Clinical Trial Protocol

	Document Number:	**c30500151-06**
EudraCT No. **Universal Trial No.**	2020-000384-23 U1111-1292-1333	
BI Trial No.	1434-0004	
BI Investigational Medicinal Product(s)	BI 764198	
Title	A multicenter, randomized, double-blind, parallel group, placebo-controlled study to assess the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics profile of BI 764198 administered orally once daily for 12 weeks in patients with focal segmental glomerulosclerosis.	
Lay Title	A study to test BI 764198 in people with a type of kidney disease called focal segmental glomerulosclerosis.	
Clinical Phase	Phase 2a	
Clinical Trial Leader	[redacted] Phone: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted]	
Current Version and Date	**Version 5.0**	**Date: 08 Jan 2024**
Original Protocol Date	**26 May 2021**	

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	26 May 2021
Revision date	08 Jan 2024
BI trial number	1434-0004
Title of trial	A multicenter, randomized, double-blind, parallel group, placebo-controlled study to assess the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics profile of BI 764198 administered orally once daily for 12 weeks in patients with focal segmental glomerulosclerosis.
Coordinating Investigator	[redacted] Phone: [redacted]
Trial sites	Multicenter, multinational trial
Clinical phase	Phase 2a
Trial rationale	Due to the mechanism of action of BI 764198 and the likely biological link between focal segmental glomerulosclerosis (FSGS) and gain of function mutations of Transient Receptor Potential Cation subfamily C, Member 6 (TRPC6), patients with primary FSGS, and patients with monogenic FSGS as a result of TRPC6 mutations have been selected for this proof of clinical principle study to establish TRPC6 inhibition as a potential mechanism to reduce excessive proteinuria.
Trial objectives	A key objective of this trial is to explore the efficacy of 3 doses (20 mg, 40 mg, and 80 mg) of BI 764198 with respect to their benefit to lower proteinuria. Additional objectives in this study are to investigate the safety, tolerability, and pharmacokinetic and pharmacodynamic profiles of BI 764198 vs placebo.
Trial endpoints	**Primary endpoint:** The primary endpoint is patients achieving at least 25% reduction in 24-hour urine protein-creatinine ratio (UPCR) relative to baseline at week 12. **Secondary endpoints:** The secondary endpoints are; • Change in 24-hour UPCR relative to visit 3 at week 12 • Change in 24-hour UPCR relative to baseline at week 13 • Change in 24-hour urinary protein excretion relative to baseline at week 12 • The following pharmacokinetic parameters of BI 764198 will be determined if feasible: - Steady state trough concentration $C_{pre,ss}$ on week 4 and week 12.
Trial design	Randomized, double-blind, parallel group study with 3 doses of BI 764198 (20 mg, 40 mg, and 80 mg) compared to placebo.

Total number of patients randomized	60 patients
Number of patients per treatment group	15 patients in each of the four treatment groups
Diagnosis	Patients with primary FSGS, and patients with monogenic FSGS as a result of TRPC6 mutations.
Main inclusion and exclusion criteria	**Main inclusion criteria:** • Signed and dated informed consent in accordance with ICH-GCP and local legislation prior to admission to the study. • Male and female patients 18 years to 75 years (both inclusive) of age on the day of signing informed consent. • Patients diagnosed with biopsy proven primary FSGS or documented TRPC6 gene mutation causing FSGS prior to screening visit. • UPCR ≥ 1000 mg/g based on first morning void during screening. • Patients treated with corticosteroids must be on a stable dose for at least 4 weeks prior to screening visit with no plan to change the dose until end of trial treatment. • Patients treated with ACE inhibitors, ARBs, finerenone, aldosterone inhibitors, or SGLT2 inhibitors should be on a stable dose for at least 4 weeks prior to screening visit with no plan to change the dose until end of trial treatment. • Body Mass Index (BMI) of ≤ 40 kg/m^2 at screening visit. • Women of childbearing potential must be willing and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. **Main exclusion criteria:** • Known monogenic (with the exception of TRPC6 gene mutation) or clinical or histologic evidence of secondary FSGS. • Documented Alport syndrome, Nail Patella syndrome, diabetic nephropathy, IgA-nephropathy, lupus nephritis, or monoclonal gammopathy (e.g., multiple myeloma). • Uncontrolled hypertension defined as an average resting systolic blood pressure >160 mmHg calculated from the last two of the triplicate sitting blood pressure measurements at screening visit. Patients with a documented history of white coat hypertension may be included. • Concomitant use of calcineurin inhibitors within 5 half-lives before screening visit. • Concomitant treatment with cytotoxic agents (cyclophosphamide, chlorambucil), or CD20 monoclonal antibody, e.g., rituximab, within 5 half-lives before screening visit. Note: use of other immunosuppression therapies considered as standard of care may be allowed as long as the patient remains on stable dose throughout the study. • Treatment with metformin or dofetilide (MATE1 or OCT2 substrates); dabigatran or digoxin (P-gp substrates with narrow therapeutic window) within 5 half-lives before screening visit.

	• Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 (CKD-EPI formula based on serum creatinine and cystatin C) at screening visit. • QTc intervals (QTcF) greater than 450 ms in males or greater than 470 ms in females, or any other clinically relevant ECG findings (at the investigator's discretion) at screening visit.
Test product	BI 764198
dose	20 mg, 40 mg, 80 mg, and matching placebo, q.d.
mode of administration	Oral (p.o)
Comparator products	Matching placebo to BI 764198
dose	Not applicable
mode of administration	Oral (p.o)
Duration of treatment	12 weeks
Statistical methods	For the primary analysis, descriptive statistics will be provided. Proportion of patients achieving at least 25% UPCR reduction relative to baseline at 12 weeks will be described. In addition, an ANOVA model for the UPCR change from baseline at 12 weeks (and other endpoints as applicable) will be used to see difference across arms. The dose-response relationship based on reduction in log of UPCR will be explored using a graphical approach.

FLOW CHART A – STUDY PROCEDURES

Trial Periods	**Screening**	**Treatment Period**						**Follow-up**
Visit[1]	**1**	**2**	**3**	**4**	**5**	**EoT**[2]	**FUP1**	**EoS**[3]☎
Week		**0**		**4**	**8**	**12**	**13**	
Days from first dose	**-30**[4]	**1**[5]	**4**	**29**	**57**	**85**	**92**	**115**
Time window for visits (days)		**0**	**+3**	**±3**	**±3**	**±3**	**±2**	**±3**
Informed consent[6]	X							
Demographics	X							
Height[7], body weight	X			X	X	X	X	
Medical history	X	X						
Review of inclusion /exclusion criteria	X	X						
Physical exam[8]	X			X		X		
Vital signs	X[28]	X	X	X	X	X	X	
12-lead ECG[9]	X	X	X	X	X	X	X	
Sampling for safety laboratory (incl. serum creatinine/cystatin C for eGFR)	X	X	X	X	X	X	X	
Pregnancy testing[10]	X	X		X	X	X	X	
Eye exams[11]	X					X[12]		X[12]
First morning void (FMV)	X							

FLOW CHART A – STUDY PROCEDURES (cont.)

Trial Periods	**Screening**	**Treatment Period**						**Follow-up**
Visit[1]	**1**	**2**	**3**	**4**	**5**	**EoT**[2]	**FUP1**	**EoS**[3]☎
Week		**0**		**4**	**8**	**12**	**13**	
Days from first dose	**-30**[4]	**1**[5]	**4**	**29**	**57**	**85**	**92**	**115**
Time window for visits (days)		**0**	**+3**	**±3**	**±3**	**±3**	**±2**	**±3**
Dispense 24-hr urine collection containers[13]	X	X			X	X		
24-hour urine collection	XX[14]		X[15]			X[16]	X[17]	
[redacted]								
Pharmacogenomics[20]		X						
PK sampling (blood)[21]		X	X	X	X	X	X[22]	
Randomization & dispense trial medication[23]		X						
Dispense/review of medication diary[24]		X	X	X	X	X		
Medication administration during study visit[25]		X	X	X	X	X		
Concomitant therapy	X	X	X	X	X	X	X	X
All AEs[26]/SAEs/AESIs	X	X	X	X	X	X	X	X
Return medication /compliance check[27]			X	X	X	X		
Completion of patient participation								X

Footnotes:

1. Study visits may be completed at the patient's home for patients participating in the trial remotely via the decentralized clinical trial (DCT) model. All trial procedures performed at the clinic can be completed by the mobile research nurse (MRN) at the patient's home. For eye examinations (see footnotes 11 and 12). Please refer to phone call visit schedule in Flow Chart B below.
2. End of Treatment (EoT) visit. Patients who discontinue trial treatment prematurely should undergo the End of Treatment (EoT) visit procedures as soon as possible.
3. End of Study (EoS) is synonym for End of Trial. EoS will be a telephone visit. For eye exams at EoS, see footnote 12. Patients who discontinue trial treatment prematurely should complete follow-up visit (FUP1) and EoS visit. Study site staff will complete the EoS visit by telephone for all patients.
4. Screening period can be shorter than 30 days. Screening period may also be extended if needed: see section 6.2.1 for more information.
5. Day of first intake of trial medication. Randomization is completed prior to visit 2 and trial medication is shipped directly to the patient. For more information, see section 4.1.4.
6. To allow collection of the first morning void sample to determine if the patient's UPCR meets the protocol inclusion criteria prior to visit 1, patients may sign a separate screening consent form (or verbally consent). Patients who are eligible per their UPCR results must sign the main consent form prior to additional screening procedures being performed. See section 8.1 for more information on the screening consenting process. Once the patient has consented to collect the first morning void urine sample, the patient is considered to be enrolled in the trial and must be registered in the IRT.
7. Height measurement collected only at the screening visit.
8. Physical exam for patients participating in the trial remotely will be performed via telemedicine (section 5.2.1).
9. ECGs will be recorded at the screening visit. Starting first dosing visit (visit 2) to EoT visit, ECGs will be recorded twice: pre-dose and at 1 to 2 hours post-dose. At the FUP1 visit, there will be one ECG recording. See additional guidelines on ECG recordings in section 5.2.4.
    a. ECGs at the screening visit will be recorded in triplicate (3 single ECGs recorded within 180 seconds). The average of the 3 readings will be used to determine eligibility (section 3.3.3)
    b. ECGs should be recorded either before or at least 10 minutes after blood sample time points to avoid blood draw related anxiety effects on ECG results.
    c. For patients participating in the trial remotely, the MRN will complete the ECG procedure at the patient's home.
10. Serum pregnancy test at screening visit (test performed at central lab), and urine pregnancy test at the study site for other visits (except visit 3 and phone visits). Menstrual cycle status (not delayed or missed period) should be checked before the first dose (visit 2). Applicable to only women of childbearing potential. See additional guidelines in section 6.1.
11. Eye exams should be completed at the study site or at another healthcare or eye care facility. If documented medical history of cataract surgery in both eyes is available at the time of screening, eye assessments are not required in this trial (section 5.2.5.1).
12. If cataract surgery in both eyes is confirmed by the eye exam at screening, patients are not required to complete the eye exams at EoT and EoS (section 5.2.5.1).

13. Patients will receive instructions on urine collection, storage, and return of the specimens to the study site. If possible, patients should be reminded (e.g., via telephone) during screening and ahead of the applicable visits to collect the 24-hour urine samples. More information and instructions for urine collection are provided in section 6.1.
14. Two separate 24-hour urine samples will be collected on separate days prior to visit 2. The 24-hour urine samples should be collected only after confirmation that the patient met all the eligibility criteria for the trial, and the collections should be close to visit 2 as much as possible. Visit 2 must be rescheduled if UPCR data is not available at least from one 24-hour urine sample.
15. One 24-hour urine sample should be collected before visit 3. For information and collection time points, see section 6.1.
16. One24-hour urine samples should be collected before EoT visit. EoT visit must be rescheduled if the 24-hour urine sample is not collected for UPCR measurements. For information and collection time points, see section 6.1.
17. One 24-hour urine sample will be collected before FUP1. For information and collection time points, see section 6.1.

[redacted]

20. One blood sample for pharmacogenomics will be taken at visit 2. If the sample is not collected at visit 2, it can be collected at a later visit.
21. Refer to Table 10.1: 1 for planned PK sampling schedule. The date and exact time of trial medication administration will be recorded in the eCRF together with the date and exact time when PK samples are drawn.
22. An additional PK sample will be collected at the FUP1 visit.
23. Randomization will be performed using the IRT Platform at least a week before the scheduled visit 2 date. Randomization call must occur only after patient eligibility (including UPCR criteria, eye exams) has been confirmed and UPCR data from central lab is available from at least one 24-hour urine sample during screening period. Trial medication will be shipped directly to the patient via a courier from a central depot unless not permitted by local/site regulations. First dose will be administered at visit 2. A telephone call (video call if possible) from site to patient should occur in about 24 hours (or next working day) after the site receives the delivery notification from the courier. For more information, see section 4.1.4.
24. A medication diary (paper) will be dispensed to the patient. Patient should record the date and time of medication intake at home for the 3 days prior to EoT, and for the previous day for all other clinic visits. Patients should bring the diary to the clinic for review. For more information, see section 4.1.4. If possible, a few days before the visit patients should be reminded (e.g., via telephone) to complete the medication diary, and to not take the study drug on the day of the study visit.
25. Patient will bring all the trial medication received directly from the central depot to the clinic for visit 2 (first dosing visit). Site will inspect all the trial medication and provide instruction to the patient on how medication is administered at home and how the medication should be brought to the clinic visits. Site will open the first bottle to administer the first dose in the clinic. When the patient is contacted after the trial medication is delivered to the patient's home (see footnote 23), they should be reminded to bring the trial medication to the clinic for visit 2. If possible, patients should be reminded (e.g. by telephone) to bring

the trial medication to the clinic before each visit. Study visits will have to be rescheduled if trial medication is not available during the applicable visits. For information on how trial medication will be handled during the course of the trial, see section 4.1.4.

26. A separate eCRF will be used to collect specific data related to acute kidney injury (section 3.3.4.1). After the FUP1 visit until the individual patient's end of trial only cancers of new histology and exacerbations of existing cancer, all trial drug related SAEs and all trial drug related AESIs will be collected (section 5.2.6.2.1).
27. Medication compliance (section 4.3) will be checked by capsule count by study site staff. For information on medication return, see section 4.1.4.
28. Assessment for uncontrolled hypertension is completed at Visit 1 only. Three blood pressure measurements will be taken approximately 2 minutes apart after the patient has rested quietly and is in a seated position for at least 5 minutes. The average of the last two measurements for the triplicate systolic blood pressure measurements should be < 160 mmHg for assessment of exclusion criteria 5 at the screening visit.

FLOW CHART B - PHONE CALL VISITS

Phone visits[1]	**3A☎**	**4A☎**	**5A☎**[2]
Week	**2**	**6**	**10**
Days from first dose	**15**	**43**	**71**
Window (days)	**±3**	**±3**	**±3**
Concomitant therapy	X	X	X
All AEs[3]/SAEs/AESIs	X	X	X

Footnotes:

1. Patients will be contacted by telephone. If there is any follow-up needed, an unscheduled visit may be scheduled. Patients should be reminded to be compliant with the intake of trial medication.
2. Patient should be reminded to collect the 24-hour urine before EOT visit.
3. Please see footnote #26 for Flow Chart A.

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

ACE	Angiotensin Converting Enzyme
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHR	Aryl Hydrocarbon Receptor
ALT	Alanine Aminotransferase
ANOVA	Analysis of Variance
ARB	Angiotensin II Receptor Blockers
AST	Aspartate Aminotransferase
AUC	Area under the Plasma Concentration Curve
$AUC_{0-\infty}$	Area under the Plasma Concentration Curve from 0 to ∞
AUC_{t1-t2}	Area under the Plasma Concentration Curve from t1 to t2
$AUC_{t1-t2,ss}$	Area under the Plasma Concentration Curve from t1 to t2 at steady state
BI	Boehringer Ingelheim
BMI	Body Mass Index
CA	Competent Authority
CAR	Constitutive Androstane Receptor
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Collaboration
C_{max}	Maximum Plasma Concentration
$C_{max,ss}$	Maximum Plasma Concentration at steady state
$C_{pre,ss}$	Pre-dose Plasma Concentration at steady state
$C_{trough,ss}$	Trough Plasma Concentration at steady state
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRO	Contract Research Organization
CSA	Cyclosporine
CT Manager	Clinical Trial Manager
CTL	Clinical Trial Leader
CYP3A4	Cytochrome P450 3A4
DCT	Decentralized Clinical Trial

DDI	Drug-Drug Interaction
DEX	Dexamethasone
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EoS	End of Study (corresponds with End of Trial)
EoT	End of Treatment
ES	Entered Set
ESKD	End Stage Kidney Disease
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSGS	Focal Segmental Glomerulosclerosis
FUP1	Follow-up Visit #1
GCP	Good Clinical Practice
gCV	Geometric Coefficient of Variation
GGT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
gMean	Geometric Mean
HA	Health Authority
HR	Heart Rate
IB	Investigator’s Brochure
ICE	Intercurrent Event
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IgA	Immunoglobulin A

IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
K-EDTA	Potassium Ethylenediaminetetraacetic Acid
LOCS III	Lens Opacities Classification System III
LPLT	Last Patient Last Treatment
MATE1	Multidrug and Toxin Extrusion 1
MATE2	Multidrug and Toxin Extrusion 2
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMF	Mycophenolate Mofetil
MRN	Mobile Research Nurse
ms	Milliseconds
mRNA	Messenger RNA
NEPTUNE	Nephrotic Syndrome Study Network
[redacted]	
NOAEL	No Observed Adverse Effect level
OCT2	Organic Cation Transporter 2
P-gp	Permeability Glycoprotein
PD	Pharmacodynamics
PE	Physical Exam
PK	Pharmacokinetics
p.o.	per os (oral)
q.d.	quaque die (once a day)
QT	Time between start of the Q-wave and end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the method of Fridericia
RA	Regulatory Authority
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sFSGS	Secondary Focal Segmental Glomerulosclerosis
SGLT2	Sodium-Glucose Cotransporter-2

SOP	Standard Operating Procedure
SULT	Sulfotransferase
SUSAR	Suspected Unexpected Serious Adverse Reactions
TS	Treated set
TRPC6	Transient Receptor Potential Cation subfamily C Member 6
TSAP	Trial Statistical Analysis Plan
$t_{1/2}$	Terminal half-Life of the analyte
t_{max}	Time to Maximum Plasma Concentration
[redacted]	
UGT	Uridine Diphosphate Glucuronosyl Transferase
ULN	Upper Level of Normal
[redacted]	
UPCR	Urine Protein-Creatinine Ratio
[redacted]	
WOCBP	Woman of Childbearing Potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Boehringer Ingelheim (BI) is developing BI 764198, an oral, small-molecule inhibitor of the transient receptor potential cation subfamily C Member 6 (TRPC6), for the treatment of proteinuric glomerular disease on top of standard of care.

Focal segmental glomerulosclerosis (FSGS) is a leading glomerular cause of End Stage Kidney Disease (ESKD) in the United States. FSGS refers to a histologic pattern that is a characteristic of perhaps distinct underlying etiologies sharing a common theme of podocyte injury and depletion (P17-08386).

FSGS is characterized by histologic lesions as opposed to a specific disease. FSGS is a pathophysiological entity which commonly explains the onset of nephrotic syndrome in adult or pediatric patients. Histological abnormalities contain sclerosis in segmental (parts) of focal (some) glomeruli as assessed by microscopic investigation of kidney biopsies.

FSGS is a frequently found histopathologic lesion in adults with nephrotic syndrome within the United States accounting for 35% of all cases and >50% among African Americans (R20-3949, and R20-3978).

The classification of FSGS in specific categories is based on various etiologies as defined below:

- Primary (idiopathic) FSGS frequently presenting with nephrotic syndrome.
- Secondary FSGS (sFSGS) or also referred to as adaptive FSGS, often presenting with non-nephrotic proteinuria and, commonly, with some extent of kidney function impairment. This category is a common adaptive response to hyperfiltration or glomerular hypertrophy and disorders characterized by renal vasodilation and/or kidney mass reduction (e.g. unilateral renal agenesis). Drug- or toxin-induced (e.g. heroin, interferon, pamidronate) and viral-induced (especially HIV) pathologies account for the other causes of sFSGS.
- Genetic (familial) FSGS, presents generally in early childhood with substantial nephrotic syndrome and proteinuria or with less severe proteinuria in adolescence or adulthood.

FSGS classification will depend on a multitude of assessments including clinical history, laboratory testing, kidney biopsy, and in some cases genetic testing. While considerable progress has been achieved with the clinical understanding of FSGS, research is still needed to identify plasma factor(s) believed to be responsible for primary FSGS, to assess the clinical utility of routine genetic testing, and to find more effective and safer therapeutic interventions for FSGS (P17-08386).

A possibly important mechanism related to glomerular dysfunction in proteinuric diseases could be the calcium overload of the podocyte. In subjects with TRPC6 mutations increased

podocyte foot process detachment and loss has been observed as a consequence of disruption of the glomerular filtration barrier [R18-1764, R18-1763]. It is hypothesized that increased TRPC6 activity could be a principal mechanism in proteinuric kidney disease driving progression to ESKD. Therefore, BI 764198 as TRPC6 inhibitor, may be a novel treatment option by limiting TRPC6 channel activity in case of pathological Ca^{2+} entry which should result in preserved podocyte function and reduced podocyte loss.

TRPC6 is expressed in several renal cell types, including podocytes which are key cells for glomerular filtration function of the kidney. Multiple gain of function mutations in TRPC6 have been demonstrated to cause FSGS by elevating intracellular calcium concentration in podocytes and inducing cytoskeletal rearrangements. This has been linked to podocyte apoptosis, foot process detachment and loss of podocytes, leading to disruption of the glomerular filtration barrier. The modulation of TRPC6 activity should therefore have the potential to improve both podocyte function and survival in proteinuric glomerular diseases and specifically in FSGS.

1.2 DRUG PROFILE

BI 764198 is an oral, small-molecule inhibitor of TRPC6. It is being developed for the treatment of advanced chronic kidney disease on top of standard of care.

Mode of action:
BI 764198 is a potent inhibitor of human TRPC6 (IC_{50}: 14.4 nM; IC_{90}: 77 nM), rat TRPC6 (IC_{50}: 12.9 nM), mouse TRPC6 (IC_{50}: 19.3 nM), dog TRPC6 (IC_{50}: 44.2 nM) and cynomolgus monkey TRPC6 (IC_{50}: 10.0 nM) in *in vitro* manual patch clamp assays using human HEK293 cells with inducible TRPC6 expression.

Key pharmacokinetic characteristics:
Following administration of single and multiple doses ranging from 1 mg to 240 mg in humans, BI 764198 was rapidly absorbed into the systemic circulation with maximum plasma concentrations occurring in the range of 0.75 h to 2 h post-dose time to maximum plasma concentration (t_{max}). BI 764198 was cleared from plasma with an apparent $t_{1/2}$ ranging from 12.7 h to 17.4 h, independent of the dose. At doses of 10 mg or higher, the exposure of BI 764198 was linear. After multiple dose administration, steady state AUC and C_{max} values increased linearly between 20 mg and 80 mg doses and BI 764198 shows time independent PK up to 80 mg. A steady state was achieved by 3-4 days with modest accumulation based on $AUC_{0\text{-}24h,}$ (1.33-1.48) and C_{max} (1.13-1.43). The fraction of BI 764198 excreted unchanged in urine over 48 h was between 14% and 30% after single dose administration and 21% to 29% over 24 h after multiple dose administration. In study 1434-0002 [redacted]), in otherwise healthy participants who had renal impairment, gMean BI 764198 AUC increased by 48% (moderate impairment) and 78% (severe impairment) and C_{max} increased by 14% (moderate renal impairment) and 12% (severe renal impairment) after a single dose of 40 mg compared with healthy controls.

After multiple doses of BI 764198 (up to 160 mg), gMeans for $AUC_{\tau,ss}$ and $C_{max,ss}$ were higher by 3-36% and 21-47% respectively, when comparing Japanese (1434-0003) and Caucasian (1434-0007) data. This may be related to the lower body weight in Japanese subjects (mean weight 63.25 kg vs. 78.08 kg in Caucasian).

The hepatic metabolic clearance of BI 764198 is predicted to be low in humans based on *in vitro* evaluation using human hepatocytes. BI 764198 is 14-30% renally excreted. BI 764198 is metabolized via glucuronidation (mostly via uridine diphosphate glucuronosyl transferase, UGT1A4), oxidation (primarily via cytochrome P450, CYP3A), and amide hydrolysis. Although co-administered drugs that inhibit CYP3A or UGT1A4 activity may increase BI 764198 plasma exposure, the effect is not expected to be substantial given the multiple elimination pathways of BI 764198. With respect to BI 764198's CYP3A induction potential, a clinical drug-drug interaction (DDI) study ([redacted] was conducted to assess the compound's effect (80 mg once daily for 10 days) on the pharmacokinetics of micro-dose midazolam, a sensitive CYP3A4 substrate. The geometric mean ratios (90% CI) of $AUC_{0-\infty}$ and C_{max} of midazolam with and without co-administration of BI 764198 are 1.04 (0.93,1.16) and 0.94 (0.84, 1.06), respectively, indicating that 80 mg BI 764198 once daily did not affect CYP3A4 activity in vivo. BI 764198 may cause clinically relevant inhibition of P-gp at a dose of 80 mg once a day (q.d.). A high fat, high caloric meal did not influence AUC or C_{max}. Therefore, BI 764198 can be administered with or without food. Relevant restrictions will be available in the investigator site file (ISF).

Drug interactions

As outlined above, 80 mg BI 764198 once daily did not alter the pharmacokinetics of midazolam, a CYP3A4 index substrate. Therefore, BI 764198 does not affect CYP3A4 activity in vivo. Based on the metabolism described above, co-administered drugs that modulate CYP3A or UGT1A4 activity may have an impact on BI 764198 plasma exposure. Strong inhibitors and strong inducers of CYP3A are excluded. BI 764198 may inhibit OCT2, MATE1, or MATE2-K at a dose of ≥40 mg once daily; and P-gp at a dose of ≥80 mg once daily. The effect of BI 764198 on the pharmacokinetics of metformin or dofetilide (MATE1/ OCT2 substrates), and dabigatran or digoxin (P-gp substrates with narrow therapeutic window) will be elucidated when data from DDI studies in healthy subjects become available; until then co-administration should be avoided.

BI 764198 is not expected to lead to a clinically relevant reduction in the exposure of oral contraceptives due to an increased metabolism via enzyme induction [redacted]). BI 764198 (80 mg once daily over 10 days) did not change the pharmacokinetics of the sensitive CYP3A4 substrate midazolam. Thus, BI 764198 is not considered to be a CYP3A4 inducer in vivo. From in vitro studies using human hepatocytes, there is no indication that BI 764198 activates other nuclear receptors (AHR or CAR) that trigger induction of other drug metabolizing enzymes involved in metabolism of oral contraceptive components, such as UGTs and sulfotransferases (SULTs).

Residual Effect Period

The Residual Effect Period (REP) of BI 764198 is 119 hours, i.e. 5 days, based on 5 times 23.8 hours, the maximum value for $t_{1/2}$ in patients with moderate renal impairment [redacted]). This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

Data from toxicology studies

The toxicity profile of BI 764198 has been assessed in a comprehensive set of safety pharmacology studies, genetic toxicology and phototoxicity studies, repeat dose general toxicology studies (up to a duration of 26 weeks in the rat and 39 weeks in the dog) embryo-foetal development toxicity studies (rat and rabbit), and a fertility and early embryonic development study (in rat). BI 764198 has been well tolerated at clinically relevant plasma exposures in toxicity studies. Exposure multiples were calculated based on the human estimated steady state C_{max} of 3650 nM and $AUC_{0\text{-}24hr}$ of 40200 nM•h for a dose of 80 mg once daily.

The IC_{50} for hERG inhibition was 7,970 nM, which is 6X human exposure for the predicted C_{max} for the unbound drug (1329 nM), demonstrating potential for blocking hERG channels at clinically relevant concentrations. While no effects to QT intervals were observed after a single dose to dogs, there was a dose and time-dependent increase in QTc intervals after repeat dosing in the 4-, 13-, and 39-week dog studies. In the 4-week dog study, there was a 12% increase in QTc interval (+24.9 milliseconds) at 17X human exposure. Prolongations of the QTc interval were less prominent in subsequent studies and reproducible only at 25 mg/kg/day. Additionally, in the 13-week dog study, it was uncertain if second-degree AV block in one female at 9X human exposure was due to BI 764198.

Studies in rats showed dose and time-dependent microscopic lens degeneration that generally correlated with cataracts at higher doses or longer duration. In the 26-week study, a dose of 10 mg/kg/day (1X human exposure) was free of lens findings while the dose of 30 mg/kg/day (4X human exposure) as tested in the 13-week study in rats, was considered to represent a threshold dose for the irreversible lens degeneration, as the 50 mg/kg/day dose when tested in the 26-week rat study was free of adverse effects in males (7X human exposure), but induced lens degeneration in females (10X human exposure). No lens effects were observed in dogs at doses up to 17X and 9X human exposure, respectively. Lacrimation was observed in both rat and dog studies.

Increases in alanine aminotransferase (ALT) and alkaline phosphatase (ALP) were seen in dog and/or rat studies. In the dog, increased ALT correlated with panlobular hepatocellular necrosis in a single animal at 17X human exposure. In rats, there have been mild decreases in red blood cell parameters and increases in leukocytes. Platelets decreased in dogs in a 2-week study, but not in studies with a longer dosing period. Platelets increased and showed decreased activation in rats. Increases in cholesterol and decreases in triglycerides have been observed in rats. Urinalysis in rat studies showed decreased urine pH and/or increased urine protein at 11X human exposure.

Reversible skin findings were preceded by clinical signs of erythema. Dermal redness was observed in rats and dogs at exposures providing 3X human exposure. In rats at higher dose levels, dermal redness affecting multiple cutaneous sites was generally accompanied by

additional skin and footpad effects such as hair thinning/loss, dermal dryness, single cell necrosis, scabbing, and/or epidermal hyperkeratosis, hyperplasia, or acanthosis at 11X human exposure. Skin ulceration and swelling were also observed in rats at 22X human exposure. Skin swelling was observed for dogs at 9X human exposure. A relation to BI 764198 was not excluded for a tricholemmoma in a female mid dose rat (11X human exposure) of the 26-week study. In rat studies only, hyperkeratosis affected the tongue at 24X human exposure.

Testing for effects on fertility and early embryonic development in rats revealed NOALEs for fertility of 7X human AUC0-24h (males) and 23X human AUC0-24h (females) as well as NOAELs for effects on early embryonic development of 7X human AUC0-24h (paternally mediated) and 0.4X human AUC0-24h (maternally mediated). In embryo-fetal development studies, where pregnant rats and rabbits were dosed BI 764198 from implantation to closure of the hard palate, there was embryolethality in rats at 3X human exposure, but no evidence of adverse effects to fetal growth or dysmorphogenesis. There was no embryolethality, effect to fetal growth, or dysmorphogenesis in rabbits at dose levels providing up to 26X human exposure. There is risk for adverse effects to embryo-fetal development at clinically relevant human exposures.

The risk of fetotoxicity induced by systemic exposure to BI 764198 via semen in female sexual partners of male trial participants has been assessed based on the recommendations of the Clinical Trials Facilitation and Coordination Group CTFG (R20-3402) and as commented in a White Paper by Bowman et al (R22-1956). It has been concluded that the exposure of female sexual partners and associated risk of fetotoxicity are negligible, indicating that condom use is not required for male trial participants with WOCBP partners.

The non-clinical safety package supports administration of BI 764198 to humans for more than 6months duration. The NOAEL in the 26-week rat study was 50 mg/kg/day in males (Cmax 32,900 nM and AUC0-24h 272,000 nM·h) and 10 mg/kg/day in females males (Cmax 12,200 nM and AUC0-24h 53,500 nM·h), corresponding to a steady state mean exposure multiple of 3X (Cmax) and 1X (AUC0-24h) the human exposure at 80 mg once daily. The NOAEL in the 39-week dog study was the high dose, 25 mg/kg/day (Cmax 86,000 and 71,700nM and AUC0-24h 1,640,000 and 1,240,000 nM·h for males and females, respectively), corresponding to a steady state mean exposure multiple of 20X (Cmax) or 31X (AUC0-24h) the human exposure at 80 mg once daily.

Data from clinical studies

To date, BI 764198 has been studied in a single rising dose trial of up to 240 mg once daily in healthy volunteers [redacted]), in a single dose trial in patients with renal impairment ([redacted]), and in a multiple rising dose/drug-drug interaction trial (midazolam) in healthy volunteers treated up to an 160 mg dose once daily for 14 days [redacted]) and in a relative bioavailability trial ([redacted]). BI 764198 was also administered orally up to 160 mg once daily to healthy Japanese volunteers up to 14 days [redacted]). In the completed phase 1 studies, a total of 171 healthy volunteers and 16 patients with renal impairment have received BI 764198. Based on completed Phase 1 clinical trials, BI 764198 was overall well tolerated up to a daily dose of 160 mg given up to 14 days in healthy volunteers with no imbalance

versus placebo in reported adverse events (AE) leading to discontinuation, drug-related AEs, or serious adverse events (SAE).

An electrocardiogram (ECG) analysis based on three Phase I trials in healthy volunteers ([redacted]), ([redacted]0), and [redacted]) indicated that BI 764198 may cause QT prolongation in a dose-dependent manner for doses ≥80 mg BI 764198 once daily. After single and multiple doses of BI 764198, a reversible, dose-dependent increase of serum creatinine was observed in Phase I trials. It is believed that BI 764198 may increase serum creatinine by decreasing renal tubular secretion of creatinine via inhibition of renal transporters (e.g. MATE1) without an impact on kidney function as measured by unchanged cystatin C levels. Cystatin C (in addition to serum creatinine measurements) will be used to assess changes in renal function in patients treated with BI 764198.

Treatment in a proof-of-concept clinical trial 1434-0009 ([redacted]) to reduce the risk/severity of acute respiratory distress syndrome in patients hospitalized for coronavirus disease 2019 (COVID-19) and requiring non-invasive oxygen therapy was terminated early, based on an independent data monitoring committee (DMC) recommendations, due to a clear lack of benefit in this critically ill patient population and a numerical imbalance of fatal events between the active and placebo treatment groups. Fatality rate was still within expected range for hospitalised COVID-19 patients on oxygen (R20-3802). Based on the totality of the data review from the study, BI has not identified to date any new safety risks for BI 764198. No adverse effects were noted to date which would impact the conduct of ongoing Phase 1 trials in healthy volunteers or the planning of Phase 2 proof-of-concept trials in chronic kidney disease (CKD).

Through favourable effects on glomerulosclerosis, delaying podocyte injury, and improving vascular function, a TRPC6 inhibitor may have the potential to slow disease progression when used on-top-of optimal therapy including ACEi/ARB. Such a therapy could be considered a notable advance in patient health and well-being by slowing progression to ESKD, improving clinical outcomes, reducing disease burden, and improving quality of life in proteinuric glomerular diseases such as FSGS.

For a more detailed description of the profile, refer to the current version of the IB ([redacted]).

1.3 RATIONALE FOR PERFORMING THE TRIAL

FSGS is one of the most common forms of acquired glomerular disease leading to ESKD and it is one of the most important causes of acquired chronic kidney disease in children and adults (R20-3912). Based on a clear biological link between FSGS and gain of function mutations of TRPC6 in this disease, BI 764198, based on its TRPC6 inhibitory mechanism of action, is expected to reduce proteinuria in FSGS thereby reducing disease burden and potential progression.

Specifically, TRPC6 is expressed in several renal cell types, including podocytes which are key cells for glomerular filtration function of the kidney. Multiple mutations in the TRPC6 channel have been demonstrated to cause FSGS. This has been linked to podocyte apoptosis, foot process detachment and loss of podocytes, leading to disruption of the glomerular filtration barrier. The modulation of TRPC6 activity should therefore have the potential to improve both podocyte function and survival in proteinuric glomerular disease.

Building on knowledge gained in preclinical investigations and first in human (FIH) phase 1 clinical studies, this phase 2 study will investigate if TRPC6 inhibition can reduce proteinuria by assessing the safety, tolerability, pharmacodynamic and pharmacokinetic profile of BI 764198 in patients with FSGS. A reduction of proteinuria in FSGS with TRPC6 inhibition will provide a sound basis for the continued investigation of this therapeutic mode of action in proteinuric glomerular diseases in future stages of clinical development.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

There is no direct benefit for individual participants in this study. The anticipated efficacy of BI 764198 in reducing proteinuria has not yet been demonstrated in patients with FSGS. However, participation in this study is of major importance to the development of a new oral drug that may improve therapeutic options for patients with FSGS and kidney disease characterized by excessive proteinuria.

1.4.2 Risks

Procedure-related risks
Blood draw may be accompanied by mild bruising and in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the needle, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period. Other observed side effects of blood draw are anxiety, dizziness, syncope.
Drug induced liver injury
Although rare, a potential for drug induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety.

Safety measures
The following safety measures will be applied in order to minimize potential risk for the trial participants:

- An extensive safety laboratory will be performed at periodic intervals as specified in the Flow Chart A. Safety laboratory tests are listed in Table 5.2.3: 1.
- Thorough ECG evaluation with central reading at every study visit including pre- and post-dose evaluations at expected drug steady state (day 4 of treatment). During the

treatment period, ECGs are also collected at the time when C_{max} of the drug is expected during study visits. Time points for ECG collection can be found in the Flow Chart A. ECG collection and central reading processes are described in section 5.2.4.

- To monitor for cardiac effects and the potential for QTc prolongation, regular ECG is evaluated by regular ECG monitoring, and specific exclusion and discontinuation criteria are in place for potential risk minimization. See section 3.3.4.1 for conditions under which trial treatment will be discontinued due to QT prolongation.
- Patients who experience clinically relevant conduction disorders (e.g. AV block ≥2nd degree, bundle branch block) will be discontinued from study treatment.
- To monitor for ocular changes, eye exams at screening, end of treatment, and 30 days after last dose of trial medication will be performed. Patients diagnosed with cataract (Lens Opacities Classification System III (LOCS III) higher than NC1/NO1, C0, P0 (R99-2093) in slit lamp eye examination will be excluded from the study at screening, and if diagnosed after inclusion in study will be discontinued from study treatment.
- To monitor for renal function, serum cystatin C and serum creatinine levels will be assessed at regular intervals and GFR estimation will be based on cystatin C values.
- There are no risks expected by stopping the study drug during the course of the trial.
- During the study, patients will be monitored for AEs.
- Females of childbearing potential who are pregnant, breast-feeding or intend to become pregnant or are not using an adequate contraceptive method throughout the trial and until 5 days after the last dose of the trial medication are excluded from the trial (section 4.2.2.3).
- Set up of an internal study safety review committee who will review unblinded data periodically to allow continuous assessment of drug exposure, efficacy, and safety. The safety review committee will include a cardiologist and an ophthalmologist. For more information, see section 8.7.

Patient participation in this trial will be consistent with local public health guidance and regulations. During screening, patients with symptoms of COVID-19 or a confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection will be excluded from participation in the trial. During participation in the study, if a patient is diagnosed with COVID-19, trial treatment will be terminated in cases where the patient has severe illness (for example patients who require hospitalization, need supplemental oxygen, have compromised lung function, etc.) and patients will be discontinued from the study. If a patient has a mild SARS-CoV-2 infection, continuation of trial treatment will be at the discretion of the investigator. The investigator will make an individual benefit-risk assessment on a case-by-case basis considering all aspects and decide if the patient should continue treatment or discontinue treatment temporarily or permanently. There are no restrictions for trial participant to receive vaccination for COVID-19 during or after the study period.

If local regulations require a SARS-Cov-2 test for patients to participate in the trial, the site investigator may order a polymerase chain reaction (PCR) test or another approved test at

screening or at any time during the study. Patients who test positive will be informed about the test result and they will not be eligible to participate in the trial.

1.4.3 Discussion

In summary, BI 764198 has the potential to become an oral treatment for patients with proteinuric glomerular disease such as FSGS based on a unique and promising mechanism of action with a clear pathophysiological disease link related to TRPC6 mutations in the context of FSGS. Patients suffering from FSGS have a high unmet medical need for safe and effective therapies to reduce disease severity and progression towards ESKD.

Based on preclinical data and first clinical data for BI 764198, mitigation strategies to minimize the potential risk for the participants will be implemented, e.g. close medical observation including frequent ECG readings and ophthalmological monitoring.

The proposed dose range selected for efficacy and safety evaluations in this trial has been primarily selected based on the tolerability and safety profile of the drug observed in completed phase 1 trials including:

- Trial 1434-0001 ([redacted]) a placebo-controlled rising dose study of single doses of BI 764198 (1 mg to 240 mg) in healthy volunteers,
- Trial 1434-0007 ([redacted]) a placebo-controlled multiple rising dose study of once daily doses of BI 764198 (20/40/80/160 mg) in healthy volunteers,
- Trial 1434-0002 ([redacted] a placebo-controlled single dose study of BI 764198 (40 mg) in subjects with normal, moderate and severe renal impairment.

Considering the medical need for an effective treatment in patients with proteinuric glomerular disease such as FSGS, the sponsor considers that the benefit outweighs the potential risks and justifies exposure of patients with FSGS to BI 764198, given the current need of drug development for effective and safe therapies in this disease.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

A key objective of this trial is to explore the efficacy of 3 doses (20 mg, 40 mg, and 80 mg) of BI 764198 with respect to their effect in lowering proteinuria. The primary endpoint is the proportion of patients achieving at least 25% reduction in 24-hour urine protein creatinine ratio (UPCR) relative to baseline at week 12 in patients with primary FSGS, and patients with monogenic FSGS as a result of TRPC6 mutations causing FSGS. Additional objectives in this study are to investigate the safety, tolerability, and pharmacokinetic and pharmacodynamic profiles of BI 764198 vs placebo.

The primary treatment comparison will be while on treatment, including all data prior to early discontinuation or lost to follow-up.

2.1.2 Primary endpoint

The primary endpoint is patients achieving at least 25% reduction in 24-hour urine protein-creatinine ratio (UPCR) relative to baseline at week 12. For details on efficacy assessments and definition of baseline, see section 5.1.1.

2.1.3 Secondary endpoints

The secondary endpoints are:

- Change in 24-hour UPCR relative to visit 3 at week12
- Change in 24-hour UPCR relative to baseline at week 13
- Change in 24-hour urinary protein excretion relative to baseline at week 12
- The following pharmacokinetic parameters of BI 764198 will be determined if feasible:
  - Steady state trough concentration $C_{pre,ss}$ on week 4 and week 12

For details on efficacy assessments and definition of baseline, see section 5.1.1.

[redacted]

[redacted]

2.2.2.2 Safety endpoints

- AEs (including clinically relevant findings from the physical examinations)
- SAEs occurring during the course of the study
- AEs leading to treatment discontinuation
- Vital signs (blood pressure, pulse rate)
- Safety laboratory tests
- 12-lead ECG
- Ophthalmological assessments

[redacted]

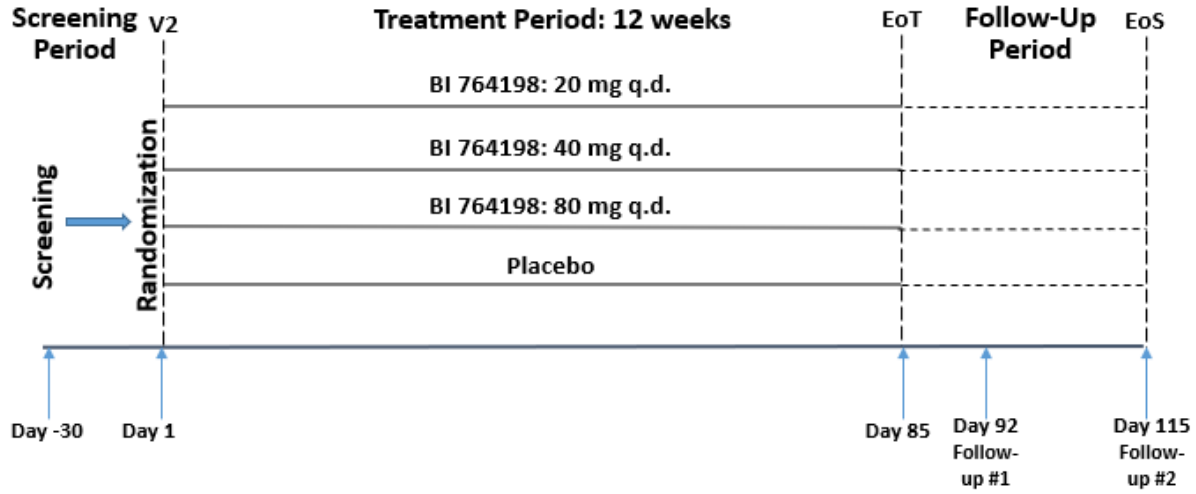
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This multicenter, randomized, double-blind, parallel group study will assess 3 doses of BI 764198 compared to placebo administered orally once daily for 12 weeks in patients with primary or TRPC6 monogenic FSGS.

After completion of all the screening procedures, eligible patients will be randomized into one of the 4 treatment groups stratified by use of corticosteroids, and treated for 12 weeks. It is planned to randomize approximately 15 patients in each treatment group. At the end of the treatment period, there will be a follow-up visit at day 7 after end of treatment. A 2nd follow-up visit will be scheduled via telephone, 30 days from end of treatment. Eye exams (section 5.2.5.1) will be completed at the 2nd follow-up visit. A schematic illustration of the trial design is presented in Figure 3.1: 1.

Figure 3.1: 1 Study design



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

A randomized, double-blind, placebo-controlled design is selected for this study. It is standard in studies at this early stage of development to use placebo as a control group in order to evaluate efficacy, safety and tolerability. The conduct of this short duration proof of clinical principle study will be on top of an array of established standard of care modalities including conservative management and steroid-based immunosuppression regimens.

Most FSGS studies on glomerular diseases have used different metrics of proteinuria including UPCR. UPCR will be measured from 24-hour urine in this study.

UPCR reduction ratio (follow-up vs. baseline) for Cyclosporine A (CSA) and mycophenolate mofetil/dexamethasone (MMF/DEX) in a study with adults and children with steroid-resistant FSGS was analyzed (P11-13071). At week 8, there were approximately 65% and 50% reduction of UPCR for CSA and MMF/DEX, respectively. A 12-week treatment to identify a reduction in UPCR should therefore be sufficient to demonstrate efficacy in the study. In addition, efficacy will further be assessed in this study by the evaluation of [redacted] 24-hour proteinuria as secondary endpoints.

3.3 SELECTION OF TRIAL POPULATION

This study will randomize approximately 60 patients with primary FSGS or with TRPC6 mutations causing FSGS. It is planned to conduct the study in approximately 55 sites in multiple countries. A sufficient number of patients will be screened to meet the randomization goal.

Study sites in selected countries will have the option of integrating a decentralized clinical trial (DCT) model where the study visits are conducted outside of a dedicated healthcare or research facility. This would allow patients to participate in the trial remotely and complete the study in their own home or residence. The DCT model can bring the clinical trial to patient's homes through telemedicine, a smartphone device, and through the deployment of mobile research nurses (MRN). The MRN will visit the patient's home and complete trial procedures in collaboration with the site principal investigator and study staff.

Sites participating in the DCT model would also continue to enroll patients using the traditional site-based approach where the patient visits the clinic at the specified time points in the protocol. Sites with DCT integration can also allow active ongoing patients in the trial to switch to remote participation. Additional operational guidelines will be provided in a separate DCT operational manual. A copy of the operational manual will be provided in the ISF.

Recruitment of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial. Patients already in screening at this time may be allowed to continue to randomization if eligible.

A log of all patients enrolled into the trial (i.e. who have signed informed consent including patients who signed a screening consent or provided verbal consent) will be maintained in the ISF irrespective of whether they have been treated with investigational drug or not. If retrospectively it is found that a patient has been randomized in error (did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on individual benefit-risk assessment, a decision will be made whether continued trial participation is possible.

3.3.1 Main diagnosis for trial entry

The study will include patients with primary FSGS, and patients with monogenic FSGS as a result of TRPC6 mutations.

Refer to section 8.3.1 for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

1. Signed and dated informed consent in accordance with ICH-GCP and local legislation prior to admission to the study.
2. Male and female patients 18 years to 75 years (both inclusive) of age on the day of signing informed consent.
3. Patients diagnosed with biopsy proven primary FSGS or documented TRPC6 gene mutation causing FSGS prior to screening visit.
4. UPCR ≥ 1000 mg/g based on first morning void urine sample during screening.
5. *Inclusion criterion 5 removed in global amendment 2. Numbering of subsequent criteria was not changed.*
6. Patients treated with corticosteroids must be on a stable dose for at least 4 weeks prior to screening visit with no plan to change the dose until end of trial treatment.
7. Patients treated with ACE inhibitors, ARBs, finerenone, aldosterone inhibitors, or SGLT2 inhibitors should be on a stable dose for at least 4 weeks prior to screening visit with no plan to change the dose until end of trial treatment.
8. Body Mass Index (BMI) of ≤ 40 kg/m^2 at screening visit.
9. Women of childbearing potential (WOCBP[1]) must be willing and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the informed consent form (ICF) and in section 4.2.2.3.

3.3.3 Exclusion criteria

1. Known monogenic (with the exception of TRPC6 gene mutations) or clinical or histologic evidence of secondary FSGS.
2. Documented Alport syndrome, Nail Patella syndrome, diabetic nephropathy, IgA-nephropathy, lupus nephritis, or monoclonal gammopathy (e.g., multiple myeloma).
3. Genito-urinary malformations with vesicoureteral reflux or renal dysplasia.
4. A history of organ transplantation or planned transplantation during the course of the study.

[1] A woman is considered of childbearing potential (WOCBP), 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 1 year without an alternative medical cause.

5. Uncontrolled hypertension defined as an average resting systolic blood pressure >160 mmHg calculated from the last two of the triplicate sitting blood pressure measurements at screening visit. Patients with a documented history of white coat hypertension may be included.
6. Concomitant use of calcineurin inhibitors within 5 half-lives before screening visit.
7. Concomitant treatment with cytotoxic agents (cyclophosphamide, chlorambucil), or CD20 monoclonal antibody, e.g., rituximab, within 5 half-lives before screening visit. Note: use of other immunosuppression therapies considered as standard of care may be allowed as long as the patient remains on stable dose throughout the study.
8. Treatment with metformin or dofetilide (MATE1 or OCT2 substrates); dabigatran or digoxin (P-gp substrates with narrow therapeutic window) within 5 half-lives before screening visit.
9. Treatment with strong inhibitors or strong inducers of CYP3A within 1 week or 5 half-lives before screening visit (whichever is longer).
10. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 (CKD-EPI formula based on serum creatinine and cystatin C) at screening visit.
11. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) >3X the upper limit of normal (ULN) at screening visit.
12. Clinically significant laboratory abnormalities or medical conditions which pose a safety risk for the patient or may interfere with the trial objectives in the investigator's opinion (except for renal function tests or deviation of clinical laboratory values that are related to FSGS) at screening visit.
13. QTc intervals (QTcF) greater than 450 ms in males or greater than 470 ms in females, or any other clinically relevant ECG findings (at the investigator's discretion) at screening visit.
14. History of congenital long QT syndrome, previous drug-induced QT prolongation, or other risk factors for Torsade de pointes (e.g. hypokalemia, bradycardia, heart failure).
15. Detection of graded cataract by LOCS III higher than NC1/NO1, C0, P0 in the slit lamp eye examination at screening visit. Planned cataract surgery during participation in the study. Patients with cataract who have undergone lens replacement are not excluded.
16. A history of gastrointestinal (GI) surgery or GI disorders that could interfere with absorption of trial medication in the investigator's opinion.
17. Major surgery (major according to the investigator's assessment, e.g. hip replacement) performed 3 months before the screening visit or planned within 6 months after entering the study.
18. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening visit, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix.
19. History of relevant allergy or hypersensitivity according to the investigator´s clinical judgment (e.g. systemic hypersensitivity reactions including anaphylaxis and anaphylactoid reactions to the excipients or any other systemically administered agent).
20. Patients who need to use restricted medications (section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the study, e.g. drugs with known QT-prolongation effects.

21. Patients not expected to comply with the protocol requirements or not expected to complete the study as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable study participant).
22. Previous enrollment in this trial, or currently enrolled in another study investigating a device or drug, or less than 30 days or 5 times half-life of the investigational drug (whichever is longer) since ending another investigational drug study. Patients participating in observational studies will not be excluded.
23. Women who are pregnant, nursing, or who plan to become pregnant while in the study.
24. A positive test for SARS-CoV-2 during the screening period and up to the randomization.

3.3.4 Discontinuation of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; see sections 3.3.4.1 and 3.3.4.2 below. Every effort should be made to keep the patients in the trial. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrollment, as well as the explanation of the consequences of withdrawal. The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and electronic case report forms (eCRF). If applicable, consider the requirements for AE collection reporting (section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment. 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 both, the investigator and sponsor representative, 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 which may increase their risk of adverse effects or interfere with the investigational medicinal product (section 4.2.2.). In cases where treatment is expected to be temporary (short course), the case should be discussed with the sponsor and a decision will be made on potentially restarting trial medication.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, serious or severe drug induced liver injury attributable to the trial drug (section 5.2.6.1.4), other AEs, other diseases, or pregnancy).
- The patient experiences confirmed QT prolongation of QTcF intervals greater than 500 ms or an increase of >60 ms compared to baseline (defined as visit 2, pre-dose measurement).
- The patient experiences clinically relevant conduction disorders (e.g. AV block ≥2nd degree, bundle branch block).

- The patient is diagnosed with cataract (graded by LOCS III higher than NC1/NO1, C0, P0) during study treatment.
- eGFR below 25 mL/min/1.73 m^2 (CKD-EPI formula based on serum cystatin C) and not improved by resolution of transient events (e.g. dehydration).
  Patient experiences acute kidney injury as per clinical judgement by the investigator and/or according to the modified Kidney Disease: Improving Global Outcomes (KDIGO) definition (R17-2439) and adapted for cystatin C as opposed to serum creatinine (R14-1203, R15-5270).
    - Increase in cystatin C to ≥ 1.5 times the baseline value, which is known or presumed to have occurred within the prior 7 days.
- The patient is diagnosed with severe COVID-19 (for example patients who require hospitalization, need supplemental oxygen, have compromised lung function, etc.). If the patient has mild illness, continuation of trial treatment is at the discretion of the investigator. Testing for SARS-CoV-2 infection must be done locally and not at the central lab. Positive test should be reported as an AE, and reason for premature withdrawal should be recorded as "other AE" if applicable.

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

If the trial treatment is permanently discontinued, patient should complete the EoT, follow-up (FUP1), and EoS visits as outlined in the Flow Chart A.

3.3.4.2 Withdrawal of consent to trial participation

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

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation. Investigator should also explain the options for continued follow-up after trial treatment discontinuation.

3.3.4.3 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrollment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment.
3. Deviations from Good Clinical Practice (GCP), the trial protocol, or the contract impairing the appropriate conduct of the trial.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The BI investigational products are provided by Boehringer Ingelheim Pharma GmbH & Co. KG.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product 1

Substance:	BI 764198
Pharmaceutical formulation:	Capsule
Unit strength:	20 mg, 40 mg, and 80 mg
Posology:	q.d.
Mode of administration:	Oral (p.o.)

Table 4.1.1: 2 Test product 2

Substance:	Placebo to match BI 764198
Pharmaceutical formulation:	Capsule
Unit strength:	Not applicable
Posology:	q.d.
Mode of administration:	Oral (p.o.)

4.1.2 Selection of doses in the trial

The proposed doses in this study, 20 mg, 40 mg, and 80 mg were chosen based on acceptable Phase 1 clinical trial safety data generated with 80 mg for up to 14 days of daily dosing in healthy volunteers and safety margins based on nonclinical toxicological findings ([redacted]).

The human therapeutic dose in patients with CKD has been estimated based on plasma exposures demonstrating efficacy in a mouse unilateral ureteral obstruction model in which BI 764198 levels above the mouse manual patch-clamp IC_{90} value (after correcting for plasma protein binding) produced a significant pharmacological effect. Coverage of the human manual patch-clamp IC_{90} value of 212 nM (equivalent to 77 nM unbound, considering an unbound fraction of 36.4% in human plasma ([redacted])) is predicted to be required in patients to provide therapeutic benefit. The conservative assumption is that the $C_{trough,ss}$ value needs to be above the IC_{90} value.

In the multiple rising dose (MRD) study ([redacted]), the gMean (gCV%) $C_{trough,ss}$ values of dose groups 20 mg, 40 mg and 80 mg were 164 nM (28.6), 351 nM (20.2) and 731 nM (29.1), respectively. Patients with primary FSGS likely have slightly higher exposures due to their impaired renal function relative to healthy subjects (see section 1.2). Simulations for patients with an eGFR of 60 mL/min/1.73 m^2 were performed based on a population PK analysis including studies 1434-0001 ([redacted]), 1434.0002 ([redacted]), and 1434-0007 ([redacted]). The predicted median $C_{trough,ss}$ (95% prediction interval) of dose groups 20 mg, 40 mg and 80 mg were 221 nM (134 - 356 nM), 432 nM (264 - 710 nM) and 867 nM (529 - 1381 nM), respectively.

Thus, the therapeutic dose of BI 764198 is estimated to be between 20 and 40 mg. However, in the absence of the possibility to assess target engagement in humans and given the uncertainty of a demonstrable pharmacodynamic effect solely based on in vitro dose estimation, a higher exposure (at multiples of IC_{90}) may be needed to observe a therapeutic response in vivo.

From an efficacy perspective, in this mechanistic study, we intend to investigate high doses of BI 764198 (above the anticipated therapeutic dose) in order to explore whether TRPC6 inhibition induces a clinically meaningful UPCR response in patients with primary or TRPC6 monogenic FSGS. Beyond the establishment of the proof of clinical principle, which is a key objective in this trial, future studies, including a dedicated Phase 2 dose finding trial will enable a thorough investigation of therapeutic doses and the establishment of the minimum effective dose.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all inclusion and exclusion criteria, each eligible patient will be randomized to one of the treatment groups according to the randomization plan in a 1:1:1:1 ratio via Interactive Response Technology (IRT). Randomization will be stratified by use of corticosteroids.

Note that the trial medication number is different from the patient number (the latter is generated during screening via the IRT System). A total of 60 patients will be randomized with approximately 15 patients in each treatment group. Patients randomized by error and did not receive any trial medication may be replaced.

4.1.4 Drug assignment and administration of doses for each patient

Table 4.1.4: 1 shows the trial medication schedule for each treatment group.

Table 4.1.4: 1 BI 764198 and placebo treatments

Dose group	Substance	Pharmaceutical form	Unit strength	Number of capsules per administration	Total daily dose
1	BI 764198	Capsule	20 mg	1 capsule q.d. for 12 weeks	20 mg
2	BI 764198	Capsule	40 mg	1 capsule q.d. for 12 weeks	40 mg
3	BI 764198	Capsule	80 mg	1 capsule q.d. for 12 weeks	80 mg
1-3	Placebo*	Capsule	--	Matching placebo for 12 weeks	--

* Subjects receiving placebo are equally distributed across all three treatment groups.

After eligibility of the patient is confirmed during the screening period, patient will be randomized in the IRT Platform at least 7 days before the scheduled visit 2 date. Randomization will initiate the direct shipment of trial medication to the patient. Each patient will receive trial medication from an external depot contracted by the sponsor. Patient's name and address will not be made available to the sponsor. Patient will receive sufficient trial medication for the entire 12-week duration of the treatment period.

Prior to shipment of the trial medication, study site staff will train the patient on handling, storage, and use of the trial medication. Site staff should contact the patient by telephone (video call if possible) in about 24 hours (or next working day) after the site receives the delivery notification from the courier. During this contact, the site should remind the patient of the proper storage requirements for the medication. The patient should also be instructed not to open the trial medication package and to bring all the medication to the clinic for visit 2.

Medication from one of the bottles will be used to dose the patient at visit 2. Site staff will inspect the shipment to ensure patient has received all the medication. All trial medication (except the capsule used for dosing at visit 2) will be returned to the patient with instructions for administration of medication at home.

- Patient will self-administer the trial medication at home. On study visit days, patient must receive the dose during the study visit (at the clinic or at home) after the pre-dose PK sample is taken.
- Patients should take one capsule a day with or without food, preferably at the same time of the day in the mornings.
- In case dosing occurs before 18:00 hours (6 p.m.), the next dose should be in the morning the next day (followed by morning dosing thereafter).
- In case dosing occurs before midnight, the next dose should be at about noon the next day (followed by morning dosing thereafter).
- If dosing does not occur on a particular day (not taken until midnight), the next dose should be in the morning the next day (followed by morning dosing thereafter).

The route of administration is by mouth (p.o.). Trial treatment may be restarted after temporary discontinuation (section 3.3.4.1). Dose reduction or increase are not allowed.

On study visit days, trial medication will be administered at the specified time (see Table 10.1: 1). Patient should be instructed to bring all used and unused bottles to the clinic for each study visit. Site staff will inspect all the trial medication and also calculate compliance (section 4.3) by capsule count. Site will destroy the empty bottles with documentation and re-dispense the remaining medication to the patient at each study visit. At the EoT visit all remaining used and unused bottles with trial medication will be collected from the patient. Study visits should be rescheduled if trial medication is not available for dosing the patient after the pre-dose PK sample is drawn.

If local regulations or site procedures or if the patient does not permit shipment of the trial medication directly to the patient, medication can be shipped to the study site. Randomization will still be completed at least 7 days before the scheduled visit 2 date to initiate trial medication shipment to the site. Site staff will dispense the trial medication to the patient. For storage conditions, see section 4.1.7.

Unscheduled supply of trial medication can be initiated by the study site in the IRT. Patient should contact the site if a need for additional medication supply arises.

A paper diary will be dispensed and collected at time points shown in the Flow Chart A. Patient will record the date and time of trial medication intake in the diary on the 3 days before EoT visit, and on the previous day for all other visits. Patients should be instructed to bring the completed diary for review by the site staff. Date and time of medication intake for the 3 days prior to EoT as well as the previous day for all other visits will be entered in the eCRF. Date and time of medication intake during the study visit will also be entered in the eCRF. A copy of the paper diary will be placed in the ISF.

For patients participating in the trial remotely via the DCT model, the MRN will visit the patient's home for the study visit and complete the trial procedures including inspection of the trial medication, providing instructions for administration of medication at home, administering trial medication at the specified time during the study visit, and review of the paper diary. Additional guidance on remote study visits will be provided in a separate DCT operational manual which will include instructions for handling used empty bottles and unused trial medication.

COVID-19 pandemic - contingency plan:

During the COVID-19 pandemic physical visits to the sites (for patients not participating in the DCT model) may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment, after discussion with the sponsor.

4.1.5 Blinding and procedures for unblinding

[redacted]

The trial has a double-blind design. The randomization schemes and medication kit lists (i.e. the treatment information) will be handled according to the sponsor's Standard Operating Procedures (SOPs).

[redacted]

Refer to section 4.1.5.2 for rules of breaking the code for an individual or for all patients in emergency situations.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must be used only in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page. If the patient is unblinded by the investigator, patient will have to be discontinued from the trial. Discontinued patients will complete the EoT and follow-up visits.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomization code for individual patients during trial conduct. The access to the

code will only be given to authorized Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated contract research organization (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice. Re-supply (if necessary) will be managed via the IRT system. 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 according to the recommended storage conditions on the medication label. Patients will be instructed to store the medication in a secure area. Site staff will train the patients on storage conditions. Patients will not maintain a temperature log.

If shipment of trial medication to the site becomes necessary (section 4.1.4), sites should store the medication in a secure limited access storage area according to the recommended storage conditions on the medication label, and maintain a temperature log until the medication is dispensed to the patient. If the storage conditions are found outside the specified range, procedure described in the ISF has to be followed and a Clinical Research Associate (CRA) should be contacted immediately.

4.1.8 Drug accountability

The patient will receive the investigational drug delivered by the sponsor when the following requirements are fulfilled at the study site:

- Approval of the clinical trial protocol by the Institutional Review Board (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 Food and Drug Administration (FDA) Form 1572 (if applicable),
- Study site has obtained a signed informed consent from the patient.

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return all unused investigational drug.

The investigator or designee must maintain records of the product's delivery to the patient, the use by each patient, and the return to the sponsor or warehouse / drug distribution center

or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution center will maintain records of the disposal. These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol and reconcile all investigational medicinal products the patient received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed in this trial.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Medication or class of medications	Restriction needs and time
Strong inhibitors and strong inducers of CYP3A4/5; immunosuppressive agents, drugs with UGT1A4 activity, drug which are known P-gp substrates of narrow therapeutic window, and OCT2, MATE1, or MATE2-K substrates.	Not allowed 1 week or 5 half-lives (whichever is longer) prior to randomization through 5 days after EOT
Investigational device or drug	Not allowed 30 days or 5 half-lives (whichever is longer) prior to randomization through 5 days after EOT
Agents known to prolong the QT interval	Not allowed 1 week or 5 half-lives (whichever is longer) prior to randomization through 5 days after EOT
Systemic corticosteroids	Dose must be stable for at least 4 weeks prior to screening visit. Dose should not change during the screening and treatment period unless the investigator feels a dose change is necessary to ensure the patient's safety.

Additional information, including a list of drugs that should be avoided, is provided in the ISF for the following classes of medications: immunosuppressive agents, strong inhibitors/inducers of CYP3A4/5, UGT1A4, drugs which are known P-gp substrates of narrow therapeutic window, and OCT2, MATE1, or MATE2-K substrates as well as agents known to prolong the QT interval.

Medications listed under the exclusion criteria (section 3.3.3), are not allowed during the trial. When possible, use of restricted medications and impact on treatment discontinuation should be discussed with the sponsor. There are no restrictions for trial participant to receive vaccination for COVID-19 during or after the study period.

4.2.2.2 Restrictions on diet and lifestyle

Patients should avoid high protein, high salt diet. Avoidance of dietary protein load and strenuous exercise is especially important within 24 hours prior to the start and until the completion of the 24-hour urine collections.

4.2.2.3 Contraception requirements

Female Patients

WOCBP (for definition refer section 3.3.2) and their male sexual partner must use two medically approved methods of birth control during the treatment period and for a period of at least 5 days after last trial drug intake. Male partner of a WOCBP trial participant who is able to father a child must use a condom.

WOCBP (trial participant) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly. Birth control methods with low user dependency, as indicated with an asterisk (*) below are preferable.

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable*)
- Intrauterine device (IUD)* or intrauterine hormone-releasing system (IUS)*
- Bilateral tubal occlusion*

Acceptable methods of birth control will include abstinence from male-female sex or having a vasectomized partner, provided that partner is the sole sexual partner of the trial participant who is a WOCBP, and that the vasectomized partner has received medical assessment of the surgical success.

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

Since BI 764198 is not expected to lead to a clinically relevant reduction in the exposure of oral contraceptives due to an increased metabolism via enzyme induction (section 1.2), oral contraceptives are allowed in this trial.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty bottles with them when attending visits. Based on capsule counts, treatment compliance will be calculated as shown in the formula below.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of capsules actually taken} \times 100}{\text{Number of capsules should have been taken as directed by the investigator}}$$

Compliance will be verified by the CRA authorized by the sponsor or delegate. The target for medication compliance should be 100%. If patient is non-compliant, site staff will explain to the patient the importance of treatment compliance. Randomized patients will not be discontinued from the trial for poor medication compliance without prior discussion with the Clinical Trial Manager (CT Manager) appointed by the sponsor.

For patients participating in the trial remotely via the DCT model, compliance will be calculated by the MRN, and all unused trial medication and empty bottles will be collected by the MRN and returned to the study site or an alternative location for disposal. Shipment schedule and guidelines will be described in the DCT operational manual. The investigator or designee must verify that all unused trial medication has been returned by the patient and that no remaining supplies are at the patient's home.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Measures of proteinuria

The primary endpoint is patients achieving at least 25% reduction in UPCR from 24-hour urine relative to baseline after 12 weeks of treatment. The baseline UPCR will be from the average of two 24-hour urine samples collected before visit 2.

Secondary and [redacted] are listed in sections 2.1.3 and [redacted]., respectively, and they will be assessed as follows:

- Change in UPCR relative to visit 3 at week 12: the samples will be from the 24-hour urine samples collected at visits 3 and 12.
- Change in UPCR relative to baseline at week 13: the samples will be the 24-hour urine samples collected at baseline and week 13.
- Change in 24-hour urinary protein excretion relative to baseline at week 12.

[redacted]

For additional information on urine sample collections and the time points, see section 6.1 and Flow Chart A.

[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 Flow Chart A. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. Measurement of height and body weight will be performed at the time points specified in the Flow Chart A. The results must be included in the source documents available at the site.

For patients participating in the trial remotely via the DCT model, a physical examination per protocol will be performed at the patient's home at the time points specified in the study protocol. The investigator or a designee (as indicated in the site trial staff list) will supervise

the physical examination remotely. A MRN will facilitate the physical examination in the patient's home.

For patients participating in the trial remotely, if during the physical examination (PE) or at any time during the trial it is deemed that the patient requires in-person follow-up, the patient will be advised to visit the study site or their healthcare provider or a local facility for consultation. When applicable, the study site staff will contact the local healthcare facility to obtain the medical records.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart A, prior to blood sampling. This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. Assessment for uncontrolled hypertension is completed at Visit 1 only. Three blood pressure measurements will be taken approximately 2 minutes apart after the patient has rested quietly and is in a seated position for at least 5 minutes. The average of the last two measurements for the triplicate systolic blood pressure measurements should be < 160 mmHg for assessment of exclusion criteria 5 at the screening visit. For subsequent visits, triplicate measurements are needed only if the first reading is >160mmHg, the average of the last two measurements are taken as the final reading. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. Sampling time points are provided in the Flow Chart A.

All analyses will be performed by a central laboratory, and the respective reference ranges will be provided in the laboratory manual. Instructions regarding sample collection, sample handling, processing, and shipping are provided in the laboratory manual.

If central lab services or the lab kits provided by the central lab are not available at the study site, safety labs may be done at a local lab. The results of the lab tests should be entered in the eCRF. Please note the local labs should be used only if it becomes necessary, and the CT Manager should be informed.

For patients participating in the trial remotely via the DCT model, laboratory kits will be made available at the patient's home for the respective visits. The MRN will collect, process, and ship lab samples to the central laboratory or the study site (when applicable). Additional information will be provided in the DCT operations manual.

Patients do not have to be fasted for the blood sampling for the safety laboratory.

The central laboratory will send laboratory reports to the investigator. It is the responsibility of the investigator to evaluate the 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 (section 5.2.6.1 and the DILI Checklist provided in the electronic data capture (EDC) system. The amount of blood taken from the patient concerned will be increased due to this additional sampling for DILI assessments. The central laboratory will transfer the data to the sponsor periodically.

For assessment of eGFR exclusion criterion (section 3.3.3), the CKD-EPI formula based on serum creatinine and serum cystatin C will be used. The serum cystatin C-based CKD-EPI formula will be used for the calculation of eGFR in the evaluation of efficacy. [redacted].

Table 5.2.3: 1 Safety laboratory tests

Functional lab group	**Test name**
Haematology	Haematocrit Haemoglobin Red blood cells (RBC) White blood cells (WBC) Platelet count MCV MCH MCHC RDW
Automatic WBC differential (relative and absolute)	Neutrophils total Lymphocytes total Eosinophils Basophils Monocytes Lymphocytes
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphonuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin Time (PT) International Normalised Ratio (INR)
Enzymes	Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase (ALP) Gamma-glutamyl transferase (GGT) Creatine Kinase (CK) Creatine kinase – MB fraction (CK-MB[1]) Lactate dehydrogenase Lipase Amylase Troponin I[1]
Substrates	Glucose HbA1c (at screening and EoT) Creatinine (enzymatic method)[2] Cystatin C eGFR - CKD-EPI formula based on serum creatinine and cystatin C[3] eGFR - CKD-EPI based on serum creatinine eGFR – CKD-EPI based on serum cystatin C[4] Urea Uric Acid

Table 5.2.3: 1 Safety laboratory tests (cont.)

Functional lab group	**Test name**
Substrates (cont.)	Total bilirubin Direct bilirubin Total protein Triglycerides Albumin Globulin Albumin / Globulin ratio C-Reactive Protein (CRP) Total cholesterol
Infectious serology[5]	Hepatitis B surface antigen Hepatitis C antibodies HIV-1/2 combination
Electrolytes	Calcium Sodium Potassium Magnesium Chloride Phosphate Bicarbonate (calculated) anion gap
Urinalysis	Urine nitrite Urine protein Urine glucose Urine ketone Urine bilirubin Urine Blood Urine leukocyte esterase Urine pH Specific gravity **Urine drug screen (screening visit only)** Cannabis Cocaine Benzodiazepine Amphetamines Barbiturates Methadone Opiates
Urine sediment (microscopic examination if erythrocytes, leukocytes, nitrate or protein are abnormal in urine)	Only positive findings will be reported (e.g. presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes).
Serum Pregnancy test (only for female participants of childbearing potential) at Visit 1, and if urine pregnancy test is positive at other visits.	Human Serum Chorionic Gonadotropin
Urine pregnancy test	Human Serum Chorionic Gonadotropin

1. If initial CK is elevated, re-test CK with CK-MB and troponin I.
2. Reported to the investigator only up to visit 2.
3. eGFR based on serum creatinine and cystatin C will be reported to the investigator only up to visit 2.
4. eGFR based on serum cystatin C will be reported to the investigator from visit 2 onwards.
5. Only at screening visit.

5.2.4 Electrocardiogram

Centralized ECG services will be provided by an external vendor. Standardized equipment and a quick guide will be provided by the vendor. ECGs should be collected according to the study-specific recommendations, using the standardized equipment provided by the vendor.

The 12-lead ECGs will be recorded at the time points shown in the Flow Chart A. ECGs should be recorded before or at least 10 minutes after blood samples are drawn. Patients should be supine for approximately 5 to 10 minutes before ECG collection. Patients should remain supine, but awake, during the ECG collection process.

After the screening visit, the investigator must review the ECG results from central reading to ensure that patient is eligible to participate in the study. Starting at visit 2, ECGs will be recorded at two time points at each study visit: pre-dose and at 1 to 2 hours post-dose. ECGs may be repeated for quality or safety reasons.

ECG recordings will be transmitted electronically to a vendor for central reading. ECGs will be centrally evaluated and rated as normal, abnormal, or unable to evaluate, and the results will be sent to the study site. The investigator should review the report from central reading. If the ECG is rated as abnormal, the investigator will determine if the abnormal findings are clinically significant. The investigator will have the responsibility to follow up with the patient if there are any clinically significant findings in the ECG report.

At the screening visit, ECGs are done in triplicate (3 single ECGs recorded within 180 seconds). The QTcF value used to check eligibility at the screening visit is the average of the three recordings. Any pre-existing conditions should be recorded as baseline conditions.

Pre-dose ECGs at the first dosing visit should be evaluated by the investigator before the patient receives the first dose. If abnormalities are observed by the investigator in the ECG readings at the first dosing visit, the investigator may wait until the results from central reading are available, and the first dosing visit may be rescheduled.

After the first dose is taken at visit 2, ECG will be done 1 to 2 hours post-dose. In each of the remaining study visits until EoT, ECG will be recorded pre-dose and 1 to 2 hours post-dose. At the FUP1 visit, ECG will be recorded only once. ECGs will not be recorded at EoS visit.

After the patient receives the first dose, if a clinically significant increase in the QTcF interval from baseline (defined as visit 2, pre-dose measurement) or any other clinically significant quantitative or qualitative change from baseline is identified the investigator will assess the symptoms (e.g., palpitations, near syncope, or syncope) and decide if the patient

will continue in the trial. The investigator must also check if the patient meets any of the treatment discontinuation criteria (section 3.3.4.1). Any new pathological findings (including clinically relevant abnormal ECG findings) or deterioration of previous findings observed during the trial will be recorded as AEs or SAEs, and should be followed up and/or treated as medically appropriate per local standards.

Although the ECGs are transmitted to the vendor for central reading, the investigator has the responsibility to complete an initial review of the ECG recordings the same day as the study visit. At any time during the trial, the investigator may decide to place a hold on further dosing of the patient if there is an indication of any new pathologic abnormalities in the ECG, and would prefer to wait until the results from the central reading are available.

All ECGs that are read in the central location will be stored in the vendor's database and will be transmitted to the sponsor periodically.

For patients participating in the trial remotely via DCT, ECGs are completed at the patient's home. The MRN will upload the ECGs to the DCT Platform (when applicable), and they will be available for the investigator or the site staff for review. If necessary, the MRN should consult with the investigator or designee before dosing the patient.

5.2.5 Other safety parameters

5.2.5.1 Ocular safety assessments

Eye exams including the evaluation of cataract by slit lamp will be performed by an ophthalmologist or an optometrist in both eyes to evaluate the presence of lens disorders and cataract during the screening period. Results from the eye exams must be available to the investigator before the patient is randomized in the IRT and trial medication shipment is initiated. The eye assessments will be repeated at EoT, and 30 days after last dose of trial medication (EoS) to monitor eye health and to observe any changes from baseline.

The eye exams do not have to be completed on the same day of the study visits. At study entry, eye exams can be completed during the screening period. For EoT and EoS visits, patients should try and complete the eye exams within the protocol allowed window (±3 days) for the respective visits. Eye exams should be completed at the study site or at another healthcare or eye care facility.

Eye assessments will be performed according to the Eye Examination Worksheet provided by the sponsor. All cataracts will be graded using LOCS III. A copy of the worksheet will be available in the ISF. The results from the eye exams should be entered in a separate eCRF. Safety related findings will be reported as AEs if applicable. If documented medical history of cataract surgery in both eyes is available at the time of screening, eye assessments are not required, and patient will not undergo eye exams during the screening period, EoT, and EoS. If it is confirmed at the screening visit (by slit lamp exam) that the patient had cataract surgery in both eyes, eye assessments are not required at EoT and EoS.

Patients participating in the trial remotely via the DCT model will complete the eye exams at a facility referred to by the investigator or patient could complete these exams at a local healthcare facility close to the patient's home. Results from the eye exams must be sent to the study site.

5.2.6 Assessment of adverse events

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.

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

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

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

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

5.2.6.1.2 Serious adverse event

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

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

5.2.6.1.3 AEs considered "Always Serious"

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

The latest list of "Always Serious AEs" can be found in the EDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in section 5.2.6.2.

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 5.2.6.2, "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:
Potential severe DILI
A potential severe Drug Induced Liver Injury (DILI) that requires follow-up defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST and/or ALT ≥3 fold upper limit normal (ULN) combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or in samples within 30 days of each other, or
- ALT and/or AST elevations ≥10-fold ULN.

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

5.2.6.1.5 Intensity (severity) of AEs

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

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated.
Moderate: Sufficient discomfort to cause interference with usual activity.

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

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the adverse event and the BI investigational compound, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.
Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

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

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

- From signing the informed consent onwards until the follow-up visit: all AEs (serious and non-serious) and all AESIs.
- After follow-up-visit 1 until the individual patient's end of trial: cancers of new histology and exacerbations of existing cancer, all trial drug related SAEs and all trial drug related AESIs.
- After the individual patient's end of trial: the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. telephone call. Those AEs should be reported on the BI SAE form (section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point within 24 hours of becoming aware of the event. Country specific process will be specified in the ISF. The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.2.6.2.3 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 medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B). The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part 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 Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

5.2.6.2.4 Additional Safety monitoring

In addition to the standard AE and SAE reporting, additional information will be collected in a separate eCRF on the following:

- Acute kidney injury (defined in section 3.3.4)
- Cataract

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Blood samples for PK will be collected according to planned dates and times provided in Table 10.1: 1. The date and clock times of drug administration and pharmacokinetic sampling will be recorded in the eCRF. The actual sampling times will be used for determination of pharmacokinetic parameters as defined in section 2.1.3. PK samples collected from this study will be also used for population PK and/or PK/PD analyses.

5.3.2 Methods of sample collection

For the quantification of BI 764198 plasma concentrations, blood samples will be collected at time points indicated in Table 10.1: 1 and the Flow Chart A. The actual sampling times and time of dosing will need to be recorded in the eCRF. At selected sites, additional samples will be taken for the exploratory investigation of the metabolite CD 7949. These additional samples will be acidified as described in the laboratory manual.

Plasma samples should be shipped to the central laboratory preferably on the same day of collection. Samples should be stored at approximately -20°C or below. Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual.

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.4.2 Pharmacogenomics biomarkers

Pharmacogenomics investigates genetic variations to explain and to predict an individual's response to drugs. Therefore, a blood sample for pharmacogenomic testing will be taken from each subject. In case of unexplainable variability of PK or PD parameters, DNA may be extracted from these samples and used for exploratory analysis of variants of genes with known association with FSGS, in particular TRPC6, and/or genes involved in absorption, distribution, metabolism and excretion of drugs.

It is not intended to include these data in the clinical trial report. However, the data may be part of the report if necessary. All DNA samples will be destroyed one year after the last patient has completed the trial.

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

5.4.2.1 Methods and timing of sample collection

One blood sample will be taken from an arm vein into a PAXgene blood DNA drawing tube, preferably at Visit 2.

[redacted]

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements except for the exploratory biomarker measurements performed during this trial are standard measurements and will be performed in order to monitor patients' safety and to determine pharmacokinetic and pharmacodynamic parameters. Sampling for the exploratory biomarkers is not associated with any additional risks. The risks related to eye exams are minimal.

The scheduled procedures and measurements will allow monitoring of changes in vital signs, standard laboratory values, eye health, and ECG parameters that might occur as a result of administration of study drug. The safety assessments are standard, and are accepted for evaluation of safety and tolerability, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined are generally used for assessments of drug exposure. Approximately 200 mL (14 tablespoons) of blood will be collected from a patient during the course of the study.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The trial consists of a screening period, treatment period, and a follow-up period. Following the screening period, patients will be randomized (prior to visit 2) to one of the four treatment arms. The treatment period is followed by a 30-day follow-up period which consists of 2 follow-up visits. The 2nd follow-up visit which is also the EoS visit will be completed by telephone except for the eye exams. Visit schedule and trial procedures are provided in the Flow Charts A and B. Schedule for PK sampling is presented in Table 10.1: 1.

Patients should make all efforts to complete the trial which includes the 2 follow-up visits. Investigators should encourage treatment compliance, and adherence to the protocol procedures. All patients should adhere to the visit schedule as specified in the Flow Charts A and B. Any deviations from the planned visit schedule should be documented.

All study visits should start preferably in the morning. Patients should be instructed to not take their trial medication at scheduled clinic visit days (from visit 2 to EoT visit). Trial medication must be administered during the clinic study visit as the time points specified in Table 10.1:1.

If any visit after the first dosing visit (visit 2) is rescheduled or missed, subsequent visits should follow the original visit date. The total treatment period (visit 2 to EoT visit) should be 12 weeks.

Unscheduled visits may be arranged, and it will be at the discretion of the investigator in order to check the safety or for other reasons.

ECGs should be recorded before blood samples are taken. Post-dose ECGs should be recorded before the PK sample is taken.

Eye exams should be completed at the study site or at another healthcare facility (section 5.2.5.1).

For patients participating in the trial remotely via the DCT model, study visits and procedures (except eye exams) will be performed by a MRN deployed by a CRO authorized by BI. Home visits may also be performed by an appropriately qualified member of the investigational site staff (e.g. investigator, study nurse). Investigative sites may also contract their own mobile research nurse to perform the study visits at the patient's home. Phone visits conducted in Flow Chart B should be conducted by site staff.

The remote visits must adhere to the visit schedule as specified in the Flow Chart A. The EoS visit by telephone will be completed by the study site staff.

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient, 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, and home healthcare nurse visits. The implementation of these measures will depend on patient's consent, operational feasibility, local law and regulations. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

First morning void – urine collection:

First morning void sample is collected during the screening period to obtain the UPCR needed to determine eligibility for the trial. The first morning void is the urination after the patient wakes up to start their day. If the patient goes back to sleep after urinating early in the morning e.g. at 4am, this void does not need to be collected and this does not need to be documented. This applies also to any urinations earlier during the night in patients who have nocturia. However, if the patient is an early riser and gets up 'for good' e.g. at 4am, this would qualify as their first morning void. There may be cases when a patient might go back to bed after their usual rising time. In those cases, the void after the usual rising time constitutes the first morning void. The FMV sample can be brought to the site by the patient or may be shipped to the study site via a courier when possible.

Patients can sign a separate screening consent for the purpose of collecting the first morning void urine sample during the screening period or provide a verbal consent (section 8.1). Site will process the urine samples and send them to central lab for UPCR analysis. The UPCR value obtained from the first morning void urine sample will be used to assess eligibility of the patient for the trial (section 3.3.2). Site staff should ensure sufficient time is available to get the UPCR results from central lab to complete the screening period within the protocol allowed window. If the patient did not meet the inclusion criteria for UPCR from the first morning void, the patient may repeat the assessment once, and the UPCR value obtained from the 2nd first morning void urine sample can be used to determine eligibility for the study.

24-hour urine collection:

The schedule for 24-hour urine collection and the time points for dispensing urine collection containers are provided in the Flow Chart A. The start and end time of the 24-hour urine collection will be recorded. Patients will be asked to empty their bladders outside the container before start of sampling and into the container during and at the end of the 24-hour collection period. Patients will receive detailed instructions on the collection, storage, and transportation of the urine samples. Processing and analyses of the 24-hour urine samples will be described in the laboratory manual.

The 24-hour urine samples where collection started the day before the study visits should be brought to the clinic by the patient for the respective study visits. Other 24-hour urine

samples (collected during the screening period) can be brought to the site by the patient or may be shipped to the study site via a courier when possible.

During the screening period, patient will collect 24-hour urine samples at two separate occasions. The 24-hour urine samples should be collected only after confirmation that the patient met all the eligibility criteria for the trial, and the collections should be close to visit 2 as much as possible. Visit 2 must be rescheduled if UPCR data is not available from at least one 24-hour urine sample.

For visits 3, EoT, and FUP1, one 24-hour urine sample will be collected. Collection should start preferably the day before the respective study visit and end on the day of the visit.

Visit 2 must be rescheduled if at least one of the 24-hour urine sample is not collected. The EoT visit must be rescheduled if the 24-hour urine sample is not collected before the visit. Visits must be rescheduled as soon as possible.

For patients participating in the trial remotely via the DCT model, urine collection containers for all the study visits will be sent to the patient's home, and the urine samples will be shipped to the study site via a courier. If patients live close to the study site, they may also pick up the urine collection containers from the study site and bring the 24-hour urine samples to the study site.

If possible, patients should be reminded (e.g. via telephone) during the screening period and ahead of the applicable visits to collect the 24-hour urine samples.

Collection of 24-hour urine samples may be repeated for logistical reasons (e.g. samples lost or patient could not complete the 24-hour collection) or technical issues (e.g. sample not fit for analysis).

Pregnancy tests

All WOCBP will undergo serum pregnancy test at the screening visit (visit 1). Patients who test positive for the serum pregnancy test will be excluded from the trial. If the patient is a WOCBP, the status of the menstrual cycle should be assessed before the administration of the first dose of trial medication (visit 2): in case of a delayed or missed period, the PI should use their clinical judgement and the results of the pregnancy test at visit 2 to assess the participants pregnancy status and confirm eligibility before intake of trial drug.

Urine pregnancy tests will be done at all study visits starting from visit 2 (except visit 3 and phone visits). If the urine pregnancy test is positive, trial medication will be stopped and a serum pregnancy test will be performed to confirm pregnancy. If the serum pregnancy test is positive, the patient will be discontinued from the trial. EoT visit will be scheduled as soon as possible, and patient should complete the EoS visit. If serum pregnancy is negative, patient may continue in the trial and resume treatment with trial medication. If the urine pregnancy

test is positive at the first dosing visit (visit 2), the patient must not be dosed unless the serum pregnancy test is negative.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period

Trial procedures to be performed during the screening period can be found in the Flow Chart A. Screening period is defined as the time between the date of informed consent (or the screening consent) to the date of first dose (visit 2). No trial procedures should be performed until the patient has consented to take part in the trial. The separate screening consent is to allow collection of the first morning void urine sample to obtain the UPCR needed to check eligibility criteria (section 3.3.2 and 8.1). Each patient will be assigned a unique patient number and enrollment will be recorded in eCRF.

For patients participating in the trial via the DCT model, the consenting process may be completed electronically (via eConsent) within the DCT Platform. Screening consent when applicable will be administered outside the DCT Platform. Prior to initiating the eConsent process, eligibility of potential patients will be assessed after review of medical records by the investigator or site staff. Once this preliminary eligibility is confirmed, a study informed consent discussion will be scheduled. The informed consent materials will be presented in the DCT Platform. The patient will review the documents and during this telephone call with the investigator or designee will have the opportunity to discuss the study, and have their questions answered. If patient agrees to participate in the trial, an electronic signature will be obtained.

Once the patient has consented to collect the first morning void urine sample for screening purposes, the patient is considered to be enrolled in the trial. The patient should be recorded on the enrollment log and be registered in the IRT.

Baseline conditions, medical history, and eligibility criteria will be assessed at visit 1. Concomitant therapy and AE (if any) will be recorded. At the conclusion of visit 1, patients should receive instructions on procedures to be followed during the screening period.

If all the eligibility criteria are met, randomization will be completed by calling the IRT. Randomization will initiate trial medication shipment to the patient and visit 2 will be scheduled. For more information on medication administration, see section 4.1.4.

Screening period may be extended for administrative reasons with approval from the CT Manager.

If screening period exceeds 30 days, the investigator should review the laboratory reports from the screening visit (visit 1) and make a determination if any labs specified in the protocol must be repeated before the first dosing visit. If deemed necessary, test samples should be drawn and sent to the central laboratory.

Discontinuation during the screening period

If patients discontinue from the trial during the screening period, no additional study visits are required, and they will be marked as screen failures. Patient will be registered as a screen failure in IRT.

Rescreening and retesting

Patients who screen failed due to a reason that was reversible and has since been resolved or those who were screen failed for administrative reasons (e.g., extended travel, life events) may be rescreened once with approval from the CT Manager or designee.

If the investigator believes that a lab test result is due to an error or other extenuating circumstances, the lab test can be repeated once without the patient having to be rescreened.

6.2.2 Treatment period.

Treatment period will begin at visit 2 and will continue for 12 weeks. Procedures to be completed at each study visit can be found in the Flow Charts A and B. There will be three phone call visits during the treatment period: visits 3A, 4A, and 5A. Please refer to Flow Chart B for details on the phone call visits.

Unscheduled visits may be arranged if necessary. Procedures completed during an unscheduled visit will depend on the circumstances under which the visit was scheduled, and at the discretion of the investigator.

EoT must be rescheduled if the 24-hour urine sample is not collected for UPCR measurements. After completion of the treatment period, the patient will enter the 30-day follow-up period.

Discontinuation during the treatment period

For discontinued patients, EoT visit must be scheduled as soon as possible. After completion of the EoT visit, patient will complete both follow-up visits (FUP1 and EoS).

6.2.3 Follow-up period and trial completion

The 30-day follow-up period extends from the EoT visit until the EoS phone call visit. The FUP1 visit should be scheduled 7 days after the EoT visit, and EoS phone call visit should be scheduled 30 days after the EoT visit. The EoS visit will be a telephone visit for all patients. For patients participating in the trial remotely, the study site staff will complete EoS visit by telephone. Procedures to be completed at the follow-up visits can be found in the Flow Chart A. Investigator should ensure that eye exams (if applicable) are completed as part of the EoS visit and the results are reviewed.

The last study visit will be the EoS visit and this will mark the end of observation period, and the patient has completed the trial.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

No confirmatory testing will be performed and hence no null and alternative hypotheses are defined since this is a non-confirmatory study.

7.2 PLANNED ANALYSES

7.2.1 General considerations

The following analysis sets will be defined for statistical analyses:

- Entered Set (ES): This patient set includes all patients who signed informed consent. The ES will be used for the analysis of patient disposition.

- Randomized Set (RS): This patient set includes all patients who signed the informed consent form and were also randomized, regardless whether the patient was treated with trial medication or not.

- Treated Set (TS): This patient set includes all patients who received at least one dose of trial medication. The TS is used for safety analyses as well as demographics and baseline characteristics.

- Full Analysis Set (FAS): This patient set includes all patients who were randomized and treated with evaluable measurements UPCR at baseline and at least one UPCR measurement after first dose. The FAS is the main analysis set for the analysis of efficacy.

- Pharmacokinetic Analysis Set (PKS): This patient set includes all patients in the TS who provide at least one PK endpoint that was not excluded due to protocol violation relevant to the evaluation of PK or due to PK non-evaluability.

For the analysis of efficacy, patients will be analyzed as randomized, without regard to any treatment changes.

7.2.2 Handling of Intercurrent Events

An intercurrent event (ICE) is defined as an event of,
- early discontinuation,
- lost to follow-up, or
- death.

The strategies for handling intercurrent events in this trial are as follows:

- Hypothetical estimand: assuming all subjects remained adherent to the assigned trial medication and the study protocol. This strategy will include all data collected until time of an ICE.
- Treatment policy estimand: using all available data including data collected after an ICE.

7.2.3 Primary endpoint analyses

An exploratory inferential analysis for the primary endpoint, in terms of proportion of patients achieving at least 25% UPCR reduction relative to baseline at 12 weeks, will be conducted by providing 95% confidence intervals from each treatment group. The primary estimand of interest is the treatment effect assuming all subjects remained adherent to the assigned trial medication and the study protocol using a hypothetical approach, i.e., study drug is taken as directed. This analysis will include all data collected until time of an ICE.

In addition, an analysis of variance (ANOVA) model (for the UPCR change from baseline at week 12) will be used to see difference across arms. Dose-response relationship based on reduction in log of UPCR may be explored using graphical approach.

7.2.3.1 Sensitivity analyses

Sensitivity analyses to be conducted to assess the robustness of the primary analysis outcome will be described in the trial statistical analysis plan (TSAP).

7.2.3.2 Supplemental analysis of primary endpoint

An additional assessment of the primary endpoint will be conducted using the treatment policy estimand, i.e., effectiveness/intention to treat. The treatment policy estimand will use all available data including data collected after an ICE. All attempts will be made to collect all data per protocol.

7.2.3.3 Subgroup analyses

No subgroup analysis planned.

7.2.4 Secondary endpoint analyses

All secondary endpoints in Section 2.1.3 except pharmacokinetic parameters of BI 764198 will be analysed by using descriptive statistics and figures.

Further details will be given in the TSAP.

[redacted]

[redacted]

7.2.6 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of study, which include a 5-day period after last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients (i.e., all patients who received at least one dose of trial medication) will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the study. Adverse events that start before first intake of trial medication and deteriorate under treatment will also be considered as ‘treatment-emergent’.

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

Laboratory data will be analyzed 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 summarized. 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 study and at the end-of-study evaluation will be assessed with regards to possible changes compared to findings before start of treatment.

[redacted]

7.3 HANDLING OF MISSING DATA

No missing data will be imputed in the UPCR, , and urinary protein excretion, analyses. Handling of missing PK data will be performed according to the relevant Corporate Procedure. PK parameters that cannot be reasonably calculated based on the available drug concentration-time data will not be imputed. Further details will be specified in the TSAP.

7.4 RANDOMIZATION

The study will be performed as a double-blind design with respect to the 3 different doses of BI 764198 and placebo in a 1:1:1:1 ratio stratified by use of corticosteroids. Patients will be randomized in blocks to double-blind treatment via the IRT system.

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

7.5 DETERMINATION OF SAMPLE SIZE

To explore the clinical principle of BI 764198 it is planned to include a total of 60 patients with FSGS. The planned sample size is not based on a power calculation. The size of 15 patients per treatment arm is considered to be sufficient to detect differences between the different treatment groups and placebo in terms of the primary endpoint.

The goal of the trial is to determine if the difference in UPCR response between at least one dose after baseline and placebo is greater than 25%. Assuming that approximately 40%, 30%, 20% of patients in 80mg, 40mg, 20mg treatment groups, respectively, achieve at least 25% UPCR reduction at 12 weeks while 9 % of patients in placebo group achieve 25% UPCR reduction, the proposed sample size provides 73.4% probability for the difference in responder rates between at least one treatment arm and placebo to be greater than 25%.

Calculations were performed using R3.6.1.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for GCP, relevant BI SOPs, the EU directive 2001/20/EC /EU regulation 536/2014, 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 as will be treated as "protocol deviation".
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

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

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

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 / Independent Ethics Committee (IEC) and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory on the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient. For patients who are also participating in the National Institutes of Health sponsored Nephrotic Syndrome Study Network (NEPTUNE), their NEPTUNE TrialLink identification number will be collected in the eCRF to enable sharing their trial data with NEPTUNE, appropriate data linkages for post-hoc analysis, and for quality assurance. For additional information on consenting patients participating in the trial remotely via the DCT model, refer to section 6.1.

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

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

When possible, a screening consent process can be used prior to signing the full consent to permit collection of the first morning void urine sample from the patient that is needed during the screening process. A screening consent form will be mailed/faxed/emailed to the patient, and site staff will discuss the urine collection process over the phone/video call. A signed screening consent form is mailed/faxed/emailed back to the site. Once the signed screening consent form is received, urine collection containers and instructions will be sent to the patient.

When it is not possible to send/return a signed screening consent form, the study site staff will verbally describe the procedure over a phone/video call and obtain a verbal consent. Site will document the conversation in medical notes. Patient will sign the screening consent form in person during the screening visit. The date of the screening consent obtained over the phone/video call is regarded as the date of screening consent. The investigator or delegated site staff will sign and date the screening consent form. All phone/video call screening consents should be documented by the site staff in patient's medical record. If a patient signs a screening consent and does not provide the first morning void urine sample before the screening visit, or if the patient did not sign a screening consent, patient will receive instructions and urine collection containers at the screening visit.

Patients participating in the trial remotely via the DCT model will follow the same screening consenting process administered by the study site staff.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

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

8.3 RECORDS

CRFs for individual 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

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data 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 CRF 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.

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

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

Data collected from patients participating in the trial remotely via the DCT model, will be entered in a DCT Platform built for this trial. The data from the DCT Platform will be transcribed into the BI EDC system by the site staff.

8.3.2 Direct access to source data and documents

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

Remote source data verification is acceptable in rare cases where onsite monitoring visits cannot take place due to the COVID-19 pandemic or other unforeseen circumstances. Remote source data verification must first be approved by the CT Manager and must be aligned with local laws and regulations.

8.3.3 Storage period of records

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the World Health Organization GCP handbook.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

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

- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trial 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

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last patient in 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 treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 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 (HA) request.

The IEC / competent authority in each participating EU member state will be notified about the 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 one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

The sponsor will establish an internal safety review committee which will include a cardiologist, ophthalmologist, member from global pharmacovigilance, and other trial or project team members. The committee will review individual and aggregated unblinded safety data at regular intervals. The primary objective of this committee will be to monitor the safety and tolerability of BI 764198. ECG data (from central reading) will be reviewed at this meeting. The safety review committee will operate under a data review plan. Information on tables, figures, and listings to be reviewed by the committee will be described in this document. An independent data monitoring committee will not be established to monitor this trial.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.
BI has appointed a Clinical Trial Leader (CTL), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of CT Managers, CRAs, and investigators of participating countries.

In the participating countries the trial will be performed by the respective local or regional BI-organization (Operating Unit) in accordance with applicable regulations and BI SOPs, or by a CRO based on a contract.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

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

A central laboratory service, a central ECG service, and an IRT vendor will be used in this trial. Details will be provided in the central laboratory manual, quick guide for ECG, and quick reference documents for IRT, respectively.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P11-13071 Gipson DS, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. Kidney Int 2011;80(8):868-878.

P17-08386 Rosenberg AZ, Kopp JB. Focal segmental glomerulosclerosis. Clin J Am Soc Nephrol 2017;12(3):502-517.

R14-1203 Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Lente F van, Zhang YL, Coresh J, Levey AS, CKD-EPI Investigators. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med 2012;367(1):20-29.

R15-5270 Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA 2015;313(8):837-846.

R17-2439 Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KIDGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2(1):1-138.

R18-1763 Jiang L, Ding J, Tsai H, Li L, Feng Q, Miao J, et al. Over-expressing transient receptor potential cation channel 6 in podocytes induces cytoskeleton rearrangement through increases of intracellular Ca^{2+} and RhoA activation. Exp Biol Med (Maywood) 2011;236:184-193.

R18-1764 Tian D, Jacobo SMP, Billing D, Rozkalne A, Gage SD, Anagnostou T, et al. Antagonistic regulation of actin dynamics and cell motility by TRPC5 and TRPC6 channels. Sci Signal 2010;3(145):ra77.

R20-3402 Recommendations related to contraception and pregnancy testing in clinical trials (version 1.1, CTFG 21/09/2020). Website: hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1.pdf (access date: 16 October 2020); Clinical Trial Facilitation Group (CTFG), Head of Medicine Agencies (HMA); 2020.

R20-3802 Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al, ACTT-1 Study Group Members. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med 2020;383(19):1813-1826.

R20-3912 Kiffel J, Rahimzada Y, Trachtman H. Focal segmental glomerulosclerosis and chronic kidney disase in pediatric patients. Adv Chronic Kidney Dis 2011;18(5):332-338.

R20-3949 Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976 - 1979 and 1995 - 1997. Am J Kidney Dis 1997;30(5) :621-631.

R20-3978 Kitiyakara C, Eggers P, Kopp JB. Twenty-one-year trend in ESRD due to focal segmental glomerulosclerosis in the United States. Am J Kidney Dis 2004;44(5):815-825.

R22-1956 Bowman CJ, Becourt-Lhote N, Boulifard V, et al. Science-based approach to harmonize contraception recommendations in clinical trials and pharmaceutical labels. Clin Pharmacol Ther 2022. doi:10.1002/cpt.2602

R99-2093 Chylack LT, Wolfe JK, Singer DM, Leske MC, Bullimore MA, Bailey IL, Friend J, McCarthy D, Wu SY, Longitudinal Study of Cataract Study Group. The lens opacities classification system III. Arch Ophthalmol (Chicago) 1993;111:831-836.

10. APPENDICES

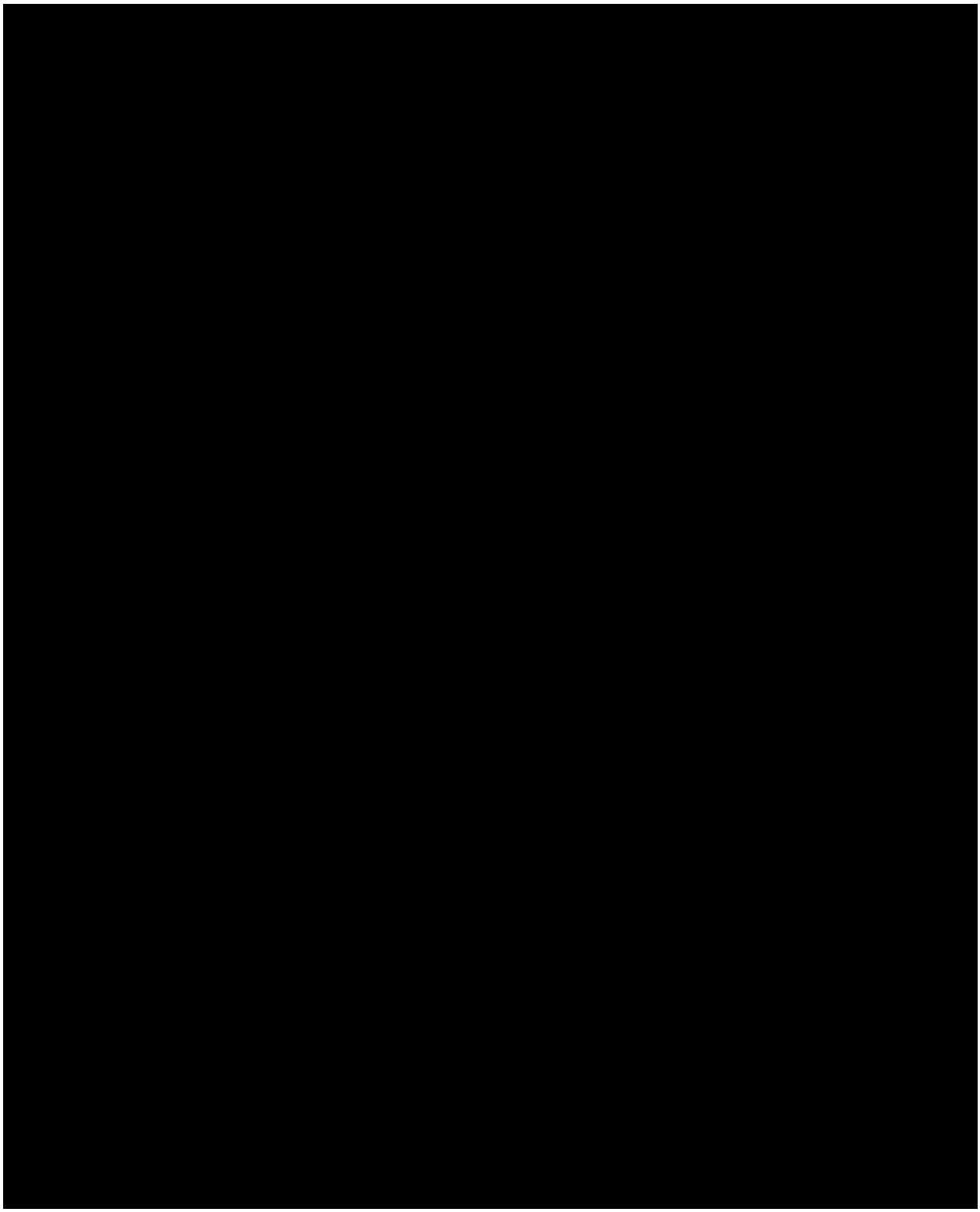
10.1 TIME SCHEDULE FOR PK BLOOD SAMPLING

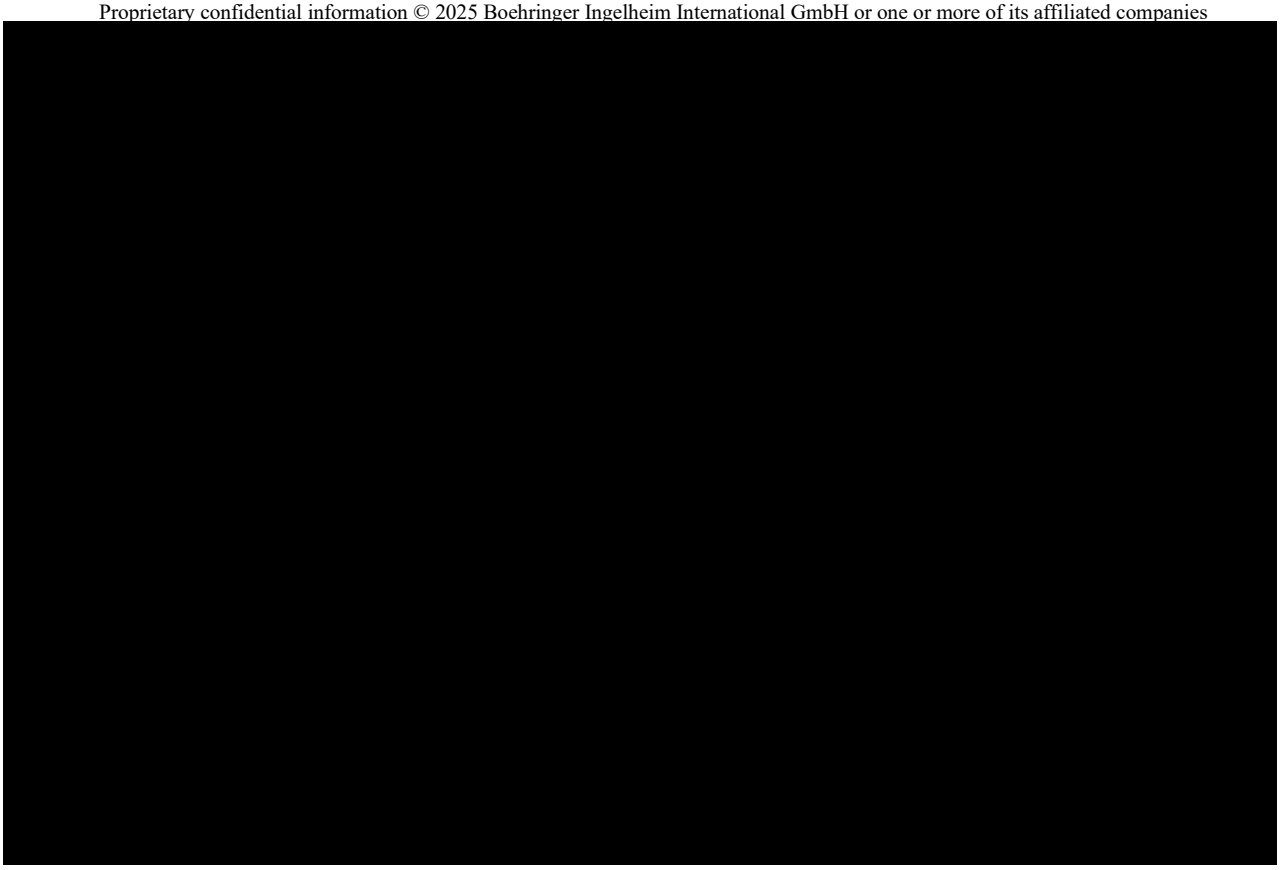
PK blood samples will be taken according to the time schedule below.

Table 10.1: 1 Time schedule for PK blood sampling during treatment course

Trial Periods	Visit	Day	Time Point [hh:min]	Planned Time	Event
Treatment period	2	1	Within 30 min before drug admin.	-0:30	PK Blood
			0:00	0:00	Drug admin.
			0:30[3]	0:30	PK Blood
			1:00[1,3]	1:00	PK Blood
			2:00[3]	2:00	PK Blood
	3	4 (+3)	Within 5 min before drug admin.	71:55	PK Blood
			0:00	72:00	Drug admin.
			1:00[3]	73:00	PK Blood
	4	29 (±3)	Within 5 min before drug admin.	671:55	PK Blood
			0:00	672:00	Drug admin.
			1:00[3]	673:00	PK Blood[2]
	5	57 (±3)	Within 5 min before drug admin.	1343:55	PK Blood[2]
			0:00	1344:00	Drug admin.
			1:00[3]	1345:00	PK Blood
	EoT	85 (±3)	Within 5 min before drug admin.	2015:55	PK Blood
			0:00	2016:00	Drug admin.
			0:30[3]	2016:30	PK Blood
			1:00[1,3]	2017:00	PK Blood
			2:00[3]	2018:00	PK Blood
			4:00[3]	2020:00	PK Blood
			6:00[3]	2022:00	PK Blood[2]
Follow-up period	FUP 1	92 (±2)	One PK sample during the visit	2184:00	PK Blood

[1] Post dose ECG should be performed either before or at least 10 min after PK blood sample.[2] At selected sites, additional PK samples at planned times 673:00, 1343:55 and 2022:00 will be taken and acidified for CD 7949 quantification. Details on the handling and acidification of these specific samples will be provided in the laboratory manual.
[3] +/- 15 minutes for post dose sample draws.





11. DESCRIPTION OF GLOBAL AMENDMENT

Date of amendment		01 December 2021
EudraCT number		2020-000384-23
BI Trial number		1434-0004
BI Investigational Medicinal Product		BI 764198
Title of protocol		A multicenter, randomized, double-blind, parallel group, placebo-controlled study to assess safety, tolerability, pharmacokinetics and pharmacodynamics of BI 764198 administered orally once daily for 12 weeks in patients with focal segmental glomerulosclerosis.
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Sections 1.2 and 4.1.2
Description of change		<u>Drug profile</u> a) Sections on drug interactions updated. Sections on toxicology and clinical studies updated. b) REP changed from 4 to 5 days. c) In section 4.1.2, preliminary results from the renal impairment study ([redacted]) is updated with final results.
Rationale for change		a) Updates based on additional data that became available. b) REP for BI 764198 is longer in patients with moderate renal impairment. c) Updated with final results consistent with the IB.
Sections to be changed		All applicable sections
Description of change		<u>Patient Population</u> Patients with primary or monogenic FSGS or with TRPC6 mutations causing FSGS will be included in the study.
Rationale for change		To include patients with TRPC6 associated FSGS.
Section to be changed		a) Flow Chart b) Table 5.2.3.1 c) Section 6.1
Description of change		<u>Trial Procedures</u> a) Pregnancy test at visit 3 removed.

		b) Urine drug screening added for screening visit. c) If urine pregnancy test is positive, trial medication should be suspended until serum pregnancy test result is available.
Rationale for change		a) Pregnancy test done 3 days before at visit 2. b) Additional safety labs added at screening. c) To ensure patient safety.
Section to be changed		a) Section 1.2 b) Sections 1.4.2, 3.3.2, and 4.2.2.3 c) Section 6.1 d) Section 4.2.2.3
Description of change		Contraception requirements a) Rationale for permitting oral contraceptives added. b) Men must use condoms, including those who are vasectomized. c) Menstrual cycle status checked at randomization visit in WOCBP. d) Preferable methods of birth control for WOCBP indicated.
Rationale for change		a) BI 764198 is not expected to lead to a clinically relevant reduction in the exposure of oral contraceptives due to an increased metabolism. b) Potential male-mediated exposure to BI 764198 in females would be conveyed by seminal fluid rather than the genetic material in the sperm cells. Therefore, the use of condoms is also required in vasectomized trial participants. c) To ensure exclusion of pregnant patients. d) Birth control methods with low user dependency are preferred.
Section to be changed		a) Section 2.2.2.2 b) Sections 2.1.3, 5.1.1, [redacted] c) Section 5.1.1
Description of change		Endpoints a) Ophthalmological assessments added to safety endpoints. b) Change in 24-hour urinary albumin excretion deleted. [redacted].

Rationale for change		a) To monitor any changes in the ocular assessments. b) [redacted]
Section to be changed		Section 3.3.3
Description of change		Exclusion criteria Cataract is graded by LOCS III system.
Rationale for change		To allow patients with age-related mild cataract to participate in the study.
Section to be changed		Section 3.3.4.1
Description of change		Discontinuation criteria Added two additional criteria: 1. The patient experiences clinically relevant conduction disorders (e.g. AV block ≥2nd degree, bundle branch block). 2. The patient is diagnosed with cataract during study treatment.
Rationale for change		Additional safety measures added for patients during their participation in the study.
Section to be changed		Section 4.2.2.1
Description of change		Restrictions List of medications or class of medications updated.
Rationale for change		Align with restricted medication guidance provided in the ISF.
Section to be changed		a) Section 5.2.5.1 b) Various
Description of change		Ocular safety assessments a) Eye assessments will be performed according to the Eye Examination Worksheet provided by the sponsor. b) Slit lamp eye exam changed to “eye exams”.
Rationale for change		Characterization of cataract using the LOCS III grading.
Section to be changed		a) Section 3.3 b) Section 3.3.4.1 c) Section 5.2.3 d) Section 8 e) Section 9.2 f) Entire document g) Flow Chart and synopsis

Description of change		Administrative a) Multinational study b) Cystatin C – compared to baseline c) Assessment of eGFR at screening and for other visits defined. Formulas to calculate eGFR has been removed: will be included in the central lab specifications document. d) European Union specific requirements are added. Collection of NEPTUNE TrialLink identification number added. e) References added. f) Abbreviations updated and typographical errors corrected. Clarifications and corrections made. Applicable changes throughout the document to reflect the changes described in Section 11. g) Changes in the main protocol have also been addressed in the Flow Chart and synopsis when applicable.
Rationale for change		Administrative

Date of amendment	25 October 2022
EudraCT number	2020-000384-23
BI Trial number	1434-0004
BI Investigational Medicinal Product	BI 764198
Title of protocol	A multicenter, randomized, double-blind, parallel group, placebo-controlled study to assess efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of BI 764198 administered orally once daily for 12 weeks in patients with focal segmental glomerulosclerosis.
Global Amendment due to urgent safety reasons	☐
Global Amendment	☒
Section to be changed	Title page and Synopsis
Description of change	Title of the protocol is revised to include efficacy assessment. Change in Clinical Trial Leader
Rationale for change	Primary endpoint includes efficacy assessment. Change in Clinical Trial Leader
Section to be changed	Sections 1.2, 1.4.2, and 3.3.4.1
Description of change	**Drug Profile:** Key pharmacokinetic characteristics updated. Data from clinical studies updated. **Risks, Discontinuation of trial treatment:** Severe Covid-19 infection defined and provided as a reason patients should be discontinued from trial treatment.
Rationale for change	Updates were made based on new clinical data.

Section to be changed	Section 3.3.1 Also clarified in the synopsis under trial rationale.
Description of change	**Main diagnosis for trial entry:** Patients with primary or monogenic FSGS as a result of TRPC6 mutations. *Changed to* Patients with primary FSGS, and patients with monogenic FSGS as a result of TRPC6 mutations.
Rationale for change	Clarification
Section to be changed	Synopsis Sections 2.1.1, 2.1.2, 2.1.3, [redacted], [redacted], 5.1.1, and 5.3.4. 7.2.1, 7.2.3, 7.2.5, 7.5
Description of change	**Trial objectives and endpoints:** Main objectives: updated to include efficacy as an objective. Primary endpoint: baseline will be based on 24-hour urine samples collected before first dose. Secondary endpoints: changed to align with revised 24-hour urine collection schedule. [redacted]
Rationale for change	Decision to have UPCR collected before first dose as the baseline for primary endpoint. [redacted]
Section to be changed	Synopsis, Flow Chart A, Sections 3.3.2, 6.1, and 6.2.1

Description of change	**Inclusion criteria:** Inclusion criteria 4, UPCR for inclusion criteria changed to 1000mg/g and will be based on first morning void. Section 6.1 provides instructions for the collection of morning void. Inclusion criteria 5 removed and 6 revised.
Rationale for change	UPCR from first morning void is sufficient to determine inclusion in the study. Inclusion criteria 6 revised to allow patients taking corticosteroids in the study if they are on a stable dose for 4 weeks.
Section to be changed	Synopsis and Section 3.3.3
Description of change	**Exclusion criteria:** Exclusion 6: exclusionary timeframe for calcineurin inhibitors prior to screening added Exclusion 7: stable therapeutic dose *changed to* stable dose Exclusion 19: revised to describe the assessment of relevant allergy or hypersensitivity. Exclusion 24: revised to clarify eligibility relative to covid-19 infection.
Rationale for change	Clarifications
Section to be changed	Section 4.2.2.1, 4.2.2.3
Description of change	**Restrictions on concomitant treatment:** restriction needs and time described in the protocol. Restriction guidelines for systemic corticosteroids added. Restriction of agents known to prolong QT interval is specified. **Contraception Requirements:** Vasectomized partner added as acceptable method of contraception.
Rationale for change	Additional information and guidance added to restricted medications.

Section to be changed	Flow Charts A and B, Section 6.1, 6.2.1, 6.2.2, 8.1
Description of change	**Study visits** Visits 4, 6, and 8 removed and visit numbers changed. Visits 3A, 4A, and 5A added as phone visits. Dispensing 24-hour urine collection kits aligned with scheduled collections. [redacted] Footnotes renumbered. FMV added during screening for determination of eligibility before proceeding with other screening procedures. Broadened potential reasons for rescreening after screen failure.
Rationale for change	Reduced the frequency of clinic visits to reduce patient burden. Phone visits have been added to follow patient safety.
Section to be changed	Table 10.1.1, Sections 4.1.4, and 5.3
Description of change	PK sampling schedule changed. Serial PK will be done only at EoT. Additional PK samples will be collected at selected sites for quantification of the CD 7949 metabolite. Schedule to record date and time of trial medication intake in the paper diary changed.
Rationale for change	Two serial PK visits removed to reduce patient burden. Additional samples were needed to quantify metabolite CD 7949. Paper diary is aligned with revised PK sampling schedule.
Section to be changed	Flow Chart A, Sections 1.3, [redacted], 5.5, and 8.5.1
Description of change	Optional biobanking samples will not be collected.

Rationale for change	Biobanking samples will be collected in future trials.
Section to be changed	Table 5.2.3: 1
Description of change	Infectious serology added to safety laboratory tests. Added to table: eGFR - CKD-EPI formula based on serum creatinine and cystatin C
Rationale for change	Additional safety parameters added. eGFR formula added for consistency with inclusion criterion.
Section to be changed	Flow Chart A, Section 1.4.2
Description of change	ECG will be performed only at clinic visits.
Rationale for change	To align with changes in the clinic visit schedule.
Section to be changed	Section 5.4.1.3
Description of change	Urine biomarkers will not be collected if study visits are conducted remotely.
Rationale for change	Logistical reasons in processing the urine samples at remote visits (e.g., patient's home) before shipment to central laboratory.
Section to be changed	Section 7.2.3
Description of change	Added 95% confidence intervals for proportion of patients achieving at least 25% UPCR reduction relative to baseline at 12 weeks from each treatment group.
Rationale for change	To have more informative statistics besides simple descriptive statistics.
Section to be changed	Sections 3.1, 4.1.3, 7.4
Description of change	Patients will be stratified by use of corticosteroids at randomisation.
Rationale for change	Ensure even distribution of patients taking corticosteroids across treatment groups.
Section to be changed	Sections 3.3, 4.1.1, 4.1.2, and 5.7
Description of change	Added more sites

	Source for Investigational Medicinal Products is corrected. Reference to 1434-0002 removed in Section 4.1.2. Blood volume corrected to align with the revised blood sampling schedule.
Rationale for change	Administrative

Date of amendment	14 Jul 2023
EudraCT number	2020-000384-23
BI Trial number	1434-0004
BI Investigational Medicinal Product	BI 764198
Title of protocol	A multicenter, randomized, double-blind, parallel group, placebo-controlled study to assess efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of BI 764198 administered orally once daily for 12 weeks in patients with focal segmental glomerulosclerosis.
Global Amendment due to urgent safety reasons	☐
Global Amendment	☒
Section to be changed	**Title page**
Description of change	1. Universal Trial Number added 2. Change in Clinical Trial Leader 3. Change in Coordinating Investigator
Rationale for change	Administrative update
Section to be changed	**Protocol Synopsis**
Description of change	Removal of male participant contraception use if female partner is WOCBP
Rationale for change	Based on emergent animal study results, the exposure of female sexual partners and associated risk of fetotoxicity are negligible, indicating that condom use is not required for male trial participants with WOCBP partners
Section to be changed	**Flowchart footnotes**

Description of change	1. Timing of collection of ECG relative to blood sampling 2. Urine pregnancy testing clarity 3. Addition of triplicate systolic blood pressure measurements at screening to support assessment of exclusion criteria 5
Rationale for change	1. Clarity to avoid ECG collection no sooner than 10 minutes after blood sampling to avoid anxiety related findings on ECG results 2. Urine pregnancy testing is not done at phone visits 3. Guidance for assessment of uncontrolled hypertension in exclusion criteria 5
Section to be changed	**1.2 Drug Profile**
Description of change	Alignment with Investigator Brochure version 7 based on completed toxicology animal study data
Rationale for change	Alignment with Investigator Brochure version 7 based on completed toxicology animal study data
Section to be changed	**1.4.2 Risks**
Description of change	Removal of male participant contraception use if female partner is WOCBP
Rationale for change	Based on emergent animal study results, the exposure of female sexual partners and associated risk of fetotoxicity are negligible, indicating that condom use is not required for male trial participants with WOCBP partners
Section to be changed	**3.3.2 Inclusion criteria**
Description of change	Removal of male participant contraception use if female partner is WOCBP
Rationale for change	Based on emergent animal study results, the exposure of female sexual partners and associated risk of fetotoxicity are

	negligible, indicating that condom use is not required for male trial participants with WOCBP partners
Section to be changed	**4.1.4 Drug assignment and administration of doses for each patient**
Description of change	Update reason why study medication may be shipped to the site instead of patient's home
Rationale for change	Update reason why study medication may be shipped to the site instead of patient's home
Section to be changed	**4.2.2.3 Contraception requirements**
Description of change	Removal of male participant contraception use if female partner is WOCBP
Rationale for change	Based on emergent animal study results, the exposure of female sexual partners and associated risk of fetotoxicity are negligible, indicating that condom use is not required for male trial participants with WOCBP partners
Section to be changed	**5.2.2 Vital Signs**
Description of change	Addition of triplicate systolic blood pressure measurements at screening to support assessment of exclusion criteria 5
Rationale for change	Guidance for assessment of uncontrolled hypertension in exclusion criteria 5
Section to be changed	**5.2.4 Electrocardiogram**
Description of change	Timing of collection of ECG relative to blood sampling
Rationale for change	Clarity to avoid ECG collection no sooner than 10 minutes after blood sampling to avoid anxiety related findings on ECG results
Section to be changed	**5.2.6.2.3 Pregnancy**
Description of change	Removal of male participant contraception use if female partner is

	WOCBP and a pregnant partner informed consent form is no longer needed
Rationale for change	Based on emergent animal study results, the exposure of female sexual partners and associated risk of fetotoxicity are negligible, indicating that condom use is not required for male trial participants with WOCBP partners
Section to be changed	**6.1 Visit schedule**
Description of change	Urine pregnancy testing clarity
Rationale for change	Urine pregnancy testing is not done at phone visits
Section to be changed	**9.1 Published references**
Description of change	Added references
Rationale for change	Administrative update
Section to be changed	**10.1 Time schedule for PK blood sampling**
Description of change	1. Addition of out of window allowance for post dose sampling 2. Clarity to avoid ECG collection no sooner than 10 minutes after blood sampling
Rationale for change	Allowance of out of window for post dose PK sampling and ECG collection

Date of amendment	08 Jan 2024
EudraCT number	2020-000384-23
BI Trial number	1434-0004
BI Investigational Medicinal Product	BI 764198
Title of protocol	A multicenter, randomized, double-blind, parallel group, placebo-controlled study to assess efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of BI 764198 administered orally once daily for 12 weeks in patients with focal segmental glomerulosclerosis.
Global Amendment due to urgent safety reasons	☐
Global Amendment	☒
Section to be changed	**Title Page**
Description of change	Change in Document Number Change in Clinical Trial Protocol Revision Date Change in Clinical Trial Leader
Rationale for change	Administrative change
Section to be changed	**Protocol Synopsis**
Description of change	Change in Clinical Trial Protocol Revision Date
Rationale for change	Administrative change

[redacted]