Clinical Trial Protocol

	Document Number:	**c21031338-02**
BI Trial No.	1407-0015	
BI Investigational Medicinal Product	BI 730357	
Title	Safety, tolerability, and pharmacokinetics of single rising oral doses of BI 730357 in Japanese healthy male subjects (double-blind, randomised, placebo-controlled, parallel group design)	
Lay Title	This study is done in healthy Japanese volunteers. It looks at how different doses of BI 730357 are taken up in the body and how well they are tolerated	
Clinical Phase	I	
Clinical Trial Leader	Address: Phone: Fax:	
Principal Investigator:	Phone: Fax:	
Status	Final Protocol (Revised protocol based on global amendment #1)	
Version and Date	Version: 2.0	Date: 13 December 2018

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	09 November 2018
Revision date	13 December 2018
BI trial number	1407-0015
BI Investigational Medicinal Product name	BI 730357
Title of trial	Safety, tolerability, and pharmacokinetics of single rising oral doses of BI 730357 in Japanese healthy male subjects (double-blind, randomised, placebo-controlled, parallel group design)
Principal Investigator	
Trial site	
Clinical phase	I
Trial rationale	This Phase I study is to investigate the safety, tolerability, and pharmacokinetics of BI 730357 in order to understand the clinical safety and pharmacokinetic profile in healthy male Japanese subjects after single-rising oral doses of BI 730357 within the dose range to be evaluated in further clinical studies with BI 730357 in the indication of psoriasis and other indications.
Trial objectives	The main objective is to investigate the safety and tolerability of BI 730357 in Japanese healthy male subjects following oral administration of single rising doses of 50 mg, 100 mg, and 200 mg. Secondary objectives are the explorations of the PK, including dose proportionality as well as investigation of linearity of BI 730357 after single dose administration.
Trial endpoints	Primary endpoint: to assess safety and tolerability of BI 730357 is the number [N (%)] of subjects with drug-related adverse events Secondary endpoints: $AUC_{0-\infty}$ and C_{max} of BI 730357
Trial design	Double-blind, randomised within dose groups, placebo-controlled, parallel-group design
Number of subjects **total entered** **each treatment**	 24 8 per dose group (6 on active drug and 2 on placebo)
Diagnosis	Not applicable

Main criteria for inclusion	Healthy male Japanese subjects, age of 20 to 45 years (inclusive), body mass index (BMI) of 18.5 to 25.0 kg/m^2 (inclusive)
Test product	BI 730357 film-coated tablet (50 mg and 100 mg formulations)
dose	50 mg (dose group [DG] 1), 100 mg (DG 2), and 200 mg (DG 3)
mode of admin.	Oral with approximately 240 mL of water after an overnight fast of at least 10 hours
Comparator product	Matching placebos
dose	Not applicable
mode of admin.	Oral with approximately 240 mL of water after an overnight fast of at least 10 hours
Duration of treatment	Single dose
Statistical methods	Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Visit	Day	Planned time (relative to drug administration [h:min]	Approximate clock time of actual day [h:min]	Event and comment	Safety laboratory test	Exclusionary laboratory tests	PK blood [8]		12-lead ECG	4 hours continuous 3-lead ECG monitoring[9]	Vital signs [11]	Questioning for AEs and concomitant therapy [5]
1	-28 to -2			Screening[1]	x	x			x		x	
2	-1	-12:00[6]	21:00	Ambulatory visit, Admission to trial site	x	x[13]						x
	1	-3:00	06:00	Allocation to treatment (randomisation)[2]	x[2]		x[2]		x[2, 7]		x[2]	x[2]
		0:00	**09:00**	**Drug administration (with app. 240 mL water)**						▲		x
		0:30	09:30				x		x[7]	|	x	x
		1:00	10:00				x		x[7]	|	x	x
		1:30	10:30				x			|	x	x
		2:00	11:00	**App.** 240 mL fluid intake			x		x[7]	|	x	x
		2:30	11:30				x			|		
		3:00	12:00				x		x[7]	|	x	x
		4:00	13:00	**App.** 240 mL fluid intake, thereafter lunch[3]	x		x		x[7]	▼	x	x
		5:00	14:00				x					x
		6:00	15:00				x		x[7]		x	x
		8:00	17:00				x		x[7]		x	x
		10:00	19:00	Dinner[3]			x					x
		12:00	21:00				x		x[7]		x	x
	2	24:00	09:00	Breakfast [3]	x		x		x		x	x
		28:00	13:00	Lunch[3]								x
		34:00	19:00				x		x		x	x
		34:30	19:30	Dinner[3]								x
	3	48:00	09:00	Breakfast [3], discharge from trial site			x		x		x	x
	4	72:00	09:00	Ambulatory visit[12]			x		x		x	x
	5	96:00	09:00	Ambulatory visit[12]			x				x	x
	8	168:00	09:00	Ambulatory visit[12]	x		x					x
3	9 to 13			End of study (EOS) examination[4]	x				x		x	x

AE: adverse event, app.: approximately, ECG: Electrocardiogram, PK: pharmacokinetic(s)

1. Subject must be informed and written informed consent obtained prior to starting any screening procedures. Screening procedures (28 to 2 days before drug administration) include physical examination, check of vital signs, ECG, safety laboratory test, exclusionary laboratory tests (including drug screening, infection serology, and alcohol breath test), demographics (including determination of body height and weight), relevant medical history, concomitant therapy and review of inclusion/exclusion criteria. Screening procedure should complete prior to Visit 2.
2. The time is approximate; the respective procedure is to be performed and completed within 3 hours prior to drug administration. Allocation to treatment may be performed at any time following enrolment but must be completed prior to drug administration.
3. If several actions are indicated at the same time point, the intake of meals will be the last action.
4. EOS examination to be performed within 1-4 days after last PK sampling; includes physical examination, vital signs, ECG, safety laboratory, recording of AEs and concomitant therapies.

5. 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. Concomitant therapy is prohibited in this trial (refer to Section 4.2.2.1) but will be recorded if taken.
6. Safety laboratory, drug screening and alcohol breath test will be performed on admission to be medically evaluation. If those tests are performed within 2 days prior to admission, they can be omitted.
7. The ECG recording has to be performed in triplicate at this time point
8. Sampling times and periods may be adapted based on information obtained during the trial (e.g., preliminary PK data)
9. It is monitored for at least 15 min before drug administration (for baseline assessment) and for 4 hours following drug administration)

11. Blood pressure (BP), pulse rate (PR), body temperature, and respiratory rate (RR).
12. Procedures on Days 4, 5 and 8 to be performed within ±3 hours from planned time
13. Only drug screening and alcohol test

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ABBREVIATIONS

AE	adverse event
AESI	adverse events of special interest
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration
$AUC_{0-\infty}$	area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
β	slope parameter associated with the power model used to evaluate dose proportionality
BI	Boehringer Ingelheim
BLQ	below the lower limit of quantification
BMI	body mass index (weight divided by height squared)
BP	blood pressure
CA	competent authority
CI	confidence interval
CNS	central nervous system
C_{max}	maximum measured concentration of the analyte in plasma
CRA	clinical research associate
CRF	case report form, paper or electronic (sometimes referred to as ‘eCRF’)
CRO	contract research organisation
CTL	clinical trial leader
CTP	clinical trial protocol
CTR	clinical trial report
DG	dose group
DILI	drug induced liver injury
ECG	electrocardiogram
eDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
EOS	end of study

GCP	Good Clinical Practice
HR	heart rate
IB	investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	independent ethics committee
ILC	innate lymphoid cell
IPD	important protocol deviation
IRB	institutional review board
IQRMP	integrated quality and risk management plan
ISF	investigator site file
LBD	ligand-binding domain
MedDRA	Medical Dictionary for Regulatory Activities
NK	natural killer
NCE	new chemical entity
NOA	not analysed
NOAEL	no observed adverse effect level
NOP	no peak detectable
NOR	no valid result
NOS	no sample available
PIF	photoirritancy factor
PK	pharmacokinetic(s)
PKS	pharmacokinetic set
PR	pulse rate
PsA	psoriatic arthritis
PsO	psoriasis
QT	time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
R	reference treatment
REP	residual effect period
RORγt	retinoic acid related orphan receptor γt
RR	respiratory rate

SAE	serious adverse event
SCR	screening
SOP	standard operating procedure
SRD	single-rising dose
ss	(at) steady state
TMF	trial master file
TSAP	trial statistical analysis plan
ULN	upper limit of normal
WoCBP	women of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Retinoic acid related orphan receptor γt (RORγt) is a nuclear hormone receptor/transcription factor expressed in Th17 cells and in distinct subsets of lymphoid cells, including natural killer (NK) cells, innate lymphoid cells (ILC), and γδT cells. RORγt sits at a key focal point, integrating multiple signals, including T cell receptor engagement and cytokines (e.g., IL-1, IL-6, IL-23), and driving the expression of multiple genes (e.g., IL-17A, IL-17F, IL-22, IL-23R). Via sitting at this focal node integrating multiple signals and effecting multiple outputs, RORγt has the potential

Boehringer Ingelheim (BI) is developing the new chemical entity (NCE), BI 730357, for the treatment of patients and other diseases. BI 730357 binds . By integrating multiple activating signals and via blocking the transcription of multiple key effector BI 730357 has the potential to be as or more efficacious than agents in the treatment of -related disease indications.

1.2 DRUG PROFILE

1.2.1 Nonclinical pharmacology

BI 730357 was profiled in cellular assays in primary human cells central to the pathogenesis underlying BI 730357 provided consistent potency across all stimuli, cell types, and species tested, including conditions. BI 730357 provided substantial inhibition of disease-relevant biomarker and histology reads in mechanistic models

BI 730357 showed good in that it exhibited and only low-level low-level and low-level No other were detected.

1.2.2 Toxicology

The toxicity profile of BI 730357 has been assessed in safety pharmacology, genetic toxicity, embryo-fetal development and repeat dose toxicity studies up to 26- and 39-weeks respectively. In general, BI 730357 appears to be well tolerated at clinically-relevant plasma exposures in toxicity studies. Effects on the gastrointestinal tract (emesis/vomitus and/or soft stool) and/or decreased food consumption associated with adverse decreases in body weight were seen (which achieved the anticipated human therapeutic exposure). In the 39-week study, at (equivalent to the anticipated human therapeutic exposure

, stomach inflammation limited to the cardia and fundus was observed, with evidence for reversibility. In the 4- and 13-week studies no stomach inflammation was seen at doses however gastrointestinal effects such as emesis/vomitus and decreased food consumption and body weight were seen. As similar gastro-intestinal effects were seen in the 39-week study the microscopic stomach inflammation may be preceded by clinically-notable effects on the gastrointestinal tract.

The results of the *in vitro* and *in vivo* genetic toxicology studies showed that BI 730357 were free of any genotoxic potential.

The phototoxic potential of BI 730357 was evaluated in *in vitro* and *in vivo* studies. BI 730357 exhibits an absorption band in the spectral region with a maximum absorbance
Quantitative tissue distribution of was investigated in male pigmented (Long Evans) rats administered a of BI 730357. Deposition of was moderate to high as was the level in the . The approximate half-lives and were long, , respectively. The half-lives in , including were significantly than those in plasma and whole blood indicating exposure in these tissues. An *in vitro* assay for phototoxic potential using and measuring as a marker of cellular toxicity when simultaneously treated with UV light yielded a mean . The photoirritancy factor (PIF) as BI 730357 was but not An *in vivo* phototoxicity study in rats was conducted in pigmented rats. Rats were administered BI 730357 by oral gavage for . On Drug skin and eyes of the anesthetized animals were exposed to UVR or sham UVR exposure. Dose-dependent cutaneous reactions were seen that were indicative of a related to the administration of BI 730357 and UVR exposure. Based on the in one animal, at could not be ruled out, however, there was no histopathologic correlate for the . No cutaneous reactions indicative of phototoxic response were seen which corresponded to mean values of respectively. No ophthalmic changes indicative of phototoxicity were seen up to which corresponded to a mean values of respectively. Based on a margin of approximately the anticipated human therapeutic exposure (based) to the no observed adverse effect level (NOAEL) of skin findings, the phototoxicity potential at therapeutic doses in humans may be low. However, trial subjects are advised to apply protection measures, such as sunscreen, while on BI 730357 therapy.

BI 730357 revealed no evidence of teratogenicity in embryo-fetal development studies in In the repeat dose studies up to 26- and 39-weeks in respectively, there were no effects on male or female reproductive organs.

In summary, non-clinical BI 730357 safety data demonstrated an acceptable profile to support clinical trials in males and females, including women of child-bearing potential (WoCBP). Human exposures up to those achieved at the NOAEL of in the 4- and 13-week dog studies in males and females

combined) are considered safe for dosing up to 13 weeks in clinical trials. For clinical trials that exceed 13 weeks duration, human exposures up to those achieved at the NOAEL of in the 39-week dogs study in males and females combined) are considered safe.

For a more detailed description of the BI 730357 toxicology, please refer to the current investigator's brochure (IB) [c09228382].

1.2.3 Nonclinical pharmacokinetics

The disposition of BI 730357 is characterized in oral bioavailability was observed across species, which suggests that following oral administration, the bioavailability of BI 730357 in humans is likely to be The plasma protein binding of BI 730357 was In a quantitative whole body autoradiography study in male BI 730357-derived radioactivity was absorbed and distributed to tissues. There was evidence of central nervous system (CNS) exposure to drug-related material. Deposition of radioactivity into melanin-containing tissues of the ocular bulb was

When incubated with human , BI 730357 undergoes predominately via This was also observed following incubations with rat, dog, and minipig-suspended . When BI 730357 was incubated with a selective inhibitor of in a human model, the overall metabolism was inhibited by ~90%, confirming that BI 730357 is mainly metabolized Therefore, if BI 730357 is primarily there is a high risk that co-administration with will significantly increase BI 730357 exposure.

The propensities of BI 730357 to inhibit, inactivate, and/or induce CYP isoforms was evaluated *in vitro*. Based on the criteria set in the regulatory authorities' drug-drug-interaction guidance documents and considering the current projected efficacious dose and exposure, BI 730357 is unlikely to be a clinically-relevant nor is it a clinically-relevant However, BI 730357 was determined to be a potentially and was also determined to be an The net effect of BI 730357 on a sensitive was estimated using a mechanistic static model as recommended in the FDA drug-drug interaction guidance. Using this model, BI 730357 is predicted to by . Induction of ; inhibition of by BI 730357 at anticipated human therapeutic exposure levels is also predicted to be [c09228382].

1.2.4 Prediction of human pharmacokinetics

For detailed information, please refer to Section 1.2.5 and the current IB [c09228382].

1.2.5 Clinical experience in humans

The Phase Ia, first-in-human, single-rising-dose (SRD) trial 1407.1 was completed. BI 730357 has been administered to 54 healthy male subjects as a single dose, while 18 subjects received placebo. An additional 12 subjects were treated with 3 individual doses of BI 730357 consecutively. The overall frequency of subjects with treatment-emergent adverse event (AE) was higher for subjects who received BI 730357 (7.4%) than for subjects who received placebo (5.6%), however no dose-dependency was evident, nor were differences observed among treatments in a bioavailability substudy. The most frequent of these was headache in 5.6% subjects receiving BI 730357 and in 5.6% in subjects receiving placebo. The only other drug-related AE was oropharyngeal pain, reported for 1 subject receiving BI 730357. AEs generally reflected commonly-occurring events of short duration, were mostly mild or moderate in severity, and were distributed without discernable trend among recipients of placebo and rising dose levels of BI 730357. There were no serious adverse events (SAE) reported. Overall, BI 730357 was well tolerated.

Preliminary safety data for recently-completed Phase Ib multiple-rising-dose trial 1407-0002 indicate that with respect to the kind, incidence and severity of the AEs, there were no notable differences among dose groups. No SAEs were reported during the trial. ECG recordings, clinical laboratory evaluation, and vital signs showed no clinically-relevant changes compared to baseline. Overall, administration of BI 730357 to healthy male subjects at doses up to 400 mg for up to 28 days was well tolerated.

In SRD trial 1407.1, exposure to BI 730357 increased in a dose-proportional manner for solution between 2 and 8 mg and for tablet up to 50 mg, and thereafter increased in a less-than-dose-proportional manner, with approximately 1.5-fold increase in exposure with each 2-fold increase in dose up to 400 mg in the fasted state. Bioavailability of the 25 mg tablet fasted was less than that of the 25 mg solution fasted. There was greater exposure following administration of the 25 mg tablet under fed than fasted conditions, suggesting a positive food effect for BI 730357. BI 730357 was also administered at 400 mg and 800 mg under fed conditions (following standardized continental and high-fat breakfasts) to further evaluate the safety and PK of higher BI 730357 exposures. These results show that exposures continue to increase at higher doses with food, suggesting a positive food effect.

In Phase Ib trial 1407-0002, preliminary PK data indicate that exposure appears to increase in an approximately dose-proportional manner from 25 mg to 100 mg dose after repeat oral dosing of BI 730357 in the fasted state, and in a less-than dose-proportional manner from the 100 mg to 200 mg dose. .
Accumulation of BI 730357 was approximately 2-fold from single dose to steady state for all dose groups.

For a more detailed description of the BI 730357 clinical trial, please refer to the current IB [c09228382].

1.2.6 Residual Effect Period

The residual effect period (REP) for BI 730357 is not known at this early stage of development and therefore conservatively defined as . This is the period which covers

more than terminal half-lives of the study drug in 1407.1. Please refer the detailed data obtained in SRD trial 1407.1 in the current IB [c09228382].

1.2.7 Drug product

BI 730357 is a white to off-white to yellow powder and practically insoluble in buffer solutions, and it is .

For a more detailed description of the BI 730357 profile, please refer to the current IB [c09228382].

1.3 RATIONALE FOR PERFORMING THE TRIAL

This Phase I study is to investigate the safety, tolerability, and PK of BI 730357, in order to understand the clinical safety and pharmacokinetic profile in healthy male Japanese subjects after single-rising oral doses of BI 730357 within the dose range to be evaluated in further clinical studies with BI 730357 in the indication .

Japanese healthy male subjects aged 20 to 45 years will be recruited for this study. This population is expected to provide a relatively stable physiological, biochemical, and hormonal basis (steady state) for studying drug effects, and to show no disease-related variation, and is not expected to use concomitant medication.

Within each dose group, all actively-treated individuals will receive the same BI 730357 dose. The next higher dose will only be administered (to the next group) if the treatment in the preceding dose groups was safe and showed acceptable tolerability. BI 730357 dose levels evaluated in this trial have been previously evaluated in first-in-human trial 1407.1, the results of which are provided in Section 1.2.5.

Dose selection

It is intended to investigate the following dose levels of BI 730357 in this trial: 50 mg, 100 mg, and 200 mg. The background for this dose selection is described in the following paragraphs.

A minimum daily dose of about may be required to achieve therapeutic systemic exposure to BI 730357. However, higher doses might still be well tolerated while providing a larger magnitude of therapeutic effects. Further, testing of doses higher than is also reasonable to compensate for any bioavailability and half-life lower than expected. Finally, even if the therapeutic dose is determined to be as low as , higher than therapeutic doses are typically explored Phase I studies to provide a safety margin for following studies e.g., drug-drug-interaction studies, studies with patients with impaired excretion function, etc., where substantial increases in exposure may be seen.

For this study 200 mg has been selected as the maximum dose, a dose that is expected to be high enough to obtain exposure in the therapeutic range, even if the bioavailability was significantly lower than the expected (refer to Section 1.2.5).

Non-clinical BI 730357 safety data demonstrated an acceptable profile to support clinical trials in males and females, including women of childbearing potential. Human exposures up to those achieved at the NOAEL in the 4- and 13-week

in males and females combined) are considered safe for dosing up to 13 weeks in clinical trials. The mean exposures after single dose administration for the 200 mg fasting dose group in 1407-0002 remain below this NOAEL.

1.4 BENEFIT - RISK ASSESSMENT

Participation in this study is without any (therapeutic) benefit for healthy subjects. Their participation in the study, however, is of major importance to the clinical development of a new orally available drug, which might improve the therapy in patients . Subjects participating in this study are exposed to the risks of the study procedures and those related to the exposure to the trial medication.

Procedure-related risks

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

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

Drug-related risks and safety measures

The nature of the target and the mechanism of action of BI 730357 are well understood from preclinical models. The safety, tolerability, and PK exposure following single-dose administration of BI 730357 have already been established in first-in-human trial 1407.1, at dose levels up to 800 mg, 4-fold higher than the maximum dose level (200 mg) to be evaluated in the current trial. Furthermore, since this is not a First-in-Human trial, the risk is relatively lower.

The pharmacological effects of BI 730357 are dose dependent and no evidence for prolonged or irreversible effects has been observed. Single dose administration of dose levels up to 800 mg BI 730357 are supported by preclinical safety data.

- Extensive safety laboratory testing will be performed with special focus on full blood exam (refer to Flow Chart).
- A thorough ECG monitoring including 4-hours continuous 3-lead ECG measurement for at least 15 min before drug administration (for baseline assessment) and for 4 hours following drug administration to cover the anticipated period of highest drug exposure, and additional repeated single 12-lead ECGs over 48 hours (during hospital stay) following drug administration. Dose escalation would be stopped as soon as at

least 2 subjects at one dose level showed relevant QT prolongation (refer to Section 3.3.4.3 for details).

- Prior to each dose escalation, a documented safety review will be performed by the principal investigator and the sponsor (clinical trial leader [CTL]). For details, refer to Section 3.1.
- Subjects will be hospitalized on Day -1 (one day before drug administration) and will be discharged on Day 3 only after a formal assessment and confirmation of fitness by an investigator or qualified designee. During in-house confinement, subjects will be under close medical observation and thoroughly monitored for both, expected and unexpected AEs.
- Only if the respective dose of BI 730357 was safe and showed acceptable tolerability and if no stopping criterion was met (refer to Section 3.3.4.3), the next higher dose will be given at least 7 days later (referring to the 1st subject of each dose group).

Since preclinical data indicate that BI 730357 has potential for phototoxicity, subjects will be advised to apply protection measures such as sunscreen, and solarium radiation are prohibited during this clinical trial until the end of the respective follow-up period.

BI 730357 was determined *in vitro* to be a substrate, an inactivator, and an inducer of , as well as an inducer of , thus there is a potential risk of clinically relevant drug-drug interactions (DDI) occurring. Whether substrates will need to be excluded/monitored in subsequent clinical trials will be determined based on results of planned the DDI trials.

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

As with other therapies, impaired is a theoretical target-related toxicity, potentially resulting in increased risk of play an important role in extracellular at mucosal surfaces IL-17 are associated with . Homozygous, but not heterozygous mice have a high incidence of T cell lymphoma, thought to originate in the thymus . While the translatability of the phenotype to pharmacological RORγ and to humans is unknown, this raises the hypothetical concern for clinical T cell lymphoma risk. The exact cause of T cell lymphomas in mice is not fully understood, but changes in homeostasis in the thymus, such as thymocyte apoptosis and proliferation, are thought to play a role. AEs and SAEs consistent with malignancy, and specifically those representing lymphoma, are to be carefully monitored and evaluated throughout the BI 730357 clinical development program, and monitoring of peripheral blood lymphocyte subsets integrated into clinical trials.

In summary, BI 730357 has the potential to become an oral treatment Based upon preclinical and clinical data for BI 730357 to date, as well as the implemented safety measures described above, healthy subjects will not be exposed to undue risks in relation to

the important information expected from this trial as a basis for further clinical development of this compound. Healthy volunteers are not expected to have any direct benefit from participation in this Phase I clinical trial with BI 730357, as is the usual case in such Phase I trials. Considering the medical need of the development of a safer and more effective treatment for patients with PsO, the sponsor considers that the benefit outweighs the potential risks and justifies exposure of healthy human volunteers.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this trial is to investigate the safety and tolerability of BI 730357 in Japanese healthy male subjects following oral administration of single rising doses of 50 mg, 100 mg, and 200 mg.

Secondary objectives are the explorations of the PK, including dose proportionality as well as investigation of linearity of BI 730357 after single dose administration.

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.

2.1.2 Primary endpoint

Primary endpoint to assess safety and tolerability of BI 730357 is the number [N (%)] of subjects with drug-related adverse events.

2.1.3 Secondary endpoints

The following pharmacokinetic parameters will be determined if feasible:

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

- C_{max} (maximum measured concentration of the analyte in plasma)

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This SRD trial is designed as double-blind, randomised within dose group, and placebo-controlled within parallel dose groups.

A total of 24 Japanese healthy male subjects is planned to participate in the trial, according to 3 sequential groups comprising 8 subjects per dose group.

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.

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
Dose (mg)	50	100	200
Number of subjects	8	8	8
Subjects receiving placebo	2	2	2
Subjects receiving active drug	6	6	6

The dose groups will be investigated consecutively in ascending order of doses, maintaining a time interval of at least 7 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 group will only be dose if, in the opinion of the investigator, no safety concerns arose in the preceding dose group(s) (i.e., no dose-limiting events occurred) and if none of the pre-specified trial-specific stopping criteria were met (refer to Section 3.3.4).

A documented safety review must take place prior to randomization in the next group. 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 AEs, etc. Dose escalation will only be permitted if no safety concerns exist in the opinion of the principal investigator (or an authorised deputy) and the sponsor.

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

- AEs in the current and preceding dose group(s) (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 EGG and 4-hours continuous 3-lead 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 sponsor after in-depth analysis of all available safety data, especially SAEs (if any), AEs, and out-of-range laboratory results (if considered clinically significant). Safety reviews can be conducted verbally (e.g., teleconference) and/or in writing (e.g., encrypted emails, facsimiles correspondences or mails). The CTL 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 investigator site file (ISF) and trial master file (TMF).

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

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

For SRD trials, the design described in Section 3.1 is viewed as 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 730357.

With the rising dose design, double-blind conditions regarding the subjects' 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.

It is standard in trials involving healthy volunteers to include a placebo group as control for the evaluation of safety and tolerability. 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. Six 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 24 Japanese healthy male subjects will enter the study. Subjects will be recruited at the trial site.

Only male subjects will be included into the study.

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 trial 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, RR, body temperature), 12-lead ECG, and clinical laboratory tests
2. Japanese ethnicity, according to the following criteria:
   - born in Japan, have lived outside of Japan <10 years, and have parents and grandparents who are Japanese
3. Age of 20 to 45 years (inclusive) at screening
4. BMI of 18.5 to 25.0 kg/m^2 (inclusive) at screening
5. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial
6. Male subject who agree to minimize the risk of female partners becoming pregnant by fulfilling any of the following criteria starting from participation to this trial and until 90 days after the trial completion:
   - Use of adequate contraception, e.g., any of the following methods plus condom: combined oral contraceptives, intrauterine device.
   - Vasectomised (vasectomy at least 1 year prior to enrolment)
   - Surgical sterilised (including hysterectomy) of the subject's female partner

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 BP outside the range of 90 to 140 mmHg, diastolic BP outside the range of 50 to 90 mmHg, or PR outside the range of 45 to 90 bpm at screening
3. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance at screening
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. Cholecystectomy and/or surgery of the gastrointestinal tract that could interfere with the pharmacokinetics of the trial medication (except appendectomy and simple hernia repair)

7. Diseases of the CNS (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders, including but not limited to mood disorders and any history of suicidality
8. History of relevant orthostatic hypotension, fainting spells, or blackouts
9. Chronic or relevant acute infections including human immunodeficiency virus (HIV), viral hepatitis, syphilis and/or tuberculosis
10. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients)
11. Use of drugs within 30 days or 5 half-lives, whichever is longer, prior to administration of trial medication, if that might reasonably influence the results of the trial (including potential for QT/QTc interval prolongation)
12. 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
13. Previous exposure to BI 730357
14. Smoker (more than 10 cigarettes or 3 cigars or 3 pipes per day)
15. Inability to refrain from smoking on specified trial days
16. Alcohol abuse (consumption of more than 30 g per day for males)
17. Drug abuse or positive drug screening
18. Whole blood donation of more than 200 mL within 30 days or 400 mL within 12 weeks, or plasmapheresis and platelet apheresis within 2 weeks prior to administration of trial medication, or intended donation during the trial
19. Intention to perform excessive physical activities within one week prior to administration of trial medication or during the trial
20. Inability to comply with dietary regimen of trial site
21. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 mseconds) or any other relevant ECG finding at screening
22. A history of additional risk factors for Torsades de Pointes (such as heart failure, hypokalemia, or family history of Long QT Syndrome)
23. 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 Withdrawal of subjects from treatment or assessments

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

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

documented and the reason for discontinuation must be recorded in the CRF; in addition, the data will be included in the CRF and will be reported in the CTR.

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

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

- The subject wants to discontinue trial treatment, without the need to justify the decision
- The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future
- The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
- The subject can no longer receive trial treatment for medical reasons (such as surgery, AEs, or diseases)
- An AE or clinically significant laboratory change or abnormality occurs that the investigator assesses as warranting not administering trial medication. This may include cases of sustained symptomatic hypotension (BP <90/50 mmHg) or hypertension (BP >180/100 mmHg), clinically relevant changes in ECG requiring intervention, or unexplained hepatic enzyme elevations at any time during the trial
- The subject has an elevation of aspartate transaminase (AST) and/or alanine transaminase (ALT) ≥3-fold upper limit of normal (ULN) and an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample), an elevation of ALT and/or AST ≥10-fold ULN, and/or needs to be followed up according to 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.

Even if the trial treatment is discontinued, the subject remains in the trial and, given his/her agreement, will follow up as outlined in the Flow Chart and Section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

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

for continued follow up after trial treatment discontinuation, please refer to Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

- New toxicological findings or SAEs 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 AEs of moderate or severe intensity, or if at least one drug-related serious AE is reported that is considered to be unacceptable
- The expected enrolment goals overall or at a particular trial site are not met
- Violation of Good Clinical Practice (GCP), or the clinical trial protocol (CTP), or the contract with BI by a trial site or investigator, disturbing the appropriate conduct of the trial
- The sponsor decides to discontinue the further development of the investigational product
- 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 mseconds from baseline in connection with absolute QT or QTc greater than 500 mseconds, 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).

For the following scenario further enrolment randomisation into the trial and treatment of already randomised subjects will be interrupted by the sponsor once the sponsor becomes aware:

- Two SAEs in two different subjects in the same system-organ-class, confirmed by both the investigator and sponsor as having a reasonable causal relationship to the trial medication administration.

- Two ‘severe’ non-serious AEs in two different subjects in the same cohort, independent of within or not within the same system-organ-class, confirmed by both the investigator and sponsor as having a reasonable causal relationship to the trial medication administration.

3.3.5 Replacement of subjects

In case some subjects do not complete the trial, the CTL together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be

replaced. A replacement subject will be assigned a unique trial subject number, and will be assigned to the same treatment as the subject he replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational products have been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Table 4.1.1: 1 Test product

Substance	**BI 730357**
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	50 mg (DG 1) or 100 mg (DG 2, DG 3)
Posology:	1-0-0 (DG 1); 1-0-0 (DG 2); 2-0-0 (DG 3)
Route of administration:	oral
Duration of use:	Day 1 (single dose)

DG: dose group

Table 4.1.1: 2 Reference product

Substance	**Placebo matching in size and weight to 50 or 100 mg film-coated tablet**
Pharmaceutical formulation:	Film-coated tablet
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	n.a.
Posology:	1-0-0 (DG 1) (matching in size and weight to 50 mg film-coated tablet) 1-0-0 (DG 2) (matching in size and weight to 100 mg film-coated tablet) 2-0-0 (DG 3) (matching in size and weight to 100 mg film-coated tablet)
Route of administration:	oral
Duration of use:	Day 1 (single dose)

DG: dose group

4.1.2 Selection of doses in the trial

Three dose groups are to be investigated in this trial. Three dose levels will cover potential therapeutic dose ranges. The number of dose levels will also allow for evaluation of dose proportionality.

This trial is designed to evaluate the safety, tolerability, and pharmacokinetics of BI 730357 in Japanese healthy male volunteers. A safe and tolerable dose achieved in previous trials, including Caucasian SRD trial (1407.1), is used as a reference for the dose selection in this trial.

For safety margins and further details on dose selection, refer to Section 1.2 and 1.3.

4.1.3 Method of assigning subjects to treatment groups

Prior to the screening visit, subjects will be contacted in writing and informed about the planned visit dates. The subjects willing to participate will be recruited to dose groups according to their temporal availability. 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.

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

The randomisation procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each subject

The treatments to be evaluated are outlined in Table 4.1.4: 1 below. The number of units for placebo corresponds to the number of units of the respective dose level.

Table 4.1.4: 1 BI 730357 and placebo treatments, oral administration

Dose group	Substance	Pharmaceutical form	Unit strength	Number of units per administration	Total daily dose
1	BI 730357	film-coated tablet	50 mg	1 tablet	50 mg
2	BI 730357	film-coated tablet	100 mg	1 tablet	100 mg
3	BI 730357	film-coated tablet	100 mg	2 tablet	200 mg
1	Placebo*	Film-coated tablet	--	identical to active treatment	--
2	Placebo*	Film-coated tablet	--	identical to active treatment	--
3	Placebo*	Film-coated tablet	--	identical to active treatment	--

* Subjects receiving placebo are equally distributed across dose groups

The trial medication will be administered to the subjects, while in a sitting position, as an oral dose together with approximately 240 mL of water, under supervision of the investigating physician or an authorised designee. The so-called four-eye principle (two-person rule) should be applied for administration of trial medication, if correct dosage cannot be ensured otherwise.

Subjects will be kept under close medical surveillance until at least 48 hours following drug administration. During the first 4 hours after drug administration, they are not allowed to lie down (i.e., no declination of the upper body of more than 45 degrees from upright posture), except, if required for trial-related measurements (e.g., recording of 12-lead ECG) or for medical reasons (e.g., AEs).

For restrictions with regard to diet, refer to Section 4.2.2.2.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The trial is designed double-blind. The treatments administered (active or placebo) will be blinded to the subjects and the investigators (outcome assessors) in order to limit the occurrence of any bias which the knowledge of treatment may have. According to the rising dose design, the current dose level will be known to subjects and investigators.

At the sponsor's site, access to the randomisation schedule is restricted to the randomisation operators, the Clinical Trial Support group and the Pharmaceutics Department.

The trial pharmacokineticist may receive the randomisation codes prior to official unblinding to perform the preliminary PK analysis. He or she will confirm in writing that the codes will be treated confidentially.

In addition, regarding the sponsor, all trial data will be handled open label. This means that trial functions of the sponsor are unblinded (trial clinical leader, data manager, statistician, bioanalyst, pharmacokineticist as well as dedicated CRO personnel). This is acceptable because they are neither in contact with subjects nor with site staff.

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

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

4.1.5.2 Unblinding and breaking the code

The investigator or designee 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 otherwise assure safety of trial participants. If the envelope for a subject is opened, the sponsor must be informed immediately. The reason for breaking the code must be documented on the envelope and/or appropriate CRF page along with the date and the initials of the person who broke the code.

PK samples will be labelled in such a way that treatment allocation cannot be derived by the analytical site.

4.1.6 Packaging, labelling, and re-supply

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

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

No re-supply is planned.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area 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 contacted immediately.

4.1.8 Drug accountability

The investigator/pharmacist who is documented in the trial staff list/investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the institutional review board (IRB),
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the trial site,
- Notification of the regulatory authority, e.g., competent authority (CA)
- Availability of the curriculum vitae of the principal investigator
- Availability of a signed and dated CTP

Only authorised personnel as documented in the form 'Trial Staff List' may dispense medication to trial subjects. The trial medication must be administered in the manner specified in the CTP. All unused medication must be returned to sponsor. Receipt, usage and return must be documented on the respective forms. Account must be given for any discrepancies.

The investigator/pharmacist who is documented in the trial staff list/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 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 that is documented in the trial staff list/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 return to the sponsor or appointed contract research organization (CRO), the investigator/pharmacist who is documented in the trial staff list/investigational drug storage manager must verify that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed. No additional treatment is planned. However, in case of AEs in need of treatment, the investigator can authorise symptomatic therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all 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. No food is allowed for at least 4 hours after drug intake.

From 1 hour before drug intake until 4 hours post-dose liquid intake is restricted to the fluid (approximately 240 mL of water) administered with the drug and an additional approximately 240 mL of water served on Day 1 at 2 hours and 4 hours post-dose (mandatory for all subjects).

From 4 hours post-dose until 24 hours post-dose water intake is restricted to 3000 mL. During the days of urine collection, total fluid intake should be at least 1500 mL and should not exceed 3500 mL.

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

Smoking is not allowed during in-house confinement at the trial site.

Methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) are not allowed from 24 hours before administration of trial medication until the end of plasma pharmacokinetic sampling of the respective visit.

Excessive physical activity (such as competitive sport) should be avoided starting 7 days before the first administration of trial medication until the end of study 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 refer to Section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

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

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

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

5.2.2 Vital signs

Systolic and diastolic BP as well as PR will be measured by a BP monitor at the times indicated in the Flow Chart, after subjects have rested for at least 10 minutes in a supine position. All recordings should be made using the same type of BP recording instrument on the same arm if possible.

Further, RR and body temperature will be monitored. Body temperature will be determined at the time points indicated in the Flow Chart using electronic thermometers. RR will be counted by trained study personal by observing the chest movements over a period of one minute (30 second x 2) after the subject has rested in the supine position for 10 minutes. Recording of the values will be done at the time points indicated in the Flow Chart.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart after the subjects have fasted for at least 10 hours. 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.

Manual differential white blood cell count will only be performed if there is an abnormality in the automatic blood cell count, i.e. if automatic count is not feasible or differential WBC is abnormal (i.e., pathological or atypical cells) and clinically relevant in the opinion of the investigator.

In case the urinalysis is positive for erythrocytes, leukocytes, nitrite or protein and clinically relevant in the opinion of the investigator, microscopic examination of the urine sediment

will be performed. Positive findings of the urine sediment examination will be monitored and if needed based on the medical judgment of the investigator an urologist may be consulted.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	Test name	SCR	A[1]	B[2]	EOS[4]
Haematology	Haematocrit	x	x	x	x
	Haemoglobin	x	x	x	x
	Red blood cell count (RBC)	x	x	x	x
	Reticulocyte count	x	x	x	x
	White blood cell count (WBC)	x	x	x	x
	Platelet count	x	x	x	x
Automatic WBC differential (relative)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes	x	x	x	x
Manual differential WBC (if automatic count is not feasible or differential WBC is abnormal and clinically relevant in the opinion of the investigator)	Polymorphnuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes				
Coagulation	Activated partial thromboplastin time (aPTT)	x	x	x	x
	Prothrombin time (Quick's test and INR)	x	x	x	x
	Fibrinogen	x	x	x	x
Enzymes	Aspartate transaminase (AST/GOT)	x	x	x	x
	Alanine transaminase (ALT/GPT)	x	x	x	x
	Alkaline phosphatase (AP)	x	x	x	x
	Gamma-glutamyl transferase (GGT/γ-GT)	x	x	x	x
	Creatine kinase (CK)	x	x	x	x
	CK-MB, only if CK is elevated	x	x	x	x
	Lactate dehydrogenase (LDH)	x	x	x	x
	Lipase	x	x	x	x
	Amylase	x	x	x	x
Hormones	Thyroid stimulating hormone (TSH)	x	--	--	--
Substrates	Plasma glucose	x	x	x	x
	Creatinine	x	x	x	x
	Blood Urea Nitrogen (BUN)	x	x	x	x
	Total bilirubin	x	x	x	x
	Direct bilirubin	x	x	x	x
	Total protein	x	x	x	x
	Albumin	x	x	x	x
	C-Reactive Protein (CRP)	x	x	x	x
	Uric acid	x	x	x	x
	Total cholesterol	x	x	x	x
	Triglycerides	x	x	x	x
Electrolytes	Sodium	x	x	x	x
	Potassium	x	x	x	x
	Calcium	x	x	x	x

Table 5.2.3: 1 Routine laboratory tests (cont).

Functional lab group	Test name	SCR	A[1]	B[2]	EOS
Urinalysis (strip of dipstick)	Urine nitrite	x	x	--	x
	Urine protein	x	x	--	x
	Urine glucose	x	x	--	x
	Urine ketone	x	x	--	x
	Urobilinogen	x	x	--	x
	Urine bilirubin	x	x	--	x
	Urine erythrocytes	x	x	--	x
	Urine leukocytes	x	x	--	x
	Urine pH	x	x	--	x
Urine sediment[3]	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)	x	x	--	x

SCR: screening, EOS: end of study

1 A: parameters to be determined at Visit 2 on Day -3 to -1, Day 1, 2, 8 (for time points refer to Flow Chart)
2 B: parameters to be determined at Visit 2, after 4 hours on Day 1 (for time points refer to Flow Chart)
3 Only if erythrocytes, leukocytes nitrite or protein are abnormal in urine and are deemed clinically necessary by the investigator

The tests listed in Table 5.2.3: 2 are exclusionary laboratory tests which may be repeated as required. The results will not be entered in the CRF/database and will not be reported in the CTR. Infection serology test will be planned during screening only. Drug screening and alcohol test will be performed at screening and prior to treatment period.

Table 5.2.3: 2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine)	Amphetamine/MDA Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamines/MDMA/XTC Opiates (Morphine) Phencyclidine Tricyclic antidepressants
Infectious serology (blood)	Hepatitis A antibodies (qualitative) Hepatitis B surface antigen (qualitative) [1] Hepatitis B surface antibody (qualitative) [1] Hepatitis B core antibody (qualitative) [1] Hepatitis C antibodies (qualitative) HIV-1 and HIV-2 antigen and/or antibody (qualitative) QuantiFERON TB-Gold or T-SPOT [2] Syphilis test (RPR, TP antibody method)
Alcohol test	Breath alcohol test

1 If hepatitis B surface antigen and/or hepatitis B core antibody is positive, subject will be not allowed participating in this study. If hepatitis B surface antibody is positive, hepatitis B surface antigen and hepatitis B core antibody is negative, and there is evidence that subject gets hepatitis B virus vaccine, subject will be allowed participating in this study.
2 If QuantiFERON® or T-SPOT® is positive; subject will be not allowed participating in this study. Subject with latent tuberculosis will be not allowed participating in this study.

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

The laboratory tests listed in Table 5.2.3: 1 and 5.2.3: 2 will be performed by the local laboratory at the trial site and/or at an external vendor designated by the site.

Laboratory data will be transmitted electronically from the trial site to BI.

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

Recording

Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph (MAC 800 ECG machines, GE Healthcare) at the time points given in the Flow Chart.

Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

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

All ECGs will be recorded for 10-second duration after the subjects have rested for at least 10 minutes in a supine position. ECG recordings will always precede all other study procedures scheduled for 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.

ECGs will be recorded as single ECGs or as triplicate ECGs (i.e., three single ECGs recorded within 180 second) as indicated in the Flow Chart.

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. For time points with triple ECGs, all three single ECGs will be repeated. The repeat ECGs are assigned to the respective scheduled time point.

Additional (unscheduled) ECGs may be collected at the discretion of the investigator for safety reasons. These ECGs are assigned to the prior scheduled time point.

Storing

All ECGs will be stored electronically on the Muse Cardiology information System (GE Medical Systems, Freiburg, Germany)

Data transfer

For time points specified in the Flow Chart, ECGs will be transferred electronically to the central ECG lab ( ) for evaluation.

All ECGs (including repeat ECGs due to quality reasons) will be sent to the central ECG lab. The investigator will judge data adoption and send the information which ECGs were adopted to the central ECG lab.

Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

Data transfer from the central ECG lab to the sponsor is described in the ECG data transfer agreement (refer to TMF).

Evaluation

a) Central ECG lab

   A post-study centralized evaluation of all 12-lead ECGs recorded after Days 1 up to 72 hours after drug administration will be performed by an independent ECG laboratory. This analysis will include the determination of cardiac axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi-automatically. With the exception of the first triplicate ECG (used as baseline before the first drug administration), only the first of the triplicate ECG at a single assessment time will be evaluated. The remaining second and third replicate ECG will be stored for additional analyses if required, e.g., by authorities at a later time point.

HR and the QT interval corrected for HR (QTc e.g., QTcF and QTcB) will be determined by the sponsor (refer also to trial statistical analysis plan [TSAP] for details).

Abnormalities detected during centralized 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.

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

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

b) Trial site

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

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

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

5.2.4.2 4-hours continuous 3-lead ECG monitoring

Cardiac rhythm (including heart rate) will be monitored by means of 4-hours continuous 3-lead ECG recording using the Central Monitor DS-8700 (Fukuda, Japan) for at least 15 min before drug administration (for baseline assessment) and for 4 hours following drug administration). This 4-hours continuous 3-lead ECG monitoring supports the early detection of adverse events such as clinically relevant bradycardia, tachycardia, or arrhythmia at the

trial site. Beyond this clinical evaluation at the trial site, no further data collection or analyses are performed based on 4-hours continuous 3-lead ECG monitoring.

ECG data from 4-hours continuous 3-lead ECG recording will not be transferred to the clinical trial database. Abnormal findings during 4-hours continuous 3-lead ECG recording will be recorded as AEs if judged clinically relevant by the Investigator.

5.2.5 Other safety parameters

Not applicable

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a subject 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.

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

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

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

5.2.6.1.2 Serious adverse event

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

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

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

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

5.2.6.1.3 AEs considered 'Always Serious'

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the trial medication and must be reported as described in Section 5.2.6.2, subsections 'AE Collection' and '**AE reporting to sponsor and timelines'**.

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

The latest list of 'Always Serious AEs' can be found in the electronic data capture (eDC) system, an electronic data capture system which allows the entry of trial data at the trial site.

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - 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, or
  - o Aminotransferase (ALT and/or AST) elevations ≥10-fold ULN

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

5.2.6.1.5 Intensity (severity) of AEs

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

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

Moderate: Sufficient discomfort to cause interference with usual activity

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

5.2.6.1.6 Causal relationship of AEs

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

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

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

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

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

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

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

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 Information required

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

5.2.6.2.4 Pregnancy

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

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

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

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

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

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 400 mL. Such changes would be implemented via non-substantial CTP Amendments.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 730357 plasma concentrations, 3 mL of blood will be taken from an antecubital or forearm vein into an ethylenediaminetetraacetic acid (EDTA)-anticoagulant blood drawing tube at the times indicated in the Flow Chart. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

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

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

After completion of the trial the plasma samples may be used for further methodological investigations**,** e.g., for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.3.2.2

The weight of the empty container will be determined, thereafter suitable volume of 10% Tween 20 will be added and the weight of the container at the end of each sampling interval will be determined. The urine collection container will be slightly mixed after each urine event. Details will be described in the lab manual.

The urine weight/volume for each collection interval will be documented (however, no correction for the specific gravity of urine is done, i.e., 1 L is defined to be equal to 1 kg). Two 0.5 mL aliquots will be stored in PP tubes for bioanalytical measurement. In case more than one collection container is used in an interval, the contents of all containers are to be mixed before aliquots are prepared. Mixing should be done by transferring the entire content of all collection containers into a single PE/PP or glass container, and stirring the mixed fractions for about 1 min (manually or using a stir bar or other stirring device out of PE, PP, Teflon or glass).

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

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

After completion of the trial the urine samples may be used for further methodological investigations, e.g., for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years upon the final study report has been signed.

5.3.3 Analytical determinations

5.3.3.1 Analytical determination of analyte plasma concentration

BI 730357 concentrations in plasma will be determined by a validated LC-MS/MS (liquid chromatography tandem mass spectrometry) assay. All details of the analytical method will be available prior to the start of sample analysis. The analysis will be performed at

.

As described in Section 4.1.5, the bioanalyst will be unblinded during sample analysis.

5.3.3.2

5.4 BIOBANKING

Not applicable.

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 study examination are given in the Flow Chart.

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

The tolerance for drug administration will be ± 1 minute on Days 1.

The acceptable deviation on Day 1 from the scheduled time for vital signs and ECG will be -15 minutes for the first 4 hours after the drug administration and - 30 minutes thereafter. After Day 2, vital signs and ECG will be ± 30 minutes from the scheduled time. Blood sampling for safety laboratory tests will be ± 30 minutes for the first 24 hours after trial drug administration. Urine sampling for safety laboratory tests will be -3 hours on Day 2 (24 hours after trial drug administration).

Procedures on Days 4, 5 and 8 to be performed within ±3 hours from planned time.

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

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

Relevant time violations will be identified and their handling discussed no later than at the (blinded) report planning meeting (refer to Section 7.4).

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening period

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

Each subject will receive one dose of the respective trial medication (BI 730357 or placebo) at Visit 2.

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

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 hours following the drug administration. The subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or his designee. On all other study days, the study will be performed in an ambulatory fashion.

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

The safety measurements performed during the treatment period are specified in Section 5.2 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 study examination.

6.2.3 End of study period

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of study period, refer to Sections 5.2.2 to 5.2.6.

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

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

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The main objectives of this trial will be assessed by calculating descriptive statistics for safety as well as for PK parameters, which will be compared between the treatment groups. Further analyses of these endpoints comprise the power model for assessment of dose proportionality.

7.2 NULL AND ALTERNATIVE HYPOTHESES

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

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

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all subjects who were randomized and treated with at least one dose of study drug. The treatment assignment will be determined based on the first treatment the subjects received. The treated set will be used for safety analyses.

- Pharmacokinetic parameter analysis set (PKS): This set includes all subjects in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol deviation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection 'Pharmacokinetics'). Thus, a subject will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment. Descriptive and model based analyses of PK parameters will be based on the PKS.

Adherence to the protocol will be assessed by the trial team. Important protocol deviations (IPD) categories will be specified in the integrated quality and risk management plan (IQRMP), IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Sections 2.1 and 2.2 for BI 730357 will be calculated according to the relevant standard operating procedure (SOP) of the Sponsor (001-MCS-36-472).

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

Relevant protocol deviations may be:

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

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

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

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

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

7.3.1 Primary endpoint analyses

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

7.3.2 Secondary endpoint analyses

Primary analyses

The secondary endpoints (refer to Section 2.1.3) will be analysed descriptively.

7.3.4 Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.2 and 2.2.2 based on the treated set (TS). Safety analyses will be descriptive in nature and will be based on BI standards.

For all analyses the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the randomised treatment will be discussed in the minutes of the report planning meeting).

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

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

Therefore, measurements planned or AEs recorded prior to intake of trial medication will be assigned to the screening period, those between trial medication intake and end of REP (refer to Section 1.2.6) will be assigned to the treatment period. Events occurring after the REP but prior to trial termination date will be assigned to ‘follow-up’. These assignments including the corresponding time intervals will be defined in detail in the TSAP. Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database.

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

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity and causal relationship of AEs will be tabulated by treatment, system organ class and preferred term. SAEs, AESIs (refer to Section 5.2.6.1) and other significant AEs (according to ICH E3) will be listed separately.

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

Laboratory data will be compared to their reference ranges. Values outside the reference range as well as possibly clinically significant values will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

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

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

7.4 INTERIM ANALYSES

No interim analysis is planned.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

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

7.5.2 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_RD-01).

Drug concentration data identified with no sample available (NOS), no valid result (NOS), not analysed (NOA), BLQ, or no peak detectable (NOP) 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).

7.5.3 Pharmacokinetics

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (001-MCS-36-472_RD-01).

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.

7.6 RANDOMISATION

Subjects will be randomised within each dose group in a 3:1 ratio (test treatment to placebo).

The sponsor will arrange for the randomisation as well as packaging and labelling of trial medication. The randomisation list will be generated using a validated system that uses a

pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

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

7.7 DETERMINATION OF SAMPLE SIZE

It is planned to include a total of 24 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 commonly used in SRD studies of the present type and is in general considered as sufficient for the exploratory evaluation of single dose safety and pharmacokinetics.

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

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonised Guideline for GCP and relevant BI SOPs, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997), and other relevant regulations. Investigators and site staff must adhere to these principles.

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

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

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

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

8.1 TRIAL APPROVAL, SUBJECT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB/independent ethics committee (IEC) and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

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

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

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

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

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

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

8.3.1 Source documents

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

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

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

Before sending or uploading those copies, the investigator must ensure that all subject identifiers (e.g., subject's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the subjects' source documents.

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

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

- Subject identification: gender, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date (mandatory), and end date (if available))
- SAEs (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of subject's participation in the trial" (end date; in case of premature discontinuation document the reason for it).

Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g., medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

8.3.2 Direct access to source data and documents

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

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND SUBJECT PRIVACY

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

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 6 and 12 of the WHO GCP handbook.
Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

8.6 TRIAL MILESTONES

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

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

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

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

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by BI.

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

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

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,

- ensure appropriate training and information of clinical trial manager (CTM), CRAs, and investigators of participating countries.

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

Safety laboratory tests will be performed by the local laboratory of the trial site or/and at an external vendor designated by the site.

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

The analyses of BI 730357 concentrations in plasma will be performed at the .

On-site monitoring will be performed by BI.

Data Management and Statistical Evaluation will be done by BI or a CRO 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 (as protocol reference, if applicable) can be found in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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R09-4830 Brown BD, Badilini F. HL7 aECG implementation guide (March 21, 2005).

R13-2643 Hueber W, Sands BE, Lewitzky S, Vandemeulebroecke M, Reinisch W, Higgins PD, et al. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomised, double-blind placebo-controlled trial. Gut. 2012; 61 (12): 1693-1700.

R16-0366 E14 Implementation Working Group. ICH E14 guideline: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: questions & answers (R3) (current version dated 10 December 2015). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1 4/E14_Q_As_R3__Step4.pdf (access date: 29 January 2016) ; Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (2015)

R16-2630 Ueda E, Kurebayashi S, Sakaue M, Backlund M, Koller B, Jetten AM. High incidence of T-cell lymphomas in mice deficient in the retinoid-related orphan receptor RORγ. Cancer Research. 2002;62: 901-909.

R16-3149 Onishi RM, Gaffen SL. IL-17 and its target genes: mechanisms of IL-17 function in disease. Immunology. 2010; 129: 311-321.

R16-3166 Miossec P. Cliical implications of Th17/IL-17. Diseases that may benefit from manipulating the Th17 pathway. Eur J Immunol. 2009; 39: 667-669.

9.2 UNPUBLISHED REFERENCES

001-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version

c09228382 Investigators´s Brochure. BI 730357. Psoriasis (ankylosing spondylitis, psoriatic arthritis, asthma, inflammatory bowel disease). Current version.

10. APPENDICES

Not applicable.

11. DESCRIPTION OF GLOBAL AMENDMENT

11.1 GLOBAL AMENDMENT 1

Date of amendment		13 December 2018
BI Trial number		1407-0015
BI Investigational Medicinal Product(s)		BI 730357
Title of protocol		Safety, tolerability, and pharmacokinetics of single rising oral doses of BI 730357 in Japanese healthy male subjects (double-blind, randomised, placebo-controlled, parallel group design)
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Section 3.1
Description of change		Changed section to be referred
Rationale for change		To correct error
Section to be changed		Section 4.1.5.1
Description of change		Added sentences to explain how to handling blind status
Rationale for change		To make charily how to handling blind status
Section to be changed		Section 5.2.4.1
Description of change		Deleted duplicate paragraphs
Rationale for change		Because of description mistake
Section to be changed		Section 5.3.3.2
Description of change		
Rationale for change		Because of description mistake

Section to be changed		Section 8.7
Description of change		Changed lab for analyte plasma and urine concentration
Rationale for change		Because of description mistake

APPROVAL / SIGNATURE PAGE

Document Number: c21031338 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-02

Title: Safety, tolerability, and pharmacokinetics of single rising oral doses of BI 730357 in Japanese healthy male subjects (double-blind, randomised, placebo-controlled parallel group design)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader		18 Dec 2018 03:09 CET
Author-Trial Statistician		18 Dec 2018 03:25 CET
Author-Trial Clinical Pharmacokineticist		18 Dec 2018 03:43 CET
Approval-Therapeutic Area		18 Dec 2018 09:55 CET
Approval-Team Member Medicine		19 Dec 2018 19:17 CET
Verification-Paper Signature Completion		25 Dec 2018 16:14 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed