Clinical Trial Protocol

	Document Number:	**c31942019-03**
BI Trial No.	1405-0003	
BI Investigational Medicinal Product	BI 1323495	
Title	Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1323495 versus placebo in healthy male Japanese subjects genotyped as poor and extensive metabolizers of UGT2B17 (single-blind, randomised, placebo-controlled [within dose groups] trial), including an investigation of drug-drug interaction with itraconazole in healthy male subjects genotyped as poor metabolizers of UGT2B17 (an open-label, two-period, fixed sequence trial)	
Lay Title	A study in healthy Japanese men to test how different doses of BI 1323495 are tolerated and how itraconazole influences the amount of BI 1323495 in the blood	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Telephone: [redacted], Fax: [redacted]	
Principal Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol (Revised Protocol (based on global amendment 2))	
Version and Date	Version: 3.0	Date: 25 FEB 2021

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	12 Aug 2020
Revision date	25 Feb 2021
BI trial number	1405-0003
Title of trial	Safety, tolerability and pharmacokinetics, of single rising oral doses and multiple oral doses of BI 1323495 versus placebo in healthy male Japanese subjects genotyped as poor and extensive metabolizers of UGT2B17 (single-blind, randomised, placebo-controlled [within dose groups] trial), including an investigation of drug-drug interaction with itraconazole in healthy male subjects genotyped as poor metabolizers of UGT2B17 (an open-label, two-period, fixed sequence trial)
Principal Investigator	[redacted]
Trial site	
Clinical phase	I
Trial rationale	SRD and MD part: The objective of this trial is to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamics (for MD part only) of BI 1323495 in healthy male Japanese subjects genotyped as poor (PM) and extensive metabolizers (EM) of UGT2B17. The chosen population of healthy male subjects receiving single rising oral doses and multiple oral doses are considered adequate to provide the basis for the clinical development program of BI 1323495 in Japan. DDI part: Based on *in vitro* data, CYP3A4 and P-gp are involved in metabolism and transport of BI 1323495, respectively. It is therefore necessary to explore in UGT2B17 PM the relative bioavailability of BI 1323495 in plasma when given alone versus when given together with a strong CYP3A4 and P-gp inhibitor.
Trial objectives	SRD and MD part: To investigate safety, tolerability, pharmacokinetics, and pharmacodynamics (for MD part only) following single rising doses and multiple oral doses of BI 1323495 in PM and EM of UGT2B17. DDI part: To investigate the relative bioavailability of a single oral dose of BI 1323495 when given alone (treatment R) or in combination with itraconazole (treatment T) in PM of UGT2B17.

Trial endpoints	SRD part: Primary endpoint to assess safety and tolerability of BI 1323495 is the percentage (%) of subjects with drug-related adverse events Secondary endpoints: C_{max}, and $AUC_{0-\infty}$ of BI 1323495 MD part: Primary endpoint to assess safety and tolerability of BI 1323495 is the percentage (%) of subjects with drug-related adverse events Secondary endpoints: After the first dose: AUC_{0-12} and C_{max} of BI 1323495 After the last dose: $AUC_{\tau,ss}$ and $C_{max,ss}$ of BI 1323495 DDI part: Primary endpoints: C_{max} and $AUC_{0-\infty}$ of BI 1323495 Secondary endpoints: AUC_{0-tz} of BI 1323495
Trial design	SRD and MD part: Single-blind, randomised within dose groups, placebo-controlled parallel-group design DDI part: Open-label, two-treatment, two-period, fixed sequence design
Number of subjects **total entered** **each treatment**	74 (SRD 36, MD 24 and DDI 14)* SRD part for PM : 8 per dose group (6 on BI 1323495 and 2 on placebo) SRD part for EM: 4 per dose group (3 on BI 1323495 and 1 on placebo) MD part for PM: 12 per dose group (9 on BI 1323495 and 3 on placebo) DDI part for PM: 14 * Additional subjects may be entered to allow additional testing 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 and none of the stopping criteria apply. Thus, the actual number of subjects entered may exceed 74, but will not exceed 90 subjects.
Diagnosis	Not applicable
Main criteria for inclusion	Healthy male subjects, age of 20 to 45 years (inclusive), body mass index (BMI) of 18.5 to 25 kg/m^2 (inclusive)
Test product 1	BI 1323495, film-coated tablets (dose strength 10 mg, 50 mg)

dose	SRD part for PM : 10 mg, 30 mg and 100 mg qd SRD part for EM: 30 mg, 70 mg and 150 mg qd MD part for PM 30 mg bid and 60 mg qd DDI part for PM: 10 mg
mode of admin.	SRD and MD part: Oral with 240 mL of water after a standardized meal DDI part: Oral with 240 mL of water after an overnight fast of at least 10 h
Test product 2 **(Only for DDI part)**	Itraconazole oral solution (ITRIZOLE® Oral Solution 1% [redacted])
dose	200 mg q.d.
mode of admin.	Oral with 240 mL of water after an overnight fast of at least 9 h
Comparator products: **(Only for SRD part)**	Matching placebo tablets
dose:	Not applicable
mode of admin.:	Oral with 240 mL of water after a standardized breakfast
Duration of treatment	SRD part; Single dose 1 day MD part: 30 mg bid; 11 days, 10 days twice daily (bid) dosing and single dose on day 11 60 mg qd; Once daily, multiple doses over 11 days DDI part; Treatment R (BI 1323495 alone): Single dose of 10 mg BI 1323495 (Day 1) Treatment T (itraconazole + BI 1323495): 10 days of itraconazole treatment (200 mg itraconazole once daily from Day -3 to Day 7) combined with a single dose of 10 mg BI 1323495 on the fourth day of the itraconazole treatment (Day 1, 1 h after the itraconazole administration) Wash-out period: Administrations of BI 1323495 will be separated by a wash-out phase of at least 11 days

Statistical methods	SRD and MD part: Descriptive statistics will be calculated for all endpoints. DDI part: Relative bioavailability will be estimated by the ratios of the geometric means (Treatment T/Treatment R) for the primary and secondary endpoints. Additionally, their two-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at a 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range are not specified. The statistical model will be an analysis of variance (ANOVA) on the logarithmic scale including effects for 'subject' and 'treatment'. CIs will be calculated based on the residual error from the ANOVA. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

SRD part

	Visit	Day	Planned time (relative to BI 1323495 or placebo administration [h:min])	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[6,9]	PK blood[8]	PK urine[10]	Medical Examination	Vital signs (BP, PR)[9]	12-lead ECG[9]	Questioning for AEs and concomitant therapy[12]
SCR	1	-28 to -8			Screening (SCR)[1] including pharmacogenomics test UGT2B17	x[A,7]			x	x	x	
Treatment period	2	-1	-18:00	15:00	Ambulatory visit[2]	x[B,7]						x
			-12:00	21:00	Admission to trial site							
		1[14]	-2:00	07:00	Allocation to treatment		x	x	x	x	x[11]	x
			-0:30	08:30	Standardized breakfast							
			0:00	**09:00**	**BI 1323495 or placebo administration[3]**			▲				
			0:20	09:20			x	|		x	x	x
			0:40	09:40			x	|		x	x	x
			1:00	10:00			x	|		x	x	x
			1:30	10:30			x	|		x	x	x
			2:00	11:00	240 mL fluid intake		x	|		x	x	x
			3:00	12:00			x	|		x	x	x
			4:00	13:00	240 mL fluid intake, thereafter lunch[4]	x[B]	x	┼		x	x	x
			5:00	14:00			x	|			x	
			6:00	15:00			x	|		x	x	x
			7:00	16:00			x	|			x	
			8:00	17:00	Snack(voluntary)[4]		x	┼		x	x	x
			9:00	18:00			x	|			x	
			10:00	19:00	Dinner[4]		x	|		x	x	x
			12:00	21:00			x	┼		x	x	x
		2	24:00	09:00	Breakfast[4]	x[B]	x	┼		x	x	x
			28:00	13:00	Lunch[4]			|				
			32:00	17:00	Snack(voluntary)			|				
			34:00	19:00	Dinner[4]		x	┼			x	x
		3	48:00	09:00	Discharge from trial site		x	▼			x	x
		4	72:00	09:00	Ambulatory visit		x				x	x
		5	96:00	09:00	Ambulatory visit		x				x	x
		6	120:00	09:00	Ambulatory visit		x[13]					x
		7	144:00	09:00	Ambulatory visit		x[13]					x
		8	168:00	09:00	Ambulatory visit	x[B]	x[13]		x	x	x	x
EOT	3	9 to 15			End of trial (EOT) examination[5]	x[A]			x	x	x	x

PK: pharmacokinetics, ECG: electrocardiogram, BP: blood pressure, PR: pulse rate, AE: adverse event
Clock time should be adjusted based on actual administration time

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include medical examination, check of vital signs, ECG (12-lead ECG), chest x-ray, safety laboratory (including drug screening), pharmacogenetic analysis for UGT2B17 genotype, demographics (including determination of body height and weight, smoking and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. Safety laboratory to be taken and to be medically evaluated on Day -1 prior to administration of BI 1323495. Axillary temperature measurement will be conducted during Day -1.
3. Oral with 240 mL of water after a standardized breakfast.
4. If several actions are indicated at the same time point, the intake of meals will be the last action.
5. EOT includes medical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
6. Letters A and B describe different sets of safety laboratory examinations (see Section 5.2.3).
7. Urine drug screening and alcohol breath test will be performed at screening and prior to dosing at Day -1 of Visit 2. A breath alcohol test may be repeated at any time during the trial at the discretion of an investigator or designee.
8. PK samples for determination of plasma level of BI 1323495 as detailed in Section 5.3.2. Sampling times and periods may be adapted based on information obtained during the trial (e.g. preliminary PK data) including addition of samples and visits as long as the total blood volume taken does not exceed approximately 400 mL per subject.
9. For allowed deviation from the scheduled time please refer to Section 6.1.
10. PK urine samples for determination of BI 1323495 amount eliminated in urine are to be taken at following time intervals: a blank urine sample is to be obtained within 3 h 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, 24-34, and 34-48 h (see Section 5.3.2.3).
11. Triplicate ECG. Three triplicate ECGs are recorded within approximately 1 h. The recordings of each triplicates should be separated by at least 15 min (refer to the Section 5.2.4) This measurement should be conducted within -12 h from administration.
12. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart.
13. PK plasma samples are to be taken in UGT2B17 PM group only.
14. PGx samples will be collected during Day 1.

DDI part

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[5,10]	PK blood, BI 1323495	PK blood, Itraconazole	Medical Examination	Vital signs (BP, PR)[10]	12-lead ECG[10]	Questioning for AEs and concomitant therapy[7]
SCR	1	-28 to -8			Screening (SCR)[1] including pharmacogenomics test UGT2B17	x[A,3]			x	x	x	
Period 1/ Treatment R (BI 1323495 alone)[8]	2	-1	-18:00	15:00	Ambulatory visit	x[B,3]						x
			-12:00	21:00	Admission to trial site							
		1	-2:00	07:00	Allocation to treatment[2]		x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
			0:00	09:00	BI 1323495 administration							
			0:20	09:20			x					
			0:40	09:40			x					
			1:00	10:00			x					
			1:30	10:30			x					
			2:00	11:00	240 mL fluid intake		x					
			3:00	12:00			x					
			4:00	13:00	240 mL fluid intake, thereafter lunch[4]		x			x	x	x
			5:00	14:00			x					
			6:00	15:00			x					
			7:00	16:00	Snack (voluntary)[4]		x					
			8:00	17:00			x					
			9:00	18:00			x					
			10:00	19:00	Dinner[4]		x					
			12:00	21:00			x					x
		2	24:00	09:00	Breakfast (voluntary)[4]	x[B]	x			x	x	x
			34:00	19:00	Discharge from trial site		x					x
		3	47:00	08:00	Ambulatory visit		x					x
		4	71:00	08:00	Ambulatory visit	x[B]	x					x
		5	95:00	08:00	Ambulatory visit		x					x
		6	119:00	08:00	Ambulatory visit		x					x
		7	143:00	08:00	Ambulatory visit		x					x
		8	167:00	08:00	Ambulatory visit		x		x			x

DDI part (cont'd)

Period	Visit	Day	Planned time (relative to drug administration) [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[5, 10]	PK blood, BI 1323495	PK blood, Itraconazole	Medical Examination	Vital signs (BP, PR)[10]	12-lead ECG[10]	Questioning for AEs and concomitant therapy[7]
Period 2/ Treatment T (BI 1323495 + itraconazole)[8]	3	-3	-72:00	09:00	Ambulatory visit, itraconazole administration	x[B,2,3]			x			x[2]
		-2	-48:00	09:00	Ambulatory visit, itraconazole administration							x[2]
		-1	-24:00	09:00	Ambulatory visit, itraconazole administration[11]	x[C,2,3]		x[9]				x[2]
			-12:00	21:00	Admission to trial site[2]							
		1[12]	-2:00	07:00			x[2]		x[2]	x[2]	x[2]	x[2]
			-1:00	08:00	Itraconazole administration			x[9]				
			0:00	09:00	BI 1323495 administration							
			0:20	09:20			x					
			0:40	09:40			x					
			1:00	10:00			x					
			1:30	10:30			x					
			2:00	11:00	240 mL fluid intake		x					
			3:00	12:00			x					
			4:00	13:00	240 mL fluid intake, thereafter lunch[4]		x			x	x	x
			5:00	14:00			x					
			6:00	15:00			x					
			7:00	16:00	Snack (voluntary)[4]		x					
			8:00	17:00			x					
			9:00	18:00			x					
			10:00	19:00	Dinner[4]		x					
			12:00	21:00			x					x
		2	23:00	08:00	Itraconazole administration	x[B,2]						x
			24:00	09:00	Breakfast (voluntary)[4]		x			x	x	x
			28:00	13:00	Lunch (voluntary)							
			31:00	16:00	Snack (voluntary)							
			34:00	19:00	Discharge from trial site		x					x
		3	47:00	08:00	Ambulatory visit, itraconazole administration		x[9]	x[9]				x
		4	71:00	08:00	Ambulatory visit, itraconazole administration	x[C,2]	x[9]					x
		5	95:00	08:00	Ambulatory visit, itraconazole administration		x[9]					x
		6	119:00	08:00	Ambulatory visit, itraconazole administration	x[C,2]	x[9]					x
		7	143:00	08:00	Ambulatory visit, itraconazole administration		x[9]	x[9]				x
		8	167:00	08:00	Ambulatory visit	x[B]	x	x				x
EOT	4	16 to 23			End of trial (EOT) examination[6]	x[A]			x	x	x	x

Clock time should be adjusted based on actual administration time

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include medical examination, check of vital signs, ECG(12-lead ECG), chest x-ray, safety laboratory (including drug screening), pharmacogenetic analysis for UGT2B17 genotype, demographics (including determination

of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; the procedure is to be performed and completed within the 3 h prior to drug administration.
3. Urine drug screening and alcohol breath test
4. If several actions are indicated at the same time, the intake of meals will be the last action.
5. Letters A, B and C define different sets of safety laboratory examinations (for details refer to Section 5.2.3)
6. At the end of trial visit the EOT examination includes medical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.
7. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the times indicated in the Flow Chart above.
8. Administration of BI 1323495 in treatment R and T will be separated by at least 11 days.
9. Blood collection takes place at the indicated times. Itraconazole will be administered immediately thereafter.
10. For allowed deviation from the scheduled time please refer to Section 6.1.
11. Axillary temperature measurement will be conducted during Day -1.
12. PGx samples will be collected during Day 1.

MD part (30 mg bid)

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[2]	PK blood,[4]	PK urine[5]	PD blood (NE activity)	12-lead ECG[7]	Medical examination	Vital signs[8]	Questioning for AEs and concomitant therapy[9]
1	**-28 to -8**			Screening (SCR)[1] including pharmacogenomics test UGT2B17	x[A]				x	x	x	
2	**-1**	-16:00	17:00	Admission to trial site	x [B, 6, 10, 11]							x
	1[20]	-01:00	08:00	Allocation to treatment[12]	x[C,12]	x[12]	x[12]	x[12]	x[12,13]	x[12]	x[12]	x[12]
		-00:30	08:30	breakfast								
		00:00	**09:00**	**First drug administration[15]**			▲					
		00:20	09:20			x	|					
		00:40	09:40			x	|					
		01:00	10:00			x	|		x		x	
		01:30	10:30			x	|					
		02:00	11:00	240 mL fluid intake	x[D]	x	|	x	x		x	x
		03:00	12:00			x	|					
		04:00	13:00	240 mL fluid intake, thereafter lunch[3]		x	+		x		x	x
		05:00	14:00			x	|					
		06:00	15:00			x	|		x		x	x
		07:00	16:00			x	|					
		08:00	17:00	Snack [3]		x	+		x		x	x
		09:00	18:00			x	|					
		10:00	19:00			x	|					
		11:30	20:30	Dinner			|					
		12:00	21:00	Drug administration	x[D]	x[14]	▼	x[14]	x		x	x
	2	23:30	08:30	Breakfast	x[B, 12]				x[12]		x[12]	x[12]
		24:00	09:00	Drug administration		x[14]						
		28:00	13:00	Lunch[3]								x
		32:00	17:00	Snack								
		35:30	20:30	Dinner								
		36:00	21:00	Drug administration		x[14]						x

MD part (30 mg bid) (cont'd)

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[2]	PK blood,[4]	PK urine[5]	PD blood (NE activity)	12-lead ECG[7]	Medical examination	Vital signs[8]	Questioning for AEs and concomitant therapy[9]
	3	47:30	08:30	Breakfast							x[12]	x[12]
		48:00	09:00	Drug administration		x[14]						
		52:00	13:00	Lunch[3]								x
		56:00	17:00	Snack								
		59:30	20:30	Dinner[3]								x
		60:00	21:00	Drug administration		x[14]						
	4	71:30	08:30	Breakfast							x[12]	x[12]
		72:00	09:00	Drug administration		x[14]						
		76:00	13:00	Lunch[3]								x
		80:00	17:00	Snack								
		83:30	20:30	Dinner[3]								x
		84:00	21:00	Drug administration								
	5	95:30	08:30	Breakfast	x[B, 12]				x[12]	x[12]	x[12]	x[12]
		96:00	09:00	Drug administration[16]		x[14]						
		100:00	13:00	Lunch[3]								x
		104:00	17:00	Snack								
		107:30	20:30	Dinner[3]								x
		108:00	21:00	Drug administration								
	6	119:15	08:15								x[12]	x[12]
		119:30	08:30	Breakfast								
		120:00	09:00	Drug administration[16]		x[14]						
		124:00	13:00	Lunch[3]								x
		128:00	17:00	Snack								
		131:30	20:30	Dinner[3]								x
		132:00	21:00	Drug administration								

MD part (30 mg bid) (cont'd)

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[2]	PK blood,[4]	PK urine[5]	PD blood (NE activity)	12-lead ECG[7]	Medical examination	Vital signs[8]	Questioning for AEs and concomitant therapy[9]
		143:15	08:15								x[12]	x[12]
		143:30	08:30	Breakfast								
		144:00	09:00	Drug administration[16]		x[14]						
	7	148:00	13:00	Lunch[3]								x
		152:00	17:00	Snack								
		155:30	20:30	Dinner[3]								x
		156:00	21:00	Drug administration								
		167:15	08:15		x[B, 12]				x[12]	x[12]	x[12]	x[12]
		167:30	08:30	Breakfast								
		168:00	09:00	Drug administration[16]		x[14]						
	8	172:00	13:00	Lunch[3]								x
		176:00	17:00	Snack								
		179:30	20:30	Dinner[3]								x
		180:00	21:00	Drug administration								
		191:15	08:15								x[12]	x[12]
		191:30	08:30	Breakfast								
		192:00	09:00	Drug administration[16]		x[14]						
	9	196:00	13:00	Lunch[3]								x
		200:00	17:00	Snack								
		203:30	20:30	Dinner[3]								x
		204:00	21:00	Drug administration								
		215:15	08:15								x[12]	x[12]
		215:30	08:30	Breakfast								
		216:00	09:00	Drug administration[16]		x[14]						
	10	220:00	13:00	Lunch[3]								x
		224:00	17:00	Snack								
		227:30	20:30	Dinner[3]								x
		228:00	21:00	Drug administration								

MD part (30 mg bid) (cont'd)

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[2]	PK blood,[4]	PK urine[5]	PD blood (NE activity)	12-lead ECG[7]	Medical examination	Vital signs[8]	Questioning for AEs and concomitant therapy[9]
		239:00	08:00						x[12,13]	x[12]	x[12]	x[12]
		239:30	08:30	Breakfast								
		240:00	**09:00**	**Last drug administration[15]**	x[B, 14]	x[14]	▲	x[14]				
		240:20	09:20			x	|					
		240:40	09:40			x	|					
		241:00	10:00			x	|		x		x	
		241:30	10:30			x	|					
		242:00	11:00	240 mL fluid intake	x[D]	x	|	x	x		x	x
		243:00	12:00			x	|					
	11	244:00	13:00	240 mL fluid intake, thereafter lunch[3]		x	+		x		x	x
		245:00	14:00			x	|					
		246:00	15:00			x	|		x		x	
		247:00	16:00			x	|					
		248:00	17:00	Snack[3]		x	+		x		x	x
		249:00	18:00			x	|					
		250:00	19:00			x	|					
		251:30	20:30	Dinner			|					
		252:00	21:00		x[D]	x	+	x	x		x	x
	12	264:00	09:00		x[D]	x	+	x	x		x	x
	13	288:00	09:00		x[B]	x	▼					x
	14	312:00	09:00		x[D]	x		x			x	x
	15	336:00	09:00			x						x
	16	360:00	09:00		x[D]	x		x			x	x
	17	384:00	09:00			x						
	18	408:00	09:00	discharge from trial site[17]	x[D]	x		x			x	x
3	**19 to 21**			End of trial (EOT) examination[18]	x[A]				x	x[19]	x	x

Clock time should be adjusted based on actual administration time

1 Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include medical examination, check of vital signs, ECG (12-lead ECG), chest x-ray, safety

laboratory (including drug screening), pharmacogenetic analysis for UGT2B17 genotype, demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.

2 Letters A, B, C and D describe different sets of safety laboratory examinations (see Section 5.2.3)

3 If several actions are indicated at the same time, the intake of meals will be the last action.

4 Sampling times and periods may be adapted based on information obtained during the trial (e.g., due to preliminary PK data) including addition of samples and visits, as long as the total blood volume taken does not exceed 400 ml per subject.

5 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 prior to administration of trial medication. Other urine samples are to be collected over the stated post-dose intervals (◄— | — | —►) 0-4, 4-8, and 8-12 h at baseline, 240-244, 244-248, 248-252, 252-264, 264-288 h at Day 11.

6 Infection Test on SARS-CoV-2 will be performed at Visit 2 Day -1.

7 At Screening visit (SCR) and EoT: ECGs recordings are performed as single ECGs. All other scheduled ECG recordings are performed as triplicate ECGs. Recording time points may be adapted based on information obtained during the trial. ECG recording will always precede all other study procedures scheduled for the same time (see Section 5.2.4).

8 Vital signs assessments will include pulse rate, systolic and diastolic blood pressure, height and weight. Height to be measured only at SCR, weight at SCR and at Day 1 and Day 11 prior to morning dose. Axillary body temperature to be measured at Day-1.

9 AEs and concomitant therapies will be recorded throughout the trial whenever reported, but will be specifically asked for at the times indicated in the Flow Chart above.

10 Urine drug screening and alcohol breath test will be performed at screening and prior to dosing at Day 1 of Visit 2. A breath alcohol test may be repeated at any time during the trial at the discretion of an investigator or designee.

11 Safety laboratory to be taken and to be medically evaluated on Day -1 prior to administration of BI 1323495.

12 The time is approximate; the procedures are to be performed and completed within 3 h prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to (first) drug administration.
Only on Day 1: PD blood (NE activity): at pre-dose time point, two samples (2x5 ml) will be collected.

13 3 triplicate ECGs are recorded within approximately one hour. The recordings should be separated by at least 15 minutes. The 15 minutes refer to the start of the first recording within a triplicate ECG.

14 Samples to be taken within 15 min prior to drug administration

15 At Day 1 and Day 11 subjects should have a normal caloric breakfast 30 minutes before drug administration in the morning. The breakfast should be consumed within 30 minutes prior to trial drug intake in the morning. Subjects will then fast for 4 hours after intake of morning dose. At Day 11, subjects will take only a single dose of study drug in the morning.

16 Morning and evening dose should be taken with a 12 h time interval (e.g. 9:00 h and 21:00 h) approximately at the same time each day during the treatment phase, within a time window of +/- 1 hour.
On days 1 to 10: subjects stay at the site and take morning and evening dose under surveillance of site staff. Drug administration should take place with food. Breakfast will be provided 30 minutes prior to the morning dose, and dinner will be provided 30 minutes prior to the evening dose.

17 Subjects are only allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or designee.

18 At EOT, the examination includes physical examination, vital signs, ECG, safety laboratory, recording of AEs, and concomitant therapies.

19 At EOT only if clinical relevant finding at EOT.

20 PGx samples will be collected during Day 1.

MD part (60 mg qd)

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[2]	PK blood,[4]	PK urine[5]	PD blood (NE activity)	12-lead ECG[7]	Medical examination	Vital signs[8]	Questioning for AEs and concomitant therapy[9]
1	**-28 to -8**			Screening (SCR)[1] including pharmacogenomics test UGT2B17	x[A]				x	x	x	
2	**-1**	-16:00	17:00	Admission to trial site	x [B, 6, 10, 11]							x
	1[20]	-01:00	08:00	Allocation to treatment[12]	x[C,12]	x[12]	x[12]	x[12]	x[12,13]	x[12]	x[12]	x[12]
		-00:30	08:30	breakfast								
		00:00	**09:00**	**First drug administration[15]**			▲					
		00:20	09:20			x	|					
		00:40	09:40			x	|					
		01:00	10:00			x	|		x		x	
		01:30	10:30			x	|					
		02:00	11:00	240 mL fluid intake	x[D]	x	|	x	x		x	x
		03:00	12:00			x	|					
		04:00	13:00	240 mL fluid intake, thereafter lunch[3]		x	+		x		x	x
		05:00	14:00			x	|					
		06:00	15:00			x	|		x		x	x
		07:00	16:00			x	|					
		08:00	17:00	Snack [3]		x	+		x		x	x
		09:00	18:00			x	|					
		10:00	19:00			x	|					
		11:30	20:30	Dinner			|					
		12:00	21:00		x[D]	x[14]	|	x[14]	x		x	x
	2	23:30	08:30	Breakfast	x[B, 12]		|		x[12]		x[12]	x[12]
		24:00	09:00	Drug administration		x[14]	▼					
		28:00	13:00	Lunch[3]								x
		32:00	17:00	Snack								
		35:30	20:30	Dinner								
		36:00	21:00									x

MD part (60 mg qd) (cont'd)

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[2]	PK blood,[4]	PK urine[5]	PD blood (NE activity)	12-lead ECG[7]	Medical examination	Vital signs[8]	Questioning for AEs and concomitant therapy[9]
	3	47:30	08:30	Breakfast							x[12]	x[12]
		48:00	09:00	Drug administration		x[14]						
		52:00	13:00	Lunch[3]								x
		56:00	17:00	Snack								
		59:30	20:30	Dinner[3]								x
		60:00	21:00									
	4	71:30	08:30	Breakfast							x[12]	x[12]
		72:00	09:00	Drug administration		x[14]						
		76:00	13:00	Lunch[3]								x
		80:00	17:00	Snack								
		83:30	20:30	Dinner[3]								x
		84:00	21:00									
	5	95:30	08:30	Breakfast	x[B, 12]				x[12]	x[12]	x[12]	x[12]
		96:00	09:00	Drug administration[16]		x[14]						
		100:00	13:00	Lunch[3]								x
		104:00	17:00	Snack								
		107:30	20:30	Dinner[3]								x
	6	119:15	08:15								x[12]	x[12]
		119:30	08:30	Breakfast								
		120:00	09:00	Drug administration[16]		x[14]						
		124:00	13:00	Lunch[3]								x
		128:00	17:00	Snack								
		131:30	20:30	Dinner[3]								x
	7	143:15	08:15								x[12]	x[12]
		143:30	08:30	Breakfast								
		144:00	09:00	Drug administration[16]		x[14]						
		148:00	13:00	Lunch[3]								x
		152:00	17:00	Snack								
		155:30	20:30	Dinner[3]								x

MD part (60 mg qd) (cont'd)

Visit	Day	Planned time (relative to first drug[6] administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[2]	PK blood,[4]	PK urine[5]	PD blood (NE activity)	12-lead ECG[7]	Medical examination	Vital signs[8]	Questioning for AEs and concomitant therapy[9]
	8	167:15	08:15		x[B, 12]				x[12]	x[12]	x[12]	x[12]
		167:30	08:30	Breakfast								
		168:00	09:00	Drug administration[16]		x[14]						
		172:00	13:00	Lunch[3]								x
		176:00	17:00	Snack								
		179:30	20:30	Dinner[3]								x
	9	191:15	08:15								x[12]	x[12]
		191:30	08:30	Breakfast								
		192:00	09:00	Drug administration[16]		x[14]						
		196:00	13:00	Lunch[3]								x
		200:00	17:00	Snack								
		203:30	20:30	Dinner[3]								x
	10	215:15	08:15								x[12]	x[12]
		215:30	08:30	Breakfast								
		216:00	09:00	Drug administration[16]		x[14]						
		220:00	13:00	Lunch[3]								x
		224:00	17:00	Snack								
		227:30	20:30	Dinner[3]								x
	11	239:00	08:00						x[12,13]	x[12]	x[12]	x[12]
		239:30	08:30	Breakfast								
		240:00	**09:00**	**Last drug administration[15]**	x[B, 14]	x[14]	▲	x[14]				
		240:20	09:20			x	|					
		240:40	09:40			x	|					
		241:00	10:00			x	|		x		x	
		241:30	10:30			x	|					
		242:00	11:00	240 mL fluid intake	x[D]	x	|	x	x		x	x
		243:00	12:00			x	|					
		244:00	13:00	240 mL fluid intake, thereafter lunch[3]		x	+		x		x	x
		245:00	14:00			x	|					
		246:00	15:00			x	|		x		x	

MD part (60 mg qd) (cont'd)

Visit	Day	Planned time (relative to first drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory[2]	PK blood,[4]	PK urine[5]	PD blood (NE activity)	12-lead ECG[7]	Medical examination	Vital signs[8]	Questioning for AEs and concomitant therapy[9]
		247:00	16:00			x	─					
		248:00	17:00	Snack[3]		x	┼		x		x	x
		249:00	18:00			x	─					
		250:00	19:00			x	─					
		251:30	20:30	Dinner			─					
		252:00	21:00		x^D	x	┼	x	x		x	x
	12	264:00	09:00		x^D	x	┼	x	x		x	x
	13	288:00	09:00		x^B	x	▼					x
	14	312:00	09:00		x^D	x		x			x	x
	15	336:00	09:00			x						x
	16	360:00	09:00		x^D	x		x			x	x
	17	384:00	09:00			x						
	18	408:00	09:00	discharge from trial site[17]	x^D	x		x			x	x
3	**19 to 21**			End of trial (EOT) examination[18]	x^A				x	x^{19}	x	x

Clock time should be adjusted based on actual administration time

1 Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures include medical examination, check of vital signs, ECG (12-lead ECG), chest x-ray, safety laboratory (including drug screening), pharmacogenetic analysis for UGT2B17 genotype, demographics (including determination of body height and weight, smoking status and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.

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3 If several actions are indicated at the same time, the intake of meals will be the last action.

4 Sampling times and periods may be adapted based on information obtained during the trial (e.g., due to preliminary PK data) including addition of samples and visits, as long as the total blood volume taken does not exceed 400 ml per subject.

5 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 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 h at baseline, 240-244, 244-248, 248-252, 252-264, 264-288 h at Day 11.

6 Infection Test on SARS-CoV-2 will be performed at Visit 2 Day -1.

7 At Screening visit (SCR) and EoT: ECGs recordings are performed as single ECGs. All other scheduled ECG recordings are performed as triplicate ECGs. Recording time points may be adapted based on information obtained during the trial. ECG recording will always precede all other study procedures scheduled for the same time (see Section 5.2.4).

8 Vital signs assessments will include pulse rate, systolic and diastolic blood pressure, height and weight. Height to be measured only at SCR, weight at SCR and at Day 1 and Day 11 prior to morning dose. Axillary body

temperature to be measured at Day-1.

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Drug administration should take place with food. Breakfast will be provided 30 minutes prior to the morning dose.

17 Subjects are only allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or designee.

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19 At EOT only if clinical relevant finding at EOT.

20 PGx samples will be collected during Day 1.

TABLE OF CONTENTS

ABBREVIATIONS

ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AESI	Adverse events of special interest
AEt1-t2	Amount of analyte that is eliminated in urine from the time interval t1 to t2
ALCOA	attributable, legible, contemporaneous, original, accurate (dimension of integrity)
ALT	Alanine transaminase
ANOVA	Analysis of variance
aPTT	activated partial thromboplastin time
AUC_{0-12}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to 12 hour after administration
AUC_{0-24}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 24 hours after drug administration
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
AUC_{ss}	Area under the concentration-time curve of the analyte in plasma at steady state
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUC_{τ}	Area under the concentration-time curve of the analyte in plasma during a dosage interval
$\%AUC_{tz-\infty}$	Percentage of $AUC_{tz-\infty}$ obtained by extrapolation
BA	Bioavailability
BI	Boehringer Ingelheim
bid	bis in die
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CA	Competent authority
CatC	Cathepsin C
CF	Cystic Fibrosis
CFTR	Cystic Fibrosis Transmembrane conductance Regulator
CI	Confidence interval
CK	Creatine Kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration

$CL_{R, t1-t2}$	renal clearance of the analyte in plasma from the time point t_1 to t_2
C_{max}	Maximum measured concentration of the analyte in plasma
COPD	Chronic obstructive pulmonary disease
[redacted]	
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as 'eCRF')
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical trial protocol
CTR	Clinical trial report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
eDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EM	Extensive metabolizer
EMA	European Medicines Agency
EOT	End of trial
FDA	Food and Drug Administration
fe_{t1-t2}	fraction of administered drug excreted unchanged in urine from time point t_1 to t_2
GCP	Good Clinical Practice
gCV	Geometric coefficient of variation
GFR	Glomerular filtration rate
GGT	Gamma-Glutamyl Transferase
GLDH	Glutamate dehydrogenase
GLP	Good Laboratory Practice
gMean	Geometric mean
GOT	Glutamic Oxaloacetic Transaminase
GPT	Glutamic Pyruvic Transaminase
hERG	human Ether-à-go-go-Related Gene
HIV	Human immunodeficiency virus
IB	Investigator's brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form

IEC	Independent Ethics Committee
IGRA	Interferon gamma release assay
INR	International Normalization Ratio
IPD	Important protocol deviation
IRB	Institutional Review Board
ISF	Investigator site file
K_2-EDTA	dipotassium ethylenediaminetetraacetic acid
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
MB	Myocardial band
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Multi rising dose
$MRT_{,ex}$	Mean residence time of the analyte in the body, extravascular
NE	Neutrophil elastase
NSP	Neutrophil serine protease
P-gp	P-glycoprotein
PD	Pharmacodynamic(s)
PE	Polyethylene
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PLS	Papillon-Lefèvre syndrome
PM	Poor metabolizer
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Polypropylene
PR	Pulse rate
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	corrected QT
R	Reference treatment
REP	Residual effect period
SAE	Serious adverse event
SCR	Screening
SOP	Standard operating procedure
SRD	Single-rising dose
T	Test product or treatment
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in plasma

$t_{1/2}$	Terminal half-life of the analyte in plasma
TMF	Trial Master File
TMM	Team Member Medicine
TS	Treated set
TSAP	Trial Statistical Analysis Plan
t_z	Time of last measurable concentration of the analyte in plasma
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
WOCBP	Woman of childbearing potential
XTC	Ecstasy
λz	Terminal rate constant in plasma

1. INTRODUCTION

BI 1323495 is an oral, reversible inhibitor of neutrophil elastase (NE). It is under development for the treatment of emphysema in patients with chronic obstructive pulmonary disease (COPD) and for the treatment of Cystic Fibrosis (CF).

1.1. MEDICAL BACKGROUND

COPD is a chronic and irreversibly progressive disease of the lung that is characterized by persistent respiratory symptoms and airflow limitation. The chronic airflow limitation is caused by a mixture of small airways disease and parenchymal destruction (emphysema). In emphysema, chronic inflammation causes destruction of the lung parenchyma. COPD is a leading cause of morbidity and mortality worldwide that induces a substantial and increasing economic and social burden [P17-01597].

The irreversible, progressive loss of lung function in COPD patients is partially attributed to an abundance of pulmonary proteinases that are not adequately inhibited by endogenous anti-proteases leading to excessive proteolysis of the lung connective tissue [R16-2239]. The increased proteolysis is the direct result of the activation of neutrophils and macrophages by extrinsic (e.g. cigarette smoke, infections) and intrinsic (e.g. inflammatory cytokines) stimuli associated with COPD.

Neutrophil elastase is one of the pulmonary proteases produced and stored in neutrophils and released in large quantities after activation. High levels of NE have been detected in sputum and bronchoalveolar lavage fluids of patients with various chronic respiratory diseases, including COPD [R16-2237], CF, bronchiectasis, and alpha1-antitrypsin deficiency, and there is a positive correlation between the level of NE activity and the clinical symptoms [R18-0132]. Besides the deleterious effect on lung connective tissue, neutrophil elastase increases mucus production in lung epithelial cells [R17-2928] and can delay the resolution phase of chronic lung inflammation [R17-2929].

Inhibition of NE by an orally available inhibitor is expected to result in reduced distal airway destruction related to damage to pulmonary elastin and connective tissue with possible secondary anti-inflammatory [R17-2929] and anti-mucus hypersecretory effects [P02-06423, R17-2928].

1.2. DRUG PROFILE

1.2.1. BI 1323495

BI 1323495 is a potent, highly selective, reversible inhibitor of the enzymatic activity of neutrophil elastase. It inhibits the isolated enzyme with an IC_{50} of 0.4 nM BI 1323495 exhibits > 4,000x selectivity versus the related neutrophil serine proteases Cathepsin G and proteinase 3 and has no activity against 44 tested unrelated receptors, transporters, and enzymes up to a concentration of 10 µM.

The toxicology program of BI 1323495 to date includes repeat-dose toxicity trials up to 13 weeks in Wistar rats and cynomolgus monkeys, the complete standard battery of

genotoxicity trials, and the *in vitro* phototoxicity assay. Pivotal trials were performed in compliance with GLP (Good Laboratory Practice).

General and safety pharmacology trials included *in vitro* hERG (human Ether-à-go-go-Related Gene) potassium channel trials, cardiovascular assessments in conscious cynomolgus monkeys, effects on the central nervous system and respiratory system in rats.

The 4- and 13week trials resulted in no observed adverse effect levels in rat or cynomolgus monkey of 300 and 200 (males)/600 (females) mg/kg/day or 250 and 300 mg/kg/day, respectively. The associated mean exposures combined for males and females from the 4-week trials were 33,000 and 54,700 nM (C_{max}) and 179,000 and 471,000 nM·h (AUC_{0-24}), respectively.

For a detailed description of the BI 1323495 profile, please refer to the current Investigator's Brochure (IB) [c21238478-05].

Clinical experience

At the time of preparing this trial protocol, three Phase I trials with administration of single doses of BI 1323495 to healthy male volunteers have been completed, trials 1405-0001 was first-in-man trial, 1405-0007 investigated relative BA (Bioavailability) and food effect, and 1405-0009 investigated drug interaction with itraconazole. In addition to this, 1405-0002, multiple rising dose (MRD) trial in healthy subjects is currently ongoing, and analysis of the DDI trial (1405-0015) with Rosuvastatin (BRCP and OATP1B1 substrate) and Dabigatran (P-gp substrate) is ongoing.

In the single rising dose (SRD) trial 1405-0001, single-dose treatment with up to 600 mg BI 1323495 or placebo was safe and well tolerated. There was no relationship between the occurrence of AEs and dose. Three AEs in subjects receiving BI 1323495 were judged as moderate in intensity, all other AEs were classified as mild. No severe or serious AEs were reported. The most frequently reported treatment-emergent AE was headache, reported for 6 out of 48 subjects (12.5%) receiving BI 1323495 and 2 out of 15 subjects (13.3%) receiving placebo. The next-most frequently reported treatment-emergent AEs were fatigue and diarrhea, each reported for 2 out of 48 subjects (4.2%) receiving BI 1323495. In one subject receiving 300 mg BI 1323495, a mild (<2-fold upper limit of normal [ULN]) and transient elevation of alanine transaminase (ALT) and glutamate dehydrogenase (GLDH) was reported.

The level of exposure to BI 1323495 was dependent on the expression pattern of the enzyme UGT2B17 in the intestine. While homozygous and heterozygous carriers of the wild type allele (UGT2B17 *1/*1 and *1/*2) could not be distinguished based on their exposures, AUCs and C_{max} were increased in subjects with homozygous deletion of UGT2B17 (*2/*2), compared with the other genotypes (Table 1.2.1: 1) [c26492551].
After the first-pass metabolism, the same pharmacokinetic properties apply to all genotypes. gMean (geometric mean) plasma exposure increased in a less than dose-proportional manner. Multiple plasma concentration peaks were observed in the profiles of nearly all subjects treated. Subjects with genotype *2/*2 did not show as many peaks as the other genotypes in the concentration-time profiles. The terminal half-life was similar over all dose groups, except for being longer in the 600 mg dose group.

Table 1.2.1: 1 $AUC_{0-\infty}$ and C_{max} for genotypes *1/*1 and *1/*2 compared with genotype *2/*2 after single oral administration of BI 1323495 in trial 1405-0001

BI 1323495 dose	Genotype	N	$AUC_{0-\infty}$ [nmol·h/L]		C_{max} [nmol/L]	
			gMean	gCV (%)	gMean	gCV (%)
10 mg	*1/*1, *1/*2	6	143	102	10.5	66.3
30 mg	*1/*1, *1/*2	3	438	95.3	24.8	89.6
	*2/*2	3	1780	21.2	142	11.2
60 mg	*1/*1, *1/*2	6	824	77.7	47.1	77.6
100 mg	*1/*1, *1/*2	5	2100	74.1	125	68.6
	*2/*2	1 [a]	4240	-	308	-
200 mg	*1/*1, *1/*2	4	2670	49.8	138	86.5
	*2/*2	2	7170	4.44	632	18.0
300 mg	*1/*1, *1/*2	5	2400	115	136	123
	*2/*2	1 [a]	11 500	-	712	-
450 mg	*1/*1, *1/*2	6	1780	102	136	74.2
600 mg	*1/*1, *1/*2	6	3820	71.9	195	90.8

[a] In dose groups with only 1 subject with genotype *2/*2, the individual values for the subject are displayed, rather than gMean and gCV.

Direct target engagement of BI 1323495 in blood was evaluated using an *ex vivo* NE activity assay. Median maximum placebo-corrected % NE inhibition ranged from 77.37% to 101.55%, and was >100% for BI 1323495 doses of 100 mg and higher. The pharmacokinetic (PK)/ Pharmacodynamics (PD) evaluation showed a clear BI 1323495 plasma concentration-NE inhibition relationship with an IC_{95} of around 70 nmol/L.
For further details on safety and tolerability as well as on pharmacokinetics and biomarker data of the SRD trial refer to the IB (c21238478-05).

In the food effect trial 1405-0007, a randomised 2-way crossover trial to compare the relative bioavailability of a single dose of 100 mg BI 1323495 (50 mg tablet) administered in the fasted state versus fed state (high-fat), maximum plasma concentrations were higher and were reached earlier in the fed state compared with in the fasted state. Median t_{max} was 2.00 h in the fed state and 3.52 h in the fasted state.

In the fed state, AUC_{0-tz} increased by 66.02% (gMean ratio: 166.02%, 90% CI: 143.17% to 192.53%); C_{max} by 135.50% (gMean ratio: 235.50%, 90% CI: 179.82% to 308.42%), and $AUC_{0-\infty}$ by 59.39% (gMean ratio: 159.39%, 90% CI: 140.11% to 181.34%) compared with in the fasted state.

Higher exposure to BI 1323495 when subjects were in the fed state held true over all genotypes. Subjects with the *2/*2 genotype had considerably higher exposures when compared with subjects with genotypes *1/*1 and *1/*2. The percentage increases in AUC_{0-tz}, C_{max}, and $AUC_{0-\infty}$ under fed conditions when compared with fasted conditions were similar for genotypes *1/*1 or *1/*2, and genotype *2/*2. Therefore, the results indicate that the food effect on AUC_{0-tz}, C_{max}, and $AUC_{0-\infty}$ was likely independent of genotype.

Treatment-emergent AEs were reported for 5 out of the 12 treated subjects (41.7%). Adverse events were reported for 3 out of 12 subjects (25.0%) in the BI 1323495 fasted treatment period and for 2 out of 11 subjects (18.2%) in the BI 1323495 fed treatment period. No subjects were reported with AEs in both treatment periods.

Infections and infestations occurred in 2 of the 12 subjects (16.7%): influenza in 1 subject in the BI 1323495 fasted treatment period, and otitis externa in 1 subject in the BI 1323495 fed treatment period. Headache was reported in 2 of the 12 subjects (16.7%), one in each treatment period. Mouth injury was reported in 1 of the 12 subjects (8.3%) in the BI 1323495 fasted treatment period. The only investigator-defined drug-related AE was mild headache reported for 1 subject [c27223001].

Trial 1405-0009, a two-period fixed sequence trial in healthy male subjects with UGT2B17 extensive metabolizer status, investigated the effects of multiple doses of itraconazole – a strong CYP3A4 and P-gp inhibitor - on the relative bioavailability of a single dose of 10 mg BI 1323495.

Preliminary results for BI 1323495 PK showed a modest increase in exposure to BI 1323495 in gMean $AUC_{0-\infty}$ and C_{max} of 1.69-fold (1.46 to 1.95) and 1.37-fold (1.21 to 1.56), respectively, when administered together with itraconazole.

Treatment-emergent AEs were reported for 6 out of the 14 treated subjects (42.9%). Investigator defined drug-related AEs were reported for 3 subjects (21.4%), all of them with mild or moderate diarrhea under treatment with itraconazole alone or itraconazole + BI 1323495. No relevant changes in vital signs, ECG, or laboratory parameters were reported [c29983104].

In summary, single doses of BI 1323495 investigated so far in clinical trials with healthy subjects were safe and well tolerated.

MRD trial 1405-0002, this trial is currently ongoing and investigates the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple twice daily oral doses of BI 1323495 in healthy subjects that are UGT2B17 EMs or PMs. The following represents an interim summary of the clinical safety data recorded until completion of 5 dose groups in EMs and 2 dose groups in PMs. In the five completed EM dose groups, 27 male healthy subjects and 15 female healthy subjects (not of child-bearing potential or using adequate contraception methods) received multiple twice daily doses of BI 1323495 of 10 mg, 30 mg, 70 mg, 120 mg, or 150 mg over 10.5 days. In the two completed PM dose groups, 6 male healthy subjects and 5 female healthy subjects (not of child-bearing potential or using adequate contraception methods) received multiple twice daily doses of BI 1323495 of 10 mg or 30 mg. 19 (14 male, 5 female) healthy EM or PM subjects received placebo.

Two subjects in the 120 mg dose group and one subject in the 150 mg dose group had AUC exposures exceeding the pre-defined exposure cap of AUC_{0-24} (11500 nM*h); no subject exceeded the predefined exposure cap for C_{max} (1900 nM). One subject in the 70 mg dose group had increased blood pressure, and one subject in the 150 mg dose group had a prolongation of the QTcB interval, both considered drug related. In the other subjects, multiple bid doses of BI 1323495 were associated with no clinically relevant changes in

safety lab, ECG, and vital signs observed. No deaths or serious AEs were reported in this trial. Any AEs were reported in 36 (64.3%) of the 56 subjects treated with BI 1323495, and 9 (47.4%) of the 19 subjects treated with placebo.

Investigator-defined drug-related AEs were reported for 11 (19.6%) of 56 subjects treated with BI 1323495 and 1 (5.3%) of 19 subjects receiving placebo. Headache of mild intensity was the most frequently reported drug related AE. No other drug related AEs were reported in more than one subject treated with BI 1323495. One subject in the placebo group had an AE of severe intensity (abdominal discomfort) that was considered related. One EM subject in the 30 mg dose group had an AE of severe intensity (headache; not considered related to study medication). All other reported AEs were of mild or moderate intensity. Overall, three AEs led to treatment discontinuation: One each in the EM dose groups 30 mg (nausea/vomiting, moderate, not considered related), 70 mg (blood pressure increased, moderate, considered related), and 150 mg (electrocardiogram QT prolonged, mild, considered related). There was no apparent relationship of the occurrence of AEs with dose. For the detail, please refer below Table 1.2. 1: 2. In summary, multiple doses of BI 1323495 investigated so far in clinical trials with healthy subjects were safe and well tolerated.

Table 1.2. 1: 2 Summary of AEs in study 1405-0002

System Organ Class / Preferred Term	Placebo	BI 1323495 (bid dosing)								Total
		Extensive metabolizers					Poor metabolizers		Total on BI 1323495	
		10 mg	30 mg	70 mg	120 mg	150 mg	10 mg	30 mg		
Number of subjects, N (%)	19 (100)	9 (100)	9 (100)	9 (100)	9 (100)	9 (100)	5 (100)	6 (100)	56 (100)	75 (100)
Total with any drug related AEs	1 (5.3)	2 (22.2)	3 (33.3)	1 (11.1)	0 (0)	4 (44.4)	0 (0)	1 (16.7)	11 (19.6)	12 (16)
Gastrointestinal disorders/	1 (5.3)		1 (11.1)			2 (22.2)		1 (16.7)	4 (7.1)	5 (6.7)
Abdominal discomfort	1 (5.3)									1 (1.3)
Abdominal pain	1 (5.3)					1 (11.1)			1 (1.8)	2 (2.7)
Abdominal pain (middle)								1 (16.7)	1 (1.8)	1 (1.3)
Abdominal pain (upper)						1 (11.1)			1 (1.8)	1 (1.3)
Diarrhea			1 (11.1)			1 (11.1)			2 (3.6)	2 (2.7)
Flatulence			1 (11.1)			1 (11.1)			2 (3.6)	2 (2.7)
Investigations/				1 (11.1)		1 (11.1)			2 (3.6)	2 (2.7)
Blood pressure increased				1 (11.1)					1 (1.8)	1 (1.3)
Electrocardiogram QT prolonged						1 (11.1)			1 (1.8)	1 (1.3)
Nervous system disorders/		2 (22.2)	3 (33.3)	1 (11.1)		1 (11.1)			7 (12.5)	7 (9.3)
Headache		1 (11.1)	3 (33.3)	1 (11.1)		1 (11.1)			6 (10.7)	6 (8)
Restless legs syndrome		1 (11.1)				1 (11.1)			2 (3.6)	2 (2.7)
Synkope		1 (11.1)							1 (1.8)	1 (1.3)

The following preliminary pharmacokinetic parameters of BI 1323495 were obtained in plasma in trial 1405-0002 (Table 1.2.1: 2).

Table 1.2. 1: 3 gMean (gCV) PK parameters after multiple bid doses of BI 1323495 in plasma of UGT2B17 EM or PM subjects

	Day 1 C_{max} [nmol/L]	**Day 1 AUC_{0-12} [nmol*h/L]**	**Day 11 $C_{max,ss}$ [nmol/L]**	**Day 11 $AUC_{\tau,ss}$ [nmol*h/L]**	**RA_{Cmaxss}&**	**$RA_{AUCt,ss}$&**
Extensive Metabolizers (*1/*1, *1/*2)						
10 mg bid [N=9]	23.5 (31.4)	118 (56.7)	37.5 (49.6)	237 (60.9)	1.59 (0.914-2.45)	2.00 (1.47-2.84)
30 mg bid [N=9]	62.0 (57.1)	264 (60.4)	64.4 (78.7)	474 (86.0)	1.06 (0.648-1.99)	1.96 (1.14-2.47)
70 mg bid [N=9]	123 (50.0)	738 (47.9)	281 (48.0)*	2500 (59.4)*	2.31 (1.44-6.06)	3.56 (2.18-6.37)
120 mg bid [N=9]	152 (67.5)	957 (65.9)	362 (77.7)	2850 (69.3)	2.38 (1.62-2.92)	2.98 (2.21-3.71)
150 mg bid [N=9]	117 (76.4)	704 (87)	265 (46.0)*	2080 (41.6)*	2.55* (1.71-7.57)	3.45* (1.96-7.70)
Poor Metabolizers (*2/*2)						
10 mg bid [N=5]	85.3 (30.1)	432 (27.2)	109 (25.4)	740 (19.4)	1.27 (1.05-1.75)	1.71 (1.28-2.26)
30 mg bid [N=6]	216 (39.7)	1310 (29.1)	300 (32.6)	2380 (28.1)	1.39 (0.629-1.97)	1.81 (1.47-2.26)

*N=8, & gMean (min-max)

Pharmacokinetic in UGT2B17 extensive metabolizer

The pharmacokinetic data showed considerable inter-individual variability . There was a less than proportional increase in exposure parameters $C_{max,ss}$ and $AUC_{\tau,ss}$ from 10 to 30 mg bid, but a more than dose proportional increase from 30 to 70 mg dose group. The 120 mg bid dose group showed less than dose proportional increase compared to the 70 mg bid DG. Following 150 mg bid dosing, the exposure was only comparable to 70 mg bid DG, that was interpreted to be caused by usage of a higher tablet strength (150 mg) with dissolution problems. Unexpected high accumulation ratios were observed for both C_{max} and AUC_{τ} for the three highest DGs (see Table 1.2.1:3) with also a high inter-individual variability.

Pharmacokinetic in UGT2B17 poor metabolizer

The inter-individual variability was considerably lower in PMs as compared to EMs. Exposure to BI 1323495 at steady state was approximately ~3 to 5-fold higher based on $C_{max,ss}$ and $AUC_{\tau,ss}$ in PMs as compared to EMs. The accumulation ratios at 10 mg bid and 30 mg bid were comparable between both PMs and EMs at the same dose level. However, the exposure in the 30 mg bid DG in PMs was at single dose twice as high as for the 70 mg

bid DG in EM, but still did not lead to such high accumulations as observed in the higher dose groups in the EMs suggesting that the UGT2B17 metabolism plays a role in the unexpected high accumulation behavior in EMs. The exposure of the 30 mg bid DG in PMs was comparable to the 70 mg bid DG in EMs.

In the seven completed dose groups, three subjects (1 subject of the 70 mg bid DG and 2 subjects of the 120 mg bid DG) exceeded the pre-defined exposure caps of AUC_{0-24} (11500 nM*h). The exposure of subject [redacted] following 150mg dosing was not observed but a predicted AUC_{0-24} at steady state, as this [redacted] subject discontinued from the study on Day 6 following PI decision linked to an AE .

Preliminary PK results do not indicate an obvious effect of gender on the pharmacokinetics of BI 1323495.

No obvious effects of genotype (*1/*1 versus *1/*2 EMs) on the pharmacokinetics of BI 1323495 was observed in the completed dose groups.

For further details refer to the IB (c21238478-05).

1.2.2. Itraconazole

Absorption of itraconazole solution is fast with maximum plasma concentration being reached within approximately 2.0 h after oral administration in fasting condition. Bioavailability of itraconazole liquid increases by 10-70% when given under fasting condition compared to administration together with food. Mean peak plasma concentrations were 738 ng/mL after a single dose of 200 mg itraconazole solution (fasting) and 2500 ng/mL after 15 days of daily treatment with 200 mg itraconazole solution (fasting). Pharmacokinetics of itraconazole is non-linear. The half-life of itraconazole after multiple doses of 200 mg once daily with solution formulation was approximately 40 h.
In the liver, itraconazole is metabolized extensively to more than 30 metabolites (R17-3743). Its main metabolite, OH-itraconazole, accounts for about twice the concentration of plasma itraconazole at trough. It has been shown *in vitro* that CYP3A4 is mainly responsible for the formation of this metabolite (R18-2644). FDA, EMA, and PMDA classify itraconazole as strong index inhibitor of CYP3A (R18-0241, P15-06991, and P15-06298). However, not only itraconazole contributes to the *in vivo* inhibition of CYP3A observed after itraconazole administration but also three of its metabolites (OH-itraconazole, keto-itraconazole, and N desalkyl-itraconazole) (R10-1102).

For further details, please refer to the package insert for ITRIZOLE® Oral Solution 1% (R20-1269).

1.2.3. 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 1323495 is approximately 7 days.

When given together with itraconazole (Treatment T), it is expected that plasma exposure of BI 1323495 could be increased (albeit within the exposures explored in the clinical trial

1405-0001), and the time of relevant plasma exposure could be prolonged. This might result in a prolonged period in which adverse effects could potentially occur.

For the use of itraconazole in Treatment T, the REP is defined as 9 days after last administration of itraconazole on Day 7 in Period 2.

1.3. RATIONALE FOR PERFORMING THE TRIAL

The UGT2B17 polymorphism is geographically unequally distributed, with differences likely driven by ethnicity. Within Asian populations, the *2/*2 genotype is predominant, with UGT2B17 extensive metabolizers (EMs; genotypes *1/*1 or *1/*2) comprising only approximately 15% of the general population (R19-1805). The three parts of this trial take into consideration the distribution of this pharmacogenetic polymorphism in the Asian population.

SRD part and MD part

The objective of this trial is to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of BI 1323495 in healthy male Japanese subjects. The chosen population of healthy male subjects receiving single rising oral doses and multiple oral doses are considered adequate to provide the basis for the clinical development program of BI 1323495 in Japan. Additionally, investigation of difference between PM and EM of UGT2B17 genotype will provide more insight to development of BI 1323495.

In 1405-0002, PK after multiple administrations were investigated in Caucasian UGT 2B17 EM and PM populations. This result indicated that PK characteristics after multiple drug administration were slightly different between UGT2B17 phenotype groups (e.g., the exposure in the 30 mg bid DG in PMs was at single dose twice as high as for the 70 mg bid DG in EM, but still did not lead to high accumulations as observed in the higher dose groups in the EMs, etc…), which might be caused by UGT2B17 metabolic capability (please see in detail in section 1.2.1). Since the UGT2B17 polymorphism is geographically unequally distributed (e.g., UGT2B17 PM is predominant in Asian population), the investigation of PK after multiple drug administrations in Japanese could provide comprehensive PK taking account into the racial PK difference, which is beneficial for clinical development program of BI 1323495 in Asian region.

In the airways affected by neutrophilic inflammation, NE is considered a major component of the pathophysiology of emphysema development in COPD and of tissue destruction and exacerbations in CF. In MD parts, the NE activity after zymosan stimulation of peripheral blood will be assessed as a pharmacodynamic outcome for the effects of BI 1323495 after multiple drug administrations in UGT 2B17 PM population, which provides comprehensive PK-PD relationship covering both UGT 2B17 genotype groups.

The dose range selected for this trial is expected to cover the potential therapeutic dose range(s) in the further clinical development program of BI 1323495 for both UGT2B17 PMs and EMs.

Drug-drug interaction (DDI) part

Based on *in vitro* data in human hepatocytes, BI 1323495 is metabolized via glucuronidation by UGT2B7 and UGT2B17 and via various phase I biotransformations by CYP 3A4. The *in vitro* ratio of metabolism via glucuronidation to oxidation was in the range of 7:1 to 2:1. Additionally, BI 1323495 is an *in vitro* substrate of P-glycoprotein (P-gp) (c21238478-05).

Therefore, in this trial, the focus is on the DDI victim potential of BI 1323495 with regard to CYP3A4 and P-gp inhibition as this may lead to clinically relevant increases in exposures with potential impact on patient safety. The victim potential of BI 1323495 upon inhibition of CYP 3A4 / P-pg in UGT2B17 EM has already been assessed (trial 1405-0009), suggesting that a modest increase in exposure to BI 1323495 in gMean $AUC_{0-\infty}$ and C_{max} of 1.69- fold and 1.37-fold, respectively, occurs when administered together with itraconazole. In addition, dedicated DDI assessment in a UGT2B17 PM population is required to evaluate the comprehensive victim potential of BI 1323495 by strong CYP3A4/P-gp inhibitor considering UGT2B17 genotypes, since UGT2B17 PM, when treated with a strong inhibitor of CYP 3A4 and P-gp, lack two main metabolic pathways and may experience a more pronounced effect of CYP 3A / P-gp inhibition on exposures to BI 1323495. This DDI assessment in UGT2B17 poor metabolizers is performed in a Japanese population as the high prevalence of UGT2B17 PM subjects in this population greatly facilitates the conduct of this assessment.
Itraconazole is chosen for this trial as perpetrator drug, as this drug is recommended as strong inhibitor of CYP3A by EMA (P15-06991), as strong index inhibitor of CYP3A by FDA (R18-0241), and as strong inhibitor of CYP3A by PMDA (P15-06298) and it is an inhibitor of P-gp (R18-0241). Moreover, safety and tolerability of itraconazole were acceptable in previous drug-drug interaction trials (c02336088, c03355329, c08928447).

1.4. BENEFIT - RISK ASSESSMENT

Participation in this clinical trial is without any (therapeutic) benefit for healthy subjects. Their participation in the trial, however, is of major importance for the development of a new orally available drug, which is expected to improve the prognosis of patients with COPD and emphysema by slowing the natural course of the disease, especially the progressive decline in lung function and lung density associated with the progression of tissue destruction. Furthermore, it is expected that patients with CF will benefit by experiencing less frequent pulmonary exacerbations and slowing of the natural course of the disease.

1.4.1. Procedure-related risks

The use of an indwelling venous catheter or venepuncture for e.g. blood sampling may result in mild bruising, and in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period, as well as in feeling of light-headedness or in syncope.

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

1.4.2. Drug-related risks and safety measures

Drug-induced liver injury

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

BI 1323495

BI 1323495 is a potent and highly selective inhibitor of NE. Taking into account the mode of action, the nature of the target, non-clinical findings, and the relevance of animal species and models, BI 1323495 is not considered a high-risk compound. Two compounds with the same mode of action as BI 1323495 have already been tested in phase I and II clinical trials with no relevant safety issues detected (c21238478-05).

The formation of active NE, together with two other neutrophil serine proteases (NSPs: Cathepsin G, Proteinase 3), is catalysed by Cathepsin C (CatC) in maturing neutrophil precursor cells in the bone marrow. A human genetic disease exists, Papillon-Lefèvre syndrome (PLS), in which patients completely lack functional NSPs (including NE) due to complete deficiency for CatC. The neutrophils of PLS patients upon activation are unable to release active NSPs, including NE. The phenotype of these patients can be looked at as a human model of a pharmacologically induced complete suppression of NE (and other NSPs). Despite this complete lack of functional neutrophil serine proteases, which may be expected to weaken the microbicidal capacity of neutrophils, the associated immunodeficiency in Papillon-Lefèvre syndrome patients is generally mild.

The target organs in the preclinical assessment of toxicity with BI 1323495 were the liver and kidney, and coagulation pathway in rodents, and as responsive organ, the immune system and coagulation pathway in the cynomolgus monkey.

Effects on the liver were indicated by increases in liver enzymes (Aspartate transaminase [AST], ALT, or GLDH), decreases in cholesterol and triglycerides, and an increase in total bilirubin in rats at 600 or 900 mg/kg/day. Biliary hyperplasia was observed in female rats given 900 mg/kg/day for 4-weeks. The liver findings were still present at the end of the 4-wk recovery period, but they were not seen in the 13-week toxicity trials although male rats achieved high exposures. The drug exposure was much higher in these animals than those expected in man and observed in the SRD trial 1405-0001.

Risk mitigation and monitoring: Although alterations are not specifically expected, liver function tests including total and direct bilirubin will be monitored as part of the standard safety laboratory assessments (see Section 5.2.3). Subjects with impaired liver function will be excluded from participation in this trial.

Effects on the kidneys at exposures with BI 1323495 high above those expected in man were accompanied by increases in creatinine levels and changes in blood urea values in the 2-week mice and rat trials. In the 4-week trial in rats, tubular basophilia was observed in the

kidneys of males and female rats at the highest dose tested. These effects were still present at the end of the 4-week recovery period. In the 13-week trial, tubular degeneration was seen in male rats at the highest dose tested but recovered fully within the 8-week recovery period.

Risk mitigation and monitoring: Serum creatinine, urea, and electrolyte levels will be assessed, and glomerular filtration rate will be estimated as part of the standard safety laboratory assessments (see Section 5.2.3). Subjects with impaired renal function will be excluded from participation in this trial.

The coagulation pathway was affected in rats, showing a dose-independent increase in fibrinogen. An increase is regarded toxicologically not relevant. A reduction in platelet counts was associated with BI 1323495 exposure in both rodent and non-rodent species. This was accompanied at very high exposures by minor increases in prothrombin time in male rats. No bleeding events occurred.

Risk mitigation and monitoring: Platelet count, prothrombin time and activated partial thromboplastin time (aPTT) will be measured as part of the standard safety laboratory assessments (see Section 5.2.3). Monitoring will be done for any signs of bleeding or bleeding-related adverse events. Use of concomitant drugs that inhibit platelet aggregation or coagulation (e.g. acetylsalicylic acid) will be prohibited (ref. Section 4.2.2).

The immune system showed an increase in the number of primarily B-lymphocytes in the cynomolgus monkey. In the spleen, increased cellularity in the lymphocyte-rich region was observed, and the lymph nodes showed an increase in germinal center development in the 13-week monkey trial at high exposures. These effects were considered to be toxicologically not relevant.

In the SRD and food effect trial, single dose administration of BI 1323495 up to 600 mg under fasted conditions and 100 mg under fasted and fed conditions was well tolerated, with no clinically relevant changes in safety lab, ECG, and vital signs observed (ref. Section 1.2.1).

As with all drugs, the potential for hypersensitivity and allergic reactions has to be taken into consideration when BI 1323495 is administered.

COVID-19

A thorough assessment has been conducted to evaluate whether the mechanism of action of BI 1323495 to inhibit NE may suggest an increased probability of contracting COVID-19 or of experiencing severe disease in case of such an infection. The key aspects of the assessment are summarised below. The full written documentation of this assessment (BI 1323495: Benefit-Risk assessment in context of COVID-19 infection) is filed in the trial master file (TMF).

NE is an important component of the innate immune system, targeting proteins and virulence factors of various bacteria and thereby helping to fend off bacterial infections.

However, it is only one among a large number of antimicrobial mechanisms of which neutrophils make use to kill bacterial pathogens.

The phenotype of patients with PLS is well described. No increased risk of viral infections has been observed in PLS patients. Likewise, no such risk has been reported in previous clinical trials (including those in populations of patients with respiratory diseases) upon treatment with inhibitors of NE or inhibitors of the mechanistically related CatC (referenced in the IB (c21238478-05)). Therefore, short-lived suppression of NE activity upon administration of single doses of BI 1323495 is not expected to be associated with an increased risk of acquiring an infection with a viral pathogen targeting the airways, e.g. SARS-CoV-2, nor of a particularly severe clinical presentation in case of such an infection.

Currently available evidence does also not suggest an increased risk of bacterial superinfection in case of COVID-19 upon treatment with BI 1323495. Suppression of NE will only be transient in this trial assessing administration of single doses and multiple doses for 11 days, and represents a limited intervention into the overall armamentarium available to neutrophils to control bacterial infection. Furthermore, high levels of active NE have even been reported to impair antibacterial defence by cleavage of CXCR1, CD14, or CD16 on neutrophils, and by cleavage of opsonins from target bacteria, thereby impairing phagocytosis. Consistent with these considerations, studies investigating the effects of CatC or NE inhibitors in healthy subjects or patients with respiratory diseases have not revealed an increased risk of bacterial infections, nor of aggravated clinical courses of influenza infections.

The healthy subject population of this study, as defined by the in- and exclusion criteria, is not affected by any clinically relevant concomitant diseases that might put them at an increased risk of experiencing a severe clinical course of COVID-19 in case of SARS-CoV-2 infection.

Based on these considerations, the benefit/risk assessment for the administration of BI 1323495 to healthy subjects remains unaltered also in face of the COVID-19 pandemic.

Risk mitigation:

Ensure that the general measures implemented by the government to control the spread of COVID-19 in the Japanese population are adhered to. COVID-19 infection testing such as PCR test will be conducted before hospitalization.

Itraconazole

In this trial itraconazole will be used in a standard clinical dose of 200 mg once daily for 10 days. Multiple dosing of 200 mg itraconazole up to 15 days was of acceptable tolerability in healthy subjects (c02336088, c03355329, c08928447, R17-3742). Addition to this, BI 1323495 will not have potential to be CYP3A4 inhibitor.

For a detailed description of the potential risks of itraconazole treatment, please refer to the package insert for ITRIZOLE® Oral Solution 1% (R20-1269).

In order to address the risk of hepatotoxicity, only subjects with normal liver enzyme values will be included into the trial. Safety laboratory parameters will be monitored closely. An individual subject will discontinue the treatment if the subject 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, see Section 3.3.4.1).

Further, most of the reported cases of serious hepatotoxicity during itraconazole treatment occurred in patients that suffered from concomitant liver diseases, had other significant diseases, or took concomitant hepatotoxic drugs. Subjects with liver diseases or a medical history of drug-induced liver failure are excluded from trial participation.

Itraconazole has shown a dose-related increase in maternal toxicity, embryotoxicity and teratogenicity in nonclinical trials at high doses, and therefore itraconazole must not be used during pregnancy. Woman of childbearing potential (WOCBP) have to use a highly effective method of contraception until the menstrual period after the last itraconazole dose (R18-2644, R18-2643). For risk mitigation, only male subjects will be included into this clinical trial.

Considering these safety measures and taking into account the reported acceptable tolerability of itraconazole, the planned administration of itraconazole does not represent an undue risk to healthy male volunteers.

1.4.3. Potential interaction between itraconazole and BI 1323495

It is likely that concomitant administration of BI 1323495 with itraconazole may cause an increase of plasma concentrations and $t_{1/2}$ of BI 1323495. The effect of itraconazole in increasing C_{max} and AUC of other drugs can be as high as 3.4-fold and 11-fold, respectively, as seen with oral midazolam, a sensitive CYP3A4 substrate, when co-administered with oral itraconazole 200 mg/d (R01-0516, R18-2644). Inhibition of P-gp may increase exposure of sensitive P-gp substrates like fexofenadine by factor 3-4 (R08-1652, P07-13746) and increase digoxin exposure by ~1.7-fold (R15-3252). Therefore, a low dose of 10 mg BI 1323495 has been selected for this trial (see Section 4.1.2). Based on the only modest effect of co-administration with oral itraconazole in UGT2B17 EMs in the DDI trial 1405-0009, the expected effect of co-administration with oral itraconazole on BI 1323495 exposures in the PM population of this trial is not expected to come close to the maximum effects observed with other drugs.

1.4.4. Benefit –Risk Assessment Summary

In summary, BI 1323495 has the potential to become an oral treatment for patients with COPD. Based upon preclinical and clinical data with BI 1323495 and clinical information from competitor compounds as well as the implemented safety measures described above, healthy subjects will not be exposed to undue risks in relation to the important information expected from this trial as a basis for further clinical development of this compound. Healthy volunteers are not expected to have any direct benefit from participation in this trial.
Considering the medical need of the development of an effective treatment to slow the progression of COPD for patients with this disease and potentially other Respiratory

diseases in the future, the Sponsor considers that the benefit outweighs the potential risks and justifies exposure of healthy male volunteers.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1. MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1. Main objectives

SRD part and MD part; To investigate safety, tolerability, pharmacokinetics, and pharmacodynamics (for MD part only) following single rising doses and multiple oral doses of BI 1323495 in healthy male Japanese subjects genotyped as PM and EM of UGT2B17.

DDI part; To investigate the relative bioavailability of a single oral dose of BI 1323495 when given alone (treatment R) or in combination with itraconazole (treatment T) in healthy male subjects genotyped as PM of UGT2B17.

2.1.2. Primary endpoint

SRD and MD part; The primary endpoint for assessment of safety and tolerability of BI 1323495 is the percentage of subjects with drug-related adverse events.

DDI part; The following pharmacokinetic parameters will be determined for BI 1323495:

- $AUC_{0-\infty}$ (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)

2.1.3. Secondary endpoint

SRD part; The following pharmacokinetic parameters will be determined if feasible:

- $AUC_{0-\infty}$ (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)

DDI part; The following pharmacokinetic parameters will be determined for BI 1323495 if feasible:

- 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)

MD part; The following pharmacokinetic parameters will be determined if feasible:

After the first dose of BI 1323495:

- AUC_{0-12} (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval of 12 h after administration of the first dose)
- C_{max} (maximum measured concentration of the analyte in plasma after the first dose)

After the last dose of BI 1323495:

- $AUC_{\tau,ss}$ (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 over a uniform dosing interval τ)

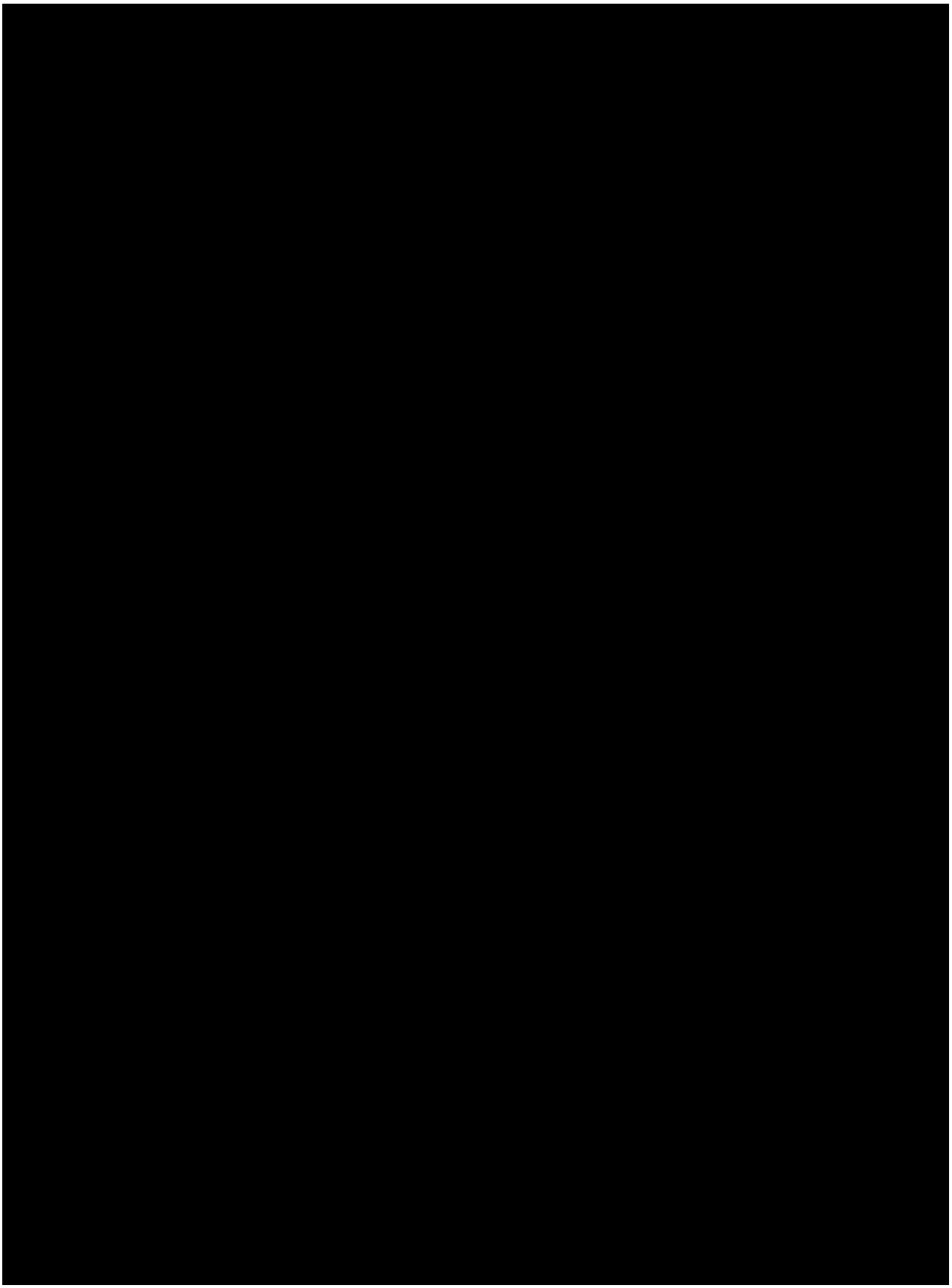
[redacted]

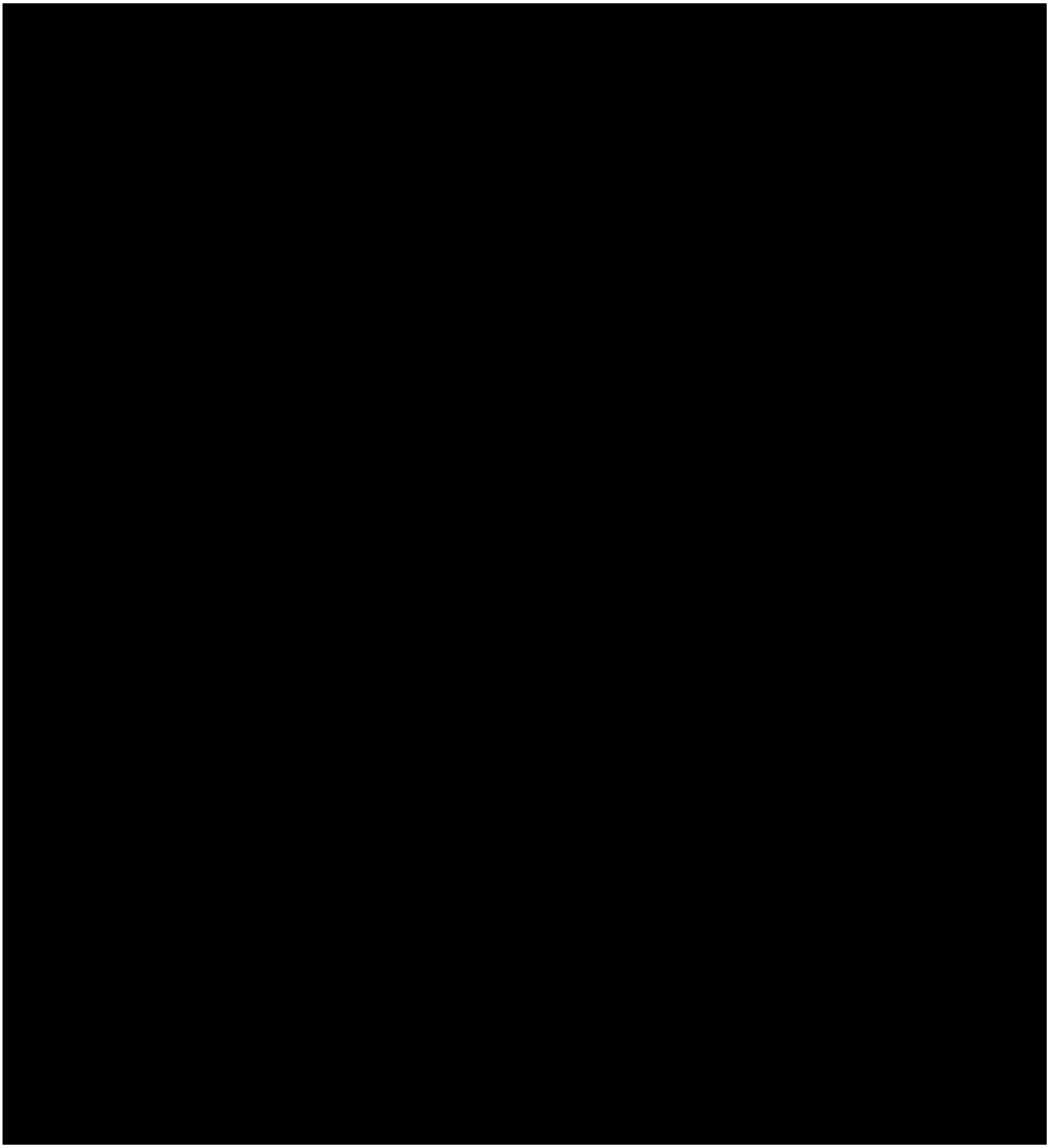
2.2.2.1. Safety and tolerability

Safety and tolerability of BI 1323495 will be assessed based on:

- Adverse events (including clinically relevant findings from the medical examination)
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate)

[redacted]





3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1. OVERALL TRIAL DESIGN AND PLAN

SRD part for PM

This single rising dose part is designed as single-blind, randomised, and placebo-controlled within dose groups.

It is planned to include a total of 24 healthy male subjects in the trial part.

The subjects will be assigned to 3 groups consisting of 8 subjects per group; the groups will be dosed sequentially (see Table 3.1: 1). Within each dose group, 6 subjects will receive BI 1323495 and 2 will receive placebo. Only one dose is tested within each dose group.

The trial schedule and design are depicted in Figure 3.1: 1.

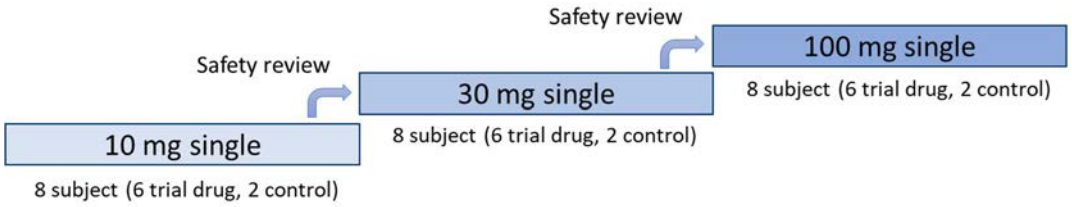


Figure 3.1: 1 Trial design “SRD part for PM”

The dose groups to be evaluated are outlined in Table 3.1: 1 below.

Table 3.1: 1 Dose groups for UGT2B17 PM

Dose Group	1	2	3
Dose (mg)	10	30	100
Number of subjects	8	8	8
Subjects receiving placebo	2	2	2
Subjects receiving active drug	6	6	6

SRD part for EM

This single rising dose part is designed as single-blind, randomised, and placebo-controlled within dose groups.

It is planned to include a total of 12 healthy male subjects in the trial part.

The subjects will be assigned to 3 groups consisting of 4 subjects per group; the groups will be dosed sequentially (see Table 3.1: 2). Within each dose group, 3 subjects will receive BI 1323495 and 1 will receive placebo. Only one dose is tested within each dose group.

The trial schedule and design is depicted in Figure 3.1: 2.

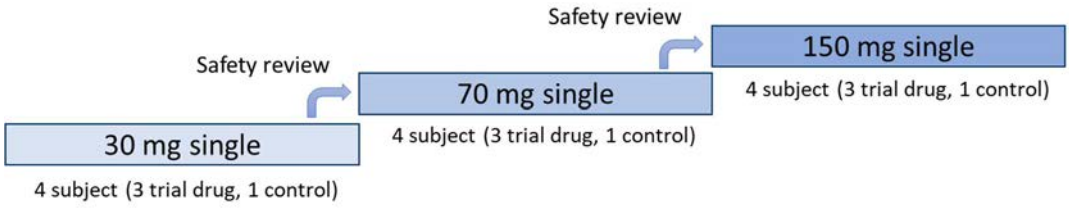


Figure 3.1: 2 Trial design "SRD part for EM"

The dose groups to be evaluated are outlined in Table 3.1: 2 below.

Table 3.1: 2 Dose groups for UGT2B17 EM

Dose Group	1	2	3
Dose (mg)	30	70	150
Number of subjects	4	4	4
Subjects receiving placebo	1	1	1
Subjects receiving active drug	3	3	3

DDI part for PM

This part will be performed as an open-label, two-treatment, two-period, fixed sequence trial in healthy male subjects in order to compare the test treatment (T) to the reference treatment (R). The treatments will be one oral single dose of 10 mg BI 1323495 administered as tablet formulation together with multiple oral doses of 200 mg itraconazole as oral solution formulation (concentration: 10 mg/mL) (T) and one single dose of 10 mg BI 1323495 as tablet formulation given alone (R). DDI part will be initiated after 10 mg safety was confirmed in SRD part for PM subjects.

In the first treatment period (Period 1, Visit 2), all subjects are planned to undergo treatment R, and in the second treatment period (Period 2, Visit 3), all subjects are planned to undergo treatment T. For details, refer to Section 4.1.

The trial schedule and design is depicted in Figure 3.1: 3.

There will be a washout period of at least 11 days between the administrations of BI 1323495.

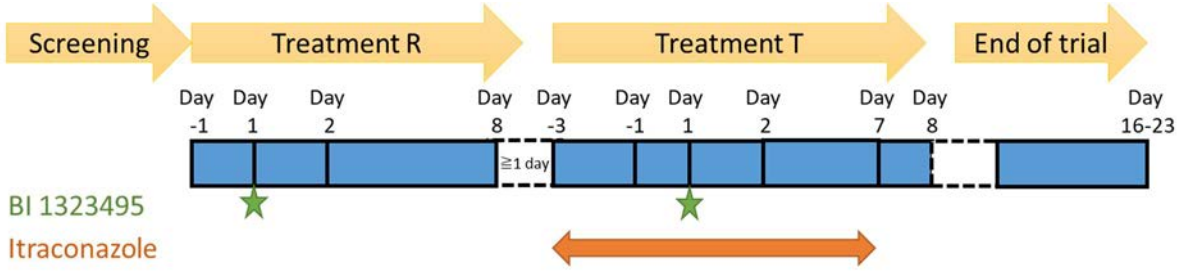


Figure 3.1: 3 Trial design "DDI part for PM"

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

MD part for PM

This multiple dose part is designed as single-blind, randomised, and placebo-controlled within dose groups.

It is planned to include a total of 24 healthy male subjects in the trial part.

The dose groups to be evaluated are 30 mg bid and 60 mg qd.

The following figures show an overview over the visit structure. Detailed schedules of all relevant trial activities are provided in the Flow Charts.

Visit No.	1	2																		3
Day	-28 to -8	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19 to 21
Drug admin			x	x	x	x	x	x	x	x	x	x	x								
Type of Visit	Ambulatory	Admission to site	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Stationary	Discharge	Amburatory

Table 3.1: 4 Overview for MD part, for details see Flow Charts

Dose escalation and safety review

The groups will be dosed consecutively in ascending order of the doses, and a time interval of at least 7 d will be maintained between the last drug administration to subjects in the previous dose group (dose group N) and the first drug administration to subjects in the subsequent dose group (dose group N+1). The decision to treat the next dose group will be based upon safety and tolerability of all the preceding dose groups. The next dose group will only be treated if, in the opinion of the Principal Investigator (or authorised deputy, sub investigator), clinical trial leader (CTL) and Team Member Medicine (TMM), no safety concerns have arisen in the preceding dose groups, i.e. no dose-limiting events occurred,

and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.1).

A documented safety review must take place prior to each dose escalation. Furthermore, an unscheduled safety review meeting can be requested anytime for any reasonable cause by the Principal Investigator, or an authorised deputy, Sub Investigator, or the sponsor of the trial, e.g. in case of any unforeseen adverse events. Dose escalation will only be permitted if no safety concerns exist in the opinion of the Principal Investigator (or an authorised deputy, Sub Investigator), the CTL and TMM.

Although no formal Safety Review meeting will take place within a given dose group, safety will be continuously monitored during this trial, and an individual will only be dosed in the absence of any safety concern, and if none of the pre-specified trial-specific stopping criteria have been met (refer to Section 3.3.4.1).

At minimum, data from 2/3 of subjects on active drug need to be available for escalation to a higher dose. The minimum data set for review consists of the following:

- AEs in the current and preceding dose groups up to at least 7 d post 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 subject to change prior to Database Lock)
- Results from 12-lead ECG in the current and preceding dose groups up to at least 3 d post dosing
- Vital signs in the current and preceding dose groups up to at least 3 d post dosing.
- Clinical laboratory tests in the current and preceding dose groups up to at least 7 d post dosing
- Review of criteria for stopping subject treatment as per Section 3.3.4.1

The decision to escalate the dose will be made jointly by the Principal Investigator, or an authorised deputy, Sub Investigator, CTL and TMM after in-depth analysis of all available safety data, especially serious adverse event (SAE)s, AEs, and out-of-range laboratory results that are considered clinically significant by the investigator. Dose escalation will only be permitted if no safety concerns exist neither in the opinion of the Principal Investigator (or an authorised deputy, Sub Investigator), CTL and TMM.

Safety Reviews can be conducted face-to-face or by video/telephone conference. The CTL is responsible for the organisation and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy, Sub Investigator), CTL and TMM, and will be filed in the investigator site file (ISF) and TMF.

Additional subjects may be entered to allow additional testing 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 and none of the stopping criteria apply. Thus, the actual number of subjects entered may exceed 50, but will not exceed 62 subjects. CTP will be amended if additional subject entry has decided.

3.2. DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

SRD part

For single -rising dose trials, the sequential rising dose design described in Section 3.1 is viewed favourably under the provision not to expose the subjects to undue risks, since the main trial objective is to investigate safety and tolerability of BI 1323495.

Single-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, subjects and investigators will be aware of the dose of the drug administered. The disadvantage of this 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 rising dose trials involving healthy subjects to include a placebo group to control for safety and tolerability of the trial medication.

SRD part for PM

Each dose group consists of 8 subjects, with 6 on active treatment, and 2 on placebo. For data analysis purposes, the placebo control group will include all subjects that were treated with placebo, regardless of the groups they were treated. Six subjects per active treatment group are generally considered to be sufficient for the exploratory evaluation of pharmacokinetics.

SRD part for EM

Each dose group consists of 4 subjects, with 3 on active treatment, and 1 on placebo. For data analysis purposes, the placebo control group will include all subjects that were treated with placebo, regardless of the groups they were treated. Three subjects per active treatment group are considered to be reasonable taking into account the low proportion of UGT2B17 EM in Japanese, and be sufficient for the exploratory evaluation of pharmacokinetics.

DDI part for PM

For relative bioavailability trials, the crossover design is preferred because of its efficiency: since each subject serves as his own control, the comparison between treatments is based on an intra-subject comparison, thus removing inter-subject variability from the comparison between treatments (R94-1529). Because of the long half-life (about 40 h) of itraconazole and its metabolites, a fixed sequence design was selected, with administration of itraconazole in the second trial period only. This design is not expected to lead to systematic errors in the estimation of the treatment effects since nonspecific time-effects are unlikely due to the short trial duration. For itraconazole trials, this design is recommended by the Innovation and Quality in Pharmaceutical Development's [redacted] (R17-3744).

For this PK drug-drug interaction part of this trial, open-label treatment is acceptable, because the primary endpoints of this trial are PK endpoints derived from measurement of

plasma concentrations of BI 1323495. These endpoints are not expected to be affected by knowledge of treatment.

MD part for PM

Single-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, subjects and investigators will be aware of the dose of the drug administered. The disadvantage of this 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 multiple dosing trials involving healthy volunteers to include a placebo group to control for safety and tolerability of the trial medication. In the MD part, each dose group consists of 12 subjects, with 9 on active treatment, and 3 on placebo. 9 subjects per active treatment group in the MRD part, is considered to be sufficient for the exploratory evaluation of safety, pharmacokinetics, and pharmacodynamics.

The treatment period of 11 days is considered adequate for collection of safety, pharmacokinetic, and pharmacodynamic data after multiple dosing at steady state to inform subsequent studies along the clinical development path. The treatment period is adequately covered by non-clinical toxicology data from animal studies.

3.3. SELECTION OF TRIAL POPULATION

It is planned that 74 healthy male genotyped UGT2B17 (62 poor metabolizers and 12 extensive metabolizers) will enter the trial. These subjects will be recruited from the volunteers' pool of the trial site.

Based on UGT2B17 genotyping, the predicted phenotypes are defined as having the following alleles: extensive metabolizers (*1/*1 or *1/*2), poor metabolizers (*2/*2).

In the SRD part, both PM and EM subjects will participate, as assessments for both UGT2B17 metabolizer groups are needed to fully characterize the pharmacokinetic properties of BI 1323495 in a Japanese population. In the DDI part, only PM subjects will participate, as the DDI effect of itraconazole in an UGT2B17 EM population has already been assessed (trial 1405-0009) and the extent of DDI is expected to be affected by the UGT2B17 metabolizer status, but not by ethnicity. In the MD part, 30 mg bid and 60 mg qd groups in UGT2B17 PM group will be investigated, which would be reasonable to ensure the safety profiles after multiple administrations of BI 1323495 in Japanese population taking account the following points; 1) majority of Japanese population is considered to be PM subjects, 2) the exposure of BI 1323495 was higher in UGT2B17 PM than in UGT2B17 EM.

Subjects who participated to one of these parts can not participate to other part.

Only male subjects will be included in the trial because no data on reproductive toxicology are available at this time.

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

3.3.1. Main diagnosis for trial entry

The trial will be performed in healthy male subjects.

3.3.2. Inclusion criteria

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

1. Healthy male subjects according to the assessment of the investigator, as based on a complete medical history, including a medical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Japanese ethnicity, according to the following criteria:
   - born in Japan, have lived outside of Japan <10 years, and have parents and grandparents who are Japanese
3. Age of 20 to 45 years (inclusive) at screening
4. BMI of 18.5 to 25.0 kg/m^2 (inclusive) at screening
5. Signed and dated written informed consent prior to admission to the trial, in accordance with Good Clinical Practice (GCP) and local legislation
6. Subjects who agree to minimize the risk of making their partner pregnant by fulfilling any of the following criteria starting from the first administration of trial medication until 90 days after last administration of trial medication

   - Use of adequate contraception, any of the following methods plus condom: intrauterine device, combined oral contraceptives that started at least 2 months prior to the first drug administration.

   - Vasectomized (vasectomy at least 1 year prior to enrolment)

   - Surgical sterilization (including bilateral tubal occlusion, hysterectomy or bilateral oophorectomy) of the subject's female partner
7. Subjects genotyped as UGT2B17 poor metabolizers, i.e. carrying allele of UGT2B17 gene (*2/*2) (DDI and MD part only)

3.3.3. Exclusion criteria

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

1. Any finding in the medical examination (including BP, PR or ECG) deviating from normal and assessed 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 40 to 90 mmHg, or pulse rate outside the range of 40 to 99 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 assessed as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Cholecystectomy or other surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy or simple hernia repair)
7. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections (Subjects who were positives to Hepatitis B surface antigen, Hepatitis B surface antibody, Hepatitis B core antibody, Hepatitis C antibodies, HIV-1 and HIV-2 antigen and/or antibody, T-SPOT and Syphilis test)
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days of planned administration of trial medication that might reasonably influence the results of the trial (including drugs that cause QT/QTc interval prolongation)
12. Intake of an investigational drug in another clinical trial within 3 months (4 months for new active ingredients) of planned administration of investigational drug in the current trial, or concurrent participation in another clinical trial in which investigational drug is administered
13. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
14. Inability to refrain from smoking on specified trial days
15. Alcohol abuse (consumption of more than 30 g per day for males)
16. Drug abuse or positive drug screening
17. Blood donation of more than 400 mL within 12 weeks or 200 mL within 30 days or plasma donation within 2 weeks prior to administration or intended blood donation during the trial
18. Intention to perform excessive physical activities within one week prior to the administration of trial medication or during the trial
19. Inability to comply with the dietary regimen of the trial site
20. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) or any other relevant ECG finding at screening
21. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome)
22. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because the subject is not considered able to understand and comply with trial requirements, or has a condition that would not allow safe participation in the trial

23. History of disease that affects the present situation

In addition, the following trial-specific exclusion criteria apply:

24. Current or history of relevant kidney, urinary tract diseases or abnormalities (e.g. nephrolithiasis, hydronephrosis, acute or chronic nephritis, renal injury, renal failure)
25. Estimated glomerular filtration rate according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI*) formula < 80 mL/min at screening
26. Within 10 days prior to administration of trial medication, use of any drug that could reasonably inhibit platelet aggregation or coagulation (e.g. acetylsalicylic acid)
27. History of drug induced liver injury
28. Liver enzymes (ALT, AST, Gamma-Glutamyl Transferase [GGT]) above upper limit of normal at the screening examination
29. Known relevant immunodeficiency, as judged by the investigator
30. History and/or presence of tuberculosis; positive result for interferon gamma release assay (IGRA) (i.e. T-SPOT), or history of pneumococcal infection
31. Axillary temperature of more than 37.7°C on Day -1
32. Subjects who have received live or live-attenuated vaccine in the 4 weeks prior to dosing
33. C-reactive protein above upper limit of laboratory reference range at screening

* Estimated glomerular filtration rate by Japanese CKD-EPI formula

For trial restrictions, refer to Section 4.2.2.

3.3.4. Withdrawal of subjects from treatment or assessments

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

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

At the time of discontinuation, a complete end of trial examination will be performed, if possible, and the information will be recorded in the CRF. If the discontinuation occurs before the end of the REP (see Section 1.2.3), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ensure collection of AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject.

3.3.4.1. Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment or trial participation, without the need to justify the decision
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The subject is no longer able to participate in the trial for other medical reasons, such as surgery, adverse events (AE)s, or diseases
5. The subject has an elevation of AST and/or ALT ≥3-fold ULN and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the DILI checklist provided in the ISF

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

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

3.3.4.2. Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for 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 at any time for any of the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New toxicological findings, serious adverse events, or any safety information invalidating the earlier positive benefit-risk assessment. Dose escalation will be terminated if more than 50% of the subjects at one dose level show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported.

3. Violation of GCP, or the CTP, or the contract with BI impairing the appropriate conduct of the trial.
4. The sponsor decides to discontinue the further development of the investigational product.
5. Dose escalation will be stopped if at least 1/3 subjects on active treatment at one dose level have relevant individual QT prolongations, i.e. a QTc increase of greater than 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, as confirmed by a repeat ECG recording.

The investigator / trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except if item 3 applies).

3.3.5. Replacement of subjects

In SRD and MD part, if some subjects do not complete the trial, or there is not a sufficient number of subjects on active within one dose group the Trial Clinical Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. In DDI part, if more than 2 subjects do not complete the trial, the CTL together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he replaces.

4. TREATMENTS

4.1. INVESTIGATIONAL TREATMENTS

The investigational product BI 1323495 as tablet formulation has been manufactured by BI Pharma GmbH & Co. KG. Itraconazole oral solution will be prepared by a site pharmacy department.

4.1.1. Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Test product 1

Substance:	BI 1323495
Pharmaceutical formulation:	Tablet, film-coated
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	10 mg and 50 mg
Posology:	1-0-0 and 1-0-1 (30 mg bid only)
Route of administration:	Oral
Duration of use:	SRD part: Single dose MD part: 11 days DDI part: Single dose for each treatment R and T

Test product 2

Name:	ITRIZOLE® Oral Solution 1% [redacted]
Substance:	Itraconazole
Pharmaceutical formulation:	Oral solution
Source:	Site pharmacy department
Holder of marketing authorisation:	[redacted]
Unit strength:	10 mg/mL
Posology:	20 mL-0-0
Route of administration:	Oral
Duration of use:	10 days in treatment T

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

Substance:	Placebo

Pharmaceutical formulation:	Tablet, film-coated
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	Not applicable
Posology:	1-0-0 and 1-0-1 (30 mg bid only)
Route of administration:	Oral
Duration of use:	SRD part: Single dose MD part: 11 days DDI part: Sing dose for each treatment R and T

4.1.2. Selection of doses in the trial and dose modification

SRD part

The doses selected for this trial are assumed to cover the therapeutic dose.

Maximum dose for each UGT2B17 genotype group

The maximum doses are 100 mg and 150 mg under fed condition for UGT2B17 PM and EM, respectively. The human exposure caps are a C_{max} gMean value of 1900 nM and AUC_{0-24} gMean value of 11500 nM·h [c21238478-05]. For the current trial, C_{max} gMean and AUC gMean are predicted to be below the exposure cap and not to exceed exposures that were already achieved (maximum values of C_{max} and AUC_{0-24} were 717 nM and 6790 nM·h, respectively) and considered safe in individual PM subjects participating in the first-in-human trial 1405-0001. The expected margins versus human exposure caps (Table 4.1.2: 1) are considered reasonable; therefore, single administration of the maximum dose in each UGT2B17 genotype group are considered safe.

Table 4.1.2: 1 Predicted PK parameters for the maximum dose group in each UGT 2B17 genotype group after single dose administration of BI 1323495 in the fed state

	AUC_{0-24}		$AUC_{0-\infty}$		C_{max}	
	Model Prediction (gMean)	Exposure multiple	Model Prediction (gMean)	Exposure multiple	Model Prediction (gMean)	Exposure multiple
UGT 2B17 PM						
100 mg	4380	2.6	7210	1.6	374	5.1
UGT 2B17 EM						
150 mg	1620	7.1	2610	4.4	142	13

Model prediction: Single dose, tablet formulation, fed condition, Male, Mean body weight 65 kg, UGT 2B17 genotype (PM or EM)
Exposure multiple: calculated as ratio of predicted exposure to exposure cap ($AUC_{0-24,ss}$: 11500 nM·h, $C_{max,ss}$: 1900 nM)

MD part

In this part, 30 mg bid and 60 mg qd under fed condition is selected as the dose to be tested for UGT2B17 PM. The human exposure caps are a C_{max} gMean value of 1900 nM and AUC_{0-24} gMean value of 11500 nM·h [c21238478-05]. For the current trial, C_{max} gMean and AUC gMean are predicted to be below the exposure cap. In addition, multiple doses of BI 1323495 investigated, including UGT2B17 PM 10 mg bid and 30 mg bid group, so far in clinical trials with healthy subjects were safe and well tolerated (please see Section 1.2.1 in detail); therefore, multiple administrations of 30 mg bid and 60 mg qd in UGT2B17 PM group are considered safe.

Table 4.1.2: 2 Predicted PK parameters for 30 mg bid and 60 mg qd in UGT 2B17 PM genotype group after multiple dose administrations of BI 1323495 in the fed state

	$AUC_{0-24,ss}$		$C_{max,ss}$	
	Model Prediction (gMean)	Exposure multiple	Model Prediction (gMean)	Exposure multiple
UGT 2B17 PM				
30 mg bid	6160	1.9	350	5.4
60 mg qd	6010	1.9	496	3.8

Model prediction: bid: twice daily, qd: once daily, assuming tablet formulation, fed condition, Male, Mean body weight 65 kg, UGT 2B17 genotype (PM)
Exposure multiple: calculated as ratio of predicted exposure to exposure cap ($AUC_{0-24,ss}$: 11500 nM·h, $C_{max,ss}$: 1900 nM)

DDI part

Perpetrator (itraconazole)

The dose of itraconazole selected for this trial reflects standard clinical doses, is considered sufficient to yield significant CYP3A and P-gp inhibition, and has been used successfully and safely in previous drug-drug-interaction trials (c02336088, c03355329, c08928447, c27223001).

Victim (BI 1323495)

For the current trial, a dose of 10 mg BI 1323495 under fasted condition is selected, which is same to that tested in trial 1405-0009. The predicted exposure of a dose 10 mg BI 1323495 alone under fasted condition in UGT2B17 PM is displayed in Table 4.1.2: 2. The exposure multiples of C_{max} and AUC were 32 and 12-19, respectively.

In trial 1405-0001, in the 200 mg dose group - the dose group with highest mean exposures - gMean values for C_{max} and AUC_{0-24} were 229 nM and 2390 nM·h, respectively. (c26492551). The ratios of these gMean plasma exposure parameters at the 200 mg dose group to the predicted exposure for the current trial (C_{max}: 59.9 nM, AUC_{0-24}: 609 nM·h) are approximately 4.

The victim potential of BI 1323495 upon inhibition of CYP 3A4 / P-pg in UGT2B17 EM has already been assessed in trial 1405-0009, suggesting that a modest increase in exposure to BI 1323495 in gMean $AUC_{0-\infty}$ and C_{max} of 1.69- fold and 1.37-fold, respectively, occurs

when BI 1323495 10 mg single administered together with itraconazole. UGT2B17 PM, when treated with a strong inhibitor of CYP 3A4 and P-gp such as itraconazole, lack two main metabolic pathways and may experience a more pronounced effect of CYP 3A / P-gp inhibition of exposures to BI 1323495. The predicted exposure after single dose administration of 10 mg BI 1323495 alone and with 200 mg itraconazole in UGT2B17 PM by PopPK model based on the clinical trials (1405-0001 and 1405-0007) are shown in Table 4.1.2: 2. In this simulation, the inhibition effect by itraconazole on PK of BI 1323495 mainly affects the bioavailability but not the elimination which was observed in UGT2B17 EM in trial 1405-0009. From this simulation, the exposure multiple of the predicted exposure with itraconazole in UGT2B17 PM are more than 5 and the predicted exposure are still lower than that experienced in trial 1405-0001. Considering these findings, it is considered to be safe for increases of BI 1323495 plasma exposures in UGT 2B17 PM when 10 mg BI 1323495 administered given together with itraconazole.

Table 4.1.2: 3 Predicted PK parameters after 10 mg BI 1323495 single administration under fasted condition (BI 1323495 alone and with itraconazole)

	AUC_{0-24}		$AUC_{0-\infty}$		C_{max}	
	Model Prediction (gMean)	Exposure multiple	Model Prediction (gMean)	Exposure multiple	Model Prediction (gMean)	Exposure multiple
UGT 2B17 PM						
10 mg	609	19	963	12	59.9	32
10 mg + 200 mg itraconazole	1260	9.1	2000	5.8	121	16

Model prediction: Single dose, tablet formulation, fasted condition, Male, Mean body weight 65 kg, UGT 2B17 PM
Exposure multiple: calculated as ratio of predicted exposure to exposure cap ($AUC_{0-24,ss}$: 11500 nM·h, $C_{max,ss}$: 1900 nM)

4.1.3. Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. During the screening, UGT2B17 genotype will be determined and subject will be categorized into 2 groups: PM (genotype *2/*2) or EM (genotype *1/*1 and *1/*2). Allocation of PM subjects to SRD part, MD part or DDI part will be decided by subject availability with 'first come first served' principle. Therefore, the allocation of PM subject is not influenced by trial personnel, but only by the subjects' temporal availability.

SRD part (For PM and EM)

The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects are allocated to 1 of the 3 dose cohorts, the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. Because the trial includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

Subjects 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. Numbers of the randomisation list will be allocated to subjects by the method 'first come first served'. Subjects are then assigned to treatment according to the randomisation list. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.6.

DDI part (For PM)

There is only one treatment sequence investigated in this part, and each subject will be allocated to the same treatment sequence (R-T). Subjects will be allocated by the method 'first come first served'. Once a subject number has been assigned, it cannot be reassigned to any other subject.

All subjects may be treated in one cohort, i.e. all subjects may receive treatment on the same calendar day. In case this is not feasible (e.g. due to logistical or recruitment reasons), the group may be split into several cohorts as required. Treatment of all subjects on the same calendar day is acceptable (for safety margin to exposure reached in previous SRD trial 1405-0001 refer to Section 1.2.1; for discussion of trial-associated risks and safety measures see Section 1.4.1 and 1.4.2).

MD part (For PM)

The subjects willing to participate will be recruited to dose group according to their temporal availability. As soon as enough subjects are allocated to 1 of the 2 dose cohorts, the following subjects will be allocated to one of the other dose cohorts. Therefore, the allocation of subjects to dose cohorts is not influenced by trial personnel, but only by the subjects' temporal availability. Because the trial includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

Subjects 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. Numbers of the randomisation list will be allocated to subjects by the method 'first come first served'. Subjects are then assigned to treatment according to the randomisation list. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.6.

4.1.4. Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Tables 4.1.4: 1, 4.1.4: 2 and 4.1.4: 3. The number of tablets for placebo corresponds to the number of tablets in the corresponding dose level.

Table 4.1.4: 1 BI 1323495 and placebo* treatments, tablets of SRD part for PM

Dose group	Substance	Pharmaceutical form	BI 1323495 10 mg	BI 1323495 50 mg	Total dose of BI 1323495
1	BI 1323495	Tablet, film-coated	1	0	10 mg
2	BI 1323495	Tablet, film-coated	3	0	30 mg
3	BI 1323495	Tablet, film-coated	0	2	100 mg
1-3	Placebo*	Tablet, film-coated	identical to active treatment		--

* Subjects receiving placebo are equally distributed across dose groups

Table 4.1.4: 2 BI 1323495 and placebo* treatments, tablets of SRD part for EM

Dose group	Substance	Pharmaceutical form	BI 1323495 10 mg	BI 1323495 50 mg	Total dose of BI 1323495
1	BI 1323495	Tablet, film-coated	3	0	30 mg
2	BI 1323495	Tablet, film-coated	2	1	70 mg
3	BI 1323495	Tablet, film-coated	0	3	150 mg
1-3	Placebo*	Tablet, film-coated	identical to active treatment		--

* Subjects receiving placebo are equally distributed across dose groups

Table 4.1.4: 3 Dosage and treatment schedule in the DDI part

Treatment period	Treatment	Substance	Formulation	Unit strength	Dosage	Total dose
1	R (Reference)	BI 1323495	Tablet, film-coated	10 mg	1 tablet as single dose (Day 1)	10 mg
2	T (Test)	BI 1323495	Tablet, film-coated	10 mg	1 tablet as single dose (Day 1)	10 mg
		Itraconazole	Oral solution	10 mg/mL	20 mL (200 mg) qd for 10 days (Days -3 to 7)	2000 mg

Table 4.1.4: 4 BI 1323495 and placebo treatments, tablets of MD part for PM

Dose group	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total daily dose of BI 1323495
1	BI 1323495	Tablet, film-coated	10 mg	3 tablets bid*	60 mg
1	Placebo	Tablet, film-coated	--	3 tablets bid*	--
2	BI 1323495	Tablet, film-coated	10 mg 50 mg	1 tablet each qd	60 mg
2	Placebo	Tablet, film-coated	--	1 tablet each qd	60 mg

*On Day 11, Subjects will receive a single dose in the morning only. On all other trial days, BI 1323495 will be administered bid.

SRD part

For BI 1323495 treatment, a standardized meal (400-500 kcal with fat contributing to ca. 150 kcal) content [P12-10638]) will be served 30 min before drug administration. The subjects must completely consume the meal prior to drug intake.

The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing /sitting position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

During the first 4 h after drug administration, the subjects 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.

Subjects will be kept under close medical surveillance until 48 h after administration of BI 1323495.

DDI part

Administration of trial medication will be performed after subjects have fasted overnight; No food is allowed within 10 h before and for at least 4 h after intake of BI 1323495. Subjects will be advised to not consume any food within 9 h before and 1 h after itraconazole administrations. The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing / sitting position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should

witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

During the first 4 h after drug administration, the subjects 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.

Subjects will be kept under close medical surveillance until 34 h after administration of BI 1323495.

MD part

The investigator (or authorised designee) will administer the trial medication as an oral dose together with about 240 mL of water to subjects who are in a standing /sitting position. For drug administration, the so-called four-eye principle (two-person rule) should be applied. For this, one authorised employee of the trial site should witness the administration of trial medication, and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise.

On first day of treatment (Day 1) and last day of treatment (Day 11), where PK profile sampling takes place, administration of BI 1323495 (Day 1, Day 11) in the morning will be performed following a standardized normal caloric meals, which is to start and be completed within 30 minutes before the scheduled dosing.

On all other treatment days and in the evening of Day 1, subjects should take the study medication with food, preferably within 30 min after a meal. On treatment days, breakfast will be provided 30 minutes prior to the morning dose administration and dinner will be provided 30 minutes prior to the evening dose administration.

Subjects should take their morning doses on all treatment days at the same time as on the first day, +/- 1 hour. The evening dose should be taken 12 hours +/-1 hour after the scheduled time of the morning dose.

Following the first administration of trial medication, subjects will stay in inhouse confinement until Day 18. During the first 4 h after drug administration, they 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 (Only for Day 1 and Day 11 morning).

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

SRD and MD part

SRD and MD part is designed single-blind. The treatments administered (active or placebo) will be blinded to subjects, but will be known to the investigators (outcome assessors). Only the current dose level will be known to the subjects due to the rising dose design.

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

All trial data will be handled open label. This means that trial functions of the sponsor are unblinded (including clinical trial manager (CTM), data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist as well as dedicated personnel of the trial site).

Access to the randomisation schedule will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF.

DDI part

DDI part will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis). This is considered acceptable because the potential for bias seems to be low and does not outweigh practical considerations.

4.1.5.2. Unblinding and breaking the code

As this trial will be conducted single blind or open-label, subjects' treatment assignments will be known to investigators. Therefore, no emergency envelopes will be provided.

4.1.6. Packaging, labelling, and re-supply

BI 1323495 tablets

BI 1323495 tablets 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 subject information form. Examples of the labels will be available in the ISF.

Itraconazole oral solution

Itraconazole oral solution will be obtained by the clinical trial site from a public pharmacy. The drug will be dispensed out of the original, unmodified packages.

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 a designee, will receive the investigational drugs from the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol (CTP) by the Institutional Review Board (IRB)
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site
- Approval/notification from the regulatory authority, e.g. competent authority (CA)
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated CTP

Only authorised personnel documented in the form 'Trial Staff List' may dispense medication to trial subjects. 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 subject, 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 subjects. The investigator, or designee, will maintain records adequately documenting that the subjects were provided the doses specified by the CTP and will 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 investigational medicinal product remains in the investigator's possession.

All unused trial medication will be disposed locally by the trial site upon written authorisation of the CTM. 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 authorize symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable.

4.2.2. Restrictions

4.2.2.1. Restrictions regarding concomitant treatment

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

Known inhibitors/inducers of CYP3A and P-gp activity, drugs with a known hepatotoxicity profile, drugs which are contraindicated to be co-administered with itraconazole (ref. R18-2644), as well as acetylsalicylic acid or other drugs that may inhibit platelet aggregation or coagulation should be avoided during the entire trial; if necessary, short term use of ibuprofen is acceptable.

4.2.2.2. Restrictions on diet and lifestyle

Poppy-seeds containing foods should not be consumed starting 3 days before the first drug administration in each treatment period, in order to avoid false-positive results in the drug-screen.

While admitted to the trial site, the subjects will be instructed not to consume any foods or drinks other than those provided by the staff. Standardized meals will be served at the times indicated in the Flow Chart.

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

Alcoholic beverages are not permitted from 7 days before the first administration of trial medication until after the last PK sample collected.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, or chocolate) are not allowed from 10 h before until 24 h after administration of BI 1323495.

Smoking is not allowed during in-house confinement.

Excessive physical activity (such as competitive sport) should be avoided from 7 days before the first 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 trial.

SRD part

From 1 h before trial medication intake until lunch, fluid intake is restricted to the water provided with standard meal, water administered with the drug, and an additional 240 mL of water served at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3 L.

During the days of urine collection, total fluid intake should be at least 1.5 litres and should not exceed 3.5 litres.

DDI part

No food is allowed within 10 h before and for at least 4 h after intake of BI 1323495. Subjects will be advised not to consume any food within 9 h before and 1 h after itraconazole administrations.

On Day 1, from 1 h before intake of BI 1323495 (Period 1) or itraconazole (Period 2), respectively, fluid intake is restricted to the water administered with the drug, water provided with standard meal, and an additional 240 mL of water at 2 h and 4 h post-dose

(mandatory for all subjects). From lunch until 23 h post-dose, total fluid intake is restricted to 3 L.

MD part

While admitted to the trial site, the subjects are restricted from consuming any other foods or beverages than those provided by the site staff. Standardised meals will be served at the time points described in Flow Chart. A standardized normal caloric breakfast (e.g., a roll with cheese or sausage, including some dietary fat) should be served and finished within 30 minutes prior to dose administration.

In the evening of Day 1 and on Days 2 to 10, drug intake should occur with food.

Breakfast will be provided 30 minutes prior to the morning dose administration and dinner will be provided 30 minutes prior to the evening dose administration.

On Days 1 and 11, from 1 h before drug intake until lunch, fluid intake is restricted to the water administered with the drug, fluid provided with food and an additional 240 mL of water served at 2 h and 4 h post-dose (mandatory for all subjects). From lunch until 24 h post-dose, total fluid intake is restricted to 3.0 litres.

During the days of urine collection, total fluid intake should be at least 1.5 litres and should not exceed 3.5 litres.

4.3. TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the trial site 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.

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

5. ASSESSMENTS

5.1. ASSESSMENT OF EFFICACY

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

5.2. ASSESSMENT OF SAFETY

5.2.1. Medical examination

At screening, the medical examination will include demographics, 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, and a physical examination. After screening, at the time pionts indicated in the Flow chart, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination.

5.2.2. 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 Chart, after subjects 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 and on the same arm, if possible.

5.2.3. Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 h, except 4 h post dosing on Day 1 of SRD part and screening. For retests, at the discretion of the investigator or designee, overnight fasting is not required. The parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 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 5.2.3: 1 Routine laboratory tests

Functional lab group	BI test name [comment/abbreviation]	A[1]	B[1]	C[1]	D[1]
Haematology	Haematocrit	X	X	--	X
	Haemoglobin	X	X	--	X
	Red Blood Cell Count/Erythrocytes	X	X	--	X
	White Blood Cells/Leucocytes	X	X	--	X
	Platelet Count/Thrombocytes (quant)	X	X	--	X
Automatic WBC relative	Neutrophils/Leukocytes; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/Leukocytes; Lymphocytes/Leukocytes	X	X	--	X
Automatic WBC differential	Neutrophil, absol.; Eosinophils, absol.; Basophils, absol.; Monocytes, absol.; Lymphocytes, absol.	X	X	--	X
Manual differential WBC *(if automatic differential WBC is abnormal and clinically relevant in the opinion of the investigator)*	Neut. Poly (segs; Neutrophils Bands; Eosinophils/Leukocytes; Basophils/ Leukocytes; Monocytes/ Leukocytes; Lymphocytes/Leukocytes;				
Coagulation	Activated Partial Thromboplastin Time	X	--	--	--
	Prothrombin time	X	--	--	--
	INR (International Normalization Ratio)	X	--	--	--
	Fibrinogen	X	X	--	--
Enzymes	AST [Aspartate transaminase] /GOT	X	X	X	--
	ALT [Alanine transaminase] /GPT	X	X	X	--
	Alkaline Phosphatase	X	X	X	--
	Gamma-Glutamyl Transferase	X	X	X	--
	Creatine Kinase [CK]	X	X	--	--
	Creatine Kinase Isoenzyme MB [only if CK is elevated and clinically relevant in the opinion of the investigator]	X	X	--	--
Hormones	Thyroid Stimulating Hormone	X	--	--	--
Substrates	Glucose (Plasma)	X	X	--	--
	Creatinine	X	X	--	--
	GFR/ CKD-EPI	X	X	--	--
	Bilirubin, Total	X	X	--	--
	Bilirubin, Direct	X	X	--	--
	Protein, Total	X	X	--	--
	C-Reactive Protein (Quant)	X	X	--	--
	Cholesterol, total	X	--	--	--
	Triglyceride	X	--	--	--
Electrolytes	Sodium	X	X	--	--
	Potassium	X	X	--	--

[1] A: parameters to be determined at Visit 1 and EOT
B: parameters to be determined at Visit 2 and 3 (for trial days and time points refer to Flow Chart)
C: parameters to be determined at Visit 3 (for trial days and time points refer to Flow Chart)
D: parameters to be determined at Visit 2 (only for MD part)

[2] Microscopic examination if erythrocytes, leukocytes, nitrite or protein in urinalysis are abnormal in urine

Table 5.2.3: 1 Routine laboratory tests (cont.)

Functional lab group	BI test name [comment/abbreviation]	A[1]	B[1]	C[1]	D[1]
Urinalysis (Stix)	Urine Nitrite (qual)	X	X	--	--
	Urine Protein (qual)	X	X	--	--
	Urine Glucose (qual)	X	X	--	--
	Urine Ketone (qual)	X	X	--	--
	Urobilinogen (qual)	X	X	--	--
	Urine Bilirubin (qual)	X	X	--	--
	Urine RBC/Erythrocytes (qual)	X	X	--	--
	Urine WBC/Leucocytes (qual)	X	X	--	--
	Urine pH	X	X	--	--
Urine sediment[2]	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)				

[1] A: parameters to be determined at Visit 1 and EOT
B: parameters to be determined at Visit 2 and 3 (for trial days and time points refer to Flow Chart)
C: parameters to be determined at Visit 3 (for trial days and time points refer to Flow Chart)
D: parameters to be determined at Visit 2 (only for MD part)

[2] Microscopic examination if erythrocytes, leukocytes, nitrite or protein in urinalysis are abnormal in urine

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests that may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Infectious serology is planned to be performed at screening only. Drug screening will be performed at screening and prior to first dose in each treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methamphetamines/MDMA/XTC Opiates Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis B surface antigen (qualitative) Hepatitis B surface antibody (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative) T-SPOT Syphilis test (RPR, TP antibody method)
Imaging test	Chest x-ray (For checking onset or history of tuberculosis)

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

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at the local laboratory of the trial site or/and at a CRO designated by the sponsor. Laboratory data will be transmitted electronically from the site to BI.

5.2.4. Electrocardiogram

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Chart. Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the trial.

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 subjects are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG recording will always precede all other trial 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.

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 recorded for safety reasons. These ECGs are assigned to the prior scheduled time point in the sponsor’s database.

Storing

All ECGs will be stored as print out.

Evaluation

All local ECGs will be evaluated by the investigator or a designee.

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

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator.

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

5.2.5. Other safety parameters

Not applicable.

5.2.6. Assessment of adverse events

5.2.6.1. Definitions of adverse event

5.2.6.1.1. Adverse event

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

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

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

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, medical 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 jeopardize 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 hospitalization or development of dependency or abuse

The following events will be handled as 'deemed serious for any other reason'. An AE that possibly leads to disability will be 'deemed serious for any other reason' and reported as an SAE.

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 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 electronic data capture (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 folds ULN combined with an elevation of total bilirubin ≥2 folds ULN measured in the same blood draw sample, or
- Aminotransferase (ALT, and/or AST) elevations ≥10 folds ULN.

These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analyzed, 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 subject's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

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

A 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 CRF(s) by the investigator:

- From signing the informed consent onwards until an individual subject's end of trial:
    - All AEs (serious and non-serious) and all AESIs
    - The only exception to this rule is AEs (serious and non-serious) and AESIs in Phase I trials in healthy volunteers, when subjects discontinue from the trial due to screening failures prior to administration of any trial medication. In these cases, the subjects' data must be collected at trial site but will not be entered in the CRF or trial database and will not be reported in the CTR.
- After the individual subject's end of trial:
    - The investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should, however, not be reported in the CRF

5.2.6.2.2. AE reporting to the sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 h) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

5.2.6.2.3. Information required

All (S)AEs, including those persisting after the individual subject's 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 a male subject has been enrolled in the clinical trial and has taken trial medication, and if a partner of the male subject becomes pregnant, the investigator must report any drug exposure during pregnancy in this partner within 24 h 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 the CRFs.

Exact times of plasma sampling will be documented in the CRFs by the medical personnel. 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 subject does not exceed approximately 400 mL. Such changes would be implemented via non-substantial CTP Amendments.

After successful analysis, the samples may be used for further methodological investigations (e.g. for stability testing or assessment of metabolites) or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations, but not later than 5 years after the CTR is archived.

5.3.2. Methods of sample collection

5.3.2.1. Blood sampling for pharmacokinetic analysis of BI 1323495

For quantification of BI 1323495 concentrations in plasma, 3 mL of blood will be drawn from an antecubital or forearm vein into a K_2-EDTA (dipotassium ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

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 process from blood collection until transfer of plasma aliquots into the freezer should be completed within 90 min, with interim storage of blood samples at room temperature. 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. Details on sample handling, processing and shipments are described in the lab manual.

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

5.3.2.2. Blood sampling for pharmacokinetic analysis of itraconazole

For quantification of itraconazole concentrations in plasma, 3 mL of blood will be drawn from an antecubital or forearm vein into a K_2-EDTA anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venepuncture with a metal needle.

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 process from blood collection until transfer of plasma aliquots into the freezer should be completed within 90 min, with interim storage of blood samples at room temperature. 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. Details on sample handling, processing and shipments are described in the lab manual.

At a minimum, the sample tube labels should list BI trial number, subject number, visit, planned sampling time, and the analyte 'Itra'.

5.3.2.3. Urine sampling for pharmacokinetic analysis

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 Chart will be collected in urine containers and stored. Patients are told to empty their bladders at the end of each sampling interval. 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 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 on a sampling interval, the contents of all containers have to be mixed before aliquots are prepared. Mixing should be done by transferring the entire content of all collection containers into a single PE/PP or glass container, and stirring the mixed fractions for about 1 min (manually of using a stir bar or other stirring device made of PE/PP, teflon or glas). Generally, the collection container should be shaken upon addition of every urine fraction to ensure proper distribution of urine.

Until transfer on dry ice to the analytical laboratory, the urine samples will be stored at about -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 about -20 °C or below until analysis. Details on sample handling, processing and shipments are described in the lab manual.

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.

5.4. ASSESSMENT OF BIOMARKER(S)

5.4.1. Biochemical and cellular biomarkers

Biomarkers will be assessed to monitor pharmacodynamic drug effects over the course of the observation time. Assessment of biomarkers in blood will be done in MD part.

Direct target engagement of BI 1323495 in blood will be evaluated in MD part of the trial using an *ex vivo* NE activity assay. For timepoints where time-matched safety lab is available, neutrophil count will be used for normalisation of NE activity. Otherwise, the last timepoint with neutrophil count closest to sampling for NE activity assessment will be used for normalisation.

5.4.1.1. Methods of sample collection

Blood samples will be taken at time points indicated in the Flow Chart.

A maximum of approximately 20 ml blood will be collected per biomarker sampling time-point per subject for the pre-specified biomarker analyses. This sums up to a total blood volume of approximately 60 mL collected for biomarker analyses over the 3 weeks observational period.

Detailed instructions for biomarker blood sampling, processing, storage and shipment of the different biofluids will be provided in the lab manual/site's ISF.

Target engagement assay

For the assessment of direct target engagement of BI 1323495, at least 5 mL of blood will be collected at the mandated time points as stated in the Flow Chart (PD blood (NE activity)). At the pre-dose time point 2 x 5 mL of blood will be collected.

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

Analyses of the biomarkers will be conducted at Boehringer Ingelheim or contractors of Boehringer Ingelheim.
After completion of the study the samples may be used for further biomarker investigations. Because this analysis is explorative, result will not be share to subjects. The study samples will be discarded after completion of any additional investigations but not later than 5 years after the CTR has been signed.

5.5. BIOBANKING

Not applicable.

5.6. OTHER ASSESSMENTS

5.6.1. UGT2B17 genotyping

In this trial, all subjects will be prospectively genotyped for UGT2B17 in order to determine their UGT2B17 allele/copy number count and their metabolizer status (poor versus extensive metabolizer). Extensive metabolizers are defined by carrying at least one functional allele/copy (*1 allele) of the UGT2B17 gene (*1/*1 homozygous and *1/*2 heterozygous individuals) whereas poor metabolizers are homozygous for the *2 allele, a non-functional deletion of the complete UGT2B17 encoding sequence, and thus lack expression of UGT2B17.
For this purpose, a sample of at most 9 mL of blood per subject will be taken at the screening examination. Genomic DNA will be extracted from blood samples according to standard molecular genetics methods and analyzed by TaqMan® or other standard genotyping technologies. Analysis will be conducted at Boehringer Ingelheim or contractors of Boehringer Ingelheim. The results will be available before inclusion of subjects into the trial and included in the final report. The result can be utilized for re-screening over screening period, if needed.
Collected sample and data will be managed with unique code number, therefore subject anonymity will be secured. As a matter of subject enrollment convenience, result will be informed to subject. If consent is withdrawn, all samples and the data that had already been collected up to the time of withdrawal of consent will still be used. The samples will not be stored upon completion of the genotype analysis and will be destroyed before the end of the clinical trial.

5.6.2. Pharmacogenomic evaluation

Pharmacogenomic investigations explore the role of genetic variation in determining an individual's response to drugs. For this purpose, a sample of at most 10 mL of blood will be obtained at the Day 1 from each subject whose genotype has not been previously determined.

DNA will be extracted from the blood sample in order to sequence genes coding for proteins that are involved in the absorption, distribution, metabolism, and excretion (ADME) of drugs.

The gene sequences to be determined include known and likely functional variations of key ADME genes and incorporate more than 90% of ADME-related genetic markers identified by the PharmaADME group (weblink.pharmaadme.org). It is not intended to include the pharmacogenomic data in the CTR. However, the data may be part of the CTR, if necessary.

5.7. APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic and pharmacodynamic 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 and pharmacodynamic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1. VISIT SCHEDULE

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

Trial measurements and assessments scheduled to occur 'before' trial medication administration at Day 1 are to be performed and completed within a 3 h-period prior to the trial medication administration (including blank values for PK and biomarker). A blank urine sample for PK will be collected within 3 h before drug administration.

The acceptable deviation from the scheduled time for vital signs and ECG will be ± 10 min for the first 4 h after trial medication administration and ± 30 min thereafter (± 60 min for MD part). For laboratory test, the acceptable deviation is ± 30 min.

If several activities are scheduled at the same time point in the Flow chart, ECG should be the first and meal the last activity. Furthermore, if several measurements including venipuncture are scheduled for the same time, venipuncture should be the last of the measurements due to its inconvenience to the subject and possible influence on physiological parameters.

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

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

6.2. DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1. Screening period

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

For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and medical examination, refer to Sections 5.2.1 to 5.2.4. All inclusion and exclusion criteria will be reviewed before treatment period.

Genotyping will be performed for all subjects who will participate to treatment period (for details, see Section 5.6).

6.2.2. Treatment period

SRD part

Each subject will receive one dose of trial medication (BI 1323495 or placebo) at Visit 2.

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

DDI part

Each subject is expected to participate in 2 treatment periods (Days -1 to 1, 2, 3, 4, 5, 6, 7 and 8 in Period 1 and Days -3, -2, -1, 1, 2, 3, 4, 5, 6, 7 , and 8 in Period 2). At least 11 days will separate BI 1323495 drug administrations in the first and second treatment period.

On Day 1 of each treatment period, trial participants will be admitted to the trial site. They will be kept under close medical surveillance for at least 34 h following administration of BI 1323495, respectively. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness. On all other trial days, subjects will be treated in an ambulatory fashion.

MD part

Trial participants will be admitted to the trial site in the evening of Day -1 and kept under close medical surveillance for at least 48 h following the first drug administration. A subject who is eligible for the study will be randomised on Day 1 and receive the first dose of BI 1323495 or placebo. For 30 mg bid group, up to Day 10, each subject will receive multiple bid doses of BI 1323495 or placebo, and a last single dose on Day 11. For 60 mg qd group, up to Day 11, each subject will receive multiple doses of BI 1323495 or placebo.

Trial medication will be taken orally by each subject under direct supervision of the investigator or [redacted] designee.

Study participants will stay at the site under medical surveillance until Day 18. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee.

For details on time points and procedures for collection of plasma and urine samples for PK analysis, refer to Flow Chart and Section 5.3.2.

The safety measurements performed during the treatment period are specified in Section 5.2 of this protocol and in the Flow Chart. For details on times of all other trial procedures, refer to the Flow Chart. 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, vital signs and medical examination during the follow-up period, see Sections 5.2.1 to 5.2.6.

Subjects 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 assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's End of Trial Visit must be followed until they have resolved, have been sufficiently characterized, or no further information can be obtained.

If a subject discontinues from the trial, the subject will be followed until the investigator, or sub-investigator, is convinced of the subject's safety. If follow-up is not possible or comes to an end, follow-up should be formally completed after discussion with the sponsor. If a subjectstops attending trial assessments, the investigator should assess the subject's status as comprehensively as possible and the well-being of the subject should be monitored. However, if the subject withdraws from the trial, it is the subject's choice whether or not to participate in further assessments; he cannot be compelled.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1. STATISTICAL DESIGN – MODEL

SRD and MD part : The main objectives of SRD and MD part will be assessed by using descriptive statistics for safety and tolerability of BI 1323495 as well as for PK parameters and PD parameters (MD part only), which will be compared between the treatment groups. Further analyses of these endpoints comprise the power model for assessment of dose proportionality.

DDI part: The main objective of this part is to investigate the relative bioavailability of BI 1323495 in plasma when given as oral single dose of 10 mg together with multiple doses of itraconazole (Test, T) as compared to when given alone as oral single dose (Reference, R) on the basis of the primary and secondary pharmacokinetic endpoints, as listed in Sections 2.1.2 and 2.1.3. This part will be evaluated statistically by use of a linear model for logarithmically transformed PK endpoints. A further objective is to evaluate and compare further pharmacokinetic parameters between the treatments. These pharmacokinetic parameters will be assessed by descriptive statistics. The assessment of safety and tolerability is a further objective of this part, and will be evaluated by descriptive statistics.

7.2. NULL AND ALTERNATIVE HYPOTHESES

SRD and MD part: Safety and tolerability of different dose groups of BI 1323495 are to be determined on the basis of the investigated parameters in comparison to placebo. It is not planned to test any statistical hypotheses with regard to these variables in a confirmatory sense. Instead, they will be described in their entirety and evaluated by descriptive statistical methods. Confidence intervals will be computed and will have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects.

DDI part: The relative bioavailability of BI 1323495 in plasma when given with multiple oral doses of itraconazole (T) versus single oral dose of BI 1323495 alone (R) will be estimated by the ratios of the geometric means (T/R), and their corresponding 2-sided 90% confidence intervals (CIs) will be provided. This method corresponds to the two one-sided t-test procedure, each at the 5% significance level. Since the main focus is on estimation and not testing, a formal hypothesis test and associated acceptance range is not specified.

7.3. PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were randomised (SRD and MD part) / allocated (DDI part) and treated with at least one dose of trial drug. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses.
- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one primary or secondary 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 subject will be included in the PKS, even if he contributes only one primary or secondary PK parameter value for one period to the statistical assessment. Descriptive and model-based analyses of PK parameters will be based on the PKS.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (IPD) categories will be suggested in the IQRM plan. IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed. Further analysis sets will be defined in TSAP, if required.

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 and 2.2 for BI 1323495 will be calculated according to BI internal SOP. Noncompartmental pharmacokinetic parameters will be calculated based on actual sampling times using a validated pharmacokinetic software (e.g. Phoenix® WinNonlin®).

Plasma and urine concentration data and parameters of a subject 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 subject's data will be documented in the CTR.

Relevant protocol deviations may be

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

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

- The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis),
- Missing samples/concentration data at important phases of PK disposition curve
- A predose concentration of BI 1323495 is >5% C_{max} value of that subject in the respective treatment period (only DDI part).

Plasma/urine concentration data and parameters of a subject which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses. Descriptive and inferential statistics of PK parameters will be based on the PKS.

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).

7.3.1. Primary endpoint analyses

SRD and MD part:

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.

DDI part:

The statistical model used for the analysis of the primary endpoints will be an analysis of variance (ANOVA) model on the logarithmic scale. That is, the PK endpoints will be log-transformed (natural logarithm) prior to fitting the ANOVA model. This model will include effects accounting for the following sources of variation: subject and treatment. The effect 'subject' will be considered as random, whereas the effect ‘treatment’ will be considered as fixed. The model is described by the following equation:

$y_{km} = \mu + s_m + \tau_k + e_{km}$, where

y_{km} = logarithm of response measured on subject m receiving treatment k,

μ = the overall mean,

s_m = the effect associated with the m^{th} subject, m = 1, 2, ..., n,

τ_k = the k^{th} treatment effect, k = 1, 2,

e_{km} = the random error associated with the m^{th} subject who received treatment k,

where $s_m \sim N(0, \sigma_B^2)$ i.i.d., $e_{km} \sim N(0, \sigma_W^2)$ i.i.d. and s_m, e_{km} are independent random variables. The indices ‘B’ and ‘W’ correspond to ‘between’ and ‘within’ variability, respectively.

Point estimates for the ratios of the geometric means (test/reference) for the primary endpoints (see Section 2.1.2) and their two-sided 90% confidence intervals (CIs) will be provided.

For each endpoint, the difference between the expected means for log(T)-log(R) will be estimated by the difference in the corresponding adjusted means (Least Squares Means). Additionally, their two-sided 90% confidence intervals will be calculated based on the residual error from the ANOVA and quantiles from the t distribution. These quantities will

then be backtransformed to the original scale to provide the point estimate and 90% CIs for each endpoint.

Sensitivity analysis

The same statistical model as stated above will be repeated for the primary endpoints but with 'subject' considered as fixed effects.

Further exploratory analyses

In addition to the model-based approach, all parameters will be calculated and analysed descriptively. Furthermore, mean plasma concentration time curves as well as individual profiles will be provided.

7.3.2. Secondary endpoint analyses

Primary analyses

The secondary endpoints (refer to Section 2.1.3) in SRD, MD and DDI parts will be calculated according to the BI internal SOP. They will be assessed descriptively. The secondary endpoint in DDI part will be assessed statistically using the same methods as described for the primary PK endpoints.

Further exploratory analyses

SRD part:

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 $AUC_{0-\infty}$ and C_{max} 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

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

where

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

DDI part:

The secondary endpoints $AUC_{0\text{-}tz}$ (refer to Section 2.1.3) will be assessed statistically using the same methods as described for the primary PK endpoints in Section 7.3.1.

[redacted]

[redacted]

7.3.4. Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.2 and 2.2.2.1 based on the treated set (TS). Safety analyses will be descriptive in nature and will be based on BI standards.

For all analyses the treatment actually administered (= treatment at onset) to the subject 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. In SRD part, the placebo group in the safety evaluation will consist of all subjects 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. In DDI part, the test treatment groups (BI 1323495+itraconazole) will be compared to the reference group (BI 1323495 alone) 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 intake of trial medication will be assigned to the screening period, those between the first trial medication intake and end of REP (see Section 1.2.3) will be assigned to the treatment period. Events occurring after the REP but prior to next intake or end of trial termination date will be assigned to 'follow-up'. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

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) 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 compared to their reference ranges. Values outside the reference range as well as values defined 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.

Relevant ECG findings will be reported as AEs.

7.3.5. Pharmacokinetic - pharmacodynamic analysis (Only MD part)

The relationship of BI 1323495 plasma concentrations and biomarker results will be investigated in an exploratory manner for the NE activity. Other correlations will be explored as applicable.

7.4. INTERIM ANALYSES

No interim analysis is planned.

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 BI internal SOP.

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

7.6. RANDOMISATION

In SRD and MD part, subjects will be randomised within each dose group in a 3:1 ratio (test treatment to placebo). In DDI part, randomisation is not applicable, because all subjects will receive the same treatment in the same order.

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 subject replacement (refer to Section 3.3.5).

7.7. DETERMINATION OF SAMPLE SIZE

SRD: It is planned to include a total of 36 subjects in this trial. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group for PM subjects (6 on active treatment, and 2 on placebo) is commonly used in single-rising dose trials of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics. The size of 4 subjects per dose group for EM subjects (3 on active treatment, and 1 on placebo) is considered sufficient for an exploratory analysis.

Additional subjects may be entered 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 subjects entered may exceed 36, but will not exceed 48 subjects entered.

MD: It is planned to include a total of 24 subjects in this part. The planned sample size is not based on a power calculation. The size of 12 subjects each in theses dose groups for PM subjects (9 on active treatment, and 3 on placebo) is commonly used in multiple dose trials of the present type and is in general considered as sufficient for the exploratory evaluation of multiple dose safety and pharmacokinetics.

DDI: It is planned to enter 14 subjects in the DDI part, accounting for up to 2 dropouts or non PK evaluable subjects. The planned sample size is not based on a power calculation but is considered sufficient to achieve the aims of this exploratory trial.

With this sample size, the following precision in estimating the ratio of geometric means (T/R) can be expected with 95% tolerance probability. Precision is defined as the ratio of upper CI limit to the relative BA estimate. Note that the precision is independent of the actual ratio of geometric means. The observed coefficient of variation (gCV%) after a single oral dose of BI 1323495 (10 mg) in trial 1405-0001 was roughly 66.3% for C_{max} and 104% for AUC. The reported variability originated from a parallel group estimates total variability. However, for this trial as a crossover trial intra-individual gCV is needed. Assuming the correlation between two responses of the same subjects ρ=0.5 for C_{max} and ρ=0.75 for AUC, we can estimate the intraindividual variability out of the total variability. The calculated values would be roughly 44.7% for C_{max} and 44.9% for AUC.

In the group of subjects treated with 10 mg BI 1323495 in trial 1405-0001, all individuals were UGT2B17 extensive metabolizer, thus the calculated intra-individual variability is representative for the subjects of this study.

The observed intra-individual coefficient of variation (gCV%) after a single oral dose of BI 1323495 (10 mg) after fed and fasted conditions in trial 1405-0007 was roughly 35% for C_{max} and 19% for $AUC_{0\text{-}tz}$.

For various assumptions for the gCV, Table 7.7: 1 provides an overview of the achievable precision for estimating the ratio of geometric means (test/reference). For illustrative

purposes, the expected 90% confidence intervals are displayed for different values of the ratios T/R of geometric means.

Table 7.7: 1 Precision that can be expected with 95% probability and illustrative two-sided 90% confidence intervals around the ratios of geometric means (T/R) for different gCVs in a two-period, fixed sequence trial (N=12)

gCV [%]	Precision upper CL / relative BA estimate	Ratio [%]*	Lower CL [%]	Upper CL [%]
30.0	1.334	100	74.99	133.36
30.0	1.334	150	112.48	200.03
30.0	1.334	200	149.98	266.71
40.0	1.459	100	68.54	145.90
40.0	1.459	150	102.81	218.85
40.0	1.459	200	137.08	291.80
50.0	1.589	100	62.93	158.91
50.0	1.589	150	94.39	238.37
50.0	1.589	200	125.85	317.83

*Ratio of geometric means (test/reference) for a PK endpoint is defined by $\exp(\mu_T)/\exp(\mu_R)$.

The expected 90% confidence interval limits in the table were derived by

$$\text{CI limit}_{\text{upper, lower}} = \exp(\ln(\theta) \pm \omega),$$

with θ being the ratio (T/R) on original scale and ω the distance from the estimate θ to either confidence interval limit on the log-scale, which was obtained from the achievable precision on the original scale.

The calculation was performed as described by Julious (R11-5230) using R Version 3.4.2.

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, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles.

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

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects 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.

The terms and conditions of the insurance coverage are made available to the investigator and the subjects, and are stored in the ISF.

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

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

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

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

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

8.2. DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

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

8.3. RECORDS

CRFs for individual subjects 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 subject 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 CRF must be consistent with the source data or the discrepancies must be explained.

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

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

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

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

8.3.2. Direct access to source data and documents

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

8.3.3. Storage period of records

Trial site:
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 SUBJECT PRIVACY

Individual subject 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 subject's personal physician or to other appropriate medical personnel responsible for the subject'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, storage and future use of biological samples and clinical data, in particular

- Sample and data usage have to be in accordance with the informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external storage 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 ICF.

8.6. TRIAL MILESTONES

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

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

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

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

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

When the trial is completed, the investigator should inform the head of the trial site in writing of the completion of the trial, and the head of the trial site should promptly inform the IRB and sponsor in writing of the completion.

8.7. ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

The trial will be conducted at [redacted] under the supervision of the Principal Investigator.

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

BI has appointed a CTL, responsible for coordinating all required trial activities, in order to

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of CTM, CRA 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.

Analyses of BI 1323495 and itraconazole concentrations and biomarker in plasma will be performed at the [redacted]

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 or contract research organization 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

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1. GLOBAL AMENDMENT 1

Date of amendment		23 SEP 2020
BI Trial number		1405-0003
BI Investigational Medicinal Product(s)		BI 1323495
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses of BI 1323495 versus placebo in healthy male Japanese subjects genotyped as poor and extensive metabolizers of UGT2B17 (single-blind, randomised, placebo-controlled [within dose groups] trial), including an investigation of drug-drug interaction with itraconazole in healthy male subjects genotyped as poor metabolizers of UGT2B17 (an open-label, two-period, fixed sequence trial)

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		Section 1.4.2
Description of change		Amended description of risk mitigation action for COVID-19.
Rationale for change		Updated to accept other than PCR testing.
Section to be changed		Section 4.1.2
Description of change		Adding more explanation about rationale of selecting 10 mg for DDI part.
Rationale for change		Based on comment from authority.
Section to be changed		Section 5.6.1

Description of change		Adding more explanation about handling of genotyping samples and result.
Rationale for change		Based on comment from authority.

11.2. GLOBAL AMENDMENT 2

Date of amendment		25 FEB 2020
BI Trial number		1405-0003
BI Investigational Medicinal Product(s)		BI 1323495
Title of protocol		Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1323495 versus placebo in healthy male Japanese subjects genotyped as poor and extensive metabolizers of UGT2B17 (single-blind, randomised, placebo-controlled [within dose groups] trial), including an investigation of drug-drug interaction with itraconazole in healthy male subjects genotyped as poor metabolizers of UGT2B17 (an open-label, two-period, fixed sequence trial)
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		Flowchart
Description of change		Minor correction due to typo to SRD part and DDI part. New Flowchart for additional MD part added.
Rationale for change		Same as above
Section to be changed		Section 1.2.1
Description of change		Updated safety and PK information from ongoing studies (1405-0002).
Rationale for change		Updated to latest information.

Section to be changed		Section 1.3
Description of change		Added rationale for additional MD part
Rationale for change		Same ad above
Section to be changed		Section 2
Description of change		Added endpoints for MD part including PD. Primary end points is same with SRD part. Secondary endpoints newly added for MD part. PK related further objectives added for MD part. PD endpoints in MD part added.
Rationale for change		Same as above
Section to be changed		Section 3.1, 3.2 and 3.3
Description of change		Added explanation of additional MD part study design.
Rationale for change		Same as above
Section to be changed		Section 4.1
Description of change		Added dose selection rationale and drug assignment for additional MD part
Rationale for change		Same as above
Section to be changed		Section 4.2
Description of change		Added explanation about restriction for additional MD part.
Rationale for change		Same as above
Section to be changed		Section 5.4.1
Description of change		Added explanation about detailed process of additional PD analysis for additional MD part.
Rationale for change		Same as above
Section to be changed		Section 6.2.2
Description of change		Added explanation about visit schedule of treatment period in additional MD part.
Rationale for change		Same as above
Section to be changed		Section 7
Description of change		Added explanation planned analysis and determination of sample size for additional MD part.

Rationale for change		Same as above

APPROVAL / SIGNATURE PAGE

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Title: Safety, tolerability and pharmacokinetics of single rising oral doses and multiple oral doses of BI 1323495 versus placebo in healthy male Japanese subjects genotyped as poor and extensive metabolizers of UGT2B17 (single-blind, randomised, placebo-controlled [within dose groups] trial), including an investigation of drug-drug interaction with itraconazole in healthy male subjects genotyped as ...

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Pharmacokineticist	[redacted]	11 Mar 2021 12:38 CET
Approval-Clinical Trial Leader		11 Mar 2021 12:39 CET
Approval-Therapeutic Area [redacted]		11 Mar 2021 14:05 CET
Author-Trial Statistician		11 Mar 2021 19:00 CET
Approval-Team Member Medicine		12 Mar 2021 09:32 CET
Verification-Paper Signature Completion		12 Mar 2021 09:35 CET

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