Clinical Trial Protocol

	Global ID_Version:	**228892_3371506_4.0**
EU Clinical Trial No. **Universal Trial Number**	2025-520658-12 U1111-1317-7542	
Trial Sponsor	Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein Germany	
Boehringer Ingelheim Trial No.	1493-0002	
Boehringer Ingelheim Investigational Medicinal Product(s)	BI 765423	
Title	A double-blind, randomised, placebo-controlled, parallel group, Phase IIa trial to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of BI 765423 administered intravenously with or without standard of care in patients with idiopathic pulmonary fibrosis	
Lay Title	A study to find out whether BI 765423 has an effect on lung function in people with idiopathic pulmonary fibrosis (IPF) with or without standard treatment	
Clinical Phase	IIa	
Clinical Trial Leader	[redacted]	
Coordinating Investigator	[redacted]	
Current Version and Date	Version 2.0, [redacted]	
Original Protocol Date	Version 1.0, [redacted]	Page 1 of **109**

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CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date **Latest revision date**	[redacted] [redacted]
Boehringer Ingelheim trial number **EU CT number** **Universal Trial Number**	1493-0002 2025-520658-12 U1111-1317-7542
Title of trial	A double-blind, randomised, placebo-controlled, parallel group, Phase IIa trial to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of BI 765423 administered intravenously with or without standard of care in patients with idiopathic pulmonary fibrosis
Coordinating Investigator	[redacted]
Trial site(s)	Approximately [redacted] sites and approximately [redacted] countries
Clinical phase	IIa
Trial rationale	1493-0002 is a trial of limited duration focused on evaluation of proof-of-clinical principle and short-term general antifibrotic efficacy, safety, and tolerability of BI 765423 (administered every [redacted] intravenously) in patients with IPF.

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Benefit-risk assessment and ethical considerations	Administration of BI 765423 is expected to [redacted] and [redacted] and to offer a benefit by [redacted] in IPF and [redacted]. However, individual benefit might not be experienced, but participation in the trial is benefitting clinical development of BI 765423/anti-IL11 in patients with pulmonary fibrosis. Based on BI 765423 non-clinical and clinical data in healthy volunteers to date, there are no identified risks. The important potential risk of embryo-foetal toxicity, hypothetical risks stemming from general safety considerations, and risks related to trial procedures have been reviewed and mitigation strategies put in place. Given the unmet medical need, anticipated benefit of BI 765423, and available non-clinical and clinical information, the benefit-risk evaluation of the compound is acceptable. Considering the medical need for the development of a better tolerated and more effective treatment for patients with IPF [redacted], the expected benefit outweighs the possible risks.
Trial objective(s)	The primary objective is to estimate the absolute difference in means of FVC change from baseline after 12 weeks between BI 765423 and placebo. The main secondary objective is to estimate the absolute difference in means of log_{10}-transformed SP-D plasma concentration change from baseline after 12 weeks between BI 765423 and placebo. [redacted]
Trial endpoints	**Primary endpoint:** • Absolute change from baseline in FVC (mL) at 12 weeks. **Main secondary endpoint:** • Absolute change from baseline in log_{10}-transformed SP-D plasma concentration at 12 weeks **Other secondary endpoints:** [redacted]

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	[redacted]
Trial design	Placebo-controlled, double-blind, randomised, parallel group design comparison of 2 groups treated [redacted].
Total number of patients randomised	Approximately [redacted]
Number of patients per treatment group	Approximately [redacted]
Diagnosis, main inclusion and exclusion criteria	**Diagnosis** Patients with IPF. **Main inclusion criteria** • 40 years of age or older at the time of informed consent signature. • Male patients or female patients of non-childbearing potential. • Patients with a documented diagnosis of IPF prior to Visit 1, confirmed by the investigator as per the 2022 ATS/ERS/JRS/ALAT Guideline (Raghu G, Remy-Jardin M, Richeldi L, *et al.*) and, if available, surgical lung biopsy or transbronchial lung cryobiopsy histopathology report. • Patients with an HRCT taken within 12 months of Visit 1 (or during the screening period, if not available) confirming "UIP" or "probable UIP" HRCT pattern consistent with the clinical diagnosis of IPF by central review (prior to Visit 2). • Patients with an extent of fibrosis ≥20% as per an HRCT of the chest performed within 12 months prior to Visit 1 or during the screening period (if not available) and confirmed by central review.

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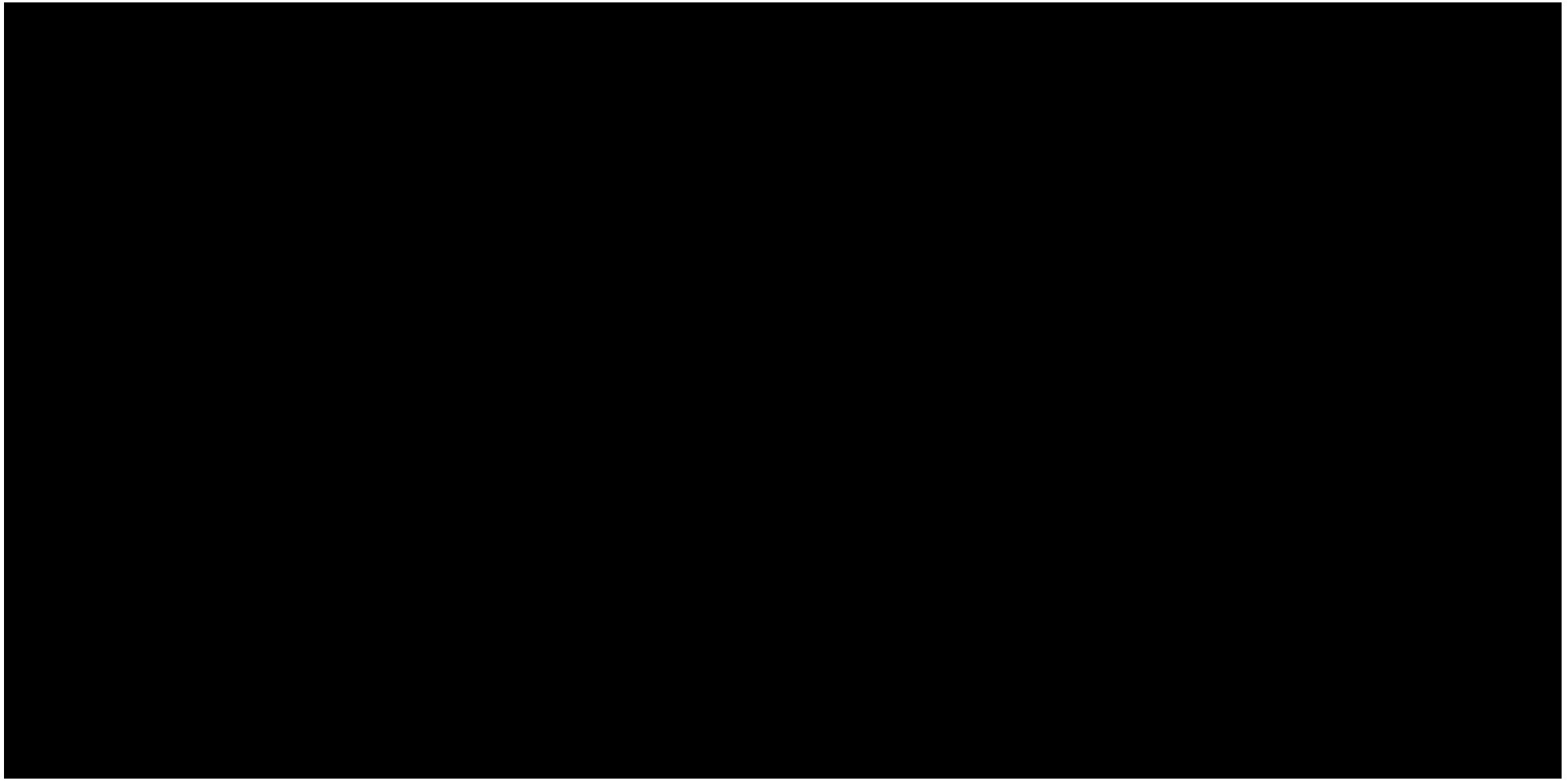
	• Patients with a FVC ≥45% predicted at Visit 1. Predicted normal values will be calculated according to GLI. • Patients with haemoglobin-corrected DL_{CO} ≥20% predicted at Visit 1. • Patients with a 6MWD ≥150 m and ≤500 m conducted at Visit 1. **Main exclusion criteria:** • Acute exacerbation of IPF within at least 12 weeks prior to Visit 1 and/or during the screening period (investigator-determined). • Relevant airways obstruction (pre-bronchodilator FEV1/FVC <0.7) at Visit 1. • Significant PH defined by any of the following: o Previous clinical or echocardiographic evidence of significant right heart failure according to investigator's judgement o History of right heart catheterisation showing a cardiac index ≤2 L/min/m² o PH requiring parenteral therapy with prostanoids • On nintedanib or pirfenidone treatment for less than 12 weeks prior Visit 1, planning to start nintedanib or pirfenidone within the first 12 weeks of IMP treatment or on combined nintedanib plus pirfenidone treatment. Newly diagnosed patients considered in need of SoC treatment during the next 12 weeks by the treating physician, who would be withheld SoC treatment only for the sake of participation in the trial, should also be excluded. • Cardiovascular comorbidities including o Severe hypertension (uncontrolled under treatment ≥160/100 mmHg at multiple occasions) within 3 months of Visit 1 o Myocardial infarction, stroke, or transient ischemic attack within 6 months of Visit 1 o Unstable cardiac angina within 6 months of Visit 1 • Life expectancy for any concomitant disease other than IPF <2.5 years (investigator assessment).

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Trial intervention and test product(s)	BI 765423 (trial intervention) [redacted])
Dose and mode of administration	[redacted] BI 765423 every [redacted] per intravenous infusion
Comparator product(s)	Placebo
Dose and mode of administration	Matching
Duration of treatment	[redacted]
Statistical methods	The primary endpoint absolute change from baseline in FVC (in mL) at 12 weeks will be evaluated descriptively and using a MMRM analysis to account for the repeated nature of the data. The model will include the fixed categorical effects of treatment at each visit, baseline type of antifibrotic treatment at each visit, as well as the fixed continuous effects of baseline FVC at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements. The adjusted mean change from baseline for each treatment group as well as difference between treatment groups (and the related standard error and 95% confidence intervals) will be calculated. [redacted]

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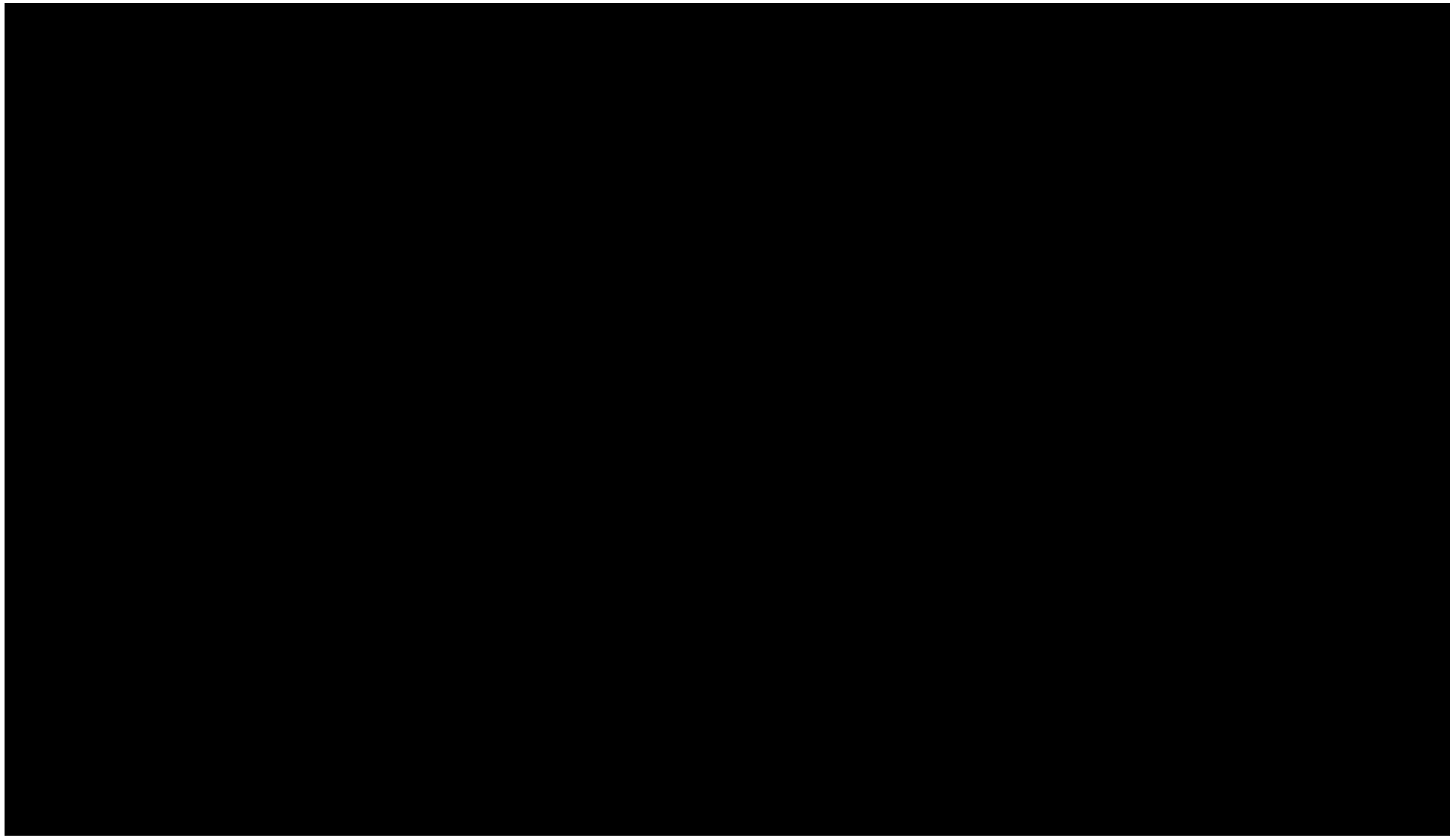
SCHEDULE OF ASSESSMENTS (SOA)



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[redacted]

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Order of assessments (OoA):

Note that the below listed assessments might not be required in all visits (see SoA for details).

The following assessments need to be done in the **indicated order** at the **visit beginning**:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

The following assessments need to be done **before blood sampling[4] and dosing**: [redacted], and vital signs (except post-dose).

The following assessments need to be done **before dosing in the following order**: physical examination, blood sampling for safety laboratory tests [redacted], biomarker, optional biobanking, [redacted], and pre-dose PK.

The following assessments need to be done **after dosing**: blood sampling for [redacted] (should be collected within 30 minutes [+5 minutes] after the end of infusion) and post-dose PK and post-dose vital signs. At the end of infusion, post-dose PK blood sampling should be performed prior to obtaining post-dose vital signs.

3 Height is to be measured at Visit 1

4 At the investigator's discretion, sites may follow their routine scheduling, however, blood sampling should not occur immediately prior to ECG. A rest period of approximately 5–10 minutes between blood sampling and ECG is recommended.

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ABBREVIATIONS AND DEFINITIONS

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
AE	Adverse event
AEP	Asset Evidence Plan
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
anti-HBc	Hepatitis B core antibody
AST	Aspartate aminotransferase
[redacted]	[redacted]
AUC	Area under the curve
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
CBC	Complete blood count
CDMS	Clinical data management system
CI	Confidence interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology
ClinRO	Clinician-reported outcome
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CMV	Cytomegalovirus
CNS	Central nervous system
COA	Clinical outcome assessment
CPL	Clinical Program Lead
CRA	Clinical research associate

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CRO	Contract Research Organisation
CRP	C-reactive protein
[redacted]	[redacted]
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Clinical Trial Leader
CTP	Clinical trial protocol
CTR	Clinical trial report
[redacted]	[redacted]
DBL	Database lock
DCT	Decentralised clinical trial
DDC	Development Decision Committee
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
[redacted]	[redacted]
DMC	Data Monitoring Committee
DMPK	Drug metabolism and pharmacokinetics
DTA	Data transfer agreement
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDMS	Electronic document management system
Eg	Exempli gratia, meaning for example
eGFR	Estimated glomerular filtration rate
EOS	End of study
EOT	End of treatment
[redacted]	[redacted]
ESMS	Emergency Unblinding Service and Medical Support
ESR	Erythrocyte sedimentation rate

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EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
[redacted]	[redacted]
FOT	Fully outsourced trial
FU1	Follow-up Visit 1
FU2	Follow-up Visit 2
FVC	Forced vital capacity
GCP	Good Clinical Practice
GD	Gestation Day
GI	Gastro-intestinal
[redacted]	[redacted]
GMP	Good Manufacturing Practice
GRL	Global Regulatory Lead
HA	Health authority
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCD	Historical control database
HCV	Hepatitis C virus
HDL	High density lipoprotein
Hgb	Hemoglobin
HHC	Home healthcare
HIV	Human immunodeficiency viruses
HRCT	High-resolution computed tomography
i.v.	Intravenous
IA	Interim analysis
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICF	Informed consent form
[redacted]	[redacted]
IEC	Independent Ethics Committee
[redacted]	[redacted]

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[redacted]	[redacted]
[redacted]	[redacted]
ILD	Interstitial lung disease
[redacted]	[redacted]
IMP	Investigational medicinal product
INR	International normalized ratio
IPD	Important protocol deviations
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IRT	Interactive response technology
ISF	Investigator site file
ISO	International Organization for Standardization
IU	International units
[redacted]	[redacted]
[redacted]	[redacted]
LDL	Low density lipoprotein
[redacted]	[redacted]
LPLT	Last patient last treatment
MAP	Meta-analytic predictive
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MMRM	Mixed model for repeated measures
m	minutes
mL	milliliters
MRI	Magnetic resonance imaging
NOAEL	No adverse effect level
NT-proBNP	N-terminal pro hormone B-type natriuretic peptide
OoA	Order of assessments
PCR	Polymerase chain reaction
PD	Pharmacodynamics
PerfOs	Performance outcomes
[redacted]	[redacted]

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PK	Pharmacokinetics
PKS	Pharmacokinetic set
PPD	Purified-protein derivative
[redacted]	[redacted]
PRO	Patient-reported outcome
PSPV	Patient Safety and Pharmacovigilance
RA	Regulatory authority
rCfB	Relative change from baseline
REML	Restricted maximum likelihood
REP	Residual effect period
[redacted]	[redacted]
SAE	Serious adverse event
SC	Steering Committee
[redacted]	[redacted]
SD	Standard deviation
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SoA	Schedule of assessments
SoC	Standard of care
SOP	Standard operating procedure
[redacted]	[redacted]
SP-D	Surfactant protein D
SRD	Single-rising dose
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Half-life time
TDM	Trial data management
t_{max}	Timepoint of maximum plasma concentration
TMF	Trial master file
TS	Treated set
TSAP	Trial statistical analysis plan
[redacted]	[redacted]
[redacted]	[redacted]

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ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

Terms synonymous with those used in this CTP are listed below.

Term	**Synonymous term**
Trial participant *or* participant	Subject *or* patient
End of study	End of trial
Investigational medicinal product	Trial medication (*or* medication), *or* trial drug (*or* drug), *or* trial treatment (*or* treatment), *or* trial intervention, *or* intervention, *or* investigational product

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1. INTRODUCTION

1.1 MEDICAL BACKGROUND

[redacted]

1.2 DRUG PROFILE

[redacted]

Refer to the investigator's brochure [206893_1863733_7.0] for further information.

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Residual Effect Period

The REP of BI 765423 is [redacted]. This is the period after the last dose where PD effects are still likely to be present, based on the estimated [redacted] of BI 765423 [redacted].

Data from non-clinical studies

Toxicology

[redacted]

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- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Summary

Based on the mode of action, the pharmacological target, and the non-clinical toxicology data, BI 765423 is not considered a high-risk compound for adverse outcomes in clinical trials.

Clinical trials

The safety profile of BI 765423 has been investigated in a Phase I SRD (1493-0007) and MRD (1493-0008) trial in healthy male volunteers:

- [redacted]

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- [redacted]

For a more detailed description of the BI 765423 profile, please refer to the IB [206893_1863733_7.0].

1.2.1 [redacted]

[redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

1493-0002 is a trial of limited duration focused on evaluation of proof-of-clinical principle and short-term [redacted], safety, and tolerability of BI 765423 (administered [redacted] intravenously) in patients with IPF, a patient population still in need for better tolerable treatments and improvement in functionality.

This trial explores tolerability, safety, and PK, as well as primarily surrogates for ILD progression, and a biomarker of epithelial injury and fibrosis (FVC, SP-D), to understand the safety and potential antifibrotic efficacy of BI 765423 in this patient population. Exploratory functional clinical endpoints ([redacted]) are included to understand potential positive effects on the [redacted], that may translate into clinical functional improvement. This trial will inform design of future studies within the clinical development of BI 765423.

The results of this trial will be used to expand the understanding of the disease IPF and the IMP(s), e.g. by learning more about the mechanism of action of the IMP or the biology of the disease, thereby allowing correlation of patient subgroups with potentially differential responses to treatment and/or prognosis and supporting subsequent trial designs regarding dose and schedule selection.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.5). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an AE, or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

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1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

[redacted]

[redacted]

Participation in this phase II trials aids in the clinical development of BI 765423/[redacted]

1.4.2 Risks

No identified risks (side effects) have been established for BI 765423, based on the non-clinical data or any clinical trials conducted for this product to date (see also Section 1.2). Embryo-foetal toxicity is considered an important potential risk based only on nonclinical findings. No other [redacted] is currently approved for marketing authorisation, therefore, the knowledge of the safety and risk profile of compounds in this class is limited.

Table 1 provides an overview of hypothetical trial-related risks based on general safety considerations [redacted] and/or characteristics of BI 765423.

To protect patients' safety, an independent DMC will periodically review safety data during trial conduct (see Section 8.7).

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Table 1 Overview of trial-related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product: BI 765423		

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Table 1 (cont'd) Overview of trial-related risks

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
[redacted]	[redacted]	[redacted]
Drug-induced liver injury	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety.
Trial procedures		
Blood sampling-related risk	Standard clinical procedure with risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected, or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain. Frequent blood collection may cause anemia (low red blood cell count), which may require blood transfusions.	Close clinical monitoring for AEs. Selection of experienced sites and site staff.
[redacted]	[redacted]	[redacted]

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Table 1 (cont'd) Overview of trial-related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]

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Table 1 (cont'd) Overview of trial- related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
[redacted]	[redacted]	[redacted]

1.4.3 Discussion

Based on the BI 765423 non-clinical and clinical data in healthy volunteers to date, there are no identified risks. The important potential risk of embryo-foetal toxicity, hypothetical risks stemming from general safety considerations, and risks related to trial procedures have been reviewed and mitigation strategies put in place.

Given the unmet medical need, anticipated benefit of BI 765423, and available non-clinical and clinical information, the benefit-risk evaluation of the compound is acceptable.

Considering the medical need for the development of a better tolerated and more effective treatment for patients with IPF [redacted], the expected benefit outweighs the possible risks.

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2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The exploratory trial will assess efficacy, safety, tolerability, PK, and PD of BI 765423 (administered intravenously) in comparison with placebo in patients with IPF with or without background SoC.

The primary objective is to estimate the absolute difference in means of FVC change from baseline after 12 weeks between BI 765423 and placebo.

The main secondary objective is to estimate the absolute difference in means of log_{10}-transformed SP-D plasma concentration change from baseline after 12 weeks between BI 765423 and placebo.

[redacted]

All treatment comparisons will be as randomized, including the effects of any changes of treatment ('treatment policy'), but excluding effects of [redacted] ('hypothetical').

2.1.2 Primary endpoint(s)

Absolute change from baseline in FVC (mL) at 12 weeks.

2.1.3 Secondary endpoint(s)

Main secondary endpoint is:

- Absolute change from baseline in log_{10}-transformed SP-D plasma concentration at 12 weeks

Other secondary endpoints are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

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- Absolute change from baseline in distance walked (m) during 6MWT at 24 weeks

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

Additional efficacy, biomarker, PK, PRO, and safety data will be collected to explore potential effects and safety over [redacted].

PK subpopulation: explore PK in patients of Japanese ethnicity.

2.2.2 Further endpoints

Efficacy - continuous

[redacted]

Efficacy - time to event

[redacted]

Efficacy – [redacted]

[redacted]

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Biomarker

- Absolute and relative change from baseline of blood-based biomarkers (listed in Section 5.4.1) over the treatment period

Patient-reported outcomes

- Absolute change from baseline in [redacted]
- Change in patient reported [redacted]

Safety

- Descriptive safety assessments as listed in Section 5.2

Pharmacokinetics

The following parameters will be determined for BI 765423 on [redacted], and other part of main study:

- $C_{pre, N}$
- $C_{t, N}$

For the **PK subpopulation [only patients of Japanese ethnicity in Japan],** the following PK parameters will be determined for BI 765423 after the first dose on Day 1, if feasible:

- AUC_{0-tz} (area under the concentration-time curve of the analyte in serum from the time point 0 after the 1 st dose to the last quantifiable analyte serum concentration)
- C_{max} (maximum measured concentration of the analyte in serum after administration)
- t_{max} (time from dosing to maximum measured concentration of the analyte in serum)
- AUC_{t1-t2} (area under the concentration-time curve of the analyte in serum over the time interval t_1 to t_2)

For the **PK subpopulation [only patients of Japanese ethnicity in Japan]**, the following PK parameters will be determined for BI 765423 after [redacted] dose if feasible:

- AUC_{0-tz} (area under the concentration-time curve of the analyte in serum from the time point 0 after the last dose to the last quantifiable analyte serum concentration)
- AUC_{τ} (area under the concentration-time curve of the analyte in serum over the dosing interval τ)
- C_{max} (maximum measured concentration of the analyte in serum after administration)

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- t_{max} (time from dosing to maximum measured concentration of the analyte in serum)
- AUC_{t1-t2} (area under the concentration-time curve of the analyte in serum over the time interval t_1 to t_2)
- λ_z (terminal rate constant in serum)
- $t_{1/2}$ (terminal half-life of the analyte in serum)
- CL_{ss} (Clearance at steady state)
- $V_{z,ss}$ (Volume of distribution at steady state)
- $R_{A,Cmax}$ (accumulation ratio based on C_{max})
- $R_{A,AUCt1-t2}$ (accumulation ratio based on $AUCt_{1-t2}$)

More details and additional further endpoints may be defined in the TSAP.

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3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This Phase IIa multi-centre, multi-national, prospective, randomised, double-blind, placebo controlled, parallel group trial is designed to evaluate BI 765423, intravenously administered at a dose of [redacted], with or without background SoC, to patients with IPF.

After signing the informed consent, patients will enter the screening period. Patients meeting eligibility criteria will be randomised at Visit 2 and enter the treatment period of the trial. The treatment period is planned to be [redacted]. Safety follow-up of patients will last [redacted] after last dose. For each patient, the trial period is from the signature of the informed consent by the patient until the patient's last visit of the study, thus, planned to be [redacted] (assuming a [redacted] screening period). Adverse events will be recorded during the entire trial period and considered treatment-emergent from first study drug intake until [redacted] last dose.

[redacted]

Approx. [redacted] patients (approx. [redacted] per treatment arm) are planned to be randomised to receive either BI 765423 or placebo. Patients will be stratified by PK subpopulation (yes/no) and by type of background antifibrotic treatment at baseline ([redacted]) for patients not part of the PK subpopulation. See Section 7.4 for further details.

To specifically assess PK in Japanese patients, sites based in Japan will include patients of Japanese ethnicity as a PK subpopulation (approx. [redacted]), all of whom will undergo additional PK assessments (see Section 5.3.3) in addition to the main trial. Sites based in Japan can also include patients of non-Japanese ethnicity, which will however not be part of the specific PK subpopulation (PK to be performed as in sites based in other countries).

Approximately [redacted] patients at selected sites in the US will undergo additional assessments to evaluate effects of BI 765423 on [redacted] done at baseline (Visit 2) and Visit 6 (see Section 5.1.6 for details). Participation in the [redacted] assessments is optional.

A recent [redacted] done during the screening period (see Section 5.6.1 for conditions) will be sent for central evaluation to confirm an [redacted]. See Section 3.3 for further details.

All visits will be in-clinic in a hospital setting or stand-alone pulmonary clinic setting fulfilling trial pre-requisites. See Section 4.1.5 for details on blinding.

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Criteria leading to premature IMP discontinuation are described in Section 3.3.4.1. All patients, including those discontinuing treatment prematurely, will have an EOT, FU1 and EOS (FU2) visit, [redacted], respectively, after last dose (see SoA).

For those patients who discontinue treatment prematurely and are unable to complete the scheduled visits, every attempt should be made to get information on vital status at [redacted] after randomization (i.e. the time of primary and secondary endpoint data collection), and at their EOS ([redacted] after last dose).

A DMC, independent from the Sponsor, will be established to review the unblinded safety data at regular intervals, and to recommend to the Sponsor whether to continue, modify, or stop the trial. The tasks and responsibilities of the DMC members are detailed in Section 8.7 and in the DMC charter. The end of trial is defined as the date the last patient completes the last visit (EOS visit). The last time point collected for the primary endpoint will be the last patient's visit after [redacted] of treatment, while secondary objective data will be collected [redacted].

[redacted]

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

Trial design and treatment allocation

This trial is a parallel group, placebo-controlled, randomised, double-blind trial to provide the highest scientific rigor and is thus considered the most appropriate design. FVC measurement over time is a widely accepted clinical endpoint in the indication of the trial for the evaluation of treatment effects on lung function. FVC assessments are supported by biomarker outcomes as well as additional lung function and functional outcome measurements ([redacted]) as secondary endpoints.

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Primary objectives will be assessed following [redacted] of treatment, with or without [redacted] as defined by stable [redacted], (refer to Section 4.2.1.3 for details). After the initial [redacted] period, restrictions on SoC become more flexible, allowing investigators to tailor treatment according to patient requirements and local SoC. This approach also facilitates exploratory evaluation of secondary endpoints after [redacted] of treatment under expanded SoC conditions. For detailed information regarding prior and concomitant therapies, please refer to Section 4.2.1.3.

A placebo-controlled trial design is considered necessary for evaluating and interpreting the AE reporting and considered justified in the trial, as it will be conducted in addition to the patient's SoC at the time of enrolment (i.e. with or without antifibrotic treatment, see Section 4.2.1.3 for details).

Stratification will be based on type of background antifibrotic treatment at baseline ([redacted]) and will facilitate the interpretation of the efficacy and safety data in patients that use BI 765423 alone or in addition to an antifibrotic treatment. The expected proportion of the respective patients with or without background antifibrotic treatment corresponds to the current treatment/prescription practices across the participating countries, so that patients can be accepted into the trial without modification of the ongoing background antifibrotic treatment.

For evaluating the efficacy and safety of BI 765423 in the target population over [redacted], a 1:1 allocation is judged appropriate for treatment comparison.

Details of the statistical approach including a sample size justification are given in Section 7.

A DMC will review unblinded safety data at regular intervals as detailed in Section 8.7.

[redacted]

The rationale for the selected BI 765423 dose is provided in Section 4.1.2.

Treatment duration

The planned duration of the placebo-controlled treatment for this exploratory study is considered sufficient to evaluate the primary endpoint of change from baseline in FVC, as well as changes in SP-D (main secondary endpoint) after [redacted] of treatment with or without SoC defined as [redacted] (refer to Section 4.2.1.3 for details) and to assess secondary objectives and the incidence of the most frequent drug-related AEs associated with BI 765423 in the trial population over total treatment duration [redacted].

Sample Size

The target sample size of approx. [redacted] patients is based on the sample size estimation for the primary evaluation of primary and main secondary endpoint (see Section 7.5).

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Patient input

This trial will include an option for patients to complete questionnaires to provide feedback on their clinical trial experience (see Section 10.1). Providing this feedback is not required for trial participation, the information collected from these questionnaires will not be analysed as part of the clinical data for the trial.

3.2.1 Patient input into trial design

Patient input to this trial has been obtained by a patient steering committee, by providing comments and questions to the trial design, eligibility criteria and assessments. Clarification and rationale for those aspects being questioned were provided to the patient steering committee.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of patients will be screened in approximately [redacted] sites and approximately [redacted] countries to randomise approximately [redacted] patients.

Once consented for the main trial, the patient should be registered in the IRT system.

The screening period to assess a patient's eligibility starts at Visit 1 and may last up to [redacted]. An extension up to [redacted] might be approved by the Sponsor in the event of logistical issues with the reporting of results by the central vendor(s) of patients who meet all other inclusion criteria and do not meet any exclusion criteria.

[redacted] should be submitted for a central review at or shortly after Visit 1. If a screening [redacted] is required (see Section 5.6.1), it should only be done once other trial eligibility criteria have been confirmed. When scheduling this [redacted] as part of screening, sufficient time should be allowed to receive the results before Visit 2.

Re-screening of screen failed patients will be permitted once providing the reasons for screen failure were reversible and have been resolved, based on investigator's judgement. The patient who will be re-screened needs to be re-consented and subsequently registered in IRT. A new patient number will be assigned, and all Visit 1 assessments must be repeated.

Retesting for eligibility (to be performed within the screening period window) will only be permitted once and limited to following tests:

- [redacted]
- [redacted]
- [redacted]
- ECG in case of quality reasons or at the discretion of the investigator (see Section 5.2.4)

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Furthermore, if the Investigator believes that an ineligible laboratory test result is the result of an error or extenuating circumstance, then the test can be repeated once without the patient having to be re-screened.

Patients who discontinue the trial following randomisation will not be replaced and may not be re-enrolled later.

Recruitment of patients for this trial will be competitive. However, screening at sites involved in additional assessments (PK subpopulation or [redacted]) may remain open longer than at other sites to ensure a sufficient number of participants has been enrolled for the additional assessments. Investigators will be notified about screening completion and will not be allowed to screen additional patients. Patients in screening will be allowed to continue to randomisation if eligible.

A log of all patients who have signed informed consent will be maintained in the ISF, irrespective of whether the patient is enrolled in the trial or IMP is administered to the patient.

The following information, at minimum, will be collected (also for screen failures): patient number, visit date, demographics, eligibility criteria, information on AEs (if applicable), and concomitant treatment relevant for the AE.

If retrospectively it is found that a patient has been randomized in error (i.e. did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment, a decision will be made as to whether continued trial participation is possible.

3.3.1 Main diagnosis for trial entry

The trial will be performed in patients with IPF, a FVC ≥45% predicted, HRCT extent of fibrosis ≥20% (confirmed by visual assessment via central review), with or without background SoC.

Please refer to Section 8.3.1 for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

Patients are eligible to be included if all the following criteria apply:

1. 40 years of age or older at the time of informed consent signature.

2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

3. Male or female patients. Male patients must not donate sperm while taking part in this study and for a period of at least [redacted] after the last dose of the IMP. Male patients with WOCBP sexual partners must use contraception (male condom) to avoid

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exposure via seminal fluid during treatment and until 131 days (19 weeks) after last drug intake (see Section 4.2.2.4). Women can only be included if they are of non-childbearing potential, defined as meeting at least one of the below conditions:

- Permanently surgically sterilised (hysterectomy, bilateral salpingectomy and/or bilateral oophorectomy)
- Postmenopausal, defined as no menses for 12 months without an alternative medical cause. In questionable cases wherein the menopausal status is uncertain and cannot be clearly determined, the following should be taken into consideration by the investigator:
    - Women not using sex hormone medication such as hormone replacement therapy may be included if a blood sample confirms levels of FSH > 40 U/L and estradiol < 30 ng/L

4. Patients with a documented diagnosis of IPF prior to Visit 1, confirmed by the investigator as per the 2022 ATS/ERS/JRS/ALAT Guideline [P22-03204] and, if available, surgical lung biopsy or transbronchial lung cryobiopsy histopathology report.

5. Patients with an HRCT taken within 12 months of Visit 1 (or during the screening period, if not available) confirming "UIP" or "probable UIP" HRCT pattern consistent with the clinical diagnosis of IPF by central review (prior to Visit 2).

    - Patients with an "indeterminate" HRCT finding are eligible if a clinical diagnosis of IPF can be confirmed based on an historical histopathology report of a surgical lung biopsy or cryobiopsy demonstrating a "UIP" or "Probable UIP" pattern or Multidisciplinary Discussion and Diagnosis as per ATS guidelines.

    - Patients with an "alternative diagnosis" HRCT finding are eligible if a clinical diagnosis of IPF can be confirmed based on an historical histopathology report of a surgical lung biopsy or cryobiopsy demonstrating a "UIP" pattern or Multidisciplinary Discussion and Diagnosis as per ATS guidelines.

6. Patients with an extent of fibrosis ≥20% as per an HRCT of the chest performed within 12 months prior to Visit 1 or during the screening period (if not available) and confirmed by central review.

7. Patients with a FVC ≥45% predicted at Visit 1. Predicted normal values will be calculated according to GLI.

8. Patients with haemoglobin-corrected DL_{CO} ≥20% predicted at Visit 1.

9. Patients with a 6MWD ≥150 m and ≤500 m conducted at Visit 1.

Inclusion criteria PK subpopulation

All patients of Japanese ethnicity in Japan will be included in the PK subpopulation:

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10. Patient of Japanese ethnicity, defined as having parents and grandparents who are Japanese, that are included in the trial from a site based in Japan

3.3.3 Exclusion criteria

Patients are excluded if any of the following criteria apply:

1. Acute exacerbation of IPF within at least 12 weeks prior to Visit 1 and/or during the screening period (investigator-determined).
2. Relevant airways obstruction (pre-bronchodilator FEV1/FVC <0.7) at Visit 1.
3. Lower respiratory tract infection requiring treatment within 4 weeks prior to Visit 1 and/or during the screening period.
4. Significant PH defined by any of the following:
   - Previous clinical or echocardiographic evidence of significant right heart failure according to investigator's judgement
   - History of right heart catheterisation showing a cardiac index ≤2 L/min/m²
   - PH requiring parenteral therapy with prostanoids
5. In the opinion of the Investigator, other clinically significant pulmonary abnormalities.
6. History of stem cell therapy for the treatment of pulmonary fibrosis.
7. On nintedanib or pirfenidone treatment for less than 12 weeks prior Visit 1, planning to start nintedanib or pirfenidone within the first 12 weeks of IMP treatment or on combined nintedanib plus pirfenidone treatment (see Section 4.2.1.3). Newly diagnosed patients considered in need of SoC treatment during the next 12 weeks by the treating physician, who would be withheld SoC treatment only for the sake of participation in the trial, should also be excluded.
8. Treated with [redacted] (see Section 4.2.2.1).
9. Previous intake of BI 765423 or any [redacted].
10. Relevant chronic or acute infections, including HIV, viral hepatitis, or other infections judged as relevant by the investigator. The corresponding laboratory tests will be performed during screening. A patient can be re-screened if the patient was treated (if not a self-limited illness) and is cured from the acute infection.
11. [redacted] (patients are required to be tested during the screening visit):
    - [redacted]. Screening tests are described in Section 5.2.3.2.
    - Patients with [redacted] should be excluded.
    - Patients with [redacted] are excluded unless they have completed treatment per local guidance for [redacted], by the time of screening.

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- Under exceptional circumstances and only after discussion with the sponsor, [redacted] are excluded unless they have completed treatment as above.
- Patients with [redacted], but this should be discussed with the sponsor on a case-by-case basis.

12. Cardiovascular comorbidities including:
    - Severe hypertension (uncontrolled under treatment ≥160/100 mmHg at multiple occasions) within 3 months of Visit 1
    - Myocardial infarction, stroke, or transient ischemic attack within 6 months of Visit 1
    - Unstable cardiac angina within 6 months of Visit 1
13. eGFR ≤30 mL/min/1.73 m^2 at Visit 1 (CKD-EPI formula or Japanese version of CKD-EPI for Japanese patients).
14. Severe, progressive, or uncontrolled hepatic disease, defined as AST, ALT, or alkaline phosphatase >3x ULN or total bilirubin >2x ULN at Visit 1.
15. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomisation or planned within the trial, e.g. hip replacement.
16. Underlying chronic moderate to severe liver disease (Child Pugh B or C liver cirrhosis).
17. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately and curatively treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or *in situ* carcinoma of uterine cervix.
18. History of allergy or hypersensitivity to the administered trial medication or its excipients.
19. Life expectancy for any concomitant disease other than IPF <2.5 years (investigator assessment).
20. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
21. Any vulnerable person (defined as: pregnant or breastfeeding women; persons deprived of their liberty; minors; persons that may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests; or unable to explicitly give consent), as per local regulation.
22. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (in the investigator's opinion).

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23. Women who are pregnant, breastfeeding, or plan to become pregnant while in the trial.
24. Currently enrolled in another investigational device or drug trial, or their Visit 1 occurs <30 days or 5 half-lives (whichever is longer) after completing a previous investigational device or drug trial or receiving other investigational treatment(s).
25. Any condition not covered by any of the other exclusion criteria which, in the investigator's opinion, might jeopardise the patient's safety or compliance with the protocol.

Exclusion criteria [redacted]

[redacted]

3.3.4 Discontinuation of patients from treatment or assessments

Patients may discontinue IMP or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications (see Sections 3.3.4.1 and 3.3.4.2).

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

The decision to discontinue trial IMP or withdraw consent to trial participation and the reason (if provided) must be documented in the patient files and eCRF. If applicable, consider the requirements for AE collection and reporting (see Section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

If a patient discontinues treatment but agrees to remain in the trial, they should attend further trial visits to ensure their safety and to collect important trial data. All patients, including those discontinuing IMP prematurely, should have an EOT, FU1 and EOS visit, [redacted], respectively, after last dose (see SoA and Section 6.2.3). For those patients who discontinue treatment prematurely and are unable to complete the scheduled visits, every attempt should be made to get information on vital status at [redacted] after randomisation (i.e. the time of primary endpoint data collection) and at their EOS ([redacted] after last dose).

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An individual patient will discontinue trial IMP if:

- The patient wants to discontinue trial IMP. The patient will be asked to explain the reasons but has the right to refuse to answer
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of the investigator, the safety of the patient cannot be guaranteed as he/she is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interacts with the IMP or other trial treatment or are restricted (see Section 4.2.2.1).
- If it is found that a patient took restricted medication, the Sponsor or delegate should be contacted. Based on an individual benefit-risk evaluation by the investigator and in consultation with the Sponsor, a decision will be made as to whether the patient should discontinue trial IMP.
- The patient [redacted] as determined by the investigator (see Section 4.2.1.4).
- The patient can no longer receive trial IMP for medical reasons such as surgery, AEs, other diseases, or pregnancy. See Section 5.2.6.2.3 regarding follow-up in case of pregnancy.
- The patient will undergo [redacted], with an assigned date of surgery.

An individual patient should discontinue trial treatment temporarily if:

- The patient fulfils the AESI definition of potential severe DILI (see Section 5.2.6.1.4).
    - Re-introduction of IMP could be considered in consultation with the Sponsor after patient recovery, individual benefit-risk evaluation by the investigator and exclusion of BI 765423-induced liver injury (see Section 5.2.6.1.4).
- [redacted]
    - Treatment of the infection should be initiated promptly according to local SoC. No further trial medication should be administered until the [redacted]. Treatment with BI 765423 may be restarted when the patient has recovered according to the investigator's assessment.

Note: Only in special circumstances the investigator, upon thorough assessment of all available clinical data and taking into consideration the potential risks associated with administration of BI 765423, may decide not to withdraw the IMP, even though one or more of the above-mentioned criteria for highly recommended IMP discontinuation are fulfilled. In such a case, continuation of IMP treatment should be discussed with the patient, and the decision and reasoning documented in the source data.

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In case of a temporary discontinuation trial IMP should be restarted if medically justified; see Section 4.1.4 also on timing to resume IMP infusion.

If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause, or discontinue the IMP for all patients or take any other appropriate action to guarantee the safety of the patients.

3.3.4.2 Withdrawal of consent to trial participation

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

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between IMP discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after IMP discontinuation (see Section 3.3.4.1).

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. New efficacy or safety information invalidating the earlier positive benefit-risk assessment; see Section 3.3.4.1
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial
4. Termination of the development of the compound in this indication

Further treatment and follow up of patients affected will occur as described in Section 3.3.4.1.

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

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4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

BI 765423 is a genetically engineered product manufactured using Chinese hamster ovary (CHO) cells. It is manufactured using standard mammalian cell culture techniques. The purification process consists of several chromatography steps, as well as steps for inactivation and removal of potential viruses.

BI 765423 concentrate for solution for infusion is a sterile, buffered, isotonic, preservative-free, colourless to slightly brown-yellow, clear to slightly opalescent solution for intravenous infusion. BI 765423 drug product is composed of the following standard pharmaceutical excipients: Sodium acetate/acetic acid, Methionine, Sucrose, Polysorbate 20, water for injection, pH 5.5.

Table 2 Test product

Substance:	BI 765423
FDA Established Pharmacologic Class (EPC):	Not available
TRT/CURTRT/COMPTRT	TRT
Pharmaceutical formulation:	Concentrate solution for infusion
Unit strength:	[redacted]
Posology:	[redacted]
Mode of administration:	Intravenous infusion administered [redacted]

Table 3 Comparator product

Substance:	Placebo
Pharmaceutical formulation:	Concentrate solution for infusion
Unit strength:	NA
Posology:	[redacted]
Mode of administration:	Intravenous infusion administered [redacted]

4.1.2 Selection of doses in the trial and dose modifications

The dose for this trial was selected to achieve the desired target engagement anticipated to be required for a therapeutic effect during the dosing interval and was considered safe and well tolerated in the SRD trial (1493-0007) and ongoing MRD trial (1493-0008, based on preliminary data).

For further details refer to the IB [206893_1863733_7.0].

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No dose modification is allowed.

Treatment might be stopped temporarily in the cases described in Section 3.3.4.1.

4.1.3 Method of assigning patients to treatment groups

After assessment of all inclusion and exclusion criteria, each eligible patient may be randomised to a treatment group according to a randomisation plan (see Section 7.4). Randomisation codes will be generated through a validated software and kept blinded to the stakeholders specified in Section 4.1.5. Access to the codes will be controlled and documented. An IRT system will be used to screen patients, create a patient number, perform treatment assignment, manage initial/re-supply ordering of IMP supplies, and handle emergency unblinding.

4.1.4 Drug assignment and administration of doses for each patient

IMP will be administered in a hospital setting or stand-alone pulmonary clinic setting fulfilling trial pre-requisites. IMP should only be administered to participating patients according to the protocol by authorised personnel as documented in the ISF. Refer to SoA for timing of dosing and OoA. No specific timing of IMP administration with respect to meals is required. See Section 5.2 for details of safety assessment, including physical examination, vital signs, safety laboratory, and ECG monitoring.

IMP will be administered every [redacted]. The treatment period is planned to be [redacted].

Start and end time of the infusion will be recorded. Refer to Section 3.3.4.1 for reasons when to temporarily discontinue IMP and when to resume dosing. Dosing should be completed in the window specified in the SoA; however, on rare occasions, at PI discretion (under exceptional circumstances and with sponsor authorization), the dosing window may be revised. Refer to Section 4.2.1.4 for considerations in case of infusion-related reaction or systemic hypersensitivity.

No dose reductions are allowed.

Patients should be closely monitored for signs and symptoms of [redacted] at Day 1 (Visit 2) and [redacted] after subsequent IMP doses. [redacted] reactions should be treated according to Section 4.2.1.4 and local medical standards.

The possibility to differentiate BI 765423 from placebo based on [redacted] of solution cannot be ruled out. Therefore, additional measures such as application of syringe blinding labels and blinding covers for infusion lines will be implemented at the trial site (see Section 4.1.5 for further details on blinding). A dedicated unblinded site staff member is required to blind the syringes and infusion lines for the IMP infusion.

IMP preparation and handling will be performed according to the “Instructions Preparation and Handling of BI 765423” filed in the ISF.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war [see Section 6]), physical visits to the sites may not be feasible or may need to be restricted to

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ensure patient safety. In such cases, based on a thorough assessment of the benefits and risks, the investigator may decide to discontinue IMP administration.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators, central reviewers, and everyone involved in the trial conduct or analysis or with any other interest in this double-blind trial will remain blinded regarding the randomised treatment assignments as specified in Table 4. The timepoint of unblinding will be documented according to Sponsor's SOPs and will be determined by the trial team on an as needed basis. The purpose of this unblinding is described below and in Section 7.2.8.

Table 4 Timing of blinding by role and function.

Role/function	**Timing of Unblinding / receiving access to the treatment information (including rationale)**
Patients	Blinded until data ready for final analysis.
Investigator/Site Staff	Blinded until data ready for final analysis.
Clinical trial/project team and clinical database	Unblinded exploratory analyses will be performed at different time points during the trial conduct (see Section 7.2.8). The release of treatment information will be documented accordingly.
Bioanalytical laboratory	Process as described below.
Unblinded site staff member	Unblinded as required for preparation of IMP, see Section 4.1.4.

Unless described otherwise in the table above, access to the randomisation code will be kept restricted until its documented release per Sponsor's SOP.

Randomisation codes will be provided to the bioanalytical laboratory before the last patient completes the trial to allow adaptation of required procedures (e.g., dilution steps) for PK samples taken from patients receiving placebo. The bioanalytical laboratory will not disclose the randomisation codes or bioanalytical results until the trial is unblinded.

Further details regarding the timepoint of unblinding the database for analysis are provided in the TSAP.

4.1.5.2 Emergency unblinding and breaking the code

Emergency unblinding will be available to the investigator via the IRT system. Using IRT, the trial investigator will be directly granted access to unblinded information about the IMP assigned to the patient without any impediment. In addition, trial investigators who are unable to access the IRT system or external healthcare professionals (in case of medical emergency outside of the trial site) can contact the ESMS. ESMS has immediate, 24/7 access to the randomization codes. It must be used only in an emergency when the identity of the trial drug must be known to provide appropriate medical treatment or otherwise assure safety of patients. The treatment allocation should not be disclosed to the sponsor unless this is

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explicitly requested. The reason for unblinding must be documented in the source documents and/or appropriate eCRF page.

Due to the requirements to report SUSARs, it may be necessary for a representative from Boehringer Ingelheim's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised PSPV representatives for processing in the pharmacovigilance database and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The IMP will be provided by Boehringer Ingelheim or a designated CRO. The IMP will be packaged and labelled in accordance with the principles of GMP.

The label will be prepared according to EU Regulation No. 536/2014, Annex 6, Section D.8., omitting certain particulars with the following justifications:

- The visit number is not relevant for the label because the product will remain at the clinical site.

- The investigator name will be omitted from the label due to the use of IRT system.

Should local regulations outside the EU require these particulars, they will be added to the country-specific label text.

Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

4.1.7 Storage conditions

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

If the storage conditions are found to be outside the specified range, immediately contact the CRA (as provided in the list of contacts) and follow the procedures for assessing and reporting temperature excursions provided in the ISF.

Storage conditions of the IMP after preparation are outlined in "Instructions Preparation and Handling of BI 765423" filed in the ISF. If the storage conditions of the IMP after preparation are found to be outside the specified range, the IMP should not be administered.

4.1.8 Drug accountability

The investigator or designee will receive the IMP delivered by the sponsor or delegate when the following requirements are fulfilled:

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

The IMP is not allowed to be used outside the context of this CTP and must not be forwarded to other investigators or clinics.

Used IMP will be destroyed at the investigator site according to its specific procedures.

The investigator or designee must maintain records of the product's delivery to the trial site, inventory at the site, use by each patient, and the return to the sponsor or warehouse/drug distribution centre or alternative disposal of unused products in alignment with the sponsor, if applicable. The sponsor or warehouse/drug distribution centre will maintain records of the disposal, if applicable.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the IMP and patients. The investigator or designee will maintain records that adequately document that patients were provided the doses specified by this CTP and reconcile all IMP supplies received from the sponsor. Unused IMP will be reconciled by the CRA and returned to the sponsor and/or appointed CRO. At the end of trial no IMP supplies will remain in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

4.2.1.1 [redacted]

[redacted]

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4.2.1.2 Rescue therapy

If AEs require treatment, the investigator can authorise appropriate therapy. In those cases, patients will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all results of medical evaluations are acceptable. See Section 4.2.1.4 for further details on emergency procedures.

4.2.1.3 Prior and concomitant therapies

Background treatment with SoC as deemed appropriate by the investigator is allowed except for those described in Section 4.2.2.1.

Treatment with [redacted] is permitted as follows:

- Patients are on a stable dose for at least 12 weeks prior to Visit 1 (and during the screening period) and plan to remain on this treatment after randomisation. Interruption and/or dose adaptation of the background antifibrotic medication are left at the discretion of the investigator, e.g. to manage side effects in line with the respective prescribing information. Combined treatment with [redacted] is not allowed.

Treatment with [redacted] can be initiated as follows:

- Treatment is initiated after [redacted] of IMP treatment because of disease worsening defined as disease under study progression and/or IPF exacerbation (by investigator's judgement), or after IMP discontinuation.

Additional details regarding concomitant non-drug therapies, such as physiotherapy and breathing therapy at screening, need to be recorded in the eCRF.

Restrictions on concomitant therapies are presented in Section 4.2.2.1.

4.2.1.4 Emergency procedures

[redacted]

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[redacted]

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4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

While enrolled in this trial, patients must not participate in another investigational drug or device trial or receive other investigational treatment(s)

All treatments are allowed in case of acute exacerbations.

Locally approved standard of care therapy for IPF can be utilized after Week 12 (Visit 6) of IMP treatment as described in Section 4.2.1.3. [redacted]

[redacted]

4.2.2.2 Restrictions on diet and lifestyle

There are no restrictions on diet and lifestyle.

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4.2.2.3 Vaccinations

Live vaccinations are not permitted 4 weeks prior to initiation of IMP treatment, until the EoS.

4.2.2.4 Contraception requirements

WOCBP are excluded from this study. A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. Tubal ligation is not a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Male patients who have sexual partners who are WOCBP must use a male condom throughout the trial and for a period of at least [redacted] after the last dose of IMP, even if the patient had a vasectomy with absence of sperm documented. Sperm donation is not allowed for the duration of the study and a period of at least 131 days (19 weeks) after the last dose of the IMP.

Male patients with sexual partners who are WOCBP may abstain from male-female sex as a form of contraception. Complete abstinence (refraining from heterosexual intercourse) is considered a highly effective method of contraception only if it is in line with the preferred and usual lifestyle of the patient. When there is complete sexual abstinence, the patient refrains from any sort of sexual activity that could involve the spill of an ejaculate, even if the spill does not occur. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to trial IMP only (i.e., sexual abstinence is not standard practice), and withdrawal are not acceptable methods of contraception.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all IMP by responsible site staff.

See Section 3.3.4.1 for conditions under which IMP will be discontinued upon patient's non-compliance.

Refer to Section 3.3.4.1 on reasons for temporary IMP discontinuation and Section 4.1.4 for timing to resume dosing.

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5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 [redacted]

[redacted]

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[redacted]

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[redacted]

5.1.5 Clinical outcome assessments

COAs must be used in the IRB/EC-approved version and format provided by the sponsor (or vendor, if applicable). COAs must not be modified, except as indicated for the administration of the assessments, as per trial instructions.

[redacted]

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[redacted]

5.1.5.3 [redacted]

[redacted]

5.1.5.4 COA rater training and qualification

[redacted]

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For each individual patient, the same qualified site staff member should handle PROs for the particular patient throughout the trial if possible. In case of unforeseen circumstances, a qualified back-up site staff member must be available throughout the trial.

5.1.5.5 COA handling

Administration of PRO questionnaires will be handled according to guidance documents from regulatory authorities and international societies (e.g. ISPOR). Patients are to complete PRO assessments (paper versions) described in Sections 5.1.5.1 and 5.1.5.3 on his/her own ([redacted] to be completed in a quiet area/room) at the frequency specified in the SoA, (order with respected to other assessments described in OoA), without being influenced by the investigator or other members of the trial team. PRO assessments are to be completed by the patient in the same language as the patient provided written consent for the trial and without any help from or interpretation/translation by other people. If this is not possible, the PRO assessments are not to be done. The scores will be recorded in the eCRF.

Adequately trained and qualified site staff are to be available at any time for general questions and to support the patient, as well as to ensure PRO completion compliance.

[redacted]

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the SoA (see OoA for order with respect to other assessments). This examination includes, at a minimum, general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.

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Measurement of height and body weight will be performed at the time points specified in the SoA.

The results must be included in the source documents available at the site.

All abnormal findings at baseline (Visit 2) will be recorded on the Baseline Condition eCRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations, if judged clinically relevant, will be recorded as adverse events on the appropriate eCRF page.

5.2.2 Vital signs

Vital signs will be evaluated at the time points and order to other assessments as specified in the SoA and OoA, respectively. At dosing visits, vital sign evaluations will be performed pre-dose and additional evaluations will be taken at the end of the infusion, and approximately [redacted]. At Visit 2 additional measurements will be performed approximately [redacted] post-dose. This includes systolic and diastolic blood pressure, respiratory rate, temperature, and pulse rate (electronically or by palpation count for 1 min) in a seated position after at least 5 min of rest. [redacted]. The results must be included in the source documents available at the site. All abnormal findings at baseline will be recorded on the Baseline Condition eCRF page. New abnormal findings or worsening of baseline conditions detected at the subsequent physical examinations, if judged clinically relevant, will be recorded as AEs on the appropriate eCRF page.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 6, and the sampling time points are shown in the SoA (see OoA for order with respect to other assessments).

Fasting before blood sampling is not required. Instructions regarding sample collection, sample handling/processing, and sample shipping are provided in the laboratory manual in the ISF.

All analyses will be performed by a central laboratory, and the respective reference ranges will be provided in the ISF.

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as AEs (refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (see Section 5.2.6.1.4 and the DILI Checklist provided in the ISF). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

The central laboratory will transfer laboratory results to the sponsor or delegate.

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Table 6 Safety laboratory tests

Functional laboratory group	Test name	Reflex
Haematology	Haematocrit	
	Haemoglobin	
	Red blood cells (RBC count)	
	Platelet count (PLT count)	
	White blood cells count	
	Mean corpuscular volume (MCV)	
	Mean corpuscular haemoglobin (MCH)	
	Mean corpuscular haemoglobin concentration (MCHC)	
	Red cell distribution width (RDW)	
	Reticulocyte count	
Automatic WBC differential (relative and absolute)	Neutrophils	
	Eosinophils	
	Basophils	
	Monocytes	
	Lymphocytes	
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphonuclear neutrophils (segs)	
	Band neutrophils (stabs)	
	Eosinophils	
	Basophils	
	Monocytes	
	Lymphocytes	
Coagulation	Prothrombin time	
	Activated partial thromboplastin time (aPTT)	
	International normalised ratio (INR)	
Enzymes	Alanine aminotransferase (ALT, SGPT)	
	Aspartate aminotransferase (AST, SGOT)	
	Alkaline phosphatase	
	Gamma-glutamyl transferase (GGT)	
	Lipase	
	Amylase	
	Creatine kinase (CK)	If increased >1 × ULN, reflex to troponin I
	Troponin I	Reflex test if CK increased >1 × ULN

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Table 6 (cont'd) Safety laboratory tests

Functional laboratory group	Test name	Reflex
Substrates	Glucose (serum)	
	Creatinine, enzymatic	
	Urea (blood, urea, nitrogen)	
	Uric acid	
	Bilirubin, total	If increased, reflex to direct/indirect fractions
	Direct bilirubin	Reflex test if total bilirubin increased
	Indirect bilirubin	Reflex test if total bilirubin increased
	Total protein	
	Albumin	
	Estimated glomerular filtration rate (eGFR)	eGFR will be calculated using Chronic Kidney Disease Epidemiology [CKD-EPI] Collaboration equation (Caucasian and Black: [R12-1392], Japanese: [R22-1536], Other races: [R22-1535])
	C-reactive protein (CRP)	As scheduled in SoA and in case of CRS
Electrolytes	Sodium	
	Potassium	
	Chloride	
	Phosphate	
	Magnesium	
	Calcium	
	Bicarbonate	
Urinalysis	Urine nitrite	
	Urine protein	
	Urine glucose	
	Urine ketone	
	Urine bilirubin	
	Urine haemoglobin	
	Urine leukocyte esterase	
	Urine pH	
	Specific gravity	
	Urine sediment microscopic examination	Reflex test if erythrocytes, leukocytes, nitrite, or protein is abnormal in urine

eGFR will be analysed and calculated by the central laboratory at the same timepoints as other safety laboratory parameters (refer to SoA). eGFR will be calculated by using the CKD-EPI formula and using the serum creatinine measurement (enzymatic method).

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5.2.3.1 Additional laboratory parameters

Additional safety laboratory tests might be required under specific circumstances as described in Table 7. The sampling time points are shown in the SoA (see OoA for order with respect to other assessments).

Table 7 Additional safety laboratory parameters (central laboratory)

Functional laboratory group	Test name	Reflex
Enzymes	Lactate dehydrogenase	As part of safety laboratory tests listed in the SoA
Substrates	Globulin Albumin/globulin ratio Total cholesterol Triglycerides LDL HDL	As part of safety laboratory tests listed in the SoA
Cardiovascular	NT Pro-BNP	As part of safety laboratory tests listed in the SoA
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Woman of non-childbearing potential	Follicle Stimulating Hormone Estradiol	In questionable cases of postmenopausal status (see Section 3.3.2)

5.2.3.2 Exclusionary laboratory tests

The investigator will use results of the exclusionary laboratory tests in Table 8 to assess each patient's eligibility for the trial. If patients are enrolled in the trial, these laboratory results

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will be reported to the sponsor. The sampling time points are shown in the SoA (see OoA for order with respect to other assessments).

Table 8 Exclusionary laboratory tests

Functional laboratory group	Test name
Infectious serology (blood)[1]	Hepatitis B surface antigen (qualitative) Hepatitis B surface antibody (qualitative)[2] Hepatitis B core antibody (qualitative) Hepatitis C antibodies (qualitative) [3] HIV1 and HIV2 antibody (qualitative) [redacted]

1 A positive hepatitis B surface antigen (HBsAg) result at screening is exclusionary. If HBsAg is negative and anti-HBc or anti-HBs is positive at screening, HBV DNA should be evaluated by PCR. Patients with detectable HBV DNA (≥10 IU/mL) will be excluded from the trial.
In patients with negative HBsAg, positive anti-HBc (or positive anti-HBs [for patients in Japan only]), and undetectable HBV DNA at screening, HBV DNA will be evaluated again at EOT visit (patients in Japan also at Visit 6).

2 Only for patients in Japan.

3 A positive hepatitis C antibody test result should be confirmed by HCV RNA PCR.

[redacted]

5.2.4 Electrocardiogram

Resting 12-lead ECGs will be conducted by a qualified technologist at timepoints shown in the SoA (see OoA for order with respect to other assessments). ECGs will be done using site's own equipment after patients have rested for at least 5 min in a supine position. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons or at the discretion of the investigator (during eligibility assessment) and used for analysis. Additional ECGs may be recorded for safety reasons.

Dated and signed printouts of ECG with findings should be documented in the patient's medical record.

Clinically relevant abnormal findings will be reported either as baseline conditions (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate. If the ECG was abnormal at Visit 1, the ECG may be repeated.

5.2.5 Local tolerability

Local tolerability at the IMP administration site will be assessed by the investigator during the IMP administration visit and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction, e.g. [redacted], and other findings should be reported as an AE.

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5.2.6 Assessment of adverse events

Data and information necessary for the thorough assessment of AEs, SAEs, and AESIs will be reported to the sponsor via eCRF. This may include specific data and information not prospectively specified in this protocol.

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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

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

The following also may be considered AEs, based on the judgement of the investigator:

- [redacted]
- Changes in vital signs, ECG, physical examination findings, and/or laboratory test results, if judged clinically relevant by the investigator.

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

5.2.6.1.2 Serious adverse event

An SAE is defined as any AE that fulfils at least one of the following criteria:

- Results in death
- Is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe
- Requires inpatient hospitalisation on or 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, based on appropriate medical judgement, that may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency

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room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse

For Japan only: An event that possibly leads to disability will be handled as "deemed serious for any other reason" and, therefore, reported as an SAE.

5.2.6.1.3 AEs considered "Always Serious"

Based on the European Medicines Agency list of Important Medical Events, Boehringer Ingelheim has set up a list of AEs (MedDRA Preferred terms), which by their nature, will be considered serious even though they may not have met one of the seriousness criteria (death, life-threatening, disability or permanent damage, hospitalization, congenital anomaly/birth defects) and could be considered as "other serious (important medical event)".

Events on this list are always classified as serious by the sponsor and need to be reported to the sponsor in the same manner as SAEs (refer to Section 5.2.6.2.2).

The Boehringer Ingelheim list of always serious events is incorporated into EDC to ensure the serious criteria for these events are evaluated. If an event is entered as non-serious but is included on the Boehringer Ingelheim Always Serious Event List, a query will be raised in EDC requesting the site to either update the AE field or update the classification from non-serious to serious with criteria 'other serious (important medical event)', and report immediately (within 24 h) to the sponsor.

A copy of the latest list of The Boehringer Ingelheim Always Serious Events will be provided upon request.

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

5.2.6.1.4 Adverse events of special interest

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

The following are considered AESIs (refer to Section 1.4.2 for rationale):

- Potential severe DILI
- [redacted]
- [redacted]
- [redacted]

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Potential severe DILI

A potential severe DILI that requires follow-up is defined by any of the following alerts (alterations) of hepatic laboratory parameters that occur after the first dose of IMP:

1. AST or ALT elevation ≥3 × ULN and total bilirubin ≥2 × ULN measured at the same visit, or in samples drawn within 30 days of each other, OR
2. AST or ALT elevation ≥3 × ULN and INR ≥1.5 × ULN measured at the same visit, or in samples drawn within 30 days of each other, OR
3. AST or ALT elevation ≥3 × ULN with new onset, or worsening of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%), OR
4. AST or ALT elevation ≥5 × ULN

These laboratory findings constitute a hepatic injury alert, and patients showing any of these laboratory abnormalities need to be followed up according to the "DILI Checklist" provided in the ISF.

In case of clinical signs or symptoms of hepatic injury (e.g. icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain) without laboratory results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary, in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI Checklist should be followed.

Additionally, with patients having a normal AST and ALT at baseline, the emergence of an isolated AST or ALT elevation between ≥3-fold and <5 × ULN requires repeat testing within 72 h. DILI Checklist is not required unless repeat testing triggers alerts 1, 2, 3, or 4.

The following events should lead to immediate discontinuation of IMP:

- Hepatic injury alert numbers 1, 2 or 3
- Hepatic injury alert number 4, if persists >2 weeks
- AST or ALT elevation >8 × ULN

Following completion of the DILI Checklist, if the Boehringer Ingelheim IMP cannot be excluded as a possible cause of the DILI event, discontinuation should be made permanent without rechallenge. If an alternate causality, e.g. acute viral hepatitis, is confirmed by the DILI Checklist evaluation, Boehringer Ingelheim IMP may be re-started, if warranted.

[redacted]

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[redacted]

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of AEs should be classified and recorded in the eCRF according to the CTCAE Version 5.0.

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the AE and the Boehringer Ingelheim IMP, 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 a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the IMP
- 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 IMP exposure
- Evidence that the event is reproducible when the IMP is reintroduced
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or comedications)
- 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 no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of IMP exposure is evident (e.g. pretreatment cases, diagnosis of cancer or chronic disease within days/weeks of IMP administration; an allergic reaction weeks after discontinuation of the IMP concerned)

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- Continuation of the event despite the withdrawal of the IMP, considering 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
- There is an alternative explanation, e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the IMP concerned
- Disappearance of the event even though trial IMP treatment continues or remains unchanged

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

Per default, SAEs/AESIs should be reported via the eCRF in the EDC system. If the EDC system is not or no longer available (e.g. after database lock), the Boehringer Ingelheim paper SAE form should be used; see Section 5.2.6.2.2. The following must be collected and documented:

- From signing the informed consent onwards until the individual patient's end of trial (usually the End-of-study Visit; see Section 6.2.3):
  All AEs (serious and non-serious) and all AESIs

- After the individual patient's end of trial:
  The investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer of new histology, IMP-related SAEs, and IMP-related AESIs of which the investigator may become aware by any means of communication, e.g. phone call.

Vital Status Data Collection

For those patients who discontinue treatment prematurely and are unable to complete the follow-up period (see Section 3.3.4.1), every attempt should be made to get information on vital status at 12 weeks after randomisation and at their EOS (19 weeks after last dose). If a patient only agrees to be contacted for vital status data collection, the investigator must report until the individual patient's EOS any occurrence of cancer, all deaths/fatal AEs regardless of relationship, IMP-related SAEs, and IMP-related AESIs the investigator becomes aware of.

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 (S)AE eCRF and on the SAE eCRF pages and report to the sponsor immediately (within 24 h of becoming aware of the event). This also applies to events that have been upgraded to a Boehringer Ingelheim Always Serious Event in the

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system. The country-specific process is described in the ISF. On specific occasions, the investigator could inform the sponsor upfront via telephone in addition.

With receipt of any further information on these events, follow-up reports must be provided. For follow-up information, the same rules and timelines apply as for initial information. All AEs/SAEs, including those persisting after an individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

Should the EDC system not be available for more than 24 h, reporting must occur via the Boehringer Ingelheim paper SAE forms.

5.2.6.2.3 Pregnancy

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

Similarly, potential IMP exposure during pregnancy must be reported if a partner of a male patient becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial-specific information and consent for the pregnant partner.

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

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

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Studies is to be completed. However, an SAE and/or AESI associated with the pregnancy must be reported as described in Section 5.2.6.2.2.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Fasting before blood sample collection is not required because BI 765423 will be administered intravenously and, thus, [redacted].

PK objectives and endpoints are described in Section 2.2.

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5.3.2 Methods of sample collection

For quantification of BI 765423 concentrations, samples will be taken at the times indicated in the SoA and in Section 10.2.1 (except for participants of the PK subpopulation; see Section 5.3.3 and Section 10.2.2). See OoA for order with respect to other assessments. Details about blood sample collection, plasma/serum preparation, required tubes, labelling of tubes, storage, and shipment (frequency and addresses) will be provided in the Laboratory Manual.

After analysis, plasma samples may be used for further methodological investigations related to BI 765423 [redacted] or to address Health Authority questions regarding the results/methodology. However, only data related to the analyte and/or its metabolite(s), [redacted] (if applicable), will be generated by these additional investigations. The samples will be discarded after completion of the additional investigations but not later than 5 years after the final clinical trial report has been signed.

5.3.3 PK subpopulation (Japan only)

All patients of Japanese ethnicity included by sites based in Japan will have an intense PK sampling described in Section 10.2.2 Table 13, instead of the PK sampling shown in Section 10.2.1 Table 12. For this purpose, some **additional site visits** are planned (see Section 10.2.2).

Patients of other ethnicities included by sites based in Japan will have PK sampling described in Section 10.2.1 Table 12.

5.3.4 Analytical determinations

Total BI 765423 concentrations will be determined by a validated immunoassay. Analyses will be performed at [redacted]. The presence of [redacted] against BI 765423 will be assessed using a validated immunoassay in a tiered approach, i.e. screening, confirmatory, and titration [redacted].

5.3.5 Pharmacokinetic – pharmacodynamic relationship

Population PK and PK/PD analyses will be performed to further characterise the PK and the exposure-response relationships of BI 765423 with selected efficacy and/or safety endpoints, [redacted], prior to the DBL. Data from this trial may be pooled with Phase I data (Trials 1493-0007 and 1493-0008). These analyses will be subject to separate analysis plans and reports and will not be part of the CTR.

5.3.6 [redacted]

For assessment of [redacted] to BI 765423, samples will be collected predose at the times indicated in the SoA (see OoA for order with respect to other assessments), close to matching

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PK sampling (see Sections 10.2.1 and 10.2.2). [redacted] samples will be collected but may not be analysed if there is no observed impact on PK, or no safety concerns associated with [redacted]. Additionally, blood for [redacted] may also be collected and assessed upon observation of [redacted], as described in Section 4.2.1.4 and listed in Table 7.

Details about blood sample collection, serum preparation, required tubes, labelling of tubes, storage, and shipment (frequency and addresses) will be provided in the Laboratory Manual.

The samples may be used to further characterise [redacted] or to address health authority questions regarding the results/methodology. However, only data related to the [redacted] to BI 765423 will be generated by these additional investigations. The samples will be discarded no later than 5 years after the final clinical trial report has been signed.

5.4 ASSESSMENT OF BIOMARKER(S)

This section refers to exploratory and probable valid biomarkers.

5.4.1 Exploratory and probable valid biomarkers

Exploratory and probable valid biomarker sampling is mandatory but not required to assess eligibility.

Blood biomarkers shown to have disease prognostic value and to be elevated in patients with IPF [redacted] [P24-05946; R15-1220; R20-3564] will be evaluated. SP-D will be explored as secondary endpoint, all other exploratory biomarkers as supportive evidence. Biomarkers will be explored in serum and plasma and association with clinical endpoints will be investigated. Results for biomarker analyses on SP-D will be reported in the CTR while all other biomarker analyses may be reported separately.

Planned exploratory or probable valid biomarker analyses may include, but is not limited to:

Probable valid

- SP-D in plasma

Exploratory

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

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[redacted]

Samples can be analysed in a staged approach, and decisions for further analysis may depend on the results of prior analyses. This may also imply that not all collected samples will be analysed, especially in case of termination of the project/trial.

Should other biomarkers become relevant in the context of the trial and/or based on new information in the scientific literature or early trial analysis, these may also be explored from the available specimens.

The trial biomarker samples will be discarded after completion of any investigations, but not later than 2 years after the final trial report has been signed. Any leftover samples or derived material from prespecified analyses (e.g. serum and plasma) may be used for method development/validation but will be destroyed no later than 2 years after the final trial report has been signed.

Exploratory and probable valid biomarker analyses will be performed by Boehringer Ingelheim or by a laboratory authorized by Boehringer Ingelheim.

Detailed instructions on sampling, preparation, processing, and shipment of the samples are provided in the laboratory manual. For sampling timepoints, see the SoA. Samples need to be taken pre-dose and exact time recorded in the eCRF.

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

Analytical results for the biomarker analyses will be described in analytical reports.

5.5 BIOBANKING

Biobanking will be performed only in countries where allowed by local laws and regulations. Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will occur only after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements.

For all countries, please refer to the country specific biobanking informed consent form for details on data protection, storage duration, withdrawal, and incidental findings.

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For Japan: Biobanking samples and the associated medical data will be pseudonymized to protect patients' identity and personal data. Samples may be kept for up to 30 years after the end of the clinical trial and will be destroyed thereafter. If patients withdraw biobanking informed consent, samples that have not been used will be destroyed. In case of incidental findings that are considered medically actionable because they have clear and immediate medical significance to patients' health, the Sponsor will take all justifiable efforts to inform the Investigator.

5.5.1 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment, and storage are provided in the laboratory manual. DNA samples will be taken once, preferably at Visit 2 (baseline) or, if not possible, at Visits 3, 4, 5, 6, or at EOT. For serum and plasma sampling timepoints, see the SoA and OoA for order with respect to other assessments.

A total of about 120 mL blood will be drawn for DNA, plasma, and serum banking purposes.

5.6 OTHER ASSESSMENTS

5.6.1 [redacted]

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

The measures conducted for primary, secondary endpoints are using standard methods. Measures conducted for exploratory further endpoints might be new methodologies already used in clinical research (e.g. [redacted]) but still not validated for IPF.

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6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstance (e.g. pandemic, war), the execution of the investigational plan as per this clinical trial protocol may not be feasible. With the consent of the patient, the sponsor and investigator may agree on alternative, back-up, or rescue methodology which may include, but will not be limited to, virtual patient visits and assessments. The implementation of these measures will depend on the patient's consent, operational feasibility, and local laws and regulations. Such alternative measures will be described in the patient information. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

The trial visit schedule is presented in the SoA. Additional site visits are planned for the PK subpopulation (see Section 10.2.2).

All patients should adhere to the visit schedule as specified in the SoA. If any visit has to be rescheduled, subsequent visits should follow the original visit schedule (counted from Visit 2). Additional (unscheduled) visits for the purpose of retesting laboratory parameters or AE monitoring may be conducted as deemed necessary by the investigator.

In the event of force majeure or other disrupting circumstance, physical visits to sites may not be feasible for patients or may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the patient may be contacted by phone. The phone call should include, at minimum, assessment of AEs and concomitant medications.

All deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Assessments to be performed at each visit are listed in the SoA. Sequence and timing of assessments is specified in the OoA. All assessments scheduled at a specific visit should be preferably performed on the same day except for the allowed retests (see Section 3.3), the imaging assessments ([redacted] [see Section 5.1.6]). In cases were [redacted] cannot be completed on the day of the visit due to the patient's health condition or technical issues, the assessment may be repeated on another day.

Drug assignment in IRT can be performed 1 day ahead of the visit if required for the preparation of IMP.

Data concerning adverse events and concomitant medications will be collected throughout the trial, as specified in the SoA. These data will be obtained at scheduled or unscheduled visits based on the information provided actively by the patient or questions asked by the investigator.

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If blood sampling for central laboratory at the trial site is not possible, safety laboratory analyses may be performed at a local laboratory. The results of the laboratory tests must be transferred to the investigator who ensures medical review and documents any clinically relevant safety issue as an AE.

6.2.1 Screening and run-in period(s)

6.2.1.1 Screening Period

During the screening visit (Visit 1), demographics information will be collected, including:

- Age (in years) on the day of informed consent
- Sex (male or female, in order to describe the patient's sex at birth)
- Gender identity (male, female, non-binary, not answered, or other in order to describe how the patient self-identifies, regardless of their genotypic or phenotypic sex) if 1) locally accepted (i.e. based on HA/EC/IRB acceptance, independent of acceptance by investigators or patients), 2) investigators are willing to ask, and 3) patients are willing to reply
- Ethnicity and race in order to sufficiently characterize the patient population, to support possible subgroup analyses if needed, and to support the calculation of the kidney function via the CKD EPI formula unless not acceptable according to local regulations

Refer to Section 3.3 for further considerations during screening, retesting and rescreening criteria. See SoA, OoA and Section 5 for details on screening assessments.

6.2.1.2 Run-In Period

Not applicable.

6.2.2 Treatment period(s)

After all screening assessments have been completed and eligibility has been confirmed, the patient can proceed to Visit 2. Randomisation in the IRT system should not be performed until eligibility is fully confirmed, as it cannot be reversed. See Section 5.1.6 for Visit 2 [redacted] (participants at selected sites only).

The treatment period starts with Visit 2 and ends with the completion of the EOT visit. It is planned to be [redacted]. The EOT visit should be conducted [redacted].

Unscheduled visits may be arranged if necessary. Procedures completed during an unscheduled visit will depend on the circumstance under which the visit was planned, and at the discretion of the investigator. No PK, biomarker or biobanking samples should be collected and no IMP should be administered at visits outside of the original visit schedule.

See SoA, OoA and Section 5 for information on assessments at specific visits.

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6.2.3 Follow-up period and trial completion

Patients should make all efforts to complete the trial including a follow-up period which extends from after the EOT visit until the EOS (FU2) visit. The REP will be fully covered by the period between the last IMP dose and the end of the follow-up period.

See SoA for assessments to be performed during the follow-up period.

Abnormal assessments or laboratory parameters judged clinically relevant by the investigator will be monitored until a return to a medically acceptable level is achieved. All AEs/SAEs, including those persisting after an individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained (see Section 5.2.6.2.2).

If needed, in the opinion of the investigator, additional visits may be scheduled after the EOS (FU2) visit for continued safety monitoring. Otherwise, the EOS (FU2) visit will be considered the final trial visit.

If it is not possible for the patient to attend the EOS (FU2) visit within the visit window, the visit should be performed later at the earliest possible occasion, for safety reasons.

See Section 3.3.4.1 for details on patients discontinuing IMP prematurely.

A patient is considered to have completed the trial if one of the following applies:

- Completion of planned follow-up period i.e. EOS (FU2) visit completed
- Lost to follow-up
- Refusal to be followed-up
- Death

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7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

No confirmatory testing is performed and hence no null and alternative hypotheses are defined. A justification of the sample size is provided in Section 7.5.

All the analyses will be performed in an exploratory fashion to better understand the efficacy and safety profile of BI 765423.

Any confidence intervals computed are to be interpreted as exploratory, i.e. as interval estimates of effects.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The following analysis sets will be defined for statistical analyses:

- **Randomised Set:** This patient set includes all entered and randomised patients.
- **Treated Set (TS)**: includes all randomised patients who received at least one dose of study treatment. The TS will be used for all safety and efficacy analyses, in which patients will be analysed according to the actual dose they received (e.g. according to actual treatment).
- **Pharmacokinetic set (PKS)**: This patient set includes all patients in the TS who provide at least one PK parameter that was not excluded because of protocol deviations relevant to PK.

Further Analysis Sets will be defined in the TSAP, if needed.

Data from patients who are screened but not randomised will be listed but not included in any summary statistics or inferential statistics. Definitions and handling of IPDs will be included in the IPD specification document and will be stored within the TMF in the EDMS. All potential important protocol deviations will be discussed during trial oversight meetings and report planning meetings. All final decisions concerning IPDs will be made before DBL and any exclusions from the analysis sets will be documented in the decision log.

7.2.2 Handling of intercurrent events

The expected intercurrent events of interest in this trial are:

- Start or change in background treatment with SoC
- Start of a restricted medication
- Treatment discontinuation

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- Death
- [redacted]
- Certain categories of important protocol deviations (iPDs)

The strategies for handling intercurrent events in this trial are as follows and summarized in Table 9. Important protocol deviations (iPDs) which would be considered as intercurrent events will be specified in TSAP.

Main strategy:

All intercurrent events except for death and [redacted] will be handled according to the treatment policy approach as defined in ICH E9 (R1). Use of the "treatment policy" approach disregards the intercurrent event and uses the value of the variable regardless of the occurrence of the intercurrent event (e.g. start of a restricted medication).

The intercurrent events of death and [redacted] will be primarily handled using hypothetical strategy, as defined in ICH E9 (R1). Use of the "hypothetical approach" considers the effect of what would have happened if the intercurrent event did not occur, this means that all data collected after the event will not be included and assumed to be missing at random.

In addition, the biomarker strategy will handle start or change in background treatment with SoC by a hypothetical approach. Remaining intercurrent events will be handled in the same way as the main strategy.

Table 9 Handling of intercurrent events as per ICH E9 (R1) within the different strategies

Intercurrent Events	Main strategy	Biomarker strategy
Death	Hypothetical	Hypothetical
[redacted]	Hypothetical	Hypothetical
Treatment Discontinuation	Treatment Policy	Treatment Policy
Start or change in background treatment with SoC	Treatment Policy	Hypothetical
Start of a restricted medication	Treatment Policy	Treatment Policy
Important protocol deviations	Treatment Policy	Treatment Policy

Each analysis will reference the strategy for handling intercurrent events that it will be estimating.

The estimand for each main analysis in this protocol is the combination of the relevant detailed clinical objective from Section 2.1 and this strategy.

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Any intercurrent events that are not listed will be decided by review prior to DBL based on the general principle outlined, and secondary strategies will be documented in the TSAP. If possible, the review will occur in a blinded manner, see Section 4.1.5 for details on blinding.

7.2.3 Primary objective analyses

7.2.3.1 Main analyses

The primary endpoint absolute change from baseline in FVC (in mL) at 12 weeks will be evaluated descriptively and by a REML based approach using a MMRM to account for covariates and the repeated nature of the data. The model will be fitted using all available data within the first [redacted]. The analysis will be performed

[redacted]

- [redacted] At the final analysis after EOT.

The last measurement before first drug administration will be considered as baseline.

The analysis will include the fixed categorical effects of treatment at each visit, baseline type of antifibrotic treatment at each visit, as well as the fixed continuous effects of baseline FVC at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

The statistical model will be as follows:

$$y_{ijk} = \beta_j S_i + \tau_{jk} + \Phi_{jm} + e_{ij}$$

With

y_{ijk}	response variable for patient i at visit j, $j = 1, \ldots, Z$ receiving treatment k
S_i	baseline measurement of patient i
β_j	coefficient of baseline effect at visit j
τ_{jk}	effect of treatment k at visit j
ϕ_{jm}	effect of stratum m at visit j
e_{ij}	random error associated with visit j of patient i.

Errors are independent between patients with $e_{ij} \sim N_Z(0, \sum)$ and $\sum$ an unstructured covariance matrix.

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. Due to the exploratory character of this trial no significance test will be done. However, least-squares means (adjusted means) per treatment group as well as treatment contrasts will be provided together with two-sided 95%-confidence intervals for each time point.

Procedures to follow if the analysis fails to converge will be described in the TSAP.

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The primary analysis will be performed on the TS. Patients will be analysed according to the stratum to which they belong (regardless of any mis-assignment to treatment based on identification of the wrong stratum), as such an error occurs before randomization and is therefore consistent with regulatory guidance.

The 'main strategy' for intercurrent events (see Section 7.2.2) will be applied to the primary endpoint analysis. This means all available data from the TS in each active treatment arm and the placebo arm within the first [redacted] will be used, including baseline and data retrieved for patients who discontinued randomized treatment and after start or change of background treatment with SoC. FVC data collected after [redacted] will not be used for analysis following a hypothetical approach. The resulting missing data from such cases and missing data after a patient died will be assumed to be missing at random.

If feasible, an additional exploratory analysis might be carried out for the primary endpoint based on a Bayesian framework including historical data from [redacted] clinical trials, as well as available results from competitor trials. Further details (including prior derivation) will be described in the TSAP.

7.2.3.2 Sensitivity analyses

Additional sensitivity analysis to explore the effect of missing data will be described in the TSAP.

7.2.3.3 Subgroup analyses

If feasible, subgroup analyses will include at least the stratification factor type of antifibrotic treatment at baseline.

Further details and a complete list of subgroup analyses will be specified in the TSAP.

7.2.4 Secondary objective analyses

Planned analyses for main secondary endpoint

The main secondary endpoint absolute change from baseline in log_{10}-transformed SP-D plasma concentration at 12 weeks will be evaluated descriptively based on the TS. Furthermore, descriptive statistics on original scale will be presented.

The MMRM analyses described above for the primary endpoint (Section 7.2.3) will be repeated for the main secondary endpoints based on the TS.

Adjusted mean estimate for each treatment group, as well as difference between treatment groups will be presented together with two-sided 95%-confidence intervals. In addition, adjusted fold change from baseline, adjusted percentage change from baseline as well as ratio in fold change and relative difference comparing treatment groups will be calculated.

The 'main strategy' for intercurrent events (see Section 7.2.2) will be applied to the main secondary endpoint analysis. This means all available data from the TS in each active

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treatment arm and the placebo arm within the first [redacted] will be used, including baseline and data retrieved for patients who discontinued randomized treatment and after start or change of SoC therapy. Biomarker data collected after [redacted] will not be used for analysis following a hypothetical approach. The resulting missing data from such cases and missing data after a patient died will be assumed to be missing at random.

In addition, a supplementary analysis will be conducted for the main secondary endpoint following the 'biomarker strategy' for intercurrent events (see Section 7.2.2). This means in contrast to the 'main strategy', data collected after start or change of background treatment with SoC will not be used for analysis following a hypothetical approach. The resulting missing data will be assumed to be missing at random.

Planned analyses for secondary endpoints

Descriptive statistics will be provided for secondary endpoints based on the TS.

As additional exploratory analysis, the MMRM analyses described above for the primary endpoint (Section 7.2.3) will be repeated for secondary efficacy endpoints based on the TS, if feasible. Least-squares means (adjusted means) per treatment group as well as treatment contrasts will be provided together with two-sided 95%-confidence intervals for each time point.

[redacted]

7.2.5 Further objective analyses

Further endpoints will be analysed descriptively based on the TS.

If deemed appropriate, continuous efficacy endpoints will additionally be analysed using an MMRM approach as described above for the primary endpoint (Section 7.2.3)

If deemed appropriate, a random slope and intercept analysis will be carried out for the rate of change in [redacted], details will be provided in the TSAP.

Time to death (all-cause mortality) will be based either on the date of death on the AE report for patients with AEs leading to death, or it will be based on the information from the vital status assessment.

Kaplan-Meier plots by treatment group will be presented for time to event endpoints.

PK endpoints of BI 765423 will be primarily analysed descriptively based on the PKS. Further details will be provided in the TSAP.

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Analyses of further safety assessments are described below in Section 7.2.6.

7.2.6 Safety analyses

AEs will be coded using the MedDRA. Standard Boehringer Ingelheim summary tables and listings will be produced.

All AEs with an onset between start of treatment and end of the REP, a period of [redacted] after the last dose of trial IMP, will be assigned to the on-treatment period for evaluation.

Safety analysis will be done by 'treatment at onset'.

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

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs, i.e. all AEs occurring between the start of treatment and the end of the REP. AEs that start before first IMP intake and deteriorate under treatment will also be considered 'treatment-emergent'.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at DBL.

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

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

Additionally, an exploratory Bayesian safety analysis will be carried out for the following safety topics, if feasible:

- Clinically significant anaemia
- Clinically significant thrombocytopaenia
- Immediate and delayed [redacted]
- [redacted]
- [redacted]
- DILI
- Malignancy

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- Impairment of wound healing

Additional topics may be selected ad-hoc depending on the ongoing safety evaluation of the study.

The AE summary statistics of interest are:

- Incidence proportion: the percentage of patients with at least one AE of interest during a specific observation period.
- Exposure adjusted event rate: the incidence of first AEs per patient-year at risk (also referred to as *incidence rate* in literature [R24-3741]).

Posterior distributions will be obtained for incidence proportions and exposure-adjusted event rates using robust MAP approach [R16-0281] for derivation of a prior based on data from previous clinical trials with [redacted] patients (informative MAP prior for placebo, non-informative MAP prior for BI 765423 treatment arm). In order to reduce bias in comparison of current and historical patients, matching of inclusion and exclusion criteria as well as other baseline characteristics of patients in the current and historical studies will be considered if feasible.

Effective sample size for incidence proportion and effective number of events for incidence rates will be calculated using the expected local information ratio method [R22-0461].

If feasible, the analyses will be repeated for the subgroups, defined by use of SoC treatment at baseline [redacted].

Further details, especially on prior derivation and potential matching, will be specified in the TSAP.

7.2.7 Other analyses

Not applicable.

7.2.8 Interim analyses

A DMC will be in place with tasks as described in Section 8.7.

[redacted]

[redacted]

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Main analysis for primary and secondary objectives (see Sections 7.2.3and7.2.4), and in addition safety data, may be conducted after end of treatment of last patient and before data base lock based on evaluable data as needed, to conduct unblinded exploratory analyses while data collection for selected other analyses is still ongoing, see Section 4.1.5 for details on unblinding.

A preliminary analysis of PK, PD and/or [redacted] data may be performed based on evaluable data prior to DBL. This analysis may be necessary to inform other activities during trial conduct or the conduct of other trials. In contrast to the analysis performed after DBL (final analysis), this preliminary analysis will be based on planned sampling times rather than on actual times; therefore, minor deviations may be present between preliminary and final data evaluation. The planning, analysis execution, and storage of results will be done according to Boehringer Ingelheim processes and will be shared with the trial team.

The preliminary analysis will provide individual and mean concentration-time profiles and summary statistics of individual values and parameters without patient identification information. No formal preliminary report will be written.

A Fast-track analysis for population PK/PD modelling is planned, i.e. a dedicated database snapshot for [redacted] The modelling activities will be planned and documented separately (see Section 5.3.5).

The described analyses above are not planned to lead to sample size recalculations or adjustment of enrolment targets.

In addition to the planned analysis described above, an administrative IA may be performed for unforeseen trial results or external results that put into question critical trial design assumptions. Examples may include unresolvable recruitment problems, unexpected patterns of efficacy or safety data, upcoming urgent drug development decision needs, or results from other trials leading to concerns about the benefit-risk of treatment groups or the trial.

The decision to conduct such an administrative IA will be documented in the decision log and accompanied by a Data Logistics Plan and Results Access Plan according to sponsor SOPs, together with details about how to protect the scientific credibility of the trial. Whether and how results of such an administrative IA will be used for a subsequent trial adaptation will be stated, which is to be planned in a protocol amendment.

7.3 HANDLING OF MISSING DATA

In the primary analysis of primary endpoint and other continuous endpoints, missing data will not be imputed.

The mixed effect model will handle missing data based on a likelihood method under the “missing at random assumption”.

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In the analysis of time-to-event endpoints, missing or incomplete data will be handled using standard survival analysis techniques (i.e. censoring).

Missing or incomplete AE dates will be imputed according to Boehringer Ingelheim standards.

Handling of missing PK and PD/biomarker data will be performed according to the relevant Boehringer Ingelheim internal procedures.

Additional details on the handling of missing data and sensitivity analysis will be specified in the TSAP.

7.4 RANDOMISATION

Patients will be randomised with a targeted [redacted] allocation ratio to either BI 765423 or placebo. The randomisation scheme will be created using the big stick design methodology [R24-2794].

This trial includes an administrative stratification for PK subpopulation (yes/no, see Section 5.3.3), this factor will not be accounted for in the statistical analysis. For the PK subpopulation an allocation ratio aiming to achieve at least [redacted] evaluable patients on the active treatment arm will be applied. To achieve this, the randomisation for this PK subpopulation will be based on a block urn design [R23-0869], targeting a [redacted] allocation for BI°765423 vs. placebo.

Randomisation will further be stratified by type of background antifibrotic treatment at baseline [redacted] for patients not part of the PK subpopulation.

Boehringer Ingelheim will arrange for the randomisation and the packaging and labelling of trial IMP. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. Specific parameters used for the creation of the randomization schedule (e.g. maximum tolerated imbalance limits for big stick design) will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

For this exploratory trial it is planned to randomise approx. [redacted] patients equally to the treatment groups placebo and BI 765423 (each group approx. [redacted]).

The total sample size of this trial is based on evaluations of the probability to observe minimum effects as specified in Table 10, under consideration of various scenarios for the treatment effect on primary and main secondary endpoint after [redacted] of treatment.

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Table 10 Minimum effect of BI 765423 for primary and main secondary endpoint

		Minimum treatment effect on:	
		Primary endpoint	**Main secondary endpoint(biomarker)**
Margin options		[redacted]	
Low	1		
	2		
Medium	1		
	2		
High	1		
	2		

aCfB: absolute change from baseline; rCfB: relative change from baseline

[redacted] If there is actually no true treatment difference, such sample size provides a success probability of [redacted] under the otherwise same conditions. This is considered acceptable for an exploratory trial.

Table 11 Success probabilities under certain scenarios

		Success probabilities ('P[Go*]') under different margin options		
Scenario	[redacted]	**Low**	**Medium**	**High**
All positive	[redacted]			
[redacted]				
No effect				

*Go: Margin options 1 or 2 are fulfilled

aCfB: absolute change from baseline;

Calculations were performed using R Version 4.2.2 [R22-0511].

Since the treatment discontinuation rate over a period of [redacted] is expected to be low (approx. 7%), and due to the nature of the main analysis strategy (a treatment policy estimand, missing measurements due to death or [redacted] will be assumed to be missing at random, see Section 7.2.2), it is expected that only approx. 5% of patients will not contribute to analysis of primary and main secondary endpoint.

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This leads to the actual information content of missing data being much less than 5% of patients, therefore the total sample size of the study was not accounted for possible dropouts.

Furthermore, the assumed SD is based on MMRM results of actual trial data (including dropouts), hence drop-out of patients is implicitly reflected in the calculation of probabilities.

For the PK subpopulation, it is planned to randomise [redacted] patients, aiming to achieve at least [redacted] evaluable patients treated with BI 765423. This size is generally considered sufficient for the exploratory evaluation of single and multiple dose PK.

For the [redacted] assessments at selected sites, it is planned to include approx. [redacted] patients. This size is generally considered sufficient for exploratory evaluation of associated endpoints.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for GCP, relevant Boehringer Ingelheim SOPs, EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997), and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP, or applicable regulations will be treated as a 'protocol deviation'.

Data protection within the EU will be handled in accordance with the EU GDPR stipulated in Regulation (EU) 2016/679.

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

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

The investigator will be responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.

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

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

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

Re-consenting may be 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 patient protection and reliability of the results, as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH GCP E6, 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 designee, IRB/IEC, or 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

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

8.3.1 Source documents

A detailed description of the transmission of electronic data (i.e. data flow) is provided in the data management plan.

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 patient. Source data as well as reported data

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should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal, and **a**ccurate. Changes to the data should be traceable (audit trail).

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

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

Copies of following source files will be provided to [redacted] vendors:

- [redacted]
- [redacted]

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

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

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

- Patient identification: sex, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dates and times of IMP administration
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and AESIs (onset date [mandatory] and end date [if available])
- SAEs (onset date [mandatory] and end date [if available])
- Concomitant therapy (start date, changes)
- Dated and signed printouts of ECG
- Original paper PRO forms
- [redacted]

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[redacted]

- [redacted]
- Documentation of physical exam findings, vital signs, height and weight measurements
- Information on collection dates and times for the individual laboratory samples
- Completion of trial participation (end date; in case of premature discontinuation, document the reason)
- Prior to allocation of a patient to a treatment in a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the patient meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient, or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial

8.3.2 Direct access to source data and documents

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

In the event of force majeure or other disrupting circumstance (e.g. pandemic or war; see Section 6), site access may be restricted, thus limiting the ability to perform standard site monitoring activities on site, such as source data review and source data verification. Therefore, some of these activities may be performed remotely or replaced by centralized monitoring to the extent possible, based on a documented risk assessment and in alignment with local regulations.

8.3.3 Storage period of records

Trial site(s):

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

Sponsor:

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

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8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

Boehringer Ingelheim is responsible for fulfilling their legal and regulatory reporting obligation in accordance with regulatory requirements. SAE/AESI are processed in the global safety database and assessed for the sponsor causal relationship, as well as the expectedness of the event according to the reference safety information. Individual case safety reports are subsequently reported according to local regulations. SUSARs will be reported to the EMA via E2B transmission of individual case safety reports to the Eudravigilance CT Module.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

- Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred
- The patient must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent
- The patient must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, appropriate IRB/IEC members, and inspectors from regulatory authorities
- The sponsor has implemented privacy and security controls designed to help protect patients' personal data, including information security controls, firewalls, incident detection, and secure transfer measures
- In the event of an accidental or unlawful destruction, loss, alteration, unauthorized disclosure, or access to personal data ("breach"), the sponsor has implemented procedures and measures to promptly address and mitigate any risk to the patient. In the event of a breach, the sponsor will notify the appropriate regulatory authorities and/or the patient(s) in accordance with applicable data protection law
- The contract between sponsor and trial sites specifies the responsibilities of the parties related to data protection, including the handling of data security breaches and respective communication and cooperation of the parties
- Information technology systems used to collect, process, and store trial-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access
- A Data Protection Impact Assessment established that data protection and mitigation measures in place by the sponsor are suitable to limit residual risk to the levels "negligible" or "limited"

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

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

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

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("last patient completed").

The "**last patient last treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial IMP (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial IMP until [redacted] days after LPLT at their site.

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

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

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

The sponsor will prepare a clinical trial report within 1 year from the end of trial.

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The sponsor will notify the IEC/competent authority in each participating EU Member State about all required trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within 1 year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim International GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany.

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

A SC consisting of independent experts and sponsor representatives will be established to support the Coordinating Investigator. The composition of the SC will be documented in the TMF. The tasks and responsibilities will be agreed in contracts between the SC members and the sponsor.

A DMC will be established and include members who are independent of the sponsor. DMC members will include physicians experienced in the treatment of the disease under investigation and a statistician.

The DMC will evaluate safety data periodically. The DMC will receive urgent, significant, safety concerns identified by the sponsor's multidisciplinary safety review committee for BI 765423 for immediate evaluation. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification, or termination of the trial as detailed in the DMC charter. DMC recommendations, as well as the final decision by the sponsor, will be reported to the appropriate RAs/HAs, IRBs/IECs, and to investigators as required by local law. The tasks and responsibilities of the DMC are specified in a charter.

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

The investigators will have access to the Boehringer Ingelheim web portal to access documents provided by the sponsor.

Boehringer Ingelheim has appointed a Clinical Trial Leader responsible for coordinating all required activities, in order to:

- Manage the trial in accordance with applicable regulations and internal SOPs

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- Direct the clinical trial team in the preparation, conduct, and reporting of the trial
- Ensure appropriate training and information of Clinical Trial Managers, CRAs, and investigators of participating countries

In the participating countries, the trial will be performed by the respective local or regional Boehringer Ingelheim organisation (Operative Unit) in accordance with applicable regulations and Boehringer Ingelheim SOPs, or by a CRO based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.

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

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

A central laboratory service, central imaging services [redacted] vendor will be used in this trial. Details will be provided in the respective manuals available in the ISF.

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9. REFERENCES

9.1 PUBLISHED REFERENCES

[redacted]

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[redacted]

9.2 UNPUBLISHED REFERENCES

206893_11324629_1.0 Safety, tolerability, pharmacokinetics, and pharmacodynamics of [redacted] doses of BI 765423 in healthy male subjects (single-blind, randomised, placebo-controlled, parallel group design). 1493-0008. Clinical Trial Report. [redacted].

206893_1863733_7.0 Investigator's Brochure 1493.P2. BI 765423. [redacted]

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c43916667-01	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising intravenous doses of BI 765423 in healthy male subjects (single-blind, randomised, placebo-controlled, parallel group design). 1493-0007. Clinical Trial Report. [redacted]

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10. APPENDICES

10.1 PATIENT FEEDBACK

Optional Patient Feedback Questionnaires:

This trial will include an option for patients to complete questionnaires, 'Patient Feedback Questionnaire', to provide feedback on their clinical trial experience. Individual patient level responses will not be reviewed by investigators. Responses will be used by the sponsor to understand where improvements can be made in the clinical trial process. These questionnaires will not collect data about the patient's disease, symptoms, treatment effect, or AEs and therefore will not be part of the trial data or clinical trial report. The questionnaires will be implemented after local regulatory approval, if required, and after consent of the patient. Providing feedback is optional and not required for participation in the trial.

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10.2 TIME SCHEDULE FOR PHARMACOKINETIC BLOOD SAMPLING

10.2.1 Blood sampling for all patients except for PK subpopulation

Table 12 Time schedule for PK blood sampling

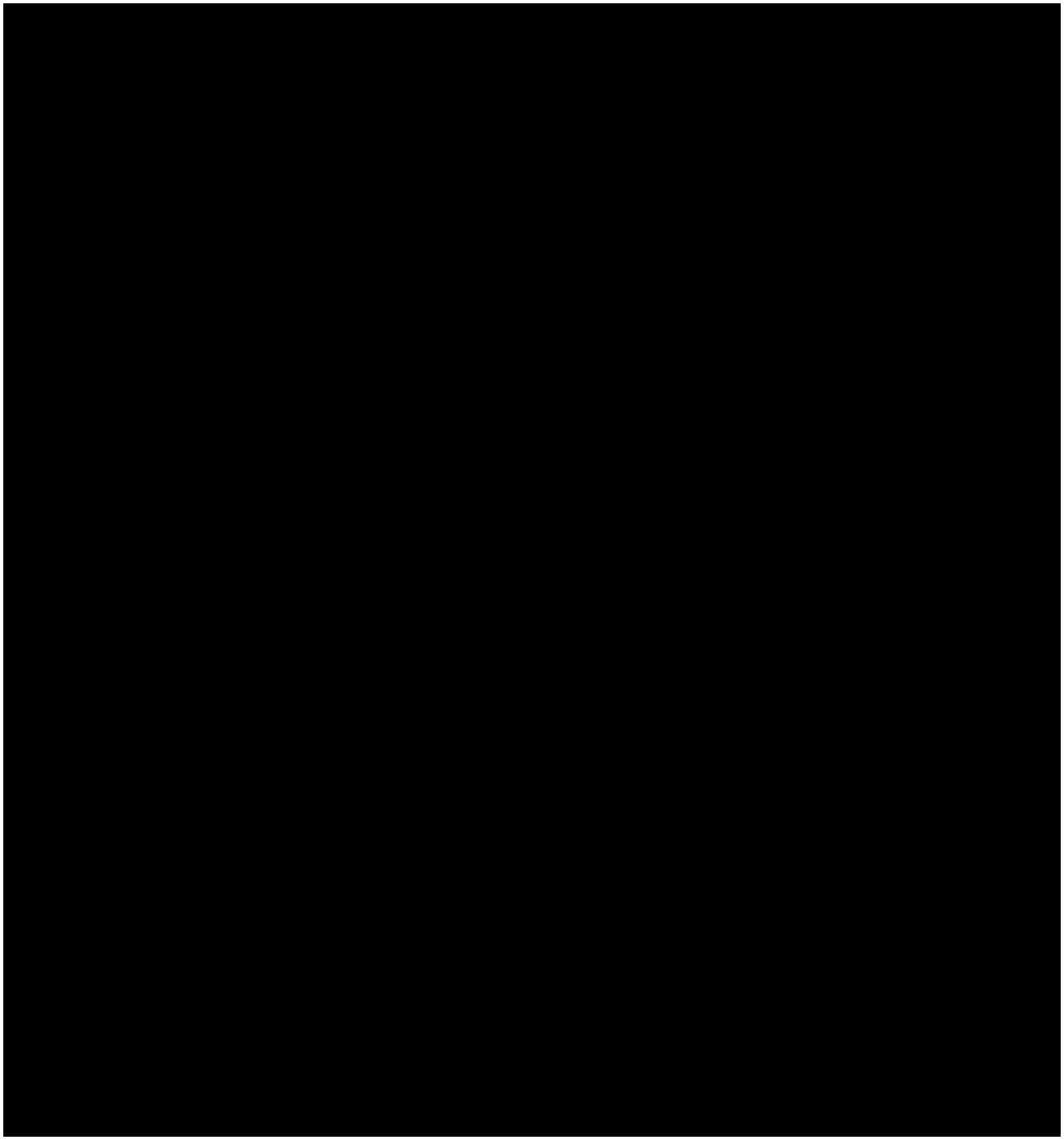
10.2.2 Blood sampling for pharmacokinetic subpopulation (Japan only)

For the PK subpopulation (see Section 5.3.3), some **additional site visits** are planned:

Assessments to be conducted during these visits as described in the footnote of Table 13.

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Table 13 Time schedule for PK blood sampling in the PK subpopulation (Japan only)



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[redacted]

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

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11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

This amendment is considered to be substantial based on the criteria set forth in Regulation (EU) No 536/2014 of the European Parliament and the Council of the European Union.

Overall rationale for the amendment:

This amendment is being revised to include some of the modifications:

- Language from the local Japanese amendment
- Clarification of eligibility criteria
- Inclusion of locally approved SoC therapies
- Clarification of operational processes
- To include a [redacted]

Amendment and date of amendment	Amendment 1 [01 Apr 2026]	
Global Amendment		X
Global Amendment due to urgent safety reasons		
Section changed	**Description of change**	**Rationale for change**
Throughout	Updated protocol version number and date	To align with the amendment
Throughout	Minor editorial and document formatting revisions	For clarity
Throughout	References updated in various section	For accuracy and citing the most recent sources
Synopsis	Update of Trial objectives Update of Trial endpoints Update of Diagnosis, and main inclusion and exclusion criteria Update of Trial design Update of Duration of treatment Update of Statistical methods	To allow trial to be more robust
Schedule of Assessment (SOA)	Removal of trial termination after [redacted] of dosing and adjustment of footnote	To align with removal of [redacted] dosing

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	Adjustment of EOS follow-up date for weeks and footnote	Due to the [redacted]
	Update of height and weight row and referral to OoA	To clarify the order of assessments
	Footnote added to IMP administration	To provide flexibility
Order of Assessments (OoA)	Added height and weight to the order of assessments and footnote Added/clarified timepoints for PK sampling and post-dose [redacted] tests including footnote	To provide flexibility and ensure accurate timing of assessments
Abbreviation	Removal and addition of abbreviations	For accuracy
1.2 Drug Profile	[redacted]	To update based on most recent information
1.4.1 Benefits	Update benefits of participation in the trial	To update based on most recent trial
2.1.1 Main objectives	Addition of secondary objectives	To better assess treatment success or failure
2.1.3 Secondary endpoints	Added changes from baseline at [redacted] of the following: Addition of FVC, [redacted], and [redacted]	To better assess treatment success or failure
2.2.2 Further endpoints	Removal of endpoints newly added to secondary endpoints	To better assess treatment success or failure
	Clarification of PK analysis in Japanese subpopulation where feasible	To permit flexibility in PK analysis in Japan
3.1 Overall Trial Design	Removal of 12-week minimum dosing Addition of [redacted] Addition of statement regarding Collection of secondary objectives	To better assess treatment success or failure
	Modification of follow-up period	Due to the [redacted]
Figure 1 Trial design schematic	Removal of 12-week minimum dosing and addition of [redacted]	To update the trial design scheme

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3.2 Discussion of trial design, including the choice of control group(s)	Addition of statement regarding primary objectives data collection at 12 weeks	To allow flexibility with SOC
	Addition of [redacted] Update of treatment duration and concomitant SoC	To better assess treatment success or failure
3.3 Selection of trial population	Added of [redacted]	To allow retesting
3.3.1 Main diagnosis for trial entry	Clarified FVC ≥45% predicted	To ensure appropriate patient selection
3.3.2 Inclusion criteria	Added explicit prohibition of sperm donation for male patients and duration	Due to the [redacted]
	Rewording of questionable menopausal status	For clarity
	Clarified eligibility of ‘indeterminate’ or ‘alternative diagnosis’ HRCT findings	For appropriate patient selection
	For Japanese PK subpopulation: removal of ‘being born in Japan’	To ensure accurate PK subpopulation definition
3.3.3 Exclusion criteria	Clarified that newly diagnosed patients considered in need of SoC during the next 12 weeks by the treating physician should be excluded	To avoid withholding standard of care
3.3.4.1 Discontinuation of trial treatment	Visit and EOS updated	Due to the [redacted]
4.1.1 Identity of the investigational medicinal products	Added background details for BI 765423	To provide scientific detail
4.1.4 Drug assignment and administration of doses for each patient	Removed minimum 16-week trial period	Updated trial design
	Dosing schedule exception	To provide flexibility

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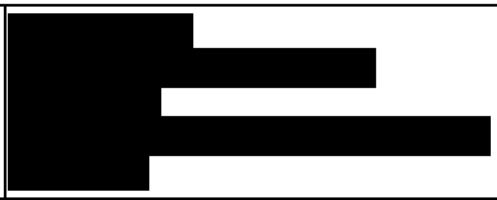
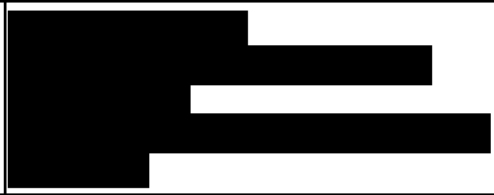
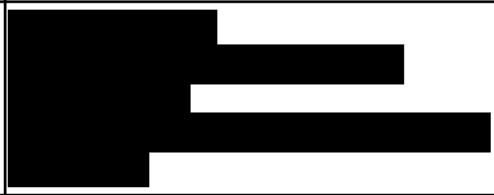
4.2.1.3 Prior and concomitant therapies	Clarified when SoC can be initiated	To ensure patients can receive appropriate care if needed
4.2.2.1 Restrictions regarding concomitant	Clarified when locally approved SoC can be utilized after Week 12 and restrictions on a class of medications	To ensure patients can receive appropriate care if needed
4.2.2.3 Vaccinations	Added explicit restriction to live vaccines	To minimize risk of infection due to immunomodulation
4.2.2.4 Contraception requirements	Updated time frame regarding male contraceptive use and added explicit prohibition regarding sperm donation	Due to the [redacted]
[redacted]	Added guidance regarding repeat assessment for [redacted] and reference to Appendix 10.3	To improve data quality and ensure consistency
Table 8 Exclusionary laboratory tests	Added HBV DNA threshold Added clarification for the [redacted]	To specify exclusion threshold
5.2.6.1.4 Adverse events of special interest	Corrected spelling of ‘leishmaniasis’	For correction
5.2.6.2.1 AE collection	Updated week of EOS	Due to [redacted]
5.3.5 Pharmacokinetic – pharmacodynamic relationship	Update of when population PK would be performed	Updated trial design
5.4.1 Exploratory and probable valid biomarkers	Clarified total blood volume noted excludes biobanking sample	For clarification
5.5 Biobanking	Updated biobanking language	To incorporate Japanese local amendment
6.2 Details of trial procedures at selected visits	Clarified that forced [redacted] may be repeated once	To provide flexibility and data completeness

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6.2.2 Treatment period(s)	Removed minimum [redacted] trial period	Updated trial design
7.2.2 Handling of intercurrent events	Addition of iPDs	To ensure robust statistical analysis
Table 9 Handling of intercurrent events as per ICH E9 (R1) within the different strategies	Addition of iPDs	To ensure a robust statistical analysis
7.2.3.1 Main analyses	Addition of [redacted]	Update of trial design
7.2.4 Secondary objective analyses	Addition of possible additional Bayesian analyses	To ensure a robust statistical analysis
7.2.8 Interim analyses	Provided details regarding the [redacted]	Addition of [redacted]
Table 11 Success probabilities under certain scenarios	Removed 2 blank rows	For formatting purposes
8.1 Trial approval, patient information, informed consent	Added paragraph immediately after 1st paragraph	Due to ICH Revision
	Removed sentence regarding trial collaborator supplementary explanation and being a signatory	Template revision
8.6 Trial milestones	Updated [redacted]	Due to the [redacted]
Published references 9.1	Addition and removal of references	To align with text
Unpublished references 9.2	Addition and removal of references	To align with text
Table 12 Time schedule for PK blood sampling	Updated table and footnote regarding sampling time	For clarity, flexibility, and the [redacted]
Table 13 Time schedule for PK blood sampling in the PK	Updated footnote regarding sampling time	For clarity, flexibility, and the [redacted]

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subpopulation (Japan only)		
Appendix 10.3 [redacted]	Added text and Table 14 [redacted]	To standardize procedures

Reason for signing: Approved	
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