Clinical Trial Protocol

	Document Number: c09105854-05
EudraCT No.:	2016-001235-12
BI Trial No.:	BI 1368.2
BI Investigational Product:	BI 655130
Title:	Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising intravenous doses of BI 655130 (double-blind, partially randomised within dose groups, placebo-controlled parallel group design) and one single intravenous dose of BI 655130 (single-blind, partially randomised, placebo-controlled) in healthy male subjects
Clinical Phase:	I
Trial Clinical Monitor:	[redacted] Phone: [redacted] Fax: [redacted]
Principal Investigator:	[redacted] Phone: [redacted] Fax: [redacted]
Status:	Final Protocol (Revised Protocol (based on global amendment 3))
Version and Date:	Version: 4.0 Date: 02 Aug 2017

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 655130			
Protocol date: 23 Jun 2016	**Trial number:** 1368.2		**Revision date:** 02 Aug 2017

Title of trial:	Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising intravenous doses of BI 655130 (double-blind, partially randomised within dose groups, placebo-controlled parallel group design) and one single intravenous dose of BI 655130 (single-blind, partially randomised, placebo-controlled) in healthy male subjects
Principal Investigator:	[redacted]
Trial site:	[redacted]
Clinical phase:	I
Objectives:	To investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple rising intravenous doses of BI 655130
Methodology:	Multiple rising dose: double-blind, randomised, placebo-controlled within dose groups Single dose: single blind, partially randomised, placebo controlled
No. of subjects:	
total entered:	40
each treatment:	8 per dose group* (6 on active drug and 2 on placebo) * Additional subjects may be entered to allow for testing of intermediate 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 be increased, but will not exceed 48 subjects.
Diagnosis:	Not applicable
Main criteria for inclusion:	Healthy male subjects, age of 18 to 50 years, body mass index (BMI) of 18.5 to 29.9 kg/m²
Test product:	BI 655130 (20 mg/mL) solution for infusion
dose:	Multiple dose: 3 mg/kg, 6 mg/kg, 10 mg/kg and 20 mg/kg body weight Single dose: 20 mg/kg body weight

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mode of admin.:	Intravenous as 30 min infusion for 3 mg/kg and 6 mg/kg multiple dose Intravenous as 60 min infusion for 10 mg/kg multiple dose and 20 mg/kg single dose Intravenous as 90 min infusion for 20 mg/kg multiple dose
Comparator product:	Matching placebo for BI 655130 solution for infusion
dose:	Not applicable
mode of admin.:	Intravenous as 30 min, 60 min or 90 min infusion
Duration of treatment:	**Dose group 3 mg, 6 mg,10 mg/kg and 20 mg/kg** Single intravenous dose once a week (within 4 weeks single intravenous doses on Day 1, Day 8, Day 15, and Day 22) **Dose group 20 mg/kg** Single intravenous dose
Criteria for pharmacokinetics:	Secondary endpoints: **Single dose (20 mg/kg b.w.)** C_{max}, $AUC_{0-\infty}$ **Multiple dose (3 mg/kg, 6 mg/kg, 10 mg/kg, 20 mg/kgb.w.)** After the first dose: $AUC_{\tau,1}$ and C_{max} After the last dose: $AUC_{\tau,ss}$ and $C_{max,ss}$ [redacted]
Criteria for pharmacodynamics:	[redacted]

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Name of finished product: Not applicable			
Name of active ingredient: BI 655130			
Protocol date: 23 Jun 2016	**Trial number:** 1368.2		**Revision date:** 02 Aug 2017
Criteria for safety:	Primary endpoint to assess safety and tolerability of BI 655130 is the number [N (%)] of subjects with drug-related adverse events (AEs). Further criteria of interest: Physical examination, vital signs (BP, PR, body temperature, continuous cardio-monitoring), 12-lead ECG, laboratory tests (including haematology, clinical chemistry, urinalysis, coagulation parameters, cytokines and ADA), adverse events and local tolerability.		
Statistical methods:	Descriptive statistics will be calculated for all endpoints. Dose proportionality of BI 655130 will be explored using a regression model. A 95% confidence interval (CI) for the slope will be computed. Linearity index will be estimated using a linear model providing a two-sided 95% CI. Attainment of steady state will be analysed by a repeated measures linear model for trough concentrations of BI 655130 with dose as an additional covariate if permissible.		

FLOW CHART

Flow Chart (3 mg and 6 mg/kg b.w. dose group, multiple dose)

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma} [4]	PD_{blood} [4]	Plasma ADA [9]	Safety laboratory/ Urinalysis [3]	Body Temperature	Body Weight	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies [12]
1	-28 to -3			screening[1]				X			X		X	
2	-2	-48:00	8:00	ambulatory visit				X[14]		X				
	-1	-12:00	20:00	admission to trial site				X[11]						X
	1	-2:00	6:00		X[2]	X[2]	X[2]	X[2, 10]	X[2]		X[2, 5]		X[2]	X[2]
		0:00	8:00	drug administration start of infusion								▲		
		0:15	8:15	▏								▏	X	X
		0:30	8:30	▼ end of infusion[15]	X	X			X		X[5]	▏	X	X
		1:00	9:00									▏	X	
		1:30	9:30									▏	X	
		2:00	10:00	light breakfast[7]					X		X[5]	▼	X	
		3:00	11:00										X	
		4:00	12:00	Lunch[7]				X[10]					X	X[6]
		6:00	14:00						X		X[5]		X	
		8:00	16:00	snack (voluntary)[7]									X	
		10:00	18:00	Dinner[7]										
		12:00	20:00		X				X		X[5]		X	X[6]
	2	24:00	8:00	Breakfast[7]	X			X[10]	X		X[5]		X	X[6]
		28:00	12:00	Lunch[7]										
		32:00	16:00	snack (voluntary)[7]					X				X	
		34:00	18:00	Dinner[7]										X
	3	48:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])							X[5]		X	X
	4	72:00	8:00	ambulatory visit				X						X
	5	96:00	8:00	ambulatory visit	X									X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma}[4]	PD_{blood}[4]	Plasma ADA[9]	Laboratory/ Urinalysis[3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
2	7	156:00	20:00	admission to trial site				X[11]					X
	8	166:00	6:00		X[2]	X[2]	X[2]	X[2, 10]	X[2]	X[2, 5]		X[2]	X[2]
		168:00	8:00	drug administration start of infusion							▲		
		168:15	8:15	▼								X	X
		168:30	8:30	end of infusion[15]	X	X			X	X[5]		X	X
		169:00	9:00									X	
		169:30	9:30									X	
		170:00	10:00	light breakfast[7]					X	X[5]	▼	X	
		171:00	11:00									X	
		172:00	12:00	Lunch[7]				X[10]				X	X[6]
		174:00	14:00						X	X[5]		X	
		176:00	16:00	snack (voluntary)[7]								X	
		178:00	18:00	Dinner[7]									
		180:00	20:00		X				X	X[5]		X	X[6]
	9	192:00	8:00	Breakfast[7]	X			X[10]	X	X[5]		X	X[6]
		196:00	12:00	Lunch[7]									
		200:00	16:00	snack (voluntary)[7]					X			X	
		202:00	18:00	Dinner[7]									X
	10	216:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])						X[5]		X	X
	11	240:00	8:00	ambulatory visit				X					X
	12	264:00	8:00	ambulatory visit	X								X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma}[4]	PD_{blood}[4]	Plasma ADA[9]	Laboratory/ Urinalysis[3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
2	14	324:00	20:00	admission to trial site				X[11]					X
	15	334:00	6:00		X[2]	X[2]	X[2]	X[2, 10]	X[2]	X[2, 5]		X[2]	X[2]
		336:00	8:00	drug administration start of infusion							▲		
		336:15	8:15	|							|	X	X
		336:30	8:30	▼ end of infusion[15]	X	X			X	X[5]	|	X	X
		337:00	9:00								|	X	
		337:30	9:30								|	X	
		338:00	10:00	light breakfast[7]					X	X[5]	▼	X	
		339:00	11:00									X	
		340:00	12:00	Lunch[7]				X[10]				X	X[6]
		342:00	14:00						X	X[5]		X	
		344:00	16:00	snack (voluntary)[7]								X	
		346:00	18:00	Dinner[7]									
		348:00	20:00		X				X	X[5]		X	X[6]
	16	360:00	8:00	Breakfast[7]	X			X[10]	X	X[5]		X	X[6]
		364:00	12:00	Lunch[7]									
		368:00	16:00	snack (voluntary)[7]					X			X	
		370:00	18:00	Dinner[7]									X
	17	384:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])						X[5]		X	X
	18	408:00	8:00	ambulatory visit				X					X
	19	432:00	8:00	ambulatory visit	X								X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma}[4]	PD_{blood}[4]	Plasma ADA[9]	Laboratory/ Urinalysis[3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
2	21	492:00	20:00	admission to trial site				X[11]					X
	22	502:00	6:00		X[2]	X[2]	X[2]	X[2, 10]	X[2]	X[2, 5]		X[2]	X[2]
		504:00	8:00	drug administration start of infusion							▲		
		504:15	8:15	▏							▏	X	X
		504:30	8:30	▼ end of infusion[15]	X	X			X	X[5]	▏	X	X
		505:00	9:00								▏	X	
		505:30	9:30								▏	X	
		506:00	10:00	light breakfast[7]					X	X[5]	▼	X	
		507:00	11:00									X	
		508:00	12:00	Lunch[7]				X[10]				X	X[6]
		510:00	14:00						X	X[5]		X	
		512:00	16:00	snack (voluntary)[7]								X	
		514:00	18:00	Dinner[7]									
		516:00	20:00		X				X	X[5]		X	X[6]
	23	528:00	8:00	Breakfast[7]	X			X[10]	X	X[5]		X	X[6]
		532:00	12:00	Lunch[7]									
		536:00	16:00	snack (voluntary)[7]					X			X	
		538:00	18:00	Dinner[7]									X
	24	552:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])						X[5]		X	X
	25	576:00	8:00	ambulatory visit				X					X
	26	600:00	8:00	ambulatory visit	X								X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma}[4]	PD_{blood}[4]	Plasma ADA[9]	Laboratory/ Urinalysis[3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
2	29	672:00	8:00	ambulatory visit	X	X	X						X
	36	840:00	8:00	ambulatory visit	X								X
	43	1008:00	8:00	ambulatory visit	X		X						X
	50	1176:00	8:00	ambulatory visit	X	X							X
	57	1344:00	8:00	ambulatory visit	X		X						
	64	1512:00	8:00	ambulatory visit	X								X
	78	1848:00	8:00	ambulatory visit	X	X	X						X
	92	2184:00	8:00	ambulatory visit	X		X						X
	120 ±3	2856:00	8:00	ambulatory visit	X	X	X						X
	148 ±3	3528:00	8:00	ambulatory visit	X		X						X
3	176 ±3	4200:00	8:00	EOT[13]	X[16]	X	X[16]	X		X		X	X

1. Screening with subject information, informed consent as the first measure, includes physical examination, check of vital signs, ECG, safety laboratory (under fasting conditions), drug screening, demographics (including determination of body height and weight, smoking and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; procedures are to be performed and completed within 3 h prior to drug administration. Within 3 hours prior to the planned dosing, planned time -2:00 will be used.
3. Laboratory tests (safety laboratory) include clinical chemistry, haematology, coagulation and urinalysis; in addition at screening: serology (HBV, HCV, HIV), and drug screening.
4. PK and PD sampling times may be adapted based on information obtained during trial conduct.
5. Triple ECG
6. Local tolerability inclusive.
7. If several actions are indicated at the same time point, the intake of meals will be the last action.
8. Confirmation of fitness includes physical examination.
9. ADAs samples will be taken at baseline, Day 8, Day 15, Day 22, Day 29, Day 43, Day 57, Day 78, Day 92, Day 120, Day 148 and Day 176 (EOT).
10. The cytokines IL1β, IL6, TNF-α and IFNγ will be collected at baseline, 4h and 24h postdose after each of the 4 single infusions. These samples are only to be analyzed in case of specific adverse events occur that are suggestive for a cytokine release.
11. Only drug screening.
12. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
13. EOT (End of trial examination) includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. EOT to be performed not before last PK sampling.
14. Safety laboratory is to be taken within three days prior to study drug administration and can be omitted, if the screening examination is performed between Day -5 to Day -3.
15. First measure after completion of infusion is collection of PK and PD sample
16. In case plasma levels still exceed LOQ additional PK and ADA samples may be collected beyond Day 176

Flow Chart (10 mg/kg b.w. dose group, multiple dose)

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma} [4]	PD_{blood} [4]	Plasma ADA[9]	Safety laboratory/ Urinalysis [3]	Body Temperature	Body Weight	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
1	-28 to -3			screening[1]				X			X		X	
2	-2	-48:00	8:00	ambulatory visit				X[14]		X				
	-1	-12:00	20:00	admission to trial site				X[11]						X
	1	-2:00	6:00		X[2]	X[2]	X[2]	X[2, 10]	X[2]		X[2, 5]		X[2]	X[2]
		0:00	8:00	drug administration start of infusion								▲		
		0:15	8:15	↓								↓	X	X
		0:30	8:30	↓					X			↓	X	X
		1:00	9:00	▼ end of infusion[15]	X	X			X		X[5]	↓	X	X
		1:30	9:30									↓	X	
		2:00	10:00	light breakfast[7]					X		X[5]	▼	X	
		3:00	11:00										X	
		4:00	12:00	Lunch[7]				X[10]					X	X[6]
		6:00	14:00						X		X[5]		X	
		8:00	16:00	snack (voluntary)[7]									X	
		10:00	18:00	Dinner[7]										
		12:00	20:00		X				X		X[5]		X	X[6]
	2	24:00	8:00	Breakfast[7]	X			X[10]	X		X[5]		X	X[6]
		28:00	12:00	Lunch[7]										
		32:00	16:00	snack (voluntary)[7]					X				X	
		34:00	18:00	Dinner[7]										X
	3	48:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])							X[5]		X	X
	4	72:00	8:00	ambulatory visit				X						X
	5	96:00	8:00	ambulatory visit	X									X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma}[4]	PD_{blood}[4]	Plasma ADA[9]	Laboratory/ Urinalysis[3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
2	7	156:00	20:00	admission to trial site				X[11]					X
	8	166:00	6:00		X[2]	X[2]	X[2]	X[2, 10]	X[2]	X[2, 5]		X[2]	X[2]
		168:00	8:00	drug administration start of infusion							▲		
		168:15	8:15	▏							▏	X	X
		168:30	8:30	▏					X		▏	X	X
		169:00	9:00	▼ end of infusion[15]	X	X			X	X[5]	▏	X	X
		169:30	9:30								▏	X	
		170:00	10:00	light breakfast[7]					X	X[5]	▼	X	
		171:00	11:00									X	
		172:00	12:00	Lunch[7]				X[10]				X	X[6]
		174:00	14:00						X	X[5]		X	
		176:00	16:00	snack (voluntary)[7]								X	
		178:00	18:00	Dinner[7]									
		180:00	20:00		X				X	X[5]		X	X[6]
	9	192:00	8:00	Breakfast[7]	X			X[10]	X	X[5]		X	X[6]
		196:00	12:00	Lunch[7]									
		200:00	16:00	snack (voluntary)[7]					X			X	
		202:00	18:00	Dinner[7]									X
	10	216:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])						X[5]		X	X
	11	240:00	8:00	ambulatory visit				X					X
	12	264:00	8:00	ambulatory visit	X								X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma}[4]	PD_{blood}[4]	Plasma ADA[9]	Laboratory/ Urinalysis[3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
2	14	324:00	20:00	admission to trial site				X[11]					X
	15	334:00	6:00		X[2]	X[2]	X[2]	X[2, 10]	X[2]	X[2, 5]		X[2]	X[2]
		336:00	8:00	drug administration start of infusion							▲		
		336:15	8:15	|							|	X	X
		336:30	8:30	|					X		|	X	X
		337:00	9:00	▼ end of infusion[15]	X	X			X	X[5]	|	X	X
		337:30	9:30								|	X	
		338:00	10:00	light breakfast[7]					X	X[5]	▼	X	
		339:00	11:00									X	
		340:00	12:00	Lunch[7]				X[10]				X	X[6]
		342:00	14:00						X	X[5]		X	
		344:00	16:00	snack (voluntary)[7]								X	
		346:00	18:00	Dinner[7]									
		348:00	20:00		X				X	X[5]		X	X[6]
	16	360:00	8:00	Breakfast[7]	X			X[10]	X	X[5]		X	X[6]
		364:00	12:00	Lunch[7]									
		368:00	16:00	snack (voluntary)[7]					X			X	
		370:00	18:00	Dinner[7]									X
	17	384:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])						X[5]		X	X
	18	408:00	8:00	ambulatory visit				X					X
	19	432:00	8:00	ambulatory visit	X								X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma}[4]	PD_{blood}[4]	Plasma ADA[9]	Laboratory/ Urinalysis[3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
2	21	492:00	20:00	admission to trial site				X[11]					X
	22	502:00	6:00		X[2]	X[2]	X[2]	X[2, 10]	X[2]	X[2, 5]		X[2]	X[2]
		504:00	8:00	drug administration start of infusion							▲		
		504:15	8:15	|							|	X	X
		504:30	8:30	|					X		|	X	X
		505:00	9:00	▼ end of infusion[15]	X	X			X	X[5]	|	X	X
		505:30	9:30								|	X	
		506:00	10:00	light breakfast[7]					X	X[5]	▼	X	
		507:00	11:00									X	
		508:00	12:00	Lunch[7]				X[10]				X	X[6]
		510:00	14:00						X	X[5]		X	
		512:00	16:00	snack (voluntary)[7]								X	
		514:00	18:00	Dinner[7]									
		516:00	20:00		X				X	X[5]		X	X[6]
	23	528:00	8:00	Breakfast[7]	X			X[10]	X	X[5]		X	X[6]
		532:00	12:00	Lunch[7]									
		536:00	16:00	snack (voluntary)[7]					X			X	
		538:00	18:00	Dinner[7]									X
	24	552:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])						X[5]		X	X
	25	576:00	8:00	ambulatory visit				X					X
	26	600:00	8:00	ambulatory visit	X								X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma} [4]	PD_{blood} [4]	Plasma ADA [9]	Laboratory/ Urinalysis [3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies [12]
2	29	672	8:00	ambulatory visit	X	X	X						X
	36	840:00	8:00	ambulatory visit	X								X
	43	1008:00	8:00	ambulatory visit	X		X						X
	50	1176:00	8:00	ambulatory visit	X	X							X
	57	1344:00	8:00	ambulatory visit	X		X						
	64	1512:00	8:00	ambulatory visit	X								X
	78	1848:00	8:00	ambulatory visit	X	X	X						X
	92	2184:00	8:00	ambulatory visit	X		X						X
	120 ±3	2856:00	8:00	ambulatory visit	X	X	X						X
	148 ±3	3528:00	8:00	ambulatory visit	X		X						X
3	176 ±3	4200:00	8:00	EOT [13]	X [16]	X	X [16]	X		X		X	X

1. Screening with subject information, informed consent as the first measure, includes physical examination, check of vital signs, ECG, safety laboratory (under fasting conditions), drug screening, demographics (including determination of body height and weight, smoking and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; procedures are to be performed and completed within 3 h prior to drug administration. Within 3 hours prior to the planned dosing, planned time -2:00 will be used.
3. Laboratory tests (safety laboratory) include clinical chemistry, haematology, coagulation and urinalysis; in addition at screening: serology (HBV, HCV, HIV), and drug screening.
4. PK and PD sampling times may be adapted based on information obtained during trial conduct.
5. Triple ECG
6. Local tolerability inclusive.
7. If several actions are indicated at the same time point, the intake of meals will be the last action.
8. Confirmation of fitness includes physical examination.
9. ADAs samples will be taken at baseline, Day 8, Day 15, Day 22, Day 29, Day 43, Day 57, Day 78, Day 92, Day 120, Day 148 and Day 176 (EOT).
10. The cytokines IL1β, IL6, TNF-α and IFNγ will be collected at baseline, 4h and 24h postdose after each of the 4 single infusions. These samples are only to be analyzed in case of specific adverse events occur that are suggestive for a cytokine release.
11. Only drug screening.
12. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
13. EOT (End of trial examination) includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. EOT to be performed not before last PK sampling.
14. Safety laboratory is to be taken within three days prior to study drug administration and can be omitted, if the screening examination is performed between Day -5 to Day -3.
15. First measure after completion of infusion collection of PK and PD sample
16. In case plasma levels still exceed LOQ additional PK and ADA samples may be collected beyond Day 176

Flow Chart (20 mg/kg b.w. dose group, multiple dose)

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma} [4]	PD_{blood} [4]	Plasma ADA[9]	Safety laboratory/ Urinalysis [3]	Body Temperature	Body Weight	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
1	-28 to -3			screening[1]				X			X		X	
2	-2	-48:00	8:00	ambulatory visit				X[14]		X				
	-1	-12:00	20:00	admission to trial site				X[11]						X
	1	-2:00	6:00		X[2]	X[2]	X[2]	X[2, 10]	X[2]		X[2, 5]		X[2]	X[2]
		0:00	8:00	drug administration start of infusion								▲		
		0:15	8:15	▼								▼	X	X
		0:30	8:30						X				X	X
		1:00	9:00										X	X
		1:30	9:30	end of infusion[15]	X	X			X		X[5]		X	X
		2:00	10:00						X		X[5]		X	
		3:00	11:00	light breakfast[7]									X	
		4:00	12:00	Lunch[7]				X[10]					X	X[6]
		6:00	14:00						X		X[5]		X	
		8:00	16:00	snack (voluntary)[7]									X	
		10:00	18:00	Dinner[7]										
		12:00	20:00		X				X		X[5]		X	X[6]
	2	24:00	8:00	Breakfast[7]	X			X[10]	X		X[5]		X	X[6]
		28:00	12:00	Lunch[7]										
		32:00	16:00	snack (voluntary)[7]					X				X	
		34:00	18:00	Dinner[7]										X
	3	48:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])							X[5]		X	X
	4	72:00	8:00	ambulatory visit				X						X
	5	96:00	8:00	ambulatory visit	X									X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma}[4]	PD_{blood}[4]	Plasma ADA[9]	Laboratory/ Urinalysis[3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
2	7	156:00	20:00	admission to trial site				X[11]					X
	8	166:00	6:00		X[2]	X[2]	X[2]	X[2, 10]	X[2]	X[2, 5]		X[2]	X[2]
		168:00	8:00	drug administration start of infusion							▲		
		168:15	8:15	▏							▏	X	X
		168:30	8:30	▏					X		▏	X	X
		169:00	9:00	▼							▏	X	X
		169:30	9:30	end of infusion[15]	X	X			X	X[5]	▏	X	X
		170:00	10:00						X	X[5]	▼	X	
		171:00	11:00	light breakfast[7]								X	
		172:00	12:00	Lunch[7]				X[10]				X	X[6]
		174:00	14:00						X	X[5]		X	
		176:00	16:00	snack (voluntary)[7]								X	
		178:00	18:00	Dinner[7]									
		180:00	20:00		X				X	X[5]		X	X[6]
	9	192:00	8:00	Breakfast[7]	X			X[10]	X	X[5]		X	X[6]
		196:00	12:00	Lunch[7]									
		200:00	16:00	snack (voluntary)[7]					X			X	
		202:00	18:00	Dinner[7]									X
	10	216:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])						X[5]		X	X
	11	240:00	8:00	ambulatory visit				X					X
	12	264:00	8:00	ambulatory visit	X								X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma}[4]	PD_{blood}[4]	Plasma ADA[9]	Laboratory/ Urinalysis[3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
2	14	324:00	20:00	admission to trial site				X[11]					X
	15	334:00	6:00		X[2]	X[2]	X[2]	X[2, 10]	X[2]	X[2, 5]		X[2]	X[2]
		336:00	8:00	drug administration start of infusion							▲		
		336:15	8:15	▏							▏	X	X
		336:30	8:30	▏					X		▏	X	X
		337:00	9:00	▼							▏	X	X
		337:30	9:30	end of infusion[15]	X	X			X	X[5]	▏	X	X
		338:00	10:00						X	X[5]	▼	X	
		339:00	11:00	light breakfast[7]								X	
		340:00	12:00	Lunch[7]				X[10]				X	X[6]
		342:00	14:00						X	X[5]		X	
		344:00	16:00	snack (voluntary)[7]								X	
		346:00	18:00	Dinner[7]									
		348:00	20:00		X				X	X[5]		X	X[6]
	16	360:00	8:00	Breakfast[7]	X			X[10]	X	X[5]		X	X[6]
		364:00	12:00	Lunch[7]									
		368:00	16:00	snack (voluntary)[7]					X			X	
		370:00	18:00	Dinner[7]									X
	17	384:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])						X[5]		X	X
	18	408:00	8:00	ambulatory visit				X					X
	19	432:00	8:00	ambulatory visit	X								X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma}[4]	PD_{blood}[4]	Plasma ADA[9]	Laboratory/ Urinalysis[3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
2	21	492:00	20:00	admission to trial site				X[11]					X
	22	502:00	6:00		X[2]	X[2]	X[2]	X[2, 10]	X[2]	X[2, 5]		X[2]	X[2]
		504:00	8:00	drug administration start of infusion							▲		
		504:15	8:15	▏							▏	X	X
		504:30	8:30	▏					X		▏	X	X
		505:00	9:00	▼							▏	X	X
		505:30	9:30	end of infusion[15]	X	X			X	X[5]	▏	X	X
		506:00	10:00						X	X[5]	▼	X	
		507:00	11:00	light breakfast[7]								X	
		508:00	12:00	Lunch[7]				X[10]				X	X[6]
		510:00	14:00						X	X[5]		X	
		512:00	16:00	snack (voluntary)[7]								X	
		514:00	18:00	Dinner[7]									
		516:00	20:00		X				X	X[5]		X	X[6]
	23	528:00	8:00	Breakfast[7]	X			X[10]	X	X[5]		X	X[6]
		532:00	12:00	Lunch[7]									
		536:00	16:00	snack (voluntary)[7]					X			X	
		538:00	18:00	Dinner[7]									X
	24	552:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])						X[5]		X	X
	25	576:00	8:00	ambulatory visit				X					X
	26	600:00	8:00	ambulatory visit	X								X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma}[4]	PD_{blood}[4]	Plasma ADA[9]	Laboratory/ Urinalysis[3]	Body Temperature	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies[12]
2	29	672	8:00	ambulatory visit	X	X	X						X
	36	840:00	8:00	ambulatory visit	X								X
	43	1008:00	8:00	ambulatory visit	X		X						X
	50	1176:00	8:00	ambulatory visit	X	X							X
	57	1344:00	8:00	ambulatory visit	X		X						
	64	1512:00	8:00	ambulatory visit	X								X
	78	1848:00	8:00	ambulatory visit	X	X	X						X
	92	2184:00	8:00	ambulatory visit	X		X						X
	120 ±3	2856:00	8:00	ambulatory visit	X	X	X						X
	148 ±3	3528:00	8:00	ambulatory visit	X		X						X
3	176 ±3	4200:00	8:00	EOT[13]	X[16]	X	X[16]	X		X		X	X

1. Screening with subject information, informed consent as the first measure, includes physical examination, check of vital signs, ECG, safety laboratory (under fasting conditions), drug screening, demographics (including determination of body height and weight, smoking and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; procedures are to be performed and completed within 3 h prior to drug administration. Within 3 hours prior to the planned dosing, planned time -2:00 will be used.
3. Laboratory tests (safety laboratory) include clinical chemistry, haematology, coagulation and urinalysis; in addition at screening: serology (HBV, HCV, HIV), and drug screening.
4. PK and PD sampling times may be adapted based on information obtained during trial conduct.
5. Triple ECG
6. Local tolerability inclusive.
7. If several actions are indicated at the same time point, the intake of meals will be the last action.
8. Confirmation of fitness includes physical examination.
9. ADAs samples will be taken at baseline, Day 8, Day 15, Day 22, Day 29, Day 43, Day 57, Day 78, Day 92, Day 120, Day 148 and Day 176 (EOT).
10. At baseline of each dosing day, cytokines (IL1β, IL6, TNF-α and IFNγ) samples will be collected together with safety lab. Additional cytokines samples IL1β, IL6, TNF-α and IFNγ will be collected at 4h and 24h post-dose after each of the 4 single infusions. Cytokines samples are only to be analysed from an individual subject in case of specific adverse events in this subject that are suggestive for a cytokine release. At 4h and 24h post-dose no safety lab needs to be taken.
11. Only drug screening.
12. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
13. EOT (End of trial examination) includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. EOT to be performed not before last PK sampling.
14. Safety laboratory is to be taken within three days prior to study drug administration and can be omitted, if the screening examination is performed between Day -5 to Day -3.
15. First measure after completion of infusion collection of PK and PD sample
16. In case plasma levels still exceed LOQ additional PK and ADA samples may be collected beyond Day 176

Flow Chart (20 mg/kg b.w. dose group, single dose)

dose group, single	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{plasma} [4]	PD_{blood} [4]	Plasma ADA [9]	Laboratory/ Urinalysis [3]	Body Temperature	Body Weight	12-lead ECG	ECG monitoring	Vital signs (BP, PR)	Query on adverse events, concomitant therapies [12]
1	-28 to -3			screening[1]				X			X		X	
2	-2	-48:00	8:00	ambulatory visit				X[14]		X				
	-1	-12:00	20:00	admission to trial site				X[11]						X
	1	-2:00	6:30		X[2]	X[2]	X[2]	X[2,10]	X[2]		X[2,5]		X[2]	X[2,6]
		0:00	8:00	drug administration start of infusion								▲		
		0:30	8:30	|					X		X[5]	|	X	X[6]
		1:00	9:00	▼ end of infusion[15]	X	X			X		X[5]	|	X	X[6]
		1:30	9:30								X[5]	|	X	
		2:00	10:00	light breakfast[7]	X				X		X[5]	▼	X	
		2:30	10:30											
		3:00	11:00		X						X[5]		X	
		4:00	12:00	Lunch[7]	X			X[10]			X[5]		X	X[6]
		6:00	14:00						X		X[5]		X	
		8:00	16:00	snack (voluntary)[7]	X						X[5]		X	
		10:00	18:00	Dinner[7]										
		12:00	20:00		X				X		X[5]		X	X[6]
	2	24:00	8:00	Breakfast[7]	X			X[10]	X		X[5]		X	X[6]
		28:00	12:00	Lunch[7]										
		32:00	16:00	snack (voluntary)[7]					X		X[5]		X	
		34:00	18:00	Dinner[7]										X
	3	48:00	8:00	Breakfast[7] discharge from trial site (confirmation of fitness[8])	X						X[5]		X	X
	4	72:00	8:00	ambulatory visit	X			X						X
	5	96:00	8:00	ambulatory visit	X									X
	8	168:00	8:00	ambulatory visit breakfast (voluntary)	X	X	X	X			X		X	X
	15	336:00	8:00	ambulatory visit	X									X
	22	504:00	8:00	ambulatory visit breakfast (voluntary)	X	X		X			X		X	X
	29	672:00	8:00	ambulatory visit breakfast (voluntary)	X	X	X	X			X		X	X

Visit	Day	Time relative to first drug administration (planned time [h:min]	Approx. time (actual time) [h:min]	Event and comment	PK_{blood} [4]	PD_{blood} [4]	Plasma ADA [9]	Laboratory/ Urinalysis [3]	Body Temperature	12-lead ECG	ECG monitoring	vital signs (BP, PR)	Query on adverse events, concomitant therapies [12]
2	36	840:00	8:00	ambulatory visit	X								X
	43	1008:00	8:00	ambulatory visit	X	X	X						X
	57	1344:00	8:00	ambulatory visit	X		X						X
	71	1680:00	8:00	ambulatory visit	X	X	X						X
	92 ±2	2184:00	8:00	ambulatory visit	X		X						X
	120 ±3	2856:00	8:00	ambulatory visit	X	X	X						X
	148 ±3	3528:00	8:00	ambulatory visit	X		X						
3	176 ±3	4200:00	8:00	EOT [13]	X [16]	X	X [16]	X		X		X	X

1. Screening with subject information, informed consent as the first measure, includes physical examination, check of vital signs, ECG, safety laboratory (under fasting conditions), drug screening, demographics (including determination of body height and weight, smoking and alcohol history), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria.
2. The time is approximate; procedures are to be performed and completed within 3 h prior to drug administration. Within 3 hours prior to the planned dosing, planned time -2:00 will be used.
3. Laboratory tests (safety laboratory) include clinical chemistry, haematology, coagulation and urinalysis; in addition at screening: serology (HBV, HCV, HIV), and drug screening.
4. PK and PD sampling times may be adapted based on information obtained during trial conduct.
5. From Day 1 (predose) to Day 3 (discharge from the unit) ECGs will be recorded as triple ECG.
6. Local tolerability inclusive.
7. If several actions are indicated at the same time point, the intake of meals will be the last action.
8. Confirmation of fitness includes physical examination.
9. ADAs samples will be taken at baseline, Day 8, Day 29, Day 43, Day 57, Day 71, Day 92, Day 120, Day 148 and Day 176 (EOT) after BI 655130 administration.
10. The cytokines IL1β, IL6, TNF-α and IFNγ will be collected at baseline, 4h and 24h postdose. At 4 h there will be only an assessment of cytokines, while at baseline and 24 h cytokines will be determined together with safety lab. The cytokine samples only to be analyzed in case of specific adverse events suggestive for cytokine release.

11 Only drug screening.

12. AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.
13. EOT (End of trial examination) includes physical examination, body weight, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies. EOT to be performed not before last PK and ADA sampling.
14. Safety laboratory is to be taken within three days prior to study drug administration and can be omitted, if the screening examination is performed between Day -5 to Day -3.
15. First measure after completion of infusion collection of PK and PD sample
16. In case plasma levels still exceed LOQ additional PK samples may be collected beyond Day 176.

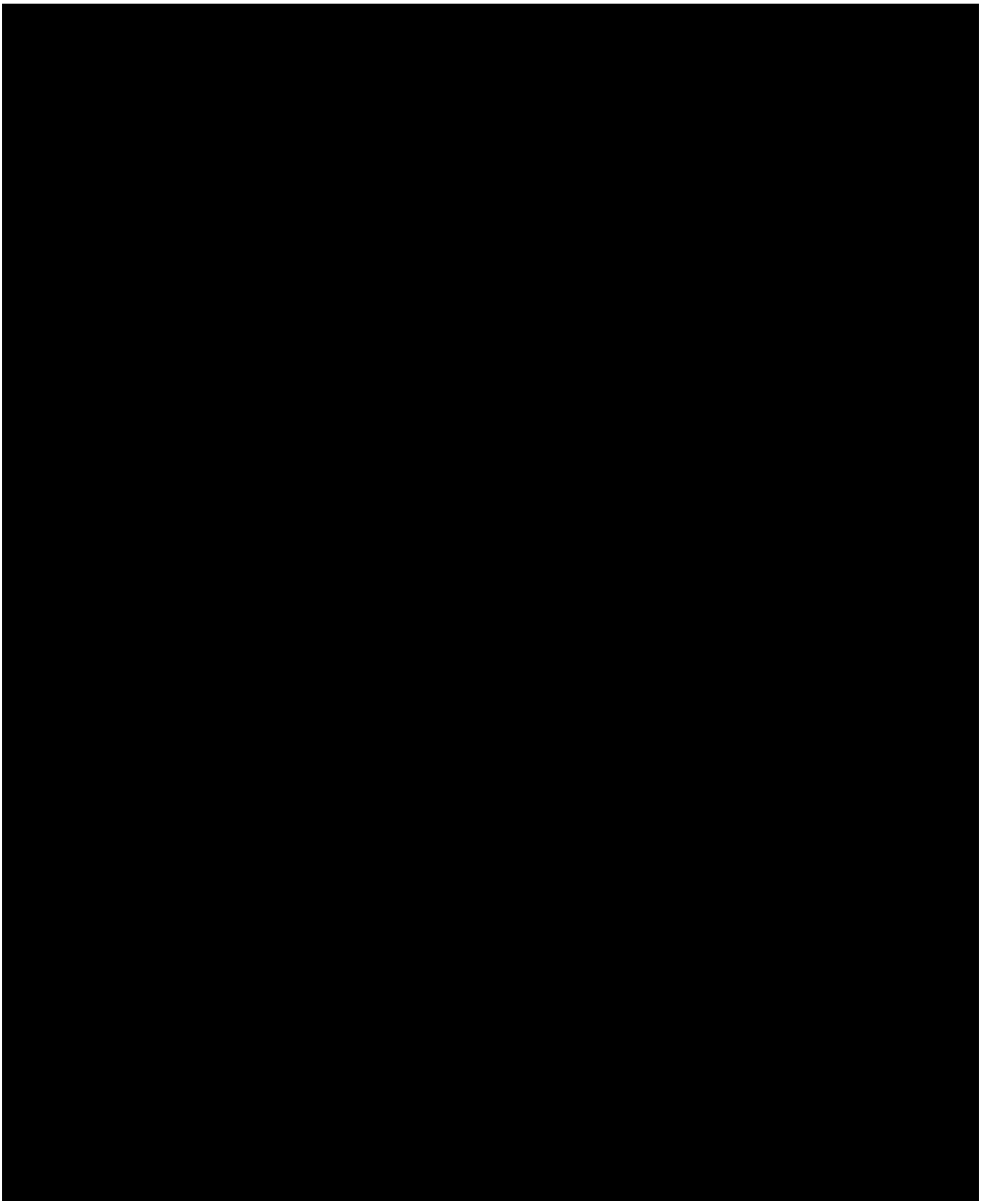
TABLE OF CONTENTS

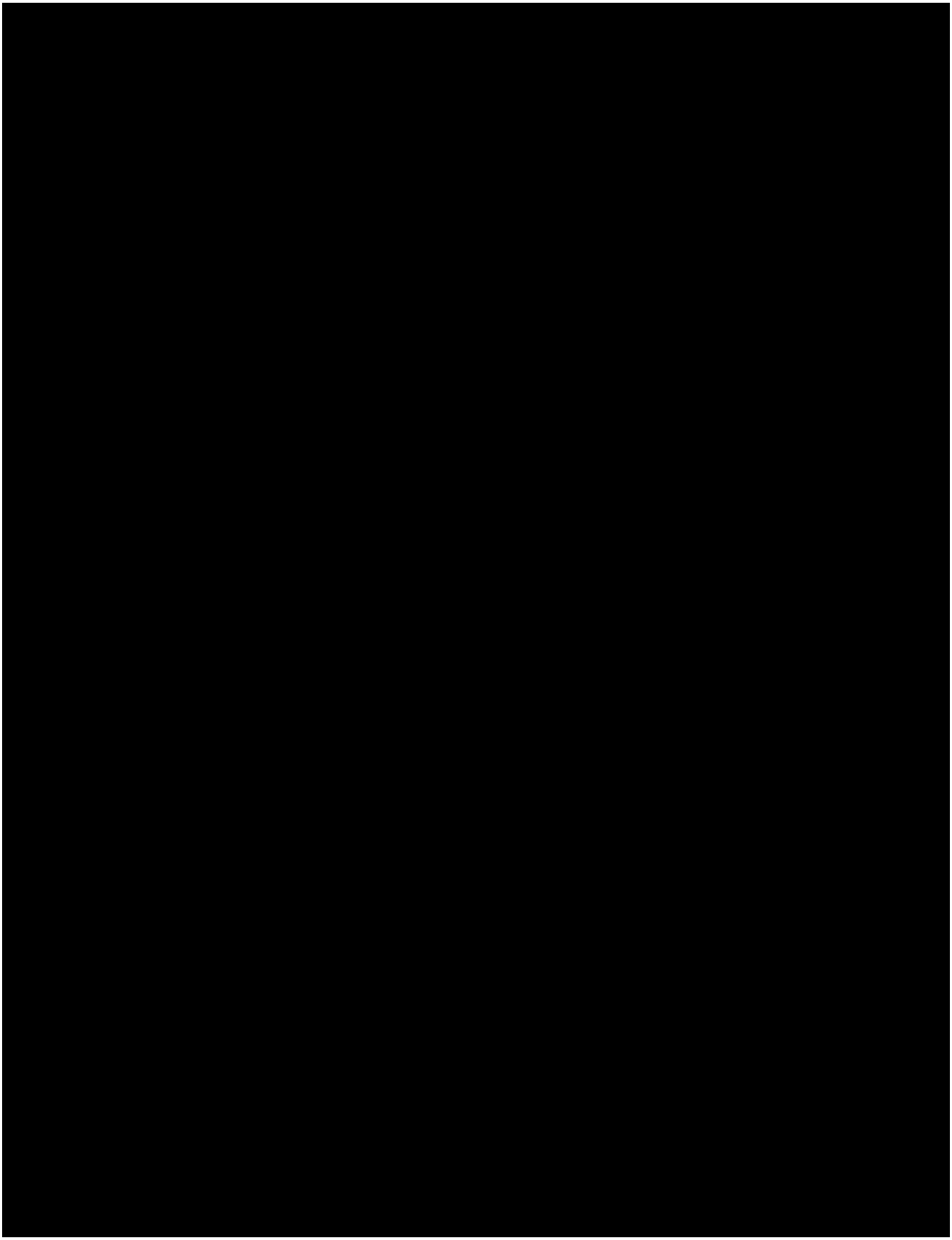
ABBREVIATIONS

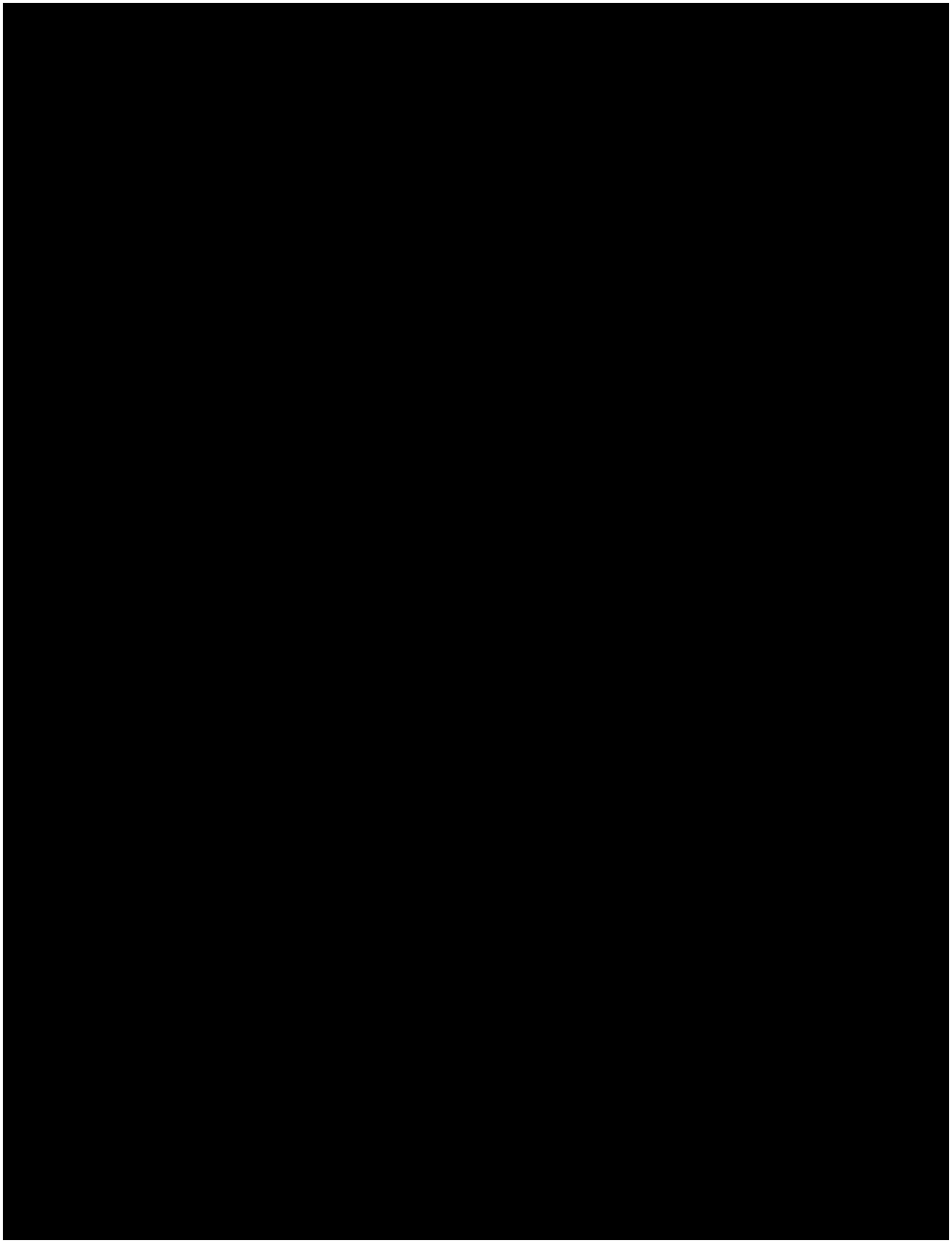
ADA	Anti-drug antibodies
ADCC	Antibody -dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine amino transferase
ANCOVA	Analysis of Covariance
API	Active Pharmaceutical Ingredient
AST	Aspartate amino transferase
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t_1 to t_2
AUCτ,ss	Area under the concentration-time curve of the analyte in plasma at steady state over a uniform dosing interval τ
AUCτ,1	Area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose
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
%AUCtz-∞	the percentage of AUC0-∞ obtained by extrapolation
β	Slope parameter associated with the power model used to evaluate dose proportionality
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
BW	Body weight
CA	Competent authority
[redacted]	[redacted]
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CL	Total clearance of the analyte in plasma after intravenous administration
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
C_{min}	Minimum measured concentration of the analyte in plasma
CPU	Clinical Pharmacology Unit
CRF	Case report form
CRO	Clinical Research Organization
CTP	Clinical trial protocol
CTR	Clinical trial report
DILI	Drug induced liver impairment
DP	Drug product

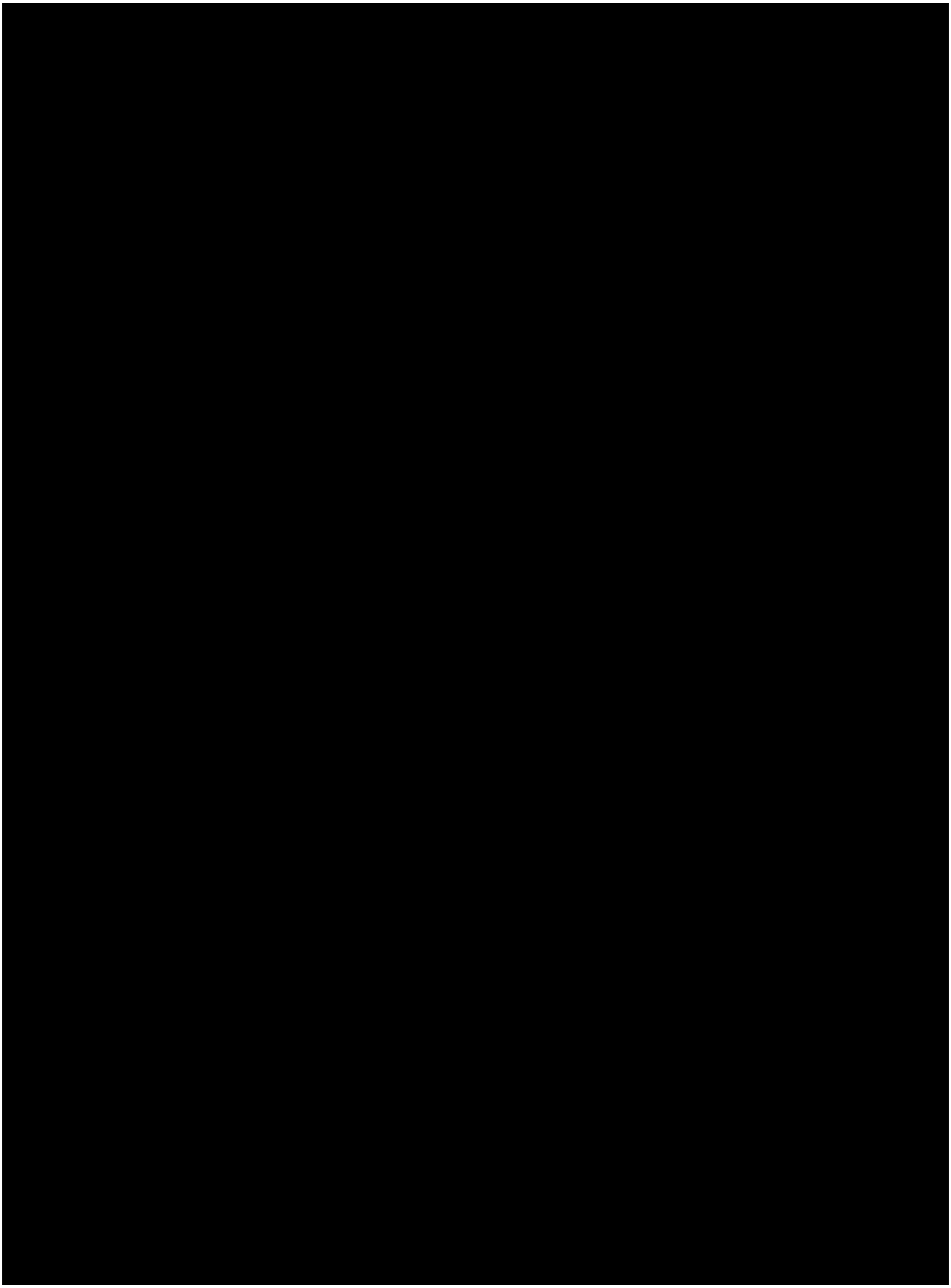
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EMEA	European Agency for the Evaluation of Medicinal Products
EOT	End of trial
FDA	Food and Drug Administration
FIH	First in Human
FIM	First in Man
GCP	Good Clinical Practice
gMean	Geometric mean
GMP	Good Manufacturing Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IB	Investigator's brochure
[redacted]	[redacted]
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
[redacted]	[redacted]
IPV	Important protocol violations
IRB	Institutional Review Board
ISF	Investigator site file
λ_z	Terminal rate constant in plasma
kDA	Kilodalton
LI	linearity index
LLOQ	Lower Limit of Quantification
LOQ	Limit of Quantification
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters Mercury
MMP	Matrix metalloproteinase
MRD	Multiple Rising Dose
MRT	Mean residence time of the analyte in the body after intravenous bolus administration
N	Number
NC	Not calculated
NF-kB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NOA	Not analysed
NOAEL	No observed adverse effect level
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PBMC	peripheral blood mononuclear cells
PD	Pharmacodynamic(s)
Ph.Eur	Pharmacopoea Europaea
PK	Pharmacokinetic(s)

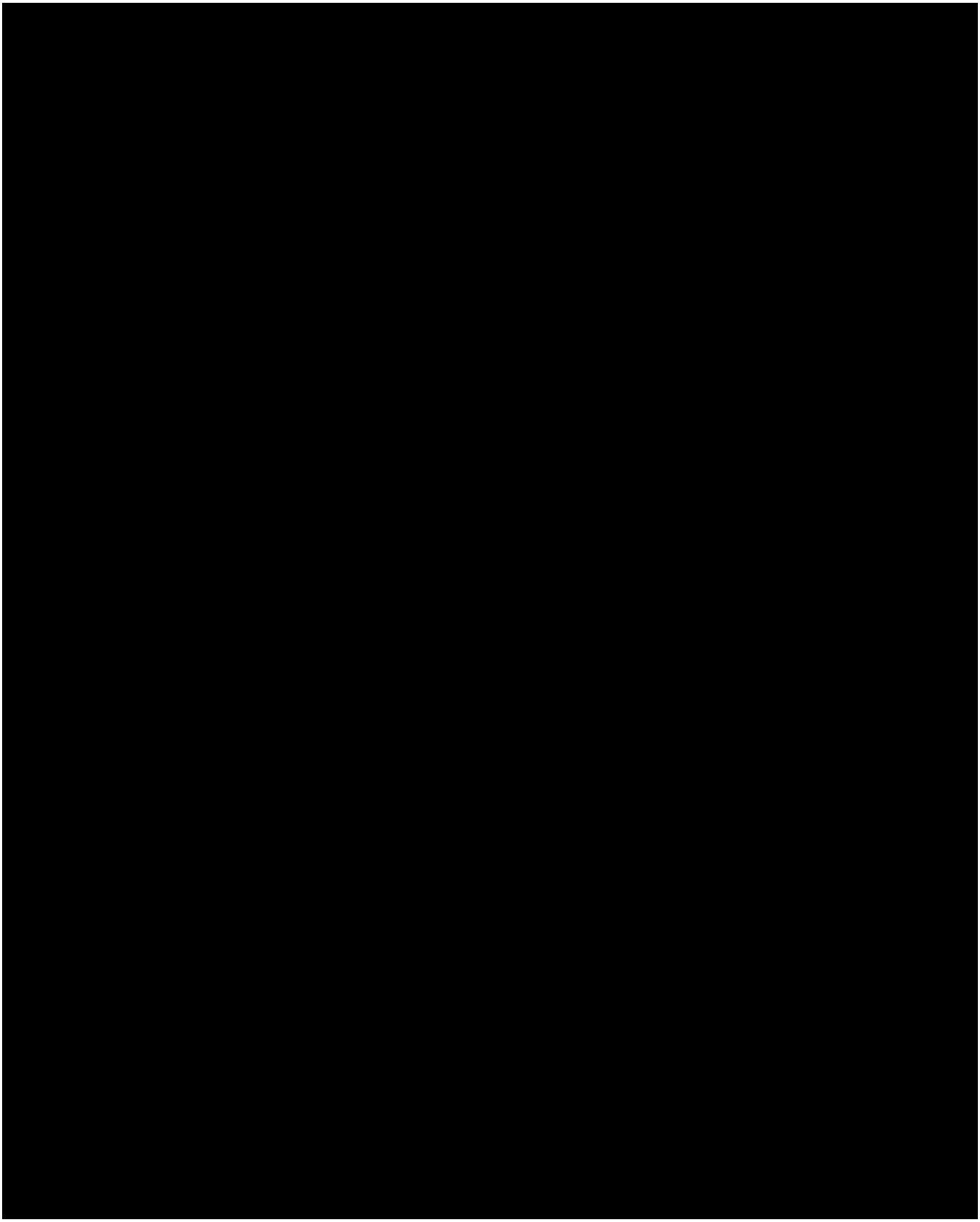
PKSD	Pharmacokinetic set for descriptive analysis
PKSI	Pharmacokinetic set for inferential analysis
pM	Picomolar
PR	Pulse rate
PTF	Peak-trough fluctuation
PTM	Planned Time
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
RA,AUC	accumulation ratio based on AUC0-τ
RA,Cmax	accumulation ratio based on Cmax,ss
REP	Residual effect period
RPM	Report Planning Meeting
RR	Riva Rocci
SAE	Serious adverse event
SCR	Screening
SOP	Standard Operating Procedure
SRD	Single-rising dose
ss	(at) steady state
[redacted]	[redacted]
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from dosing to maximum measured concentration of the analyte in plasma
TDMAP	Trial Data Management and Analysis Plan
TGF	Transforming growth factor
TMDD	Target mediated drug disposition
TMF	Trial Master File
TSAP	Trial statistical analysis plan
UC	Ulcerative colitis
ULN	Upper limit of normal
USP	United States Pharmacopeia
Vss	Volume of distribution at steady state after single intravenous administration
V_z	Volume of distribution during the terminal phase after intravascular administration
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration
WBC	White Blood Cells
WFI	Water for Injection

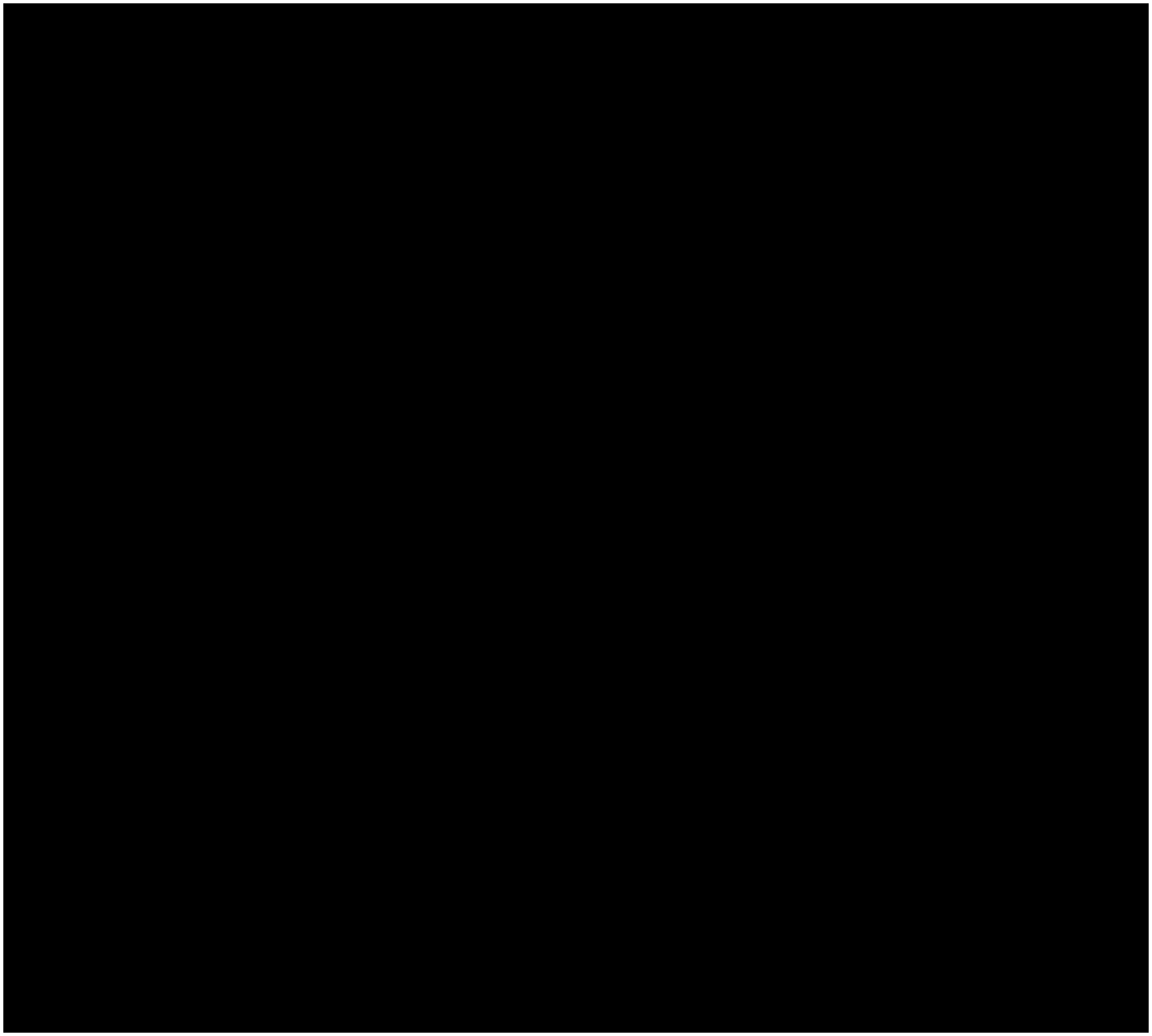


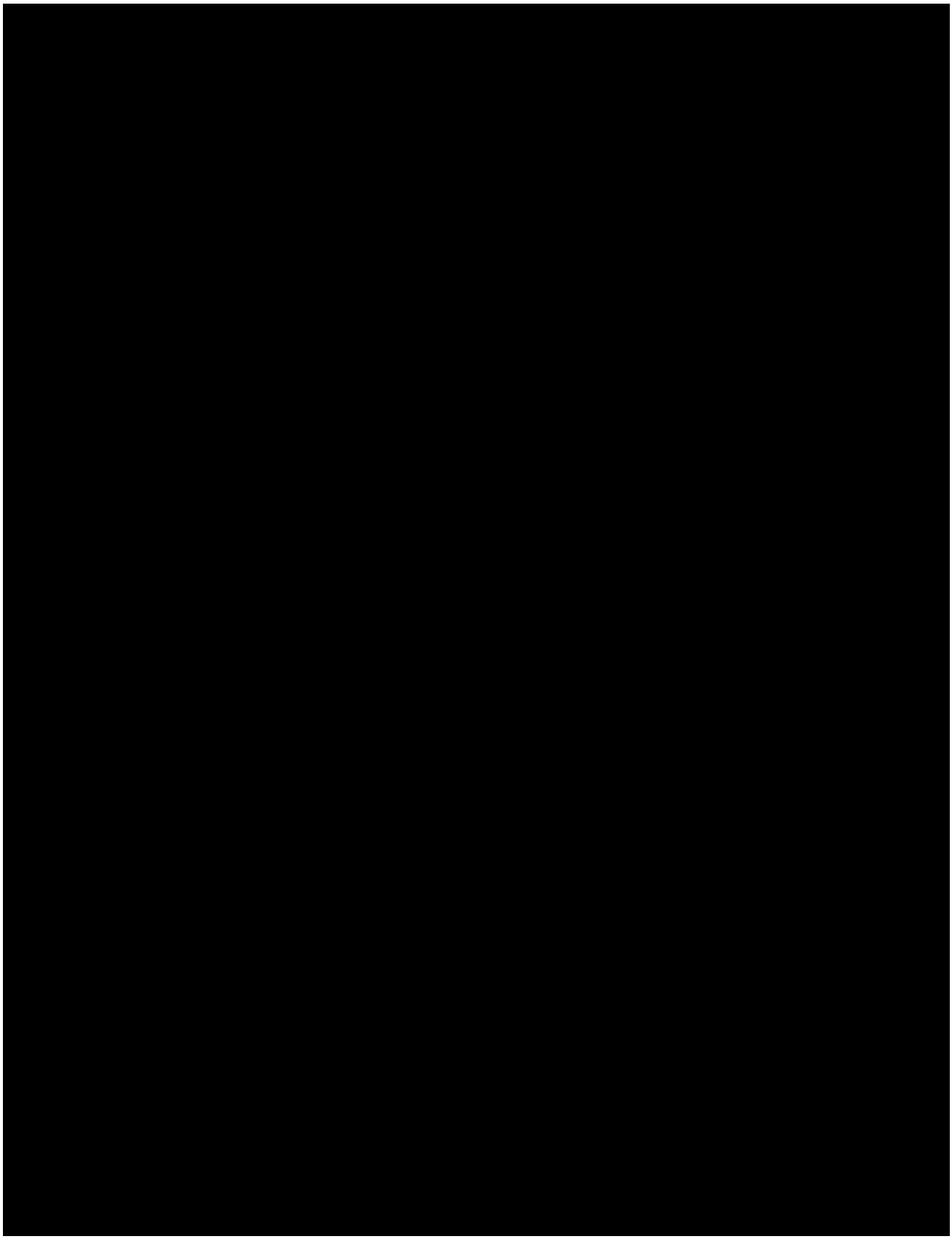




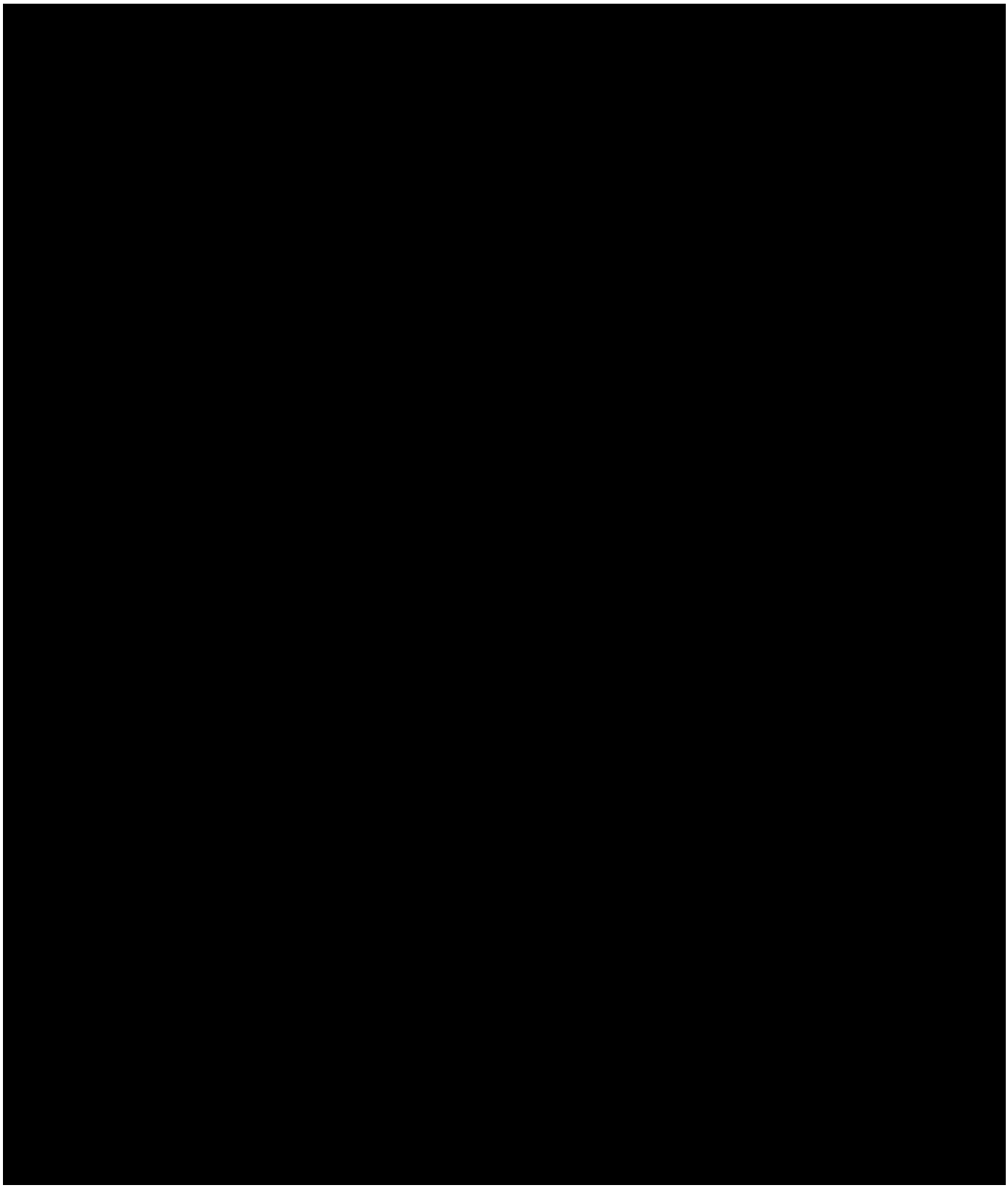








2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT



[redacted]

2.2 TRIAL OBJECTIVES

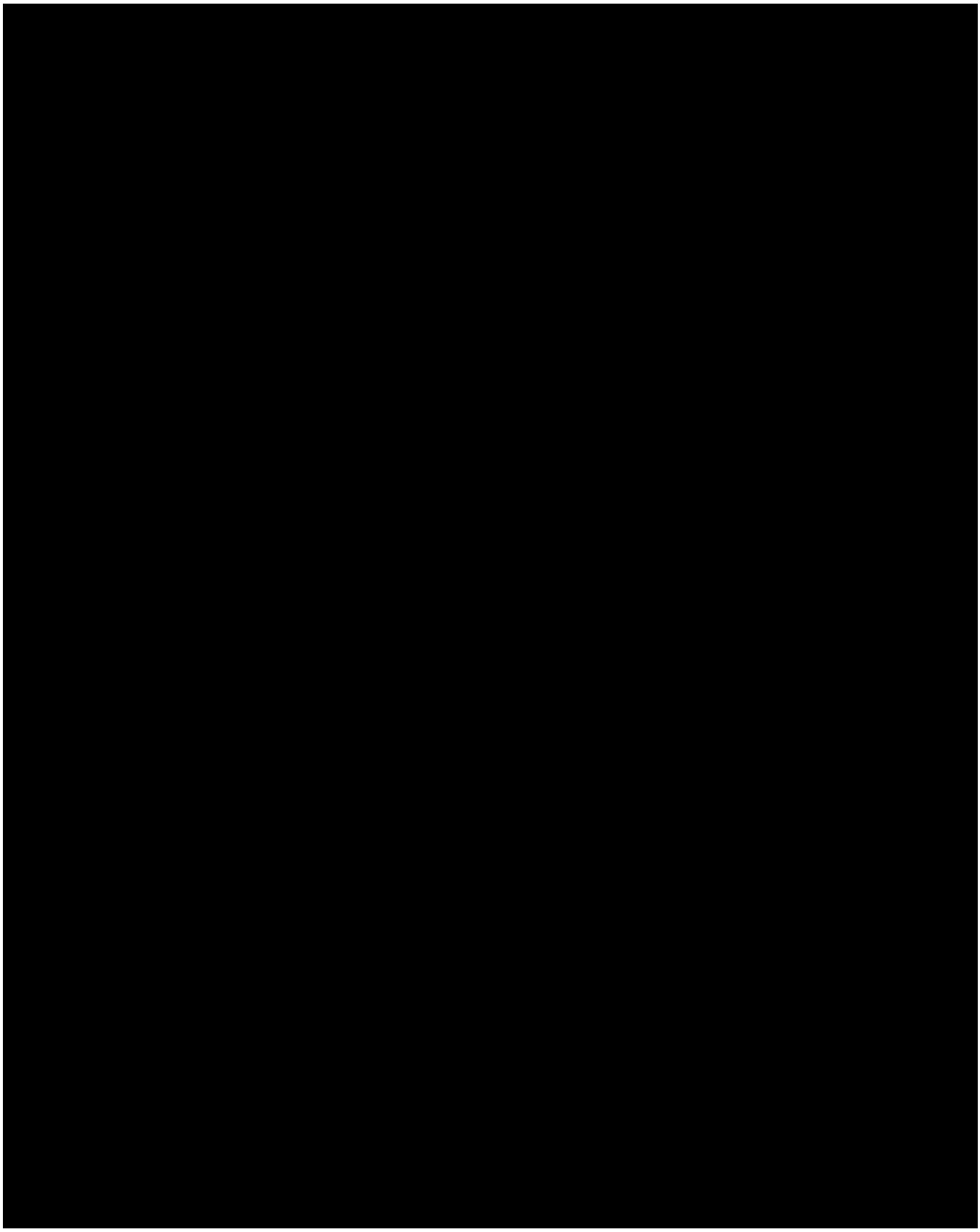
The primary objective of this trial is to investigate the safety and tolerability of BI 655130 in healthy male subjects following IV administration of multiple rising doses of 3 mg/kg, 6 mg/kg and 10 mg/kg b.w.. The study will also explore safety and tolerability following a single IV administration of 20 mg/kg b.w.. In case previous doses were shown to be safe and well tolerated multiple doses of 20 mg/kg may be studied as well to provide a further safety window to potential therapeutic doses in patients.

Secondary objectives are the exploration of the pharmacokinetics of BI 655130 after single and multiple IV administration.

A further objective is the exploration of pharmacodynamics and the evaluation of additional pharmacokinetic parameters beyond those already covered in secondary objectives.

A description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in Section 5.

[redacted]



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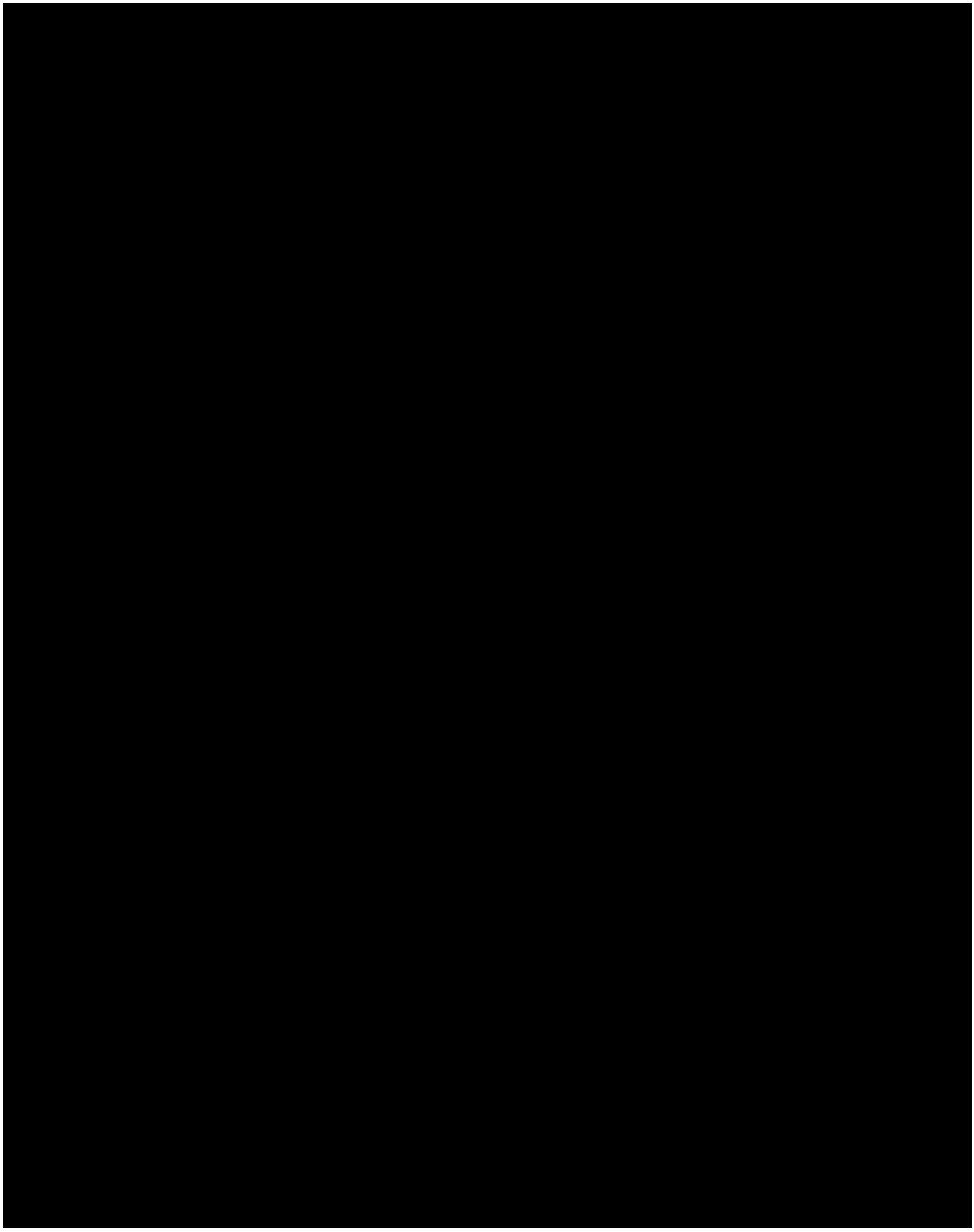


3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The multiple-rising dose part of the trial is designed as double-blind, randomised, and placebo-controlled within parallel dose group. The placebo-controlled single dose part will be conducted single-blind and partially randomised.

A total of 40 healthy male subjects is planned to participate in the trial, according to 5 sequential groups comprising 8 subjects per group. However, additional subjects may be entered to allow testing of additional intermediate doses based 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 40, but will not exceed 48 subjects. Such changes may be implemented via non-substantial CTP Amendments.

Within each dose group, 6 subjects will receive the active drug and 2 will receive placebo. Only one dose is tested within each dose group. Each dose group of the MRD part up to 20 mg/kg b.w. (within 4 weeks single intravenous doses on Day 1, Day 8, Day 15, and Day 22) will consist of 2 cohorts (in each cohort 3 on active and one on placebo) which will be treated subsequently for safety reasons. Dose group 4 (single dose of 20 mg/kg of BI 655130 or placebo) will consist of 3 cohorts (see section 2.3).

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

Table 3.1: 1 Dose groups

Dose Group	1	2	3	4	5
Dose regimen	MRD	MRD	MRD	SD	MRD
Dose (mg/kg b.w.)	3	6	10	20	20
Number of subjects	8	8	8	8	8
Subjects receiving placebo	2	2	2	2	2
Subjects receiving active drug	6	6	6	6	6

The dose groups will be investigated consecutively in ascending order of doses, maintaining a time interval of at least 14 days between the last drug administration in the previous dose group and the first drug administration of the subsequent dose group. The decision to proceed to the next dose group will be based upon the safety and tolerability data of the preceding dose groups. The next dose will only be given if, in the opinion of the investigator, no safety concerns arose in the preceding dose group (i.e. no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to Section 3.3.4.2).

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) or the sponsor of the study, e.g. because 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) and the trial clinical monitor (or an authorised deputy). In addition, at least 6 evaluable subjects per dose level are required to decide about dose escalation to the next higher dose level.

The minimum data set for review consists of the following data:

- AEs in the current and preceding dose groups (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 and continuous ECG monitoring in the current and preceding dose groups.
- Vital signs in the current and preceding dose groups
- Clinical laboratory tests in the current and preceding dose groups
- Check 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) and the trial clinical monitor (or an authorised deputy) after in-depth analysis of all available safety data, especially SAEs (if occurred), AEs and out-of-range laboratory results (if considered clinically significant). Safety Reviews can be conducted face-to-face or by video/telephone conference. The trial clinical monitor is responsible for organization and minutes of the reviews. Minutes will be signed off by the Principal Investigator (or an authorised deputy) and filed in the ISF and TMF.

The investigator (after consultation with the sponsor) is allowed to alter the scheduled dose levels (e.g. add low and/or intermediate dose levels) on the basis of experience gained during the study, provided the planned and approved highest dose is not exceeded. In this case, the total number of subjects in this trial might increase. The investigator and/or the sponsor should stop further dosing in case the safety evaluation leads to concerns that would not allow further dosing.

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

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI) Pharma GmbH & Co. KG, Germany.

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

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and participating trial sites.

The trial will be conducted at the [redacted] under the supervision of the principal investigator ([redacted]).

The trial medication will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany.

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

Safety laboratory tests will be performed by ZNA Klinisch Laboratorium, Lindendreef 1, 2020 Antwerpen, Belgium.

[redacted]

The analyses of BI 655130 concentrations in plasma will be performed at QPS in Newark, DE 19711, USA.

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

The trial is sponsored by Boehringer Ingelheim Pharma GmbH & Co. KG, Germany.

Data management and statistical evaluation will be done by BI according to BI SOPs.

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

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

For multiple-rising dose trials, the design described in Section 3.1 is viewed favourable under the provision not to expose the subjects involved to undue risks since the main study objective is to investigate safety and tolerability of BI 655130.

With the rising dose design, double-blind conditions regarding the subject's treatment (active or placebo) are maintained within each dose group. However, the current dose level will be known to subjects and investigators. The disadvantage of this trial design is a possible observer bias with regard to the dose-depending effects as well as time effects, but it has the virtue of minimizing subject risk by sequentially studying ascending doses. As time-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.

After completion of the second dose group of the multiple-rising dose part the single dose part (20 mg/kg b.w. dose group) will start, which is conducted single-blind and partially randomised. This design was selected because a single infusion of 20 mg/kg b.w. was not tested in the preceding FIH study (section 1.2).

Provided that infusions of BI 655130 were well tolerated in the preceding dose groups the study may continue with dose group 5 (multiple doses of 20 mg/kg).

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety, tolerability and pharmacodynamic effects. Each dose group consists of 8 subjects with 6 on active treatment, and 2 on placebo. The placebo control group includes all subjects of all dose groups treated with placebo. 6 subjects per active treatment group are in general considered as sufficient for the exploratory evaluation of pharmacokinetics.

3.3 SELECTION OF TRIAL POPULATION

It is planned that 40 healthy male subjects will enter the study. The actual number of subjects entered may exceed the total of 40 if additional intermediate doses will be tested (see Section 3.1). Thus, the actual number of subjects entered may be increased, but will not exceed 48 subjects. Subjects will be recruited from the volunteers' pool of the trial site.

Only male subjects will be included into the study because hitherto no data on reproductive toxicology are available.

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

3.3.1 Main diagnosis for study entry

The study will be performed in healthy subjects.

3.3.2 Inclusion criteria

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

1. Healthy male subjects according to the investigator’s assessment, based on a complete medical history including a physical examination, vital signs (BP, PR), 12-lead ECG, and clinical laboratory tests
2. Age of 18 to 50 years (incl.)
3. BMI of 18.5 to 29.9 kg/m^2 (incl.)
4. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation

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) is deviating from normal and judged as clinically relevant by the investigator
2. Repeated measurement of systolic blood pressure outside the range of 90 to 140 mmHg, diastolic blood pressure outside the range of 50 to 90 mmHg, or pulse rate outside the range of 45 to 90 bpm
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance
4. Any evidence of a concomitant disease judged as clinically relevant by the investigator
5. Gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological or hormonal disorders
6. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders
7. History of relevant orthostatic hypotension, fainting spells, or blackouts
8. Chronic or relevant acute infections
9. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
10. Use of drugs within 30 days prior to administration of trial medication if that might reasonably influence the results of the trial (incl. QT/QTc interval prolongation)
11. Participation in another trial where an investigational drug has been administered within 60 days prior to planned administration of trial medication, or current participation in another trial involving administration of investigational drug.
12. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
13. Inability to refrain from smoking on specified trial days
14. Alcohol abuse (consumption of more than 30 g per day)
15. Drug abuse or positive drug screening
16. Blood donation of more than 100 mL within 30 days prior to administration of trial medication or intended donation during the trial
17. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
18. Inability to comply with dietary regimen of trial site
19. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males) or any other relevant ECG finding at screening
20. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
21. Subject is assessed as unsuitable for inclusion by the investigator, for instance, because considered not able to understand and comply with study requirements, or has a condition that would not allow safe participation in the study

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

An individual subject is to be removed from the trial if:

1. The subject withdraws consent for trial treatment or trial participation, without the need to justify the decision
2. The subject needs to take concomitant drugs that interfere with the investigational product or other trial medication
3. The subject is no longer able to participate for other medical reasons (such as surgery, adverse events, or diseases)
4. An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg) or of clinically relevant changes in ECG requiring intervention as well as unexplained liver enzyme elevations at any time during the trial.
5. 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) and/or needs to be followed up according to Appendix 10.1 of this clinical trial protocol and the 'DILI checklist' provided in the ISF.

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

Infusion reactions should also lead to the removal of an individual subject. However, in mild transient cases of infusion reactions (with clinical symptoms such as dizziness, headache, nausea) requiring no treatment the clinical investigator may pause the infusion or continue with a reduced infusion rate as described for other therapeutic proteins [P16-06636]. However, the overall infusion time (including time of discontinuation) must not exceed 45 minutes for 3 mg/kg b.w. and 6 mg/kg b.w. multiple dose and 90 minutes for 10 mg/kg b.w. multiple dose and 20 mg/kg b.w. single dose and 120 minutes for 20 mg/kg b.w. multiple dose.

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

If a subject is removed from or withdraws from the trial prior to first administration of trial medication, the data of this subject will not be entered in the case report form (CRF) or trial database and will not be reported in the clinical trial report (CTR). If a subject is removed from or withdraws from the trial after first administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. In this case, the data will be included in the CRF/trial database and will be reported in the CTR. At the time of discontinuation a complete end of trial examination will be performed if possible and the information will be recorded in the CRFs. If the discontinuation occurs before the end of the REP (see Section 5.2.2.2), the discontinued subject should if possible be questioned for AEs and concomitant therapies at or after the end of the REP in order to ascertain collection of

AEs and concomitant therapies throughout the REP, if not contrary to any consent withdrawal of the subject. These discontinuations will be discussed in the CTR.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the subjects 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 that is considered to be unacceptable.
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP, or the contract with BI by a trial site or investigator, disturbing 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 as soon as at least 2 subjects at one dose level on active drug showed relevant individual QT prolongation, i.e. a QTc increase of greater 60 ms from baseline in connection with absolute QT or QTc greater than 500 ms, which has been confirmed by a repeat ECG recording.

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

3.3.5 Replacement of subjects

In case some subjects do not complete the trial, the trial clinical monitor 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 study subject number, and will be assigned to the same treatment as the subject[redacted] replaces.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The investigational product has been manufactured by BI Pharma GmbH & Co. KG. The BI 655130 molecule is a heterodimer with a molecular weight of approximately 146 kDa.

4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test product are given below:

Substance:	BI 655130
Pharmaceutical formulation:	solution for infusion
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	150 mg/7.5 mL (per 10 mL vial)
Posology:	1-0-0
Route of administration:	IV infusion
Duration of use:	Single dose (20 mg/kg b.w.)
	Multiple dose (4 single IV administrations one week apart)

At the time of use, the IV solution for dosing will be prepared as detailed in the instruction given in Appendix 10.2.

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

Substance:	Placebo (citrate buffer, pH 6.5)
Pharmaceutical formulation:	solution for infusion
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	not applicable
Posology:	1-0-0
Route of administration:	IV infusion
Duration of use:	Single dose (20 mg/kg b.w.)
	Multiple dose (4 single IV administrations one week apart)

4.1.2 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. The subjects willing to participate will be recruited to dose groups according to their temporal availability. As soon as enough subjects have been allocated to 1 of the 11 dose cohorts (2 cohorts per dose group in the MRD part, 3 cohorts in the SRD part), 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. As the study includes healthy subjects from a homogenous population, relevant imbalances between the dose groups are not expected.

The randomisation list with study subject numbers and allocated treatments (SRD part) and the list of subject and medication numbers (MRD part) will be provided to the trial site in advance. The allocation of subjects to study subject numbers will be performed prior to the first administration of trial medication. For this purpose, the subjects will be allocated to a study subject number by drawing lots. Once a subject number has been assigned, it cannot be reassigned to any other subject.

The randomisation procedure is described in Section 7.5.

4.1.3 Selection of doses in the trial

The doses selected for this trial cover the subtherapeutic as well as the estimated therapeutic range and include a safety margin (see Section 1.2).

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. The dose volume for placebo corresponds to the dose volume of the respective dose level. For further details concerning timing see Flow Chart. Start and time of the infusion will be recorded.

Detailed instructions for the dilution of the trial product, the preparation of the infusion solution, the volume to be administered and the infusion rate is provided in Appendix 10.2. In all subjects the infusion solution will be intravenously administered over 30 minutes for dose group 3 mg/kg b.w. multiple dose and 6 mg/kg b.w. multiple dose and over 60 minutes for dose group 10 mg/kg b.w. multiple dose and 20 mg/kg b.w. single dose approximately between 8.00 h and 10.30 h of the respective study day. Multiple doses of 20 mg/kg b.w. will be administered over 90 minutes between 8.00 h and 12.00 h of the respective study day.

In case of safety concerns, e.g. due to infusion reactions, it is in the discretion of the investigator or his/her designee to adapt the infusion scheme, including but not limited slowing down the infusion rate, stopping of the infusion and provided no further safety concern exist restarting at a slower rate. Further based on [redacted] medical judgment he/she will provide medications such as steroids, etc. as needed.

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

The administration of the trial medication on all study days will be done under supervision of the investigating physician or a designee. The so-called four-eye principle (two-person rule)

should be applied for administration of trial medication and – if applicable – its preparation (e.g. reconstitution), if correct dosage cannot be ensured otherwise. For the purpose of drug accountability, the infusion set will be weighed before and after drug administration.

Table 4.1.4: 1 Preparation of infusion solution containing active drug

Dose group	Final dose of BI 655130 [mg/kg]	Concentration of Application solution in infusion bag	Infusion volume [mL]*/ Total dose [mg]
1	3	20 mg/mL	9 mL → 180 mg
2	6	20 mg/mL	18 mL → 360 mg
3	10	20 mg/mL	30 mL → 600 mg
4	20	20 mg/mL	60 mL → 1200 mg
5	20	20 mg/mL	60 mL → 1200 mg

*Infusion volume for a body weight of 60 kg.

Water is allowed except for 1 hour before start of infusion and 1.5 h after end of infusion. On Day 1 for all dose groups and in addition Day 8, Day 15 and Day 22 for subjects receiving repeated doses (dose group 1 to 3) , from 2 hours post-dose, liquid intake is restricted at additional 3000 mL until the morning of Day 2. Standardised meals will be served as outlined in the Flow Chart. Subjects will be kept under close medical surveillance until 48 h following drug administration. Thereafter subjects will be discharged from the CPU and further assessments will be conducted in an ambulatory fashion. For restrictions with regard to diet see also Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

For the MRD part, the trial is designed double-blind with regard to the subjects and the investigators (as well as the research staff at the trial site) in order to eliminate observer or performance bias. This means avoiding systematic differences in assessments regarding the subject's treatment (active or placebo).

The administration of the 20 mg single dose (active or placebo) will be single-blind (to assure single-blind conditions, subjects will not be informed about treatment assignment on the study days, i.e. subjects will not be aware that the second cohort of each dose level will only receive active treatment).

According to the rising dose design, the current dose level will be known to subjects and investigators.

At the trial site, access to the randomisation schedule is restricted to unblinded pharmacists, pharmacy staff members or staff who will reconstitute the drug solution. Access to the codes will be controlled and documented by a signed confidentiality statement, which will be stored

in the TMF. Persons directly involved in the clinical conduct of the trial will not have access to the treatment allocation prior to database lock.

Within the ECG laboratory, the staff involved with interval measurements and assessments will be blinded for the MRD part and unblinded for the SRD part with respect to the treatment and also with regard to the recording date and time as well as the time points of the ECGs. The interval measurements for a given subject will be performed in a random and blinded sequence by a single technician. No more than two different blinded readers will evaluate the ECGs of the study.

In addition, the trial bioanalyst will request the randomisation codes prior to official unblinding to perform the interim / preliminary PK analysis. He or she will confirm in writing that the codes will be treated confidentially.

Regarding the sponsor, the database of this trial will be handled open-label, meaning that the trial functions of the sponsor are unblinded (including clinical monitor, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist as well as dedicated CRO personnel). The objective of the trial is not expected to be affected.

4.1.5.2 Procedures for emergency unblinding

For blinded trials, the investigator will be supplied with a set of sealed envelopes containing the medication codes for each subject according to the randomisation scheme. The envelopes will be kept unopened at the trial site until the end of data collection. An envelope may only be opened in emergency situations when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or to assure safety of trial participants. If the envelope for a subject is opened, the sponsor must be informed immediately. The reason for opening the code break must be documented on the envelope or appropriate CRF page along with the date and the initials of the person who broke the code. At the close-out visit all envelopes are collected.

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The required information according to Annex 13/EU GMP Guideline will be provided on the containers. Smaller boxes within the clinical trial supply containers will be labelled with:

- BI trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration
- Term ‘For Clinical Trial Use’ (domestic language)
- Sponsor name and address
- Storage conditions

- Use-by date
- Batch
- Investigator

The vials are labelled with reduced requirements.

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

Re-supply is planned.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended (labelled) storage conditions. Where 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 immediately contacted.

4.1.8 Drug accountability

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

- Approval of the study protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre
- Approval/notification of the regulatory authority, e.g. competent authority
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated clinical trial protocol or immediately imminent signing of the clinical trial protocol

Only authorised personnel as documented in the form ‘Site Delegation Log’ may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication will be disposed locally by the trial site upon written authorization by the clinical monitor. Receipt, usage and disposal must be documented on the respective forms. Account must be given for any discrepancies.

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

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

investigator / pharmacist / investigational drug storage manager must verify that no remaining supplies are in the investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

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

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 study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

While admitted to the trial site the subjects are restricted from consuming any other foods or drinks than those provided by the staff. Standardised meals will be served at the time points described in the Flow Chart. On Day 1 for all subjects and on Day 8, Day 15 and Day 22 for subjects receiving multiple doses of BI 655130, no food is allowed for at least 10 h before and 1.5 h after administration of the study drug (= end of infusion).

On all days of drug administration, starting from 1 hour before drug administration until 1.5 h after end of infusion liquid intake is not allowed. From breakfast until 24 hours post-dose water intake will be within 1000 to 3000 mL. Total fluid intake on all 24 hours inhouse days is recommended to be at least 1.5 liters and should not exceed 3.5 liters.

Smoking is not allowed during in-house confinement at the trial site. On the ambulatory days it is restricted to not more than 10 cigarettes or 3 cigars or 3 pipes per day

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed during inhouse confinement. Alcoholic beverages are not permitted starting 7 days before the first administration of trial medication until Day 28. From Day 28 onwards, alcohol consumption is restricted to 20 g alcohol per day corresponding to 0.5 L beer or 0.2 L of white wine per day.

Excessive physical activity (such as competitive sport) should be avoided starting 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 study.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured plasma concentrations 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. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

No efficacy endpoints will be evaluated in this trial.

5.1.2 Assessment of efficacy

Not applicable.

5.2 SAFETY

5.2.1 Endpoints of safety

Primary endpoint to assess safety and tolerability of BI 655130 is the number [N (%)] of subjects with drug-related AEs.

Further criteria of interest:

- AEs (including clinically relevant findings from the physical examination)
- Safety laboratory tests
- 12-lead ECG
- Continuous ECG monitoring
- Vital signs (blood pressure, pulse rate)

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

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

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

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity
- is a congenital anomaly/birth defect,

  or
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered ‘Always Serious’

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

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 given above.

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

Adverse events of special interest (AESIs)

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

The following are considered as AESIs in this trial:

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

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

Intensity of AEs

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

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

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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 diminished).

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

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).

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

5.2.2.2 Adverse event collection and reporting

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

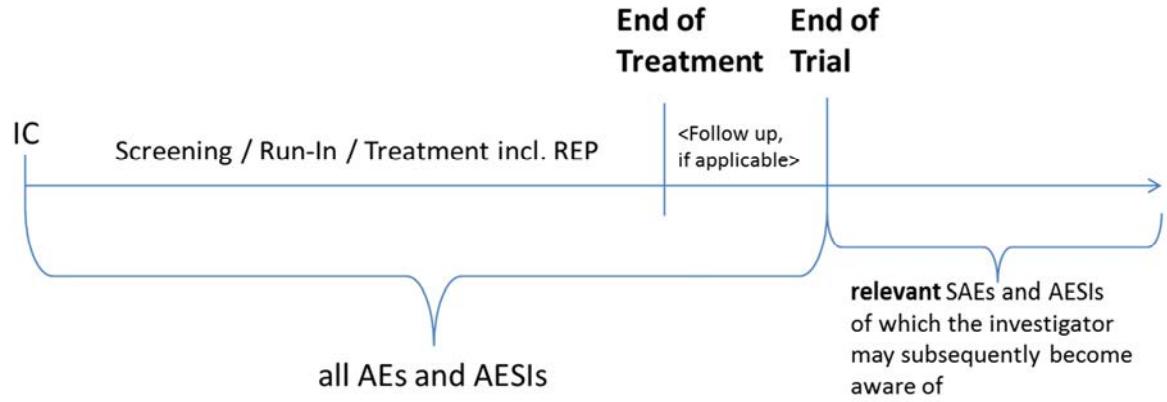
A careful written record of all AEs shall be kept by the investigator in charge of the trial. Records of AEs shall include data on the time of onset, end time, and intensity of the event as well as any treatment or action required for the event and its outcome.

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

- From signing the informed consent onwards through the residual effect period (REP), until individual subject's end of trial:
  - All AEs (serious and non-serious) and all AESIs.
  - The only exception to this rule are AEs (serious and non-serious) and AESIs in Phase I trials in healthy 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 AEs but should only report relevant SAEs and relevant AESIs of which [redacted] may become aware of.



The REP for BI 655130, when measurable drug levels or PD effects are still likely to be present after the last administration, is not known at this early stage of development. Therefore, all AEs reported until the end of trial examination will be considered on treatment; please see Section 7.3.3.

The follow-up period describes the period of time from the last administration of trial medication including the REP until the end of trial examination (last per protocol visit).

AE reporting to sponsor and timelines

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

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

Information required

For each AE, the investigator should provide the information requested on the appropriate CRF pages and the BI SAE form (if applicable). The investigator should determine the causal relationship to the trial medication. The following should also be recorded as an (S)AE in the CRF and on the SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions

- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

All (S)AEs, including those persisting after individual subject's end of trial must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

5.2.3 Assessment of safety laboratory parameters

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

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

Table 5.2.3: 1 Routine laboratory tests (cont).

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

[1] Only at screening

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Drug screening will be performed at screening and at admission to trial site the day prior to each treatment.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Opiates
Infectious serology (blood)[1]	Hepatitis B surface antigen (qualitative) Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antibody (qualitative)

[1] Only at screening

To encourage compliance with alcoholic restrictions, a breath alcohol test (Dräger Alcotest® 6510 and Alcotest® 5510, Belgium) will be performed at screening and at start of the inhouse period (Day -1), and may be repeated at any time during the study at the discretion of an investigator or designate. The results will not be included in the CTR.

In case of a potential systemic allergic reaction blood samples for determination of serum tryptase will be collected 0.5 h, 2 h, 6 h and 24 h after onset of the event.

The laboratory tests listed in Tables 5.2.3: 1 and 5.2.3: 2 will be performed at ZNA Klinisch Laboratorium, Antwerpen, with the exception of the drug screening tests. These tests will be performed at the trial site using “Alere Triage TOX Drug Screen”. Laboratory data will be transmitted electronically from the laboratory to the trial site.

The cytokines IL1β, IL6, TNF-α and IFNγ will be collected at baseline, 4h and 24h postdose after each infusion (for all subjects on Day 1, for subjects receiving multiple doses also on Day 8/9, Day 14/15 and Day 22/23. The cytokine samples will be only analyzed in case of specific adverse events suggestive for cytokine release.

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (MAC 5500, GE Healthcare) at the time points given in the Flow Chart.

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

Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

Triple ECGs (recorded within 180 sec) will be recorded as the baseline before any drug administration part up to 48 h after dosing. At all other time points single ECGs will be recorded.

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

ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation). For time points with triple ECGs, all three single ECGs will be repeated. For the repeats due to quality reasons, only the repeated ECG recordings will be analyzed by the central ECG lab, whereas the initially recorded ECGs will be discarded.

Additional (unscheduled) ECGs may be collected by the investigator for safety reasons. These ECGs are assigned to the prior scheduled time point. Unscheduled ECGs will not be included into the statistical analysis of interval lengths.

For the inclusion or exclusion (see Section 3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcB values generated by the ECG machines or their manual corrections by the investigators will be used. In doubtful cases, ECGs may be sent upfront for centralised evaluation (see below). In this case, these centrally measured results would overrule any other results obtained.

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.

In addition, a centralised evaluation of all 12-lead ECGs recorded from baseline up to 48 h after each dosing will be performed by an independent ECG laboratory. For this analysis, RR and QTall intervals will be determined semi-automatically, whereas PR and QRS intervals are determined by a validated GE 12-SL-algorithm or equivalent by the ECG core lab. Other parameters (e.g. cardiac axis) are determined by a validated GE 12-SL-algorithm or equivalent but do not undergo semi-automatic evaluation. For each QT interval, the RR interval preceding the QT will be measured to calculate the respective frequency corrected QTc intervals 'QTcF' according to Fridericia's formula (QTcF = QT / RR1/3) and 'QTcB' according to Bazett's formula (QTcB = QT / RR1/2). The QTcF correction will be used for evaluation and reporting. Abnormalities detected during centralised ECG evaluation will not necessarily qualify as AE. All interval measurements in one subject will be performed on the same lead. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. The lead actually used will be reported in the CTR.

Within the ECG laboratory, the staff involved with ECG interval measurements and assessments will be blinded with regard to treatment, date and time as well as time points of the ECG measurements. The interval measurements for a given subject will be performed in random sequence by a single technician. No more than two different blinded readers will evaluate all ECGs of the study. For quality assurance and control of the measurements, all ECGs of a subject will be subsequently reviewed by the ECG technician supervisor or his/her designee with respect to the overall variance of the measured intervals, in order to detect accidentally switching of leads and/or false subject assignments of the ECGs. After the quality control the fiducial point markings will be reviewed by the cardiologist assigned to the study.

Assessed ECGs will comply with the ICH E14 guidance document and supplements [R05-2311], [R13-0801], [R13-4095] as well as the FDA requirements for annotated digital ECGs [R09-4830].

5.2.4.2 Continuous ECG monitoring and oxygen monitoring

Cardiac rhythm (including heart rate) will be monitored by means of continuous 2-lead ECG recording for at least 15 min before (for baseline assessment) and 2 h following start of infusion using the Dräger Telemetry monitoring system, Infinity M300. Oxygen saturation will be monitored by pulse oximetry using either Type NT1 handheld pulse oximeter from Newtech or Oxytrue A from Bluepoint Medical.

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Systolic and diastolic blood pressures (BP) as well as pulse rate (PR) or heart rate (heart rate is considered to be equal to pulse rate in healthy volunteers) will be measured by a blood pressure monitor (Welch Allyn 530TP and 530TO devices) 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 on the same arm if possible.

5.2.5.2 Medical examinations

At the screening visit, the medical examination will include demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. At the end of trial examination, it will include review of vital signs, 12-lead ECG, laboratory tests, and a physical examination with determination of weight.

5.2.5.3 Local tolerability

Local tolerability will be assessed by the investigator according to 'swelling', 'induration', 'heat', 'redness', 'pain', or 'other findings'.

5.2.5.4 Oral body temperature

Oral body temperature will be measured at the times indicated in the Flow Chart using a standard device.

5.3 OTHER

5.3.1 Pharmacogenomic evaluation

Not applicable.

5.3.2 Other endpoints

Not applicable.

5.3.3 Other assessments

Not applicable.

5.4 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 parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure. The biomarkers and

pharmacodynamic parameters and measurements outlined in Section 5.6 and 5.7 are of exploratory nature only.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded in the CRFs.

Exact time points of plasma sampling will be derived from electronic data capturing system LabPas and documented in the CRFs by the site personnel or sent as electronic files to the trial data manager. The actual sampling times will be used for determination of pharmacokinetic parameters.

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

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic parameters will be determined if feasible:

5.5.1.1 Secondary endpoints

Single dose part (20 mg/kg b.w.):

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

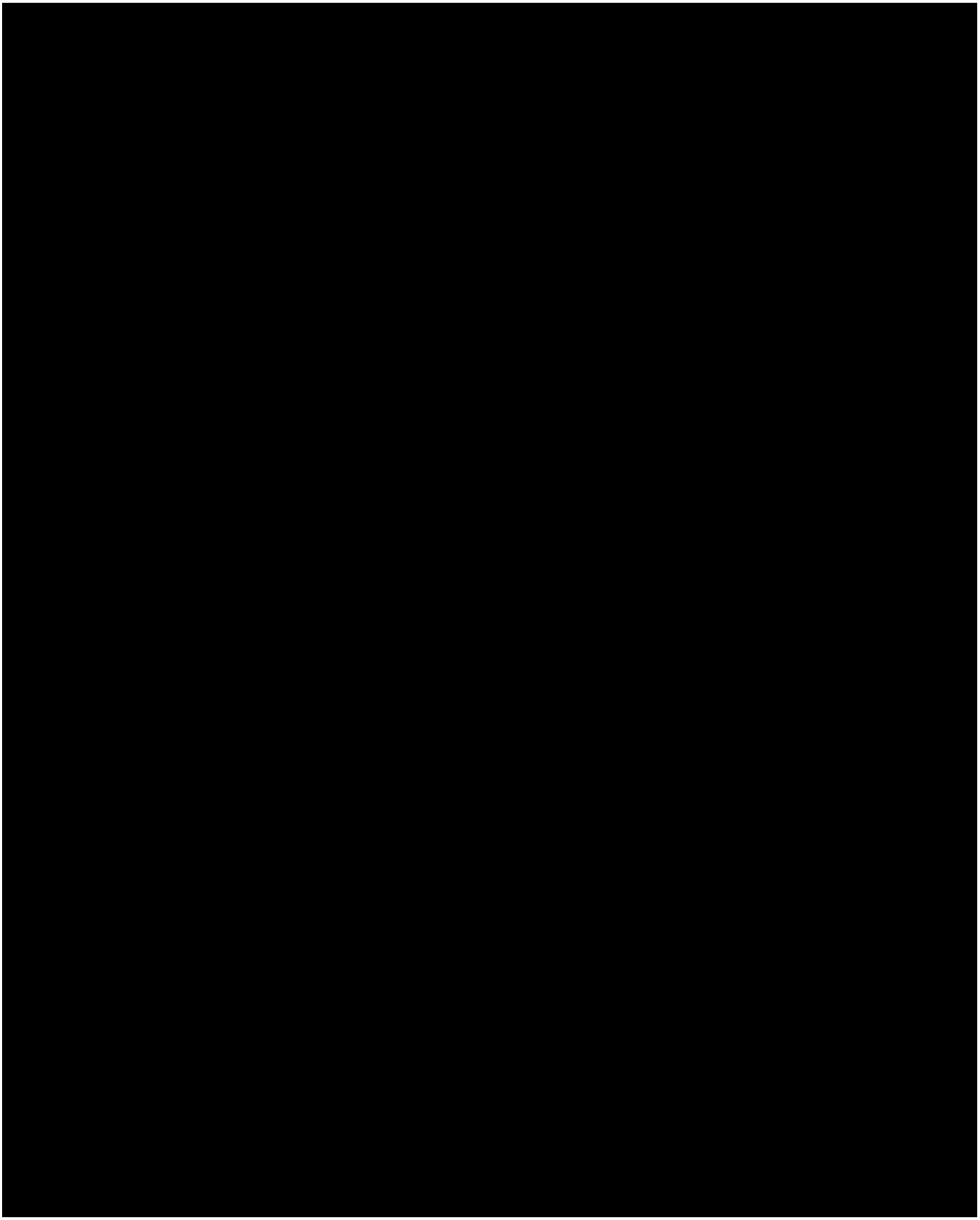
Multiple dose part (3 mg/kg, 6 mg/kg, 10 mg/kg, 20 mg/kg b.w.):

After the first dose:

- $AUC_{\tau,1}$ (area under the concentration-time curve of the analyte in plasma over a uniform dosing interval τ after administration of the first dose)
- C_{max} (maximum measured concentration of the analyte in plasma)

After the last dose:

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



5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 655130 plasma concentrations, approximately 3.0 mL of blood will be taken from a forearm vein into a K2EDTA (ethylendiaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in the Flow Chart under plasma PK.

Mix the K2EDTA-anticoagulated blood samples gently and place on ice until centrifugation at about +4°C. The blood should be centrifuged to produce plasma as soon as possible after collection, but not later than 30 minutes after withdrawal. Centrifugation will last for approximately 10 minutes (at 2000 to 4000 x g) at about +4°C. Two aliquots of EDTA plasma sample will be obtained in two labelled polypropylene cryotubes. At a minimum, the sample tube labels should list the following information: BI trial number, subject number, visit, PTM, aliquot #1 or #2, plasma and PK.

The two aliquots should contain approximately 0.5 mL of plasma each. The plasma samples will be stored in a freezer set to -20°C or below at the clinical site(s) until shipment on dry ice to the central lab (with dry ice sufficient for at least 3 days transit), then stored in a freezer set to -20°C or below at the site until shipment to the analytical laboratory. Both aliquots will be shipped (in separate shipments with dry ice sufficient for 3 days transit) to the analytical laboratory for the determination of BI 655130. Both aliquots will be stored in in a freezer set to -20°C or below at the analytical laboratory until the finalization of the clinical trial report.

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

5.5.2.2 Plasma sampling for ADA assessment

For ADA assessment, approximately 3.0 mL of blood will be taken from a forearm vein into a K2EDTA anticoagulant blood-drawing tube at the time points listed in the Flow Chart under plasma ADA.

Mix the K2EDTA-anticoagulated blood samples gently and place on ice until centrifugation at approximately +4°C. The blood should be centrifuged to produce plasma as soon as possible after collection, but not later than 30 minutes after withdrawal. Centrifugation will last for approximately 10 minutes (at 2000 to 4000 x g) at approximately +4°C. Two aliquots of EDTA plasma samples will be obtained in two labelled (label to include: trial number, subject number, visit, PTM, aliquot #1 or #2, plasma, and ADA) polypropylene cryotubes. The two aliquots should contain approximately 0.5 mL of plasma each. The plasma samples will be stored in a freezer set to -20°C or below at the clinical site(s) until shipment on dry ice to the central lab (with dry ice sufficient for at least 3 days transit), then stored in a freezer set to -20°C or below at the central lab until shipment to the analytical laboratory. Both aliquots will be shipped (in separate shipments with dry ice sufficient for 3 days transit) to the analytical laboratory for assessment of potential ADA to BI 655130. Once received at the analytical laboratory, both aliquots will be stored in in a freezer set to -20°C or below.

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

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of BI 655130 plasma concentration

BI 655130 concentrations will be determined by a validated Gyros affinity flow-through immunoassay. Analyses will be performed at QPS in Newark, DE 19711, USA.

5.5.3.2 Assessment of ADA to BI 655130

The presence of ADA to BI 655130 will be assessed via their detection using a validated immunoassay in a tiered approach (screening, confirmatory, and titration analysis as appropriate). Analyses will be performed at Charles River Laboratories, US.

[redacted]

[redacted]

5.7 PHARMACODYNAMICS

[redacted]

5.7.2 Methods of sample collection

Please refer to Section 5.6.3.

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

The PK and PD data from this study may be used for an exploratory investigation of PK/PD relationship of BI 655130, however, it is not planned to report the results of this investigation into the clinical trial report of this study.

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 end of trial examination are given in the Flow Chart.

Multiple dose part

Study measurements and assessments scheduled to occur 'before' trial medication administration on Day 1, 8, 15 and 22 are to be performed and completed within a 3h-period prior to the trial drug administration (including blank and trough values for PK and biomarkers).

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

- ±15 min up to including 12 h after dosing after each dosing
- ±30 min from 12h up to including 48 h after each dosing
- ±60 min from 48 h up to Day 7 after each dosing
- ±24h from 8 days after last dosing (=from Day 30 onwards) up to Day 92
- ±72h from Day 120 up to the last measurements

The tolerance for pharmacokinetic/laboratory parameters will be:

- ±1 min up to including 30 min after each dosing
- ±5 min up to including 12 h after each dosing
- ±15 min up to including 48 h after each dosing
- ±60 min from 48 h up to Day 7 after each dosing
- ±24h from 8 days after last dosing (=from Day 30 onwards) up to Day 92
- ±72h from Day 120 up to the last measurements

Single dose part

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

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

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

The tolerance for pharmacokinetic/laboratory parameters will be:

- ±1 min up to including 30 min
- ±5 min up to including12 h
- ±15 min up to including 48 h

- ±60 min from 48 h up to Day 8
- ±24h from Day 8 up to Day 71
- ±48h on Day 92
- ±72h from Day 120 up to the last measurements

Single/multiple dose part

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

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

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening

After having been informed about the trial, all subjects will give their written informed consent in accordance with GCP and local legislation prior to enrolment in the study.
For information regarding laboratory tests (including drug and virus screening), ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

6.2.2 Treatment period

Multiple dose part

Each subject will receive a single dose of BI 655130 or placebo once weekly during Visit 2 on Day 1, Day 8, Day 15 and Day 22.

Study participants will be admitted to the trial site in the evening before dosing (Day -1, Day 7, Day 14, Day 21) and kept under close medical surveillance for at least 48 h following after each dosing. The subjects will be kept hospitalized from the evening of Day -1 to the morning of Day 3, the evening of Day 7 to the morning of Day 10, the evening of Day 14 to the morning of Day 17, the evening of Day 21 to morning of Day 24. On all other time periods the study will be performed in an ambulatory fashion provided there are no medical reasons preventing the discharge from the unit.

Single dose part

Study 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 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 study days, the study will be performed in an ambulatory fashion.

Single/multiple dose part

Trial medication will be administered as IV infusion by the investigating physician or [redacted] designee. Details on treatments and procedures of administration are described in Section 4.1.4.

For details on time points and procedures for collection of plasma analysis, refer to Flow Chart and Section 5.5.2.

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

6.2.3 End of trial and follow-up period

For AE assessment, laboratory tests, collection of PK and ADA samples, recording of ECG and vital signs, and physical examination during the end of trial period, see Sections 5.2.2 to 5.2.5.

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

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. Adverse events persisting after trial completion must be monitored until they have normalised or have been sufficiently characterised.

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

7.1.1 Objectives

The primary objective of this trial is to investigate the safety and tolerability of BI 655130 by using descriptive statistics for all endpoints comparing active dose groups to placebo in healthy male subjects. The study will also explore safety and tolerability following a single IV administration of 20 mg/kg b.w. The primary endpoint is defined in Section 5.2.1. Inferential statistics is not planned (as explained in Section 7.2).

Secondary objectives are the exploration of the pharmacokinetics of BI 655130 after single and multiple IV administration.

A further objective is the exploration of pharmacodynamics and the evaluation of additional pharmacokinetic parameters beyond those already covered in secondary objectives.

The secondary objective is the exploration of the pharmacokinetics (PK) and pharmacodynamics (PD) of BI 655130. Endpoints as specified in 5.5.1 and 5.7.1 will be analysed by descriptive statistics. Secondary endpoints as defined in Section 5.5.1.1 will be subjected to analysis of dose proportionality by use of the power model. Trough concentration values will be analysed regarding attainment of steady state as a pre-requisite for calculation of steady state parameters. Additionally, the linearity index will be estimated.

7.2 NULL AND ALTERNATIVE HYPOTHESES

Safety and tolerability of 5 different dose groups of BI 655130 (Section 3.1) 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.

7.3 PLANNED ANALYSES

All individual data will be listed.

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol violations (IPVs) will be identified no later than in the Blinded Report Planning Meeting and provided in the TSAP.

7.3.1 Primary analyses

Analysis of safety and tolerability is described in Section 7.3.3.

7.3.2 Secondary analyses

The secondary parameters (refer to Section 5.5.1) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472). Analyses will be performed for parent drug.

Pharmacokinetic parameters of a subject will be included in the analysis unless the subject has an important protocol violation relevant for the evaluation. Whether a protocol violation is important will be decided no later than in the Blinded Report Planning Meeting.

Reasons for exclusion of single pharmacokinetic parameters may be:

- The subject experiences emesis at or before two times median t_{max}. Median t_{max} is to be determined for the test product excluding the subjects experiencing emesis.
- The subject experiences emesis at any time during the labelled dosing interval.
- Time deviations
- Use of restricted medications

The subject set for the evaluation of PK endpoints (PKS) will include all treated subjects that provide at least one observation for at least one secondary endpoint without important protocol violations with respect to the statistical evaluation of PK endpoints. It will be decided in the Blinded Report Planning Meeting which subjects are to be included in the PKS.

Excluded subjects will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical assessment.

Assessment of dose proportionality

Dose proportionality will be assessed using the pharmacokinetic endpoints as specified in 5.5.1.1.

The basic model for the investigation of dose proportionality will be a power model that describes the functional relationship between the dose and PK endpoints.

$$\exp(Y_{ij}) = \alpha' * \exp(X_i)^{\beta} * \varepsilon'_{ij}$$

The model consists of a regression model applied to log-transformed data. The corresponding ANCOVA model includes the logarithm of the dose as a covariate.

Together with $\alpha' = \exp(\alpha)$ and $\varepsilon'_{ij} = \exp(\varepsilon_{ij})$, taking natural logarithms converts this model to a linear form as follows:

$$Y_{ij} = \alpha + \beta * X_i + \varepsilon_{ij}$$

where

Y_{ij}	logarithm of the pharmacokinetic endpoint for subject j at dose level i; where number of dose groups i = 1, 2, …, 4, and j = 1, 2, …, N where N is the number of subjects per dose group;
α	intercept parameter;
β	slope parameter;
X_i	logarithm of dose i;
ε_{ij}	random error associated with subject j at dose level i (assumed to be independent and identically normally distributed).

This equation can be fit as a linear regression model.

Based on the estimate for slope parameter (β), a 2-sided 95% CI for the slope will be computed. Perfect dose proportionality would correspond to a slope of 1. The assumption of a linear relationship between the log-transformed pharmacokinetic endpoint and the log-transformed dose will be checked.

If dose proportionality over the entire dose range investigated cannot be shown, an attempt will be made to identify dose range(s), where dose proportionality can be assumed.

Linearity index

Linearity with respect to multiple administration will be explored using the linearity index (LI) that will be computed as follows:

$$LI = \frac{AUC_{\tau,ss}}{AUC_{0-\infty}}$$

In order to construct a confidence interval for LI, a statistical model using $AUC_{\tau,ss}$ and $AUC_{0-\infty}$ will be set up: A linear model on the logarithmic scale including effects for 'subject' and 'AUC type' can be applied, where 'subject' is a random and 'AUC type' a fixed effect.

[1] $Y_{ij} = \mu + \tau_i + s_j + e_{ij}$, where

Y_{ij}	logarithm of the response (AUC after first dose, AUC after last dose) for subject j and AUC type i; where i = 1 (after first dose) or 2 (after last dose) and j=1, 2,…, n
μ	the overall mean
τ_i	the AUC type i
s_j	the effect associated with subject j (random effect)
e_{ij}	random error associated with subject j at AUC type i (assumed to be independent and identically normally distributed).

A pairwise comparison of both areas via the log transformed difference

$\log(\frac{AUC_{\tau,ss}}{AUC_{0-\infty}}) = \log(AUC_{\tau,ss}) - \log(AUC_{0-\infty})$

will then be performed including calculation of a 2-sided 95% CI. The back transformed point estimate then represents the estimate of LI. Perfect linearity with respect to multiple administrations holds true if this index equals unity.

Generally, this model will be applied to each dose level separately. If there is evidence that the areas are comparable across dose levels, they can be analysed simultaneously. The corresponding model will then include the log transformed dose as (additional) covariate

Attainment of steady state

Attainment of steady state will be explored for the three dose-groups undergoing multiple dose administrations by using the trough concentrations of BI 655130 between days 4 and 22 and the concentrations taken directly at the end of the first and the last dosing interval ($C_{\tau,1}$, $C_{\tau,22}$) for each dose level. Pairwise comparisons of concentrations are performed using 2-sided 95% CIs based on the t-distribution. The calculation is based on a repeated measures linear model on the logarithmic scale.

$Y_{ij} = \mu + \tau_i + s_j + e_{ij}$, where

- Y_{ij} logarithm of the concentrations for subject j at time i, i = 1, 2, …I and j=1, 2,…, n_k , where I is the number of measured time points and n_k is the number of subjects in dose group k
- μ the overall mean,
- τ_i the effect associated with time point i (repeated effect),
- s_j (random) effect of subject j, j=1, 2, ..., n_k, where n_k is the number of subjects in dose group k
- e_{ij} random error associated with subject j at time i (assumed to be independent and identically normally distributed).

Dose can be included as an additional covariate if there is evidence that the trough concentration profiles are comparable across dose levels.

The model will be used to explore the time to steady state by pairwise comparing concentrations from different time points: log-transformed differences between all subsequent time points ($\log(C_{pre,i}/C_{pre,j}) = \log(C_{pre,i}) - \log(C_{pre,j})$, where j>i) will be compared and adjusted means (Least Squares Means) as well as 2-sided 95% CIs will be calculated. Thereafter, these quantities will be back-transformed by exponentiation to give the corresponding (adjusted) ratio and CI.

Comparisons which reveal CIs (for the adjusted ratio) not including 100% will be inspected to determine if the differences between time points are resulting from not yet attaining steady-state.

For further details refer to the TSAP (such as selection of covariance structure and comparison of time points).

Investigation of relative bioavailability for single i.v. dose of 20 mg/kg weight

The investigation of relative bioavailability will be done on the secondary pharmacokinetic endpoints listed in Section 5.5.1.1 for the 20 mg/kg of weight dose group.

The statistical model used for the analysis of relative bioavailability of BI 655130 will be an ANOVA (analysis of variance) model on the logarithmic scale.

7.3.3 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. All treated subjects (that is, all subjects who received at least one dose of study drug), will be included in the safety evaluation. Safety analyses will be descriptive in nature and will be based on BI standards.

Treatments will be compared in a descriptive way. The placebo control group in the safety evaluation will consist of all placebo treated subjects, regardless of the dose group in which they were treated. The active treatment groups will be compared to the placebo group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data. Separate listings will be provided for subjects under multiple drug administration and the ones with a single dose of 20 mg/kg.

The analyses will be done by ‘treatment at onset’.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs).

Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening', those between first trial medication intake until the end of trial visit will be assigned to the treatment period, and those after the end of trial examination will be assigned to ‘post-study’. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

Additionally, further treatment intervals (analysing treatments) may be defined in order to provide summary statistics for time intervals, such as combined treatments, on-treatment totals or periods without treatment effects (such as screening and post-study intervals). Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, intensity and causal relationship of AEs will be tabulated by treatment, primary system organ class and preferred term. SAEs, AESIs (see Section 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

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

For vital signs, the differences from baseline will be evaluated.

A centralised evaluation of all 12-lead ECGs recordings (see Section 5.2.4) will be the basis for the derivation of further ECG parameters based on the ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR. The baseline value of an ECG variable is defined as the mean of the triple ECG measurements prior to drug administration. The derivation of the quantitative and qualitative ECG endpoints and their analyses will be described in the TSAP.

7.3.4 Interim analyses

No interim analysis is planned.

7.3.5 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 655130 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

Subjects who are not included in the PKS (refer to Section 7.3.1.) will be reported with their individual plasma and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma, pharmacokinetic parameters or other statistical assessment.

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 provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

If a predose concentration value is greater than 5% of C_{max}, the subject's pharmacokinetic data will be not included in any statistical evaluations, in accordance with international guidances. The individual pharmacokinetic parameters of such a subject will be calculated and listed separately. If a predose concentration is above BLQ, but less than or equal to 5% of the subject's C_{max} value, the subject's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

With respect to safety evaluations, it is not planned to impute missing values.

7.4.2 Plasma/urine drug concentration - time profiles

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

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

7.4.3 Pharmacokinetic parameters

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

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be ignored. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.5 RANDOMISATION

Subjects will be randomised within each dose group in a 3:1 ratio, which reflects the ratio of subjects receiving active drug to placebo.

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves 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).

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 40 subjects in this trial. The planned sample size is not based on a power calculation. The size of 8 subjects per dose group (6 on active treatment, and 2 on placebo) is considered as sufficient for the exploratory evaluation of multiple dose safety and pharmacokinetics [R95-0013].

Additional subjects may be entered to allow testing of intermediate doses within the planned and approved dose range on the basis of experience gained during trial conduct (e.g. preliminary PK data), i.e. the actual number of subjects entered may exceed 40.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

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

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

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in a separate agreement between the investigator or the trial site and the sponsor. As a general rule, no trial results should be published prior to finalisation of the CTR.

Insurance Coverage: The terms and conditions of the insurance coverage must be given to each subject and are made available to the investigator via documentation in the ISF.

8.1 STUDY APPROVAL, SUBJECT INFORMATION, AND INFORMED CONSENT

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

Prior to a 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 are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative.

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

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

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/IECs, 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.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the TMF.

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

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

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate/on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage period of records

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

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 regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY

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

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

8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last subject/subject out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

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10. APPENDICES

10.1 CLINICAL EVALUATION OF LIVER INJURY

10.1.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (Protocol-specified AESIs), are to be further evaluated using the following procedures:

10.1.2 Procedures

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

In addition,

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

and report these via the CRF.

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

Serology
Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody

Epstein Barr Virus (VCA IgG, VCA IgM), cytomegalovirus (IgG, IgM), herpes simplex virus (IgG, IgM), varicella (IgG, IgM), parvovirus (IgG, IgM), toxoplasmosis (IgG, IgM)

Hormones, tumormarker
TSH

Haematology
Thrombocytes, eosinophils

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm.
- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (total and direct) at least weekly until the laboratory ALT and/or AST abnormalities stabilize or return to normal, then monitor further as specified in the CTP. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

10.2 RECONSTITUTION INSTRUCTION(S)

Preparation instructions for 3 mg/kg dose (drug concentration in infusion solution 5 mg/mL BI 655130):

Necessary Materials:

Drug Product and Dilution Media:

3 vials BI 655130 Solution for Infusion 20 mg/mL (correlates to 3 x 150 mg BI 655130)

1 bottle 0.9% sodium chloride solution (e.g. 500 mL, B.Braun, 401734)

Consumables:

1 x Blunt Fill needle 18 G (material: stainless steel/Polypropylene - e.g. BD, 305180)

2 x 1 mL syringe (material: Polycarbonate/Polypropylene - e.g. BD, 309628)

1 x 10 mL syringe (material: Polypropylene - e.g. BD, 300912)

2 x 20 mL syringe (material: Polypropylene - e.g. BD, 300629)

1 x 50 mL syringe (material: Polypropylene - e.g. Omnifix B.Braun, 4617509F)

5 x syringe closure (material: Polyethylene - e.g. Combi-Stopper B.Braun, 4495101)

4 x Spike (material: Polyolefine - e.g. Mini-Spike, 0.45 µm Air Filter B.Braun, 4550242)

Empty EVA (Ethylene vinyl acetate) infusion bag:

e.g. Freka Mix Monolayer (Fresenius-Kabi, F2859061)

Preparation overview:

Dilution: 22.5 mL of BI 655130 Solution for Infusion 20 mg/mL + 67.5 mL 0.9% sodium chloride → 90 mL 5.0 mg/mL BI 655130 (in infusion bag)

1) Put a Mini-Spike on a bottle containing 500 mL 0.9% sodium chloride solution
2) Attach a 50 mL syringe to the Mini-Spike, withdraw 50 mL of the 0.9% sodium chloride Solution and disconnect the filled syringe. Close it with a Combi-Stopper.
3) Attach a 20 mL syringe to the Mini-Spike, withdraw 17.0 mL of the 0.9% sodium chloride solution and disconnect the filled syringe. Close it with a Combi-Stopper.
4) Attach a 1 ml syringe to the Mini-Spike, withdraw 0.5 mL of the sodium chloride solution and disconnect the filled syringe. Close it with a Combi-Stopper.
5) Put a Mini-Spike on each of two vials containing BI 655130 Solution for Infusion 20 mg/mL and connect one 20 mL syringe to the Mini-Spike.
6) Withdraw 7.5 mL of BI 655130 Solution for Infusion 20 mg/mL from each of the two so the total volume in the syringe is 15.0 mL (= 300 mg BI 655130).
7) Disconnect the syringe and lock the syringe with a Combi-Stopper.
8) Put a Mini-Spike on the third vial containing BI 655130 Solution for Infusion 20 mg/mL and connect one 10 mL syringe to the Mini-Spike.
9) withdraw 7.0 mL of BI 655130 Solution for Infusion 20 mg/mL from the vial (= 140 mg BI 655130)
10) Disconnect the syringe and lock the syringe with a Combi-Stopper.
11) Attach a 1 mL syringe to the Mini-Spike, withdraw 0.5 mL of BI 655130 Solution for Infusion 20mg/mL from the vial (= 10 mg BI 655130) and disconnect the filled syringe. Close it with a Combi-Stopper.
12) Lock the fill port of the empty infusion bag close to the bag. Open the injection port of the bag.
13) Remove the Combi-Stopper from the syringe obtained in step 6, attach an 18 G needle and transfer the complete contents of the syringe into the infusion bag via the injection port.
14) Disconnect the empty syringe from the needle and close the needle using a Combi-Stopper. Keep bag in an upright position to prevent leakage.

15) Connect consecutively the second syringe containing BI 655130 Solution for Infusion (step 9) to the needle of the infusion bag containing BI 655130 Solution for Infusion 20 mg/mL (step 13) and transfer the content of the syringes completely into the infusion bag. Disconnect the empty syringe.
16) Connect the third syringe containing BI 655130 Solution for Infusion (step 11) to the needle of the infusion bag containing BI 655130 Solution for Infusion 20 mg/mL (step 12) and transfer the content of the syringe completely into the infusion bag. Disconnect the empty syringe.
17) Connect consecutively the syringes containing 0.9% sodium chloride solution (step 2, 3 and 4) to the needle of the infusion bag containing BI 655130 Solution for Infusion 20 mg/mL (step 13) and transfer the contents of the syringes completely into the infusion bag. Disconnect the empty syringe.
18) Remove the needle and mix solution in the bag by gently kneading and turning it.

Preparation instructions for 6 mg/kg dose (drug concentration in infusion solution 10 mg/mL BI 655130):

Necessary Materials:

Drug Product and Dilution Media:

6 vials BI 655130 Solution for Infusion 20 mg/mL (correlates to 6 x 150 mg BI 655130)

1 bottle 0.9% sodium chloride solution (e.g. 500 mL, B.Braun, 401734)

Consumables:

1 x Blunt Fill needle 18 G (material: Stainless Steel/Polypropylene - e.g. BD, 305180)

2 x 50 mL syringe (material: Polypropylene - e.g. Omnifix B.Braun, 4617509F)

3 x syringe closure (material: Polyethylene - e.g. Combi-Stopper B.Braun, 4495101)

7 x Spike (material: Polyolefine - e.g. Mini-Spike, 0.45 µm Air Filter B.Braun, 4550242)

Empty EVA (Ethylene vinyl acetate) infusion bag:

e.g. Freka Mix Monolayer (Fresenius-Kabi, F2859061)

Preparation overview:

Dilution: 45 mL of BI 655130 Solution for Infusion 20 mg/mL + 45 mL 0.9% sodium chloride → 90 mL 10.0 mg/mL BI 655130 (in infusion bag)

1) Put a Mini-Spike on a bottle containing 500 mL 0.9% sodium chloride solution
2) Attach a 50 mL syringe to the Mini-Spike, withdraw 45 mL of the 0.9% sodium chloride Solution and disconnect the filled syringe. Close it with a Combi-Stopper.
3) Put a Mini-Spike on each of the 6 vials containing BI 655130 Solution for Infusion 20 mg/mL and connect one 50 mL syringe to the Mini-Spike.
4) Withdraw 7.5 mL of BI 655130 Solution for Infusion 20 mg/mL from each of the 6 vials so the total volume in the syringe is 45.0 mL (= 900 mg BI 655130).
5) Disconnect the syringe and lock the syringe with a Combi-Stopper.
6) Lock the fill port of the empty infusion bag close to the bag. Open the injection port of the bag.
7) Remove the Combi-Stopper from the syringe obtained in step 4, attach an 18 G needle and transfer the complete contents of the syringe into the infusion bag via the injection port.
8) Disconnect the empty syringe from the needle and close the needle using a Combi-Stopper. Keep bag in an upright position to prevent leakage.
9) Connect the syringe containing 0.9% sodium chloride solution (step 2) to the needle of the infusion bag containing BI 655130 Solution for Infusion 20 mg/mL (step 8) and transfer the contents of the syringe completely into the infusion bag. Disconnect the empty syringe.
10) Remove the needle and mix solution in the bag by gently kneading and turning it.

Preparation instructions for 10 mg/kg dose (drug concentration in infusion solution 20 mg/mL BI 655130):

Necessary Materials:

Drug Product:

10 vials BI 655130 Solution for Infusion 20 mg/mL (correlates to 10 x 150 mg BI 655130)

Consumables:

1 x Blunt Fill needle 18 G (material: Stainless Steel/Polypropylene - e.g. BD, 305180)

2 x 50 mL syringe (material: Polypropylene - e.g. Omnifix B.Braun, 4617509F)

3 x syringe closure (material: Polyethylene - e.g. Combi-Stopper B.Braun, 4495101)

10 x Spike (material: Polyolefine - e.g. Mini-Spike, 0.45 µm Air Filter B.Braun, 4550242)

Empty EVA (Ethylene vinyl acetate) infusion bag:

e.g. Freka Mix Monolayer (Fresenius-Kabi, F2859061)

Preparation overview:

75 mL of BI 655130 Solution for Infusion 20 mg/mL → 20.0 mg/mL BI 655130 (in infusion bag)

1) Put a Mini-Spike on each of 10 vials containing BI 655130 Solution for Infusion 20 mg/mL and connect one 50 mL syringe to one of the Mini-Spikes.
2) Withdraw 7.5 mL of BI 655130 Solution for Infusion 20 mg/mL from each of 6 vials so the total volume in the syringe is 45 mL (= 900 mg BI 655130).
3) Disconnect the syringe and lock the syringe with a Combi-Stopper.
4) Withdraw 7.5 mL of BI 655130 Solution for Infusion 20 mg/mL from each of 4 vials so the total volume in the syringe is 30 mL (= 600 mg BI 655130).
5) Disconnect the syringe and lock the syringe with a Combi-Stopper.
6) Lock the fill port of the empty infusion bag close to the bag. Open the injection port of the bag.
7) Remove the Combi-Stopper from the syringe obtained in step 3, attach an 18 G needle and transfer the complete contents of the syringe into the infusion bag via the injection port.
8) Disconnect the empty syringe from the needle and close the needle using a Combi-Stopper. Keep bag in an upright position to prevent leakage.
9) Connect consecutively the second syringe containing BI 655130 Solution for Infusion (step 5) to the needle of the infusion bag containing BI 655130 Solution for Infusion 20 mg/mL (step 7) and transfer the content of the syringes completely into the infusion bag. Disconnect the empty syringe.
10) Remove the needle.

Preparation instructions for 20 mg/kg dose (drug concentration in infusion solution 20 mg/mL BI 655130):

Necessary Materials:

Drug Product:

17 vials BI 655130 Solution for Infusion 20 mg/mL (correlates to 17 x 150 mg BI 655130)

Consumables:

1 x Blunt Fill needle 18 G (material: Stainless Steel/Polypropylene - e.g. BD, 305180)

3 x 50 mL syringe (material: Polypropylene - e.g. Omnifix B.Braun, 4617509F)

4 x syringe closure (material: Polyethylene - e.g. Combi-Stopper B.Braun, 4495101)

17 x Spike (material: Polyolefine - e.g. Mini-Spike, 0.45 µm Air Filter B.Braun, 4550242)

Empty EVA (Ethylene vinyl acetate) infusion bag:

e.g. Freka Mix Monolayer (Fresenius-Kabi, F2859061)

Preparation overview:

125 mL of BI 655130 Solution for Infusion 20 mg/mL → 20.0 mg/mL BI 655130 (in infusion bag)

1) Put a Mini-Spike on each of 6 vials containing BI 655130 Solution for Infusion 20 mg/mL and connect one 50 mL syringe to one of the Mini-Spikes.
2) Withdraw 7.5 mL of BI 655130 Solution for Infusion 20 mg/mL from each of 6 vials so the total volume in the syringe is 45 mL (= 900 mg BI 655130).
3) Disconnect the syringe and lock the syringe with a Combi-Stopper.
4) Repeat Steps 1-3.
5) Put a Mini-Spike on each of 5 vials containing BI 655130 Solution for Infusion 20 mg/mL and connect one 50 mL syringe to the Mini-Spike.
6) Withdraw 7.5 mL of BI 655130 Solution for Infusion 20 mg/mL from each of 4 vials and 5 mL from a 5th vial so the total volume in the syringe is 35 mL (= 700 mg BI 655130).
7) Disconnect the syringe and lock the syringe with a Combi-Stopper.
8) Lock the fill port of the empty infusion bag close to the bag. Open the injection port of the bag.
9) Remove the Combi-Stopper from the syringe obtained in step 3, attach an 18 G needle and transfer the complete content of the syringe in the infusion bag via the injection port.
10) Disconnect the empty syringe from the needle and close the needle using a Combi-Stopper. Keep bag in an upright position to prevent leakage.
11) Connect consecutively the second syringe containing BI 655130 Solution for Infusion (step 4) to the needle of the infusion bag containing BI 655130 Solution for Infusion 20 mg/mL (step 10) and transfer the content of the syringe completely into the infusion bag. Disconnect the empty syringe. Close the needle using a Combi-Stopper.
12) Connect the third syringe containing BI 655130 Solution for Infusion (step 7) to the needle of the infusion bag containing BI 655130 Solution for Infusion 20 mg/mL (step 11) and transfer the content of the syringes completely into the infusion bag. Disconnect the empty syringe.
13) Remove the needle.

Infusion Information:

Dose (mg/kg)	In-line Filter Used?	Approximate Pre-flush Volume (mL)	Concentration of the ready to use i.v. bag BI 655130 (mg/mL)	Volume Delivered (mL/kg body weight)	Infusion Time (min)
3	Yes	30	5	0.6	Up to 240
6	Yes	15	10	0.6	Up to 240
10	Yes	15	20	0.5	Up to 240
20	Yes	15	20	1	Up to 240

After preparation, the solution for infusion may be stored at 2-8°C for up to 24 hours. After removal from 2-8°C storage or preparation, the solution must be administered within 60 minutes if stored at ≤ 25°C. Do not freeze.
Chemical and physical in-use stability has been demonstrated for 60 minutes at ≤ 25°C. In addition the time for infusion must not exceed 240 minutes at ≤ 25°C.
From a microbiological point of view the drug should be used immediately. If not used immediately, the in-use storage times and conditions prior to use are the responsibility of the user, and would normally not be longer than 24 hours at 2-8°C (36-46°F), unless preparation has taken place in controlled and validated aseptic conditions.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		11 Oct 2016
EudraCT number		2016-001235-12
BI Trial number		1368.2
BI Investigational Product(s)		BI 655130
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising intravenous doses of BI 655130 (double-blind, partially randomised within dose groups, placebo-controlled parallel group design) and one single intravenous dose of BI 655130 (single-blind, partially randomised, placebo-controlled) in healthy male subjects
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		1. Synopsis; Flow Chart; Section 2.3 ; Section 3.3.4 ; Section 4.1.4 2. Section 10.2 3. Section 10.2 4. Flow Chart ; Section 6.1 5. Section 1.2.5 ; Section 3.1 ; Section 4.1.4 ; Section 4.1.5.1 ; Section 5.2.3 ; Section 5.2.4 ; Section 6.1 ; Section 6.2.2 6. Section 5.5.2.2 7. Section 1.2.5

Number of global amendment		1
Description of change		1. Infusion time for dose groups 10 mg/kg b.w. multiple doses and 20 mg/kg b.w. single dose was prolonged to 60 minutes 2. Update of reconstitution instructions: a. 1 mL syringe was added in 3 mg dose group b. Material information for consumables was added c. Infusion time was updated 3. Update of stability of reconstituted/diluted solution / In-Use-Stability 4. Update of study flow chart: a. Additional visits for follow-up observation (until 20 weeks after last dosing) with respective time-windows were included for all dose groups b. Infusion time for dose group 10 mg/kg b.w. multiple doses and 20 mg/kg b.w. single dose was extended to 60 minutes. c. Body weight measurement was included at visit 2/day -2 d. Time window for procedures performed before drug administration was adapted 5. Correction of inconsistencies and typing errors throughout the document 6. Update regarding blood sampling 7. Update to align with final data after database lock in July 2016
Rationale for change		1. Updated In-Use Stability Study with date from 24 August 2016 2. Updated In-Use Stability Study with date from 24 August 2016 3. Updated In-Use Stability Study with date from 24 August 2016 4. a. PK results from 1368.1 trial suggest a half-life of BI 655130 of about 4 weeks for doses tested in the study. The evaluation is ongoing. However as precautionary measure we have

Number of global amendment		1
		extended the observation period to Day 176 to cover at least 5 half-lifes b. Updated In-Use Stability Study with date from 24 August 2016 c. Correction to align with eCRF d. For logistical reasons 5. A few inconsistencies and typing errors were corrected 6. Left over blood samples will be discarded after 5 years instead of 3 years 7. Data were aligned with final data after database lock

Number of global amendment		2
Date of CTP revision		05 Dec 2016
EudraCT number		2016-001235-12
BI Trial number		1368.2
BI Investigational Product(s)		BI 655130
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising intravenous doses of BI 655130 (double-blind, partially randomised within dose groups, placebo-controlled parallel group design) and one single intravenous dose of BI 655130 (single-blind, partially randomised, placebo-controlled) in healthy male subjects
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		1. Synopsis, Flow Chart, Section 2.1, Section 2.2, Section 2.3, Section 3.1, Section 3.2, Section 3.3, Section 3.3.4, Section 4.1.2, Section 4.1.4, Section 5.5.1.1 and Section 7.6
Description of change		1. 20 mg/kg b.w. MRD (multiple dose group) added. To limit the amount of protein infused per minute the infusion time was prolonged to 90 minutes. Blood volume withdrawn during the study increases from 400 ml to 430 ml. 2. A few inconsistencies and typing errors were corrected throughout the document.
Rationale for change		1. This optional final dose group of 20

Number of global amendment		2
		mg/kg multiple dose may further widen the safety margin in patients with [redacted] who may require higher doses ≥ 10 mg/kg due to protein loss, up-regulation of the target, and a potentially higher clearance. The prolongation of the infusion time to 90 minutes has been implemented to reduce the theoretical risk of an infusion reaction. 2. With amendment number 2 a few inconsistencies and typing errors were corrected throughout the document.

Number of global amendment		3
Date of CTP revision		02 August 2017
EudraCT number		2016-001235-12
BI Trial number		1368.2
BI Investigational Product(s)		BI 655130
Title of protocol		Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising intravenous doses of BI 655130 (double-blind, partially randomised within dose groups, placebo-controlled parallel group design) and one single intravenous dose of BI 655130 (single-blind, partially randomised, placebo-controlled) in healthy male subjects
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		1. Abbreviations 2. Section 5.5.3.1
Description of change		The PK testing platform will change from ELISA (enzyme linked immunosorbent assay) to Gyros affinity flow-through immunoassay. The PK testing will be conducted at QPS, Newark, DE 19711, USA.
Rationale for change		Logistical reasons.

APPROVAL / SIGNATURE PAGE

Document Number: c09105854 **Technical Version Number:5.0**

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

Title: Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising intravenous doses of BI 655130 (double-blind, partially randomised within dose groups, placebo-controlled parallel group design) and one single intravenous dose of BI 655130(single-blind, partially randomised, placebo-controlled) in healthy male subjects

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	02 Aug 2017 10:54 CEST
Approval-Team Member Medicine		02 Aug 2017 11:11 CEST
Approval-Therapeutic Area [redacted]		02 Aug 2017 14:51 CEST
Author-Trial Clinical Pharmacokineticist		02 Aug 2017 15:10 CEST
Author-Trial Clinical Monitor		03 Aug 2017 09:44 CEST
Verification-Paper Signature Completion		10 Aug 2017 14:35 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed