Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c31864883-06**
EudraCT No. **EU Trial No.**	2020-002723-11	
BI Trial No.	1404-0043	
BI Investigational Medicinal Product(s)	BI 456906	
Title	Multicenter, double-blind, parallel-group, randomised, 48 weeks, dose-ranging, placebo-controlled phase II trial to evaluate efficacy, safety and tolerability of multiple subcutaneous (s.c.) doses of BI 456906 in patients with non-alcoholic steatohepatitis (NASH) and fibrosis	
Lay Title	A study to test whether different doses of BI 456906 are effective in people with a liver disease called non-alcoholic steatohepatitis (NASH) and liver fibrosis	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted] Email: [redacted]	
Coordinating Investigator	[redacted] s Phone: [redacted] Email: [redacted]	
Version and Date	**Version: 6.0**	**Date: 27 Jul 2023**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	14 September 2020
Revision date	27 July 2023
BI trial number	1404-0043
Title of trial	Multicenter, double-blind, parallel-group, randomised, 48 weeks, dose-ranging, placebo-controlled phase II trial to evaluate efficacy, safety and tolerability of multiple subcutaneous (s.c.) doses of BI 456906 in patients with non-alcoholic steatohepatitis (NASH) and fibrosis
Coordinating Investigator	[redacted] Phone: [redacted] Email:
Trial site(s)	Multi-center trial conducted globally
Clinical phase	II
Trial rationale	The prevalence of non-alcoholic steatohepatitis (NASH) is increasing worldwide. Currently, the cornerstone treatment is lifestyle modifications focusing on diet and exercise resulting in weight loss, however, weight loss is difficult to achieve and maintain. Thus, novel therapeutic approaches are highly demanded. This trial will serve as a proof of clinical concept, as it will investigate potential improvement in liver histology in patients with NASH and fibrosis following treatment with BI 456906. Furthermore, it will help to determine the most suitable dose that will be used in phase III trial(s). Liver biopsy and imaging will be used to confirm the diagnosis of NASH at baseline and to assess the treatment response. The 48-week treatment duration is expected to be sufficient to show improvement in NASH with no worsening of fibrosis.
Trial objective(s)	The main trial objectives are to demonstrate a non-flat dose response curve, to evaluate the size of the treatment effect (using the absolute difference in proportions of patients with histological improvement between BI 456906 and placebo at Week 48), and to characterize the dose-response relationship.
Trial endpoints	The primary endpoint is the improvement (yes/ no) from baseline in liver histological findings based on liver biopsy after 48 weeks of treatment in patients with NASH (NAS $\geq$ 4, fibrosis F1-F3). Improvement in histological findings is defined as a composite of: Improvement in NASH: Decrease of at least two points in NAS, with at least one point

	decrease in NAS sub-score for lobular inflammation or ballooning and No worsening of fibrosis, defined as an absence of any increase in the fibrosis stage Secondary efficacy endpoints include: • Improvement of liver fat content (yes/ no) defined as at least 30% relative reduction in liver fat content after 48 weeks of treatment compared to baseline assessed by magnetic resonance imaging proton density fat fraction measurement (MRI-PDFF) • Absolute and relative change of liver fat content from baseline after 48 weeks of treatment assessed by MRI-PDFF • Improvement of fibrosis (yes/ no) defined as at least one stage decrease in fibrosis stage after 48 weeks of treatment assessed by liver biopsy • Absolute change from baseline in NAS after 48 weeks of treatment assessed by liver biopsy
Trial design	Multi-center, randomised, dose-ranging, double blind, placebo-controlled, parallel-group trial
Total number of patients randomised	240 patients
Number of patients on each treatment	60 patients on BI 456906 2.4 mg (Group 1) 60 patients on BI 456906 4.8 mg (Group 2) 60 patients on BI 456906 6.0 mg (Group 3) 60 patients on placebo (Group 4)
Diagnosis	Non-alcoholic steatohepatitis (NASH) and fibrosis
Main in- and exclusion criteria	Inclusion criteria: • Male or female patients ≥ 18 years (or who are of legal age in countries where that is greater than 18 years) and ≤ 80 years of age at time of consent. • Diagnosis of NASH (NAS ≥ 4, with at least 1 point in inflammation and ballooning each) and fibrosis stage F1–F3 proven by a biopsy conducted during the screening period or by a historical biopsy conducted within the last 6 months prior to randomization and stable body weight defined as less than 5% self-reported change in body weight between the historical biopsy and randomization if a historical biopsy is used. • Liver fat fraction ≥ 8% measured by MRI-PDFF and liver stiffness > 6.0 kPa measured by FibroScan® at Visit 1 (if biopsy is scheduled during the screening period MRI-PDFF and FibroScan® assessments have to be performed prior to the biopsy). However, the diagnosis of NASH and fibrosis at liver biopsy (including historical biopsy) is the primary assessment to establish patient eligibility. • Patients willing and able to undergo liver biopsies per protocol as judged by the Investigator. • BMI ≥ 25 kg/m^2 and a body weight ≥ 70 kg at Visit 1.

	Exclusion criteria: • Current or history of significant alcohol consumption (defined as intake of > 210 g/ week in males and > 140 g/ week in females on average over a consecutive period of more than 3 months) or inability to reliably quantify alcohol consumption based on Investigator judgement within the last 5 years. • Intake of medications historically associated with liver injury, hepatic steatosis, or steatohepatitis within 12 weeks prior to Visit 1. Intake of restricted medications or any medications considered likely to interfere with the safe conduct of the trial. • History of other forms of chronic liver disease (e.g., viral hepatitis, autoimmune liver disease, primary biliary sclerosis, primary sclerosing cholangitis, Wilson`s disease, hemochromatosis, A1At deficiency, history of liver transplantation). • Suspicion, diagnosis, or history of hepatocellular carcinoma (HCC), or any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix. • Diagnosis of a serious or unstable disease including hepatic (other than NASH), renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, psychiatric, immunologic, or hematologic disease and other conditions that, in the clinical judgment of the Investigator, are likely to interfere with the analyses of safety and efficacy in this trial. Patients with a history of organ transplantation except for corneal transplantation and patients with an expected life expectancy of less than 2 years are also excluded.
Test product(s)	Solution for injection BI 456906: 0.6 mg/mL, 1.8 mg/mL, 3.6 mg/mL, 4.8 mg/mL and 6.0 mg/mL Pre-filled syringes, 0.5 mL fill volume
dose	Group 1: Starting dose of 0.3 mg followed by a dose escalation up to the maintenance dose of 2.4 mg, two pre-filled syringes once weekly Group 2: Starting dose of 0.3 mg followed by a dose escalation up to the maintenance dose of 4.8 mg, two pre-filled syringes once weekly Group 3: Starting dose of 0.3 mg followed by a dose escalation up to the maintenance dose of 6.0 mg, two pre-filled syringes once weekly
mode of administration	Subcutaneous, s.c.
Comparator product(s)	Group 4: Placebo
dose	Matching
mode of administration	Subcutaneous, s.c.
Duration of treatment	48 weeks of treatment consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period

Statistical methods	The primary analysis of the primary endpoint (improvement from baseline in liver histological findings based on liver biopsy after 48 weeks) will be performed using multiple comparison and modelling techniques (MCPMod), whereby several possible dose response models (patterns) will be evaluated while keeping full control of the type I error at 5% (one-sided), to identify the best-fitting model or subset of models. A plausible and diverse range of monotone dose response patterns will be used for this purpose, as well as one non-monotone dose response pattern. The placebo response rate is assumed to be 20%, and the maximum BI 456906 response rate is assumed to be 45%. A logistic regression analysis will first be carried out. Covariate-adjusted estimates of the log odds for each dose and the covariance matrix will be extracted from the logistic regression fit and used for the subsequent MCPMod analysis. The MCPMod analysis will be carried out on the logit scale, and the results converted back to the original response scale for interpretation. The logistic regression model will be fitted without an intercept and will include presence of diabetes of any type (yes, no) and baseline fibrosis stage (F1, F2, F3), as well as the dose group, as factors. If a non-flat dose-response relationship is established, the statistically significant (best fitting) model(s) will be refitted to the data to generate new estimates for all model parameters from the data. The target dose(s) will be estimated from the best fitting model(s) by incorporating information on the minimum clinically relevant effect ("delta") and accounting for safety. The primary analysis will be performed using the full analysis set, defined as all patients who were randomised and treated. Patients will be assigned to the actual maintenance dose received. All post-baseline biopsy data will be included, without restriction on how late after discontinuing or completing treatment the biopsy was done and using all available biopsy results for patients who discontinued treatment early. Patients without a post-baseline biopsy will be imputed as non-responders, regardless of whether a biopsy result was expected or not. Supporting and sensitivity analyses will also be performed on the primary endpoint to investigate various aspects including assignment of patients to randomised (rather than actual) maintenance dose [redacted] Analysis of the responder secondary endpoint (30% reduction in liver fat content from MRI-PDFF after 48 weeks) will be performed similarly to the primary endpoint. The same dose response patterns will be used for the MCPMod, with the placebo response rate assumed to be 15%, and the maximum BI 456906 response rate

	assumed to be 50%. For the other binary secondary endpoint of improvement of fibrosis, a logistic regression analysis will be performed. For the continuous secondary endpoints measured repeatedly over time, a mixed model for repeated measures (MMRM) analysis will be performed. One interim analysis will be performed by the Sponsor for internal planning purposes after approximately half of randomised patients have reached Week 28. [redacted] Safety and tolerability will be summarised descriptively only.

FLOW CHART

Trial Period	**Screening**		**Treatment – Dose escalation**															
Visit	**1**	**1a[1]**	**2[2]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Week (w)[4]	**Up to -10w[6]**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Day (d)			**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**
Visit window (in days)				±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Visit Type[5]	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**T**	**S**	**T**	**S**	**T**	**S**	**T**	**S**	**T**	**T**	**T**
Informed consent[7]	X																	
Demographics	X																	
Medical history	X																	
Physical examination[8]	X																	
Vital signs[9]	X	X	X	X	X	X	X		X		X		X		X			
Height	X																	
Weight[10]	X		X								X							
Waist and hip circumference[11]	X		X								X							
Laboratory tests (safety)[12, 13, 14]	X		X		X		X		X		X		X		X			
12-lead ECG[15]	X		X		X		X		X		X		X		X			
In-/exclusion criteria review	X	X	X															
Randomization			X															
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
All AEs/SAEs/AESIs[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy testing[17]	Xs		Xu				Xu				Xu				Xu			
IRT call[18]	X		X	X	X	X	X		X		X		X		X		(X)	
Dispense trial medication[18, 19]			X	X	X	X	X		X		X		X		X		(X)	

FLOW CHART (cont.)

Trial Period	**Screening**		**Treatment – Dose escalation**															
Visit	**1**	**1a[1]**	**2[2]**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
Week (w)[4]	**Up to -10w[6]**			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Day (d)			**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**	**85**	**92**	**99**	**106**
Visit window (in days)				±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2
Visit Type[5]	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**T**	**S**	**T**	**S**	**T**	**S**	**T**	**S**	**T**	**T**	**T**
Self-administration training[20]			X	X	X	X	X		X									
Medication compliance check[21]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smartphone App training/ set-up[22]			X															
Review patient diary				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS completion[23]	X		X		X		X		X		X		X		X			
[redacted]			[redacted]															
Dispense SMBG device[25]			X															
[redacted]			[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]		[redacted]			
[redacted]			[redacted]				[redacted]				[redacted]				[redacted]			
[redacted]			[redacted]															
Biobanking, blood (optional)[13, 27]			X															
Biobanking, stool (optional)[28]			X															
Liver biopsy[3, 29]		X																
MR imaging[3, 30]	X																	
[redacted]	[redacted]																	
Trial completion																		

FLOW CHART (cont.)

Trial Period	**Treatment – Dose escalation**								**Treatment - Maintenance**							**Follow-up**
Visit	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32[3] (EOT/ED)**	**33**
Week (w)[4]	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**EOT/ED+4**
Day (d)	**113**	**120**	**127**	**134**	**141**	**148**	**155**	**162**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**EOT/ED+28**
Visit window (in days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	+5
Visit Type[5]	**S**	**T**	**T**	**T**	**S**	**T**	**T**	**T**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**
Informed consent[7]																
Demographics																
Medical history																
Physical examination[8]																
Vital signs[9]	X				X				X	X	X	X	X	X	X	X
Height																
Weight[10]	X									X					X	X
Waist and hip circumference[11]	X									X					X	X
Laboratory tests (safety)[12, 13, 14]	X				X				X	X	X	X	X	X	X	X
12-lead ECG[15]	X				X				X	X	X	X	X	X	X	
In-/exclusion criteria review																
Randomization																
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
All AEs/SAEs/AESIs[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy testing[17]	Xu				Xu				Xu	Xu	Xu	Xu	Xu	Xu	Xu	Xu
IRT call[18]	X		(X)		X		(X)		X	X	X	X	X	X	X	
Dispense trial medication[18, 19]	X		(X)		X		(X)		X	X	X	X	X	X		

FLOW CHART (cont.)

Trial Period	**Treatment – Dose escalation**								**Treatment - Maintenance**							**Follow-up**
Visit	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**31**	**32[3] (EOT/ED)**	**33**
Week (w)[4]	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**EOT/ED+4**
Day (d)	**113**	**120**	**127**	**134**	**141**	**148**	**155**	**162**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**EOT/ED+28**
Visit window (in days)	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	+5
Visit Type[5]	**S**	**T**	**T**	**T**	**S**	**T**	**T**	**T**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**
Self-administration training[20]																
Medication compliance check[21]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Smartphone App training/ set-up[22]																
Review patient diary	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS completion[23]	X				X				X	X	X	X	X	X	X	X
[redacted]										[redacted]					[redacted]	
Dispense SMBG device[25]																
[redacted]	[redacted]				[redacted]				[redacted]	[redacted]		[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]				[redacted]					[redacted]		[redacted]			[redacted]	[redacted]
[redacted]															[redacted]	
Biobanking, blood (optional)[13, 27]	X									X					X	
Biobanking, stool (optional)[28]										X					X	
Liver biopsy[3, 29]															X	
MR imaging[3, 30]										X					X	
[redacted]	[redacted]									[redacted]					[redacted]	
Trial completion																X

Footnotes for Flow Chart:

1. Visit 1a is not required if a historical biopsy with sufficient and analysable material was collected within the last 6 months prior to randomisation (refer to Section 3.3.1 and 5.1.1).

2. Day of randomisation and the first administration of trial medication.

3. In case of early discontinuation (ED), Visit 32 should be completed instead of the planned treatment period visit, as soon as possible after trial medication is stopped. Liver biopsy should be performed at the ED visit providing the patient has been on treatment with trial medication for at least 40 weeks. MR imaging does not need to be performed at the ED visit if the patient discontinues before Visit 22 or if another MR imaging was performed within 12 weeks before the ED. [redacted] Follow-up Visit 33 should be performed 4 weeks/28 days after the ED visit.

4. Number of weeks since randomization.

5. Trial visits will be conducted in two ways: 1/ at site (indicated by "S" in the Flow Chart) and 2/ remotely via telemedicine from patient's home (indicated by "T" in the Flow Chart). Method of visit conduct (on-site or remote) can be modified. Modifications from an on-site to a remote visit require Sponsor approval.

6. Visit 1 can be conducted within less than 10 weeks of randomization. Before randomization, the Investigator should ensure that all safety laboratory results, ECG reading, imaging and liver biopsy results are available to ensure that the patient meets all inclusion criteria and does not meet any exclusion criteria. In the event of logistical issues with the reporting of results by the central vendor(s) a patient who meets all inclusion criteria and does not meet any exclusion criteria should be considered for participation in the clinical trial even if he/ she exceeds the screening period of 10 weeks. Extension of the screening period requires a Sponsor approval. If more than 12 weeks elapse from Visit 1 safety laboratory tests, ECG and vital signs should be repeated and results should be available before randomization.

7. Patient must be informed and written informed consent must be obtained prior to starting any trial procedure. Fasting is considered part of a trial procedure. For the historical biopsy, if applicable, a written non-trial specific informed consent has been obtained (per local standard).

8. Physical examination after screening is required only if patient reports symptoms.

9. Vital signs measurement should be performed prior to blood sample collection. At dosing visits a second vital signs measurement should be performed approx. 10 minutes post-dose. Vital signs include DBP/ SBP measurement and pulse rate. Vital signs measurement at Visit 1a is optional but recommended.

10. Body mass index will be calculated automatically. For weight measurement, follow guidelines in Section 5.1.4.

11. For waist and hip circumference measurement, follow guidelines in Section 5.1.5.

12. Safety laboratory tests include haematology, clinical chemistry, coagulation, lipids and urinalysis. For details refer to Table 5.2.3:1.
In the event of systemic hypersensitivity ADAs, NAbs, level of BI 456906, IgE, histamine, serum tryptase, and complement components will be analyzed as detailed in the laboratory manual.

13. All blood samples should be collected before the administration of trial medication. Fasting condition is not required for routine trial blood sample collection.

14. RT-PCR test on SARS-CoV-2 will be performed at Visit 1.

15. ECG should be recorded in triplicate at Visit 1. ECG should be recorded before blood samples are taken. ECG recording may be repeated by the Investigator for medical or quality reasons. For ECG measurement, follow guidelines in Section 5.2.4.

16. After the individual patient's end of the trial the Investigator should report only any cancers of new histology and exacerbations of existing cancer, trial treatment related SAEs and trial treatment related AESIs of which the Investigator may become aware of and only via the SAE form.

17. For female patients of childbearing potential only. Xs = serum testing, Xu = urine testing. Serum pregnancy testing will be performed at Visit 1 and thereafter as a reflex test when urine testing is positive. Pregnancy testing must be completed prior to trial medication intake. Refer to Section 6.1.

18. At Visit 16, 20 and 24 the IRT call will only be made if a patient visits the site due to tolerability issues and requires a new assignment of trial medication.

19. During site visits IRT will assign trial medication kits for use until the next scheduled site visit. For example, kits assigned at Visit 14 will include trial medication to be administered at the site for Visit 14 and trial medication needed for the patient for use at home at Visit 15, 16 and 17. However, if a patient experiences tolerability issues with the dose administered at Visit 14 and 15, new trial medication kits will be dispensed to him/ her at Visit 16.

20. Patient and/ or designated person should be trained on how to administer the trial medication. If the patient is not willing to self-administer the injections, he/ she should be given the option to visit the site and/or to have the medication administered by a qualified site personnel or designated person. During site visits the trial medication should be preferably administered by a qualified site personnel.

21. Medication compliance should be monitored throughout the treatment period to ensure the required compliance criteria are met (refer to Section 4.3).

22. Patients will be using a smartphone for trial-related application (Science 37 platform which may include patient diary, [redacted] patient-facing materials). Training will be provided to patients on how to use the application.

23. C-SSRS, Columbia-Suicide Severity Rating Scale questionnaires will be administered at Visit 1 using the “baseline/screening” version. The “since last visit” version will be used at the following visits. Paper forms will be used for the assessment of C-SSRS (refer to Section 5.2.5.1).

[redacted]

25. T2DM patients taking antidiabetic medication will be provided with a self-monitoring blood glucose (SMBG) device for use at home during the treatment period. Patients may also use their own device for self-monitoring of blood glucose.

[redacted]

27. Blood sample collection for biobanking is optional and requires a separate informed consent for biobanking. It consists of plasma, serum and DNA biobanking. Plasma and serum samples should only be collected at the planned visits. If a sample is missed, continue with the sample collection at the next scheduled collection timepoint. Do not make up for missed samples. DNA biobanking requires only one blood sample. If it is not possible to collect the DNA biobanking sample at Visit 2, it may also be collected at a later visit.

28. Stool samples should be collected before the administration of trial medication. Patient should be asked to collect the stool sample at home 1-2 days prior to the visit and bring it to the site at the visit. Stool sample does not have to be refrigerated. Stool sample collection can also occur at the site during the visit. If a sample is missed, continue with the sample collection at the next scheduled collection timepoint. Do not make up for missed samples. Stool sample collection for biobanking is optional and requires a separate informed consent for biobanking.

29. If the liver biopsy is performed as part of screening, it should only be done after Visit 1 results are available and the patient is deemed eligible for the trial. When scheduling a liver biopsy as part of screening procedures sufficient time should be allowed to receive the results before proceeding to Visit 2. The liver biopsy at the end of treatment should be performed during Visit 32 or up to 14 days after the visit. Patients should be fasting overnight before the liver biopsy, if required by local standard.

30. [redacted] MR imaging should be performed on the day of the planned visit or up to 14 days after the visit. The 14 days time window for [redacted] MR imaging is not applicable during the screening period. [redacted] Patients should be fasting for at least 6 hours before [redacted] MR imaging.

TABLE OF CONTENTS

[redacted]

[redacted]

ABBREVIATIONS

A1At	Alpha-1 Antitrypsin
ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AMLN	Amylin Liver NASH
AP	Alkaline Phosphatase
[redacted]	[redacted]
AST	Aspartate Aminotransferase
AUC	Area under the Curve
AV	Atrioventricular
BI	Boehringer Ingelheim
BMI	Body Mass Index
C_{max}	Maximum measured concentration of the analyte in plasma
C_{min}	Minimum measured concentration of the analyte in plasma
CA	Competent Authority
[redacted]	[redacted]
CCS	Canadian Cardiovascular Society
CEC	Clinical Event Committee
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COVID-19	Coronavirus Disease 19
[redacted]	[redacted]
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as eCRF")
CRN	Clinical Research Network
CRO	Contract Research Organisation
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CT Leader	Clinical Trial Leader

CT Manager	Clinical Trial Manager
CTR	Clinical Trial Report
[redacted]	[redacted]
DILI	Drug Induced Liver Injury
DIO	Diet Induced Obesity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
ED	Early Discontinuation
EDTA	Ethylenediaminetetraacetic Acid
[redacted]	[redacted]
EOT	End of Treatment
[redacted]	[redacted]
EudraCT	European Clinical Trials Database
F1, F2…	Fibrosis stage 1, 2…
FAS	Full Analysis Set
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
GCP	Good Clinical Practice
GCGR	Glucagon Receptor
γ-GT	Gamma-Glutamyl Transferase
GI	Gastrointestinal
GLP-1R	Glucagon-like-peptide 1 Receptor
GMP	Good Manufacturing Practice
HA	Health Authority
HbA_{1c}	Glycosylated Haemoglobin
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus

HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IgE	Immunoglobulin E
IPD	Important Protocol Deviation
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
iSTAT	Independent Statistician
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IV	Intravenous
LDL	Low-Density Lipoprotein
LPLT	Last Patient Last Treatment
MAR	Missing at Random
MCPMod	Multiple Comparison Procedures and Modelling Techniques
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed Model For Repeated Measurements
MRD	Multiple Rising Dose
MRI	Magnetic Resonance Imaging
NAb	Neutralizing Antibody
NAFLD	Non-alcoholic Fatty Liver Disease
NAS	NAFLD Activity Score
NASH	Non-Alcoholic Steatohepatitis
NOAEL	No Observed Adverse Effect Limit
NYHA	New York Heart Association
OPU	Operative Unit
PD	Pharmacodynamics

PDFF	Proton Density Fat Fraction
PFS	Pre-filled syringe
PG	Pharmacogenomics
[redacted]	[redacted]
PK	Pharmacokinetics
[redacted]	[redacted]
PPS	Per Protocol Set
[redacted]	[redacted]
[redacted]	[redacted]
q.d.	Quaque die (once a day)
q2d	Every other day
QT	Time between start of the Q-wave and end of the T-wave in electrocardiogram
QTcF	QT interval corrected for heart rate using the method of Fridericia
RA	Regulatory Authority
REP	Residual Effect Period
RPM	Report Planning Meeting
RT-PCR	Reverse Transcription Polymerase Chain Reaction
s.c.	Subcutaneous
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SCD	Skin to Liver Capsule Distance
SGLT-2	Sodium-Glucose Co-Transporter 2
SMBG	Self-Monitoring of Blood Glucose
SOC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
T2DM	Type 2 Diabetes Mellitus
[redacted]	[redacted]
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Level of Normal
VCTE	Vibration Controlled Transient Elastography

VLDL	Very-Low-Density Lipoprotein
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

BI 456906 is being developed in two indications, namely NASH and obesity. The target indications read as follows:

1) Non-alcoholic steatohepatitis (NASH) in NASH patients (NAFLD activity score (NAS) ≥ 4, with at least one point in ballooning and inflammation each) with advanced liver fibrosis (fibrosis stages 2 and 3). A relevant subpopulation has to be defined.
2) Weight management in patients with obesity or overweight with co-morbidities, plus cardiovascular risk reduction in patients with increased cardiovascular risk.

These diseases are highly prevalent and are increasing at an alarming rate. Non-alcoholic fatty liver disease (NAFLD), the hepatic component of the metabolic syndrome, is the most common chronic liver disease. Currently, no approved pharmacotherapy for NASH, the progressive form of NAFLD, is available, relying on treatment of the comorbidities of the metabolic syndrome. Obesity is associated with a variety of medical conditions, including all components of the metabolic syndrome, cardiovascular, pulmonary, gastrointestinal, endocrine, joint and psychosocial disorders. Currently, the available weight loss medications lack sufficient efficacy, safety, tolerability, and convenience to reduce body weight and improve its associated co-morbidities/ conditions.

1.1 MEDICAL BACKGROUND

It is estimated that about 1/3 of the population (in US, EU5, Japan and urban China) have NAFLD, and about 17 Mio. (2-5%) have NASH with advanced fibrosis (F2 and F3). It is also estimated that this number will double (approx. 36 Mio) within the next 15 years [R20-1255].

Approximately 1-2% of patients with NASH and advanced fibrosis (F2 and F3) are at risk to develop cirrhosis, with its complications including decompensation, need for transplantation, HCC and liver–related death.

In addition to these late complications, patients with NASH have little to no liver-related symptoms, however, more and more data suggest that the quality of life in patients with NASH is reduced. These new data have led to a shift in the paradigm from characterizing patients with NASH as asymptomatic to exhibiting non-specific symptoms. Most common symptoms are fatigue, abdominal discomfort, and pain. The reduction in quality of life experienced by NASH patients is also probably associated with the comorbidities such as obesity, type 2 diabetes and others. In addition, some studies suggest that NASH itself is a risk factor for cardiovascular complications.

1.2 DRUG PROFILE

Mode of action
BI 456906 is a dual agonist of Glucagon-like-Peptide 1 (GLP-1) and Glucagon (GCG) receptors. GLP-1R agonists lower body weight by the inhibition of food intake and also by delaying gastric emptying and intestinal transit. GCGR agonist is expected to reduce body

weight by increasing energy expenditure and might directly increase the fatty acid oxidation in the liver, potentially reducing the lipotoxicity.

BI 456906 leads to full activation of the GLP-1R at the predicted therapeutic exposure, but only to a partial activation of the GCGR, which seems sufficient to achieve more efficacy compared to GLP-1R activation alone. Simultaneous dual activation of GLP-1R and GCGR by BI 456906 is anticipated to improve glycemic control, body weight loss as well as NASH and fibrosis.

Key pharmacokinetic characteristics

Pharmacokinetics of BI 456906 were investigated after single subcutaneous doses of 0.3, 0.5 and 1.2 mg. T_{max} was reached between 9 and 60 hours. C_{max} was 7, 13 and 34 nM, respectively. $T_{1/2}$ ranged from 10 to 15h. Dose proportionality was demonstrated for C_{max}, AUC0-168, and AUC0-∞. Further details, also on multiple dosing, can be found in the Investigator's Brochure (IB).

Drug interactions

GLP-1R agonism reduces gastric emptying. This was assessed by measuring the effect of BI 456906 on the absorption of paracetamol. Paracetamol C_{max}, AUC0-10, and AUC0-∞ were slightly lower after a single dose of 0.3 mg BI 456906, and strongly decreased after a single dose of 1.2 mg BI 456906 compared with administration of paracetamol alone.

Residual Effect Period

The Residual Effect Period (REP) of BI 456906 is 28 days. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

Data from non-clinical studies

Liver steatosis improvement was more pronounced by BI 456906 than with liraglutide. In a 4-week study in Diet Induced Obesity (DIO) mice, BI 456906 at a subcutaneous dose of 10 nmol/kg q.d. (C_{min} 109 nM) reduced liver triglycerides by 31% (from 203 mg/g in vehicle-treated animals to 140 mg/g) and Alanine Aminotransferase (ALT) in plasma by 62% (from 403 U/l in vehicle-treated animals to 154 U/l). These effects were superior to those of liraglutide (176 mg/g; 215 U/l) at supra-therapeutic exposure (10 nmol/kg bid; C_{min} 39 nM). Overall, the effects on plasma lipids of BI 456906 at predicted therapeutic exposure were comparable to liraglutide at supra-therapeutic exposure (n00254747-01). In C57Bl/6J mice on Amylin Liver NASH diet ([AMLN], a high fat, high fructose, high cholesterol diet) as a DIO NASH model, BI 456906 at 20, 30 and 40 nmol/kg q.d. was compared with liraglutide at 100 nmol/kg q.d. and dulaglutide at 2 nmol/kg q2d. After 8 weeks of treatment, body weight vs. vehicle-treated animals on AMLN diet was reduced by 10% and 13% with dulaglutide and liraglutide, and dose-dependently by 15-21% with BI 456906. C_{min} exposure was 160 nM, 234 nM, 321 nM and 322 nM, respectively, for low, medium and high dose BI 456906 and liraglutide. ALT and Aspartate Aminotransferase (AST) in plasma were significantly reduced by all treatments. Liver triglycerides were dose-dependently reduced by 51-66% with BI 456906 compared to liraglutide (-33%) and dulaglutide (-10%, not significant). Thus, the effect of BI 456906 on body weight and liver triglyceride content was superior to liraglutide/dulaglutide. Histological analysis of the liver for the lowest dose of BI 456906 showed an improvement of the steatosis score in all animals vs. the pre-treatment value (6/13 animals improved by one unit, 7/13 animals improved by two units). The effects for the medium and high dose of BI 456906 were comparable to the low dose but with a higher share

of animals in improving their steatosis score by two units. BI 456906 had a better effect on improvement of liver steatosis score than liraglutide or dulaglutide. All treatments prevented worsening of the liver inflammation score between pre-treatment and post-treatment analysis. Inflammation score was comparably improved by one unit in some animals. Overall, BI 456906, liraglutide and dulaglutide showed comparable effects on liver inflammation (n00267699-01).

BI 456906 was well tolerated in safety pharmacology studies and the effects observed mainly reflected the intended pharmacological activity of the compound. There were no toxicologically meaningful cardiovascular effects in cynomolgus monkey. BI 456906 is considered to have a low pro-arrhythmic potential (c14085752).

Data from clinical studies

GLP-1R agonists are known to be associated with gastrointestinal (GI) and cardiac side effects. Multiple studies and clinical experience from GLP-1R agonists suggest that GI side effects including nausea, vomiting and diarrhea, appear to be dose dependent. Moreover, dose escalation has been shown to significantly improve tolerability in clinical practice for a number of these compounds. For example, the proportion of patients reporting nausea was 20% lower for semaglutide with dose escalation than without dose escalation [R17-4311].

Cardiac conduction disorders were described for GLP-1R agonists in clinical trials and in the prescribing information for Saxenda [R19-1407], reported as first-degree atrioventricular block, right bundle branch block, or left bundle branch block as well as QT-prolongation.

BI 456906 has been studied in healthy volunteers in a single rising dose trial (c15175923-02). Similar to other GLP-1R agonists, nausea and vomiting were seen with increasing doses up to 1.2 mg and the trial was discontinued early due to severe nausea and vomiting in a number of healthy volunteers. Currently, BI 456906 is being studied in a multiple rising dose trial (c21168858-05) with dose escalation to investigate the safety and tolerability of different dose escalation schemes in otherwise healthy patients with obesity/overweight to determine a dose escalation scheme that minimizes gastrointestinal adverse events (AEs).

Preliminary data out of the multiple rising dose (MRD) trial (c21168858-05) trial where BI 456906 was administered for 6 weeks in 4 different titration schemas (one once-daily dose group and three once-weekly dose groups, all with weekly dose escalation) showed the frequent AEs were gastrointestinal disorders. Specifically, symptoms included nausea in up to 70% of patients on BI 456906 vs 23% on placebo, dyspepsia in up to 39% vs. 8% in placebo, and abdominal distention in up to 37% vs. 8% in placebo, all of mild to moderate intensity. Among other frequently reported AEs in the metabolism and nutrition disorders class were decreased appetite in up to 67% vs 39% in placebo, and early satiety in up to 46% vs 15% on placebo. Mild fatigue was reported in 8% of patients on BI 456906 and 15% of patients on placebo while moderate fatigue was reported only on BI 456906 in only 6% of patients. Cardiac disorders were only reported in the BI 456906 treated group with 9% AV block first degree, 9% AV block second degree, 8% sinus tachycardia and 6% ventricular extrasystoles (c28750666).

Most of the reported AEs were mild or moderate in intensity. Severe AEs diarrhea (2) and vomiting (1) were reported for 3 out of 67 patients treated with BI 456906. No deaths, serious

adverse events (SAEs), protocol-specified adverse event of special interest (AESI), or other significant AEs were reported in this trial to date (c28750666).

For a more detailed description of the profile, please refer to the current Investigator's Brochure for BI 456906.

1.3 RATIONALE FOR PERFORMING THE TRIAL

BI 456906 is a dual GLP-1R and GCGR agonist being evaluated in the indications of glycemic control in patients with Type 2 Diabetes Mellitus (T2DM), chronic weight management in patients with obesity/overweight and treatment of patients with NASH and fibrosis.

This trial is a 48-week phase II trial to examine three dose levels of BI 456906 administered once weekly compared to placebo in patients with NASH and fibrosis.

It is designed to evaluate safety, tolerability, [redacted] of BI 456906 in male and female patients with NASH and fibrosis using multiple escalation schemes and doses and will function as dose-finding trial for phase III clinical development of BI 456906 in patients with NASH and fibrosis.

There is still no treatment approved for patients with NASH and fibrosis, leaving a huge unmet medical need to develop treatments. This dose-finding trial is important to assess the most suitable dose to be brought forward in the pivotal phase III/IV trial, in which the histological improvement as well as long-term outcomes will be evaluated. It also functions as confirmatory trial to the planned pivotal trial for approval.

Multiple clinical trials indicate that GLP-1 receptor agonists improve NASH and weight, however, there is no data available for a dual agonist with agonism on GLP-1 and GCG receptors for patients with NASH and fibrosis. It is anticipated that patients participating in this trial, if on active treatment, will have benefit in their weight management, metabolic status as well as NASH. GLP-1R agonism achieves glucose lowering by inducing glucose-dependent insulin-secretion at the pancreatic β-cell. In addition, GLP-1R activation lowers body weight by inducing inhibition of food intake at the hypothalamic appetite regulation centers and also by inducing delay of gastric emptying and intestinal transit. In addition, GCGR agonism reduces body weight by increasing energy expenditure and is supposed to increase fatty acid oxidation in the liver, and subsequently reducing lipotoxicity. In patients with NASH and fibrosis, dual agonism at the GLP-1R and GCGR is expected to result in improvements in glycemic control, reduction of body weight and improvement of NASH and fibrosis, thereby targeting not only NASH, but also the underlying metabolic syndrome.

Patients with NASH and any pre-cirrhotic stage of fibrosis (F1 to F3) will be included in this trial. The targeted patient population for the compound however is patients with NASH and advanced fibrosis. This patient population will be investigated in phase III, especially in regards of long-term outcome events as histological progression to cirrhosis, liver transplantation, all-cause mortality. However, as no significant number of events are anticipated in this trial due to the treatment duration of 48 weeks and the sample size of about 240, the primary outcome of this trial is improvement of NASH, which is anticipated to be

related to these long-term outcome events. This can be also seen in patients with earlier disease stage (F1), therefore, these patients are also allowed to participate in this trial.

This trial investigates adult patients of both genders, pediatric development will be initiated at a later timepoint with supportive data from the adult trials.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.6). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g., to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

In the proposed patient population with NASH and fibrosis, improvements in NASH and fibrosis, as well as body weight and metabolic status, are anticipated. The expected benefit for the selected patient population is improvement of NASH with no worsening of fibrosis, as well as exploratory resolution of NASH and improvement of fibrosis. Body weight and metabolic status are also anticipated to be improved in patients with NASH and fibrosis, therefore, improving the overall health of the patients.

This trial functions as a dose-finding trial for phase III and beyond, therefore, more than one dose is being tested. To achieve a proper dose finding, at least 3 doses should be compared. Also, as currently no gold standard, besides any approved therapy is available, placebo is chosen as comparator.

Patients on placebo will receive standard of care (SOC), which is currently stable diet and exercise (lifestyle) regimen and will be guided by their physicians as per local standard. Also, these patients will be assessed and monitored extensively, which has been shown in addition to SOC to already have a substantial effect on NASH and fibrosis in clinical trials.

Patients receiving 2.4 mg/ week as maintenance dose are anticipated to have benefit on their metabolic status, as this dose is most likely equivalent to the doses of the available GLP-1R agonists for T2DM, as well as on their weight. The effect on NASH however is anticipated to be not statistically significant compared to placebo.

Patients in the higher dose groups (4.8 mg/ week and 6.0 mg/ week) are anticipated to have a substantial benefit regarding their metabolic status, weight and NASH and fibrosis.

1.4.2 Risks

There is no identified risk for BI 456906, based on the toxicology programme or any clinical trials conducted for this product to date. There are three important potential risks based on other GLP-1 receptor agonists currently approved, providing information on identified and

potential risks in molecules of this class. The three important potential risks include medullary thyroid cancer (C-cell carcinogenicity), pancreatic cancer, and acute pancreatitis.

NASH diagnosis and assessment of treatment response is based on liver biopsies. Liver biopsy is an invasive procedure and represents certain risks for patients such as bleeding, pain or organ perforation. To minimize those risks sites will be expected to follow local standard processes considering the suitability of a patient for the procedure, and whilst conducting the procedure. In this trial the initial biopsy will be performed only after all other eligibility parameters have been confrmed for a patient. Furthermore, use of historical biopsy will be permitted, if sufficient and analysable material is available from that biopsy and if it was performed within 6 months of randomization.

Patients will undergo magnetic resonance imaging (MRI) examinations. While exposure to a high magnet field does not pose additional risks to patients, contraindications to MRI exist; patients with these contraindications will be excluded from the trial (refer to Section 3.3.3).

The risks for patients caused by the trial procedures and the risks related to the exposure to the trial medication are reasonably low and do not outweigh the potential benefits. The expected side effects are known to be temporary, dose dependent, easy to monitor and manageable in clinical trials.

Among the expected and well-known side effects for GLP-1R agonist-based therapies are:

- Gastrointestinal disorders, as delayed gastric emptying, nausea and vomiting, as well as diarrhea or obstipation. Also, pancreatitis (acute and acute-on-chronic) is known to occur under treatment with GLP-1R agonists.
- Metabolism and nutrition disorders, as low blood glucose in patients with diabetes, delayed absorption of nutrition or medications
- Cardiac disorders, as cardiac conduct disorder (e.g., AV-block, prolonged QTc time)
- C-cell tumors of the thyroid, black box warning in established GLP-1R agonist, due to findings in rodents and of unknown risk to humans
- Administration site conditions, as rash, itching, infection
- Anti-drug antibodies (ADA) and neutralizing antibodies (NAb), peptides as BI 456906 are able to induce antibody development

These side effects, which are known to be dose dependent, can be reduced by careful dose escalation, are easy to monitor, and, therefore, are manageable in clinical trials. In addition, tolerability and safety data is very important in this drug class and plays an essential role in the optimal dose finding. It is also well known that the gastrointestinal disorders are temporary, and most patients adapt to GLP-1R agonist-based compounds during dose escalation and/ or maintenance period.

In this trial the following safety measures will be applied in order to minimize the risk for trial patients:

- An extensive safety laboratory testing will be performed at all site visits.
- Patients with T2DM taking antidiabetic medication will be recommended to measure their fasted blood glucose at home daily and to contact the Investigator for safety related measures.

- If patients develop persistent or recurrent severe hypoglycemic episodes (fasted blood glucose level of 54 mg/dL (3.0 mmol/L) or below) they will be asked to reduce the dose of or discontinue any concomitant antidiabetic medication. Antidiabetic medications are allowed to be interrupted under certain clinical circumstances in order to avoid hypoglycemia. Investigators may decide to keep patients solely on trial treatment if there is evidence of glycemic normalization, which is a well-known effect of glucagon receptor agonists. Hypoglycemic episodes as well as their relationship to the trial treatment will be strictly monitored by investigators and appropriately reported. In patients experiencing hypoglycemia, characteristics of episodes, including frequency and severity, will determine whether hypoglycemia needs to be classified as treatment-related adverse events.
- Patients in the placebo group will remain on standard of care that includes diet and exercise counseling as per local standard, and thorough surveillance.
- There are no risks expected by stopping the trial medication during the course of the trial and no down titration is needed.
- Electrocardiogram (ECG) monitoring will be performed at screening, randomization and at all site visits during the trial, and criteria for heart rate, QT prolongation and cardiac conduction disorders are defined.
- To minimize the risk of development of C-cell tumors in patients, patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, manifest hypo- or hyperthyroidism at screening visit will not be enrolled.
- Dose escalation will happen in small increments (0.3 mg/ dose escalation step at the beginning, 0.6mg/ dose escalation step at higher doses) and at a slow pace (every two weeks) to improve the tolerability and safety of the patients.
- Patients will be on-site or have a virtual visit to choose the correct pre-filled syringes (PFS) to minimize the risk of wrong dosing.
- The patients will be thoroughly trained on handling and administration of the doses via the PFS within the first 4 weeks of the treatment period. The patient can come to the site, if he/she feels uncomfortable self-administrating.
- Patients who do not tolerate the assigned maintenance dose are allowed to reduce the maintenance dose to the next lower dose after Visit 14 (during dose escalation until Visit 14, no dose reduction is allowed. If the patients do not tolerate the dose escalation until Visit 14, they will be discontinued from the trial).
- During the trial, patients will be under medical observation and thoroughly monitored for both expected and unexpected AEs.
- Consistent with the FDA draft guidance intitled “Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials”, prospective assessment of suicidal ideation and behaviour is included in this trial using the C-SSRS.
- ADA and NAb are assessed throughout the trial and analysed for safety and effect on efficacy.
- Pediatric patients are excluded from the trial.
- 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 including the 4-week follow-up period are excluded from the trial (Section 4.2.2.3).

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety. Section 10.1 provides guidance for the investigators on how to evaluate and treat patients with suspected DILI.

Based on the pharmacological mechanism of BI 456906, the review of the non-clinical and clinical data available so far for this compound and considering the clinical and post-marketing data derived from the GLP-1 receptor agonists available on the market, there is no indication that BI 456906 could increase the risk of severe viral infections such as COVID-19 infection. There are no restrictions for trial participants to receive vaccination for COVID-19 during or after treatment period.

1.4.3 Discussion

BI 456906 was well tolerated in safety pharmacology and toxicology studies and the main effects seen reflected the intended pharmacology of the compound. Single s.c. doses of 0.3 mg and 0.5 mg, but not 1.2 mg of BI 456906 was well tolerated in a single rising dose trial. In a multiple rising dose trial with weekly dose escalation up to 4.8 mg once a week, BI 456906 did not reveal relevant safety signals although drug-related gastrointestinal and cardiac side effects were reported. All side effects were expected in nature such as nausea, dyspepsia, decreased appetite, heart rate increase and conduction disorders and are in line with other GLP-1R agonist-based therapies. Most of the reported AEs were mild or moderate in intensity. Severe AEs diarrhea (2) and vomiting (1) were reported for 3 out of 67 patients treated with BI 456906. No deaths, SAEs, protocol-specified AESIs, or other significant AEs were reported in this trial to date.

The above-mentioned risks will be closely monitored, and it is anticipated, that the benefit will outweigh the risks, especially as the GI tolerability issues are temporary and most patients adapt to the medication.

The expected benefit for the selected patient population is improvement in NASH and improvement of fibrosis, improved metabolic status and body weight loss.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

This trial will characterize the dose response curve for BI 456906 in patients with NASH (NAS ≥ 4, fibrosis F1-F3) by assessing three doses and placebo. The response is the proportion of patients with improvement from baseline in liver histological findings after 48 weeks (as defined in Section 2.1.2).

The main trial objectives are to demonstrate a non-flat dose response curve, to evaluate the size of the treatment effect (using the absolute difference in proportions of patients with histological improvement between BI 456906 and placebo at Week 48), and to characterize the dose-response relationship.

2.1.2 Primary endpoint(s)

The primary endpoint is the improvement (yes/ no) from baseline in liver histological findings based on liver biopsy after 48 weeks of treatment in patients with NASH (NAS ≥ 4, fibrosis F1-F3). NAFLD activity score (NAS) represents the sum of scores for steatosis (0-3), lobular inflammation (0-3) and ballooning (0-2), refer to Table 5.1.1: 1 for NAS and fibrosis stage.

Improvement in histological findings is defined as a composite of:

Improvement in NASH:

Decrease of at least 2 points in NAS with at least 1 point decrease in NAS sub-score of either lobular inflammation or ballooning

AND

No worsening of fibrosis, defined as absence of any increase in the fibrosis stage.

A patient who has improvement in histological findings after 48 weeks of treatment will be defined as a responder. A patient with the intercurrent event of early discontinuation of the treatment for any reason will be defined as a non-responder unless biopsy results are available, in which case they will be used to determine responder status.

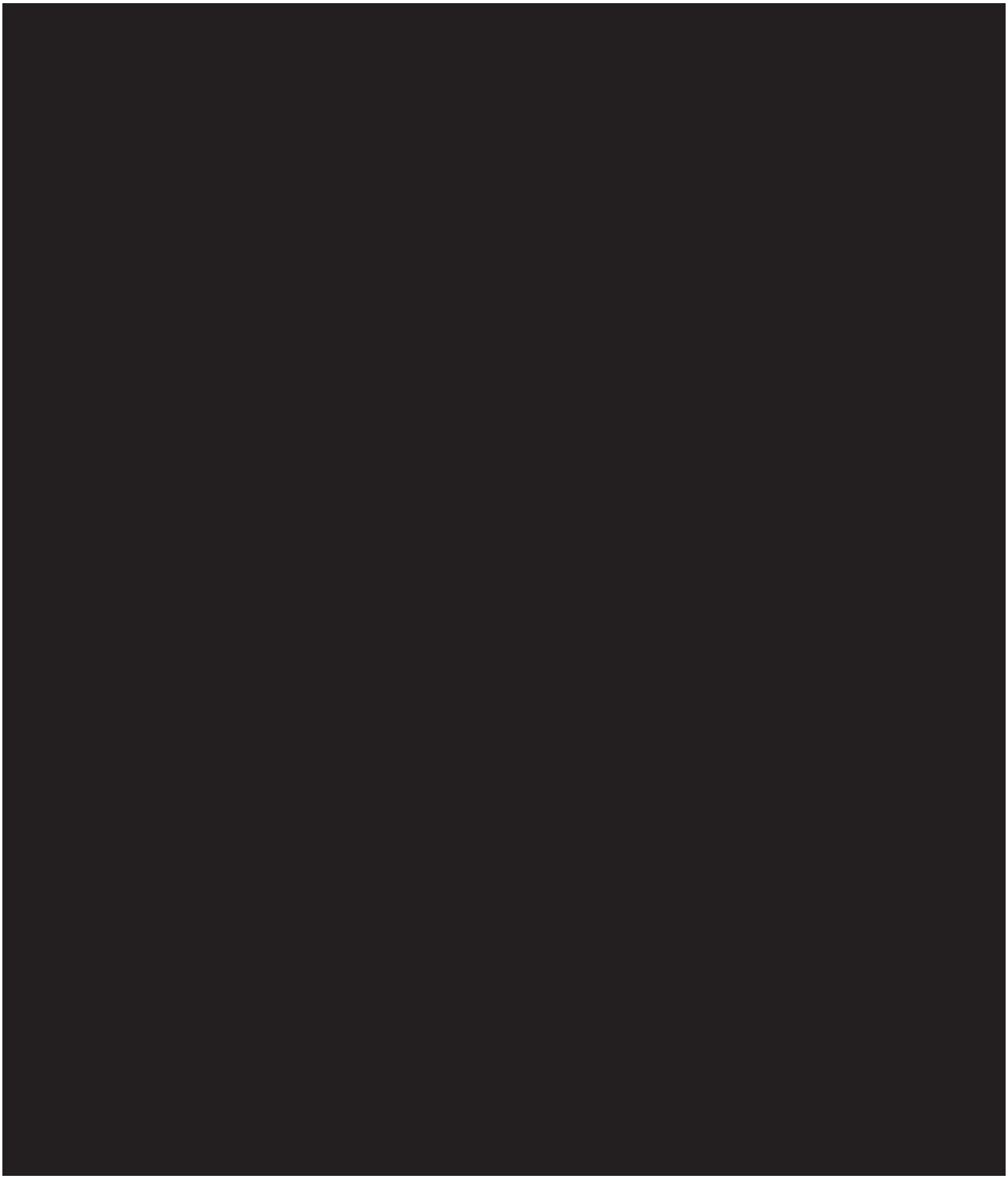
2.1.3 Secondary endpoint(s)

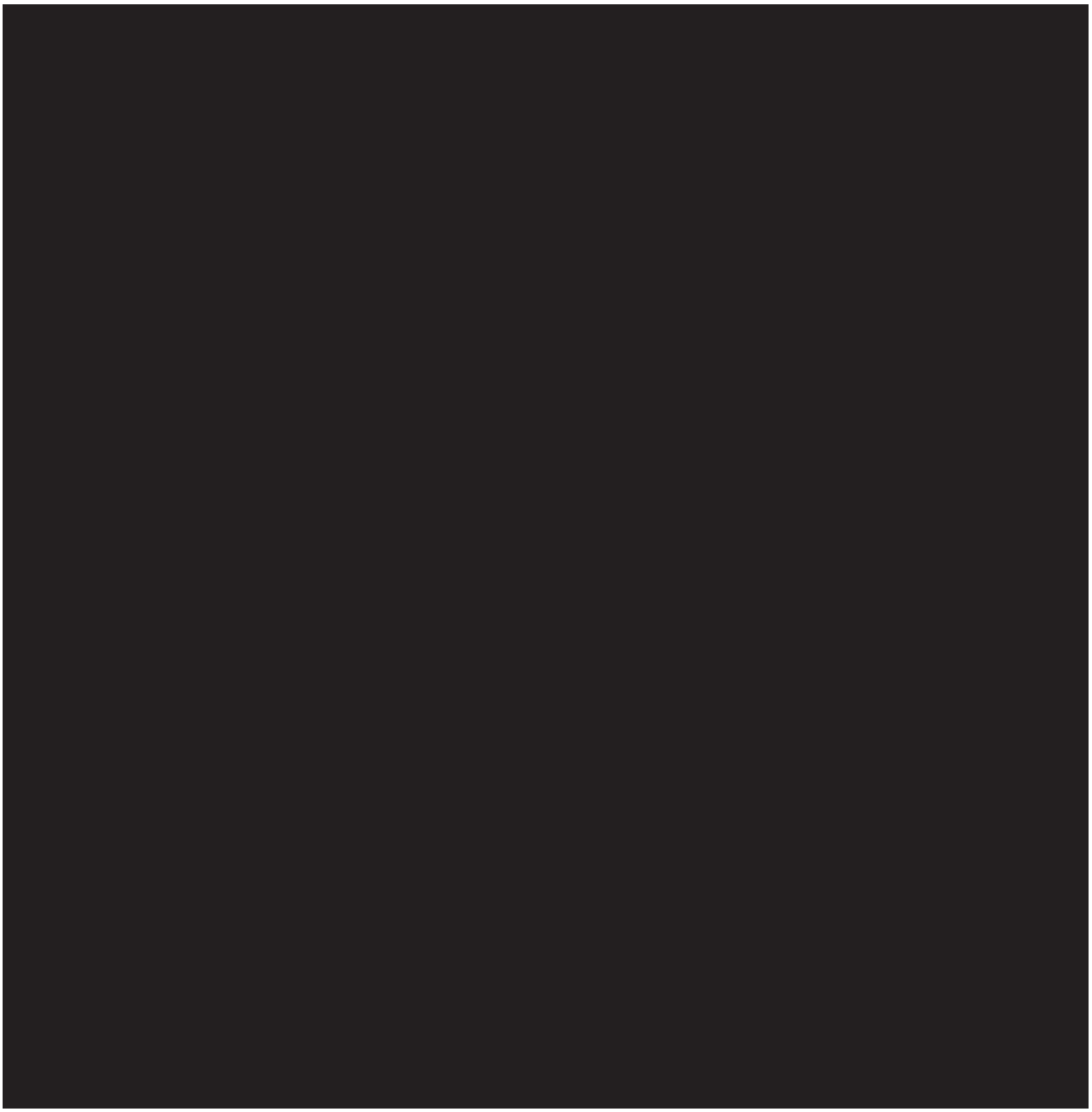
Secondary efficacy endpoints include:

- Improvement of liver fat content (yes/ no) defined as at least 30% relative reduction in liver fat content after 48 weeks of treatment compared to baseline assessed by magnetic resonance imaging proton density fat fraction measurement (MRI-PDFF)
- Absolute and relative change of liver fat content from baseline after 48 weeks of treatment assessed by MRI-PDFF

- Improvement of fibrosis (yes/ no) defined as at least one stage decrease in fibrosis stage after 48 weeks of treatment assessed by liver biopsy
- Absolute change from baseline in NAS after 48 weeks of treatment assessed by liver biopsy

For the responder secondary endpoints, patients who meet the criteria of the endpoint definition are responders. The handling of intercurrent events for these responder secondary endpoints is similar to the primary endpoint.

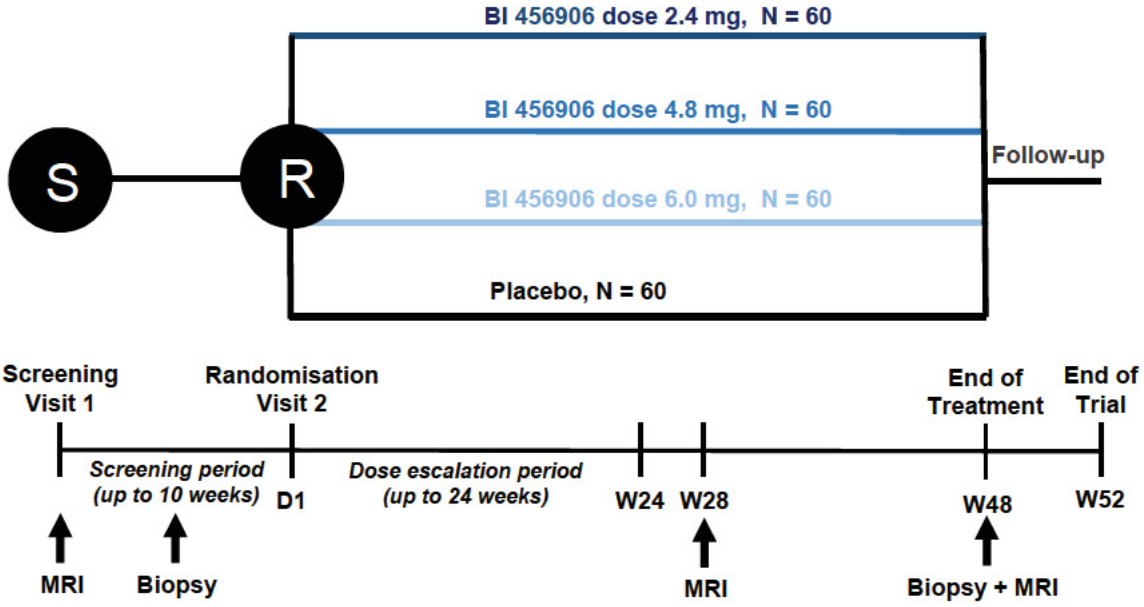




3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

Figure 3.1:1 Trial design



This is a 48-week, multi-center, randomised, dose-ranging, double blind, placebo-controlled, parallel-group trial in patients with NASH. Main parameters for inclusion of patients and for evaluation of treatment response are based on the histological evaluation from the liver biopsy and noninvasive imaging modalities. Patients who meet the eligibility criteria following a screening visit (Visit 1) will have a second screening visit (Visit 1a) for liver biopsy, if no sufficient material from a historical biopsy within the last 6 months prior to randomization is available. If they are found to be eligible based on the liver biopsy results, they will be randomised to one of the four treatment groups (placebo, BI 456906 dose 2.4 mg, BI 456906 dose 4.8 mg or BI 456906 dose 6.0 mg). Treatment duration is 48 weeks consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period. Another liver biopsy will be performed at the end of the treatment for efficacy evaluation. All liver biopsies will be centrally assessed. After the end of treatment, patients will complete a follow-up period of 4 weeks.

Dose escalation schemes are described in Section 4.1.4.

The consecutive screening approach allows to limit the number of liver biopsies at screening, i.e., ineligible patients will be screen-failed before undergoing a biopsy.

MR imaging will be performed at screening, after 28 weeks of treatment and at the end of the treatment and will be assessed centrally.

One interim analysis will be performed during the trial. Please refer to Section 7.2.7.

The end of the trial is defined as "last patient out", i.e., the last Follow-up visit (Visit 33) completed by the last patient in the trial.

The trial will apply a hybrid trial management approach that will employ telemedicine technology for interactions between the Investigator/ trial personnel and patients. The method of telemedicine allows for practice of medicine using technology to deliver care remotely at a distance. For further details refer to Section 6.1.

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

A randomised, double blind, placebo-controlled design was chosen for this trial as an accepted standard trial design for a phase II trial.

The treatment duration of 48 weeks was chosen as sufficient to potentially show changes in liver pathology.

A placebo control was chosen to be included in order to evaluate the absolute effects of BI 456906 on safety and efficacy and to better characterize the nature of the dose response relationship. This is acceptable as no standard treatment for NASH and/or fibrosis is available and in accordance with the guidelines provided by regulatory authorities.

The hybrid trial management approach was chosen in order to make the trial participation more convenient for patients by reducing travel burden and time spent at the site. Furthermore, as some trial procedures will be performed at patient's home, the site burden will also be reduced. Approximately 60% of the visits is expected to occur at the site. The remaining visits should be conducted remotely at patient's home, the patient will interact with the Investigator and/or site personnel via a video conferencing feature. For the method of visit conduct (on-site or remote) please refer to the Flow Chart. Modifications from on-site to remote visits require Sponsor approval.

Data Monitoring Committee
A Data Monitoring Committee (DMC), independent from the Sponsor, will be established to review the safety unblinded data at regular intervals, and to recommend to the Sponsor whether to continue, modify, or stop the trial. An unplanned DMC meeting may be called if there is an emergency concern on the safety of the patients (Section 3.3.4.1). The tasks and responsibilities of the DMC members will be detailed in the DMC charter. Please refer to Section 8.7.

Clinical Event Committee
The trial will be set-up with prospective adjudication of all cardiovascular, pancreatic, thyroid and oncological trigger events as described in Section 5.2.6.1.5. The prospectively defined adjudication process will assess cardiovascular, pancreatic, thyroid and oncological events through an independent, blinded, external Clinical Event Committee (CEC). Details on the composition of the committee, its procedures and interactions will be provided in a separate CEC charter. Adjudication was implemented in the trial in accordance with the FDA draft

guidance for industry and in order to support future discussions with compentent authorities related to patient safety.

3.3 SELECTION OF TRIAL POPULATION

240 patients with biopsy proven NASH and fibrosis will be randomised to one of the four treatment groups in a 1:1:1:1 ratio. Approximately 180 sites in multiple countries are planned to participate in the trial.

It is anticipated that approximately two patients will be randomised at each site. If enrolment is delayed additional sites may be recruited. Permission to randomise more than 20 patients per site must be obtained from the Sponsor. This will only be allowed after a careful review of the enrolment status.

Recruitment of patients for this trial will be competitive, i.e., screening for the trial will stop at all sites at the same time once a sufficient number of patients has been randomised. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

Re-testing during the screening period and re-screening, if a patient is not eligible initially, is each allowed once.

If a patient is randomised in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the Sponsor should be contacted immediately.

Patients who discontinue following randomization will not be replaced and may not be re-enrolled at a later date.

To ensure sufficient enrolment of patients with advanced fibrosis, recruitment of patients with fibrosis stage F1 will be capped at 30% of randomized patients.

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

3.3.1 Main diagnosis for trial entry

The trial will include patients with NASH with NAS $\geq$ 4 (with at least 1 point in ballooning and inflammation each) and fibrosis stage F1-F3, as confirmed by liver biopsy conducted during the screening period or from a historical biopsy conducted within the last 6 months prior to randomization.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

1. Male or female patients ≥ 18 years (or who are of legal age in countries where that is greater than 18 years) and ≤ 80 years of age at time of consent.
2. Diagnosis of NASH (NAS ≥ 4, with at least 1 point in inflammation and ballooning each) and fibrosis stage F1–F3 proven by a biopsy conducted during the screening period or by a historical biopsy conducted within the last 6 months prior to randomization and stable body weight defined as less than 5% self-reported change in body weight between the historical biopsy and randomization, if a historical biopsy is used.
3. Liver fat fraction ≥ 8% measured by MRI-PDFF and liver stiffness > 6.0 kPa measured by FibroScan® at Visit 1 (if biopsy is scheduled during the screening period MRI-PDFF and FibroScan® assessments have to be performed prior to the biopsy). However, the diagnosis of NASH and fibrosis at liver biopsy (including historical biopsy) is the primary assessment to establish patient eligibility.
4. Patients willing and able to undergo liver biopsies per protocol as judged by the Investigator.
5. BMI ≥ 25 kg/m^2 and a body weight ≥ 70 kg at Visit 1.
6. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
7. Women of childbearing potential (WOCBP)[1] must be willing and able to use two forms of effective contraception where at least one form is 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 patient information.

3.3.3 Exclusion criteria

1. Current or history of significant alcohol consumption (defined as intake of > 210 g/ week in males and > 140 g/ week in females on average over a consecutive period of more than 3 months) or inability to reliably quantify alcohol consumption based on Investigator judgement within the last 5 years.
2. Intake of medications historically associated with liver injury, hepatic steatosis or steatohepatitis within 12 weeks prior to Visit 1. Intake of restricted medications or any medications considered likely to interfere with the safe conduct of the trial; please refer to Section 4.2.2.
3. History of other forms of chronic liver disease (e.g., viral hepatitis, autoimmune liver disease, primary biliary sclerosis, primary sclerosing cholangitis, Wilson's disease,

[1]A woman is considered of childbearing potential (WOCBP), i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Please note that tubal ligation is NOT accepted as a method of permanent sterilisation and therefore a woman who underwent tubal ligation is still considered as WOCBP. However tubal ligation is considered as a method of highly effective birth control.

hemochromatosis, A1At deficiency, history of liver transplantation). Hepatitis B and C testing will be done at Visit 1. Patients with positive HBsAg should be excluded. Patients treated for hepatitis C must have a negative RNA test at screening and also be HCV RNA negative for at least 3 years prior to screening in order to be eligible for the trial.

4. Suspicion, diagnosis, or history of hepatocellular carcinoma (HCC), or any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix.
5. Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, manifest hypo- or hyperthyroidism at Visit 1.
6. History of chronic or acute pancreatitis or elevation of serum lipase/amylase > 2x ULN or fasting serum triglyceride levels of > 500 mg/dL (> 5.65 mmol/L) at screening.
7. Known history of HIV (Human Immunodeficiency Virus) infection and/or tuberculosis and/or an acute COVID-19 infection at Visit 1 (confirmed by SARS CoV-2 RT-PCR test, see Section 5.2.3).
8. Abnormal laboratory values at Visit 1 as listed below:
   a) Estimated Glomerular Filtration Rate (eGFR) < 45 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] formula);
   b) Platelet count < 150.000/µL (< 150x10^9/L);
   c) Bilirubin level > 1.5x ULN (except for known Gilbert's syndrome with a conjugated bilirubin of < 0.3 mg/dL (< 5.13 µmol/L);
   d) ALT and/or AST > 5x ULN;
   e) Glycosylated haemoglobin (HbA1c) ≥ 9.5%;
   f) Calcitonin ≥ 20pg/mL (≥ 5.84 pmol/L).
9. Diagnosis of a serious or unstable disease including hepatic (other than NASH), renal, gastroenterologic, respiratory, cardiovascular (including ischemic heart disease), endocrinologic, neurologic, psychiatric, immunologic, or hematologic disease and other conditions that, in the clinical judgment of the Investigator, are likely to interfere with the analyses of safety and efficacy in this trial. Patients with a history of organ transplantation except for corneal transplantation and patients with an expected life expectancy of less than 2 years are also excluded.
10. Any suicidal behavior or history of major depressive disorder requiring inpatient treatment or escalation of care in the past 2 years before randomization, any suicidal ideation of type 4 or 5 in the C-SSRS in the past 3 months prior to Visit 1.
11. Bariatric surgery, prior to or planned during trial conduct; except gastric-band surgery more than 2 years prior to screening (including adjustments) with a stable body weight within the last 12 months. Any other major surgery (major according to Investigator's assessment) performed within 12 weeks prior to randomization or planned during trial conduct.

12. Resting heart rate > 100 beats per minute (bpm) and/or blood pressure ≥ 160/ 95 mmHg at Visit 1. Blood pressure measurement should be repeated 10 minutes apart. Patient should be excluded only if the second measurement confirms a blood pressure ≥ 160/ 95 mmHg.
13. A marked prolongation of QT/ QTc (Fridericia) interval that is greater than 450 ms at Visit 1 or any other abnormal clinically significant ECG finding at Visit 1 (e.g., type 2 second-degree AV block (Type Mobitz II) or third-degree AV block).
14. History of ventricular tachycardia, type 2 second-degree AV block (Type Mobitz II), third-degree AV block or congestive heart failure NYHA III-IV.
15. Heart rhythm disturbances (e.g., bradycardia with baseline heart rate < 50 bpm, in the absence of heart rate lowering medications), tachycardia or tachyarrhythmia (e.g., atrial fibrillation, atrial flutter or ventricular tachycardia), considered by the Investigator indicative of relevant cardiac disease or with abnormalities that may interfere with the interpretation of changes in ECG intervals at Visit 1. Family history of long QT syndrome, use of prescription or over-the-counter medications known to significantly prolong the QT/ QTc interval at Visit 1.
16. Any of the following conditions or procedures within the last six months prior to Visit 1: myocardial infarction, unstable angina (e.g., Canadian Cardiovascular Society (CCS) grading of Angina pectoris grade III and IV), artery bypass (e.g., coronary artery bypass graft, carotid bypass, peripheral artery bypass), percutaneous coronary intervention (diagnostic angiograms are permitted), transient ischaemic attack, cerebrovascular accident (stroke) or decompensated congestive heart failure.
17. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
18. Contraindication to magnetic resonance imaging including, but not limited to severe claustrophobia, extensive tattoos, inner ear implant, pacemakers or other implanted cardiac rhythm management devices, intracranial aneurism clips incompatible with MRI, any other metallic, non-MR compatible implanted devices (e.g., insulin pump, hip joint replacement), a history of intra-orbital metal fragments that have not been removed, and weight or girth that exceeds scanner capabilities.
19. Ongoing participation in another interventional device or drug trial or prior participation during the previous 6 months or 5 times the half-life of the investigational drug, whichever is longer, before Visit 1.
20. Any other clinical condition that, in the opinion of the Investigator, would jeopardize patient safety while participating in the trial.

3.3.4 Withdrawal 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; please see Section 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the patients in the trial, if possible, on treatment. Measures to control the withdrawal rate include careful patient selection, appropriate

explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal. Patients should be made aware of potential anticipated GI side effects and investigators should provide guidance on how to avoid or overcome them.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and eCRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Section 5.2.6.2.1 and 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, without the need to justify the decision.
- An AE (CTCAE Grade 3 or higher) occurred, and the AE was assessed by the Investigator as related to the trial treatment (Section 5.2.6.1.6 and 5.2.6.1.7).
- A clinically significant laboratory change or abnormality occurred and the Investigator judges to warrant discontinuation of trial treatment.
- The patient develops a sinus tachycardia (HR >120/min in two consesutive measurements 5 minutes apart and/or tachyarrhythmia (HR >110/min) or cardiac condition requiring medical intervention.
- Ventricular tachycardia is seen on ECG or syncope.
- Clinically relevant changes are seen on the ECG (QTcF prolongation >500 ms or an increase of 60 ms from baseline (Visit 2), or Type Mobitz II, or third-degree AV block, or Torsade de Pointes) or the patient develops any symptomatic AV block, atrial fibrillation or atrial flutter requiring medical intervention.
- The patient develops a clinically relevant coronary artery disease (e.g., CCS grading of Angina pectoris grade III-IV, or congestive heart failure NYHA class III-IY, or any major adverse cardiovascular event)
- Signs of suicidal behaviour or ideation are detected.
- The patient develops a malignant neoplasm.
- The patient experiences systemic hypersensitivity. Refer to Section 4.2.1.
- The patient develops a clinically significant elevation of liver enzymes. Refer to Section 10.1.
- The patient experiences an infection with SARS-CoV-2 (as confirmed by RT-PCR test) and presents with signs or symptoms requiring discontinuation of trial treatment as per Investigator's discretion.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the Investigator and Sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the trial treatment for more than 2 weeks. Refer to Section 4.2.2.1 and 4.2.2.2.
- The patient experiences tolerance issues with the dose due to AEs over 2 weeks within the treatment period before Visit 14 (Section 4.1.2).
- The patient is out of compliance with trial medication (missing doses), please see Section 4.3.

The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events and other diseases not mentioned above, or pregnancy). If the patient becomes pregnant during the trial the trial medication must be stopped, the patient will be discontinued from the trial and followed up until birth or otherwise termination of the pregnancy. For further information, including the process for follow-up of the outcome of the pregnancy please see Section 5.2.6.2.3.

If the trial treatment is permanently discontinued, the patient should undergo the procedures of the EOT and Follow-up visit (Visit 32 and 33 resp.) as outlined in the Flow Chart and Section 6.2.3.

In case of a temporary reason, trial treatment should be restarted if it is possible from the compliance perspective and if medically justified, please refer to Section 4.1.4.

Boehringer Ingelheim will closely monitor and medically review all adverse events CTCAE Grade 3 and higher.

If one of the following occurs:

1) three patients who were randomised to any of the three active treatment groups develop the same Grade 3 CTCAE adverse event* assessed by the Investigator as related to the trial treatment;
2) two patients who were randomised to any of the three active treatment groups develop any Grade 4 CTCAE adverse event assessed by the Investigator related to the trial treatment;
3) one patient who was randomised to one of the three active treatment groups develops any Grade 5 CTCAE adverse event assessed by the Investigator related to the trial treatment.

Boehringer Ingelheim will pause the enrolment of new patients in the trial and, taking into consideration the DMC recommendations, discontinue the trial treatment for all patients, if needed.

*For adverse events of nausea, vomiting, diarrhoea, constipation, or anorexia, hospitalization or prolongation of hospitalization caused by these respective events plus at least one of the following additional criteria specified below it is required to pause enrolment of new patients in the trial.

- Nausea: IV hydration; tube feeding, or total parenteral nutrition indicated
- Vomiting: IV hydration; tube feeding, or total parenteral nutrition indicated
- Diarrhoea: IV hydration; increase of ≥ 7 stools per day over baseline
- Constipation: obstipation with manual evacuation indicated
- Anorexia: IV hydration; tube feeding, or total parenteral nutrition indicated

Trial-specific procedures have been defined in case of increased liver enzymes after randomization. For details refer to Section 10.1.

If new efficacy/safety information becomes available, Boehringer Ingelheim 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.

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, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the Sponsor

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

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

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

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 Test product

Substance:	BI 456906
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	BI 456906 0.6 mg/mL, 1.8 mg/mL, 3.6 mg/mL, 4.8 mg/mL, 6.0 mg/mL Pre-filled syringes, 0.5 mL fill volume
Posology:	One dose weekly (two pre-filled syringes)
Mode of administration:	s.c. injection

Table 4.1.1:2 Reference product

Substance:	Placebo to match BI 456906
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Unit strength:	Placebo to match BI 456906 Pre-filled syringes, 0.5 mL fill volume
Posology:	One dose weekly (two pre-filled syringes)
Mode of administration:	s.c. injection

4.1.2 Selection of doses in the trial and dose modifications

For this trial, target maintenance doses of 2.4 mg, 4.8 mg and 6.0 mg once weekly dosing were selected based on the following considerations:

Safety and tolerability of BI 456906 is being evaluated in healthy volunteers with obesity or overweight up to 6 weeks for doses ranging from 0.7 to 3.15 mg/ week (daily administration)

and 0.3 to 3.0 mg/ week (weekly administration) and up to 16 weeks for doses ranging from 0.6 to 4.8 mg/ week (once or twice weekly administration) in trial 1404-0003 (c21168858-05). The first part of the trial with the treatment duration up to 6 weeks has already been completed. The available clinical data indicate that the estimated human dose for maintenance in obesity might be reached with 4.8 mg/ week to achieve the anticipated exposure.

The safety margin for the 4.8 mg/ week dose has an exposure multiple of 5.3 fold ($C_{max,ss}$) and 4.1 fold ($AUC_{\tau,ss}$) to the no-observed-adverse-effect level in mice and cynomolgus monkeys.

However, pre-clinical models showed that higher exposures than in obesity might be needed in NASH to show meaningful efficacy (n00254747-01 and n00267699-01). This is potentially based on the effect of the GCGR agonism which is assumed to increase directly the lipid and fatty acid oxidation in the liver. The effect of the GCGR agonism is anticipated to be more pronounced at higher doses. Since this trial is intended to be a dose-finding trial, 6.0 mg/ week dose was selected.

The safety margin for the 6.0 mg/ week dose has an exposure multiple of 3.1 fold ($C_{max,ss}$) and 3.1 fold ($AUC_{\tau,ss}$) to the no-observed-adverse-effect level of the 26-week toxicological study in mice. Safety margins to the no-observed-adverse-effect level of the 39-week toxicological study of 2.4 and 0.8 based on C_{max} and 2.6 and 0.7 based on AUC were derived for male and female cynomolgus monkeys, respectively. These calculations are based on a population PK model, set up with PK data from trial 1404-0001 (c22991258-01) and 1404-0003 (c21168858-05). It should be noted that the expected C_{max} and AUC refer to the enrolment criteria (70 kg and BMI 25 kg/m^2) and is hence a worst-case scenario. A heavier individual will have lower C_{max} and AUC.

The NOAEL for BI 456906 in cynomolgus monkeys is only limited by the effect on body weight loss which reflects the pharmacology of the compound. Obviously, especially female monkeys with a profound lower initial body weight than male monkeys have to be considered oversensitive.

The lowest dose of 2.4 mg/ week in this trial is predicted to achieve sub-therapeutic PD response comparable to placebo in patients with NASH and fibrosis, however, still providing weight loss and improvement in the metabolic status.

The results from the 1404-0003 indicate that the most common GI adverse events such as nausea and vomiting occur at the beginning of the drug exposure and can be mitigated by a careful dose escalation. The tolerability of GLP-1 receptor agonists is known to improve over time, so is assumed that even higher doses of BI 456906 will be tolerated [R20-0479]. In addition, close monitoring is implemented in this trial to assure patients´ safety.

Overall, the three selected maintenance doses are anticipated to support robust dose-exposure-response analyses for multiple safety and efficacy measures to serve as a basis for selection of the suitable dose regimen for the phase III trial.

Selected doses cover a safe starting dose of 0.3 mg/ week with different dose escalation schemes up to the target maintenance dose. The first 10 weeks of the dose escalation period will be identical for all three active treatment groups. The duration of the dose escalation up to the target maintenance dose differs among the active treatment groups from 14 to 22 weeks.

Dose adjustment will be allowed in all groups during the dose escalation period after Visit 14 as well as any time during the maintenance period based on the occurrence of AEs. If a patient does not tolerate a dose due to AEs in the previous two weeks and wishes to reduce the dose, then the dose should be decreased to the next lower tolerated target maintenance dose. The assignment of the lower dose will occur in a blinded fashion via IRT.
Examples:

- If a patient who does not tolerate a dose of 2.4 mg over two weeks during the dose escalation period and wishes to reduce the dose will be changed to placebo;
- If a patient who does not tolerate a dose of 3.6 mg over two weeks during the dose escalation period and wishes to reduce the dose will be changed to 2.4 mg;
- If a patient who does not tolerate a dose of 4.8 mg over two weeks during the maintenance period and wishes to reduce the dose will be changed to 2.4 mg.

Dose adjustment should be done at the site. A patient is allowed to adjust the dose two times during the entire treatment period, once during the dose escalation and once during the maintenance period.

Dose escalation period
During the dose escalation period a dose adjustment may only occur at Visit 16, 18, 20, 22 and 24. If a patient experiences tolerance issues with a dose due to AEs over the last two weeks before a remote visit (i.e., Visit 16, 20 or 24) and believes that a dose adjustment is needed, the patient will be asked to come to the site and to return the unused trial medication dispensed to him/ her during the previous site visit. The Investigator will assess together with the patient, if a dose adjustment is needed, and a new trial medication will be dispensed to the patient for the next two administrations.

If a patient experiences tolerance issues with a dose due to AEs over two weeks within the treatment period before Visit 14, the trial medication should be discontinued, and the patient should undergo the procedures of the EOT and Follow-up visit (Visit 32 and 33 resp.).

Maintenance period
If required, a dose adjustment during the maintenance period should occur at the site either during a planned or an unscheduled visit.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised to treatment groups according to a randomisation plan in a 1:1:1:1 ratio at Visit 2 via Interactive Response Technology (IRT). Details on randomization are provided in Section 7.4. Patient assignment to the treatment groups will be determined by a computer-generated random sequence. Access to the randomization code will be controlled and documented. For further details please refer to Section 4.1.5.

4.1.4 Drug assignment and administration of doses for each patient

Table 4.1.4: 1 shows the dose escalation scheme within each dose group.

Table 4.1.4: 1 Dose escalation schemes

Target dose	Visit											
	2	3	4	5	6	7	8	9	10	11	12	13
	Weeks on treatment											
		1	2	3	4	5	6	7	8	9	10	11
	Weekly dose (in mg)											
2.4 mg	0.3	0.3	0.6	0.6	0.9	0.9	1.2	1.2	1.8	1.8	1.8	1.8
4.8 mg	0.3	0.3	0.6	0.6	0.9	0.9	1.2	1.2	1.8	1.8	2.4	2.4
6.0 mg	0.3	0.3	0.6	0.6	0.9	0.9	1.2	1.2	1.8	1.8	2.4	2.4

Target dose	Visit											
	14	15	16	17	18	19	20	21	22	23	24	25
	Weeks on treatment											
	12	13	14	15	16	17	18	19	20	21	22	23
	Weekly dose (in mg)											
2.4 mg	2.1	2.1	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4
4.8 mg	3.0	3.0	3.6	3.6	4.2	4.2	4.8	4.8	4.8	4.8	4.8	4.8
6.0 mg	3.0	3.0	3.6	3.6	4.2	4.2	4.8	4.8	5.4	5.4	6.0	6.0

BI 456906 or placebo will be provided in pre-filled syringes. Each patient will be administered two injections at every dosing day. Trial medication will be administered preferably by a qualified site personnel during site visits. During remote visits and between site visits during the maintenance period trial medication will be administered by the patient or a designated person. Patient and a designated person (if appointed) will be properly trained before starting the administration at home. Furthermore, during remote visits the administration of trial medication will be monitored by a qualified site personnel via the video conferencing function available on the Science 37 platform. If the patient is not willing to self-administer the injections, he/ she should be given the option to visit the site and to have the medication administered by a qualified site personnel.

“Instructions for Use” (IFU) with step-by-step instructions on how to use the pre-filled syringe will be provided to each patient. A copy of the IFU will be placed in the ISF. The IFU will also contain important safety information and storage instructions. The injection site should be the abdomen, as shown in the instructions. Each dose (both pre-filled syringes) should be administered on one side of the abdomen, and the next dose should be administered on the alternate side of the abdomen.

Electronic diary (eDiary) will be maintained by the patient. Date and time of administration (of the first of two pre-filled syringes) and site of injection will be recorded by the patient when the trial medication is administered at patients' home. Patient should also answer questions regarding side effects in the eDiary. The Investigator will have immediate access to the eDiary through Science 37 platform. In case of technical issues with the platform, a paper diary will be used.

Dose escalation period

During the dose escalation period the treatment with trial medication may be interrupted at maximum two occasions. On each occasion only one dose of trial medication can be missed. At the re-start the patient will continue with the dose escalation scheme without any changes. Examples:

- If a patient misses a dose at Visit 15, he/ she should re-start the treatment at Visit 16 with the planned dose of Visit 16.
- If a patient misses Visit 14, he/ she should come to the site not later than at Visit 15 to re-start the treatment with the planned dose of Visit 15 and to pick-up the trial medication for self-administration during the next two remote visits (Visit 16 and 17).

Maintenance period

During the maintenance period the treatment with trial medication may also be interrupted on maximum two occasions. Two consecutive doses of trial medication may be missed at each occasion. In the event of one missed dose the patient should re-start at the dose from before the temporary discontinuation. In the event of two missed consecutive doses, the dose at re-start will be decreased by two dose escalation steps and re-escalated to the maintenance dose in weekly steps within two weeks.

Examples:

- If a patient misses two consecutive doses at Week 25 and 26, he/ she should come for the next dose administration at Week 27 to the site (unscheduled visit) and return the unused trial medication to the site. During the unscheduled visit a new trial medication (reduced dose) will be administered to the patient. Then patient will continue with the planned visit schedule, i.e., Week 28 visit (Visit 27) will occur at the site. From Week 29 on the patient will be back at the maintenance dose.
- If a patient misses two consecutive doses at Week 27 and 28, he/she should come for the next dose administration at Week 29 to the site (unscheduled visit) and return the unused trial medication to the site. During the unscheduled visit a new trial medication (reduced dose) will be administered and trial medication for the next two administrations at Week 30 and 31 will be dispensed to the patient. Then patient will continue with the planned visit schedule, i.e., Week 32 visit (Visit 28) will occur at the site. From Week 31 on the patient will be back at the maintenance dose.

If a patient misses the last dose from the dose escalation period and the first dose from the maintenance period, this should be handled like two missed consecutive maintenance doses.

During the COVID-19 pandemic, visits to the sites may need to be replaced by remote visits to ensure patient safety. Based on a thorough assessment of the benefits and risks, the

Investigator may still decide to continue the trial treatment and trial medication may be shipped to the patient's home if acceptable according to local law and regulations.

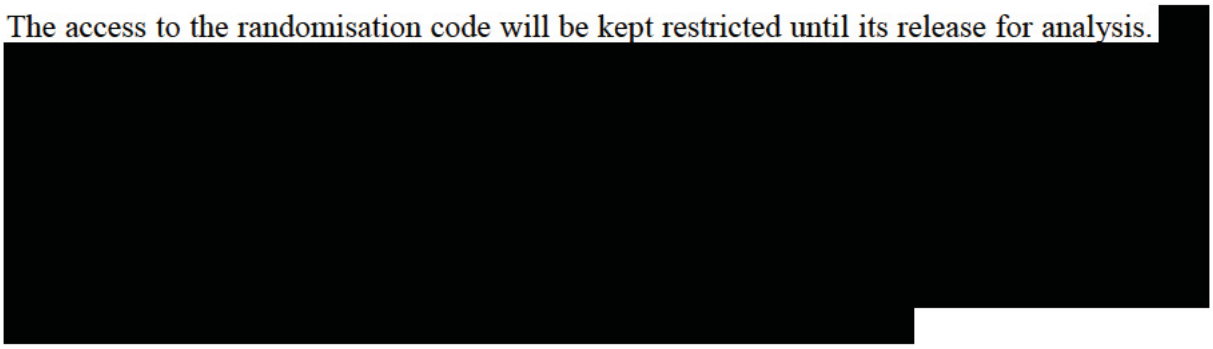
4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This trial has a double-blind design across dose groups. Patients, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial (except as noted below) will remain blinded with regard to the randomised treatment assignments until after the main database lock.

One interim analysis will be performed by an independent statistics and programming team at the Sponsor after approximately half of randomised patients have reached Week 28.

The access to the randomisation code will be kept restricted until its release for analysis.



An external DMC will perform an unblinded safety asessment at regular intervals or upon request, i.e., at the occurrence of adverse events that may lead to the trial discontinuation, as specified in the DMC charter in order to ensure that patients are protected from potential harm. For further details, please refer to Section 8.7. Randomization codes will be provided to the trial independent statistician (iSTAT) who will be in charge of preparing tables and listings as well as summary reports for the DMC based on the agreed upon format and layout. Information, including adverse events and results from laboratory and other assessments, will be provided in an unblinded fashion. This will be accomplished by using code labels and providing the decoding information separately, if needed.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator via IRT. It must only be used in an emergency situation when the identity of the trial medication 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 eCRF page. If the patient is unblinded by the Investigator, the patient will have to be discontinued from the trial. Discontinued patients will complete the early discontinuation assessments of the EOT visit as specified in the Flow Chart and the Follow-up visit.

In case the automated unblinding option via IRT is malfunctioning, the IRT service provider can be contacted (24/7 coverage) and the treatment allocation can be obtained. IRT support has direct access to the database and the treatment information can be manually obtained.
Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs) and the assessment of pre-defined stopping criteria, it may be necessary for a representative from BI's Pharmacovigilance group or independent statistician to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system or for assessment of a safety signal and will not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via the IRT system, which will also monitor expiry dates of supplies available at the sites.

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation. If the storage conditions are found to be outside the specified range, the procedure described in the ISF has to be followed and the Clinical Research Associate (CRA), as provided in the list of contacts, should be contacted immediately.

Pre-filled syringes dispensed to the patient at site visits (Flow Chart) should be transported in insulated bags with cooling gel packs (or other similar cooling tools) from the site to patient's home. Patients should store the medication at home according to the recommended storage conditions on the medication label as instructed by the site personnel. Patients will not maintain a temperature log.

4.1.8 Drug accountability

The Investigator or designee will receive the trial medication delivered by the Sponsor when the following requirements are fulfilled:
- Approval of the clinical trial protocol by the IRB / ethics committee;
- Availability of a signed and dated clinical trial contract between the Sponsor and the investigational site;
- Approval/notification of the regulatory authority, e.g., competent authority;
- Availability of the curriculum vitae of the Principal Investigator;
- Availability of a signed and dated clinical trial protocol;
- Availability of the proof of a medical license for the Principal Investigator;
- Availability of FDA Form 1572 (if applicable).

Trial medication is not allowed to be used outside the context of this clinical trial protocol. It must not be forwarded to other investigators or clinics. Transfers of trial medication between sites should occur in exceptional events only and should be coordinated by the Sponsor.
Patients should be instructed to return all unused trial medication (cartons with the pre-filled syringes), and the empty cartons from used trial medication, to the site at the next site visit. The sharps container (dispensed to the patient) where the used pre-filled syringes are stored should be returned to the site when it is full or at Visit 32.

The Investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or warehouse/ drug distribution centre or alternative disposal of unused products. If applicable, the Sponsor or warehouse/ drug distribution centre 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 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 clinical trial 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

No rescue medication, emergency procedure or additional treatments are foreseen for this trial.

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation (refer to Section 3.3) are permissible. All concomitant therapy should be carefully evaluated by the Investigator and the Sponsor should be contacted when there are questions.

In case of AEs in need of treatment, symptomatic therapy according to Investigator judgment will be permitted. All concomitant therapies will be recorded on the appropriate pages of the eCRF.

Malignancies
In case of occurrence of malignant neoplasm, the Investigator should discontinue treatment with the trial medication, and notify the Sponsor. Diagnostics and treatment should be initiated according to local standard of care.

Suicidality
In case of signals of suicidal ideation or behaviour, the Investigator should discontinue treatment with the trial medication, notify the Sponsor and the patient should be referred to an appropriate psychiatric clinic.

Hypoglycemic events
T2DM patients should contact the site any time their fasted blood glucose level measured with a SMBG device drops below 70 mg/dL (3.9 mmol/L).

Investigators are asked to assess the frequency of detection of the glucose alert value of 70 mg/dL (3.9 mmol/L) or less and to carefully assess hypoglycemic episodes following the 2017 American Diabetes Association position statement on glycemic targets. Investigators should consider lowering the dose of or to discontinue the concomitant antidiabetic medication and to implement additional glucose monitoring as needed.

Systemic hypersensitivity incl. anaphylactic reaction
In case of systemic hypersensitivity including anaphylactic reaction emerging during or after injection(s) of trial medication, the Investigator should consider in accordance with severity of the reaction and local standard of care to:

- immediately stop further injections;
- treat with systemic antihistamines, i.v. steroids, and in case of a severe allergic reaction (e.g., anaphylactic reaction) epinephrine.

Blood will be drawn for the analysis of ADAs, NAbs, level of BI 456906, IgE, histamine, serum tryptase, and complement components as detailed in the laboratory manual.

In the event of systemic hypersensitivity, based on patient's clinical course and medical judgment, the injection(s) may be continued in case of mild or moderate systemic hypersensitivity.

In the event of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA [R11-4890] suspected to be caused by the trial medication, the Investigator should permanently discontinue treatment with the BI456906.

When a non-acute hypersensitivity reaction related to immune complexes (i.e., serum sickness) is suspected, please draw a sample for the laboratory assessment for circulating immune complexes.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The following medications are prohibited during the entire duration of the trial:

- Amiodarone, methotrexate, systemic glucocorticoids for more than 2 weeks, tetracyclines, tamoxifen, estrogens (excluding estrogen substitution with serum estrogen levels within the normal range), anabolic steroids, valproic acid and anti-obesity medications
- Pioglitazone or GLP-1R agonists within 6 months of randomization
- Initiation of SGLT-2 inhibitors within 6 months of randomization
- Beta-blockers, verapamil and diltiazem, unless indicated for heart rate control or hypertension treatment

- Initiation or change in dose of Vitamin E
- Oral medications with Narrow Therapeutic Index (NTI), unless dosing can be adapted according to standard of care monitoring (e.g., levothyroxine dosing appropriately adapted to thyroid hormone levels)
- Medications known to significantly prolong the QT/ QTc interval (website.crediblemeds.org)

4.2.2.2 Restrictions on diet and lifestyle

Patients participating in this trial should refrain from donating blood during the entire duration of the trial including the follow-up period.

Dietary supplements that potentially induce change in body weight, over-the-counter or prescribed weight loss products, and products including St. John's wort (Hypericum perforatum) are not permitted starting 4 days before the first administration of trial medication until the end of the trial.

There are no other restrictions on diet, exercise, alcohol consumption or smoking except that the patient's usual habits, including nicotine, alcohol, and caffeine intake, should be within acceptable daily amounts and not be drastically changed throughout the trial conduct. All patients should be on a stable (i.e., no changes within 6 months of randomization) diet and exercise (lifestyle) regimen according to the sites standard of care throughout the trial, without substantial modifications. Assessing the restrictions on diet and lifestyle of trial patients is left to the Investigator. Counceling by the site staff on lifestyle per local standard of care should be documented in the patient´s source documents.

4.2.2.3 Contraception requirements

Female patients

Women of child-bearing potential (WOCBP, for the definition please refer to Section 3.3.2) and their male sexual partner able to father a child must use two medically approved methods of birth control throughout the trial and for a period of at least 5 weeks after last trial medication intake. Male partner of a female trial participant must use a condom if his sexual partner is a WOCBP or be vasectomised with documented absence of sperm.

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 if their sexual partner is a man able to father a child. A list of contraception methods meeting these criteria is provided in the patient information.

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

WOCBP who use oral contraceptives at screening visit should change to non-oral contraceptives listed above. Oral contraceptives are not permitted in female participants during the trial.

Or

Patients must abstain from male-female sex. This 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 trial medication; and withdrawal are not acceptable.

Male patients
There are no specific contraceptive requirements for male participants and their female partners.

4.3 TREATMENT COMPLIANCE

Patients should be encouraged to be fully compliant with the trial medication dosing schedule (Flow Chart).

If a dose is missed on the planned dosing day, patients should take the planned dose within two days. If more time has elapsed since the missed dose, then the patients should wait to take the next planned dose. A minimum of five days between doses is required.

Patients are considered out of compliance, and should be discontinued from the trial:

1) if they miss two or more consecutive doses OR if they miss one dose at more than two occasions during dose escalation period;
2) if they miss three or more consecutive doses OR if they miss one dose or two consecutive doses at more than two occasions during maintenance period.

The total maximum number of allowable missed doses during the entire treatment period is six, i.e., two during the dose escalation and four during the maintenance period.

Patients should be instructed to return all unused trial medication (cartons with the pre-filled syringes), and the empty cartons from used trial medication, to the site at the next site visit. Compliance will be determined by the site personnel.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Liver biopsy

Liver biopsy specimens will be collected at the time points specified in the Flow Chart. A large needle, preferably 16G but not less than 18G, should be used and a biopsy core with a total length of at least 20 mm, not too much fragmented (1 to 3 fragments) should be obtained in order to meet the quality requirements for an accurate histological evaluation. Unstained slides will be prepared locally and sent to the central pathology laboratory. Alternatively, biopsy blocks can be sent to the central pathology laboratory. Guidelines for biopsy specimen collection and preparation are provided in the manuals from the central pathology laboratory. If a historical biopsy is intended to be used for eligibility assessment and as a baseline, sufficient and suitable material must be available for this purpose. Central pathology laboratory will process the biopsy specimens for reading by the central pathologist.

Assessment of liver biopsy specimens will be set-up in a blinded fashion. It will be based on the NAFLD scoring system (NAS), developed by the NASH clinical research network (CRN). The NAS represents the sum of scores for steatosis, lobular inflammation and ballooning, and ranges from 0 to 8. The total score for the fibrosis stage ranges from 0 to 4 (Table 5.1.1: 1).

Table 5.1.1: 1 NAFLD scoring system (NAS) for liver biopsies

	Steatosis		Lobular inflammation		Ballooning		Total
	Degree	Description (% hepatocytes)	Degree	Description	Degree	Description	
	0	<5	0	0/20×[a]	0	0	
	1	5–33	1	<2 foci/200×	1	Few/inapparent	
	2	34–66	2	2–4 foci/200×	2	Easily noted/many	
	3	>67	3	>4 foci/200×			
NAS score	0–3		0–3		0–2		0–8

Stage	Fibrosis location
1A	Zone 3, perisinusoidal, delicate
1B	Zone 3, perisinusoidal, dense
1C	Portal, periportal only
2	Zone 3, perisinusoidal + portal, periportal only
3	Bridging fibrosis
4	Cirrhosis

[a] Optical field

Gene expression analysis

A fraction of the liver tissue collected during biopsy will be used to conduct gene expression analysis (refer to Liver biopsy in the Flow Chart). For any liver biopsies conducted during the trial, the generation of slides for the histological staging of NASH will take precedence over sample collection for gene expression analysis. For further details refer to Section 5.5.3.

5.1.2 Fibroscan Assessment of Liver Stiffness [redacted]

The liver will be evaluated using the FibroScan® device, a non-invasive technique using Vibration Controlled Transient Elastography (VCTE™) technology (to measure liver stiffness) [redacted]

The following measurements will be made:

- Fibrosis will be measured using Vibration-Controlled Transient Elastography (VCTE) which is an advanced ultrasound technique that measures liver stiffness.

[redacted]

Sites must have the expertise in using the FibroScan® device, i.e., the operator should be duly trained. If possible, the same operator should perform the Fibroscan® assessments on one patient.

Correct probes should be selected corresponding to the patient's body type (follow the automatic probe selection tool displayed in real time, based on the Skin to Liver Capsule Distance (SCD), and not on patient's BMI). Sites should ensure that the probes are calibrated.

If the FibroScan® device is not available at the site, it will be provided by the Sponsor for the duration of the trial.

5.1.3 Magnetic resonance imaging

MR imaging will be used to assess the liver fat content in the whole liver by way of proton density fat fraction (PDFF) at the time points specified in the Flow Chart. Therefore, sites must be equipped or collaborating with a site equipped with an MRI scanner from the following manufacturers: General Electric, Philips or Siemens. Ideally the MRI scanner should be equipped with a manufacturer specific MRI-PDFF package also known as multi-echo, multi-peak Dixon techniques. All imaging sites will undergo a quality assessment process prior to trial initiation based on a review of MRI hardware and software.

MR images to compute the whole liver volume (by way of 3D image acquisition) will also be collected from each subject in the same MRI session in order to compute the liver fat volume. Other MR image sequences may be collected for additional exploratory analyses if required. MR image acquisition, including preparation time, is estimated to take no longer than 30 minutes. MR images will be sent to an external vendor for centralized reading.

5.1.4 Weight

Weight measurements should always be done on the same scales for one patient whenever possible. Mechanical and digital scales are acceptable. In order to get comparable body weight values, shoes, coats/jackets, and any headgear should be taken off, and pockets should be emptied of heavy objects (i.e., keys, coins etc.). Headgear worn for religious reasons are

acceptable, but this should be worn for all weight measurements in the trial. The patient should empty the bladder before weight is measured.

5.1.5 Waist and hip circumference

Waist circumference should be determined by measuring the midpoint between the lowest rib and the iliac crest. The measuring tape should be made of a material that is not easily stretched. The tape should be placed perpendicular to the long axis of the body and horizontal to the floor and applied with sufficient tension to conform to the measurement surface. Waist circumference measurements should be made around a patient's bare midriff, after the patient exhales while standing without shoes and with both feet touching the ground and arms hanging freely.

Hip circumference measurement should be taken around the widest portion of the buttocks.

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at the screening visit. Further physical examinations during the trial are required only if patient reports symptoms (please refer to in the Flow Chart). The physical examination should be conducted according to the local medical practice. 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. The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be assessed at the time points specified in the Flow Chart, prior to blood sampling. Blood pressure will be measured twice at Visit 1 (10 minutes apart). Vital signs measurement at Visit 1a is optional but recommended. At dosing visits another vital signs assessment will be done approx. 10 minutes post dose (i.e., after the administration of the second of two pre-filed syringes). Vital signs assessment consists of systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position without crossed legs, after 5 minutes of rest. 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. For the sampling time points please see the Flow Chart. Patients do not have to be fasted for the blood sampling for the safety laboratory.

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

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

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1) and the DILI Checklist provided in the ISF. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

The central laboratory will transfer the laboratory data to the Sponsor periodically.

Table 5.2.3:1 Safety laboratory tests

Category	Test name
Haematology	Haematocrit Hemoglobin MCV (Mean Corpuscular Volume) MCH (Mean Corpuscular Haemoglobin) MCHC (Mean Cellular Haemoglobin Concentration) Red Blood Cell Distribution Width (RDW) Red Blood Cells (RBC) Count/ Erythrocytes WBC Count/ Leukocytes Platelet Count / Thrombocytes Differential Automatic (relative and absolute count): Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes
Clinical chemistry	Albumin Alkaline phosphatase Amylase ALT (alanine aminotransaminase, SGPT) AST (aspartate aminotransaminase, SGOT) Bicarbonate Bilirubin total, fractionated if increased Calcium
Clinical chemistry	Chloride Creatinine Creatine kinase (CK) CK-MB, troponin (reflex tests if CK is elevated) Ferritin γ-GT (gamma-glutamyl transferase) Glucose (plasma, not fasted) HbA1c/ Insulin/ C-Peptide** Lactate dehydrogenase (LDH) Lipase Magnesium Phosphate Serum Free Fatty Acids Potassium Protein total Sodium Urea (blood urea nitrogen, BUN) Uric acid Thyroid stimulating hormone (TSH)* Calcitonin* eGFR (CKD-EPI formula)
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin Time (INR) Fibrinogen
Lipids	Cholesterol (total) HDL cholesterol LDL cholesterol (including VLDL) Triglycerides

Table 5.2.3:1 Safety laboratory tests (cont.)

Infectious serology	Hepatitis B surface antigen (HBsAg)* Hepatitis B surface antibodies (anti-HBs)* Total hepatitis B core antibodies (anti-HBs)* Hepatitis C antibodies (anti-HCV)*
Urinalysis	**Semi quantitative** Nitrite Protein Ketone Urine pH Leukocyte esterase (for WBC) Blood (erythrocytes) **Quantitative***** Albumin Creatinine **Urine drug screen*** Cannabis Cocaine Benzodiazepine Amphetamines Barbiturates Methadone Opiates

* Measured only at Visit 1.

** Measured only at Visit 1, Visit 2, Visit 27 and at the EOT/ED visit.

*** Albumin/creatinine ratio in spot urine will be calculated at the central laboratory.

SARS-CoV-2 RT PCR test will be performed at Visit 1.

ADAs, NAbs, level of BI 456906, IgE, histamine, serum tryptase, and complement components will be analyzed in the event of systemic hypersensitivity.

If the assessment of safety laboratory tests in the central laboratory is not possible due to emergency, pandemic or other unforeseen circumstances, the assessment will be performed in the local laboratories.

5.2.4 Electrocardiogram

The 12-lead ECG should be collected at the time points specified in the Flow Chart. ECG will be recorded in triplicate at the screening visit, but as a single measurement at the following visits.

Centralized ECG services will be provided by an external vendor for all site visits (including unscheduled visits). Standardized equipment and user manual will be provided by the vendor.

ECG should be collected according to the trial-specific recommendations, using the standardized equipment provided by the vendor. ECGs may be repeated for quality or safety reasons. Patients should be supine for approximately 5-10 minutes before ECG collection. Patients should remain supine, but awake, during the ECG collection process.

ECG recordings will be transmitted electronically to a vendor for central reading. The ECG recordings will be centrally evaluated and rated as normal, abnormal, or unable to evaluate, and the results will be sent to the site. The Investigator should review the report. If the ECG is rated as abnormal, the Investigator will have to 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.

After the screening visit, the Investigator must review the ECG results from central reading to ensure patient has met all the entry criteria for the trial. Any pre-existing conditions should be recorded as baseline conditions. ECG recorded at the randomization visit should be evaluated by the Investigator before the patient receives the first dose of trial medication. If abnormalities are observed by the Investigator in the ECG reading at randomization visit, the Investigator may wait until the results from central reading are available, and the randomization visit may be rescheduled.

After the patient is randomised, if a clinically significant increase in the QT/QTc interval from baseline or any other clinically significant quantitative or qualitative change from baseline is identified, the Investigator will assess the symptoms (e.g., palpitations, near syncope, and syncope) and decide if the patient will continue in the trial. The Investigator must also ensure that patient does not meet any of the stopping criteria, such as tachycardia, arrhythmia or conduction disorders (Section 3.3.4.1). Any new 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 as soon as the ECG recordings are obtained at the site 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 significant 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.

5.2.5 Other safety parameters

5.2.5.1 Suicidal risk assessment and reporting

The C-SSRS is an investigator-rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behavior and suicidal ideation. It does not give a global score but provides some categorical and some severity information specifically for behavior and ideation.

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counselor, nurse, or research coordinator with C-SSRS training. It has a typical duration of five minutes and causes only a low burden on patients. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4

related to suicidal behavior and may be expanded to up to 17 items in case of positive responses. In this trial paper forms will be used for the assessment of the C-SSRS.

The C-SSRS has been widely used in large multinational clinical trials. The C-SSRS will be administered at the screening visit (using the "baseline/screening" version) with the aim to exclude subjects with a lifetime history of suicidal ideation and behavior. After the baseline visit, the assessment "since last visit" will be performed at clinic visits as specified in the Flow Chart. The Investigator is to review positive and negative reports for plausibility and clinical relevance. Doubtful reports may be repeated, or reports may be validated by a consulting psychiatrist. If there is a positive report of suicidal behavior or suicidal ideation type 4 or 5 after start of trial, the Investigator is to immediately interview the patient during the clinic visit and advise the patient to consult with a psychiatrist. If the positive report is confirmed, appropriate actions for the patient's safety must be initiated. Treatment with trial medication should be stopped and patient should be discontinued from the trial. Additionally, all C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior must be reported as separate SAEs by the Investigator. For 'Self-injurious behavior, no suicidal intent' (Type 11) standard AE / SAE reporting rules are to be applied. For each negative report (suicidal ideation type 1, 2 or 3) after start of the trial, the Investigator is to decide based on clinical judgment whether it represents an AE as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

5.2.5.2 Self-monitoring of blood glucose

T2DM patients taking antidiabetic medication will be provided with a SMBG device for use at home during the treatment period for self-measurement of blood glucose. Patients may also use their own device for SMBG monitoring. The SMBG device will be dispensed to the patients at randomization (Visit 2). Instructions on the proper use of the SMBG equipment will be provided to the patient by the site staff.

SMBG measurements in a fasted state (fasting for at least 10 hours) should be performed regularly. Recommendations are as follows:

- daily during the treatment period;
- at any time, they experience signs/ symptoms of hypoglycemia.

Refer to Section 4.2.1 for information on handling of hypoglycemic events.

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 eCRF 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 hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event 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 hospitalisation or development of dependency or abuse.

For Japan only: the following events will be handled as “deemed serious for any other reason”. AEs which possibly lead to disability will be reported as SAEs.

5.2.6.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim 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 trial medication and must be reported

as described in Section 5.2.6.2, subsections "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, please see Section 5.2.6.2.2.

Hepatic injury is considered as AESI. It is defined by the following alterations of hepatic laboratory parameters as defined by the removal and stopping criteria in Section 3.3.4.1. and Section 10.1.

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

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

5.2.6.1.5 Adverse events requiring adjudication

Pre-specified AEs critical for the assessment of safety of BI 456906 will be centrally adjudicated in a blinded fashion by an independent external Clinical Event Committee (CEC).
Definitions of the adjudicated events and the principles of standardised data collection in the centralised CEC adjudication process are outlined in the separate CEC Charter. For further details refer to Section 8.7.

AEs requiring adjudication

- All-cause death
- Cardiovascular event
- Cerebrovascular disease
- Heart failure requiring hospitalisation
- Pancreatitis
- Neoplasm
- Thyroid mass requiring surgery

5.2.6.1.6 Intensity (severity) of AEs

The intensity (severity) of adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 released on 27 November 2017 [R18-1357].

5.2.6.1.7 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given trial treatment, 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 eCRF(s) by the Investigator:

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

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 immediately (within 24 hours) to the Sponsor's unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

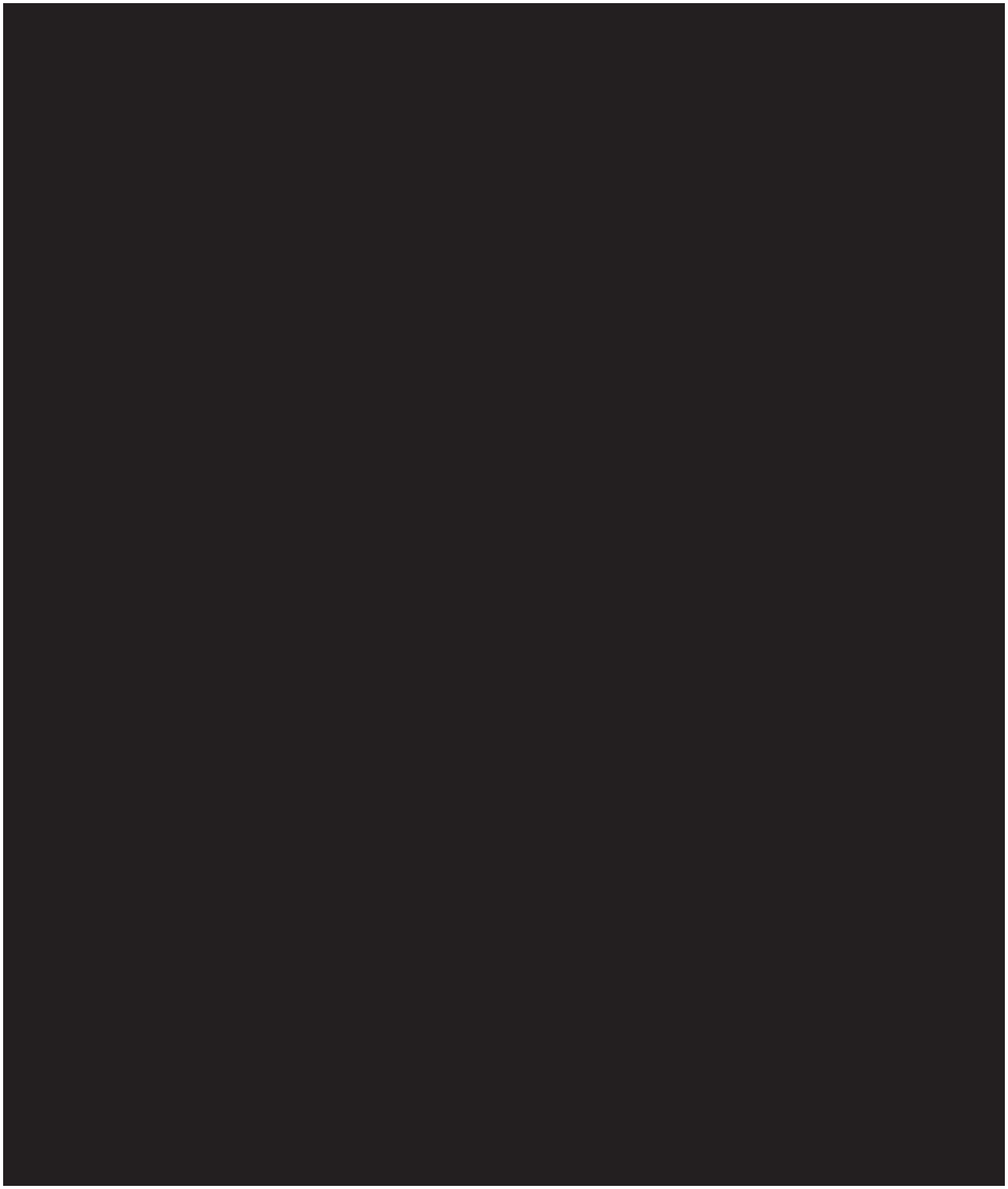
With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have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

5.2.6.2.3 Pregnancy

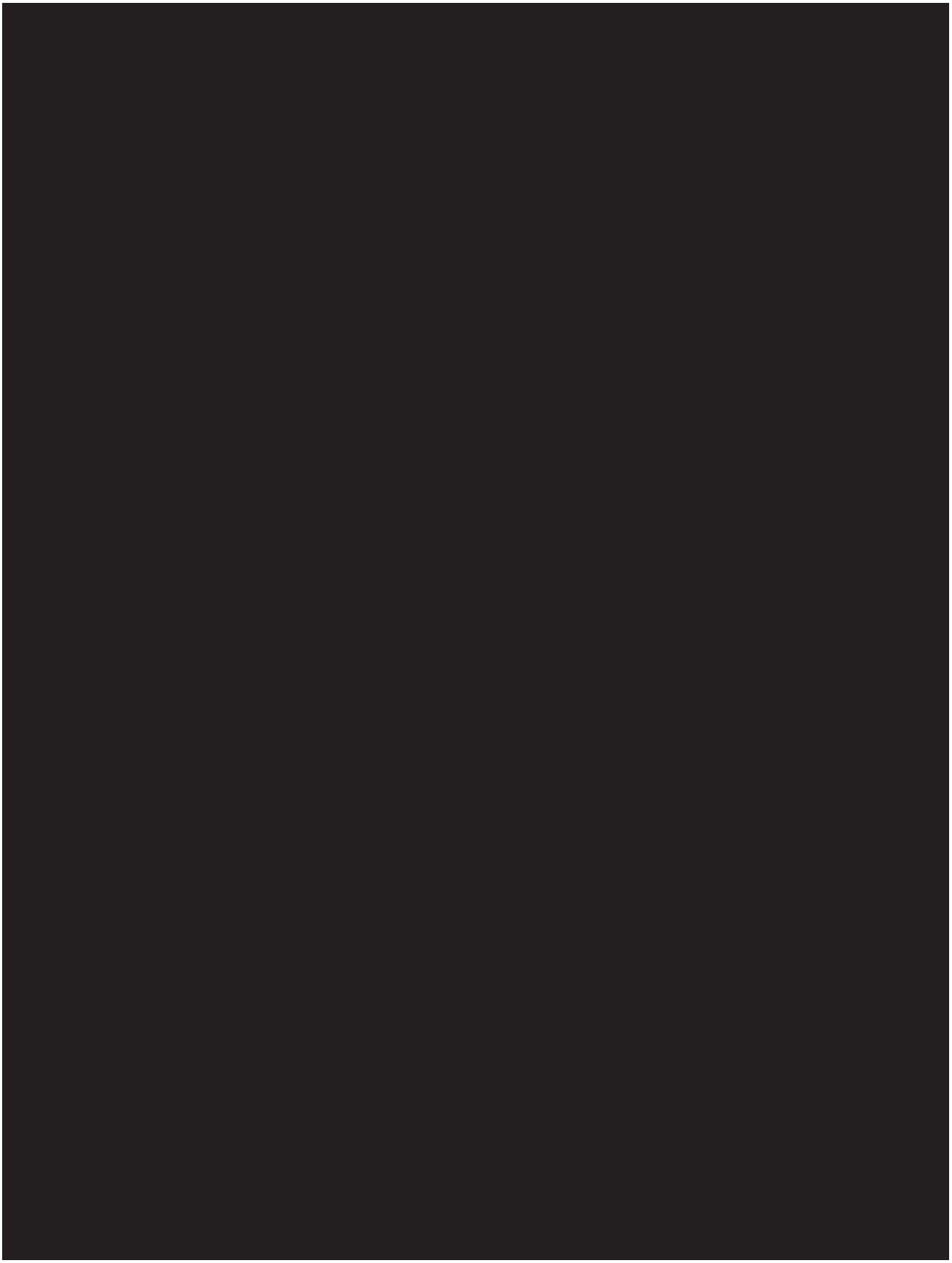
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the Investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring 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.



[redacted]



5.6 BIOBANKING

Participation in sampling for biobanking is voluntary and not a prerequisite for participation in the trial. Samples (blood and stool) will be collected only after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements. Countries may opt out of biobanking sample collection based on regulatory requirements.

5.6.1 Methods and timing of sample collection

Detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. For sampling timepoints see Flow Chart.

Approximately 83 mL of blood will be drawn for DNA, plasma and serum banking purposes. In addition, stool samples will be biobanked for fecal biomarker assessments at Visit 2, 27 and 32 as indicated in the Flow Chart.

5.8 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are considered standard measurements in the clinical development of a treatment for NASH and will be performed in order to monitor safety aspects and to determine efficacy [redacted] Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The trial consists of a screening period, treatment period with a dose escalation and a maintenance period, and a follow-up period:

Screening :	up to 10 weeks
Dose escalation :	up to 24 weeks
Maintenance :	at least 24 weeks
Follow-up :	4 weeks

All patients are to adhere to the visit schedule specified in the Flow Chart with a time window for rescheduling. Any deviations from the planned visit schedule are to be documented. If any visit has to be rescheduled, subsequent visits should follow the original visit schedule (calculated from the randomization Visit 2). Additional visits for the purpose of retesting laboratory paramaters or AE monitoring may be included as deemed necessary by the Investigator.

Approximately 40% of the visits is expected to be conducted remotely from patient's home through Science 37 platform. The platform offers the patient a direct line of communication with the Investigator and/or site personnel via a video conferencing feature. If the patient does not feel comfortable with remote visits, these can be replaced by site visits. However, such modification has to be arranged with the site personnel in a timely manner.

If visits to site are impossible because of COVID-19 or other unforeseen circumstances posing safety risks to patients, these visits may be performed as remote visits from patient's home via Science 37 platform. When scheduling such visits every effort should be made to ensure a continuous supply of trial medication for the patient, whilst also taking into account that the next kit(s) of trial medication may need to be shipped to the patient's home (refer to Section 4.1.4) and, that medical prerequisites, i.e., at minimum monthly safety laboratory tests and ECGs, should be fulfilled prior to shipment of new supplies.

All COVID-19 related deviations from the original schedule of visits and trial procedures will be documented, and the implications will be considered for the analysis of trial data.

Science 37 application will be installed on patient's smartphone. Alternatively, a smartphone can be provisioned to the patient for the duration of the trial. Apart from using the video conferencing function, patients will complete eDiary [redacted] through the smartphone's Science 37 app. Patients will be instructed on the use and access of Science 37 platform and on the use of the installed app at Visit 2.

For detailed description of trial procedures, please refer to the Flow Chart.

Vital signs measurement and ECG recording should be performed before blood samples are taken.

[redacted]

Pregnancy tests:
All women of childbearing potential will undergo serum pregnancy test at the screening visit (Visit 1). The test will be done in the central laboratory. Patients with a positive result of the serum pregnancy test will be excluded from the trial. Urine pregnancy tests will be done monthly starting from Visit 2. They will be done locally. If the urine pregnancy test is positive, a serum pregnancy test will be done in the central laboratory to confirm pregnancy. If the serum pregnancy test is positive, trial medication will be discontinued, and patient will be discontinued from the trial. If the serum pregnancy test is negative, the patient may continue in the trial. If the urine pregnancy test is positive at the randomization visit (Visit 2), the patient must not be randomised into the trial unless the serum pregnancy test is negative.

In the event of disruptive circumstances (e.g., pandemic, war) the investigational plan as per this clinical trial protocol may not be feasible at a site. In this case, Sponsor, and Investigator, with the informed consent of the patient, may agree on alternative, back-up methodology which may include but will not be limited to allowing local labs for safety assessments, providing options to either consider paper diaries or paper PROs for patients, and other measures that may be required to ensure trial continuity while mainitaining patient safety and data integrity of primary endpoint.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Screening Period:
All patients must sign an informed consent consistent with ICH-GCP guidelines prior to any trial specific procedures. Please refer to Section 8.1 for details. If a patient is willing to provide blood and/or stool samples for biobanking, a separate consent must be obtained.

Once the patient has consented, the patient is considered as enrolled in the trial. The patient should be recorded on the enrolment log and registered in IRT.

The screening period, i.e., the period before the first administration of trial medication, starts at Visit 1 and may be as long as 10 weeks, but should be kept as short as possible. After all Visit 1 results including MR imaging are received and the patient is considered eligible, the Visit 1a for liver biopsy should be scheduled. When scheduling a liver biopsy as part of screening procedures sufficient time should be allowed to receive the results before preceding to Visit 2. In the event of logistical issues with the reporting of results by the central vendor(s) a patient who meets all inclusion criteria and does not meet any exclusion criteria should be considered for participation in the clinical trial even if he/ she exceeds the screening period of 10 weeks. Extension of the screening period requires a Sponsor approval. If more than 12 weeks elapse from Visit 1 safety laboratory tests, ECG and vital signs should be repeated and results should be available before randomization.

Run-in Period:
There will be no run-in period in this trial.

Demographics and Medical Conditions:
Information on race (if allowed by local law) will be collected because certain ethnic groups are at higher risk for NASH. Moreover, this information is required for the calculation of eGFR (CKD-EPI formula).

The following medical conditions will be specifically asked for: type and history of diabetes mellitus, history of arterial hypertension, history of hyperlipidemia, history of cardiac dysrhythmias, and metabolic syndrome, alcohol and caffeine consumption, and nicotine use. In addition, information will be collected in the eCRF for relevant chronic diseases, current observable conditions and other relevant conditions (as per Investigator's judgment) which may not be necessarily manifest at the day of examination, e.g., because therapy is given.

Re-screening and re-testing:
If patients discontinue from the trial during the screening period, no additional assessments or site visits are required. The patients will be marked as screen failures and registered as such in IRT. A patient may be re-screened once with the approval from the Clinical Trial Leader. Re-screening of a previously screen failed patients will be permitted providing the reasons for screen failure were reversible and have been resolved, based on Investigator's judgement. The patient who will be re-screened needs to be re-consented and subsequently registered in IRT. A new patient number will be assigned. All procedures of Visit 1 must be repeated except for FibroScan® and MR imaging. FibroScan® and MR imaging from the initial screening can be used if the assessments were performed within 1 month prior to re-screening.

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

6.2.2 Treatment period(s)

Patients who meet all eligibility criteria will be randomised at Visit 2. After randomization, patients will start the treatment period which includes a dose escalation, followed by the maintenance period as shown in Figure 3.1: 1.

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

[redacted]

Measurement of vital signs should be performed before blood samples are taken (pre-dose) and approx. 10 minutes after dosing (post-dose).

Data concerning adverse events and concomitant medications will be collected throughout the trial, as specified in the Flow Chart. These data will be obtained at scheduled or

unscheduled visits based on the information provided actively by the patient or as a result of questioning the patient.

After completion of the treatment period or after a premature trial discontinuation, patient will have the End of Treatment visit (Visit 32) and will be registered as completed or discontinued in IRT, as applicable. Trial medication will not be administered at Visit 32, the last administration of the trial medication will occur one week before the visit.

6.2.3 Follow-up period and trial completion

The patients should make all efforts to complete the trial including the 4-week follow-up period which extends from Visit 32 until Visit 33. The residual effect period (REP) of 28 days will be fully covered by the period between the last administration of the trial medication and the end of the follow-up period. Procedures to be completed at the Follow-up visit (Visit 33) can be found in the Flow Chart. The sequence of the procedures will be the same as in the treatment period. With the conduct of Visit 33 the observation period has ended. Trial completion should be recorded on the corresponding eCRF page.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The main trial objectives are to demonstrate a non-flat dose response curve, to evaluate the size of the treatment effect (using the absolute difference in proportions of patients with histological improvement between BI 456906 and placebo at Week 48), and to characterize the dose-response relationship. For this purpose, the primary analysis uses methodology for dose finding employing both multiple comparison procedures and modelling techniques (MCPMod).

7.1 NULL AND ALTERNATIVE HYPOTHESES

For both the primary endpoint (improvement from baseline in NASH and no worsening in fibrosis at Week 48) and the secondary endpoint (at least 30% reduction in liver fat content assessed by MRI-PDFF at Week 48), the null hypothesis is that there is a flat dose response curve across the placebo and the BI 456906 dose groups. The alternative hypothesis is that there is a non-flat dose response curve indicating a benefit of BI 456906 over placebo.

The MCPMod procedure allows for simultaneous evaluation of different potential dose response patterns, whilst protecting the overall probability of Type I error (one sided 5%). Additionally, the probability to continue the program with a non-effective drug is further limited by specifying that an effect of at least “delta” relative to placebo is achieved (see Section 7.5 for details). The pre-specified models and their parameters used are outlined in Section 7.2.2 and Section 7.2.3, respectively.

No confirmatory hypothesis testing is planned to be performed in this trial. Where p-values are given, these are to be interpreted as exploratory. Given the exploratory nature of the trial, no adjustment will be made to Type I error levels for the testing of the null hypothesis of flat dose response on more than one endpoint.

7.2 PLANNED ANALYSES

7.2.1 General considerations

Analysis Sets
Statistical analysis will be based on the following analysis sets:

The Full Analysis Set (FAS) is defined as all randomised patients who received at least one dose of trial treatment (efficacy analysis).

The Treated Set (TS) is defined the same as the FAS (safety analysis).

The Per Protocol Set (PPS) is defined as all patients in the FAS who were without an important protocol deviation relevant for efficacy.

[redacted]

Important Protocol Deviations
Important protocol deviation (IPD) categories will be defined in the IPD [redacted] specified in the IPD specification document. IPDs will be identified no later than in the Report Planning Meeting (RPM).

IPDs may include (but not necessarily be limited to) the following:

- Violation of inclusion or exclusion criteria
- Major deviations from scheduled timing of assessments
- Non-compliance with trial medication
- Treatment dispensing errors
- Use of prohibited or restricted concomitant medication.

Definition of baseline
In general, unless otherwise specified in the TSAP, the last non-missing measurement on or prior to the date of first dose of study treatment will be used as baseline for efficacy and safety variables.

Definition of on-treatment
For the purposes of on-treatment efficacy analyses, the definition of "on-treatment" will be given in the TSAP.

For the purposes of on-treatment safety analyses, an assessment (or AE start date) will be considered "on-treatment" if the assessment date (or AE start date) is between the date of first dose and 28 days after the date of last dose of trial treatment.

7.2.2 Primary endpoint analyses

The primary analysis of the primary endpoint will be performed using multiple comparison and modelling techniques (MCPMod), whereby several possible dose response models (patterns) will be evaluated while keeping full control of the type I error at 5% (one-sided), to identify the best-fitting model or subset of models.

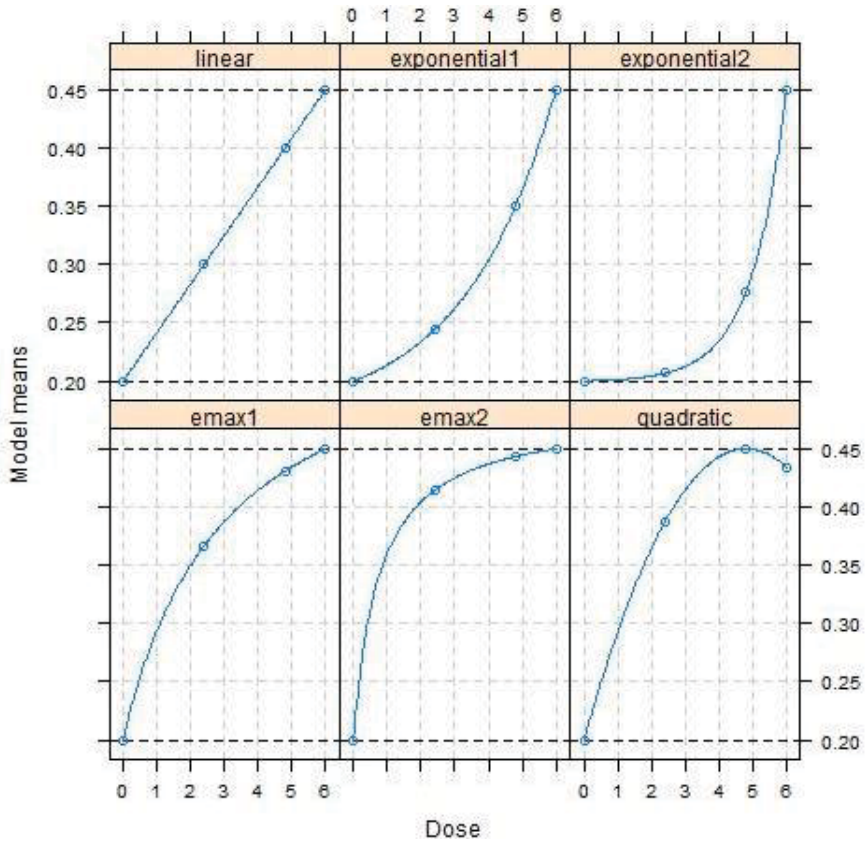
A logistic regression analysis will first be carried out on the primary endpoint. Covariate-adjusted estimates of the log odds for each dose and the covariance matrix will be extracted from the logistic regression fit and used for the subsequent MCPMod analysis. The MCPMod analysis will be carried out on the logit scale, and the results converted back to the original response scale for interpretation. The logistic regression model will be fitted without an intercept and will include presence of diabetes of any type (yes, no) and baseline fibrosis stage (F1, F2, F3), as well as the dose group, as factors.

The basic shape of each of the models to be tested must be pre-defined. The following model assumptions and resulting graphs (Figure 7.2.2: 1) have been selected to cover a plausible and

diverse range of dose response patterns, with placebo response rate assumed to be 20% [R16-5487; R16-5489; R18-2781] and maximum BI 456906 response rate assumed to be 45%. The maximum BI 456906 response rate occurs at the highest BI 456906 dose under monotone assumptions; one non-monotone dose response pattern is also included here, to allow for the possibility that this is not the case. Note: specifications here are made on the original response scale, but the MCPMod analysis itself must use the logit scale, i.e., in which the assumed placebo response rate is log(0.20/(1-0.20)) and the maximum BI 456906 response rate is log(0.45/(1-0.45)):

- Linear
- Exponential1: 25% of maximum effect achieved at dose 3.0 mg (Note: a 3.0 mg dose is only used to specify the models here and below. This dose is not proposed for inclusion in the trial.)
- Exponential2: 5% of maximum effect achieved at dose 3.0 mg
- Emax1: 50% of maximum effect achieved at dose 3.0 mg
- Emax2: 80% of maximum effect achieved at dose 3.0 mg
- Quadratic: Maximum effect achieved at dose 4.8 mg.

Figure 7.2.2: 1 Dose response patterns considered for the MCPMod analysis of the primary endpoint



A non-flat dose response relationship will be established if at least one model is statistically significant, rejecting the null hypothesis of a flat dose response relationship jointly over the candidate dose response models, with a contrast test controlled for the family–wise type I error rate at one sided $\alpha = 5\%$.

If a non-flat dose-response relationship is established, the statistically significant (best fitting) model(s) from the above candidate set will be refitted to the data to generate new estimates for all model parameters from the data. The target dose(s) will be estimated from the best fitting model(s) by incorporating information on the minimum clinically relevant effect ("delta") and accounting for safety.

The primary analysis will be performed using the FAS, as defined in Section 7.2.1.

The primary MCPMod analysis will use the actual maintenance dose (i.e., as treated). Actual maintenance dose is defined as the dose the patient was receiving at the start of the maintenance period (which is expected to be one of the planned maintenance doses). Rules for handling any special situations (e.g., any patient who was not receiving the same dose at the end of the maintenance period as at the start of the maintenance period) will be addressed in the TSAP. Any patient who discontinued treatment prior to starting the maintenance period will be assigned to the next target maintenance dose up from the last dose which was tolerated during the dose escalation period. For example, if a patient was randomised to a

maintenance BI 456906 dose of 6.0 mg and discontinued during the dose escalation period, having tolerated a dose of 2.4 mg but not tolerated a dose of 3.0 mg, this patient will be assigned to an actual maintenance dose of 4.8 mg in the analysis.

A sensitivity MCPMod analysis will be performed which uses randomised maintenance dose, irrespective of whether this dose was reached/tolerated. [redacted]

The primary analysis will use all available post-baseline biopsy data, regardless of whether it was done within the protocol scheduled window, specifically 1) with no restriction on how late after discontinuing or completing treatment the biopsy was done, and 2) using all available biopsy results for patients who discontinued treatment early irrespective of timing (although not expected to be available before Week 40). Patients without a post-baseline biopsy will be imputed as non-responders in the primary analysis, regardless of whether a biopsy result was expected (missing data) or not expected (intercurrent event of early treatment discontinuation, according to the protocol schedule). This essentially specifies a treatment policy strategy for an intercurrent event of early treatment discontinuation.

[redacted]

[redacted]

In addition to the above analyses, pairwise comparisons of all BI 456906 dose groups versus placebo will be provided in an explorative manner without adjusting for multiplicity.

The primary endpoint will be summarised descriptively overall, and [redacted]

7.2.3 Secondary endpoint analyses

MRI-PDFF responder secondary endpoint

MCPMod analysis of the secondary endpoint of 30% reduction in liver fat content assessed by MRI-PDFF at Week 48 will be performed in the same way as for the primary analysis in Section 7.2.2, and where the methodology is the same, it is not repeated here.

Covariate-adjusted estimates of the log odds for each dose and the covariance matrix will be extracted from a logistic regression fit and used for the MCPMod analysis, similarly to the primary analysis in Section 7.2.2. The same baseline factors will be used in the logistic regression model, plus an additional linear covariate for baseline liver fat content (from MRI-PDFF).

The same model assumptions and resulting graphs will be used as specified in Section 7.2.2 for the primary endpoint, except that the placebo response rate is assumed to be 15% and the maximum BI 456906 response rate is assumed to be 50%. As before, the MCPMod analysis itself must use the logit scale, i.e., in which the assumed placebo response rate is log(0.15/(1-0.15)) and the maximum BI 456906 response rate is log(0.50/(1-0.50)).

The analysis of this secondary MRI-PDFF responder endpoint will be performed using the FAS, and will use the actual maintenance dose (i.e., as treated).

[redacted]

Other secondary endpoints

For the continuous secondary endpoints measured repeatedly over time, a mixed model for repeated measures (MMRM) analysis will be performed and used to obtain covariate-adjusted mean estimates of differences between active BI 456906 doses and placebo at Week 48. The MMRM will include fixed effects for the baseline value of the endpoint (i.e., baseline liver fat content or baseline NAS, as relevant) and baseline by visit interaction as continuous covariates, and treatment, presence of diabetes (yes, no), baseline fibrosis stage (F1, F2, F3), visit and treatment-by-visit interaction as factors. Unstructured covariance will be used to model the relationship between pairs of endpoint measurements taken at different visits on the same patient. The Kenward-Roger approximation will be used to estimate the

denominator degrees of freedom. The TSAP will specify approaches to be taken to resolve possible non-convergence issues, including, if necessary, the selection of a simpler covariance structure.

For the binary secondary endpoint of a one stage decrease in fibrosis stage after 48 weeks, a logistic regression analysis will be performed and used to obtain covariate-adjusted odds ratios between active BI 456906 doses and placebo. The logistic regression model will include the same model terms as specified in Section 7.2.2. Where biopsy data are available between Week 40 and Week 48 for patients who prematurely discontinued early, these data will be used directly to determine the response for such patients (similarly to Section 7.2.2).

MCPMod dose finding analyses are not planned to be performed for secondary endpoints, other than as specified above for the MRI-PDFF responder endpoint. If additional MCPMod analyses are required, these will be specified in the TSAP, together with the dose response shapes to be evaluated.

All secondary endpoints will be summarised descriptively.

Secondary endpoints will be analysed using the FAS.

7.2.5 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 the residual effect period (REP), a period of 28 days after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

Safety analyses will be performed on the TS, using the actual maintenance treatment received. Key safety analyses will also be performed using the randomised maintenance treatment (if this is different for any patient).

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 REP.

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 Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

The adjudicated events will be summarised descriptively for each treatment group.

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

Vital signs, physical examinations and 12-lead ECG observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.2.6 Other Analyses

Exploratory analyses may be performed which investigate the relationship between endpoints derived from liver imaging (MRI-PDFF, [redacted]) and those obtained from biopsy. This may form part of a separate analysis plan and not be part of the CTR.

Intra-rater variability of biopsy readings
To assess the intra-rater variability of the screening biopsy reading, the screening and end of treatment biopsies will be read at the end of the trial, fully blinded to the initial eligibility biopsy reading, and to patient identification and visit timing. Intra-class correlation coefficients will be calculated. Further details will be provided in the TSAP.

[redacted]

7.2.7 Interim Analyses

Data Monitoring Committee
An external DMC will be implemented, with tasks and administrative details as briefly described in Section 8.7. Full details will be specified in the DMC Charter. The primary role of the DMC is the ongoing evaluation of safety.

Interim Analysis
One interim analysis will be performed after approximately half of randomised patients have reached Week 28.

[redacted]

[redacted]

All available data will be cleaned prior to interim database lock.

The interim analysis results are not intended to be used to stop the trial.

The interim analysis will be performed by the Sponsor, using the steps below to protect the integrity of the trial. The external DMC will be informed of the results of the interim analysis and will be given opportunity to review them at the scheduled DMC meeting following their availability.

The interim analysis will be performed by an independent statistics and programming team within BI. Personnel involved with trial conduct at study sites will not have access to unblinded data from the interim analysis, until after the end of treatment of the last patient in the trial. The trial team at BI will have access to aggregate unblinded interim results after the end of treatment of the last patient in the trial. Secure folders with restricted access will be used for the storage of unblinded interim data and results.

7.3 HANDLING OF MISSING DATA

For the primary analysis of the primary endpoint (see Section 7.2.2), all available post-baseline data will be used irrespective of timing. Patients without data with which to make the responder determination will be imputed as non-responders, regardless of whether a biopsy result was expected (missing data) or not expected (intercurrent event of early treatment discontinuation, according to the protocol schedule).

[redacted]

Missing data (whether related to handling of early treatment discontinuation or not) will be handled similarly for the MRI-PDFF responder secondary endpoint.

[redacted]

[redacted]

7.4 RANDOMISATION

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list(s) will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report (CTR). Access to the codes will be controlled and documented.

Patients will be randomised in blocks using equal allocations to one of 4 double-blind treatment groups. Randomisation will be performed at the start of the dose escalation period, with allocation to one of the following maintenance period treatments:

- Placebo once weekly
- BI 456906 2.4 mg once weekly
- BI 456906 4.8 mg once weekly
- BI 456906 6.0 mg once weekly.

Randomisation will be stratified by presence of any type of diabetes (Yes, No).

7.5 DETERMINATION OF SAMPLE SIZE

Calculations were performed using R Version 3.6.1.

One aim of this trial is to show a significant non-flat dose-response curve across the different doses and placebo. Additionally to that, at least one modelled dose within the dose range considered should show a benefit of at least "delta" in the primary endpoint responder rate compared to placebo. The probability of success of this trial is therefore defined as the probability to (1) obtain a significant test for non-flat dose-response curve and (2) to observe for at least one of the modelled doses an effect difference of at least delta compared to placebo.

The sample size calculation is based on an assumed maximum difference in the primary endpoint responder rate (BI 456906 vs. placebo) of 25%, as well as on the pre-specified models listed in Section 7.2.2. For placebo, a response rate of 20% at Week 48 will be considered [R16-5487; R16-5489; R18-2781].

Using a total sample size of 240 evaluable patients (60 per treatment group), the probability of a successful trial (as defined above) was estimated using simulations. For each dose group, samples of the required size were drawn from a binomial distribution.

Based on these assumptions, the success probability under a delta of 20% (i.e., non-flat curve achieved, and at least one BI 456906 dose shows a difference to placebo of at least 20%) is approximately 76% when assuming a linear dose response curve. Assuming a different form

for the underlying dose response curve (Emax, exponential, quadratic), the success probability is between 73% and 82% (data not shown). For a delta of 10% the respective success probability is 92% assuming a linear dose response shape, and between 92% and 95% for the other dose response shapes (data not shown).

If the difference between placebo and active BI456906 doses is low, i.e., 5% (which is assumed to be clinically not relevant) the success probability is approximately 2% and 16% for a delta of 20% and 10%, respectively (assuming a linear dose response curve). In the case that there is no treatment benefit, the false positive probability is limited by the α-level for the significance testing of the non-flat dose-response curve of 5% (one-sided). Additionally, this probability is further reduced by requesting an effect of at least delta. Thereby, the probability of a false decision for a non-effective drug is reduced to less than 1% for a delta of 20% and remains at less than 5% for a delta of 10%.

Due to tolerability issues it is possible that not all patients in the higher dose groups can be uptitrated to their randomised dose. Since the primary analysis is planned "as treated", this may result in lower sample sizes in highest dose groups and respectively higher sample sizes in lower dose groups. Therefore, in addition to the intended equal allocation, four variations of this sampling ratio have been considered. The first 2 variations assume that tolerability issues occur at the highest dose only (i.e., 60-60-70-50 and 60-70-70-40 for placebo, BI 456906 2.4 mg, BI 456906 4.8 mg and BI 456906 6.0 mg, respectively). The second 2 variations assume that tolerability issues could occur at either of the highest two doses (60-80-50-50 and 60-90-50-40 for placebo, BI 456906 2.4 mg, BI 456906 4.8 mg and BI 456906 6.0 mg, respectively). The resulting overall success probabilities do not differ meaningfully from those of the originally planned sampling sheme.
Table 7.5: 1 provides success probabilities under different scenarios (i.e., different treatment effects and allocation ratios).

Table 7.5: 1 Multiplicity-adjusted success probability given expected primary endpoint response rate at week 48 and a total sample size of 240 patients based on MCPMod nominal alpha-level of 5% (one-sided) and additional treatment effect threshold (delta).

Sample size per dose group	Expected primary endpoint response rate (in %)		Exp. max. Response Difference	Delta	Probability of positive MCPMod test (multiplicity adjusted)	Multiplicity adjusted overall success probability*
	Placebo	High dose BI				
60/60/60/60	20	45	25	20	92.1%	75.9%
60/60/60/60	20	50	30	20	97.9%	90.9%
60/60/70/50	20	45	25	20	91.1%	75.7%
60/70/70/40	20	45	25	20	89.5%	75.4%
60/80/50/50	20	45	25	20	90.4%	74.9%
60/90/50/40	20	45	25	20	88.1%	74.6%
60/60/60/60	20	25	5	20	15.6%	2.2%

60/60/60/60	20	20	0	20	4.5%	0.2%
60/60/60/60	20	45	25	10	92.1%	92.1%
60/60/60/60	20	50	30	10	97.9%	97.9%
60/60/70/50	20	45	25	10	91.1%	91.1%
60/70/70/40	20	45	25	10	89.5%	89.5%
60/80/50/50	20	45	25	10	90.4%	90.4%
60/90/50/40	20	45	25	10	88.1%	88.1%
60/60/60/60	20	25	5	10	15.6%	15.6%
60/60/60/60	20	20	0	10	4.5%	4.5%

*Success probabilities under different efficacy assumptions for the defined success criteria of 1) Significant non-flat dose-response achieved based on at least one of the candidate set models AND 2) Treatment benefit of at least 'delta' compared to placebo for at least one modelled dose within the considered dose range. Success probabilities have been calculated assuming a linear dose response relationship. All calculations have been done using R Version 3.6.1 based on simulations (10000 simulations per scenario). Thereby the calculations for the MCPMod step have been performed using DoseFinding R-package 0.9-16 [R15-2001]

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

The trial will be conducted in compliance with the clinical trial protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice, relevant BI SOPs, the EU directive 2001/20/EC/EU regulation 536/2014 and other relevant regulations. Investigators and site personnel must adhere to these principles. Deviation from the clinical trial protocol, the principles of ICH GCP or applicable regulations 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.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

Prior to patient participation in the trial, written informed consent must be obtained from each patient according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional 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.

The patient must be given sufficient time to consider participation in the trial. The Investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator or [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.

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

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 (IQRMP) 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

Electronic 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 eCRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the Investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the Investigator must make at least one documented attempt to retrieve previous medical records. If this fails, verbal feedback from the patient, documented in their medical records, would be acceptable.

Copies of source documents necessary for adjudication will be provided to the adjudication vendor. Before sending or uploading those copies, the Investigator must ensure that all patient identifiers (e.g., patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

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

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

- Patient identification: 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 AESIs (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)
- Completed C-SSRS questionnaires (paper record) and completed [redacted] diaries (if paper documents are used)
- 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 the clinical trial protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

The electronic version of the ECG is regarded as source data. Dated and signed printouts will be stored in the patient's medical file.

Data entered into Science 37 platform (i.e., [redacted], eDiary) will be regarded as source data.

8.3.2 Direct access to source data and documents

The Investigator/ Institution will allow site trial-related monitoring, audits, IRB/ IEC review and regulatory inspections. Direct access must be provided to the eCRF and all source documents/data, including progress notes, 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 eCRFs 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 clinical trial protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to 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 WHO GCP handbook.

Individual patient data obtained as a result of this clinical 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 clinical 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, biobanking and future use of biological samples and clinical data, in particular:

- Sample and data usage has to be in accordance with the separate biobanking informed consent
- 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, including audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The **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 clinical trial 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 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.

An independent external committee (Clinical Event Committee, [CEC]) will be established, jointly with trial 1404-0036 (c31754142-02), to adjudicate all cardiovascular, pancreatic, thyroid, and oncological trigger events identified by abnormal laboratory values and/ or adverse events. In order to assess the trigger events relevant source documents will be requested from investigators. They may include laboratory reports, reports from histology, ultrasound, CT, MRI or scintigraphy assessments, hospital discharge letters and medical reports from other physicians. The assessment will be blinded to treatment allocation. The process of identifying the events for adjudication and the adjudication process will be detailed in the CEC charter.

Data Monitoring Committee (DMC) will be established, jointly with trial 1404-0036 (c31754142-02). The DMC members are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician. The DMC will evaluate safety data and will receive urgent significant safety concerns, and cases of DILI, for immediate evaluation. While DMC members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend continuation, modification, or termination of the trial. DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs/ ECs, and to investigators as requested by local law. Tasks and responsibilities of the DMC will be specified in the DMC charter.

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 (CT Leader), responsible for coordinating all required activities, in order to:

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

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

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

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

Central services for laboratory, pathology, MR imaging and ECG and an IRT vendor will be used in this trial. Details will be provided in the respective manuals that will be available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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R20-1255 Younossi ZM. Non-alcoholic fatty liver disease - a global public health perspective. J Hepatol 2019;70:531-544.

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9.2 UNPUBLISHED REFERENCES

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10. APPENDICES

10.1 REMOVAL OF INDIVIDUAL PATIENTS IN CASE OF INCREASED LIVER ENZYMES

Trial-specific procedures have been defined in case of increased liver enzymes after randomisation as outlined below.

- Normal aminotransferases at baseline

New elevations of aminotransferases to ≥ 5x ULN (total bilirubin normal* and no liver-related symptoms) should be followed by a repeat testing within 48 to 72 hours. If elevations persist, other causes of aminotransferase elevations should be evaluated along with tests of hepatic functions. If no other cause is identified, the patient should be monitored closely.

Treatment with trial medication should be discontinued if:

- ALT or AST increases to ≥ 8x ULN
- ALT or AST increases to ≥ 5x ULN for more than 2 weeks
- ALT or AST increases to ≥ 3x ULN and the increase is accompanied by a concomitant increase in total bilirubin to ≥ 2x ULN** or INR to > 1.5
- ALT or AST increases to ≥ 3x ULN and the increase is accompanied by the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

- Abnormal aminotransferases at baseline

If a patient develops elevations of ALT or AST to ≥ 3x baseline or ≥ 300 U/L (whichever is lower) with total bilirubin normal* and no liver-related symptoms, the testing should be repeated within 48 to 72 hours. If elevations persist, then close observation (testing and physical examination 2 to 3 times a week) should be implemented, and discontinuation of trial medication should be considered. Decision to discontinue the trial medication should be considered based on factors that include how much higher than baseline ALT and AST values were relative to ULN and how much the on-treatment ALT and AST values have increased relative to baseline.

Treatment with trial medication should be discontinued if:

- baseline values were < 2x ULN, and ALT or AST increases to ≥ 5x baseline values
- baseline values were ≥ 2x ULN but ≤ 5x ULN, and ALT or AST increases to ≥ 3x baseline values
- ALT or AST increases ≥ 2x baseline values or ≥ 300 U/L (whichever is lower) and the increase is accompanied by a concomitant increase in total bilirubin to ≥ 2x ULN** or INR concomitantly increases by > 0.2 (to prevent false positive results, another sample should be tested within 24 hours)
- ALT or AST increases ≥ 2x baseline values or ≥ 300 U/L (whichever is lower) and patient develops signs and symptoms of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

Patients should be followed up until resolution of symptoms or signs in the above stated situations [P09-12413]. Treatment with trial medication may be restarted only if another aetiology is clearly identified and the liver values have returned to baseline [R20-1981]. Otherwise, after resolution or stabilisation the patient should complete the procedures for the EOT and Follow-up visit (Visit 32 and 33 resp.) as outlined in the Flow Chart and Section 3.3.4.1 and 6.2.3.

* Patients with Gilbert's syndrome: no change from baseline total bilirubin
** Patients with Gilbert's syndrome: doubling of direct (conjugated) bilirubin

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		18 December 2020
EudraCT number **EU number**		2020-002723-11
BI Trial number		1404-0043
BI Investigational Medicinal Product(s)		BI 456906
Title of protocol		Multicenter, double-blind, parallel-group, randomised, 48 weeks, dose-ranging, placebo-controlled phase II trial to evaluate efficacy, safety and tolerability of multiple subcutaneous (s.c.) doses of BI 456906 in patients with non-alcoholic steatohepatitis (NASH) and fibrosis
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Flow Chart
Description of change		1. Dispensation of SMBG device at Visit 2 added to the flow chart 2. Footnote #23: Statement about C-SSRS questionnaire administration “at each site visit” deleted (C-SSRS questionnaire not administered at Visit 3 and 5) 3. Footnote #25: Clarification regarding use of SMBG device added 4. Footnotes #25 and higher re-numbered 5. “Screening” or “screening visit” replaced with “Visit 1” in footnotes
Rationale for change		Ad 1 and 3: Implementation of additional safety measure Ad 2, 4 and 5: Corrections and clarifications
Section to be changed		Section 1.4.2
Description of change		Regular SMBG measurements in T2DM patients on antidiabetic medication and safety measures in case of hypoglycemic events added
Rationale for change		Request from Health Authority regarding safety risk monitoring and mitigation in patients vulnerable to hypoglycemia
Sections to be changed		Section 3.1
Description of change		“Visit 1” and “Visit 1a” added to the first and second screening visit resp.
Rationale for change		Clarification
Sections to be changed		Sections 3.2 and 4.1.5.1
Description of change		Information added regarding unplanned DMC

		meeting and unblinded safety assessment by DMC at the occurrence of adverse events that may lead to trial discontinuation
Rationale for change		Request from Health Authority regarding trial stopping criteria and process
Sections to be changed		Section 3.3.2 and synopsis
Description of change		1. Cut-off for age increased to legal age for countries with legal age above 18 years 2. BMI cut-off increased to 25 kg/m^2 3. "Screening visit" replaced with "Visit 1"
Rationale for change		Ad 1/ Legal age clarification Ad 2/ The previous BMI cut-off included normal weight Caucasians while overweight Asians. BMI cut-off of 25 kg/m^2 will homogenously include overweight patients of all ethnicities. Ad 3/ Clarification
Section to be changed		Section 3.3.3 and synopsis
Description of change		1. Text regarding acute COVID-19 infection and testing slightly re-worded 2. Cut-off for eGFR increased to 60 mL/min/1.73m^2 3. Exclusion of patients with history of organ transplantation except for corneal transplantation added to the criteria 4. Description "requiring inpatient treatment or escalation of care" added for patients with history of major depressive disorder in the past 2 years 5. SI units added to conventional units 6. "Screening visit" replaced with "Visit 1"
Rationale for change		Ad 1 and 6: Clarifications Ad 2 and 3: Request from Health Authority Ad 4: Further specification added for identification of patients with history of major depressive disorder Ad 5: Laboratory units relevant for investigator decisions (e.g., on patient eligibility) aligned with units used by the central laboratory when reporting results
Section to be changed		Section 3.3.4.1
Description of change		1. Occurrence of an adverse event CTCAE Grade 3 related to trial treatment added to the trial treatment discontinuation criteria for individual patients 2. Trial treatment discontinuation criterion for individual patients regarding clinically relevant ECG changes corrected, QTcF increase from

		baseline changed to 60 ms, Visit 2 defined as baseline 3. Information added about close monitoring and medical review of all adverse events CTCAE Grade 3 and higher. Triggers for discontinuation of trial treatment for all patients specified.
Rationale for change		Ad 1 and 3: Request from Health Authority regarding trial treatment discontinuation criteria Ad 2: Correction
Section to be changed		Section 4.1.2
Description of change		Duration of escalation period in active treatment groups changed to "16 to 22 weeks"
Rationale for change		Correction
Section to be changed		Section 4.1.4
Description of change		Number of weeks on treatment added to Table 4.1.4.:1 "Dose escalation schemes"
Rationale for change		Clarification
Section to be changed		Section 4.1.5.2
Description of change		Information added regarding unblinding by pharmacovigilance group or independent statistician for assessment of adverse events that may lead to trial discontinuation
Rationale for change		Process clarification
Section to be changed		Sections 4.2.1 and 5.2.5.2
Description of change		Guidance for regular SMBG measurements in T2DM patients and safety measures in case of hypoglycemic events added
Rationale for change		Request from Health Authority on safety risk monitoring and mitigation in patients vulnerable to hypoglycemia
Section to be changed		Section 4.3
Description of change		The word "allowable" added in the sentence describing the total maximum number of missed doses during the entire treatment period
Rationale for change		Clarification
Section to be changed		Section 5.1.1
Description of change		Minimum requirement for collection of liver biopsy specimen (i.e., size of biopsy needle, size of biopsy specimen) added to define the quality standards for an accurate histology evaluation
Rationale for change		Request from Health Authority regarding biopsy collection
Sections to be changed		Section 5.2.3
Description of change		1. SARS-CoV-2 RT PCR test deleted from the serology subsection of Table 5.2.3:1 "Safety laboratory tests" and added below the table

		2. "Screening visit" and "screening" replaced with "Visit 1", and "randomisation" replaced with "Visit 2"
Rationale for change		Correction and clarification
Section to be changed		Section 5.5.1
Description of change		Patients from sites in China excluded from collection of blood samples for evaluation of exploratory biomarkers, but Fib-4 index and APRI will be calculated.
Rationale for change		Clarification
Section to be changed		Section 7.2.6
Description of change		Brief statement added regarding blinded biopsy readings and subsequent analysis of intra-class correlation coefficient.
Rationale for change		Clarification of process and planned evaluation of intra-rater variability.
Section to be changed		Synopsis, Abbreviations, Sections 7.2.1, 7.2.2, 7.2.3, 7.2.4 and 7.2.5
Description of change		Redefine analysis set labels for full analysis set (FAS) and treated set (TS) to include rather than exclude patients from sites in China. Note: this is a labelling issue only and does not change any statements about whether patients from sites in China are actually included or excluded from the specified analyses.
Rationale for change		Consistency with other trials in project
Section to be changed		Section 9.1
Description of change		Reference added to FDA's drug-induced liver injury (DILI) guidance
Rationale for change		Administrative change
Section to be changed		Section 10.1
Description of change		Guidelines for removal of individual patients in case of increased liver enzymes revised. Trial treatment discontinuation criteria defined for individual patients in the event of drug-induced liver injury.
Rationale for change		Request from Health Authority regarding DILI
Sections to be changed		Cover page, Abbreviations, multiple sections
Description of change		1. Clinical Trial Protocol version and date changed 2. "SMBG" and "QTcF" added to abbreviations, QT explanation re-worded 3. Typos corrected
Rationale for change		Administrative changes

11.2 GLOBAL AMENDMENT 2

Date of amendment		14 May 2021
EudraCT number **EU number**		2020-002723-11
BI Trial number		1404-0043
BI Investigational Medicinal Product(s)		BI 456906
Title of protocol		Multicenter, double-blind, parallel-group, randomised, 48 weeks, dose-ranging, placebo-controlled phase II trial to evaluate efficacy, safety and tolerability of multiple subcutaneous (s.c.) doses of BI 456906 in patients with non-alcoholic steatohepatitis (NASH) and fibrosis
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis – total number of patients
Description of change		Removed statement that up to 24 additional patients from sites in China will be randomised.
Rationale for change		Patients from sites in China are now part of the 240 patients planned to be randomised in the trial.
Section to be changed		Synopsis – inclusion criteria
Description of change		Replaced “Screening visit” with “Visit 1”.
Rationale for change		Clarification
Section to be changed		Synopsis – statistical methods
Description of change		Amended definition of full analysis set (FAS) to include all randomised and treated patients and removed reference to China in the FAS definition. Removed statement that a sensitivity analysis of the primary endpoint will be performed including patients from sites in China.
Rationale for change		Patients from sites in China will now be included in the primary analysis and are expected to provide timely biopsy data to enable this. There is no longer any reason to consider separate analyses of the primary endpoint with and without patients from sites in China.
Section to be changed		Synopsis – statistical methods
Description of change		Removed wording that the trigger for interim analysis (approximately half of randomised patients having reached Week 28) will exclude patients from sites in China. Removed statement that the interim analysis will exclude data from patients from sites in China.

Rationale for change		If any patients from China have reached Week 28 before the interim analysis trigger has been met, they will be included in the count of half of the planned randomised patients. Irrespective of whether or not any patients from China have reached Week 28 by the time the interim analysis is triggered, patients from sites in China will be included in the interim analysis as far as their available data permit. Since the primary analysis will now include patients from sites in China, there is no longer any reason to consider a different requirement for the interim analysis with regard to those countries included.
Section to be changed		Flowchart incl. footnotes
Description of change		1. Extended the screening period to 10 weeks 2. Clarified that measurement of vital signs at Visit 1a is optional [redacted] 4. Deleted the requirement to perform imaging assessments at the same time of the day 5. Added urine pregnancy test at V33 (Follow-Up Visit)
Rationale for change		1. Consecutive screening approach and central assessments may require more time than 8 weeks. 2. Measurement of vital signs at the primary site on the day of the screening biopsy may not be always possible. [redacted] 4. Requirement is not necessary. 5. Pregnancy test should be performed at the end of the relevant systemic exposure.
Section to be changed		Sections 1.4.1 and 4.2.2.2
Description of change		Aligned wording in both sections, added information on diet restrictions and removed "modifications" of lifestyle. Added wording regarding dietary supplements.
Rationale for change		Correction and clarification
Section to be changed		Section 1.4.2
Description of change		Added information on vaccination for COVID-19 during and after treatment period

Rationale for change		Request from Health Authority
Section to be changed		Sections 3.1, 6.1 and 6.2.1
Description of change		Extended the screening period to 10 weeks
Rationale for change		Consecutive screening approach and central assessments may require more time than 8 weeks.
Section to be changed		Section 3.3
Description of change		Removed text regarding additional recruitment in China and increased the number of sites. Removed information on a separate cap for patients from China.
Rationale for change		Patients from China will be part of the 240 patients planned randomised in the trial. There is no longer any reason to separate processes for sites from China.
Section to be changed		Section 3.3.3
Description of change		1. Added information on treated hepatitis C patients 2. Replaced “Visit 1” with “screening” 3. Added congestive heart failure NYHA class III-IV to exclusion criteria
Rationale for change		1. Clarification 2. Fasting condition is not required for blood samples collection at any visit. However, serum triglycerides may be re-tested at fasting condition during screening if the levels at Visit 1 exceed 500 mg/dL (5.65 mmol/L). 3. Alignment of exclusion criteria across trials using the same compound
Section to be changed		Sections 3.3.3 and 5.2.2
Description of change		Added information on a second blood pressure measurement at Visit 1
Rationale for change		Increase of blood pressure measurement accuracy
Section to be changed		Section 3.3.4.1
Description of change		1. Added Torsade de Pointes and any major adverse cardiovascular events to trial treatment discontinuation criteria. 2. Added clinically significant elevation of liver enzymes and tolerance issues with the dose to trial treatment discontinuation criteria.
Rationale for change		1. Request from Health Authority 2. This information is mentioned in other sections of the clinical trial protocol. It was added to the list of treatment discontinuation criteria in this section for the sake of completeness.
Section to be changed		Section 4.1.2
Description of change		Corrected information on toxicology studies. Added information on the selection of 6 mg dose in

		the trial.
Rationale for change		Request from Health Authority
Section to be changed		Section 4.1.4
Description of change		1. Removed wording that Instructions for Use (IFU) will be provided to patients via platform. 2. Added paper diary as an alternative option to eDiary.
Rationale for change		1. Use of both, electronic and a paper document, should be possible. 2. In case of non-availability of eDiary backup solution should be in place.
Section to be changed		Section 4.1.5.1
Description of change		Removed wording that the trigger for interim analysis (approximately half of randomised patients having reached Week 28) will exclude patients from sites in China.
Rationale for change		If any patients from China have reached Week 28 before the interim analysis trigger has been met, they will be included in the count of half of the planned randomised patients.
Section to be changed		Section 5.1.1
Description of change		1. Added alternative option to provide biopsy blocks to the central pathology laboratory 2. Removed wording on biopsy process for sites in China 3. Removed wording on collection of tissue specimens for gene expression analysis in China
Rationale for change		1. Consistency with the manuals from the central pathology laboratory 2. Detailed information will be included in the manuals from the central pathology laboratory. 3. Any restrictions on specimen collection in a specific country will be subject of a local amendment.
Section to be changed		Section 5.1.3
Description of change		Removed wording on MRI procedure in China
Rationale for change		Redundant wording
Section to be changed		Section 5.2.2
Description of change		Clarified that measurement of vital signs at Visit 1a is optional
Rationale for change		Measurement of vital signs at the primary site on the day of the screening biopsy may not be always possible.
Section to be changed		Section 5.2.3
Description of change		Added information on the possibility to conduct safety laboratory tests in local laboratories

Rationale for change		Implemented measures ensuring trial continuity while maintaining patient safety in the event of disruptive circumstancies
Section to be changed		Section 5.5.1
Description of change		Removed wording on collection of samples for biomarker assessment in China
Rationale for change		Any restrictions on sample collection in a specific country will be subject of a local amendment.
Section to be changed		Section 5.6
Description of change		Removed wording on collection of samples for biobanking in China
Rationale for change		Restrictions are applicable in several participating countries. Collection of samples for biobanking is optional.
Section to be changed		Section 5.7
Description of change		[redacted]
Rationale for change		
Section to be changed		Section 6.1
Description of change		Added information on the use of local laboratories, paper diaries and PROs
Rationale for change		Implemented measures ensuring trial continuity while maintaining patient safety in the event of disruptive circumstancies
Section to be changed		Section 7.2.1
Description of change		Amended definition of full analysis set (FAS) to include all randomised and treated patients and removed reference to China in the FAS definition. Removed references to a separate main and final analysis with and without patients from sites in China. Similar changes made regarding treated set (TS).
Rationale for change		Patients from sites in China will now be included in all analyses and are expected to provide timely biopsy data to enable inclusion in the primary analysis. There is no longer any reason to consider separate analyses with and without patients from sites in China.
Section to be changed		Section 7.2.1
Description of change		Statement that important protocol deviations (IPDs) leading to exclusion from the per protocol analysis set will be defined in the TSAP changed to

		require definition in the IPD specification document.
Rationale for change		Update to Sponsor process.
Section to be changed		Section 7.2.2
Description of change		Removed reference to China in FAS definition. Removed reference to a main analysis in which patients from China are not included in the primary analysis. Removed reference to a final analysis in which patients from China are included as a sensitivity analysis. Removed subsequent reference to a logistic regression model in which an additional factor (China, Rest of World) in included.
Rationale for change		Patients from sites in China will now be included in the primary analysis and are expected to provide timely biopsy data to enable this. There is no longer any reason to consider separate analyses of the primary endpoint with and without patients from sites in China. Statistical analysis models are updated to reflect stratification changes in Section 7.4 (see separate description of change).
Section to be changed		Section 7.2.3
Description of change		Removed reference to China in FAS definition. Removed reference to a main analysis in which patients from China are not included. Removed reference to a final analysis in which patients from China are included. These changes made 1) to the description of analysis of the secondary MRI-PDFF responder endpoint, and 2) to the description of analysis of other secondary endpoints.
Rationale for change		Patients from sites in China will now be included in all analyses. There is no longer any reason to consider separate analyses with and without patients from sites in China.
Section to be changed		[redacted]
Description of change		

		[redacted]
Rationale for change		
Section to be changed		Section 7.2.5
Description of change		Removed reference to China in TS definition. Removed reference to a main analysis in which patients from China are not included. Removed reference to a final analysis in which patients from China are included.
Rationale for change		Patients from sites in China will now be included in all analyses. There is no longer any reason to consider separate analyses with and without patients from sites in China.
Section to be changed		Section 7.2.7
Description of change		Removed wording that the trigger for interim analysis (approximately half of randomised patients having reached Week 28) will exclude patients from sites in China. Removed statement that the interim analysis will exclude data from patients from sites in China. Amended statement that data for the interim analysis would only be cleaned for patients not from sites in China.
Rationale for change		If any patients from China have reached Week 28 before the interim analysis trigger has been met, they will be included in the count of half of the planned randomised patients. Irrespective of whether or not any patients from China have reached Week 28 by the time the interim analysis is triggered, patients from sites in China will be included in the interim analysis as far as their available data permit. Data will be cleaned

		for this purpose accordingly. Since the primary analysis will now include patients from sites in China, there is no longer any reason to consider a different requirement for the interim analysis with regard to those countries included.
Section to be changed		Section 7.2.7
Description of change		Removed considerations relating to the timing of liver biopsy results. Removed reference to a main analysis in which patients from China are not included. Removed reference to a final analysis in which patients from China are included. Removed descriptions of separate database locks to handle the above items.
Rationale for change		It is expected that timely reading of liver biopsy slides by the central pathologist is possible in all proposed countries. There is no longer any reason to consider separate analyses with and without patients from sites in China.
Section to be changed		Section 7.4
Description of change		Removed stratification variable for country (Rest of World/China). Only presence of diabetes (Yes/No) is retained for stratification purposes, irrespective of country.
Rationale for change		Since China is not being handled differently from other countries with regard to 1) inclusion in the primary analysis and the expected timely availability of biopsy data to permit this, and 2) the use of the same central pathology reader as other countries, there is no longer any reason for the additional stratification.
Section to be changed		Section 7.5
Description of change		Statement removed that the 240 randomised patients planned according to statistical considerations does not include patients from sites in China. Statement deleted that up to 24 additional patients from sites in China will be randomised.
Rationale for change		Patients from sites in China will be included in the

		primary analysis and, as such, are now part of the 240 patients planned to be randomised.
Section to be changed		Section 8.1
Description of change		Removed wording on the provision of a signed copy of the informed consent to the patient's legally accepted representative
Rationale for change		Legally accepted representative will not be involved.
Section to be changed		Section 8.3.1
Description of change		Added paper [redacted] diaries to source documents
Rationale for change		In case of non-availability of [redacted] diaries paper documents may be used.
Section to be changed		Section 8.6
Description of change		Statement deleted that data from patients at sites in China will not be included in the final report.
Rationale for change		All patients will be included in the clinical trial report, regardless of location.
Section to be changed		All sections
Description of change		Corrected typographical errors
Rationale for change		Quality improvement of the document

11.3 GLOBAL AMENDMENT 3

Date of amendment		24 May 2022
EudraCT number **EU number**		2020-002723-11
BI Trial number		1404-0043
BI Investigational Medicinal Product(s)		BI 456906
Title of protocol		Multicenter, double-blind, parallel-group, randomised, 48 weeks, dose-ranging, placebo-controlled phase II trial to evaluate efficacy, safety and tolerability of multiple subcutaneous (s.c.) doses of BI 456906 in patients with non-alcoholic steatohepatitis (NASH) and fibrosis
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis and Section 3.3.2
Description of change		Added information to the inclusion criterion that liver biopsy findings should always be taken into account as primary assessment for the decision of the eligibility of patients in case there is not agreement between histology and non-invasive assessments.
Rationale for change		It is well known that both FibroScan® and MRI-PDFF are surrogate of liver biopsy findings, which are nevertheless more accurate in staging and grading NASH and liver fibrosis.
Section to be changed		Flowchart - footnotes
Description of change		1. Added information about possible extension of the screening period 2. [redacted] 3. Added information on the collection of biobanking samples (blood and stool) 4. Specified timepoint of the FibroScan® and MR imaging measurement during the screening period
Rationale for change		1. Logistical issues may cause delays in the provision of results by the central vendor(s). Eligible patients who underwent a liver biopsy during the screening period should be considered for participation in the trial even if results were received more than 10 weeks after Visit 1 (ethical aspect). 2. Items 2 - 4 required further clarification
Section to be changed		Section 1.3
Description of change		Added the source of knowledge about GLP-1

		receptor agonists
Rationale for change		Accuracy of statement
Section to be changed		Section 3.3
Description of change		Changed the number of sites participating in the trial
Rationale for change		More sites are required to reach the patient recruitment target.
Section to be changed		Section 3.3.3
Description of change		1. Added information on hepatitis B patients 2. Corrected numbering of exclusion criteria from No. 3 to No. 20 3. Modified the cut-off for eGFR 4. Modified the cut-off for platelet count 5. Added information on patient participation in another interventional trial
Rationale for change		1. Clarification 2. Correction of the previous formatting error 3. Patients with mild or moderate renal impairment represent a relevant part of our target patient population. Data from a recently completed clinical trial in patients with T2DM that included patients with a baseline eGFR of 45 mL/min/1.73m^2 or higher show that the overall summary of adverse events in patients with eGFR < 60 mL/min/1.73m^2 was largely in line with that of patients with eGFR ≥ 60 mL/min/1.73m^2. Furthermore, publicly available eligibility criteria of other GLP-1R agonist based compounds included patients with eGFR between 45 and 60 mL/min/1.73m^2 and this did not represent a safety concern for the patients. GLP-1R agonists with a marketing authorization do not require dose adjustments for patients with mild or moderate renal impairment. 4. Liver cirrhosis is accurately ruled out by histology in our trial, therefore patients without any sign of liver cirrhosis and a platelet count > 110 x10^9/L are assumed to have a non-significant risk of suffering from portal hypertension. 5. Clarification
Section to be changed		Section 3.3.4.1
Description of change		1. Added information on trial treatment discontinuation of individual patients who experience an infection with SARS-CoV-2

		2. Modified stopping rules of the trial. Instead of stopping the trial treatment in all patients further enrolment of new patients in the trial will be stopped until receiving the DMC recommendation. Timeline for the ad-hoc DMC meeting has not changed, it will take place within one week. Individual patients who experience an AE of CTCAE Grade 3 or higher that was assessed by the Investigator as related to the trial treatment will discontinue the trial treatment. 3. Specified criteria for Grade 3 CTCAE adverse events of nausea, vomiting, diarrhoea, constipation, or anorexia
Rationale for change		1. Investigator will take the totality of information related to the patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment in order to determine whether the patient should continue to participate in the trial. Alignment with the latest COVID-19 benefit-risk assessment for BI 456906 2. GLP-1R agonist compounds require an accurate dose-escalation scheme before reaching the maintenance dose. In addition, certain tolerance is reached with time. Sudden stop and possible restart of the trial treatment in all patients may lead to drug tolerability issues in many patients. Alignment of stopping rules with another BI 456906 trial in patients with hepatic impairment 3. For the purpose of triggerring an ad-hoc DMC evaluation the CTCAE grading was put into a more clinically meaningful context to give the right value to the AEs which need to be considered for stopping the enrolment of new patients in the trial and potentially stopping the trial following DMC recommendation. Alignment with another BI 456906 trial in patients with hepatic impairment
Rationale for change		Section 4.1.4 and 5.7
Section to be changed		Added information on the use of paper [redacted] diaries in case of technical issues with the Science 37 platform
Description of change		Clarification
Section to be changed		Sect. 4.1.5.1

Description of change		Added information on the exclusion of ADA and NAb samples taken from placebo patients from the analyses
Rationale for change		Consistency with PK samples
Section to be changed		Sect. 4.2.2.1
Description of change		1. Removed SGLT-2 inhibitors from the list of restricted concomitant medications 2. Added medications known to significantly prolong the QT/ QTc interval to the list of restricted concomitant medications
Rationale for change		1. There are no clinical concerns supporting the complete exclusion of T2DM patients treated with SGLT-2 inhibitors. 2. Alignment with exclusion criterion No. 15
Section to be changed		Section 5.2.3
Description of change		Corrected the type of specimen for Free Fatty Acids
Rationale for change		Consistency with the central laboratory documents
Section to be changed		Section 5.2.4
Description of change		Added information on a single ECG measurement at visits following Visit 1
Rationale for change		Clarification
Section to be changed		Section 5.3.2
Description of change		Removed the timepoint when PK samples may be used for further methodological investigations
Rationale for change		There is no reason to restrict the use of the samples only after the completion of the trial
Section to be changed		Section 6.1
Description of change		Added information on the minimum medical prerequisites that should be fulfilled in order to ship trial medication to the patient's home when a patient cannot visit the site due to safety risks
Rationale for change		Clarification
Section to be changed		Section 6.2.1
Description of change		1. Added information about possible extension of the screening period 2. Specified requirement for FibroScan® and MR imaging at re-screening
Rationale for change		1. Logistical issues may cause delays in the provision of results by the central vendor(s). Eligible patients who underwent a liver biopsy during the screening period should be considered for participation in the trial even if results were received more than 10 weeks after Visit 1 (ethical aspect). 2. Reduction of addional burden for patients. FibroScan® and MR imaging do not have to be

		repeated at re-screening if the assessments were performed within previous 1 month during the initial screening.
Section to be changed		Section 7.2.7
Description of change		Added information on the population PK/PD analysis that should be performed during the interim analysis
Rationale for change		Clarification
Section to be changed		Section 9.1
Description of change		Added reference to the consensus guideline for detection, assessment and management of suspected acute drug-induced liver injury (DILI) during clinical trials in patients with NASH
Rationale for change		Administrative change
Section to be changed		Section 10.1
Description of change		Revised guidelines for removal of individual patients in case of increased liver enzymes
Rationale for change		Alignment with the consensus guidelines including provisions for patients with Gilbert's syndrome
Section to be changed		Cover page, Synopsis, Abbreviations
Description of change		1. Changed Clinical Trial Protocol version and date 2. Added "IV" to abbreviations
Rationale for change		Administrative changes
Section to be changed		Multiple sections
Description of change		Corrected grammatical and typographical errors
Rationale for change		Quality improvement of the document

11.4 GLOBAL AMENDMENT 4

Date of amendment		04 August 2022
EudraCT number **EU number**		2020-002723-11
BI Trial number		1404-0043
BI Investigational Medicinal Product(s)		BI 456906
Title of protocol		Multicenter, double-blind, parallel-group, randomised, 48 weeks, dose-ranging, placebo-controlled phase II trial to evaluate efficacy, safety and tolerability of multiple subcutaneous (s.c.) doses of BI 456906 in patients with non-alcoholic steatohepatitis (NASH) and fibrosis
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Section 1.3
Description of change		Corrected sample size to 240
Rationale for change		Correction was missed during the last two protocol amendments.
Section to be changed		Section 3.3.3
Description of change		Modified the cut-off for platelet count to the original level
Rationale for change		The trial is in the final stage of recruitment. Implementation of alternative non-invasive tests and/ or imaging tools for the exclusion of portal hypertension as requested by Health Authority would require more time than the remaining available time for recruitment.
Section to be changed		Sect. 4.2.2.1
Description of change		Patients recently started on SGLT-2 inhibitors will be excluded.
Rationale for change		Recommendation from Health Authority

11.5 GLOBAL AMENDMENT 5

Date of amendment		27 July 2023
EudraCT number **EU number**		2020-002723-11
BI Trial number		1404-0043
BI Investigational Medicinal Product(s)		BI 456906
Title of protocol		Multicenter, double-blind, parallel-group, randomised, 48 weeks, dose-ranging, placebo-controlled phase II trial to evaluate efficacy, safety and tolerability of multiple subcutaneous (s.c.) doses of BI 456906 in patients with non-alcoholic steatohepatitis (NASH) and fibrosis
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Section 4.1.5.1 and 7.2.7
Description of change		Modified information on purpose of the interim analysis and access to unblinded data from the interim analysis
Rationale for change		Considering that the mean BMI of patients recruited in this trial is approx. 36 kg/m^2, data on liver fat reduction (and liver benefit in general) in this patient category are very informative for the future development program of BI 456906 in chronic weight management, going into phase III by Q4/2023. The availability of this data will help enrolling the best patient population into the trial(s), targeting patients who may benefit most. As the phase II trial in chronic weight management (1404-0036) has not generated liver data, as opposed to 1404-0043, it is important to inform investigators, study personnel, patients and their relatives involved in the phase III program of BI 456906 in chronic weight management about these benefits in a timely manner, considering that the updated version of the Investigator Brochure (planned issue in Q4 2023) will not include interim analysis data and, importantly, will not be able to appropriately reach and inform patients and caregivers. The availability of this data will help positioning BI 456906 among the available drugs in development for chronic weight management, independently of the NASH indication.
Section to be changed		Section 5.2.3 (Table 5.2.3:1)
Description of change		Corrected information on availability of eGFR

		results
Rationale for change		Typographical error

APPROVAL / SIGNATURE PAGE

Document Number: c31864883 **Technical Version Number:6.0**

Document Name: clinical-trial-protocol-version-06

Title: Multicenter, double-blind, parallel-group, randomised, 48 weeks, dose-ranging, placebo-controlled phase II trial to evaluate efficacy, safety and tolerability of multiple subcutaneous (s.c.) doses of BI 456906 in patients with non-alcoholic steatohepatitis (NASH) and fibrosis

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	31 Jul 2023 13:08 CEST
Approval-Clinical Program [redacted]		31 Jul 2023 15:42 CEST
Author-Trial Statistician		31 Jul 2023 16:05 CEST
Verification-Paper Signature Completion		03 Aug 2023 10:49 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed