Clinical Trial Protocol

	Document Number:	**c26686857-02**
EudraCT No.	2019-002390-60	
BI Trial No.	1404-0002	
BI Investigational Medicinal Product(s)	BI 456906	
Title	A Phase II, randomized, parallel group, dose-finding study of subcutaneously administered BI 456906 for 16 weeks, compared with placebo and open-label semaglutide in patients with type 2 diabetes mellitus.	
Lay Title	A study to test whether different doses of BI 456906 are effective in treating adults with type 2 diabetes.	
Clinical Phase	Phase II	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol (revised protocol based on global amendment 1)	
Version and Date	**Version: 2**	**Date: 28 September 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	28 August 2019
Revision date	28 Sep 2020
BI trial number	1404-0002
Title of trial	A Phase II, randomized, parallel group, dose-finding study of subcutaneously administered BI 456906 for 16 weeks, compared with placebo and open-label semaglutide in patients with type 2 diabetes mellitus.
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]
Trial site(s)	Multicenter trial conducted in approximately 14 countries
Clinical phase	II
Trial rationale	The trial is designed to evaluate safety, tolerability, PK and PD of BI 456906 in male and female patients with type 2 diabetes mellitus (T2DM) using multiple escalation schemes and doses, and will support dose selection for phase 3 clinical development of BI 456906.
Trial objective	The primary objective is to demonstrate proof of clinical concept with respect to a non-flat dose response curve and to define a suitable dose escalation scheme and dose range for BI 456906 regarding safety, tolerability, and efficacy, for further pivotal testing in phase 3 studies.
Trial endpoints	**Primary endpoint:** 1. Absolute change in HbA1c from baseline to 16 weeks. **Secondary endpoints:** 1. The relative body weight change from baseline to 16 weeks (key secondary endpoint). 2. The absolute body weight change from baseline to 16 weeks. 3. The absolute change in waist circumference from baseline to 16 weeks. 4. The percentage of patients with 5% or greater body weight loss from baseline to 16 weeks. 5. The percentage of patients with 10% or greater body weight loss from baseline to 16 weeks.
Trial design	Randomized, double blind within dose groups, parallel, placebo and active comparator controlled trial
Total number of patients randomized	Approximately 410

Number of patients on each treatment	60 patients in each of the six BI 456906/placebo dose groups 50 patients in the semaglutide group
Diagnosis	Type 2 diabetes mellitus
Main inclusion- and exclusion criteria	**Inclusion criteria:** 1. Signed and dated written informed consent in accordance with ICH GCP and local legislation. 2. Male and female patients 18 years to 75 years (both inclusive) of age on the day of signing informed consent. 3. Diagnosis of T2DM at least 6 months prior to informed consent. 4. HbA1c 7.0%-10.0% (both inclusive) at screening. 5. Treatment with a stable dose of metformin ≥ 1000mg/day for at least 3 months prior to screening. 6. Body mass index (BMI) 25 kg/m^2-50 kg/m^2 (both inclusive) at screening. **7.** Women of childbearing potential must be ready and able to use highly effective methods of birth control. **Exclusion criteria:** 1. Patients with type 1 diabetes. 2. Exposure to semaglutide, or other GLP-1R agonists (including combination products) within 3 months prior to screening, or any previous exposure to BI 456906. 3. Any additional oral anti-hyperglycemic medication beyond metformin within 3 months prior to screening. 4. Use of insulin for glycemic control within 12 months prior to screening. 5. Resting Heart Rate >100 bpm or blood pressure ≥160/95 mm Hg at screening. 6. A marked prolongation of QT/QTc (Fridericia) interval or any other clinically significant ECG finding at screening. 7. Body weight change of +/- 5% or more in the past 3 months or on anti-obesity therapies at any time during the 6 months prior to screening. 8. Continuous oral pharmacotherapy to treat any clinical condition during the trial. Following medications are allowed: • metformin • anti-hypertensives* • hormone replacement therapy including thyroid hormone • lipid lowering • proton pump inhibitors • H2 blockers for GERD • analgesics • sleep medications • antihistamines

	• selective alpha receptor blocker for benign prostatic hyperplasia Patients must be on a stable dose for at least 3 months prior to screening. *Any medications known to cause heart block or bradycardia such as beta-blockers, verapamil and diltiazem are excluded unless used to treat heart rate control or hypertension. 9. Any suicidal behavior in the past 2 years, any suicidal ideation of type 4 or 5 in the C-SSRS in the past 3 months at screening. 10. Chronic or relevant acute infections. 11. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
Test products	BI 456906 or matching placebo
dose	Multiple doses
mode of administration	Subcutaneous injection
Comparator product	Semaglutide
dose	Multiple doses
mode of administration	Subcutaneous injection
Duration of treatment	16 weeks
Statistical methods	For the primary analysis, the analyses for dose-finding 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 2.5%, one-sided to identify the best-fitting model or subset of models. To account for the repeated nature of the data and the covariates in the model, mixed model repeated measures (MMRM) analysis will be carried out and covariate adjusted fixed effect estimates of average response for each dose group and the covariance matrix will be extracted from the fit and used for MCPMod analysis. The analysis will be repeated for the relative body weight change from baseline to 16 weeks. Descriptive statistics will be presented for primary and secondary endpoints.

FLOW CHART

Trial Period	**Screening**	**Treatment Period**											**Follow-up[29]**
Visit[1]	**1[3]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[4]**	**10[5]**	**11[6]**	**12[7] (EOT)**	**13**
Days	-14 days	1	8	15	22	29	36	43	50	78	106	113	141
Study Week[2]	- 2 weeks	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 12	Week 16	Week 17	Week 21
Time window for visits		N/A	± 1 day	± 1 day	±1 day	± 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	+ 4 days
Informed consent[8]	X												
Demographics	X												
Medical history	X												
Inclusion/Exclusion	X	X											
Physical examination	X	X					X					X	
Pregnancy testing[9]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X												
Body Weight[10]	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference[11]	X	X					X					X	
Laboratory tests (safety labs)[12]	X	X				X			X	X	X	X	X
HbA1c	X	X				X			X	X	X	X	X
12-lead ECG[13]	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X											
Medication kit allocation (IRT)[14]		X	X	X	X	X	X	X	X	X	X		
Study drug administration[15]		X	X	X	X	X	X	X	X	X	X		
s.c., injection training[16]									X	X	X		
Check injection site reactions		X	X	X	X	X	X	X	X	X	X	X	X
Blood sampling for PK[17]		X	X	X	X	X	X	X	X	X	X	X	X

FLOW CHART (cont.)

Trial Period	**Screening**	**Treatment Period**											**Follow-up[29]**
Visit[1]	**1[3]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9[4]**	**10[5]**	**11[6]**	**12[7] (EOT)**	**13**
Days	-14 days	1	8	15	22	29	36	43	50	78	106	113	141
Week[2]	- 2 weeks	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 12	Week 16	Week 17	Week 21
Time window for visits		N/A	± 1 day	± 1 day	±1 day	± 1 day	± 1 day	± 1 day	± 1 day	± 2 days	± 2 days	± 2 days	+ 4 days
Blood sampling for ADA/NAb[18]		X		X		X		X		X		X	X
Blood sampling, biomarkers[19, 20]		X				X			X	X		X	X
Blood sampling for pharmacogenomics (pre-specified)[21]		X											
Blood sampling for biobanking[22] (unspecified, optional)		X										X	
Diet/exercise counseling[30]		X		X		X			X	X	X	X	X
Dispense patient diary (IMP-self administration)									X	X	X[23]		
Dispense SMBG patient diary & review[24]	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense blood glucose monitor[24]	X												
[redacted]		[redacted]									[redacted]		
[redacted]		[redacted]				[redacted]			[redacted]			[redacted]	
AEs/SAEs/AESIs	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS[27]	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication compliance check[28]			X	X	X	X	X	X	X	X	X	X	
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Completion of participation													X

Footnotes for Flow Chart

1. In dose groups 5 and 6 (twice weekly dosing), every 2nd dose (of a particular week) taken by the patient at a clinic visit, will be recorded in eCRF under visit 2A, 3A, 4A, 5A, 6A, 7A, and 8A. Any AEs or changes in concomitant medications, and self monitoring of blood glucose (SMBG) diary will be checked when patient comes to the clinic for the 2nd dose.
2. Study week indicates start of the week.
3. Screening visit can be less than 14 days from the randomization. Before randomization, investigator should ensure that all safety lab results and central ECG reading are available, and all required medical records are available to ensure that patient has met all the inclusion criteria and does not meet any of the exclusion criteria.
4. All patients will self administer the injections (twice a week for dose groups 5 and 6) at home between visits 9 and 10 (Day 57, Day 64, and Day 71). Patients will have the option to visit the clinic on the specified days (±1 day), if they want the injection to be administered by qualified staff at the clinic. Patients will maintain a diary (dispensed at the site) to record date, time, and site of injection. Patients should also make note of any injection site reactions in the diary.
5. All patients will self administer the injections (twice a week for dose groups 5 and 6) at home between visits 10 and 11 (Day 85, Day 92, and Day 99). Patients will have the option to visit the clinic on the specified days (±1 day), if they want the injection to be administered by qualified staff at the clinic. Patients will maintain a diary (dispensed at the site) to record date, time, and site of injection. Patients should also make note of any injection site reactions in the diary.
6. In dose groups 5 and 6 (twice a week dosing), patients will self administer the second dose of the injections at home between visits 11 and 12 (Day 109 or Day 110). Patients will have the option to visit the clinic on the specified day (±1 day), if they want the injection to be administered by qualified staff at the clinic. Patients will maintain a diary (dispensed at the site) to record date, time, and site of injection. Patients should also make note of any injection site reactions in the diary.
7. Patients in dose groups 5 and 6 (twice weekly dosing) will also have the end of treatment (EOT) visit scheduled on Day 113 as in other dose groups. If patients discontinue from the trial during the treatment period, they should complete the EOT visit, and complete trial procedures associated with EOT visit before entering the follow-up period.
8. Patient must be informed and written informed consent obtained prior to starting any screening procedures.
9. Serum pregnancy test at screening visit (test performed at central lab), and urine pregnancy test in the clinic for other visits. Please see additional guidelines in section 6.1.
10. Body mass index will be calculated automatically. For weight measurement, follow guidelines in section 5.1.2.
11. For waist circumference measurement, follow guidelines in section 5.1.2.
12. Fasting is not required at visits when safety labs are drawn (including screening visit). However, some of these visits will coincide with visits when samples for biomarker analysis are collected or PRO questionnaires are administered when fasting is required (see footnote 20).

13. ECG should be recorded in triplicate (i.e. three single ECGs recorded within 180 seconds) at the screening visit. ECGs should be recorded before blood samples are taken. ECG recording may be repeated by investigator for medical or quality reasons. For ECG measurements, follow guidelines in section 5.2.4.
14. At visits 9, 10, and 11, IRT will assign medication kits for use at home until the next scheduled clinic visit. For example, at visit 9, kits assigned will include the medication to be administered in the clinic for visit 9 and all the medication needed for the patient for use at home until visit 10. IRT will assign semaglutide kits only at visits 2, 6, 9, and 10.
15. Patients randomized to dose groups 5 and 6 will be dosed twice a week. The first dose of each week will be administered on the days shown in the Flow Chart, and all visit procedures for that day will be completed as indicated in the Flow Chart. The 2nd dose of each week will be administered 3 or 4 days after the 1st dose of each week. Patient will visit the clinic for the 2nd injection except between visits 9 and 10, between visits 10 and 11, and between visits 11 and 12.
16. Patients should be trained on how to self administer the medication provided as pre-filled syringes. If the patient is not willing to self administer the injections, the patient should be given the option to visit the clinic and have the medication administered by the qualified site staff. Training at visit 11 is only for patients in dose groups 5 and 6 (twice weekly dosing).
17. Pre-dose PK samples (except Visits 12 and 13). PK samples will not be collected on dosing days between visits 9 and 10, between visits 10 and 11, and between visits 11 and 12. PK samples will not be collected when patients in dose groups 5 and 6 (twice a week dosing) come to the clinic for their 2nd dose (see footnote 1).
18. Blood sample for anti-drug antibody (ADA) analysis and NAbs (see section 5.4). Blood samples for ADA analysis and NAbs will **not** be taken from patients in dose group 7 (semaglutide, open-label).
19. Blood samples for the exploratory biomarkers. The first biomarker sample at randomization visit should be taken before the administration of study drug as this will serve as the baseline.
20. Patients should be instructed to come in the fasting state after at least 10 hours without regular food intake, at the visits biomarker samples are drawn, or at the visits when PRO questionnaires are completed. On days when fasting is required, patients should plan on taking their metformin dose (if applicable) after the blood draws and PRO questionnaires are completed.
21. Sample for pre-specified pharmacogenomics testing. This sample is collected from all patients participating in the study.
22. Blood samples for biobanking. Samples collected at visit 2 and end of treatment. Samples collected for biobanking at end of treatment will include only two samples (1 x 4 ml K2-EDTA tube and 1 x 4 ml serum tube). Sample for DNA banking will not be collected at the end of treatment visit. This testing is optional for the patients, and the samples are collected only if the patient has signed a separate consent form (see section 5.6).
23. Only for patients in dose groups 5 and 6 (twice a week dosing).
24. All patients will be provided with SMBG monitoring device for use at home during the study. Patients may also use their own device for self monitoring of blood glucose. Patients will enter measurements from the blood glucose monitor in a patient diary. Site staff will review the diary at each clinic visit.
25. [redacted]

[redacted]

27. C-SSRS, Columbia-Suicide Severity Rating Scale. Questionnaires will be provided in the ISF. The C-SSRS will be administered at the screening visit using the "baseline/screening" version. After the screening visit, the assessment "since last visit" will be performed at clinic visits.
28. Medication compliance (study drug administration in the clinic and at home) should be monitored throughout the treatment period to ensure the required compliance criteria are met (section 4.3).
29. Visit 13, Follow-up visit is the End of Study visit.
30. Diet and exercise counseling should be performed per local guidelines.

TABLE OF CONTENTS

ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BI	Boehringer Ingelheim
BMI	Body mass index
BPM	Beats per minute
CCS	Canadian cardiovascular society
CK	Creatine kinase
C_{max}	Maximum (or peak) serum concentration
COVID-19	Corona virus disease 2019
CRA	Clinical research associate
CRO	Contract research organization
C-SSRS	Columbia-suicide severity rating scale
CTR	Clinical trial report
DDPi	Dipeptidyl peptidase inhibitor
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eDC	Electronic data capture
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
ELF	Enhanced liver fibrosis
EOT	End of treatment
EU	European Union
EudraCT	European clinical trials database
FBG	Fasting blood glucose
FDA	Food and Drug Administration
FGF-21	Fibroblast growth factor 21
GCGR	Glucagon receptor
GCP	Good clinical practice
GERD	Gastric esophageal reflux disease
GI	Gastrointestinal
GLP-1R	Glucagon-like-peptide 1 receptor
Hb	Hemoglobin
HbA1c	Glycosylated hemoglobin A1c
HDL	High density lipoprotein
HIV/AIDS	Human immunodeficiency virus/acquired immune deficiency syndrome

ICH	International conference on harmonization
IEC	Independent ethics committee
IFU	Instructions for use
IRB	Institutional review board
IRT	Interactive response technology
ISF	Investigator site file
LDL	Low density lipoprotein
LPLT	Last patient last treatment
MCPMod	Multiple comparison and modelling techniques
MMRM	Mixed model repeated measures
MRD	Multiple rising dose
NAb	Neutralizing antibody
NTI	Narrow therapeutic index
NYHA	New York health association
PD	Pharmacodynamics
[redacted]	[redacted]
PK	Pharmacokinetics
PK/PD	Pharmacokinetics/Pharmacodynamics
PoCC	Proof of clinical concept
PRO	Patient reported outcome
Qw	Quantum Well (once a week)
QT	Time between start of the Q-wave and end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using the method of Fridericia
s.c.	Subcutaneous
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SGLT-2i	Sodium-glucose cotransporter-2 inhibitors
SMBG	Self monitoring of blood glucose
SMC	Safety monitoring committee
SOP	Standard operating procedure
SUSARs	Suspected unexpected serious adverse reactions
SU	Sulfonylureas
T2DM	Type 2 diabetes mellitus
[redacted]	[redacted]
TSAP	Trial statistical analysis plan
ULN	Upper limit normal
[redacted]	[redacted]
WBC	White blood cells
WOCBP	Women of child-bearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Type 2 diabetes mellitus (T2DM) is a highly prevalent disease affecting 30.3 million Americans, or 9.4% of the US population in 2015. According to the American Diabetes Association, about 1.5 million Americans are newly diagnosed with type 2 diabetes every year.

T2DM is associated with a variety of medical conditions, including all components of the metabolic syndrome, obesity, cardiovascular, pulmonary, gastrointestinal (GI), endocrine, musculo-skeletal as well as psychosocial diseases. Although some of these conditions can be treated by currently available medications, others including obesity are very difficult to treat and pose a significant challenge to caregivers. T2DM is also an important health condition for the aging population, as approximately one-quarter of people over the age of 65 years have T2DM and one-half of older adults have prediabetes. Patients with T2DM have higher rates of premature death, functional disability, and coexisting illnesses.

The first treatment for T2DM is often dietary intervention, physical activity, and weight loss. Most of the time these measures are not enough to bring blood glucose levels and body weight down to the normal range. The next step is taking a medicine that lowers blood glucose levels. Recommended first line therapy is metformin, followed by other oral anti-hyperglycemic medication or injectable medication such as glucagon-like-peptide 1 receptor agonist or insulin.

The proportion of patients with T2DM who achieve recommended glycosylated hemoglobin A1c (HbA1c), blood pressure, and low density lipoprotein (LDL) cholesterol levels has increased in recent years. Nevertheless, a 2013 report found that 33–49% of patients still did not meet general targets for glycemic, blood pressure, or cholesterol control, and only 14% met targets for all three measures while also avoiding smoking. Therefore, T2DM still poses a significant clinical and economic burden to individuals and society. After adjusting for inflation, economic costs of T2DM increased by 26% from 2012 to 2017. This is attributed to the increased prevalence of T2DM and the increased cost for care per person with T2DM (P19-01871).

There is strong and consistent evidence that obesity management is beneficial in the treatment of type 2 diabetes. In patients with type 2 diabetes who have obesity/overweight, modest and sustained weight loss has been shown to improve glycemic control and to reduce the need for glucose-lowering medications.

BI 456906 is a dual glucagon-like-peptide 1 receptor (GLP-1R) and glucagon receptor (GCGR) agonist that is being evaluated for the indications of glycemic control in T2DM and chronic weight management in obesity/overweight. GLP-1R agonism achieves glucose lowering by inducing glucose-dependent insulin-secretion acting at the pancreatic β-cell. In addition, GLP-1R agonists lower body weight by the inhibition of food intake and also by delaying gastric emptying and intestinal transit. GCGR agonism is expected to reduce body

weight by increasing energy expenditure, and might positively affect lipid metabolism resulting in lowering of plasma and liver triglycerides and plasma cholesterol.

In patients with T2DM and obesity/overweight, dual agonism at the GLP-1R and GCGR is anticipated to result in lower HbA1c and body weight (c14085752-06) that is expected to be of greater magnitude than compared to GLP-1R agonism alone.

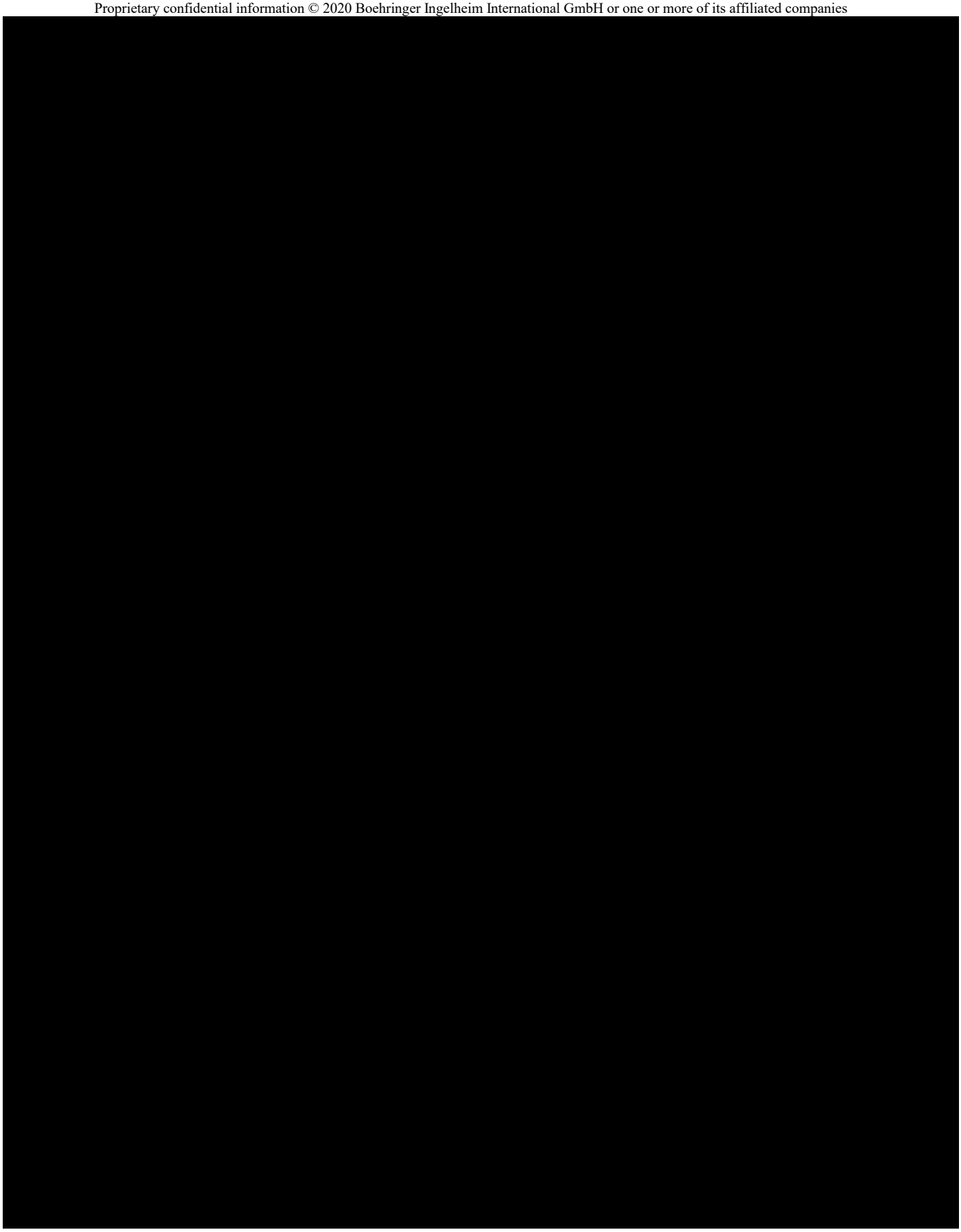
1.2 DRUG PROFILE

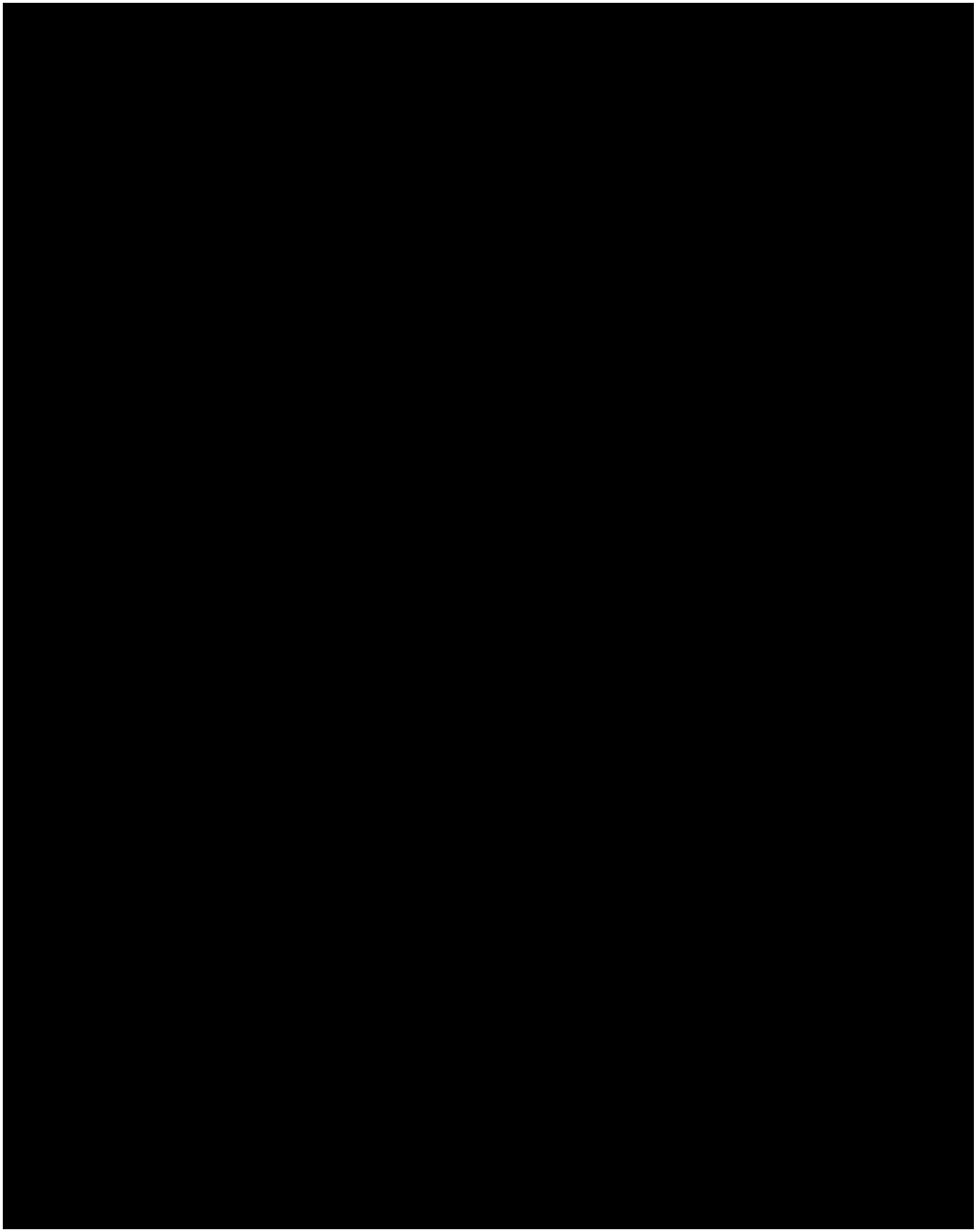
Mode of action

[redacted]s

Semaglutide is a GLP-1R agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. Semaglutide has demonstrated improved glycemic control and body weight loss. The most common adverse reactions, reported in ≥5% of patients treated with semaglutide are: nausea, vomiting, diarrhea, abdominal pain and constipation. BI 456906 and semaglutide are considered as investigational medicinal product in this trial.

[redacted]





[redacted]

For a more detailed description of the profile, please refer to the current Investigator's Brochure for BI 456906, and the Summary of Product Characteristics (SmPC) or US Package Insert for semaglutide.

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 T2DM and chronic weight management in obesity/overweight.

[redacted]

This study is a 16-week phase 2 study to examine up to 6 dose levels of BI 456906 administered once or twice weekly compared to placebo and open-label semaglutide in patients with T2DM who are inadequately controlled with diet and exercise and stable doses of metformin.

It is designed to evaluate safety, tolerability, PK and PD of BI 456906 in male and female patients with T2DM using multiple escalation schemes and doses, and will support dose selection for phase 3 clinical development of BI 456906.

1.4 BENEFIT - RISK ASSESSMENT

More information on the benefits, risks, and known AEs will be presented in the Investigator's Brochure. The US prescribing information for semaglutide will be provided which gives more information on the known and expected benefits and risks of semaglutide.

1.4.1 Benefits

In the proposed patient population with T2DM, improvements in hyperglycemia and body weight are anticipated. The expected benefit for the selected patient population is improved glycemic control and body weight loss, and an improvement of the associated metabolic risk factors and patient reported outcomes.

In addition, participation in the study is of major importance to the development of a new subcutaneous (s.c.) once-weekly medication, which might improve the future therapy in patients with T2DM and obesity/overweight.

1.4.2 Risks

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

Among the expected and well known side effects for GLP1-R agonist based therapies are:

- Gastrointestinal disorders
- Metabolism and nutrition disorders
- Cardiac disorders
- Administration site conditions

These side effects can be reduced by careful dose escalation, are known to be dose dependent, are easy to monitor and manageable in clinical trials.

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

- An extensive safety laboratory will be performed.
- Patients with severe hypoglycemia within 6 months prior to screening, or a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms are excluded from the trial.
- Self monitoring of blood glucose (SMBG) devices will be provided to patients (section 5.2.5.2). Patients can also use their own device.
- Rescue medication in case of hyperglycemia can be initiated during the treatment period of the trial (section 4.2.1).
- Patients in the placebo group will remain on standard of care that includes metformin therapy, and diet and exercise counseling.
- There are no risks expected by stopping the study drug during the course of the trial.
- Electrocardiogram (ECG) monitoring will be performed at screening, randomization and within predefined intervals during the trial, and criteria for heart rate, QT prolongation and cardiac conduction disorders are defined.
- Dose adjustment in the highest weekly dose group and the highest twice weekly dosing group is allowed (section 4.1.2)
- During the study, patients will be under medical observation and thoroughly monitored for both expected and unexpected AEs including administration and evaluation of the Columbia-Suicide Severity Rating Scale (C-SSRS).
- 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.

The mechanism of action of BI 456906, and available preclinical and clinical data for BI 456906 are not indicating an increased risk of infections. 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 available 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.

Patient participation in this trial will be consistent with local public health guidance and regulations. Patients with symptoms of SARS-CoV-2 infection will be excluded from participation in the trial. During participation in the study, if a patient is diagnosed with COVID-19, or is suspected to have SARS-CoV-2 infection when diagnostic testing is not available, trial treatment will be terminated and the patient will be discontinued from the study.

If local regulations require a SARS-Cov-2 test for patients to participate in the trial, the site investigator may order a polymerase chain reaction (PCR) test or another test to diagnose acute infection that will be performed locally at screening. Patients who test positive will be informed about the test result and they will not be eligible to participate in the trial in accordance to exclusion criterion 27 in the protocol.

A safety monitoring committee (SMC) will be established, comprising of trial investigators, members of the BI trial team, and trial independent members. The SMC will review blinded safety data at regular intervals (section 8.7).

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. [redacted] In a multiple rising dose trial with weekly dose escalation up to 3.0 mg q.w., 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-1 R 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 expected benefit for the selected patient population is improved glycemic control and body weight loss, and an improvement of the associated metabolic risk factors and patient reported outcomes.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of the trial is to demonstrate a dose-relationship of BI 456906 on HbA1c (absolute change) from baseline to 16 weeks relative to placebo in patients with T2DM. Secondary objectives are to assess the effect of BI 456906 on change in body weight. An open-label comparator (semaglutide) will allow for comparison of the effects against a pure GLP-1R agonist.

This trial is to demonstrate proof of clinical concept (PoCC) with respect to a non-flat dose response curve and to define a suitable dose escalation scheme and dose range for BI 456906 regarding safety, tolerability and efficacy. For this purpose, a multiple comparison procedure with modelling techniques (MCPMod) approach is considered.

2.1.2 Primary endpoint

- Absolute change in HbA1c from baseline to 16 weeks.

2.1.3 Secondary endpoints

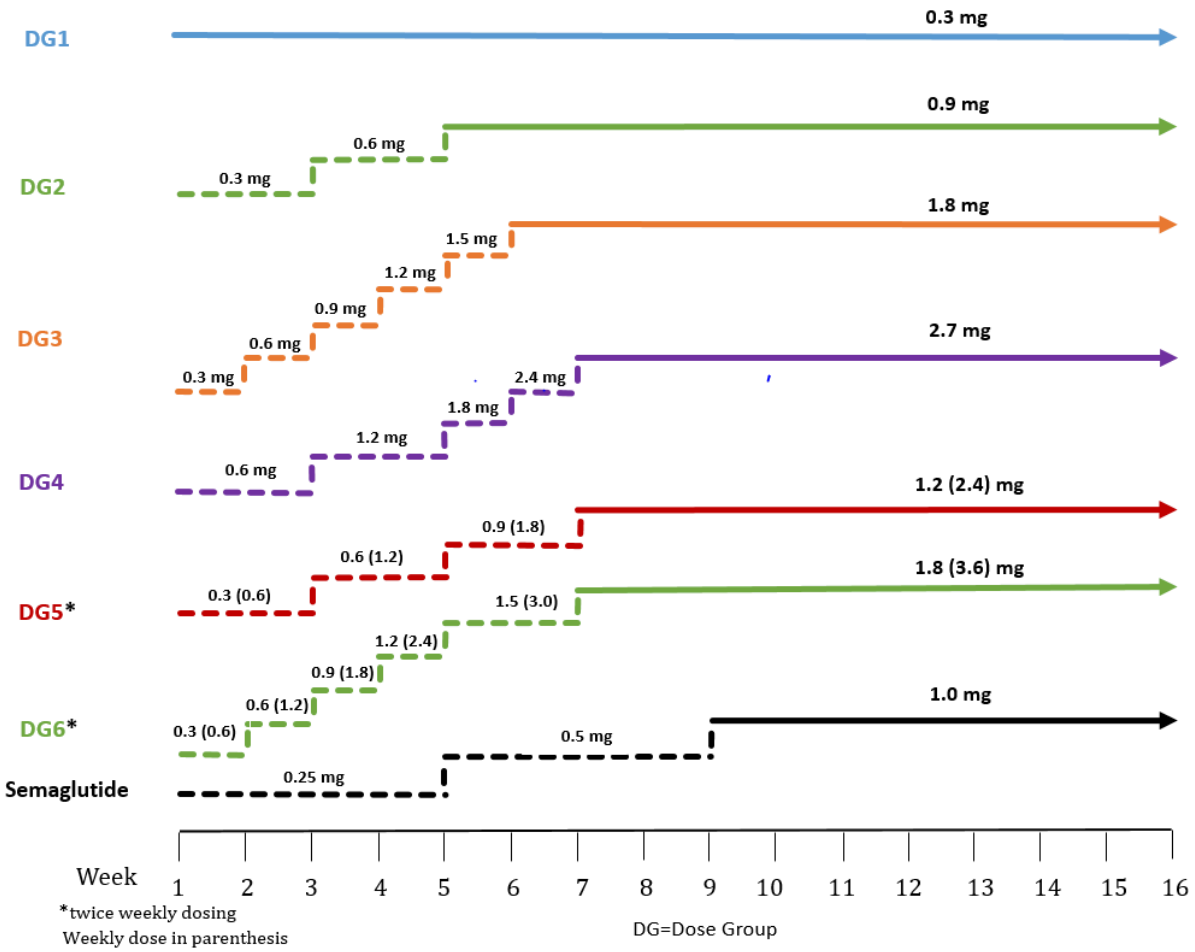
1. The relative body weight change from baseline to 16 weeks (key secondary endpoint).
2. The absolute body weight change from baseline to 16 weeks.
3. The absolute change in waist circumference from baseline to 16 weeks.
4. The percentage of patients with 5% or greater body weight loss from baseline to 16 weeks.
5. The percentage of patients with 10% or greater body weight loss from baseline to 16 weeks.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial is a multicenter, randomized, double-blinded within dose groups, parallel, placebo-controlled clinical trial with dose-escalation schemes in patients with T2DM. In addition, an open-label GLP-1R (semaglutide) group will be included as benchmark to compare response curves and support assumptions for phase 3 design. A schematic illustration of the dose escalation scheme is presented in Figure 3.1: 1. The different treatment arms and the doses are also presented in Table 4.1.4: 1.

Figure 3.1: 1 Dose escalation scheme



Additional exploratory endpoints will include changes in liver biomarkers, lipid profiles, anti-drug antibody measurements, as well as patient reported outcome measures.

The results of this dose-finding study will serve as PoCC in patients with T2DM, and will provide the basis for decision making to proceed to the next phase based on safety, tolerability, and also efficacy including HbA1c and body weight. In addition, the dose escalation scheme identified in this trial is expected to be extrapolated to associated indications such as chronic weight management. Due to the fact that GLP-1R agonist based therapies are associated with gastrointestinal side effects like nausea and vomiting, all doses above 0.6 mg will be reached through dose escalation.

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

This trial is designed to evaluate safety, tolerability, PK and PD of BI 456906 in male and female patients with T2DM using multiple escalation schemes and doses, and will support dose selection for phase 3 clinical development of BI 456906. To compare the effect on glycemic control and body weight reduction to established GLP-1R agonists, an open label active comparator (semaglutide) was chosen. Semaglutide currently represents the most efficacious GLP-1R agonist with once-weekly posology and is approved in the indication for glycemic control in patients with T2DM. To optimize for the well known gastrointestinal side effects with GLP-1 based therapies, especially at the beginning of treatment, 6 dose escalation schemes with different dose escalation phases were selected to define the most favorable dose escalation in terms of tolerability and PD for phase 3 trials.

3.3 SELECTION OF TRIAL POPULATION

It is planned to screen 615 patients and randomize 410 patients with type 2 diabetes in this clinical trial. Enrollment will be competitive and patients will be enrolled in approximately 80 study sites in multiple countries. Additional study sites may be added for patient recruitment, or initiated sites may be closed for lack of enrollment. Although the trial is targeting glycemic control as its primary endpoint, many patients with elevated body mass index (BMI) are expected to enter the trial, which will benefit in the assessment of weight loss criteria as secondary endpoints.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the investigator site file at the investigational site irrespective of whether or not they have been treated with investigational drug. If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrollment), the sponsor should be contacted immediately by the investigator to determine whether the patient may continue in the trial. If both agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor to allow the wrongly enrolled patient to continue in the trial.

3.3.1 Main diagnosis for trial entry

Patients with T2DM who have insufficient glycemic control despite diet, exercise and metformin treatment.

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. Signed and dated written informed consent in accordance with ICH GCP and local legislation prior to admission to the trial.
2. Male and female patients 18 years to 75 years (both inclusive) of age on the day of signing informed consent.
3. Diagnosis of T2DM at least 6 months prior to informed consent.
4. HbA1c 7.0%-10.0% (both inclusive) at screening.
5. Treatment with a stable dose of metformin ≥ 1000mg/day (either immediate release or extended release) for at least 3 months prior to screening.
6. BMI 25 kg/m^2-50 kg/m^2 (both inclusive) at screening.
7. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information and in section 4.2.2.3.

3.3.3 Exclusion criteria

1. Patients with type 1 diabetes.
2. Exposure to semaglutide, or other GLP-1R agonists (including combination products) within 3 months prior to screening, or any previous exposure to BI 456906, or history of relevant allergy or hypersensitivity (including allergy, intolerability or lack of efficacy to study drug or drugs that belong to the GLP-1R agonist class).
3. Any additional oral anti-hypergylcemic medication beyond metformin (e.g. SUs, DDPi, SGLT-2i, GLP-1s, a-glucosidase inhibitors, meglitinides) within the 3 months prior to screening.
4. Use of insulin for glycemic control within 12 months prior to screening. Short-term (up to 14 days) use of insulin for acute conditions (e.g. hospitalization and/or surgery) is allowed.
5. More than one episode of ketoacidosis or hyperosmolar state requiring hospitalization within 6 months prior to screening.
6. More than one episode of severe hypoglycemia, defined as the occurrence of neuroglycopenic symptoms requiring the assistance of another person for recovery in the 6 months prior to screening, or any history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms in the 6 months prior to screening.
7. Resting Heart Rate >100 beats per minute (bpm) or blood pressure ≥160/95 mm Hg at screening, or renal artery stenosis or evidence of labile blood pressure including

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilization.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

symptomatic hypotension, or history of relevant orthostatic hypotension, fainting spells, or blackouts.

8. A marked prolongation of QT/QTc (Fridericia) interval that are greater than 450 ms at the screening or at the randomization visit) or any other abnormal or clinically significant ECG finding at screening (e.g., type 2 second-degree AV block (Type Mobitz II) or third-degree AV block).
9. Heart rhythm disturbances (e.g., bradycardia with baseline HR < 50 bpm (in the absence of medications that lower the heart rate), supraventricular 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 screening. Family history of long QT-syndrome, use of prescription or over-the-counter medications known to significantly prolong the QT or QTc interval at screening.
10. Any of the following conditions or procedures within the last 6 months prior to screening: myocardial infarction, unstable angina, clinically relevant coronary artery disease (e.g. CCS grading of Angina pectoris grade III and IV), coronary artery bypass graft, urgent percutaneous coronary intervention (diagnostic angiograms and elective coronary interventions are permitted), transient ischaemic attack, cerebrovascular accident (stroke) or decompensated congestive heart failure.
11. History or currently diagnosed with congestive heart failure, New York Health Association (NYHA) class III-IV. History of symptomatic ventricular tachycardia, or history of type 2 second degree AV block (Type Mobitz II) or third degree AV block.
12. Body weight change of +/- 5% or more in the past 3 months or on anti-obesity therapies at any time during the 6 months prior to screening (including all kinds of medication and weight loss surgery, aggressive diet regimen, etc.).
13. Ongoing oral pharmacotherapy treatments or within 3 months prior to screening.

    Examples of excluded medications:
    - *anti-hyperglycaemic agents (except metformin)*
    - *anti-depressants*
    - *central nervous system stimulants*
    - *anti-psychotics*
    - *anticonvulsants (except gabapentin)*
    - *diuretics (except thiazides)*
    - *systemic corticosteroids*
    - *antithrombotics (except low dose aspirin)*

14. Major surgery (according to the investigator's assessment) performed within 12 weeks prior to randomization or planned within 6 months after screening, e.g., hip replacement.
15. Prior surgery of the GI tract (including minimally invasive/endoscopic bariatric devices, bariatric surgery) that could interfere with body weight except appendectomy, simple hernia repair, and simple cholecystectomy.
16. Known significant autonomic neuropathy as evidenced by urinary retention, resting tachycardia, orthostatic hypotension, diabetic diarrhoea, diagnosis of gastroparesis, or clinically significant gastric emptying abnormalities.

17. Acute proliferative diabetic retinopathy or expected medical intervention/surgery during the trial.
18. History of chronic or acute pancreatitis or elevation of serum lipase/amylase > 2x upper limit normal (ULN), or serum triglyceride levels of > 500 mg/dl at screening. Doses for lipid lowering medication must be stable for 3 months prior to screening.
19. Estimated glomerular filtration rate (eGFR) of <45 mL/min/1·73 m^2, or a level of serum creatinine or eGFR that would contraindicate the use of metformin.
20. Have calcitonin ≥20 pg/mL at screening.
21. Have symptoms of liver disease, chronic or acute hepatitis, or serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) above 2.5 x ULN at screening.
22. Personal or family history of medullary thyroid carcinoma or history of multiple endocrine neoplasia syndrome type 2, acromegalie, morbus cushing or pheochromocytoma, manifest hypo- or hyperthyroidism at screening.
23. Continuous oral pharmacotherapy to treat any clinical condition during the trial. Following medications are allowed:
    - *metformin*
    - *anti-hypertensives**
    - *hormone replacement therapy including thyroid hormone*
    - *lipid lowering*
    - *proton pump inhibitors*
    - *H2 blockers for GERD*
    - *analgesics*
    - *sleep medications*
    - *antihistamines*
    - *selective alpha receptor blocker for benign prostatic hyperplasia*

    Patients must be on a stable dose of continuous oral pharmacotherapy for at least 3 months prior to screening.

    **Any medications known to cause heart block or bradycardia such as beta-blockers, verapamil and diltiazem are excluded unless used to treat heart rate control or hypertension.*

24. Use of drugs with narrow therapeutic index (NTI), except levothyroxine (see exclusion criteria 23). A list of NTI drugs can be found under the link https://www.drugbank.ca/categories/DBCAT003972. The list of NTI drugs will be provided in the investigator site file (ISF).
25. Diseases of the central nervous system (including but not limited to any kind of seizures or stroke), and other relevant neurological or psychiatric disorders.
26. Any suicidal behavior in the past 2 years, any suicidal ideation of type 4 or 5 in the C-SSRS in the past 3 months at screening.
27. Chronic or relevant acute infections (including but not limited to respiratory tract infections, urinary tract infection, bladder infection, diabetic foot syndrome,

enterocolitis, abscess, tuberculosis, meningitis, influenza, Epstein-Barr virus, HIV/AIDS, and hepatitis B or C).

28. A history of atopy (severe or multiple allergic manifestations) or clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis).
29. History of organ transplant (corneal transplants [keratoplasty] is allowed).
30. Participation in another trial where an investigational drug has been administered within 60 days or 5 half-lives (whichever is longer), or involving an investigational device within 30 days prior to planned administration of study drug, or current participation in another trial involving administration of an investigational drug or device, or receiving other investigational treatments.
31. Alcohol, drug or confectionary liquorice abuse within the 3 months prior to screening that would interfere with trial participation or any ongoing condition leading to a decreased compliance to study procedures or study drug intake in the investigator's opinion.
32. 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.
33. Blood donation of 450 ml or more within 3 months prior to screening visit or any blood donation within the prior month.
34. Blood transfusion or severe blood loss within 3 months prior to screening, or have known haemoglobinopathy, haemolytic anemia, sickle cell anemia, or have a hemoglobin (Hb) value <11 g/dl (males) and <10 g/dl (females), or any other condition known to interfere with HbA1c methodology.
35. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
36. Patients who must or wish to continue the intake of restricted medications or any drug considered likely to interfere with the safe conduct of the trial.
37. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant).
38. Previous enrollment in this trial, except under the re-screening criteria for this study (section 6.2.1).
39. Patient had confirmed active infection with SARS-CoV-2 within the past 3 months from screening.

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. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrollment, as well as the explanation of the consequences of withdrawal. Patients should be made aware of potential anticipated GI symptoms during the trial, and investigator 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 electronic case report form (eCRF). If applicable, consider the requirements for AE collection reporting (please see sections 5.2.6.2.1 and 5.2.6.2.2).

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 or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of trial treatment.
- Sustained symptomatic hypotension or hypertension: For hypotension, episode of symptoms (such as light-headedness or dizziness) associated with a systolic blood pressure <100 mm Hg for > 60 minutes or for hypertension, episode of symptoms such as headaches, shortness of breath or nosebleeds associated with a systolic blood pressure > 160 mm Hg in at least three consecutive measurements, each at least 30 minutes apart.
- Clinically relevant changes in ECG (QTcF prolongation >500 ms or an increase of 60 ms versus baseline (randomization), or Type Mobitz II, or third-degree AV block), or any symptomatic AV block, newly developed atrial fibrillation, or atrial flutter that require medical intervention.
- Sinus tachycardia (HR >120/min in two consecutive assessments 5 minutes apart) and/or tachyarrhythmia (HR >110/min) or cardiac conditions requiring medical intervention.
- Ventricular tachycardia in ECG or syncope.
- Clinically relevant coronary artery disease (e.g. CCS grading of Angina pectoris grade III and IV or congestive heart failure, NYHA class III-IV).
- The patient shows an elevation of AST and/or ALT ≥3-fold ULN combined with an elevation of total bilirubin ≥2-fold ULN (measured in the same blood sample) and/or needs to be followed up according to the 'DILI checklist' provided in the ISF.
- The patient is diagnosed with COVID-19, or is suspected to have SARS-CoV-2 infection when diagnostic testing is not available (see section 5.2.3), trial treatment will be terminated and the patient will be discontinued from the study. Positive test should be reported as an AE, and reason for premature withdrawal should be recorded as "other AE". If the patient tests negative, trial treatment will be resumed and the interruption of trial medication should be documented in the medication compliance page.
- 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 investigational medicinal product or other trial treatment for more than two weeks. This includes agents that have been demonstrated to lower blood glucose and body weight (and includes rescue therapy).
- Change in dose of metformin for more than 2 consecutive weeks during the trial which includes the screening and treatment periods (change to an equivalent dose strength but with different release formulation is allowed).
- Out of compliance with study drug (missing doses), please see section 4.3.

- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).

If the trial treatment is discontinued, the patient should remain in the trial to complete the EOT visit (visit 12) and follow-up period, and given his/her agreement, will undergo the procedures for the EOT and follow-up visit (visit 13) as outlined in the Flow Chart and section 6.2.3.

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.

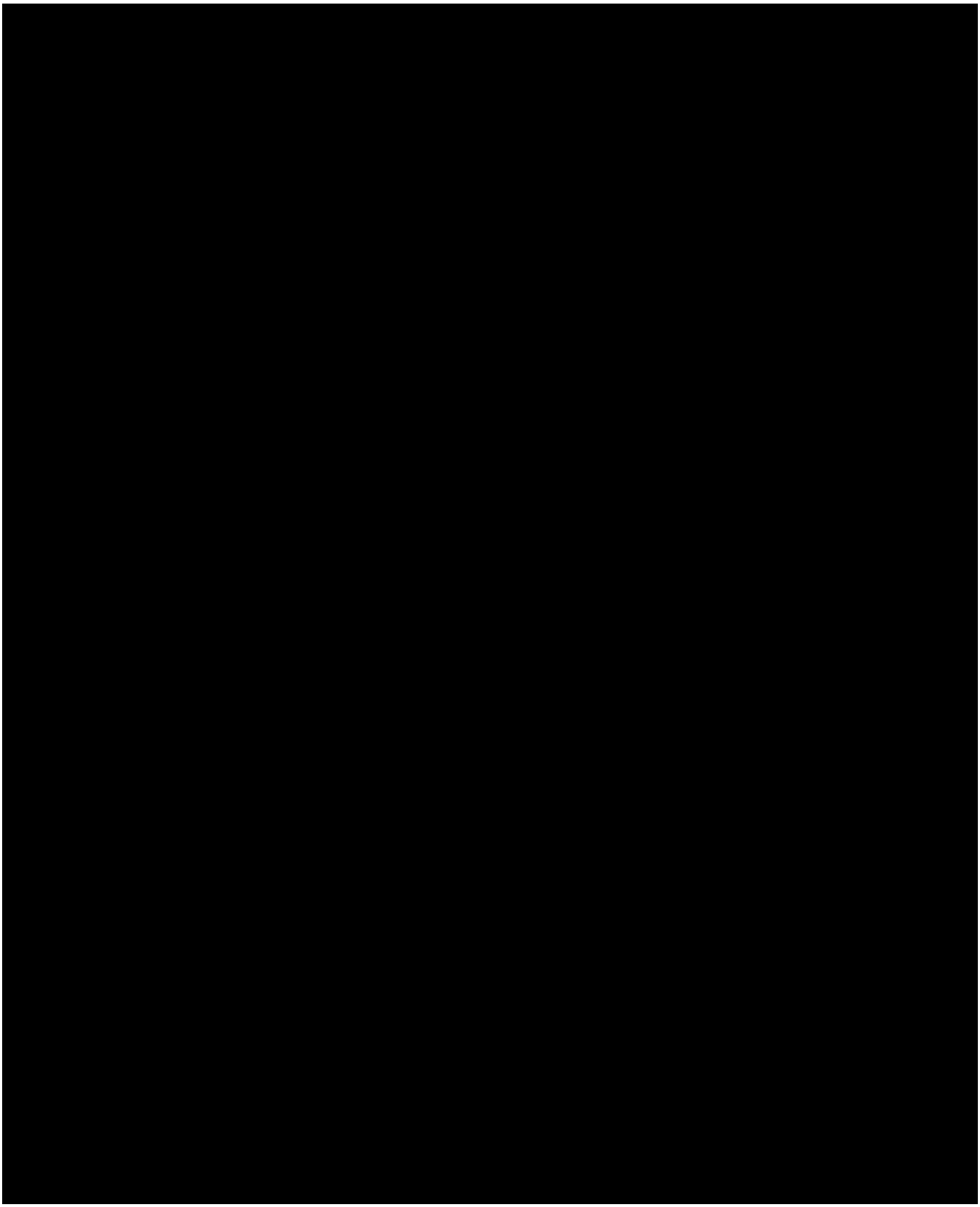
3.3.4.3 Discontinuation of the trial by the sponsor

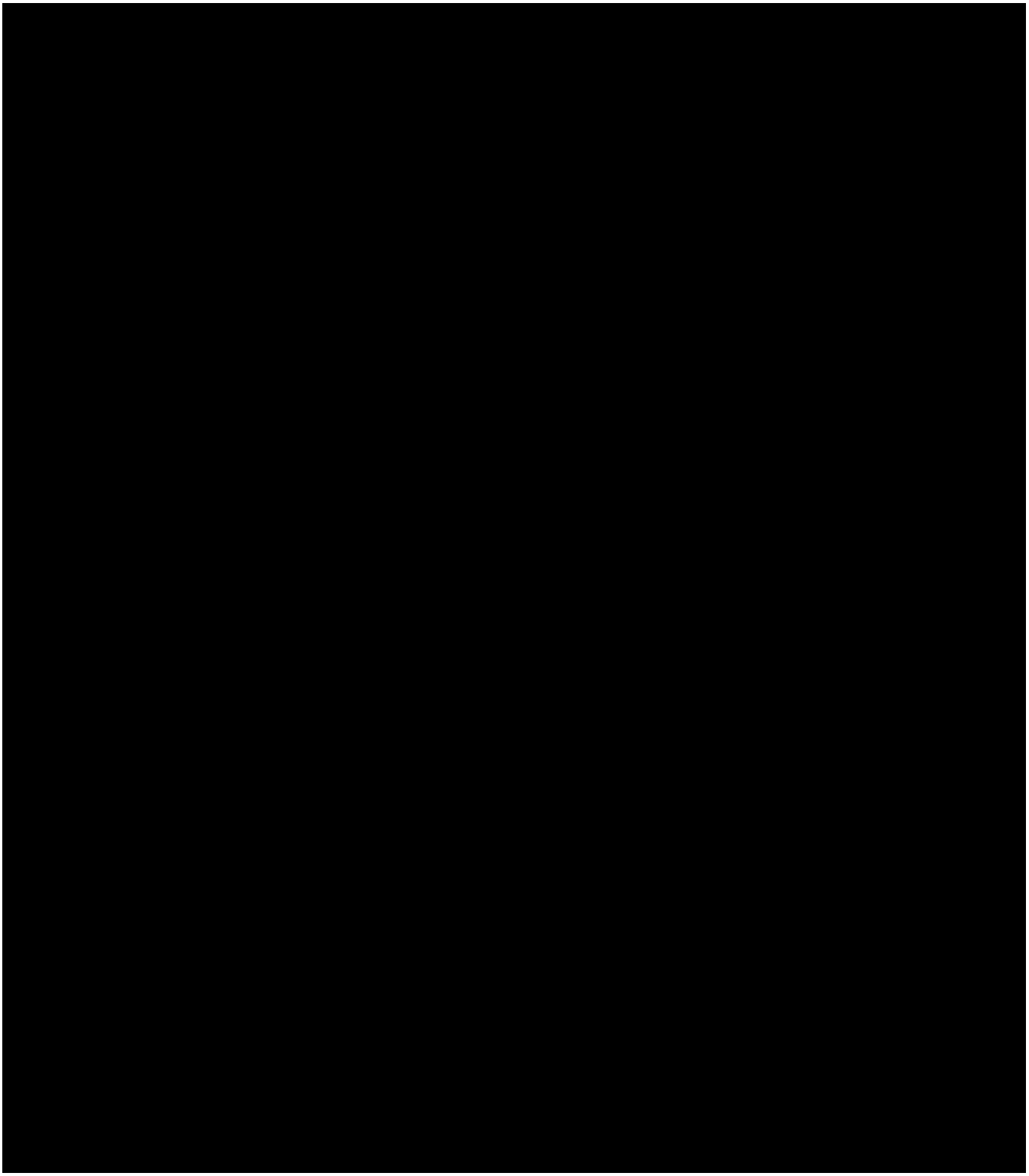
Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrollment goals overall or at a particular trial site.
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial.
3. Sponsor decides to discontinue further development of the investigational product.
4. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

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

4. TREATMENTS





[redacted]

4.1.2 Selection of doses in the trial and dose modifications

Doses from 0.3 mg to 3.6 mg were selected for weekly or twice-weekly dosing based on the following considerations:

Safety and tolerability of BI 456906 was evaluated in healthy subjects and patients with obesity/overweight up to 16 weeks for doses up to 3.15 mg/week (daily dosing) and up to 4.8 mg /week (weekly dosing), ie exceeding the highest dose planned for 1404-0002. The results indicate that the most common GI side effects could be mitigated by a more gradual increase in exposure.

The lowest dose of 0.3 mg in this trial was selected to support modelling of exposure-response (MCPMod dose-response and population PK/PD modelling) and is predicted to achieve sub-therapeutic PD response comparable to placebo.

[redacted]

The selection of different dose levels and uptitration schemes to be investigated will support a robust dose-exposure-response analysis of multiple safety and efficacy measures to support selection of a suitable dose regimen for BI 456906. This will allow for optimizing

benefit/risk (especially towards tolerability for GI side effects) for further clinical development.

Dose adjustment will be allowed for patients assigned only to the two highest dose groups (dose groups 4 and 6, Table 4.1.4: 1). In dose groups 4 and 6, if a patient does not tolerate the target titrated dose at the end week 6 (visit 8) due to moderate to severe nausea and/or vomiting in the previous two weeks, and the investigator does not believe that the patient will tolerate the pre-planned dose with further increasing exposure, dose adjustment is allowed.

In dose group 4, the weekly target dose may be reduced to 1.8 mg at the beginning of week 7

[redacted]

If in the opinion of the investigator the patient does not tolerate the reduced dose in dose groups 4 and 6, patient will be discontinued from treatment, and the patient will complete the end of treatment visit, and the follow-up period. Dose adjustment is allowed only at the end of week 6 (visit 7), and only in dose groups 4 and 6. The actual dose received by the patient (weekly or twice weekly) should be recorded in the eCRF.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all inclusion and exclusion criteria, each eligible patient will be randomized to one of the dose groups (dose groups 1 to 6 or semaglutide). Within dose groups 1 to 6, patients will be randomized to active or placebo in a 5:1 ratio. Semaglutide group (dose group 7) will be open label without placebo. In each of the dose groups from 1 to 6, a total of 60 patients will be randomized (50 active and 10 placebo). A total of 50 patients will be randomized to dose group 7, the open label semaglutide group.

For patients discontinued during the treatment period (does not include follow-up period), additional patients may be added. In each dose group, additional patients may be added after 5 patients discontinue from the trial (starting with the 6th discontinued patient in that particular dose group). The number of patients added in each dose group should not exceed 12 patients in dose groups 1 to 6, or 10 patients in dose group 7, which is 20% of the total planned randomized in each dose group. Patients in the screening period may be allowed to continue and be randomized in the study even if the maximum limit is reached in each dose group. For dose groups 1 to 6, added patients will be randomized using Interactive Response Technology (IRT). It is not guaranteed that the added patient will be assigned to the same treatment as the discontinued patient.

Randomization will be performed using the IRT at visit 2. Randomization is not stratified in this trial. Note that the medication kit number is different from the patient number (patient

number is generated during the screening visit via the IRT System, and medication kit numbers will be assigned via IRT).

4.1.4 Drug assignment and administration of doses for each patient

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

Table 4.1.4: 1 Dose escalation scheme*

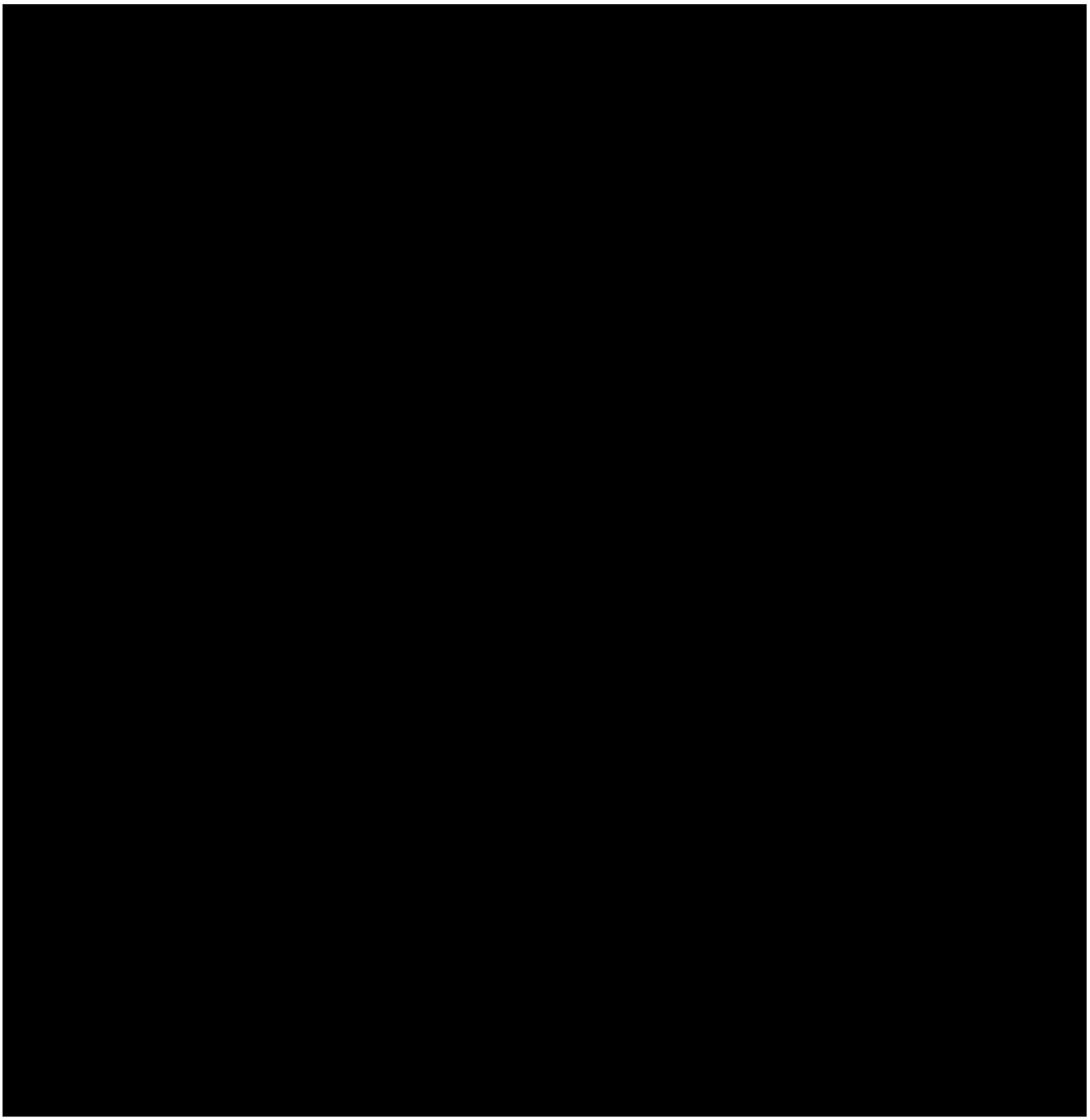
Treatment group	Weekly/twice weekly dosing in (mg)						
	Week 1	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Weeks 7-16**
Dose group 1	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Dose group 2	0.3	0.3	0.6	0.6	0.9	0.9	0.9
Dose group 3	0.3	0.6	0.9	1.2	1.5	1.8	1.8
Dose group 4	0.6	0.6	1.2	1.2	1.8	2.4	2.7
Dose group 5 twice weekly**	0.3 (0.6)	0.3 (0.6)	0.6 (1.2)	0.6 (1.2)	0.9 (1.8)	0.9 (1.8)	1.2 (2.4)
Dose group 6 twice weekly**	0.3 (0.6)	0.6 (1.2)	0.9 (1.8)	1.2 (2.4)	1.5 (3.0)	1.5 (3.0)	1.8 (3.6)
Dose group 7 Semaglutide	0.25	0.25	0.25	0.25	0.5	0.5	0.5/1.0§

*Patients in dose groups 1 to 6 will receive BI 456906 or placebo (blinded within dose groups). All patients in the semaglutide group will receive semaglutide (open label).
**Weekly dose in parenthesis.
§Semaglutide dosing: 0.5 mg at Weeks 7 and 8; 1 mg at Weeks 9 to 16.

[redacted]

[redacted]

[redacted]



COVID-19 pandemic: contingency plan:

During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment, and trial medication may be shipped to the patient's home if acceptable according to local law and regulations. The decision to ship trial medication to the patient's home will be made by the sponsor in consultation with the site investigator. Vials containing BI 456906 or matching placebo cannot be shipped to the patient's home as they are not suitable for self administration. Only pre-filled syringes and semaglutide pens can be shipped.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

The trial has a double blind design within each dose group (dose groups 1 to 6). Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this trial will remain blinded with regard to the randomized treatment assignments until after database lock. The semaglutide group (dose group 7) is open label.

Patients in dose groups 1 to 6 will receive medication from vials that contain active or placebo from weeks 1 to 6, and this randomized treatment assignment will remain blinded. The volume which should be administered at each visit will be known to the study site staff who administers the injection. Therefore the blinding will be maintained within each dose group, but not across dose groups.

For weeks 7 to 16, patients in dose groups 1 to 6 will receive medication from pre-filled syringes (0.5 mL fill volume) that contain active medication or placebo. Each patient will receive 2 injections (active/active, or active/placebo, or placebo/placebo) once a week (dose groups 1 to 4) or twice a week (dose group 5 and 6) for 10 weeks.

The particular dose group (1 to 6) to which the patient was randomized should not be made available to the patient. Patient will know if they are randomized to the open label semaglutide group, or to one of the two twice weekly dosing groups (5 and 6). Patients assigned to the open label semaglutide group will receive single-patient-use pens from which the respective dose for each week is administered.

The access to the randomization code will be kept restricted until its release for final analysis. The randomization codes will be provided to bioanalytics group during the course of the trial to allow for the exclusion from the analyses samples from placebo patients. Bioanalytics will not disclose the randomization code or the results of their measurements until the trial is unblinded after database lock. The randomization codes may be provided to the unblinded team if a decision was made to conduct interim analysis (Section 7.2.7).

4.1.5.2 Unblinding and breaking the code

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

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomization code for individual patients during trial conduct. The access to the code will only be given to authorized pharmacovigilance representatives for processing in the pharmacovigilance database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated contract research organization (CRO). They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice. Re-supply 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 at the site 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 at the study site 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 a Clinical Research Associate (CRA), as provided in the list of contacts should be contacted immediately.

Pre-filled syringes dispensed to patients at specific visits (Flow Chart) should be transported in insulated bags with cooling gel packs (or other similar cooling methods) from the site to the home. Patient should store the medication at home according to the recommended storage conditions on the medication label. Patients will not maintain a temperature log.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the Institutional Review Board (IRB) / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of Food and Drug Administration (FDA) Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be sent to other investigators or clinics. Patients should be instructed to return all unused investigational medication (carton with the pre-filled syringes or single-patient-use pens), and the empty cartons from used medication, at the next clinic visit. The sharps container (dispensed to the patient) where the used pre-filled syringes or the single-patient-use pens are stored should be returned to the clinic when it is full or at the end of treatment visit.

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 center or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution center will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol and reconcile all investigational medicinal products 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

Rescue medication, for the treatment of hyperglycemia, can be initiated in patients that meet the following criteria:

- The patient is fully compliant with assigned therapeutic regimen, and
- Either of the following measurements for fasting blood glucose (FBG) occurs in the absence of any acute condition that is known to raise blood glucose levels:
    - During the first 6 weeks post-randomization: FBG above 270 mg/dl (15 mmol/L) or
    - During weeks 7 to 16 post-randomization: FBG above 240 mg/dl (13.3 mmol/L).

Patients will receive a self monitoring blood glucose device or they can use their own device to measure FBG levels. All patients will receive a paper diary to record the measurements (section 5.2.5.2).

- Randomized treatment period: weekly blood glucose measurements in a fasted state (fasting for at least 10 hours).
- Follow-up period: at least one blood glucose measurement in a fasted state (fasting for at least 10 hours).
- At any time patient is symptomatic, i.e. experiences signs/symptoms of hyper- or hypoglycemia
- Patient should contact the site any time FBG is above 240 mg/dl (>13.3 mmol/L) or below 70 mg/dl (3.9 mmol/L)

Hypoglycemic Events:

Hypoglycemic Events will be recorded in the eCRF using the definitions below (R18-1820):

Level 1	A glucose alert value of 70 mg/dL (3.9 mmol/L) or less
Level 2	A glucose level of 54 mg/dL (3.0 mmol/L) is sufficiently low to indicate serious, clinically important hypoglycemia

Level 3	Severe hypoglycemia, as defined by the American Diabetes Association, denotes severe cognitive impairment requiring external assistance for recovery

Hypoglycemic events should be treated and additional glucose monitoring should be implemented per investigator discretion and medical judgement.

Investigator should make a determination if a hyperglycemic or a hypoglycemic event should be reported as an AE.

A fasting plasma glucose sample and a HbA1c sample should be taken before initiation of rescue therapy and sent to the central laboratory for analysis. The HbA1c sample is not required if the test was performed by the central laboratory within the last 4 weeks.

Rescue medication can be used from when treatment is initiated until the end of the treatment. The choice of rescue medication and its dosage will be left to the discretion of the investigator, depending upon existing concomitant medications. Regardless of the choice made, rescue medication should be taken in accordance with the local prescribing information of that respective medication, taking into account potential contraindications.

If, in the investigator's clinical opinion, no further effect from the rescue medication is anticipated and the patient's hyperglycaemia cannot be controlled, study medication should be permanently discontinued, and the patient should be discontinued from the trial. If continuous additional anti-hyperglycemic medication is instituted, study medication should be permanently discontinued, and the patient should be discontinued from the trial. If a decision is made to discontinue the patient from the trial, patient should complete the end of treatment visit and complete the follow-up period.

Any rescue medication or any change in dose (i.e. reduction/increase) of antidiabetic medication (including background therapy) will be recorded in the source documents and on the appropriate pages of the eCRF.
Rescue medication will not be provided as part of the clinical trial supplies, unless required by local laws and regulations.

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Patients should continue to take the same dose of metformin that they were on at the time of randomization in the trial. Investigator may reduce the dose if hypoglycemic episodes are observed. However, the metformin dose should be at least 1000 mg/day. If there is change in the formulation (e.g. immediate release to extended release), the investigator should determine the comparable dose.

4.2.2.2 Restrictions on diet and life style

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

Patients will receive dietary and exercise counseling for management of T2DM, at clinic visits specified in the Flow Chart.

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 first drug administration until the end of trial.

Excessive physical activity and manual labor outside usual amount should be avoided from randomization until the end of trial.

4.2.2.3 Contraception requirements

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 study drug intake, one male barrier method or male vasectomy, and one highly effective non-barrier method. Oral contraceptives are not permitted in female participants of the study.

Men (partner of a trial participant) must be vasectomised with documented absence of sperm or use a condom if their sexual partner is a WOCBP. Contraception is not required for males participating in the study.

WOCBP (trial participant or partner of a 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.

- Combined (estrogen 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

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 study drug; and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

Patients should be encouraged to be fully compliant with the medication dosing schedule. Patients should be compliant on clinic visits within the protocol allowed time window.

Patients should be compliant on the dosing schedule when they self administer the study drug at home with pre-filled syringes or single-patient-use-pen.

If a dose is missed on the planned dosing day, patients should take the planned dose within 2 days for weekly dosing groups (1 to 4, and 7) or within 1 day for twice a week dosing groups (5 and 6). If more time has elapsed since the missed dose, then patients should wait to take the next planned dose.

A minimum of 5 days between weekly doses and a minimum of 2 days between twice weekly doses is required. A 24-hour period is considered as one day.

In dose groups 1 to 4, and 7 (weekly dosing), patients are considered out of compliance, and should be discontinued from the trial if they miss 2 of the first 6 planned doses (first 6 weeks of dosing) or miss more than 2 doses during weeks 7 to 16. In dose groups 1 to 4, and 7, the total missed doses during the trial cannot exceed 4 doses.

In dose groups 5 and 6 (twice a week dosing), patients are considered out of compliance, and should be discontinued from the trial if they miss 4 doses of the first 12 planned doses (first 6 weeks of dosing) or miss 4 doses during weeks 7 to 16. In dose groups 5 and 6, the total missed doses during the trial cannot exceed 8 doses.

Discontinued patients due to noncompliance should stop taking study drug, complete EOT visit (visit 12), and also complete the follow up visit (visit 13) 5 weeks after the last dose.

At visits 9 and 10, pre-filled syringes (BI 456906 or matching placebo) or single-patient-use-pens (semaglutide) are dispensed to the patients in all dose groups to self administer the injections for the 3 weeks before the next clinic visit. At visit 11, pre-filled syringes are dispensed to patients in dose groups 5 and 6 (twice a week dosing) for the last dose to be taken after visit 11. Date, time, and site of injection will be recorded by the patients in a diary that will be dispensed at visits 9, 10, and 11. Patients should bring the diary to the clinic at the following visit. A copy of the paper diary will be placed in the ISF.

Patients should be instructed to return all unused investigational medication (carton with the pre-filled syringes or single-patient-use pens), and the empty cartons from the used medication at the next clinic visit. Compliance will be determined by the study site staff.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

The primary endpoint is the absolute change in HbA1c from baseline to 16 weeks. Throughout the protocol, the term "baseline" refers to the last observation prior to administration of the first dose of the study drug.

Secondary endpoints are directed towards assessment of body weight changes, and the endpoints are as follows:

1. The relative body weight change from baseline to 16 weeks (key secondary endpoint).
2. The absolute body weight change from baseline to 16 weeks.
3. The absolute change in waist circumference from baseline to 16 weeks.
4. The percentage of patients with 5% or greater body weight loss from baseline to 16 weeks.
5. The percentage of patients with 10% or greater body weight loss from baseline to 16 weeks.

5.1.1 HbA1c

Blood samples will be taken from patients for the determination of HbA1c at the central laboratory. Further details about sample collection, handling, shipment, and assay procedures can be found in the central laboratory manual.

5.1.2 Weight and waist circumference

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. Patient should empty the bladder before weight is measured.

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.

5.2 ASSESSMENT OF SAFETY

5.2.1 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling. This includes systolic and diastolic blood pressure, pulse rate (electronically or by palpation count for 1 minute) in a seated position without crossed legs after 5 minutes of rest, respiratory rate, and temperature. The results must be included in the source documents available at the site.

5.2.2 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. The physical examination should be conducted according to the local medical practice. It should include at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin including visual check for skin rashes. Skin rashes will be recorded in the eCRF as an AE.

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.

5.2.3 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.

All analyses will be performed by a central laboratory, and 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 (section 5.2.6.1 and the DILI Checklist is provided in the electronic data capture (eDC) system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

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

Table 5.2.3: 1 Safety laboratory parameters

Category	Test name
Haematology	Haematocrit Hemoglobin Reticulocyte Count (reflex test if Hb outside normal range) Red Blood Cells (RBC) / Erythrocytes WBC / 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 Chloride Creatinine Creatine kinase (CK) CK-MB, troponin (reflex tests if CK is elevated) γ-GT (gamma-glutamyl transferase) Glucose (plasma, not fasted) Lactate dehydrogenase (LDH) Lipase Magnesium Phosphate Potassium Protein total Sodium Urea (blood urea nitrogen, BUN) Uric acid Thyroid stimulating hormone (TSH) Calcitonin* eGFR* C-Reactive Protein*
Infectious serology	Hepatitis B surface antigen* Hepatitis C antibodies* HIV-1/2 combination*
Lipids	Cholesterol (total) HDL cholesterol LDL cholesterol (including VLDL) Triglycerides

Table 5.2.3: 1 Safety laboratory parameters: (cont.)

Category	Test name
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
Other	SARS-CoV-2 testing (when applicable, see Section 3.3.4.1) will be performed locally. Samples must **not** be shipped to central lab for testing.

*Measured only at the screening visit.
**Albumin/creatinine ratio in spot urine will be calculated at the central lab.

5.2.4 Electrocardiogram

A 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 (i.e. three single ECGs recorded within 180 seconds).

Centralized ECG services will be provided by an external vendor for all clinic visits (including unscheduled visits). Standardized equipment and an ECG machine quick guide will be provided by the vendor.

ECGs should be collected according to the study-specific recommendations, using the standardized equipment provided by the vendor. 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 study site. The site investigator should review the report. If the ECG is rated as abnormal, the site investigator will have to determine if the abnormal

findings are clinically significant. The site 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 study. The QTcF value at the screening visit is the average of the three recordings. 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. 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 randomized, if a clinically significant increase in the QTcF 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 clinic visit. At any time during the trial, the investigator may decide to place a hold on further dosing of the patient if there is an indication of any 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

There has been no suicidal risk identified for BI 456906 in clinical data obtained to date. However, evaluation of suicidal behavior and ideation is important in clinical development and the Columbia-Suicide Severity Rating Scale, C-SSRS, will be used to prospectively assess suicidal behaviour and ideation (R12-4395).

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.

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 life time 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 study drug 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

All patients will be provided an electronic blood glucose monitoring device and supplies for use at home during the trial for self-measurement of blood glucose. Patients may also use their own device for SMBG monitoring. The SMBG device is dispensed to the patient at the screening visit (visit 1). Instructions on the proper use of the SMBG equipment will be provided to the patient by the site staff. A paper diary will be dispensed along with the device, and the patient will enter the blood glucose measurements done at home in the diary.

SMBG should be performed regularly. Recommendations are as follows:

- Randomized treatment period: weekly blood glucose measurements in a fasted state (fasting for at least 10 hours).
- Follow-up period: at least one blood glucose measurement in a fasted state (fasting for at least 10 hours).
- At any time patient is symptomatic, i.e. experiences signs/symptoms of hyper- or hypoglycemia.

The patient will be informed to watch for these signs and symptoms, to test their blood sugar if they experience them, and to enter data from the SMBG device to a patient paper diary. Blood glucose measurements recorded in the patient diary (other than the seven-point measurements) are not entered in eCRFs unless it is related to an AE or SAE.

Throughout the trial, the patient should bring the paper diary to every clinic visit. Study site staff should review the diary at each visit and follow-up if necessary. Site staff should provide additional instructions or training to the patient if needed.

Refer to section 4.2.1 for information on handling of hyperglycemia and hypoglycemia events.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a 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 unfavorable 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, and physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

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

5.2.6.1.2 Serious adverse event

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

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require

medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

5.2.6.1.3 AEs considered "Always Serious"

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

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

5.2.6.1.4 Adverse events of special interest

AESIs 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.

The following are considered as AESIs:

- Pancreatitis
- Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST and/or ALT ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

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

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

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:
Mild: Awareness of sign(s) or symptom(s) that is/are generally tolerated.
Moderate: Sufficient discomfort to cause interference with usual activity.
Severe: Incapacitating or causing inability to work or to perform usual activities.

As GI and cardiac AEs have been shown to be associated with pharmacological doses of GLP-1R agonists and glucagon, the intensity of such AEs are defined as follows for this clinical trial:

Nausea
Mild: Queasy sensation and/or the urge to vomit without decreased oral fluid or caloric intake
Moderate: Queasy sensation and/or urge to vomit with decreased oral intake, but able to maintain adequate fluid and caloric intake without dehydration or malnutrition; may require pharmacologic intervention
Severe: Queasy sensation and/or urge to vomit with prolonged inadequate oral fluid or caloric intake; severe or medically significant but not immediately life-threatening; requiring i.v. fluids or is resistant to anti-nausea treatment, hospitalization (different from trial site) indicated

Vomiting
Mild: Less than 3 episodes in 24 hours (individual episodes separated by at least 30 min)
Moderate: 3 to 5 episodes in 24 hours (individual episodes separated by at least 30 min); may require pharmacologic intervention
Severe: Six or more episodes in 24 hours (individual episodes separated by at least 30 min); severe or medically significant but not immediately life-threatening; requiring i.v. fluids, or is resistant to antiemetic treatment, hospitalization (different from trial site) indicated

Diarrhea
Mild: Increase of <3 stools in 24 hours over baseline
Moderate: Increase of 3 to 5 stools in 24 hours over baseline; may require pharmacologic intervention
Severe: Increase of ≥6 stools in 24 hours over baseline; severe or medically significant but not immediately life-threatening; requiring i.v. fluids, or is resistant to anti-diarrheal treatment, hospitalization (different from trial site) indicated

Mobitz (type) I atrioventricular block
Mild: Asymptomatic, intervention not indicated
Moderate: Symptomatic, medical intervention indicated
Severe: Symptomatic and incompletely controlled medically or controlled with device (e.g., pacemaker)

Mobitz (type) II atrioventricular block
Mild: Asymptomatic, intervention not indicated
Moderate: Symptomatic, medical intervention indicated

Severe: Symptomatic and incompletely controlled medically or controlled with device (e.g., pacemaker)

Sinus tachycardia
Mild: Asymptomatic, intervention not indicated
Moderate: Symptomatic, non-urgent medical intervention indicated
Severe: Urgent medical intervention indicated

Electrocardiogram QT corrected interval prolonged
Mild: QTcF increase from baseline of more than 30s and QTcF 450-480 ms
Moderate: QTcF increase from baseline of more than 30s and QTcF 481-500 ms
Severe: QTcF increase from baseline of more than 60s and QTcF >= 501 ms on at least two separate ECGs

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the AE and the given study 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 study 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 occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication (e.g. phone call). Those AEs should be reported on the BI SAE form (see 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.

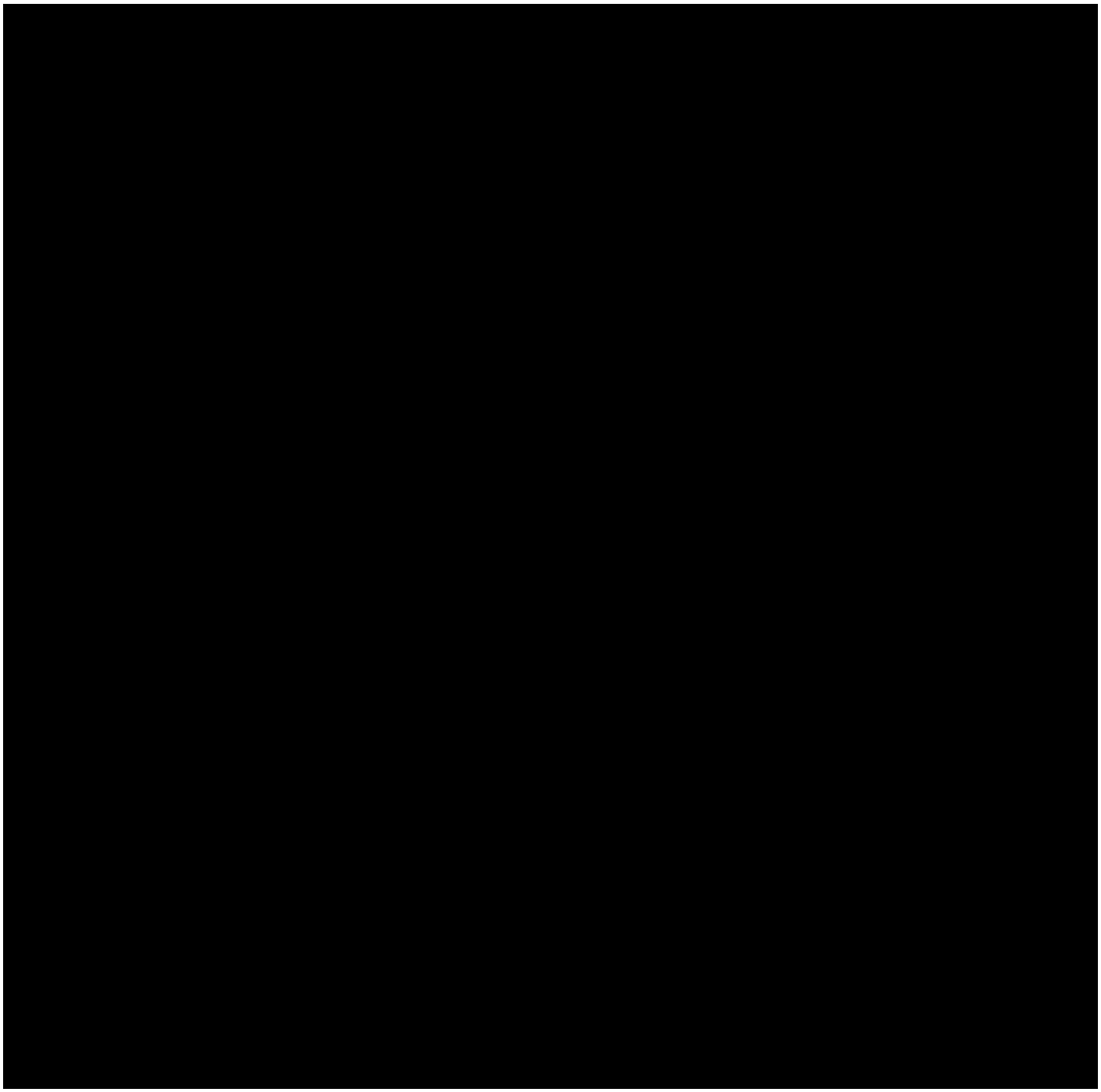
5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken study drug, 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 Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (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 Trials and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must also be completed.



[redacted]

[redacted]

5.4 IMMUNOGENICITY

5.4.1 Timing of immunogenicity measures

Blood samples from patients will be obtained from patients receiving BI 456906 or placebo for the determination of ADA and neutralizing antibody (NAb) at the time points detailed in Flow Chart. Blood samples will not be taken from patients in the semaglutide group (dose group 7) for ADA and NAb assessments. [redacted]

[redacted]

[redacted]

5.5 ASSESSMENT OF BIOMARKERS

Several exploratory biomarkers will be determined as indirect response to study drug administration. Samples will be collected for biomarker analysis as shown in the Flow Chart.

[redacted]

5.8 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor patients' safety and to determine pharmacokinetic and pharmacodynamic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that

might occur as a result of administration of study drug. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an s.c. administered drug, and are widely used in clinical trials. [redacted]

[redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

The trial consists of a screening period, treatment period, and a follow-up period. Following the 2-week screening period, patients will be randomized (visit 2) to one of the dose groups (dose groups 1 to 6 or semaglutide). During the treatment period, there will be a dose escalation period (for dose groups 2 to 7) followed by a dose maintenance period. The treatment period is followed by a 4-week follow-up period.

Patients should make all efforts to complete the trial which includes the 4-week follow-up period. Investigators should encourage treatment compliance, and adherence to the protocol procedures. All patients should adhere to the visit schedule as specified in the Flow Chart. Any deviations from the planned visit schedule should be documented.

In exceptional cases, if standard clinic visits at the trial sites are impossible or in situations where an individual patient is unable or unwilling to attend a clinic visit due to COVID-19 related safety risks, the investigator must assess the risk-benefit for the individual patient and may decide to perform a visit remotely if this is in the best interests of the patient and if agreed with the sponsor.

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

If any visit after randomization is rescheduled, subsequent visits should follow the original visit date.

At all clinic visits blood pressure should be measured, and ECG recorded before blood samples are taken.

[redacted]

Diet and exercise counseling will be provided to patients by a dietician or a trained staff member at the study site at visits specified in the Flow Chart. Patients should be reminded at every clinic visit to follow the recommended diet and exercise regimen.

Pregnancy tests

All women of child bearing potential will undergo serum pregnancy test at the screening visit (visit 1). Patients who test positive for the serum pregnancy test will be excluded from the trial. Urine pregnancy tests will be done at all visits in the clinic starting from visit 2. There will not be a pregnancy test when patients in dose groups 5 and 6 (twice a week dosing) come to the clinic for their second dose of each week. If the urine pregnancy test is positive, a serum pregnancy test will be done to confirm pregnancy. If the serum pregnancy test is positive, study drug will be discontinued and patient will be discontinued from the trial. If serum pregnancy is negative, patient may continue in the trial. If the urine pregnancy test is

positive at the randomization visit (visit 2), the patient must not be randomized into the trial unless the serum pregnancy test is negative.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period

Screening (visit 1)

No trial procedures should be performed until the patient has consented to take part in the trial. If the patient is willing to provide a blood sample for unspecified pharmacogenomics and biomarker testing (biobanking), a separate consent must be obtained. Each patient will be assigned a unique patient number and enrollment will be recorded in eCRF.

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

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

If the patient has met all the eligibility criteria, randomization visit (visit 2) will be scheduled.

Screening period may be extended by two weeks for administrative reasons after consultation with the Clinical Trial Manager. Total screening period should not exceed 4 weeks (informed consent to randomization) unless written approval is obtained from the Clinical Trial Leader.

If screening period is extended for more than two weeks, the investigator should review the laboratory reports from the screening visit (visit 1), and make a determination if any labs specified in the protocol must be repeated before the randomization visit. If deemed necessary, test samples should be drawn and sent to the central laboratory.

Discontinuation during the screening period

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

Rescreening and retesting

A patient may be rescreened once with approval from the Clinical Trial Manager. Patients who met all the inclusion criteria but were screen failed due to acute medical conditions that have since been resolved or those who were screen failed for administrative reasons (e.g., extended travel, life events) will be good candidates for re-screening.

If the investigator believes that an ineligible lab test result is the result of an error or extenuating circumstance, then that lab test can be retested once without the patient having to be rescreened. Patients who do not meet to HbA1c inclusion criteria cannot be retested or rescreened.

6.2.2 Treatment period

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

Procedures to be completed at each clinic visit can be found in the Flow Chart.

At visits specified in the Flow Chart, patients should be instructed to come in the fasting state after at least 10 hours without food intake. Water intake is allowed. Fasting is required when patients attend visits when samples for biomarkers are collected or when PRO questionnaires are administered.

[redacted]

At each clinic visit, patients should be advised to follow the recommended diet and exercise plan. Diet and exercise counseling sessions are held at visits indicated in the Flow Chart. All clinic visits during the treatment period should preferably be on the same day of the week. On days when fasting is required, the clinic visit should ideally be scheduled in the mornings, if this is convenient for the patient.

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

After completion of the treatment period, patients will have the End of Treatment visit (visit 12). All patients will then enter the 4-week follow-up period, and complete the observation period with the follow-up visit (visit 13).

Discontinuation during the treatment period

If patients discontinue from the trial during the treatment period (dose escalation phase or maintenance phase), they should complete the End of Treatment visit (visit 12), and a follow up visit (corresponding to visit 13) will be scheduled 5 weeks after the last dose of study drug. Every effort should be made to complete all the procedures at the EOT and follow-up visits.

6.2.3 Follow-up period and trial completion

The four-week follow-up period extends from visit 12 until visit 13. Visit 13 will be 5 weeks after the last dose (visit 11) which is the residual effect period in this trial. Procedures to be completed at the follow-up visit can be found in the Flow Chart. The sequence of visit procedures will be the same as in the treatment period. The last clinic visit will be visit 13, the end of the study visit and this will mark the end of observation period, and the patient has completed the trial.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The primary trial objective includes demonstration of PoCC with respect to a non-flat dose response curve, characterization of the dose-response relationship within the therapeutic range, and selection of the dose range for phase III development. For this purpose, the primary analysis uses methodology for dose finding employing MCPMod.

7.1 NULL AND ALTERNATIVE HYPOTHESES

The null hypothesis is that there is a flat dose response curve comparing 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 α of 2.5%). The pre-specified models and their parameters used for this test are outlined in Section 7.2.2.

7.2 PLANNED ANALYSES

7.2.1 General considerations

For the dose-finding all randomized patients with at least 1 post-baseline measurement according to the treatment the patients were assigned will be included in the primary analysis. More details and all other analysis sets will be specified in the TSAP.

7.2.2 Primary endpoint analyses

The analyses for PoCC and dose-finding will be performed using MCPMod [R10-1424] whereby several possible dose response models (patterns) will be evaluated, while keeping full control of the type I error at 2.5%, one-sided) to identify the best-fitting model or subset of models.

To account for the repeated nature of the data and the covariates in the model, mixed model repeated measurements (MMRM) analysis will be carried out and covariate adjusted fixed effect estimates of average response for each dose group and the covariance matrix will be extracted from the fit and used for MCPMod analysis. For the twice weekly dosing schemes the total dose per week will be considered for the MCPMod analysis.

For this analysis a restricted maximum likelihood (REML) based approach using MMRM comparing the change from baseline of HbA1c at different timepoints of treatment.
The analysis will include the fixed, categorical effects of treatment and the fixed continuous effects of baseline at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within patient measurements.

The statistical model will be as follows:

$$y_{ijk} = \beta_j S_i + \tau_{jk} + \mathrm{e_{ij}}$$
$$e_{ij} \sim N_Z\,(\mathbf{0}, \mathbf{\Sigma}).$$

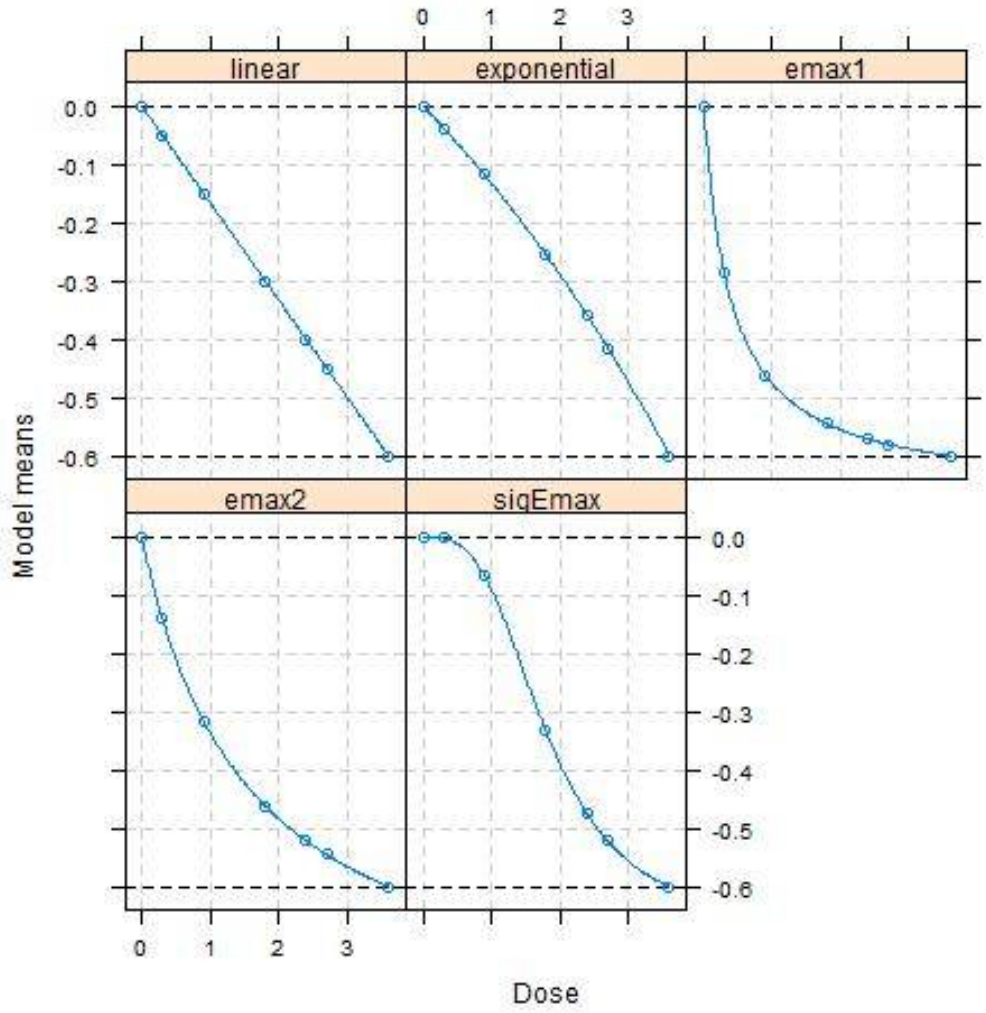
y_{ijk}	response variable at visit j receiving treatment k for subject i
S_i	the baseline measurement of subject i, i=1,2,..,
β_j	coefficient of baseline effect at visit j
τ_k	coefficient of treatment k at visit j, j=1,…,Z and k = 1, ..,Y ,
$\mathrm{e_{ij}}$	the random error associated with the j^{th} visit of the i^{th} subject. Errors are independent between subjects
$\mathbf{\Sigma}$	an unstructured covariance matrix

The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. The treatment comparison to placebo will be the contrast between treatments at the different visits and will be presented with 95% confidence intervals. The primary comparison will be performed at the visit of the primary interest.

For the PoCC testing and for the sample size calculation, the basic shape of each of the models to be tested must be pre-defined. Following models will be considered for this analysis

- The following model assumptions and resulting graphs (Figure 7.2.2: 1) have been selected to cover both plausible and a diverse range of dose response patterns.
  - Linear: the maximum effect is achieved at 3.6 mg dose
  - Exponential: 90% of the maximum effect is achieved at 3.6 mg dose
  - Emax1: 90% of the maximum effect is achieved at 3.6 mg dose
  - Emax2: 70% of the maximum effect is achieved at 3.6 mg dose
  - SigEmax: 50% of the maximum effect is achieved at 1.8 mg and 90% of the maximum effect is achieved at 3.6 mg dose

Figure 7.2.2: 1 Shape of the considered dose response patterns for the MCPMod analysis.



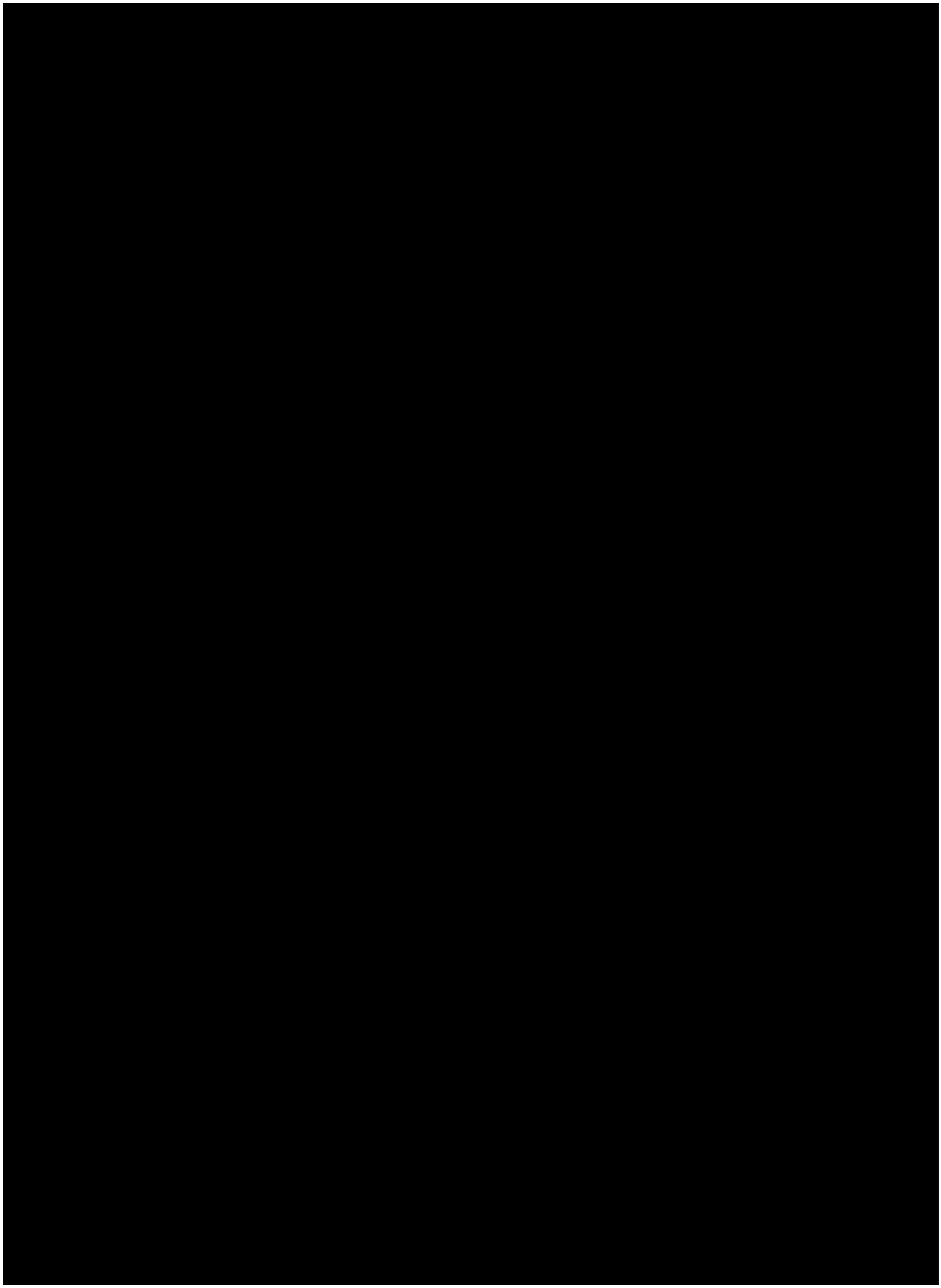
PoCC is established if at least one model is statistically significant, rejecting the null hypothesis of a flat dose response relationship over HbA1c jointly for each of the candidate dose response models with a contrast test controlled for the family–wise type I error rate at one sided $\alpha = 2.5\%$.

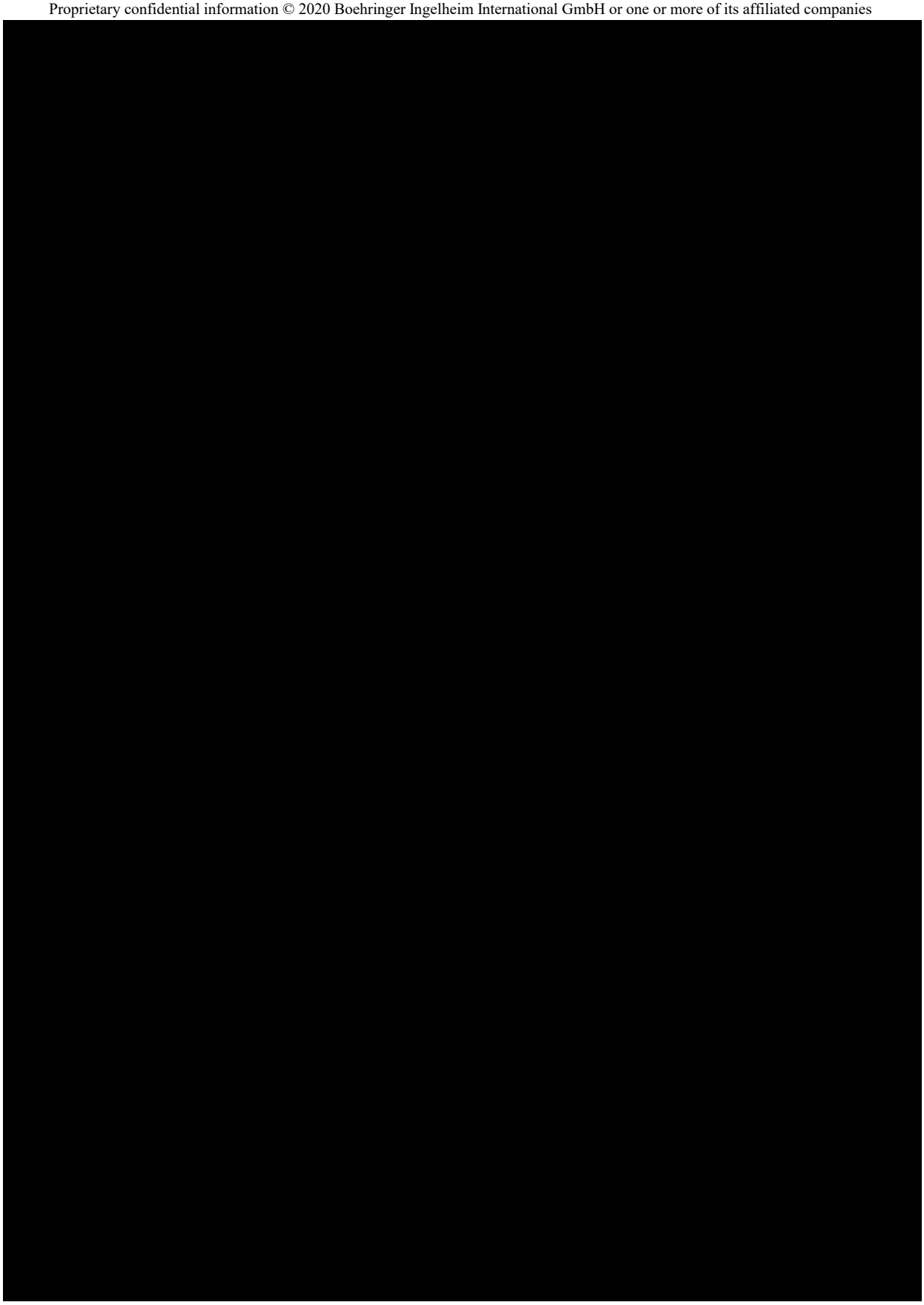
For the open label arm, descriptive statistics for the respective endpoint will be presented.

7.2.3 Secondary endpoint analyses

For the key secondary endpoint body weight, analyses similar to the primary analysis of HbA1c will be performed.

The absolute and relative body weight change as well as change in waist circumference will be assessed using an MMRM analysis as for the primary endpoint analysis. The estimates of average response to 16 weeks for each dose group will be presented.





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 REP, a period of 5 weeks after the last dose of study drug, will be assigned to the on-treatment period for evaluation.

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

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

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

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

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

[redacted]

The PRO endpoints analyses are of exploratory nature and details will be provided in the TSAP.

7.2.7 Interim Analyses

Interim analyses may be performed during the conduct of this trial. A limited number of the sponsor staff will be unblinded for the conduct of the interim analysis. Investigators, study site staff, trial team, and patients will remain blinded. If a decision is made to perform an interim analysis, more details will be specified in the interim analysis logistics plan. The data from interim analysis may allow planning future trials and reporting key results but will not include MCPMod analyses.

7.3 HANDLING OF MISSING DATA

For the primary endpoint the MMRM will be used to handle missing values. The imputation rules for secondary and further endpoints will be specified in the TSAP.

7.4 RANDOMIZATION

BI will arrange for the randomization and the packaging and labelling of study drug. The randomization 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 CTR Access to the codes will be controlled and documented (sections 4.1.3 and 4.1.5)

7.5 PATIENTS DETERMINATION OF SAMPLE SIZE

The sample size calculation is based on an assumed maximum effect size of BI 456906 vs. placebo of 0.5% change in HbA1c for the primary endpoint, as well as on the pre-specified models listed in section 5.1.2. The maximum effect size is assumed to be 0.5% with the standard deviation (SD) 1% (R17-4311).

For the contrast test (one-sided 2.5% alpha level), a sample size of 45 evaluable patients is needed in order to reach 94% average power for the assumed effect size of 0.6%. The powers for each model shape under different assumptions (different effect size and sample size) are summarized in the table below.

Table 7.5: 1 Power of MCPMod for each candidate set model and min, max, average power.

Model	**Assumption 1** **Max effect = 0.6%, SD=1%, n=45**	**Assumption 2** **Max effect = 0.6%, SD=1%, n=40**	**Assumption 3** **Max effect = 0.5%, SD=1%, n=45**	**Assumption 4** **Max effect = 0.5%, SD=1%, n=40**
Linear	93.7%	91.7%	84.0%	76.2%
Exponential	91.6%	90.7%	81.8%	77.4%
Emax 1	93.5%	91.7%	81.7%	78.3%
Emax 2	95.7%	93.6%	88.1%	81.8%
Sigmoid Emax	98.9%	97.0%	92.3%	89.6%
Min	91.6%	90.7%	81.7%	76.2%
Max	98.9%	97.0%	92.3%	89.6%

The calculations for the PoCC step have been performed using Dose Finding R-package (R15-2001) with 1000 repetitions.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice, relevant BI SOPs, the EU directive 2001/20/EC / EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations 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 Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / Independent Ethics Committee (IEC) and competent authority, 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.

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 participant 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 three documented attempts to retrieve previous medical records. If this fails, a verbal feedback from the patient which is documented in their medical records at the study site, would be acceptable.

During the site visit the sponsor's CRA or auditor must be granted access to the original patient file (please see section 8.3.2). 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 before sending them to the sponsor.

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

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

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 protocol and GCP.

8.3.3 Storage period of records

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

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

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

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

Measures are in place to comply with the applicable rules for the collection, 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 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 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.

A safety monitoring committee (SMC) composed of participating investigators, members of the BI trial team and trial independent members will be established to review individual and aggregated safety data at regular intervals to determine the safety profile, and recommend appropriateness of further enrollment. A separate SMC charter will define SMC membership and SMC roles and responsibilities. The SMC will operate under the principles specified in the charter, and the primary objective is to ensure and protect the safety and well being of the patients participating in the trial.

An independent data monitoring committee will not be established to monitor this trial.

Relevant documentation on the participating Principal Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) which will serve as a temporary location to access sponsor provided documents before and during the trial.

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

- manage the trial in accordance with applicable regulations and internal SOPs,
- 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), CRAs, and investigators of participating countries.

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

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

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

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

9. REFERENCES

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R19-1407 Saxenda (liraglutide [rDNA origin] injection), solution for subcutaneous use (Novo Nordisk) (U.S. prescribing information, revised: 12/2014). https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206321Orig1s000lbl.pdf (access date: 17 April 2019) (2014)

9.2 UNPUBLISHED REFERENCES

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n00264884 [redacted].: BI 456906: Assessment of CYP suppression potential in primary human hepatocytes using the basic model F0.5 according to EMA guidance.

10. APPENDICES

Not applicable

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		28 September 2020
EudraCT number **EU number**		2019-002390-60
BI Trial number		1404-0002
BI Investigational Medicinal Product(s)		BI 456906
Title of protocol		A Phase II, randomized, parallel group, dose-finding study of subcutaneously administered BI 456906 for 16 weeks, compared with placebo and open-label semaglutide in patients with type 2 diabetes mellitus.
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Flow Chart
Description of change		1. Check injection site reactions added to Visit 2 2. Footnote #30 added to indicate diet and exercise counselling should be performed per local guidelines. 3. Footnote #9: clarified that serum pregnancy test is performed at central lab for the screening visit. 4. Footnote #14: deleted “More details can be found in the IRT user manual”. 5. Footnote #17: Clarified PK samples drawn at Visits 12 and 13 are not pre-dose samples as there is no dosing scheduled for these visits.
Rationale for change		Corrections and clarifications.
Section to be changed		Section 1.2
Description of change		Additional safety data from Part B of the MRD study added.
Rationale for change		Part B of the MRD trial was completed.
Sections to be changed		Sections 1.4.2, 4.1.4, 5.2.3, and 6.1
Description of change		1. Section 1.4.2: addition to the risk section indicating that BI 456906 does not increase the risk of severe viral infections. Guidance is provided if local regulations require SARS-CoV-2 testing for study entry. 2. Section 4.1.4: Circumstances under which trial medication can be sent to patient’s home when physical visits are not possible due to the COVID-19 pandemic. 3. Section 5.2.3: SARS-CoV-2 tests will be done

		locally. 4. Section 6.1: Circumstances under which a clinic visit can be performed remotely when physical visits are not possible due to the COVID-19 pandemic. All COVID-19 related deviations will be documented and the implications considered for the analysis of data.
Rationale for change		Measures taken due to the COVID-19 pandemic.
Sections to be changed		Sections 3.3.2, 3.3.3, and synopsis
Description of change		The following changes were made to the inclusion/exclusion criteria: 1. Inclusion #4: added "at screening" 2. Inclusion #7: deleted "men able to father a child": male trial participants do not require contraception. 3. Exclusion #7: "supine" position removed, and deleted "or a change in antihypertensive medication 30 days prior to screening". 4. Exclusion #8: revisions include QTcF interval changed from 470 ms in males and 490 ms in females to 450ms in both males and females. Deleted "an increase of 30 ms versus screening". 5. Exclusion #9: added "supraventricular tachycardia" and "(e.g. atrial fibrillation, atrial flutter) to description of heart rhythm disturbances. Deleted "with baseline HR >100/min". 6. Exclusion #12: +/- 5% changed to "+/- 5% or more". 6 months prior to randomization changed to 6 months prior to screening. 7. Exclusion #13: anticonvulsants (except gabapentin), systemic corticosteroids, and antithrombotics (except low dose aspirin) added to the excluded medications list. Diuretics are still excluded except thiazides. Deleted "potentially induce a change in body weight". Criteria for thyroid replacement therapy moved to exclusion #23. 8. Exclusion #23: sleep medications, antihistamines, selective alpha receptor blocker for benign prostatic hyperplasia, and hormone replacement therapy including thyroid hormone are allowed. Inhaled respiratory medications are still allowed. Added "any medications known to cause heart block or bradycardia such as beta-blockers, verapamil and diltiazem are

		excluded unless used to treat heart rate control or hypertension". 9. Exclusion #24: levothyroxine is allowed. 10. Exclusion #39: new exclusion criteria, patients with confirmed SARS-CoV-2 infection in the 3 months prior to screening cannot be included.
Rationale for change		Most changes are based on feedback from Health Authorities. New criteria added and a few clarifications.
Sections to be changed		Sections 3.3.4.1 and 1.4.2
Description of change		1. Sustained symptomatic hypotension or hypertension is defined. 2. QTcF change from baseline changed from 30 ms to 60 ms. Clarified baseline is randomization. 3. Trial treatment will be terminated and patient will be discontinued if patient has symptoms of SARS-CoV-2 infection or diagnosed with COVID-19. Patients can resume treatment if the results are negative.
Rationale for change		Changes 1 and 2 are based on feedback from Health Authorities. Change 3 is an added criterion for discontinuation.
Section to be changed		Section 4.1.2
Description of change		First part of 2nd paragraph was revised as follows: Safety and tolerability of BI 456906 was evaluated in healthy subjects and patients with obesity/overweight up to 16 weeks for doses up to 3.15 mg/week (daily dosing) and up to 4.8 mg /week (weekly dosing), i.e. exceeding the highest dose planned for 1404-0002.
Rationale for change		Additional rationale for doses selected in the high dose groups in this trial.
Section to be changed		Section 4.1.4
Description of change		1. …..injected into the skin fold "over at least 15 seconds" changed to "over 5 to 10 seconds". 2. Instructions for medication administration from vials revised as follows: If the volume exceeds 1.0 mL, the dose may be divided into two syringes and will be injected into two different injection sites on the same side of the abdomen. The next dose should be administered on the alternate side of the abdomen. 3. Added the following: The placebo solution for BI 456906 is filled either into a vial or a syringe, and their composition is identical. The vials are used from week 1 to 6, and the pre-

		filled syringes are used from week 7 to 16.
Rationale for change		Further clarification provided on the site of medication administration. Clarified that the placebo for BI 456906 is the same in the vials and pre-filled syringes.
Section to be changed		Section 4.2.1
Description of change		1. Criteria for initiating treatment for hyperglycemia changed. 2. Guidance for self monitoring of blood glucose revised. 3. Patient should also contact the site when FBG is below 70 mg/dl (3.9 mmol/L). 4. Hypoglycemic events classified using standard definitions as Levels 1, 2, and 3. 5. Added the following: Hypoglycemic events should be treated and additional glucose monitoring should be implemented per investigator discretion and medical judgement. Investigator should make a determination if a hyperglycemic or a hypoglycemic event should be reported as an AE.
Rationale for change		Procedures to follow in the monitoring of hyperglycemic and hypoglycemic events have been revised.
Section to be changed		Section 4.2.2.2
Description of change		1. Dietary supplements that potentially induce change in body weight are not permitted. Over-the-counter and prescribed weight loss products are not permitted.
Rationale for change		Clarification on restrictions.
Section to be changed		Sections 4.2.2.3, 3.3.2, 5.2.6.2.3, and synopsis,
Description of change		Contraception is not required for male participants in the trial. Revisions have been made to align with this change.
Rationale for change		Reproductive and developmental toxicity studies show that male and female fertility was unaffected. BI 45906 is not genotoxic or teratogenic.
Section to be changed		Sections 5.2.1, 5.2.2, and flowchart
Description of change		1. Section 5.2.1: Respiratory rate and temperature added to vital signs. 2. Flow chart and section 5.2.2: Assessment of skin rashes added to physical examination. Skin rashes will be recorded in the CRF as an AE.
Rationale for change		Assessment of skin rashes was a request from Health Authority.

		Respiratory rate and temperature added in the evaluation of vital signs.
Section to be changed		Section 5.2.3
Description of change		Added in Table 5.2.3: 1: C-Reactive Protein test at screening visit only.
Rationale for change		Additional safety parameter added.
Sections to be changed		Section 5.2.4 and flowchart
Description of change		1. Footnote #13 in flowchart and Section 5.2.4: added "three single ECGs recorded within 180 seconds". 2. Section 5.2.4: added "The QTcF value at the screening visit is the average of the three recordings". Replaced user manual with ECG machine quick guide. QT/QTc replaced with QTcF.
Rationale for change		Provided time window for the three ECGs at screening visit. Clarified the baseline QTc value, and corrected the name of the ECG user guide. Clarified QTc measurements.
Section to be changed		Section 5.2.5.1
Description of change		Added the following, "There has been no suicidal risk identified for BI 456906 in clinical data obtained to date. However, evaluation of suicidal behavior and ideation is important in clinical development and the Columbia-Suicide Severity Rating Scale, C-SSRS, will be used to prospectively assess suicidal behaviour and ideation (R12-4395)."
Rationale for change		Added rationale for using the C-SSRS in this trial.
Section to be changed		Sections 5.2.5.2, 1.4.2, 4.2.1, and flowchart
Description of change		Patients may also use their own device for SMBG monitoring". Section 5.2.5.2: Guidance for self monitoring of blood glucose revised. Patients need not return the glucometers at the end of the study.
Rationale for change		Added more flexibility for patients to let them use their own glucometer if it is their preference. Did not want to dispense the used glucometer to another patient due to COVID-19.
Section to be changed		Section 5.2.6.1.5
Description of change		Electrocardiogram QT corrected interval prolonged: QTc changed to QTcF. In the severe category, increase from baseline changed from 30 ms to 60 ms.
Rationale for change		QTc formula clarified, severe category revised.
Section to be changed		[redacted]

Description of change		[redacted]
Rationale for change		
Section to be changed		Sections 9.1 and 9.2
Description of change		Section 9.1: added two references: R18-1820 and R12-4395. Section 9.2: reference for Investigator's Brochure updated.
Rationale for change		Added references to support changes in the amendment.
Sections to be changed		Protocol, synopsis, Abbreviations, Sections 3.3, 5.2.6.2.2, and 8.7
Description of change		1. Protocol version and date changed. 2. Abbreviations: COVID-19, SARS-CoV-2, QTcF added. QTcB deleted. 3. Section 3.3: number of sites increased from 70 to 80. 4. Section 3.3, exclusion #36: "see section 4.2.2.1" deleted (was an error). 5. Section 5.2.6.2.2: AE reporting process changed. 6. Section 8.7: IRT user manual and ECG user manual changed to IRT quick reference document and ECG quick guide respectively. The name of the documents are corrected. 7. Typos in the protocol corrected.
Rationale for change		Administrative changes
Section to be changed		Flow chart, Sections 4.3, and 6.2.3
Description of change		1. Flow chart: a) footnote #20, added guidance on metformin dosing on days fasting is required. 2. Section 4.3: Added "A 24-hour period is considered one day". 3. Flow chart and Section 6.2.3: Last clinic visit is also the "end of study visit"
Rationale for change		Clarifications

APPROVAL / SIGNATURE PAGE

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