4410 (48.6)	299 (42.7)
25 mg t.i.d.	14400 (19.8)	985 (19.4)
50 mg t.i.d.	16200 (33.5)	1290 (52.1)

* Results from preliminary pharmacokinetic non-compartmental analysis

4.1.3 Method of assigning patients to treatment groups

Prior to the screening visit, patients will be contacted in writing and informed about the planned visit dates. The patients willing to participate will be recruited to the dose groups (3 cohorts per dose group) according to their temporal availability. As soon as enough patients are allocated to 1 of the 24 dose cohorts, the following patients will be allocated to one of the other dose cohorts. Therefore, the allocation of patients to dose cohorts is not influenced by trial personnel, but only by the patients' temporal availability. Because the study includes

patients from a homogenous population, relevant imbalances between the dose groups are not expected.

Patients will be assigned to treatments (active treatment or placebo) prior to the first administration of trial medication. For this purpose, the randomisation list will be provided to the trial site in advance. Patients are then assigned to treatment according to the predefined randomisation list.

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each patient

The treatments to be evaluated are outlined in Table 4.1.4: 1 (SRD part) and 4.1.4: 2 (MRD part). The number of units for placebo corresponds to the number of units of the corresponding dose level.

Table 4.1.4: 1 BI 894416 and placebo* treatments, tablets to be administered in SRD part

Dose group	Substance	BI 894416 10 mg	BI 894416 25 mg	BI 894416 100 mg	Total dose of BI 894416	Total **daily** dose of BI 894416
SRD 1	BI 894416	0	3	0	75 mg	75 mg
SRD 2	BI 894416	0	1	1	125 mg	125 mg
SRD 5	BI 894416	2	2	1	170 mg	170 mg
SRD 3	BI 894416	0	3	1	175 mg	175 mg
SRD 4	BI 894416	0	1	2	225 mg	225 mg

* Placebo is given to the 2nd patient of first cohort and to one patient of last cohort (randomised)

Table 4.1.4: 2 BI 894416 and placebo* treatments, tablets to be administered in MRD

Dose group	Substance	BI 894416 10 mg	BI 894416 25 mg	BI 894416 100 mg	Total **daily** dose of BI 894416
MRD 1	BI 894416	1 t.i.d.	0	0	30 mg
MRD 2	BI 894416	0	1 t.i.d.	0	75 mg
MRD 3	BI 894416	0	2 t.i.d.	0	150 mg
MRD 5	BI 894416	1 t.i.d.	2 t.i.d.	0	180 mg
MRD 4	BI 894416	2 t.i.d.	2 t.i.d.	0	210 mg

* Placebo is given to the 2nd patient of first cohort and to one patient of last cohort (randomised)

The trial medication will be administered to the patients, while in a sitting or standing position, as an oral dose together with about 240 mL of water under supervision of the investigating physician or an authorised designee (please refer to Flow Charts). The so-called four-eye principle (two person rule) should be applied for administration of trial medication.

For this, 1 authorised employee of the trial site should witness the administration of trial medication, and its preparation, if correct dosage cannot be ensured otherwise.

SRD: Administration of BI 894416 or placebo will be performed after patients have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing.

SRD: During the first 4 h after drug administration, the patients are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination), or to sleep.

Patients will be kept under close medical surveillance until 34 h after dosing in SRD part.

MRD: Administration of BI 894416 or placebo on Days 1 (single dose) and 9 (single dose) will be performed after patients have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing. On the other study days, no food is allowed for at least 2 h before and 1 h after each intake of BI 894416 or placebo.

MRD: In MRD dose group patients will be hospitalized from Day -1 until Day 10. At Day 1 and Day 9 a single dose will be administered to patients whereas from Day 2 until Day 8 BI 894416 will be administered tid.

Patients will be kept under close medical surveillance until Day 10 in MRD part (please refer to MRD Flow Chart).

MRD: During the first 4 h after BI 894416 administration on Day 1 and Day 9, the patients are not allowed to lie down (i.e. no declination of the upper body of more than 45 degrees from upright posture except for medical examination), or to sleep.

For restrictions with regard to diet, see Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

A single–blind design is considered acceptable because the potential bias in this type of study is expected to be low and according to study procedures it is assured that the investigator's knowledge of the next treatment does not influence the decision to enter a patient.

At the trial site, administration and preparation of trial medication will be performed as described in Section 4.1.4 to ensure blinding of patients.

All trial data will be handled open label. This means that trial functions of the sponsor are unblinded (including clinical trial leader, trial data manager, trial statistician, bioanalyst, trial pharmacokineticist, trial pharmacometrician, [redacted] safety monitoring committee member, as well as dedicated personnel of the trial site).

In addition, the trial pharmacokineticist, trial bioanalyst and trial pharmacometrician may receive the randomisation codes to perform the interim / preliminary PK analysis.

Within the central ECG lab, the staff involved with interval measurements will be blinded with respect to the treatment and also with regard to the recording date and time as well as planned time points of the ECGs. The interval measurements for a given patient will be performed in a random and blinded sequence by a single technician.

If an interim safety analysis of ECG data is required, a part of the staff of the central ECG lab may be unblinded. This part of the staff will be strictly separated from the blinded staff members who are involved with ECG interval measurements and assessments of ECGs.

Access to the randomisation schedule will be controlled and documented.

4.1.5.2 Unblinding and breaking the code

As this trial will be conducted single-blind, patients' treatment assignments will be known to investigators. Therefore, no emergency envelopes will be provided. There will be a 24h/7d contact number of the site be provided on the patients' trial identification card in case emergency healthcare professionals need to unblind a patient.

4.1.6 Packaging, labelling, and re-supply

BI 894416 tablets

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

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

The telephone number of the sponsor and the name, address and telephone number of the trial site are provided in the patient information form. The EudraCT number is indicated on the title page of this protocol as well as on the patient information and informed consent forms. Examples of the labels will be available in the ISF.

No re-supply is planned.

4.1.7 Storage conditions

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

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs from 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

Only authorised personnel documented in the form 'Trial Staff List' may dispense medication to trial patients. The trial medication must be administered in the manner specified in the CTP.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the disposal of unused products.These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational medicinal products received from the sponsor. At the time of disposal of remaining trial medication, the investigator or designee must verify that no remaining supplies are in the investigator's possession.

All unused trial medication will be disposed of locally by the trial site upon written authorisation of the clinical trial leader. Receipt, usage, and disposal of trial medication must be documented on the appropriate forms. Account must be given for any discrepancies.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, if adverse events require treatment, the investigator can authorise symptomatic therapy. In those cases, patients will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Besides allowed low dose inhaled corticosteroids (please refer to GINA guidelines), no concomitant therapy is allowed. All concomitant or rescue therapies will be recorded (including time of intake on study days) on the appropriate pages of the eCRF if adverse events require treatment, the investigator can authorise symptomatic therapy.

In the event of rescue medication use, patients should be washed out of any inhaled short-acting β2-adrenergic agonist for at least 6 hours prior to reversibility and lung function tests.

Acetylsalicylic acid or other drugs that may inhibit platelet aggregation or coagulation **should be avoided** during the entire study. If necessary, paracetamol may be given occasional if adverse event require treatment.

Drugs that may increase exposure of BI 894416 should be avoided during the entire study. Based on *in vitro* data, CYP3A is involved in metabolism of BI 894416. In addition, BI 894416 is an in vitro substrate of P-glycoprotein. Data of drug-drug interaction trial 1371-0004 (see Section 1.2.1) indicate that inhibition of CYP3A and P-glycoprotein may cause mild increases of BI 894416 plasma concentrations. Therefore administration of CYP3A and P-glycoprotein inhibitors should be avoided during the entire study in emergency cases.

BI 894416 is also a substrate of organic cation transporter 2 (OCT2). It is not excluded that inhibition of OCT2 could increase BI 894416 plasma exposure. Therefore administration of inhibitors of OCT2 should be avoided during the entire study.

4.2.2.2 Restrictions on diet and life style

Poppy-seeds containing foods should not be consumed starting 3 days before (first) trial drug administration until the last PK sampling of the trial to avoid positive drug screening tests.

While admitted to the trial site the patients are restricted from consuming any foods or drinks other than those provided. Standardised meals will be served at the time points described in the Flow Charts.

After availability of preliminary PK data of separate clinical trial 1371-0021 (clinical phase I trial in healthy volunteers investigating the effect of a high-fat, high-calorie breakfast on BI 894416 bioavailability) the time of food in relation to drug intake (e.g. earlier breakfast) may be adapted by clarification letter or by non-substantial amendment to the CTP.

For SRD: No food is allowed for at least 10 h before and 4 h after trial medication intake.

For SRD: From 1 h before drug intake until 4 h after trial medication intake, fluid intake is restricted to the water administered with the trial medication, and an additional 240 mL of water served at 2 h and 4 h post-dose (mandatory for all patients). From 4 h after drug intake on Day 1 until 24 h post-dose, fluid intake is restricted to 3,000 mL.

For MRD: On Days 1 and 9, no food is allowed for at least 10 h before and 4 h after BI 894416 or placebo intake. On all other study days, no food is allowed for at least 2 h before and 1 h after drug intake.

For MRD:

- On Days 1 and 9, from 1 h before BI 894416 or placebo intake until 4 h after BI 894416 or placebo intake, fluid intake is restricted to the water administered with BI 894416 or placebo, and an additional 240 mL of water served at 1 h and 3 h after BI 894416 or placebo dosing (mandatory for all patients). From 4 h after drug intake on Days 1 and 9 until 24 h post-dose, fluid intake is restricted to 3,000 mL.
- On all other study days, fluid intake from 30 min before drug administration until 30 min after drug administration is restricted to the water administered with the drug.

[redacted]

Green tea, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products including St. John's wort (Hypericum perforatum) are not permitted starting 7 days before the (first) administration of trial medication until after the last PK sample is collected.

Alcoholic beverages are not allowed starting 48 h before the (first) trial drug administration until after the last PK sample is collected.

Smoking is not allowed during the trial.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed during the in-house confinement at the trial site.

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

Direct exposure to the sun or exposure to solarium radiation should be avoided during the entire study.

4.3 TREATMENT COMPLIANCE

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

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Bodyplethysmography [redacted]

ATS/ERS criteria [P05-12782] are to be fulfilled (including calibration). Spirometry will be conducted with the patient in a seated position and it is preferable that the same trained individual performs the tests for a given patient. Maneuvers will be conducted in triplicate. The highest FEV_1 and FVC from an acceptable maneuver will be selected regardless of whether they come from different maneuvers or from the same maneuver (with a maximum of five attempts).

Calculations will be based on Global Lung Function Initiative (GLI) formula [R15-0845].

Reversibility testing [P05-12782] for the qualifying PFT at the Screening Visit (Visit 1): the procedure is described in Appendix 10.3.

Constant-volume variable-pressure body plethysmography will be used in the trial, following the methodology and calibration procedures described by Coates et al. 1997 [R98-1487]. Body plethysmography will be performed during the Screening visit (Visit 1) and for patients in MRD at Day -1, at Day 9 and at Visit 8.

MRD part: [redacted] (secondary endpoint) (Section 2.2.2, Appendix 10.3).

[redacted]

5.2 ASSESSMENT OF SAFETY

5.2.1 Medical examinations

At screening, the medical examination will include demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, a physical examination (including a echocardiography followed by a echocardiography stress test in patients aged 45 and older), and a neurological examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, a physical examination, and a neurological examination.

5.2.2 Neurological examination

At the time points specified in the Flow Charts, a physical neurological examination will be performed.

The neurological examination will include the following assessments:

- General level of arousal
- Orientation
- Eye movement
- Pupil size and pupil reactivity
- Reflexes
- Assessment of muscle strength
- Gait
- Romberg test
- Tremor
- Point-to-point movements
- Sensitivity

Documentation, Assessment and Reporting
Results will be documented in source data at the clinical trial site and assessed for clinical relevance by an investigator, deputy investigator or sub-investigator. Clinically relevant findings of the neurological examination will be reported as Adverse Events (during the trial) or as baseline conditions (at screening). Case narratives may be written if necessary.

5.2.3 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) will be measured by a blood pressure monitor at the times indicated in the Flow Charts, after patients have rested for at least 5 min in a supine position. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible.

5.2.4 Safety laboratory parameters

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

The parameters that will be determined are listed in Tables 5.2.4: 1 and 5.2.4: 2. Reference ranges will be provided in the ISF, Section 10.

Manual differential white blood cell count or urine sediment examinations will only be performed if there is an abnormality in the automatic blood cell count or in the urinalysis, respectively.

Table 5.2.4: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A[1]	B[1]	C[1]
Haematology	Haematocrit	X	X	X
	Haemoglobin	X	X	X
	Red Blood Cell Count (RBC)	X	X	X
	Reticulocytes (relative and absolute)	X	X	X
	White Blood Cells (WBC)	X	X	X
	Platelet Count/Thrombocytes (quant)	X	X	X
Automatic WBC differential, relative and absolute	Neutrophil; eosinophils; basophils; monocytes; lymphocytes	X	X	X
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes			
Immunoglobulins in serum	IgA	X	--	X
	IgD	X	--	X
	IgE, total and specific	X	--	X
	IgG	X	--	X
	IgM	X	--	X
Lymphocyte differentiation (relative and absolute; except for ratio)	T cells (CD3+), T helper cells (CD3+CD4+), cytotoxic T cells (CD3+CD8+), B cells (CD19+), natural killer cells (CD16+CD56+CD3-), CD4:CD8 ratio	X	--	X
Coagulation	Activated partial thromboplastin time (aPTT)	X	X	X
	Prothrombin time (Quick's test and INR)	X	X	X
	Platelet Function (via Platelet Function Assay)	See below		
Enzymes	AST [Aspartate transaminase]/GOT, SGOT	X	X	X
	ALT [Alanine transaminase]/GPT, SGPT	X	X	X
	Alkaline phosphatase (AP)	X	X	X
	Gamma-glutamyl transferase (GGT)	X	X	X
	Creatine kinase [CK]; CK-MB only if CK is elevated]	X	--	X
	Lactate dehydrogenase	X	--	X
	Lipase	X	--	X
	Amylase	X	--	X
Hormones	Thyroid Stimulating Hormone (TSH)	X	--	--
Molecular Diagnostics	PCR test for the detection of SARS-CoV-2		X	
Substrates	Plasma glucose	X	X	X
	Creatinine	X	X	X
	Total bilirubin	X	X	X
	Direct bilirubin	X	X	X
	Total protein	X	--	X
	C-Reactive Protein (CRP)	X	X	X
	Uric acid	X	--	X
	Total cholesterol	X	--	X
	Triglycerides	X	--	X
Electrolytes	Sodium	X	X	X
	Potassium	X	X	X
	Calcium	X	X	X
	Inorganic phosphate	X	--	X

[1] A, B and C are different sets of laboratory values. The Flow Charts defines at what time point which set is to be investigated

Table 5.2.4: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A[1]	B[1]	C[1]
Infectious serology (blood)	QuantiFERON-TB Gold	X	--	--
	Hepatitis B surface antigen (qualitative)	X	--	--
	Hepatitis B core antibody (qualitative)	X	--	--
	Hepatitis C antibodies (qualitative)	X	--	--
	HIV-1 and HIV-2 antibody (qualitative)	X	--	--
Urinalysis (Stix)	Urine nitrite	X	--	X
	Urine protein	X	--	X
	Urine glucose	X	--	X
	Urine ketone	X	--	X
	Urobilinogen	X	--	X
	Urine bilirubin	X	--	X
	Urine erythrocytes	X	--	X
	Urine leucocytes	X	--	X
	Urine pH	X	--	X
Urine sediment[1] (microscopic examination if erythrocytes, leukocytes nitrite or protein are abnormal in urine)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)			

[1] A, B and C are different sets of laboratory values. The Flow Charts defines at what time point which set is to be investigated

The tests listed in Table 5.2.4: 2 are screening laboratory tests to check eligibility, which may be repeated as required. The results will not be entered in the eCRF/database and will not be reported in the CTR.

Table 5.2.4: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA
	Barbiturates
	Benzodiazepine
	Cannabis
	Cocaine
	Methadone
	Methamphetamines/MDMA/XTC
	Opiates
	Phencyclidine
	Tricyclic antidepressants

To encourage compliance with alcohol restrictions, a breath alcohol test will be performed during Screening Visit and before (first) drug administration (SRD and MRD part) and may be repeated at any time during the study at the discretion of an investigator or designee. The results will not be included in the CTR.

The laboratory tests listed in Table 5.2.4: 1 and 5.2.4: 2 will be performed at [redacted] or at

[redacted] & [redacted]. The drug screening tests will be performed at the trial site.

[redacted]

Cotinine Test
A qualitative urine cotinine test will be performed on all patients at Visit 1, and Visit 3.1, and Visit 3.9 prior to the (first) morning dose. If the qualitative test is positive at Visit 1, the site should discuss the result regarding potential exposure to nicotine and remind the patient to refrain from smoking according to inclusion criterion #6.
If the qualitative test at Visit 3.1. is positive, the site should consider to not randomize the patient.
All randomized patients with a positive qualitative cotinine test should be referred to a quantitative cotinine test. Results of the quantitative test are not decisive for patient eligibility but should support the interpretation of PK parameter analysis.
The tests will be performed at the facilities of the [redacted] and at the [redacted] & [redacted].

Molecular test for SARS-CoV-2
The test will be performed on all eligible patients at Visit 2. The result must be available prior to randomization. If positive, the patient must not be randomized.
The test will be conducted according to the recommendations of Robert-Koch-Institute in Germany (https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Entlassmanagement.html) i.e. performed on two swabs obtained at the same time from oro- and nasopharynx (single PCR test sufficient after transfer of two swabs from oro- and nasopharynx to the same transport media, or use of the same swab in both oro- and nasopharynx).

5.2.5 [redacted]

5.2.5.1 12-lead resting ECG

Recording
Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Charts. Precise electrode placement will be performed according to the method of Wilson, Goldberger and

Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). In the SRD and MRD part, precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

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

All ECGs will be recorded for a 10 sec duration after patients have rested for at least 5 min in a supine position. ECG recording will always precede all other study procedures scheduled for the same time (except for blood drawing from an intravenous cannula that is already in place) to avoid compromising ECG quality.

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in the Flow Chart of the SRD and/or MRD part.

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. For repetition within triplicate ECGs the time window of 180 sec applies as well. The repeat ECGs are assigned to the respective scheduled time point.

Additional (unscheduled) ECGs may be collected by the investigator for safety reasons. These ECGs are assigned to the prior scheduled time point in the Sponsor's database.

Storage
All ECGs will be stored electronically in the System provided by [redacted].

Data transfer
All triplicate ECGs will be transferred electronically to the central ECG laboratory ([redacted]) for evaluation.

In case of repeat ECGs due to quality reasons, only the repeated ECG recordings will be transferred to the central ECG lab, whereas the initially recorded ECGs will be discarded. Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

Data transfer from the central ECG lab to the sponsor is described in a document that is filed in the TMF.

Evaluation
a) Central ECG lab
   Central ECG lab evaluation will be performed (during the study and/or after the study) for the first of three replicate ECGs per time point. For baseline, all three ECGs of the triplicate ECG on Day 1 pre-dose will be evaluated. For the three triplicate ECGs on Day -3 to -1 all ECGs will be evaluated. This will include the determination of cardiac QRS-axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS

and QT measured semi-automatically. Heart rate (HR) and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor (see TSAP for details).

All semi-automatic interval measurements in one patient will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR. For automatic interval measurements no lead will be provided

For blinding arrangements see Section 4.1.5.1. No more than two blinded readers will evaluate all ECGs of the study. ECGs from a particular patient should be evaluated by a single reader. For quality assurance and control of the measurements, all ECGs of a patient will be subsequently reviewed by the ECG technician supervisor or his/her designee to assess the overall variance of the measured intervals and, to detect accidental switching of leads and/or false patient assignments of the ECGs. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study.

Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the FDA requirements for annotated digital ECGs [R09-4830].

b) Trial site (SRD and MRD part)
All local ECGs will be evaluated by the investigator or a designee.

For the inclusion or exclusion (see Section 3.3) of a patient and for the assessment of cardiac safety during the study, the QT and QTcB values generated by the computerised ECG system or their manual corrections by the investigators will be used. In doubtful cases, ECGs may be sent upfront (i.e. prior to the regular data transfer) for cardiologic assessment by the central lab. In this case, these centrally measured results would overrule any other results obtained.

Abnormal findings, irrespective of whether they originate from central or local evaluation, will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator.

Any ECG abnormalities will be monitored carefully and, if necessary, the patient will be removed from the trial and will receive the appropriate medical treatment.

5.2.5.2 Continuous ECG monitoring

In the SRD part, cardiac rhythm (including heart rate) will be monitored by means of continuous 3-lead ECG recording for at least 15 min before drug administration (for baseline assessment) and for 4 h following drug administration). This continuous ECG monitoring supports the early detection of adverse events such as clinically relevant bradycardia, tachycardia, or arrhythmia at the trial site. Beyond this clinical evaluation at the trial site, no further data collection or analyses are performed based on continuous ECG monitoring.

ECG data from continuous ECG recording will be transferred to the clinical trial database. Abnormal findings during continuous ECG recording will be recorded as AEs if judged clinically relevant by the Investigator.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

The following should also be recorded as an AE in the eCRF 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.

5.2.6.1.2 Serious adverse event

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

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- Requires inpatient hospitalisation
- Requires prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

5.2.6.1.3 AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in Section 5.2.6.2, 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, an electronic data capture system which allows the entry of trial data at the trial site. These events should always be reported as SAEs as described above.

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

- Hepatic injury

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

  - An elevation of AST (aspartate transaminase) and/or ALT (alanine transaminase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or
  - Aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the 'DILI checklist' provided in the ISF or in eDC, as applicable. 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 that these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.6.1.5 Intensity (severity) of AEs

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

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated

Moderate: Sufficient discomfort to cause interference with usual activity

Severe: Incapacitating or causing inability to work or to perform usual activities

5.2.6.1.6 Causal relationship of AEs

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

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

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

- From signing the informed consent onwards until an individual patient's end of trial:
  - All AEs (serious and non-serious) and all AESIs
- After the individual patient's end of trial:
  - The investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the eCRF

5.2.6.2.2 AE reporting to the sponsor and timelines

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

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

Once the male patient has been enrolled in the clinical trial and has taken trial medication, and if a partner of the male trial participant becomes pregnant within 28 days after last drug intake, the investigator must report any drug exposure during pregnancy in a partner of the male trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point, after a written consent of the pregnant partner.

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B) as well as non-trial specific information and consent for the pregnant partner.

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Date and clock times of drug administration and pharmacokinetic sampling will be recorded in Source data and in the eCRFs.

Exact times of plasma sampling will be documented in the eCRFs by the medical personnel or sent as electronic files to the trial data manager. The actual sampling times will be used for determination of pharmacokinetic parameters.

PK sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. as a result of preliminary PK data), including addition of samples and visits, as long as the total blood volume taken per patient does not exceed 500 mL. Such changes would be implemented via non-substantial CTP Amendments.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

BI 894416

For quantification of BI 894416 concentrations in plasma, 2.7 mL of blood will be drawn from an antecubital or forearm vein into an K_2-EDTA (tripotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Charts and Appendix 10.2. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

Minor changes to the sampling methodology, which do not affect the results, may be made and communicated to the investigator without need for a protocol amendment.

The EDTA-anticoagulated blood samples will be centrifuged for approximately 10 min at approximately 2000 g to 4000 g and at 4 to 8 °C. Two plasma aliquots will be obtained and stored in polypropylene tubes. The first aliquot should contain at least 0.5 mL of plasma. The second aliquot should contain remaining plasma. The process from blood collection until transfer of plasma aliquots into the freezer should be completed within 60 min, with interim storage of blood samples in ice water or on ice. The time each aliquot was placed in the freezer will be documented. Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at approximately -20°C or below at the trial site. The second aliquot will be transferred to the analytical laboratory after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the plasma samples will be stored at approximately -20°C or below until analysis.

At a minimum, the sample tube labels should list BI trial number, patient number, visit, and planned sampling time. Further information such as matrix and analyte may also be provided. After completion of the trial, the plasma samples may be used for further methodological investigations (e.g., for stability testing [redacted]. The study samples will be discarded after completion of the additional investigations, but not later than 5 years after the CTR is archived.

[redacted]

[redacted]

5.3.2.3 Urine sampling for pharmacokinetic analysis

BI894416

A blank urine sample will be collected before administration of trial medication (within 3 h before drug dosing) and two 0.5 mL aliquots will be retained to check for analytical interference by concomitant or rescue medication.

All urine voided during the sampling intervals indicated in the Flow Charts and Appendix 10.2 will be collected in 2 L polyethylene (PE) containers and stored at room temperature. Patients are told to empty their bladders at the end of each sampling interval.

Due to the known adsorption of the drug to the container wall, 10 mL of 10% Tween 20 solution will be added to each 2 L collection container prior to the start of urine sampling. The weight of the empty container will be determined, thereafter 10 mL 10% Tween 20 will be added and the weight of the container at the end of each sampling interval will be determined.

The urine weight/volume for each collection interval will be documented (however, no correction for the specific gravity of urine is done; i.e., 1 L is defined to be equal to 1 kg). Two 0.5 mL aliquots will be stored in polypropylene (PP) tubes for bioanalytical measurements. If more than one collection container is used in an interval, the contents of all containers are to be mixed before aliquots are prepared. Mixing should be done by transferring the entire content of all collection containers into a single polyethylene) (PE)/PP

or glass container, and stirring the mixed fractions for about 1 min (manually or using a stir bar or other stirring device made of PE, PP, Teflon, or glass).

At a minimum, the sample tube labels should list BI trial number, patient number, visit, and planned collection time. Further information, such as matrix and analyte may also be provided.

Until transfer on dry ice to the analytical laboratory, the urine samples will be stored at approximately -20°C or below at the trial site. The second aliquot will be transferred after the bioanalyst has acknowledged safe arrival of the first aliquot. At the analytical laboratory, the urine samples will be stored at approximately -20°C or below until analysis.

After completion of the trial, the urine samples may be used for further methodological investigations (e.g., for stability testing [redacted] The study samples will be discarded after completion of the additional investigations but not later than 5 years after the CTR has been archived.

[redacted]

[redacted]

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

5.6.1 Pharmacogenomic evaluation

Pharmacogenomics investigates genetic variations to explain and to predict an individual's response to drugs. Therefore, a blood sample for **optional** pharmacogenomic testing will be taken from each patient. In case of unexplainable variability of PK parameters, DNA may be extracted from these samples and used for exploratory analysis of variants of the SYK gene and genes involved in Absorption, Distribution, Metabolism and Excretion (ADME) of drugs. It is not intended to include these data in the final report. However, the data may be part of the report if necessary.

Detailed instructions for pharmacogenomics sampling, including handling and shipment of samples will be provided in the laboratory manual in the ISF.

5.6.1.1 Methods and timing of sample collection

One blood sample of 8.5 mL will be taken from an arm vein in a PAXgene blood DNA drawing tube as indicated in the Flow Charts.

5.6.1.2 Analytical determinations

Genomic DNA will be extracted from blood samples according to standard molecular genetics methods and analysed by Drug Metabolism Enzymes and Transporters (DMETTM) analysis or other standard genotyping technologies.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Charts. Each visit date (with its window) is to be counted from Day 1. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

Exact times of measurements outside the permitted time windows will be documented. The acceptable time windows for screening and the end of trial examination are provided in the Flow Charts.

If Screening Visit is performed on Day -3 (within 76 hours) prior to administration of trial drug, the ambulatory Visit 2 can be omitted.

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1 are to be performed and completed within a 3 h-period prior to the trial drug administration (including blank values for PK [redacted]

In the SRD part, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 15 min for the first 4 h after trial drug administration, ± 30 min thereafter on Day 1 and ± 90 min on Day 2.

The acceptable deviation from the scheduled time for neurological tests in the SRD part is ± 45 min on Day 1 and ± 90 min on Day 2.

Starting from 48 h post administration a time window of ±120 min will be allowed for all study activities (incl. PK [redacted] sampling) in the SRD part.

In the MRD part, the acceptable deviation from the scheduled time for vital signs, ECG, and laboratory tests will be ± 15 min for the first 4 h after trial drug administration on Day 1 and Day 9, ± 30 min thereafter on Day 1 and Day 9, ± 90 min on Day 2 and on Day 10 and ± 120 min from Day 11 onwards.

The acceptable deviation from the scheduled time for neurological tests in MRD part is ± 45 min on Day 1, and ± 90 min on Day 2.

From Day 3 until Day 8 and from 48 h post last administration on Day 9 a time window of ±120 min will be allowed for all study activities (incl. PK [redacted] sampling) in the MRD part, except PK samples taken pre dose on Days 5, 7 and 8. Pre dose PK samples are taken within a time window of 15 min prior to drug administration.

If several activities are scheduled at the same time point in the Flow Charts, ECG should be the first and meal the last activity. Urine collection can be done prior to the ECG, if not within 5 min of the start of the ECG recording. Furthermore, if several measurements

including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the patient and possible influence on physiological parameters.

For planned individual plasma concentration sampling times and urine collection intervals refer to the Flow Charts. While the nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

Informed Consent

- After having been informed in detail about the trial, all patients will provide written informed consent in accordance with GCP and local legislation prior to enrolment in the study. Patients will be asked to give Informed Consent to SRD, MRD, and to pharmacogenomics sampling (optional).
- The patient should be recorded on the enrolment log.
- Upon obtaining Informed Consent the patient will receive a trial identification card.

Further Procedures at Visit 1

- After the informed consent process is complete and written informed consent is obtained, the patients will be assessed for study eligibility including assessments summarized in the Flow Charts of SRD and MRD.
- A preliminary check of in-/exclusion criteria is recommended at Screening to avoid to avoid unnecessary procedures and assessments in non-eligible patients.
- Patients who fail screening following Visit 1 assessments should be registered as screen failures in eCRF. 1 Re-screening attempt is allowed.
- For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, medical examination, and neurological examination refer to Sections 5.2.
- Demographic data (inclusive height, weight (both measured at site), smoking and alcohol history), Medical history and baseline medication are to be obtained.
- [redacted]
- Reversibility Testing (please refer to Appendix 10.3)
- Body plethysmography measurements will be conducted using the site's own equipment [R98-1487]. Body plethysmography measurements will be taken as described in Flow Charts, Section 5.1.1 and in Appendix 10.4.
- Echocardiography and echocardiography stress test after all other screening procedures have been completed.

6.2.2 Treatment period

Each patient may participate in one SRD dose group and in one MRD dose group. In case of planned participation in the MRD part in this trial the previous participation in one dose group of the SRD part is allowed if BI 894416 has been administered more than 21 days prior to planned administration of BI 894416 in the MRD part (Participation in an SRD dose group after the patient has participated in the MRD part is not allowed).

Trial medication will be taken orally by each patient under direct supervision of the investigator or his designee. Details on treatments and procedures of administration are described in Section 4.1.4.

SRD: Study participants will be admitted to the trial site in the morning of Day 1 and kept under close medical surveillance for at least 34 h following drug administration. The patients will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or his designee. On all other study days, the study will be performed in an ambulatory fashion in the SRD part.

MRD: Study participants will be admitted to the trial site on Day -1 and kept under close medical surveillance until Day 10 (please refer to the Flow Chart). The patients will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or his designee. On all other study days, the study will be performed in an ambulatory fashion in the MRD part.

For details on time points and procedures for collection and processing of blood and urine samples for PK [redacted] analysis, refer to Section 5.3 or 5.4, respectively, to Appendix 10.2 and to the Flow Charts.

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

6.2.3 Follow-up period and trial completion

For AE assessment, laboratory tests, recording of ECG and vital signs, physical examination and neurological examination during the end of trial period, see Section 5.2.

Patients who discontinue treatment before the end of the planned treatment period should undergo the end of trial visit.

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objectives (refer to Section 2.1) of this trial will be assessed by calculating descriptive statistics for safety as well as for PK, [redacted], which will be compared between the treatment groups.

As further analyses, PK endpoints will be explored regarding dose proportionality by the power model. Linear modelling will be used for exploring the attainment of steady state and for estimation of the linearity index.

7.2 NULL AND ALTERNATIVE HYPOTHESES

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

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

7.3 PLANNED ANALYSES

In general, the two trial parts (SRD and MRD) will be evaluated separately if not stated otherwise.

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all patients who were randomised and treated with at least one dose of study drug. The treatment assignment will be determined based on the first treatment the patients received. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all patients in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a patient will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.
- Biomarker set (BMS): This patient set includes all patients in the TS who provide at [redacted]

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be specified in the iQRMP, iPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and Section 2.2 for drug BI 894416 will be calculated according to the relevant SOP of the Sponsor (001-MCS-36-472).

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

Relevant protocol deviations may be

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

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

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

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

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

[redacted]

7.3.1 Primary endpoint analyses

The primary endpoint as specified in Section 2.1.2 will be derived according to BI standards. The analysis will be based on the treated set (TS) and will be descriptive in nature.

7.3.2 Secondary endpoint analyses

Primary analyses

The secondary efficacy endpoints (refer to Section 2.1.3) will be analysed descriptively based on the TS.

The secondary PK endpoints (refer to Section 2.1.3) will be analysed descriptively based on the PKS. Analyses will be performed for the parent drug.

Further exploratory analyses

Dose proportionality will be explored via graphical checks and if applicable via the power model stated below. The analysis will be performed for the pharmacokinetic endpoints $AUC_{0-\infty}$, C_{max} (SRD part) and $AUC_{\tau,ss}$, $C_{max,ss}$ (MRD part) of BI 894416 specified in Section 2.1.3.

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

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

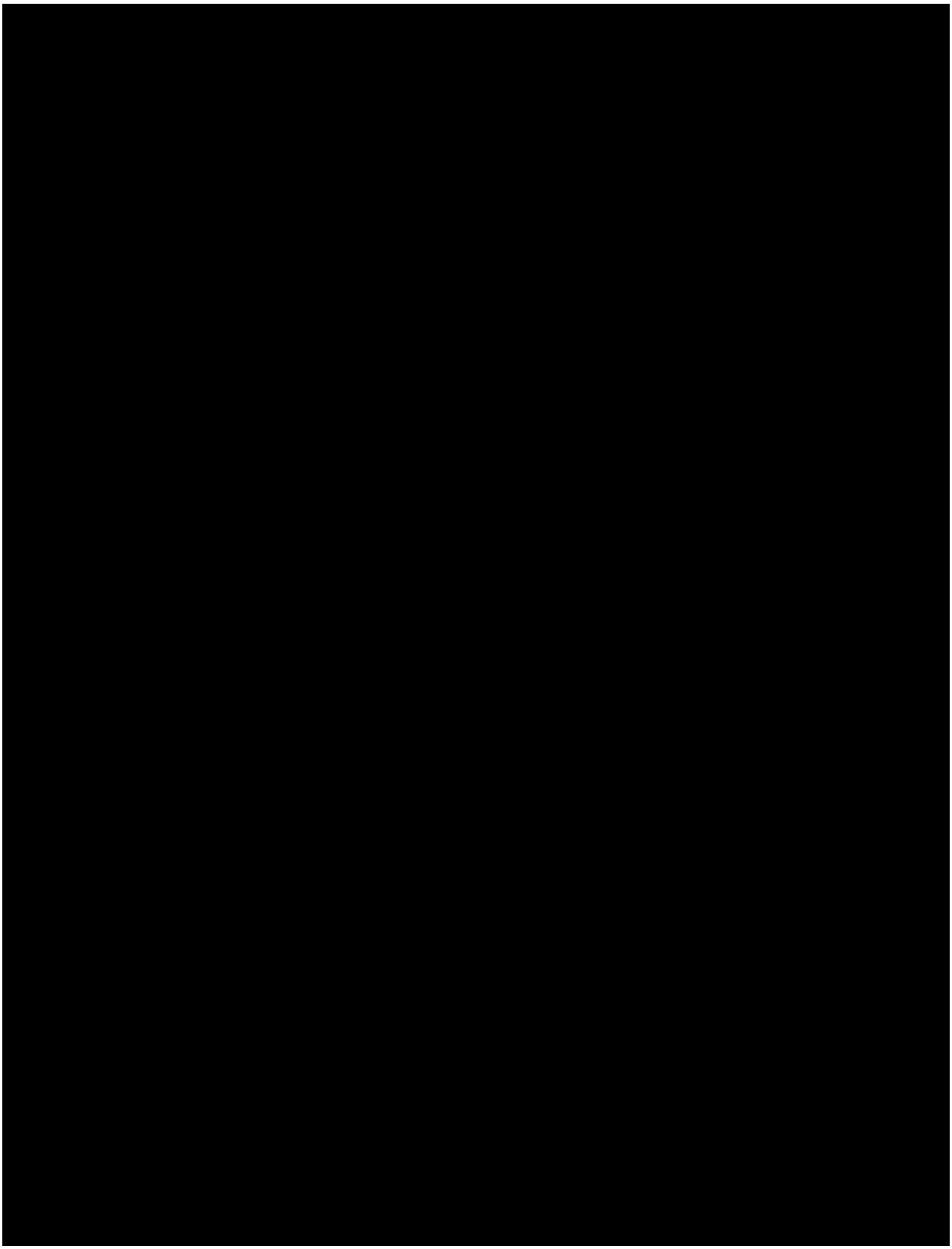
where

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

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

As some small doses at the beginning and/or some doses at the upper end might not contribute to the linear relationship between dose and PK, dose proportionality over the entire

dose range investigated might not be shown. In that case an attempt will be made to identify a subrange of at least 3 consecutive doses where dose proportionality can be concluded.



7.3.4 Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.2 and 2.2.2 based on the treated set (TS). Safety analyses will be descriptive in nature and will be based on BI standards. All adverse events with an onset between start of treatment will be assigned to the on-treatment period for evaluation. For residual effect period (REP) information is listed in Section 1.2.2.

For all analyses the treatment actually administered (= treatment at onset) to the patient will be used (any deviations from the randomised treatment will be discussed in the minutes of the Report Planning Meeting).

Treatments will be compared in a descriptive way. The placebo group in the safety evaluation will consist of all patients treated with placebo, regardless of the dose group in which they were treated. The test treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECGs, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment-emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to the screening period, those between the first trial medication intake and the trial termination date will be assigned to the treatment period. These assignments including

the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

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 possibly clinically significant values will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

The ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR obtained from the centralised evaluation of 12-lead ECG recordings will be the basis for the derivation of quantitative and categorical ECG endpoints. These endpoints and their analyses will be described in the TSAP.

[redacted]

7.4 INTERIM ANALYSES

No official interim analysis of PK parameters will be done. A preliminary analysis of PK parameters (AUC_{0-24} and $C_{max,}$ single dose; $AUC_{t,ss}$, $AUC_{0-24,ss}$ and $C_{max,\ ss,}$ multiple dose of BI 894419), provided as individual values and geometric means per dose level, will be performed for each dose level before proceeding to the next level for SRD and MRD part. $AUC_{0-24,ss}$ will be calculated from $AUC_{t,ss}$ after last dose.

Data from at least 6 actively dosed patients at the current dose level are required in order to proceed to the next dose level.

In contrast to the final PK calculations, the preliminary analysis will be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows. Therefore, minor deviations may occur between preliminary and final results. The preliminary analysis will provide individual and mean concentration -time profiles and summary statistics of individual values without patient identification information. The preliminary results will be distributed to the investigator and the trial team.

The pharmacokinetic parameters will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' [redacted] The non-compartmental analysis will be performed using a validated software program such as [redacted] A quality check of the preliminary data will be performed.

Modelling of all available data from the current trial and the previously performed SRD study in healthy volunteers (1371-0001) will be used as basis for prediction of exposure of next higher dose group. Further details are described in a separate analysis plan.

Depending on the results of available preliminary PK analyses and the tolerability and safety of the compound, changes to the dosing schedule (e.g., additional intermediate doses),) and additional PK/[redacted]preliminary analysis may be performed if requested by the Clinical Trial Leader, the investigator, or Trial Clinical Pharmacokineticist. Preliminary PK results will not be reported in the CTR.

No inferential statistical interim analysis is planned. However, after completion of each dose group the investigator (or his or her deputy) is allowed to postpone further dose progression until a preliminary analysis of the data has been performed.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 Pharmacokinetics

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

PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed.

7.6 RANDOMISATION

The first 5 patients per dose level will not be randomised to maintain a treatment sequence of active-placebo-active-active-active due to safety reasons. The remaining 5 patients of each dose level will be randomised in a 4:1 ratio (test treatment to placebo).

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system that uses a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

The randomisation list will contain additional blocks to allow for patient replacement (refer to Section 3.3.5).

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 40 patients in each trial part (maximum 80 for the overall study). The planned sample size is not based on a power calculation. The size of 10 patients per dose group (8 on active treatment, and 2 on placebo) is commonly used in single- and multiple-rising dose studies of the present type and is in general considered as sufficient for the exploratory evaluation of single and multiple dose safety and pharmacokinetics.

Additional patients may be entered to extend the number of patients within a dose group or to allow testing of additional doses on the basis of experience gained during the trial conduct (e.g. preliminary PK data), provided the planned and approved highest dose in the respective trial part will not be exceeded. Thus, the actual number of patients entered may exceed 80 (may exceed 40 per trial part) but is not to exceed 100 (is not to exceed 50 per trial part).

Based on amended CTP version 3.0, following SRD 2, an interim dose group (SRD 5) with additional 10 subjects was added, i.e. planned sample size is 50 in the SRD part (please refer to Section 4.1.2 and Figure 3.1:1).

Based on amended CTP version 5.0, following MRD 3, an interim dose group (MRD 5) with additional 10 subjects was added, i.e. planned sample size is 50 in the MRD part (please refer to Section 4.1.2 and Figure 3.1:1).

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles.

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

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

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to archiving of the CTR.

Insurance Coverage: The terms and conditions of the insurance coverage are made available to the investigator and the patients, and are 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 responsible Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to a patient's participation in the trial, written informed consent must be obtained from each 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 patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or his delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

8.2 DATA QUALITY ASSURANCE

A Clinical Research Associate appointed by Boehringer Ingelheim will visit the site at a regular basis and will support site staff in questions in first instance and will review medical records documented at trial site(s). Further, the medical records may be examined by other authorized monitors as Clinical Trial Managers, Site Monitoring Lead or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

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.

Training will be provided to investigators, coordinators and CRAs to ensure consistency and accuracy of the data. The data will be source verified by the CRAs.

8.3 RECORDS

eCRFs for individual patients will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records for each trial patient that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. Changes to the data should be traceable (audit trail).

Data reported on the eCRF 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.

Before providing any copy of patients' source documents to the sponsor, the investigator must ensure that all patient identifiers (e.g., patient's name, initials, address, phone number, and social security number) have properly been removed or redacted to ensure patient confidentiality.

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 eCRF, data must be derived from source documents, for example:

- Patient identification: sex, 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
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- ECG results (original or copies of printouts)
- Completion of patient's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- 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.
- Reversibility Test results
- Body plethysmography results
- and others (refer to Flow Chart)

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the eCRF 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 Clinical Research Associate, auditor and regulatory inspector (e.g. FDA). They may review all eCRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted in Section 8.7.

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.

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

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

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

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

8.6 TRIAL MILESTONES

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

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

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

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

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

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

A final report of the clinical trial data will be written only after all patients have completed the trial, so that all data can be incorporated and considered in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at the [redacted], under the supervision of the Principal Investigator. Relevant documentation on the participating (Principal) Investigator(s) (e.g. their curricula vitae) will be filed in the ISF.

BI has appointed a Clinical Trial Manager, responsible for coordinating all required trial activities, in order to

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates, and investigators of participating trial sites

The trial medication will be provided by the [redacted]

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

Analyses of BI 894416, [redacted] will be performed at [redacted].

[redacted]

The digitally recorded 12-lead ECGs will be sent to a specialised contract research organisation ([redacted]) for evaluation.

On-site monitoring will be performed by BI or a contract research organisation appointed by BI.

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.

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10. APPENDICES

10.1 RECRUITMENT, COHORT AND TIME-INTERVAL SCHEME

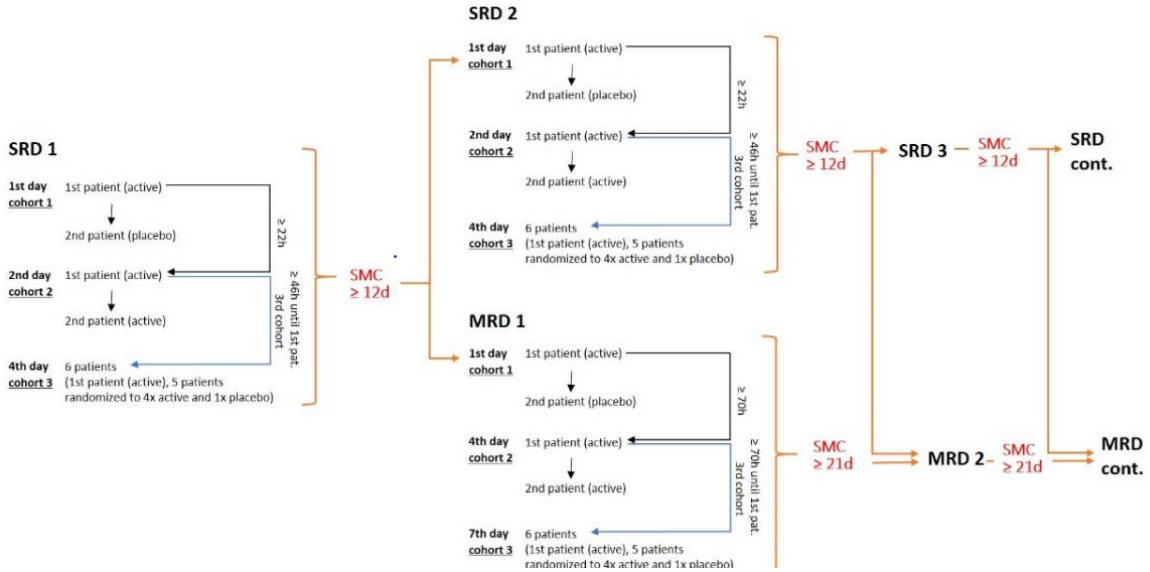

Figure 10.1: 1 Recruitment, Cohort and time-interval Scheme

The figure shows the recruitment plan, cohort schemes and time-intervals between cohorts and next dose group (interim doses are not shown but follow the same principle, please refer to Figure 3.1:1)

10.2 TIME SCHEDULES FOR PHARMACOKINETIK (PK) [redacted]

Table 10.2: 1 Time schedule for PK blood and urine samplings, [redacted] – MRD part

				Blood samples				Urine samples	
Visit	**Day**	**Time Point [hh:mm]/ event**	**eCRF Time/ PTM**	**BI 894416**	[redacted]	[redacted]	[redacted]	**BI 894416**	[redacted]
3	1	Predose	-1:00					X	[redacted]
		Predose	-0:05	X	[redacted]		[redacted]		
		BI 894416 intake	0:00					▲	
		0:15	0:15	X				|	
		0:30	0:30	X				|	
		0:45	0:45	X				|	
		240 ml fluid intake	1:00	X				|	
		1:30	1:30	X				|	
		2:00	2:00	X	[redacted]			|	
		2:30	2:30	X				|	
		240 ml fluid intake	3:00	X				|	
		4:00	4:00	X	[redacted]			▼▲	
		6:00	6:00	X				|	
		8:00	8:00	X	[redacted]			▼▲	
		10:00	10:00	X				|	
		12:00	12:00	X				▼▲	
	2	Predose	23:55	X	[redacted]			|	
		BI 894416 intake	24:00					▼	
	5	Predose	95:55	X	[redacted]				
		BI 894416 intake	96:00						
	7	Predose	143:55	X	[redacted]				
		BI 894416 intake	144:00						
	8	Predose	167:55	X	[redacted]				
		BI 894416 intake	168:00						
		Predose	175:55	X	[redacted]				
		BI 894416 intake	176:00						
		Predose	183:55	X					
		BI 894416 intake	184:00						

Table 10.2: 1 (cont.) Time schedule for PK blood and urine samplings, [redacted] – MRD part

				Blood samples				Urine samples	
Visit	**Day**	**Time Point [hh:mm]/ event**	**eCRF Time/ PTM**	**BI 894416**	[redacted]	[redacted]	[redacted]	**BI 894416**	[redacted]
	9	190:30	190:30					X	
		Predose	191:55	X					
		BI 894416 intake	192:00					▲	
		192:15	192:15	X					
		192:30	192:30	X					
		192:45	192:45	X					
		240 ml fluid intake	193:00	X					
		193:30	193:30	X					
		194:00	194:00	X					
		194:30	194:30	X					
		240 ml fluid intake	195:00	X					
		196:00	196:00	X				▼▲	
		198:00	198:00	X					
		200:00	200:00	X				▼▲	
		202:00	202:00	X					
		204:00	204:00	X				▼▲	
	10	Discharge from site	216:00	X				▼	
4	11	Ambula-tory Visit	240:00	X					
5	12	Ambula-tory Visit	264:00	X					
6	13	Ambula-tory Visit	288:00	X					

10.3 REVERSIBILITY TESTING [P05-12782]

At the screening visit (Visit 1), following the completion of three acceptable prebronchodilator forced expiratory manoeuvres, salbutamol (albuterol) will be administered to each patient in order to document the degree of reversibility. Immediately after (within 10 min) pre-bronchodilator forced expiratory manoeuvres and after a gentle and incomplete expiration, a dose of 100 µg of salbutamol (albuterol) is inhaled in one breath to total lung capacity (TLC). The breath is then held for 5–10 s before the patient exhales. Four separate doses (total dose 400 µg) are delivered at approximately 30-s intervals (this dose ensures that the response is high on the salbutamol [albuterol] dose–response curve). Three additional, acceptable post-bronchodilator forced expiratory manoeuvre tests are recorded ≥10 min and up to 15 min after the last dose of salbutamol (albuterol) is inhaled.

Calculations will be based on Global Lung Function Initiative (GLI) formula [R15-0845].

10.4 BODY PLETHYSMOGRAPHY MEASUREMENT TECHNIQUE AND SPIROMETRY

The body plethysmography procedures will be performed in "linked" manoeuvers, i.e. without the patient coming off the mouthpiece prior to the completion of the manoeuvers. The body plethysmography procedures will comprise (Figure 10.4: 1):

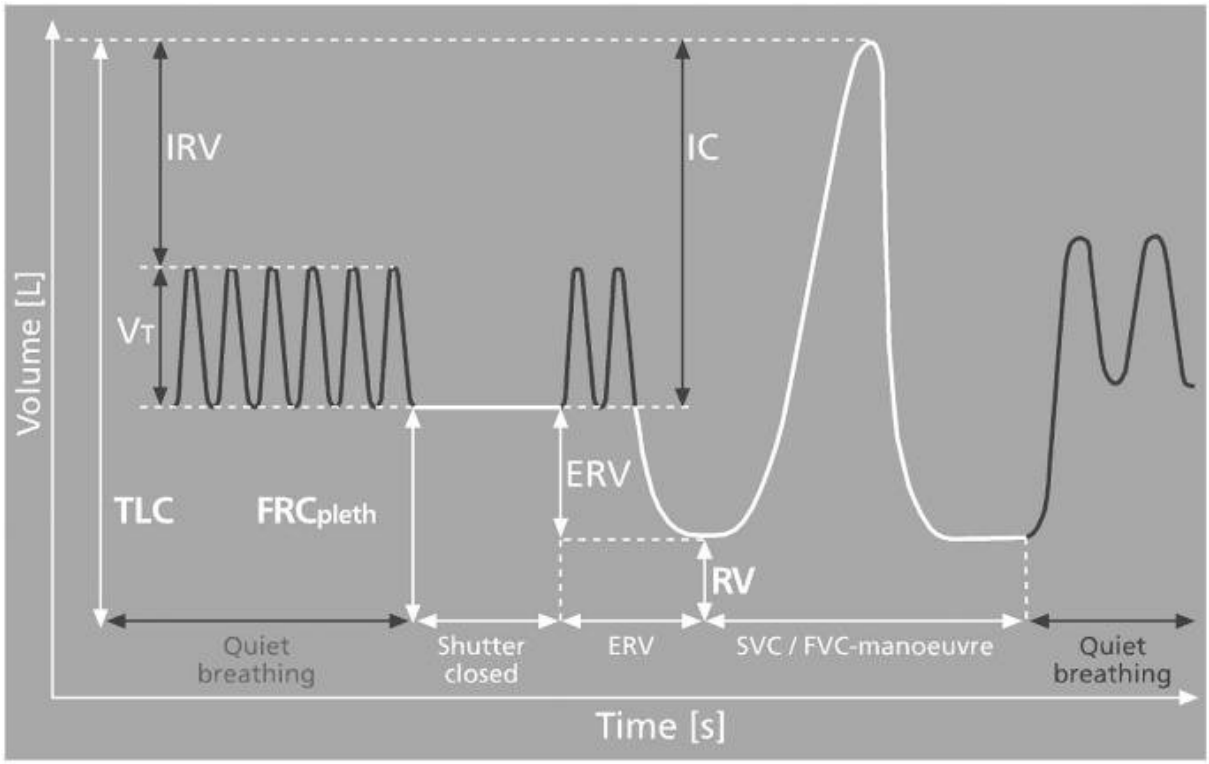

Figure 10.4: 1 Example of body plethysmography maneuver [R08-1121]

- quiet tidal volume breathing, End-expiratory Lung Volume (EELV), followed by
- shutter closing at EELV and panting with hands over cheeks, followed by
- opening of the shutter and return to quiet tidal breathing (ensuring stable EELVs, which are at the same position as those prior to shutter closing), followed by
- an Expiratory Reserve Volume (ERV) manoeuver, followed by a SVC/FVC manoeuvre (slow inspiration followed by a forced expiration)

Note:
The term "body plethysmography" is being used for specified measurements in the body box (MRD) or as well for "normal" spirometric measurements.

Spirometry (FEV1, FVC, [redacted] will be performed using the body box system or via a stand-alone spirometer.

The following parameter will be determined/ calculated (in MRD part only) at screening, at Day -1, after 9 days of treatment and at Visit 8:

- FEV1/FVC
- FEV1: the highest FEV1 from an acceptable maneuver
- FEF 25-75
- Raw: secondary (efficacy) endpoint

10.5 STANDARD CONVERSION TABLE FOR DIFFERENT ALCOHOL TYPES

For conversion of different alcohol types the electronical calculation by the validated system ClinBase™ is used.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Number of global amendment		1
Date of CTP revision		18 June 2019
EudraCT number		2019-000805-60
BI Trial number		1371-0008
BI Investigational Product(s)		BI 894416
Title of protocol		Safety, tolerability, pharmacokinetics [redacted] of single rising oral doses and multiple rising oral doses of BI 894416 versus placebo in male patients with asthma [redacted] (single-blind, randomised, placebo-controlled, parallel group design).
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		- Title page - Synopsis - Flowchart SRD - Flowchart SRD/Timeschedule - Flowchart MRD - Flowchart MRD/Timeschedule - Flowcharts MRD+Midazolam - Section 1 - Section 2.1.1 - Section 2.2.2 - Section 3.1 - Section 3.3

Number of global amendment		1
		- Section 3.3.3 - Section 3.3.4.1 - Section 3.3.4.4 - Section 3.3.5 - Section 4.1.1 - Section 4.1.4 - Section 4.1.6 - Section 4.2.2 - Section 5.1.2 - Section 5.2.1 - Section 5.2.5.2 - Section 5.3.1 - Section 5.3.2.1 - Section 5.3.3.1 - Section 6.1 - Section 6.2.1 - Section 7.3.3.1 - Section 8.7 - Section 9 - Section 10.2 - Section 10.6
Description of change		- Title page: Title adapted - Synopsis: Title adapted, description of treatment adapted - Flowchart SRD and SRD/Timeschedule: Insertion of echocardiography assessment, extension of screening period to 4 weeks, addition of assessment at Follow-Up visit. - Flowchart MRD: addition of several screening assessments at FU visits and insertion of echocardiography assessment, extension of screening period to 4 weeks - Flowchart MRD/Timeschedule: urine PK sampling at timepoint 191h removed, insertion of several screening assessments at FU visits and echocardiography assessment, extension of screening period to 4 weeks. - Flowchart MRD+[redacted]: deleted - Section 1, 2.2.2, 3.1; 4.1.1, 4.1.4, 4.1.6, 4.2.2, 5.1.2, 5.3.2.1, 5.3.3.1, 6.1, 6.2.1, 7.3.3.1, 8.7, 9, 10.2, and 10.6: [redacted] - Section 1.4: insertion of benefit statement

Number of global amendment		1
		- Section 1.4.1: Insertion of benefit-risk statement for patients with higher age and BMI - Section 1.4.2: insertion of risks related to echocardiography - Section 1.4.3.1: Insertion of risk statement - Section: 1.4.3.3: Insertion of echocardiography assessment - Section 2.1.1: clarification of main objectives - Section 3.3: clarification on selected study population - Section 3.3.3: EXCL 1, 5 and 12 adapted, addition of EXCL 6 - Section 3.3.4.1: added treatment stopping rule - Section 3.3.4.4: reworded trial discontinuation stopping rule - Section 3.3.5: included maximum no of patients to be replaced - Section 5.2.1: Insertion of echocardiography assessment - Section 5.2.5.2: changed rule for storage of continuous ECG data - Section 5.3.1: deletion of ClinBase™ - Section 6.2.1: addition of echocardiography
Rationale for change		- Flowchart MRD/time schedule: correction as this assessment is not planned at this time point. - Section 5.3.1: correction - All other changes were made based on clarification letters from German Competent Authority (BfArM) and EC and after internal discussion to meet the requirements of the regulators.

11.2 GLOBAL AMENDMENT 2

Number of global amendment		2
Date of CTP revision		22 November 2019
EudraCT number		2019-000805-60
BI Trial number		1371-0008
BI Investigational Product(s)		BI 894416
Title of protocol		Safety, tolerability, pharmacokinetics [redacted] of single rising oral doses and multiple rising oral doses of BI 894416 versus placebo in male patients with asthma [redacted] (single-blind, randomised, placebo-controlled, parallel group design).
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		- Title page - Synopsis - Flowchart MRD/Timeschedule - Table 3.1: 1 - Figure 3.1: 1 - Section 3.3.1 - Section 4.1.2 - Table 4.1.2: 1 - Table 4.1.4: 1 - Section 7.7 - Figure 10.1: 1
Description of change		- Title page: document number, version number and date adapted - Synopsis: revision date adapted, insertion of interim dose 170mg

Number of global amendment		2
		- Flowchart MRD/Timeschedule: correction (Vital signs at visit 2). - Table 3.1: 1: information on 170 mg dose added - Figure 3.1: 1: information on 170 mg dose added - Section 3.3.1: correction - Section 4.1.2: information on 170 mg dose added - Table 4.1.2: 1: information on 170 mg dose added, predicted PK parameters adapted - Table 4.1.4: 1: information on 170 mg dose added - Section 7.7: information on 170 mg dose added - Figure 10.1: 1: information on 170 mg dose added
Rationale for change		With the exception of the corrections, all changes were made based on the decision to reduce the dose of the next planned SRD 3 dose level according to the rules for dose reduction outlined in sections 3.1 and 4.1.2

11.3 GLOBAL AMENDMENT 3

Number of global amendment		3
Date of CTP revision		23 January 2020
EudraCT number		2019-000805-60
BI Trial number		1371-0008
BI Investigational Product(s)		BI 894416
Title of protocol		Safety, tolerability, pharmacokinetics [redacted] of single rising oral doses and multiple rising oral doses of BI 894416 versus placebo in male patients with asthma [redacted] single-blind, randomised, placebo-controlled, parallel group design).
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		- Title page - Flowchart SRD/Overview - Section 3.3.4.5 - Section 4.1.2, Interim Dose Levels - Table 5.2.4: 1 - Section 5.2.4 - Section 5.2.6.2.2 - Section 5.3.2.3, [redacted]1 - Section 6.2.1, Further Procedures at Visit 1 - Section 7.7
Description of change		- Title page: document number, version number and date adapted - Flowchart SRD/Overview: subclause in

Number of global amendment		3
		footnote 3 deleted - Section: 3.3.4.5: new discontinuation rule added - Section 4.1.2, Interim Dose Levels: wording added regarding escalation mode - Table 5.2.4: 1: new test added - Section 5.2.4: text deleted - Section 5.2.6.2.2: text in first paragraph adapted - Section 5.3.2.3, [redacted] - Section 6.2.1, Further Procedures at Visit 1: 3rd bullet point, text added - Section 7.7: text added in the 3rd paragraph
Rationale for change		- Title page: adaptations regarding protocol amendment - Flowchart SRD/Overview/ Section 6.2.1, Further Procedures at Visit 1: changes to allow for one re-screening attempt - Section: 3.3.4.5: text added to allow to stop a study part in case escalation to the next dose group is possible but meaningful knowledge gain is not expected. - Section 4.1.2, Interim Dose Levels: wording added to describe the linkage between interim SRD5 and MRD3 - Table 5.2.4: 1: assay added to allow for platelet function testing - Section 5.2.4: correction, obsolete text - Section 5.2.6.2.2: adapted text according to new BI standard to reflect, that fax transmissions are no longer supported in some countries. - Section 5.3.2.3, [redacted] clarification - Section 7.7: clarification

11.4 GLOBAL AMENDMENT 4

Number of global amendment		4
Date of CTP revision		15 May 2020
EudraCT number		2019-000805-60
BI Trial number		1371-0008
BI Investigational Product(s)		BI 894416
Title of protocol		Safety, tolerability, pharmacokinetics [redacted] s of single rising oral doses and multiple rising oral doses of BI 894416 versus placebo in male patients with asthma [redacted] (single-blind, randomised, placebo-controlled, parallel group design).
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		- Title page - Protocol Synopsis - Flow Chart SRD - Overview - Flow Chart MRD – Overview - Flow Chart MRD – Time Schedule - Section 1.4.4 and 1.4.5 - Section 3.1 – Part 2 (MRD Portion) - Figure 3.1: 1 - Table 3.1: 2 - Section 3.3.4.1 - Section 4.1.2 - Table 4.1.2: 1 - Table 4.1.2: 2 - Table 4.1.2: 3 - Table 4.1.2: 4

Number of global amendment		4
		- Table 4.1.4: 2 - Table 5.2.4: 1 - Section 5.2.4 - Section 5.3.2.2 - Section 6.1 - Section 7.7 - Section 8.7 - Appendix 10.2 – Table 10.2 : 1
Description of change		- Title page: document number, version number and date adapted - Protocol Synopsis: addition of interim dose group, administrative changes - Flow Chart SRD and MRD/Overviews: addition of cotinine test and SARS-CoV-2 test - [redacted] - Section 1.4.4 and 1.4.5: risk section added - Section 3.1 – Part 2 (MRD Portion): changed wording - Figure 3.1: 1: updated study design - Table 3.1: 2: new values added - Section 3.3.4.1: new discontinuation rule added - Section 4.1.2: Interim Dose Levels: wording added regarding escalation mode - Table 4.1.2: 1 and 4.1.2: 3: new values added - Table 4.1.2: 2 and Table 4.1.2: 4: new tables added - Table 4.1.4: 2: updated table - Table 5.2.4: 1: updated table - Section 5.2.4: text regarding additional tests/test lab added - Section 5.3.2.2: new dose group added - Section 6.1: new wording describing the order of assessments - Section 7.7 added text regarding MRD5 - Section 8.7: added text regarding use of laboratory - Appendix 10.2 – Table 10.2 : 1: new information regarding test mode
Rationale for change		- Title page: adaptations regarding protocol amendment - Protocol Synopsis: interim dose group

Number of global amendment		4
		based on descriptions in Section 3.1 – Part 2 (MRD Portion) - Flow Charts SRD/MRD Overview: new safety measures re SARS-Cov-2 pandemic and supportive lab value for exclusion of current smokers. - [redacted] - Section 1.4.4 and 1.4.5: description of risks and safety measures related to SARS-CoV-2 and COVID-19 - Section 3.1 – Part 2 (MRD Portion): clarification regarding exposures from SRD covering exposures from MRD dose groups - Figure 3.1: 1: addition of MRD5 - Table 3.1: 2: information for new MRD 5 (60 mg tid) interim dose added - Section 3.3.4.1: rule regarding discontinuation of SARS-CoV-2 positive patients - Section 4.1.2, Interim Dose Levels: wording added to describe the linkage between interim SRD and MRD - Table 4.1.2: 1 and 4.1.2: 3 values were updated based on the latest predictions including all completed dose groups - Table 4.1.2: 2 and Table 4.1.2: 4: new values for obtained PK parameters added from all completed dose groups - Table 4.1.4: 2: information for new dose group added - Table 5.2.4: 1: new test for SARS-CoV-2 added - Section 5.2.4: addition of the lab responsible for SARS-CoV-2 testing and change of the lab for PFA. Description of additional tests for cotinine and SARS-CoV2. - [redacted] - Section 6.1: wording to allow urine sampling prior to ECG

Number of global amendment		4
		- Section 7.7: description of changed samples size due to MRD5 - Section 8.7: information on 2nd site of local laboratory added - [redacted]

11.5 GLOBAL AMENDMENT 5

Number of global amendment		5
Date of CTP revision		14 October 2020
EudraCT number		2019-000805-60
BI Trial number		1371-0008
BI Investigational Product(s)		BI 894416
Title of protocol		Safety, tolerability, pharmacokinetics [redacted] of single rising oral doses and multiple rising oral doses of BI 894416 versus placebo in male patients with asthma [redacted] single-blind, randomised, placebo-controlled, parallel group design).
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☒
Section to be changed		- 5.3.2.1 Blood sampling for pharmacokinetic analysis
Description of change		- [redacted]
Rationale for change		- Expand the use of PK plasma samples

APPROVAL / SIGNATURE PAGE

Document Number: c21616656 **Technical Version Number:6.0**

Document Name: clinical-trial-protocol-version-06

Title: Safety, tolerability, pharmacokinetics [redacted] of single rising oral doses and multiple rising oral doses of BI 894416 versus placebo in male patients with asthma (single-blind, randomised, placebo-controlled, parallel group design).

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area Head	[redacted]	15 Oct 2020 14:46 CEST
Approval-Clinical Trial Leader		15 Oct 2020 15:39 CEST
Author-Trial Statistician		16 Oct 2020 08:15 CEST
Approval-Team Member Medicine		19 Oct 2020 03:57 CEST
Author-Clinical Pharmacokineticist		19 Oct 2020 10:38 CEST
Verification-Paper Signature Completion		26 Oct 2020 14:13 CET

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Meaning of Signature	Signed by	Date Signed