Clinical Trial Protocol

	Document Number:	**c44205431-01**
EU Clinical Trial No. **Universal Trial Number**	2024-513739-25-00 U1111-1306-9071	
Trial Sponsor	Boehringer Ingelheim Pharma GmbH & Co. KG Binger Straße 173 55216 Ingelheim am Rhein Germany	
Boehringer Ingelheim Trial No.	1404-0044	
Boehringer Ingelheim Investigational Medicinal Product	Survodutide (BI 456906)	
Title	A randomised, double-blind, placebo-controlled, multicentre, Phase III trial evaluating long-term efficacy and safety of survodutide weekly injections in adult participants with non-cirrhotic non-alcoholic steatohepatitis/metabolic associated steatohepatitis (NASH/MASH) and (F2) - (F3) stage of liver fibrosis	
Lay Title	A study to test whether survodutide helps people with a liver disease called NASH/MASH who have moderate or advanced liver fibrosis	
Clinical Phase	III	
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Coordinating Investigator	Prof Jörn Schattenberg II. Medizinische Klinik Universität des Saarlandes Kirrberger Straße 100, Gebäude 41 66421 Homburg, Germany Phone: +49-6841-16-15021 Email: joern.schattenberg@uks.eu	

Current Version and Date	Final Version 1.0	
Original Protocol Date	27 May 2024	Page 1 of **165**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original protocol date **Latest revision date**	27 May 2024 Not applicable
Boehringer Ingelheim trial number **EU CT number** **Universal Trial Number**	1404-0044 2024-513739-25-00 U1111-1306-9071
Title of trial	A randomised, double-blind, placebo-controlled, multicentre, Phase III trial evaluating long-term efficacy and safety of Survodutide weekly injections in adult participants with non-cirrhotic non-alcoholic steatohepatitis/metabolic associated steatohepatitis (NASH/MASH) and (F2) - (F3) stage of liver fibrosis
Coordinating Investigator	Prof Jörn Schattenberg II. Medizinische Klinik Universität des Saarlandes Kirrberger Straße 100, Gebäude 41 66421 Homburg, Germany Phone: +49-6841-16-15021 Email: joern.schattenberg@uks.eu
Trial sites	Multi-centre trial conducted in approximately 450 sites and up to 40 countries
Clinical phase	III
Trial rationale	MASH is a liver disease associated with obesity related disorders, such as type-2 diabetes mellitus (T2DM) and the metabolic syndrome and is characterised by the accumulation of fat in the liver with ongoing liver cell injury (lobular inflammation and ballooning) leading to progressive liver fibrosis and in the later stage cirrhosis. MASH is associated with an increased risk of all-cause, cardiovascular, and cancer-related mortality related to the presence of obesity and T2DM. In parallel, patients with MASH and at least stage 2 fibrosis have a higher risk of liver-related morbidity and mortality. Up today, pharmacological therapy for MASH with liver fibrosis is very limited and usually non-liver-specific pharmacological management including weight loss, lifestyle changes and pharmacotherapies associated with metabolic syndrome components is followed.

	This Phase III trial aims to investigate the efficacy and safety of survodutide (BI 456906) once weekly versus placebo on defined as resolution of steatohepatitis, reduction of liver fibrosis in liver biopsy and long-term improvement in clinical liver outcomes observed in trial participants with MASH and fibrosis stage F2-F3.
Benefit-risk assessment and ethical considerations	Trial participants with a MASH defined as NAS ≥4 and fibrosis stage F2-F3 in liver biopsy treated with survodutide are expected to achieve resolution of steatohepatitis and fibrosis reduction assessed in liver biopsy compared with prior to their trial participation. They are also expected to have a lower progression rate to cirrhosis compared with participants treated on placebo. The risks for participants caused by participation in the trial, including the trial procedures and exposure to the trial drug, are reasonably low and do not outweigh the potential benefits. The inclusion of the placebo comparator helps to better identify the difference between treated active arm with lifestyle modification versus lifestyle modification only in the placebo arm. Overall, the potential benefits, coupled with an acceptable safety profile and a well-controlled clinical trial environment support the initiation of the trial.
Trial objectives	**Primary objectives** The primary objectives are to evaluate survodutide in adults with MASH and liver fibrosis stages 2 or 3. <u>Part 1:</u> To demonstrate superiority of survodutide compared with placebo on: • The odds ratio (survodutide vs. placebo) for MASH resolution without worsening of liver fibrosis from baseline at Week 52 • The odds ratio (survodutide vs. placebo) for improvement in fibrosis with no worsening of MASH from baseline at Week 52 <u>Part 2:</u> To demonstrate superiority of survodutide compared with placebo by means of the hazard ratio (survodutide vs. placebo) of a time to first occurrence of any of components of composite endpoint that includes progression to cirrhosis, liver-related clinical outcome events, and all-cause mortality. **Key secondary objectives** <u>Part 1:</u> To demonstrate the superiority of survodutide compared with placebo from baseline to Week 52 on:

	• The difference of means for percentage change in body weight • The difference of means for absolute change in haemoglobin A1c (HbA1c; in participants with T2DM) • The difference of means for absolute change in ELF score • The difference of means for absolute change in liver stiffness assessed by vibration-controlled transient elastography (VCTE) • The odds ratio (survodutide vs. placebo) for no progression of fibrosis at Week 52 assessed by central pathology <u>Part 2:</u> To demonstrate the superiority of survodutide from baseline to Week 114/EoT/EoS compared with placebo on: • The difference of means for percentage change in body weight (Week 114) • The difference of means for absolute change in HbA1c (in participants with T2DM) (Week 114) • The difference of means for absolute change in ELF score (Week 114) • The difference of means for absolute change in liver stiffness assessed by VCTE (Week 114) • The odds ratio (survodutide vs. placebo) for no progression of fibrosis assessed by central pathology (at end of treatment [EoT]) • Occurrence of all-cause hospitalisation (first and recurrent) (at EoS) • Time to first occurrence of any of the adjudicated components of the composite endpoint consisting of: CV death, non-fatal stroke, non-fatal MI, ischaemia related coronary revascularisation, or HFE (this includes HHF, emergency room visit, urgent care visit, or urgent outpatient HF visit) (5P-MACE) (at EoS)
Trial endpoints	**Primary endpoints** <u>Part 1:</u> (at Week 52) • Resolution of MASH without worsening of liver fibrosis on MASH Clinical Research Network (CRN) fibrosis score • At least a 1-point improvement in fibrosis stage with no worsening of MASH

	Part 2: (at EoS) Time to first occurrence of any of components of the composite endpoint consisting of: • Progression to cirrhosis (defined as histological fibrosis score CRN F4) • All-cause mortality • Liver transplant • Hepatic decompensation event(s) (including ascites requiring treatment, hepatic encephalopathy [HE] requiring treatment, portal hypertension-related upper gastrointestinal [GI] bleeding, including events of bleeding from oesophageal varices, gastric varices, and portal hypertensive gastropathy) • Worsening of Model for End-stage Liver Disease (MELD) score to ≥15 • Progression to clinically significant portal hypertension, defined as 'high-risk' gastroesophageal varices confirmed in upper gastrointestinal endoscopy. **Key secondary endpoints** Part 1: (at Week 52) • Percentage change from baseline in body weight • Absolute change from baseline in HbA1c (in participants with T2DM) • Absolute change from baseline in ELF score • Absolute change from baseline in liver stiffness assessed by VCTE • Achievement of no progression of fibrosis assessed by central pathology (yes/no) Part 2: (at Week 114/EoT/EoS) • Percentage change from baseline in body weight (Week 114) • Absolute change from baseline in HbA1c (in participants with T2DM) (Week 114) • Absolute change from baseline in ELF score (Week 114) • Absolute change from baseline in liver stiffness assessed by VCTE (Week 114) • Achievement of no progression of fibrosis assessed by central pathology (yes/no; at EoT) • Occurrence of all-cause hospitalisation (first and recurrent) (EoS) • Time to first occurrence of any of the adjudicated components of the composite endpoint consisting of: CV

	death, non-fatal stroke, non-fatal MI, ischaemia related coronary revascularisation, or HFE (this includes HHF, emergency room visit, urgent care visit, or urgent outpatient HF visit) (5P-MACE) (EoS) **Additional secondary endpoints** In Part 1 (at Week 52) and In Part 2 (at Week 114): • Improvement of liver fat content (LFC) defined as at least 30% relative reduction in LFC compared with baseline assessed by MRI-PDFF (subset of participants with MRI) • Absolute change from baseline in LFC in MRI-PDFF (subset of participants with MRI) • Absolute change from baseline in Alanine aminotransferase (ALT) [U/L] • Absolute change from baseline in Aspartate aminotransferase (AST) [U/L] • Absolute change from baseline in systolic blood pressure (SBP) [mmHg] • Absolute change from baseline in diastolic blood pressure (DBP) [mmHg] • Absolute changes from baseline in lipids (including but not limited to: total cholesterol, low-density lipoprotein cholesterol, very low density lipoprotein, high-density lipoprotein cholesterol, triglycerides) • Absolute change from baseline in free fatty acids [mg/dL] • Progression to cirrhosis (defined as histological fibrosis score CRN F4) (yes/no), only at Week 52
Trial design	Placebo-controlled, randomised, double-blind, parallel-group design comparison of 2 arms over 7 years
Total number of trial participants randomised	Approximately 1800
Number of trial participants per treatment group	Approximately 1200 randomised to survodutide approximately 600 randomised to placebo

Diagnosis, main inclusion and exclusion criteria	**Main diagnosis** Adult participants with non-cirrhotic MASH and F2 or F3 stage of liver fibrosis **Main inclusion criteria** • Male or female participants ≥18 years (or who are of legal age in countries where that is greater than 18 years) of age at time of consent. • Diagnosis of MASH (NAS ≥4, with at least 1 point in inflammation and ballooning each) and fibrosis stage F2-F3 proven by a biopsy conducted during the screening period or by a historical biopsy conducted within the last 6 months prior to randomisation. • Stable body weight defined as less than 5% self-reported change in body weight 3 months prior to the screening or during the period between the historical biopsy and randomisation, if a historical biopsy is used. • The participants will be randomised following screening parameters which needs to be met in consecutive order: AST >20 U/L, liver stiffness measured by FibroScan® VCTE ≥7.5k Pa and FAST >0.36 at screening) and liver fat fraction ≥8% measured by MRI-PDFF prior to scheduling the screening biopsy. • Be willing to maintain a stable diet and physical activity levels throughout the entire trial. **Main exclusion criteria** • Any of the following liver laboratory test abnormalities at screening: o Serum AST and/or ALT elevation ≥5x ULN o Platelet count <140 000/mm^3 (<140 GI/L) o Alkaline phosphatase >2x ULN o Abnormal synthetic liver function as defined by screening central laboratory evaluation: - Albumin below <3.5 g/dL (35.0 g/L) - OR International normalised ratio (INR) of prothrombin time >1.3 (unless participant is on anticoagulants) - OR total serum bilirubin concentration ≥1.5x ULN (participants with a documented history of Gilbert's syndrome can be enrolled if the direct bilirubin is within normal reference range) • Any history or evidence of acute or chronic liver disease other than MASH.

	• Histologically documented liver cirrhosis (fibrosis stage F4), either at screening or in a historical biopsy • History of or current diagnosis of hepatocellular carcinoma • History of or planned liver transplant • Inability or unwillingness to undergo a liver biopsy at screening (if a suitable historical biopsy is unavailable for central review), or during trial conduct. • History of portal hypertension or presence of decompensated liver disease (including hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis) • MELD score ≥12 due to liver disease Note: MELD of ≥12 must be the result of liver disease to be exclusionary, NOT isolated laboratory abnormalities such as elevated creatinine due to chronic kidney disease, INR abnormality secondary to anticoagulants or laboratory error, and bilirubin elevation due to Gilbert's Syndrome • Treatment with any medication for the indication obesity within 3 months before screening biopsy or historical biopsy time point. • HbA1c >10% (>86 mmol/mol) as measured by the central laboratory at screening. • Impaired renal function, defined as eGFR <30 mL/min/1.73 m^2 ($CKD\text{-}EPI_{cr}$) at screening or trial participants requiring dialysis • History of either chronic or acute pancreatitis or elevation of serum lipase or amylase >2x ULN as measured by the central laboratory at screening • Uncontrolled hypertension (mean SBP ≥160 mmHg and/or mean DBP ≥100 mmHg) at screening (at least two measurements 5 minutes apart). • Major surgery (in the opinion of the investigator) performed within 3 months prior to screening or planned during the trial
Trial intervention and test product	Survodutide
Dose and mode of administration	Subcutaneous maintenance dose of 6.0 mg once weekly
Comparator product	Placebo

Dose and mode of administration	Matching subcutaneous injection
Duration of treatment	The trial is event-driven, and all randomised trial participants will remain in the trial until the defined number of primary endpoint events is projected to be reached. The estimated trial duration is about 7 years with a recruitment period of approximately 36 months. The trial duration may be prolonged or shortened depending on when the required minimum number of 394 clinical events for the primary endpoint (of Part 2) has been reached. The estimated trial duration and length of double-blind treatment for each trial participant will vary accordingly.
Statistical methods	Efficacy will be shown based on primary 'Treatment-Regimen' Estimand I for both Part 1 and Part 2, respectively. The main estimation aligned with the 'Treatment-Regimen' Estimand I for Part 1 will firstly impute the missing biopsy data at Week 52 using multiple imputation with full conditional specification approach. Secondly, a logistic regression will be used to test if there is a difference between treatments regarding the binary endpoints in Part 1 adjusting for categorical covariates of region, fibrosis stage at baseline, and presence of T2DM at baseline. For each endpoint, results obtained from multiple imputation runs are summarised into a single estimate for the respective treatment effect (odds ratio with corresponding confidence interval and p-value, respectively). The main estimation aligned with the 'Treatment-Regimen' Estimand I for Part 2 will be provided using a Cox regression model including treatment, region, fibrosis stage at baseline and presence of T2DM at baseline. The primary treatment comparison in Part 1 and Part 2 will be as randomised. All key secondary binary endpoints will be analysed using the logistic regression model adjusting for covariates of region, fibrosis stage and presence of T2DM at baseline and evaluated based on 'Treatment-Regimen' Estimand I of Part 1; all key secondary continuous endpoints will be analysed using the ANCOVA model adjusting for covariates of region, fibrosis stage, presence of T2DM at baseline and baseline corresponding measurements and evaluated based on 'Treatment-Regimen' Estimand III; all key secondary recurrent event endpoint will be analysed using a semi-parametric regression model named Lin-Wei-Yang-Ying model (LWYY) adjusting for covariates of region, fibrosis stage and presence of T2DM at baseline and evaluated based on 'Treatment-Regimen' Estimand IV'; all key

	secondary time-to-event endpoint will be analysed using Cox regression model including treatment, region, fibrosis stage at baseline and presence of T2DM at baseline and evaluated based on ‘‘Treatment-Regimen‘ Estimand I of Part 2’. The trial consists of two parts. There are two planned analyses. At the end of Part 1, an interim analysis is planned, with an overall significance level of 0.01. At the end of Part 2, the final analysis is planned, with an overall significance level of 0.04 + certain alpha propagated from the Part 1 analysis level. The multiple testing procedure for the primary endpoints and all key secondary endpoints will be implemented in terms of truncated Hochberg procedure and hierarchical testing strategy for Part 1 and in terms of hierarchical testing strategy for Part 2 which controls the family-wise error rate at the overall two-sided significance level α of 5% in the strong sense.

SCHEDULE OF ASSESSMENTS

	Screening and randomisation		**Dose escalation**								**Maintenance period**									**Follow-up**	
	Screening (in-clinic)	Randomisation (in-clinic)	Remote	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic	In-clinic	Remote	In-clinic	Remote	In-clinic	In clinic (biopsy)	In clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic
Visit[1]	**V1[2]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 Rep. every 12 w until EoT[3]**	**V18 Rep. every 12 w until EoT[3]**	**EoT[3]**	**ETD[3]**	**FU[3]/ EoS[4]**
Timing of visits (weeks)	-10	0	2	4	6	8	12	16	20	24	30	36	42	48	52	54	60	66			EoT +21 days OR ETD +21 days
Timing of visits (days)	-70	1	15	29	43	57	85	113	141	169	211	253	295	337	365	379	421	463			
Visit window (days)		+/-0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-14	+/-7	+/-7	+/-7	+7		+7
Informed consent[5]	X																				
Review inclusion/exclusion criteria	X	X																			
Demographics	X																				
Medical history[6]	X																				
Physical examination	X	X[7]					X			X[7]		X[7]		X	X	X		X[7]	X[7]	X[7]	X
Height		X																			
Weight[8]	X	X		X		X	X	X	X	X		X		X	X	X		X	X	X	X

	Screening and randomisation		**Dose escalation**								**Maintenance period**									**Follow-up**	
	Screening (in-clinic)	Randomisation (in-clinic)	Remote	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic	In-clinic	Remote	In-clinic	Remote	In-clinic	In-clinic (biopsy)	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic
Visits[1]	**V1[2]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 Rep. every 12 w until EoT[3]**	**V18 Rep. every 12 w until EoT[3]**	**EoT[3]**	**ETD[3]**	**FU[3]/ EoS[4]**
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Visit window (days)		+/-0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-14	+/-7	+/-7	+/-7	+7		+7
Waist and hip circumference	X	X		X		X	X	X	X	X		X		X	X	X		X	X	X	X
Vital signs (SBP, DBP, pulse)[9]	X	X		X		X	X	X	X	X		X		X	X	X		X	X	X	X
12-lead ECG[10]	X	X		X			X			X		X				X		X[10a]	X	X	X
Concomitant therapy[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of lipid-lowering treatment[12]		X					X			X		X		X	X	X		X	X	X	X
Evaluation of anti-hypertension treatment[12]		X					X			X		X		X	X	X		X	X	X	X

	Screening and randomisation		**Dose escalation**								**Maintenance period**									**Follow-up**	
	Screening (in-clinic)	Randomisation (in-clinic)	Remote	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic	In-clinic	Remote	In-clinic	Remote	In-clinic	In-clinic (biopsy)	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic
Visits[1]	**V1[2]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 Rep. every 12 w until EoT[3]**	**V18 Rep. every 12 w until EoT[3]**	**EoT[3]**	**ETD[3]**	**FU[3]/ EoS[4]**
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Visit window (days)		+/-0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-14	+/-7	+/-7	+/-7	+7		+7
Evaluation of anti-hyperglycaemic treatment[12]		X					X			X		X		X	X	X		X	X	X	X
Assessment of obesity staging[13]		X																	X	X	
All AEs/SAEs/AESIs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X3
Check for injection site reaction		X		X		X	X	X	X	X		X		X	X	X	.	X	X	X	X
Randomisation		X																			
Laboratory tests[14]																					
Safety laboratory tests[15]	X	X		X		X	X	X	X	X		X		X	X	X		X	X	X	X
Pregnancy testing[16]	X	X		X		X	X	X	X	X		X		X	X	X		X	X	X	X

	Screening and randomisation		**Dose escalation**								**Maintenance period**									**Follow-up**	
	Screening (in-clinic)	Randomisation (in-clinic)	Remote	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic	In-clinic	Remote	In-clinic	Remote	In-clinic	In-clinic (biopsy)	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic
Visits[1]	**V1[2]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 Rep. every 12 w until EoT[3]**	**V18 Rep. every 12 w until EoT[3]**	**EoT[3]**	**ETD[3]**	**FU[3]/ EoS[4]**
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Timing of visits (days	-70	1	15	29	43	57	85	113	141	169	211	253	295	337	365	379	421	463			
Visit window (days)		+/-0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-14	+/-7	+/-7	+/-7	+7		+7
HBV, HCV, HIV	X																				
Liver tests (ALT, AST, GGT, ALP, total bilirubin)	X	X		X		X	X	X	X	X		X		X	X	X		X	X	X	X
HbA1c, FPG, FPI, fasting C-peptide, HOMA-IR, HOMA-β	X[17]	X					X			X		X		X	X	X		X	X	X	X
Lipids tests: total cholesterol, HDL, LDL, VLDL, triglycerides, and free fatty acids		X					X			X		X		X	X	X		X	X	X	X
$eGFR_{cr}$, $eGFR_{cys}$	X	X		X		X	X	X	X	X		X		X	X	X		X	X	X	X

	Screening and randomisation		**Dose escalation**								**Maintenance period**									**Follow-up**	
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Visits[1]	**V1[2]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 Rep. every 12 w until EoT[3]**	**V18 Rep. every 12 w until EoT[3]**	**EoT[3]**	**ETD[3]**	**FU[3]/ EoS[4]**
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Visit window (days)		+/-0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-14	+/-7	+/-7	+/-7	+7		+7
Urine analysis[18], UACR		X					X			X		X		X	X	X		X	X	X	X
ELF score[19]		X					X			X					X			X[19]	X	X	
Other biomarker samples[20]		X					X			X					X			X[20]	X	X[20]	
Optional biobanking samples[21]		X								X									X	X	
PK, ADA, NAb samples[22]		X		X			X			X		X			X			X[22]	X	X[22]	X
FSH[23]	X																				
Liver biopsy[24]	X[24a]														X[24b, 24c]				X[24d]	X[24e]	

	Screening and randomisation		**Dose escalation**								**Maintenance period**									**Follow-up**	
	Screening (in-clinic)	Randomisation (in-clinic)	Remote	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic	In-clinic	Remote	In-clinic	Remote	In-clinic	In-clinic (biopsy)	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic
Visits[1]	**V1[2]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 Rep. every 12 w until EoT[3]**	**V18 Rep. every 12 w until EoT[3]**	**EoT[3]**	**ETD[3]**	**FU[3]/ EoS[4]**
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Timing of visits (days	-70	1	15	29	43	57	85	113	141	169	211	253	295	337	365	379	421	463			
Visit window (days)		+/-0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-14	+/-7	+/-7	+/-7	+7		+7
Blood sample for Pharmacogenomics[25]		X																			
MRI-PDFF[26]	X																				
MRI-PDFF, MRE, cT1, liver volume (for subset of participants)[27]		X								X					X			X[27a]	X	X	
FibroScan® (VCTE – LSM) and CAP28)	X									X					X			X[28a]	X	X	
MELD scores	X	X		X		X	X	X	X	X		X		X	X	X		X	X	X	
Assess ascites, hepatic encephalopathy	X	X		X		X	X	X	X	X		X		X	X	X		X	X	X	

	Screening and randomisation		**Dose escalation**								**Maintenance period**									**Follow-up**	
	Screening (in-clinic)	Randomisation (in-clinic)	Remote	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic	In-clinic	Remote	In-clinic	Remote	In-clinic	In-clinic (biopsy)	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic
Visits[1]	**V1[2]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 Rep. every 12 w until EoT[3]**	**V18 Rep. every 12 w until EoT[3]**	**EoT[3]**	**ETD[3]**	**FU[3]/ EoS[4]**
Timing of visits (weeks)	-10	0	2	4	6	8	12	16	20	24	30	36	42	48	52	54	60	66			EoT +21 days OR ETD +21 days
Timing of visits (days	-70	1	15	29	43	57	85	113	141	169	211	253	295	337	365	379	421	463			
Visit window (days)		+/-0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-14	+/-7	+/-7	+/-7	+7		+7
Liver disease progression assessment[29]		X								X				X				X[29a]	X	X	
UGE and abdominal scan (only for participants who progressed to cirrhosis)[30]																		X[30]	X[30]	X[30]	
Eye examination[31]	X									X								X[31a]	X	X	
HCC screening (alpha-fetoprotein)[32]	X	X								X				X				X[32]	X	X	

	Screening and randomisation		**Dose escalation**								**Maintenance period**									**Follow-up**	
	Screening (in-clinic)	Randomisation (in-clinic)	Remote	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic	In-clinic	Remote	In-clinic	Remote	In-clinic	In-clinic (biopsy)	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic
Visits[1]	**V1[2]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 Rep. every 12 w until EoT[3]**	**V18 Rep. every 12 w until EoT[3]**	**EoT[3]**	**ETD[3]**	**FU[3]/ EoS[4]**
Timing of visits (weeks)	-10	0	2	4	6	8	12	16	20	24	30	36	42	48	52	54	60	66			EoT +21 days OR ETD +21 days
Timing of visits (days	-70	1	15	29	43	57	85	113	141	169	211	253	295	337	365	379	421	463			
Visit window (days)		+/-0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-14	+/-7	+/-7	+/-7	+7		+7
Questionnaires[33]																					
NASH-CHECK Questionnaire		X					X			X				X	X			X[33a]	X	X	
CLDQ NAFLD-NASH		X					X			X				X	X			X[33a]	X	X	
PHQ-9	X	X[34]					X			X		X		X		X		X	X	X	X
C-SSRS	X	X[34]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Other assessments and procedures																					
Training in/observe pre-filled syringe administration[35]		X	X	X	X																

	Screening and randomisation		**Dose escalation**								**Maintenance period**									**Follow-up**	
	Screening (in-clinic)	Randomisation (in-clinic)	Remote	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic	In-clinic	Remote	In-clinic	Remote	In-clinic	In-clinic (biopsy)	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic
Visits[1]	**V1[2]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 Rep. every 12 w until EoT[3]**	**V18 Rep. every 12 w until EoT[3]**	**EoT[3]**	**ETD[3]**	**FU[3]/ EoS[4]**
Timing of visits (weeks)	-10	0	2	4	6	8	12	16	20	24	30	36	42	48	52	54	60	66			EoT +21 days OR ETD +21 days
Timing of visits (days	-70	1	15	29	43	57	85	113	141	169	211	253	295	337	365	379	421	463			
Visit window (days)		+/-0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-14	+/-7	+/-7	+/-7	+7		+7
Hand out IFU – pre-filled syringe		X																			
IRT call and dispense IMP[36]	X[37]	X		X		X	X	X	X	X		X		X		X		X			
eDiary review (IMP administration, injection, injection site reactions and compliance check)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diet and physical activity counselling[38]		X		X		X	X	X	X	X		X		X		X		X	X	X	

	Screening and randomisation		**Dose escalation**								**Maintenance period**									**Follow-up**	
	Screening (in-clinic)	Randomisation (in-clinic)	Remote	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic	In-clinic	Remote	In-clinic	Remote	In-clinic	In-clinic (biopsy)	In-clinic	Remote	In-clinic	In-clinic	In-clinic	In-clinic
Visits[1]	**V1[2]**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17 Rep. every 12 w until EoT[3]**	**V18 Rep. every 12 w until EoT[3]**	**EoT[3]**	**ETD[3]**	**FU[3]/ EoS[4]**
Timing of visits (weeks)	-10	0	2	4	6	8	12	16	20	24	30	36	42	48	52	54	60	66			EoT +21 days OR ETD +21 days
Timing of visits (days	-70	1	15	29	43	57	85	113	141	169	211	253	295	337	365	379	421	463			
Visit window (days)		+/-0	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-7	+/-7	+/-7	+/-7	+/-14	+/-7	+/-7	+/-7	+7		+7
Hand out of SMBG (self-monitoring blood glucose) device (trial participants with T2DM), and trial participant materials[39]	X	X																			
Hyper-/hypoglycaemic episode review (eDiary – trial participants with T2DM)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital status																					X

Note:
For in-clinic visits after randomisation and review of inclusion/exclusion criteria, the suggested order of assessments is described in Section 6.2.2.
If remote visits are not allowed per local regulation, they will be performed as in-clinic visits. If a participant requests on-site visit instead of remote visit, this request can be accepted by the investigator. In both cases if remote visits are completed as in-clinic visits, only procedures designated for the remote visit should be completed in the clinic. If a participant is not able to come to the site for a specific trial visit, the participant must be invited for an unscheduled visit to perform the corresponding tests/assessments.

1 If the IMP administration is scheduled on the day of the visit, the trial participant has to be informed to come to the trial site prior to the IMP administration so that the blood samples is obtained prior to IMP administration. Participants will be instructed to inject the IMP once weekly at the same day of the week to the extent possible (+/-1 day).
All in-clinic visits, except screening, should be at fasting state (at least 8 hours without food or liquid intake, except water). In the case a participant was in a non-fasted state at the screening visit and some laboratory values are exclusionary, retesting on fasting state can occur during the screening period as per investigator judgment.

2 In the event of logistical issues with the reporting of results by the central vendor(s) a patient who meets all inclusion criteria and does not meet any exclusion criteria should be considered for participation in the clinical trial even if he/ she exceeds the screening period of 10 weeks. Extension of the screening period requires a sponsor approval.

3 The trial is event-driven, and all randomised trial participants will remain in the trial until the defined number of primary endpoint events has been reached. The estimated trial duration is about 7 years (includes estimated screening and treatment period, and follow-up period). After the first 700 randomised participants have experienced 52 weeks of treatment (or terminated earlier), an interim analysis will be performed for efficacy assessment purpose based on histological assessment of liver biopsy. Recruitment will continue without interruption until the entire planned 1800 participants have been randomised. All trial participants will have an FU/EoS Visit at least 28 days after the last dose of IMP.

- Trial participants who prematurely discontinue IMP will have an ETD Visit up to 7 days after the last dose of IMP, FU Visit, and then continue with scheduled visits until the trial is stopped, and then complete the FU/EoS Visit once the trial has ended.
- Trial participants who prematurely discontinue the IMP and are not willing to attend scheduled visits, remote visits (if allowed per local regulations) or telephone calls must be made to document any occurrence of outcome events, vital status, and adverse events (AEs). If the participant chooses not to continue with all the scheduled visits, attempt should be made to conduct at least yearly trial visits via remote visits (if allowed per local regulations) or over the phone for review of medical records (Section 3.3.4.1).
- Trial participants who discontinue IMP and choose not to continue with the trial visits, should complete the ETD Visit within 7 days after last dose and FU/EoS visit should be completed 21 days after ETD Visit. If the participant is not willing to attend these scheduled visits, conduct ETD and FUP/EoS Visit via a remote visit (if allowed per local regulations) or over the phone for review of medical records (Section 3.3.4.1).

If the trial continues beyond 7 years, visits are to be repeated with same intervals as from Week 60 and onwards, i.e. an in-clinic visit every 12 weeks alternated by a remote visit (if allowed per local regulations) every 12 weeks. If remote visits are not allowed, trial participants should attend the clinic to complete these visits.

The time point for the EoS will be communicated via an investigator letter when the sponsor is confident that the required number of events will be reached within an expected timeframe.

4 After the EoS Visit (i.e. the individual trial participant's EoS), the investigator should only report any occurrence of cancer of new histology, IMP related SAEs, and IMP related AESIs of which the investigator may become aware of (Section 5.2.6.2.1).

5 A separate informed consent is required for obtaining biobanking samples and for participants in the MRI substudy.

6 Medical history includes assessment of pre-existing conditions (special attention to be paid to medical conditions requested by in-/exclusion criteria and other important medical conditions, e.g. history of gallbladder disease, CVD, history of psychiatric disorder, MTC, and history of any cancer other than MTC). In addition, if a mammogram or colonoscopy was performed within 2 years prior to screening as part of routine clinical practice, data should be recorded in the eCRF.

7 The physical examination at Visit 2, Visit 10, Visit 15, Visit 26 and at EoT/ETD Visit should include assessment of substance usage (such as smoking, nicotine and alcohol use). From Visit 18 this assessment to be done once a year until EoT. Height should be measured at Visit 2 for the calculation of BMI.

8 Weight measurements should be obtained per the instructions in Section 5.1.6.1. Body weight must be measured in fasting state (except the screening visit).

9 Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing including PK samples (per the instructions in Section 5.2.2).

10 ECG at the screening visit will be done in triplicate. ECG measurements should be obtained per the instructions in Section 5.2.4. ECGs should be collected prior to collection of blood samples for laboratory testing, including PK samples.

10a) From Visit 18 onward to be performed every 6 months.

11 Concomitant therapy: special attention has to be paid if medication which has a narrow therapeutic index is used. Refer to Section 4.2.2.1 for details.

12 Changes of the medication including dose in anti-hypertension, lipid-lowering, and anti-hyperglycaemic drugs have to be assessed for increase/decrease/no change and captured in the eCRF. Refer to Section 5.6.3 for details

13 Assessment of obesity staging: for participants with BMI ≥30 kg/m^2 (≥25 kg/m^2 for Asian ethnicity)

14 Laboratory tests: all laboratory samples should be collected in a fasting state, except at screening visit. Trial participants should be instructed to come after at least 8 hours without food or liquid intake, except water, and without administering anti-hyperglycaemia medications (as applicable), which will be taken in the clinic. The IMP dose administration (if scheduled within the day of the visit) should be withheld in the morning of the clinic visit until blood sampling has been performed. If a trial participant has come to the in-clinic visit in non-fasting state, procedures that require fasting (blood sampling) should be performed on another day within the visit window. All laboratory assessments will be performed by a central laboratory. Instruction regarding sample collection, sample handling/processing, and sample shipments will be provided in the respective laboratory manuals. In the case a subject was in a non-fasted state at the screening visit and some laboratory values are exclusionary, retesting can occur during the screening period as per investigator judgment.

15 Refer to Table 11 for all safety laboratory parameters to be assessed.

16 Pregnancy testing: for WOCBP only. A urine pregnancy test will be done during screening. If it is positive, the trial participant will be considered a screen failure. If it is negative, a serum pregnancy test will be done. Urine pregnancy tests will be performed at all other in-clinic visits. If the urine pregnancy test is positive, IMP should be paused, and a serum pregnancy test will be done. If the serum pregnancy test is positive, the participant needs to be discontinued from IMP treatment. Pregnancy tests can be done more frequently if required by local regulations.

17 At the screening visit, only HbA1c will be assessed.

18 Urine sample should be collected in the clinic from the second morning void (preferably) and if not possible, from spot urine.

19 ELF (hyaluronic acid [HA], procollagen III terminale peptide [PIIINP], tissue inhibitor of metalloproteinase [TIMP 1]) samples are to be taken prior to IMP administration at baseline (Visit 2), Week 12 (Visit 7), Week 24 (Visit 10), Week 52 (Visit 15), Week 66 (Visit 18), Week 90 (Visit 22), and Week 114 (Visit 26). Then yearly during in-clinic visit till the EoT/ETD visit.

20 Other biomarker samples (N-terminal propeptide of type III collagen [Pro-C3], N-terminal pro hormone B-type natriuretic peptide [NT-proBNP], cystatin C) are to be taken prior to IMP administration at baseline (Visit 2), Week 12 (Visit 7), Week 24 (Visit 10), Week 52 (Visit 15), Week 66 (Visit 18), Week 90 (Visit 22) and Week 114 (Visit 26). Then yearly till the EoT/ETD Visit. Samples for glucagon analysis will be taken in a fasting state prior to IMP administration at baseline (Visit 2), Week 12 (Visit 7), Week 24 (Visit 10), and Week 52 (Visit 15) visits. If a participant has discontinued IMP prematurely biomarkers samples will not be taken after ETD. If a sample is not taken as scheduled, this sample will be omitted and defined schedule of assessment should be followed.

21 Optional banking samples: DNA sample for biobanking will only be collected once at Visit 2 while plasma/serum samples for biobanking will be collected at Visit 2 and at the Week 24 and EOT Visit. Collection of DNA samples at Visit 2 is preferred but also possible at later visits. Samples will be collected prior to IMP administration.

22 PK, ADA, Nab samples: If the IMP administration is scheduled during the day of the visit, then the trial participant will come to the trial site prior to IMP administration and sampling for PK, ADA, and Nab will be done prior to IMP administration (if IMP administration has occurred prior to PK sampling despite the instruction, this has to be

documented in trial participant's eDiary.). PK, ADA, and Nab samples are to be taken at baseline (Visit 2) and at Weeks 4, 12, 24, 36, 52, and from Week 66 to be repeated every 24 weeks, EoT/ETD, and FU/EoS.

- If a participant has discontinued the IMP prematurely, sampling for PK, ADA, and Nab testing should only be performed during the ETD and FU/EoS (if scheduled 21 days after ETD). Additionally, sampling for ADA and Nab testing (but no PK testing) should be performed 4 months after last IMP administration (for this purpose unscheduled visit to be planned or routine in-clinic visit can be used if the participant agreed to continue to follow trial visit and the visit timing correspond to 4 months after IMP stopped.
- In addition, a PK sample must be obtained at the time of potential DILI event for later analysis of excessive exposure.

23 FSH: For women between age 40 and 55 years with no menses for 12 months, perform FSH test to confirm if they are postmenopausal. If the participant is on Hormone Replacement Therapy (HRT), HRT must be withheld intermittently in order to allow confirmation of menopausal status via FSH testing before enrolment. If pausing HRT for this purpose is not possible or not accepted by the participant, the participant will have to use nonestrogen hormonal highly effective contraception methods. Women ≥55 with no menses for at least 12 months without alternative medical cause do not need FSH testing but can be assumed to be postmenopausal. FSH testing is not required for women who are permanently sterile (for definition of being permanently sterile, refer to Section 3.3.2).

24 Liver biopsy: Randomised participant will have a minimum of 2 biopsies:

24a) At screening (if no historical biopsy available), a centrally read eligible biopsy is required prior to randomisation. Liver biopsy should only be done after all Visit 1 results are available and the participant is deemed eligible for the trial. When scheduling a liver biopsy as part of screening procedures sufficient time should be allowed to receive the results before proceeding to Visit 2. Historical biopsies performed in the 6 months prior to randomisation are acceptable and will be sent to central reading.

24b) At Week 52 for the first 700 randomised participants (for Part 1 assessment); may be performed 2 weeks prior to or after the Week 52 visit (i.e. Week 50-54 from randomisation).

24c) From Week 52 onwards, a **triggered biopsy** is to be scheduled if NITs assessment from 6 months liver disease progression assessment visit suggests progression to cirrhosis:

- LSM (VCTE) >25 kPa OR MRE ≥5kPa
- LSM (VCTE) >20 kPa with delta change from baseline ≥30%

  (if a participant has been enrolled into the trial with baseline LSM (VCTE) >20 kPa then platelet count <150 000/mm^3 or ELF ≥11.3 to be added)
- LSM (VCTE) 15–20 kPa associated with a platelet count <150 000/mm^3 OR with ELF ≥11.3
- Cross sectional imaging (CT or MRI or ultrasound) evidence of nodular liver contour, right hepatic lobe atrophy +/- left hepatic lobe hypertrophy and coarse liver parenchyma)

If any of above criterion is met the liver stiffness examination and related laboratory is to be repeated 4 weeks later (at an unscheduled visit), and if the results confirm a suspected diagnosis of cirrhosis the liver biopsy is to be scheduled no later than within 3 months from the liver disease progression assessment visit. (in all such cases discussion with sponsor is needed prior to schedule triggered biopsy visit):

24d) Biopsy at the EoT Visit; may be performed 6 months prior to the EoT Visit unless there is previous confirmation of progression to F4 based on liver biopsy or any liver clinical outcome event defined under primary composite endpoint.

24e) Biopsy at the ETD Visit will be performed as follows:

- A participant who discontinues from the trial before Week 24 should not undergo a biopsy.
- A participant who discontinues from the treatment after Week 24 should undergo a biopsy within 15 days after the last IMP intake unless there is an available biopsy within the past 6 months.

25 For all participants who consent in the trial, mandatory pharmacogenomic (PGx) samples are collected. One PGx sample for analysis of prespecified genes will be collected at Visit 2. In exceptional cases the sample may be collected at a later visit. Refer to Section 5.4.2 for details.

26 MRI PDFF will be performed as a part of screening procedure prior to liver biopsy (participants with contraindications to an MRI-PDFF (e.g. metal prosthetics or uncontrolled claustrophobia) examination or screened at an investigative site where MRI-PDFF is not available are eligible for a liver biopsy if they have a FibroScan® with CAP ≥300.). All MRI techniques should be performed following fasting for at least 4 hours.

27 MRI PDFF, MRE, liver volume and cT1 to be performed as per SoA visits (subset of participants). A separate informed consent is required for participation in MRI-substudy. For the participants with MRI PDFF available from screening visit, MRI PDFF won't be repeated at Visit 2 and screening MRI PDFF will be used as baseline. All MRI techniques should be performed following fasting for at least 4 hours.

27a) MRI PDFF, MRE, and cT1 will be performed at W114 (V26) and then every 18 months during in-clinic visit till the EoT Visit (there won't be MRI PDFF, MRE and cT1 assessment at Visit 18).

28 Fibroscan® (LSM [VCTE] and CAP) will be performed as per SoA visits. Prior to FibroScan® measurements, 3 hours of fasting is required.

28a) From Visit 18 onwards to be performed every 6 months at Week 66 (Visit 18), Week 90 (Visit 22), Week 114 (Visit 26) and then every 6 months during in-clinic visit till the EoS Visit.

29 Liver disease progression assessment will be recorded every 6 months starting from baseline till EoT. During the visit, participant will have the disease progression assessment done based on clinical conditions and available NITs (MRI-PDFF, MRE, liver stiffness [VCTE], ELF, platelets). MELD score, stiffness progression, presence of ascites and HE will be assessed.

If performed assessment suggest progression to cirrhosis (for criterion please refer to SoA footnote: 24c) , the examination is to be repeated 4 weeks later (at an unscheduled visit), and if the results confirm a suspected diagnosis of cirrhosis the liver biopsy is to be scheduled no later than within 3 months from the liver disease progression assessment visit (after consultation with sponsor medical monitor).

29a) From Visit 18 onwards every 6 months during in-clinic visit till the EoT Visit.

30 Only for participants who have progressed to cirrhosis. All participants who have progressed to cirrhosis during trial duration should be followed as per recommended SoC (6-month abdominal ultrasound for HCC screening) and UGE performed at the diagnosis of cirrhosis, then yearly and at EoT/ETD visit for progression to CSPH assessment.

31 Only for participants with T2DM in medical history or diagnosed at screening: The eye examination has to be performed in the period between screening and randomisation, if not performed within the past 3 months before screening, to verify uncontrolled and potentially unstable diabetic retinopathy or maculopathy. For future visits, eye examination can be performed within a time window of +/-1 month of the visit.

31a) From Visit 18 the eye-exam to be performed on yearly basis or when the participant experiences worsening of vision and at EoT/ETD.

32 Alpha fetoprotein as HCC screening assessment will be performed every 6 months during in-clinic visit till the EoT Visit. Confirmatory imaging via CT scan or MRI should be performed if there is suspicion of HCC on elevated α-fetoprotein. Participants who have progressed during trial conduct to cirrhosis should have abdominal scan performed each 6 months.

33 Completion of the questionnaires should be performed prior to any other assessment scheduled for the in-clinic visit and preferably in the following order: 1) NASH-CHECK Questionnaire, 2) CLDQ NAFLD-NASH, 3) PHQ-9, and 4) C-SSRS. If PHQ-9 score is ≥15 and/or type 4 or 5 of suicidal ideation in C-SSRS, the trial participant needs to be referred to an MHP visit. If the trial participant refuses to be referred to an MHP, this needs to be documented in the medical records and the investigator has to assess, if it is safe for the participant to continue the trial or if the participant should be discontinued. In case of technical issues or participant refusal of electronic version of questionnaires use, paper questionnaires will be used during the visit.

33a) NASH-CHECK questionnaire and CLDQ NAFLD-NASH to be done every 6 months.

34 It must be re-confirmed at baseline (i.e. before randomisation) that exclusion criteria 15, 16, and 17 are not met.

35 Each trial participant will receive training on the administration of the pre-filled syringes. Site staff will observe the trial participant administering the pre-filled syringe in the clinic at Visit 2. The remote visits (if allowed per local regulations) are to be performed as video phone calls. IMP administration may be observed by site staff during Visits 3, 4,

and 5. Site staff and the trial participant might plan to schedule Visits 3, 4, and 5 on the day of planned IMP administration to allow site staff to observe administration of the injection at these visits

36 Trial participants will receive enough IMP to cover the time period until the next scheduled visit. The investigator should explain the storage temperature conditions for the IMP and instruct the trial participants about the IMP storage temperature requirements. Trial participants should be instructed about the necessity to return all used and unused IMP related packaging.

37 At the screening visit no IMP will be dispensed.

38 All trial participants with BMI ≥27 kg/m^2 will receive diet and physical activity counselling which should be performed by a dietician or equivalent qualified delegate. The counselling on diet and physical activity may be performed on a separate day from the rest of the visit's trial procedures but must occur within the visit window. The trial personnel should provide reinforcement and encouragement for lifestyle modifications.

39 Trial participant materials include: 1: Instructions for IMP use and eDiary to record IMP dosing information, 2: Trial participant identification card, 3: Instructions and trial participant brochure for control of sickness, recognition and handling of hyperglycaemia and hypoglycaemia. 4) Dietary materials and paper food and exercise diary to record physical activity and dietary compliance. In addition, for trial participants with T2DM at baseline, the blood glucose monitoring device including the device manual will be provided (weekly testing is recommended, additional measurements should be taken if necessary and in case of hypo- or hyperglycaemia-related symptoms, trial participants should be informed about the need to contact investigator). Participants who develop T2DM during the course of the trial will receive a blood glucose monitoring device after the diagnosis is confirmed.

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ABBREVIATIONS AND DEFINITIONS

3P-MACE	3-point major adverse cardiac event
4P-MACE	4-point major adverse cardiac event
5P-MACE	5-point major adverse cardiac event
AASLD	American Association for the Study of Liver Diseases
ADA	Anti-drug antibody
ADA/EASD	American Diabetes Association/European Association for the Study of Diabetes
AE	Adverse event
AESI	Adverse event of special interest
AI	Artificial intelligence
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APAC	Asia-Pacific
Apo	Apolipoprotein
APRI	Aspartate aminotransferase to platelet ratio index
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUROC	Area under the curve of the receiver operating characteristic
AVH	Acute varices haemorrhage
BI	Boehringer Ingelheim
BMI	Body mass index
BMR	Basal metabolic rate
CAP	Controlled attenuation parameter
CCLO	Composite clinical liver outcomes
CEC	Clinical events committee
CHE	Covert hepatic encephalopathy
CHESS	Clinical hepatic encephalopathy staging scale
CK	Creatine phosphokinase
CKD	Chronic kidney disease
CKD-EPI$_{cr}$	Chronic kidney disease epidemiology collaboration creatinine equation

CK-MB	Isoenzyme of creatine phosphokinase with subunits M and B
CLDQ	Chronic liver disease questionnaire
$C_{max,ss}$	Maximal concentration at steady state
COMPTRT	Comparative treatment name
CPI	C-peptide index
CRN	Clinical research network
CSPH	Clinically significant portal hypertension
C-SSRS	Columbia-suicide severity rating scale
cT1	Corrected T1
CT	Computer tomography
CTA	Clinical trial application
CTCAE	Common terminology criteria for adverse events
CTP	Child-Turcotte-Pugh
CTR	Clinical trial report
CURTRT	Current therapy or treatment (‘The literal identifier of the therapy or medication that is currently being given per protocol’)
CV	Cardiovascular
CVD	Cardiovascular disease
CYP	Cytochrome
DBL	Data base lock
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidylpeptidase 4
eCOA	Electronic clinical outcome assessment
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture/collection
eDiary	Electronic diary
eGFR	Estimated glomerular filtration rate
$eGFR_{cr}$	Creatinine based equation for eGFR calculation
$eGFR_{cys}$	Cystatin based equation for eGFR calculation
ELF	Enhanced liver fibrosis score

EMA	European Medicines Agency
EoS	End of study
EoT	End of treatment
ePRO	Electronic patient-reported outcome
ETD	Early treatment discontinuation
F2	Advanced fibrosis stage 2
F3	Advanced fibrosis stage 3
F4	Advanced fibrosis stage 4
FDA	Food and Drug Administration
FIB-4	Fibrosis-4
FPG	Fasting plasma glucose
FPI	Fasting plasma insulin
FSH	Follicle stimulating hormone
FU	Follow up
GCGR	Glucagon receptor
GCP	Good clinical practice
GE	Gastric emptying
GGT	Gamma glutamyltransferase
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like-peptide 1
GLP-1R	Glucagon-like-peptide 1 receptor
GOV	Gastroesophageal varice
HA	Hyaluronic acid
HbA1c	Glycosylated haemoglobin
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HE	Hepatic encephalopathy
HF	Heart failure
HFE	Heart failure events
HHF	Hospitalisation for heart failure
HIV	Human immunodeficiency virus

HOMA-β	Homeostasis model assessment-beta
HOMA-IR	Homeostasis model assessment-insulin resistance
HRT	Hormone replacement therapy
hsCRP	High-sensitivity C-reactive protein
HSI	Hepatic steatoses index
HRQoL	Health-related quality of life
HVPG	Hepatic venous pressure gradient
ICE	Intercurrent event
ICH	International Council for Harmonisation
IFU	Instruction for use
IMP	Investigational medicinal product
INR	International normalised ratio
IPD	Important protocol deviation
IRT	Interactive response technology
ISF	Investigational site file
i.v.	Intravenous
kPa	Kilopascal
LC-MS/MS	Liquid chromatography combined with tandem mass spectrometry
LDL	Low-density lipoprotein
LFC	Liver fat content
LSM	Liver stiffness measurement
LT	Liver transplant
LWYY	Lin-Wei-Yang-Ying
MACE	Major adverse cardiovascular event
MALO	Major adverse liver outcomes
MASH	Metabolic dysfunction-associated steatohepatitis
MASLD	Metabolic dysfunction associated steatotic liver disease
MedDRA	Medical dictionary for regulatory activities
MELD	Model for end-stage liver disease
MEN-2	Multiple endocrine neoplasia syndrome type 2
MHP	Mental health professional
MI	Myocardial infarction
MNAR	Missing not at random

MR	Magnetic resonance
MRE	Magnetic resonance elastography
MRI	Magnetic resonance imaging
MRI-PDFF	Magnetic resonance imaging proton density fat fraction
MTC	Medullary thyroid cancer
MTD	Maximum target dose
NAbs	Neutralising antibodies
NAFL	Non-alcoholic fatty liver
NAFLD	Non-alcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Non-alcoholic steatohepatitis
NIT	Non-invasive test
NSBB	Non-selective beta blocker
NT-proBNP	N-terminal pro hormone B-type natriuretic peptide
NYHA	New York Heart Association
OHE	Overt hepatic encephalopathy
PD	Pharmacodynamic
PDFF	Proton density fat fraction
Peth	Phosphatidylethanol
PGx	Pharmacogenomic
PHES	Psychometric test
PHQ-9	Patient health questionnaire 9
PII	Personable identifiable information
PIIINP	Procollagen III terminal peptide
PK	Pharmacokinetic
PRC	Pathology review committee
PRO	Patient-reported outcome
Pro-C3	N-terminal propeptide of type III collagen
q	Quantitative
QTcF	QT interval corrected for heart rate according to Fridericia's formula
QoL	Quality of life
RBC	Red blood cell
RDB	Randomised double blind

RDW	Red blood cell distribution width
REP	Residual effective period
RNA	Ribonucleic acid
RS	Randomised set
RWD	Real world data
SAE	Serious adverse event
SBP	Systolic blood pressure
SGLT2i	Sodium-glucose co-transporter-2 inhibitors
SHG	Second harmonic generation
SIB	Suicidal ideation and behaviour
SMBG	Self-monitoring blood glucose
SoA	Schedule of assessments
SOP	Standard operating procedure
T1DM	Type-1 diabetes mellitus
T2DM	Type-2 diabetes mellitus
TBA	Trial bioanalyst
TEE	Total energy expenditure
TG	Triglycerides
TIMP 1	Tissue inhibitor of metalloproteinase 1
TRT	Investigational therapy or treatment (‘The investigational product under study’)
TS	Treated set
TSAP	Trial statistical analysis plan
UACR	Urine albumin creatinine ratio
UGE	Upper gastrointestinal endoscopy
ULN	Upper limit of normal
VCTE	Vibration-controlled transient elastography
VLDL	Very low density lipoprotein
WHR	Waist-to-hip ratio
WOCBP	Women of childbearing potential

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

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

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Non-alcoholic fatty liver disease/metabolic dysfunction-associated steatotic liver disease (NAFLD/MASLD, further considered as MASLD) is a common, often "silent", liver disease associated with obesity related disorders, such as type-2 diabetes mellitus (T2DM) and metabolic syndrome, occurring in people who consume little or no alcohol, and is characterised by the accumulation of fat in the liver with no other apparent causes [P13-02280, R15-6044, R18-0878, R18-0901, R23-3446, R23-3447, R23-3448, R23-3449, R23-3450, R23-3451, R24-0157]. It is a multisystem disease that encompasses a wide range of liver histological changes, from isolated steatosis or metabolic dysfunction associated steatosis, previously known as non-alcoholic fatty liver (NAFL), to the inflammatory phenotype, non-alcoholic steatohepatitis/metabolic dysfunction-associated steatohepatitis (NASH/MASH, further considered as MASH), also showing evidence of ongoing liver cell injury (lobular inflammation and ballooning) [R23-1502, R24-0157]. The latter can potentially lead to progressive liver fibrosis and cirrhosis, and it is associated with adverse clinical, economic, and patient-reported outcomes [R23-0537, R23-1197, R23-1198].

MASLD is associated with an increased risk of all-cause, cardiovascular, and cancer-related mortality [R23-1197]. Liver fibrosis is the main determinant of adverse outcomes, and its occurrence and progression are related to the presence of obesity and T2DM [P16-03251]. Patients with MASH and at least stage 2 fibrosis (F2 or significant fibrosis), have a higher risk of liver-related morbidity and mortality [R22-2617, R23-1503, R23-1504].

The rising prevalence of obesity-related disorders has contributed to a rapid increase in the prevalence of MASH. Approximately 10% to 20% of subjects with MASLD will progress to MASH.

The proportion of MASH patients who progressed to fibrosis ranged from 22.5% [R18-0937] to 50% [R18-0895]. The proportion of patients who developed cirrhosis within 15 years of follow-up ranged from 7.1% [R21-2552] (Denmark) to 10.8% [R18-0736], and who progressed to hepatocellular carcinoma (HCC) from 12.8% [R18-0743] (US) to 30.9% [R18-0987] (Japan). The frequency of MASH as the primary indication for liver transplant (LT) increased over time from 0% in 2000 to 23.4% in 2012. Patients with MASH are also at increased risk of HCC, even in the absence of cirrhosis [R15-5365]. The progression rate for patients with MASH and advanced fibrosis (F3) to long-term outcome events is assumed to be 10% per year. Most of these long-term outcome events are histological progressions to cirrhosis (approximately 90%). The risk of liver-related death in Western patients with MASH ranges from 10% over 13.7 years to 18% over 18.5 years [P13-02280].

1.2 DRUG PROFILE

Mode of action

Survodutide is a dual glucagon receptor (GCGR) and glucagon-like-peptide 1 receptor (GLP-1R) agonist being developed for the indications of obesity and MASH, and future additional indications are under evaluation. GLP-1R agonists lower body weight by the inhibition of food intake at the hypothalamic appetite regulation centres and also by

inhibition of gastric emptying (GE) and intestinal transit. GCGR agonism reduces body weight by increasing energy expenditure and might positively affect lipid metabolism resulting in lowering of plasma and liver triglycerides and plasma cholesterol. In addition, GLP-1R agonism achieves glucose lowering by inducing glucose-dependent insulin secretion acting at the pancreatic β-cell.

Survodutide leads to full activation of the GLP-1R at the predicted therapeutic exposure, and partial activation of the GCGR. The GCGR receptor activation particularly on the liver hepatocytes is expected to enhance the efficacy due to GLP-1R activation alone. In participants with MASH and fibrosis, dual agonism at the GLP-1R and GCGR is targeting improvements of steatohepatitis and fibrosis, reduction of body weight and blood pressure and improvement in glycaemic control, thereby targeting not only MASH, but also the underlying metabolic syndrome.

Key PK characteristics

PK of survodutide were investigated after single s.c. doses of 0.3, 0.5, and 1.2 mg in the single rising dose trial [c22991258]. T_{max} was reached between 28 and 34 hours. C_{max} was 7, 13, and 34 nM, respectively. $T_{1/2}$ ranged from 109 to 115 hours. Dose proportionality was demonstrated for C_{max}, AUC_{0-168h}, and $AUC_{0-\infty}$.

In the trial in healthy Japanese volunteers [c33609485], a slightly higher average exposure was observed in Japanese compared with Caucasians. In a population analysis including data from the single rising dose trial [c22991258], the multiple rising dose trial [c26759941], and the trial in healthy Japanese volunteers [c33609485], survodutide PK was not different in Japanese and non-Japanese subjects after accounting for body weight effects [c37765403].

Further details, also on multiple dosing, can be found in the IB [c14085752].

Drug interactions

GLP-1R agonism reduces gastric emptying. This was assessed by measuring the effect of survodutide on the absorption of paracetamol in the single rising dose trial [c22991258]. Paracetamol C_{max} and AUC_{0-10} were slightly lower after a single dose of 0.3 mg survodutide, and strongly decreased after a single dose of 1.2 mg survodutide compared with administration of paracetamol alone. The effect of survodutide on gastric emptying decreases with multiple dosing [c26759941].

A population PK/PD analysis based on data from Japanese and non-Japanese subjects did not indicate meaningful ethnic differences in the survodutide effect on gastric emptying, as measured with the paracetamol absorption test [c37765403].

Residual Effect Period

The REP of survodutide is 28 days (half-life of 112 hours). This is the period after the last dose with measurable IMP levels and/or PD effects still likely to be present.

Data from non-clinical studies

In toxicity studies of up to 26 weeks in mice and up to 39 weeks in Cynomolgus monkeys, survodutide induced reduced food consumption and body weight loss or reduced body weight gain. These intended pharmacological effects limited the highest dose assessed in the toxicity studies performed in healthy (non-obese) animals and, therefore, only low exposure multiples to clinical use could be tested. All findings seen in the toxicity studies have been recorded in studies where food has been intentionally restricted or with treatments inducing unspecific stress, and therefore were interpreted as secondary effects. These observations included signs of metabolic stress for the liver, as indicated by hepatocellular vacuolation, slight increase of plasma bilirubin or changes in hepatocellular glycogen content, or changes of haematopoiesis in bone marrow, spleen, and thymus, as well as atrophy of the ovary. Cynomolgus monkeys – especially female monkeys – are considered oversensitive with regard to limiting body weight effects due to their low total body fat content (5.6% ± 3.81%) compared with humans and even more to participants with obesity.

In the non-clinical studies on embryofoetal development, there were no adverse effects on maternal toxicity and embryofoetal development up to and including the high dosage levels of 1498 µg/kg/week in mice and 252 µg/kg/week in rabbits, indicating that the compound is not teratogenic.

Data from clinical studies

Survodutide has been studied in healthy volunteers in the single rising dose trial [c22991258]. Similar to other GLP-1R agonists, nausea and vomiting were seen with increasing doses up to 1.2 mg, and planned dose escalation to further levels was stopped due to severe nausea and vomiting in a number of healthy volunteers.

Survodutide has also been studied in otherwise healthy volunteers with obesity or overweight in the multiple rising dose trial [c26759941] with dose escalation to investigate the safety and tolerability of different dose escalation schemes to determine a dose escalation scheme that minimises Gi AEs. In Part A of the trial, survodutide was administered for 6 weeks in 4 different titration schemes (1 once-daily dose group and 3 once-weekly dose groups with weekly dose escalation). The most frequent AEs were GI disorders, such as nausea, dyspepsia, abdominal distention, and vomiting. Cardiac disorders were reported in the survodutide treated group with 9% AV block first-degree, 9% second-degree, 8% sinus tachycardia, and 6% ventricular extrasystoles. All of the cardiac AEs were considered mild to moderate in intensity, none was reported as severe. An independent review of 24 hour Holter recordings of trial subjects in Part A of the study with ECG findings noted at the site using a 12-lead telemetry system was conducted by an independent cardiologist at a central ECG laboratory. It was concluded that the IMP given at 4 different doses did not show a notable increase in the findings reported by the cardiologist. The incidences in the categories are similar to those occurring at baseline and also not significantly different from those seen in the placebo-treated participants. In Part B of this trial, survodutide was administered for 16 weeks in 3 different titration schemes. As in Part A, the most frequent AEs were GI disorders, in this case nausea, vomiting, dyspepsia, diarrhoea, and eructation. No deaths or protocol specified AESIs were reported in this trial.

Survodutide was studied in healthy Japanese volunteers [c33609485]. GI disorders (decreased appetite, dyspepsia, diarrhoea, and nausea) were the most commonly reported type of AEs in this trial. There were no clinically relevant cardiac disorders reported. No unexpected safety or tolerability concerns were noted.

Survodutide was studied in 411 subjects with T2DM and obesity/overweight in a Phase II dose-finding trial [c36750061]. Survodutide showed an overall good safety profile during the trial with GI events (nausea, vomiting, and diarrhoea) being the most common AEs. Dose dependent HbA1c reductions were observed with survodutide treatment in participants with T2DM and overweight/obesity. Weekly injections with survodutide effectively lowered absolute HbA1c by up to –1.88% (Week 16) compared with the reduction of –1.47% with open-label semaglutide [P22-07379]. Treatment with survodutide induced greater body weight loss than open-label semaglutide after 16 weeks of treatment: −8.95% with the highest 3.6 mg dose vs. −5.40% with semaglutide 1.0 mg [P22-08755] Severe and serious AEs were reported at low frequencies, 5.3% and 3.6% in all participants treated with shrouded, respectively, with similar frequencies reported in the placebo group. There were no cases of pancreatitis. There were no serious or severe cardiac AEs. Of note, 11.9% of participants treated with survodutide discontinued treatment due to gI AEs.

Survodutide was studied in a Phase II trial in 387 participants with obesity and overweight (BMI ≥27kg/m^2) without T2DM [c40424795]. The therapeutic benefit of survodutide compared with placebo was shown by a non-flat dose response curve of percentage change in body weight from baseline to Week 46. Survodutide was associated with body weight reductions of up to 14.9% (treatment as randomised) after 46 weeks of treatment in the 4.8 mg group. The tolerability profile of survodutide was acceptable and most discontinuations due to AEs (mainly GI-related) occurred in the dose escalation period. There were no serious or severe AEs related to the CV system SOC.

Survodutide was studied in a Phase II dose-finding trial in 289 participants with biopsy confirmed MASH and F1-F3 stage fibrosis.

The therapeutic benefit of survodutide compared with placebo was shown by histological assessment of resolution of MASH and fibrosis reduction. Following improvement in key efficacy parameters was observed at Week 48:

1. at least 1 stage decrease in fibrosis with no worsening of MASH (survodutide 6.0 mg dose group: 42.3% responders, placebo: 17.7% responders),
2. MASH resolution with the absence of increase in fibrosis and at least 2 point improvement in NAS, after 48 weeks (survodutide 6.0 mg dose group: 51.9% responders, placebo: 6.3% responders)

The frequency of AEs in the 6.0 mg survodutide dose group was comparable with other dose groups, with GI events being the most frequently reported. Overall, no significant difference in the incidence of SAEs between survodutide treatment groups and the placebo group was noted, and no unexpected safety issues were identified.

The data from above-described Phase II dose-finding trial has been supported by the 1404-0010 hepatic impairment trial where safety and PK have been evaluated in participants with Child-Pugh A-B cirrhosis. During 28 weeks of treatment with survodutide 6.0 mg,

24 participants with cirrhosis Child-Pugh A-B (out of these participants more than 80% had cirrhosis due to MASH) were compared against 17 volunteers with normal liver function.

For a more detailed description of the survodutide profile, please refer to the current version of the IB [c14085752].

1.3 RATIONALE FOR PERFORMING THE TRIAL

Due to the growing epidemic of obesity and diabetes worldwide, MASH is projected to become the most common cause of advanced liver disease and the most common indication for liver transplantation. The burden of MASH represents an important unmet medical need [R18-0763, R18-0975, R21-2600, R23-3452].

As of now there is very limited available pharmacotherapies for the treatment of MASH and the long-term clinical benefits are still to be proven in this large unmet medical condition. The strong interface of MASH with metabolic syndrome, obesity, and T2DM requires multisystemic approach addressing not only liver inflammation and liver fibrosis but also non-liver-specific pharmacological management including weight loss, lifestyle changes and pharmacotherapies associated with metabolic syndrome components [P23-02853, R23-1381].

Survodutide, a dual GCGR and GLP-1R agonist, presents a promising therapeutic approach for the treatment of obesity, MASH and liver fibrosis. Based on the mechanism of action, including body weight reduction, increase of energy expenditure and improvement of metabolic parameters, it is expected to result in the resolution of steatohepatitis, improvement in liver fibrosis, and body weight loss, thereby targeting not only MASH but also the underlying metabolic syndrome. In clinical trial 1404-0043, survodutide has demonstrated MASH resolution and improvement in fibrosis in participants with MASH and fibrosis stages F1 to F3 after 48 weeks of treatment.

Overall, the safety profile of survodutide in patients with MASH and fibrosis was acceptable. Most common AEs were GI disorders [c14085752] and no other unexpected safety or tolerability concerns were raised.

In Phase II clinical trials in participants living with overweight and obesity survodutide has demonstrated the potential to improve underlying metabolic syndrome by improvements in parameters such as weight, HbA1c, and blood pressure. Improvements of comorbidities such as obesity, T2DM, and others may address quality of life issues experienced by MASH patients and improve overall survival.

The positive effect on the liver histology together with improvement in obesity-related underlying metabolic conditions is expected to reduce disease progression by demonstration of less liver-related clinical outcomes in longer follow up period.

Taken together, survodutide has demonstrated the potential to become best in class treatment for MASH, after meeting its primary and secondary endpoints in a dedicated MASH Phase II trial and showing significant results for treating participants with obesity in another Phase II trial.

In order to expand the understanding of the disease MASH and the IMP, e.g. by learning more about the mechanism of action of the IMP or the biology of the disease, exploratory and probable valid biomarkers will be study as hypothesis-generating or supportive endpoints. In order to be able to address future scientific questions, trial participants will be asked to voluntarily donate biospecimens for banking (please see Section 5.5). If the trial participant agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an AE, or to gain a mechanistic or genetic understanding of the product's effects and thereby better match patients with therapies.

1.4 BENEFIT – RISK ASSESSMENT

The overall benefits and safety profile of survodutide have been outlined in previous sections. More information on the benefits, risks, and known AEs is presented in the latest version of the IB [c14085752].

1.4.1 Benefits

Results from the Phase II trial 1404-0043 demonstrated histology-proven liver benefit from survodutide treatment comparing with placebo defined as MASH resolution and fibrosis improvement. The trial tested maintenance doses of 2.4 mg, 4.8 mg, and 6.0 mg of survodutide against placebo in 293 participants with MASH with F1-F3 fibrosis using once weekly injections.

In parallel to histological proven liver related benefits, the improvement in non-invasive liver related clinical parameters like reduction in AST/ALT, reduction in ELF score, and body weight reduction was observed in participants treated with survodutide compared with placebo.

In addition, body weight and metabolic parameters are also anticipated to improve in participants with pre-cirrhotic MASH. All trial participants with overweight/obesity will benefit also from participation through close contact with the trial site and counselling by a dietician or a similar qualified healthcare professional, all of which will most likely result in positive lifestyle modification.

1.4.2 Risks

There are no important identified risks specific for BI 456906, based on the toxicology program or any clinical trials conducted for this product to date.

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

An overview of trial related risks, including important potential risks, is presented in Table 1. For more details refer to Section 5.2.6.

Table 1 Overview of trial related risks

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Survodutide		
GI disorders (nausea, vomiting, and diarrhoea)	Well-known side effects for GLP-1R agonist-based therapies, mostly during the dose escalation phase	Slow and careful dose escalation. Instructions to be given on management of GI symptoms (Section 4.1.4.1, Appendix 10.2).
Acute pancreatitis and pancreatic cancer	Acute pancreatitis is a known side effect for GLP-1R agonist-based therapies. Pancreatic cancer is not a recognised risk in humans.	An extensive safety laboratory will be performed. Timely detection, evaluation, and follow-up of laboratory alterations in selected laboratory parameters to ensure trial participants´ safety.
Medullary thyroid carcinoma	To date there is no evidence that survodutide causes such AEs. MTC is a known side effect for GLP-1R agonist-based therapies in rodents. GLP-1R agonist-based therapies are contraindicated in patients with a personal or family history of MTC.	An extensive safety laboratory will be performed. Timely detection, evaluation, and follow-up of laboratory alterations in selected laboratory parameters to ensure trial participants´ safety.
Acute kidney injury (pre-renal) due to dehydration	Related to severe GI AEs of GLP-1R agonist class (severe vomiting may cause dehydration)	In case of vomiting, nausea, and diarrhoea, fluid intake should be increased (see Section 5.2.6.1.7. Decreased renal function will be monitored.’

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

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Survodutide		
Cardiac disorders (tachycardia and conduction disorders)	Tachycardia is a known side effect for GLP-1R agonist-based therapies. Cardiac conduction disorders were described for GLP-1R agonists in clinical trials and in the prescribing information for liraglutide (Saxenda) [R22-0131], reported as first degree atrioventricular block, right bundle branch block, or left bundle branch block. Survodutide has a low pro-arrhythmic potential based on animal studies No risk of cardiac arrhythmias based on Phase II trials	Centralised ECG monitoring will be performed at screening, randomisation and at selected in-clinic visits during the dose escalation and maintenance periods (see SoA), and criteria for QT prolongation are defined.
Acute gallbladder disease	Well-known side effects for GLP-1R agonist-based therapies, and well-known AE of rapid significant weight loss with any modalities.	An extensive safety laboratory will be performed. Timely detection, evaluation, and follow-up of laboratory alterations in selected laboratory parameters to ensure trial participants´ safety
Systemic hypersensitivity reaction	After administration of any biologic agent or protein, there is a possibility of occurrence of adverse immune reactions which can be local (e.g. redness, pruritus, and or swelling at the injection site) or systemic (e.g. anaphylactic reactions).	Trial participants with a history of allergy/hypersensitivity to the systemically administered IMP agent or its excipients are excluded from the trial. In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of IMP, the investigator should consider in accordance with severity of the reaction and local standard of care to interrupt the IMP treatment and treat the condition.
Trial procedures		
Injection site reactions	Well-known side effects for injectables	Instructions on self-administration will be given. Injection site will be monitored during every in-clinic visit.’

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

Possible or known risks of clinical relevance for this trial	**Summary of data, rationale for the risk**	**Mitigation strategy**
Other risks		
Drug-induced liver injury	Rare but severe event, thus under constant surveillance by sponsors and regulators	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure trial participants´ safety. Section 5.2.6.1.4 provides guidance for the investigators on how to evaluate and treat trial participants with suspected DILI.
Suicide risk, depression, and mood disorder	Not observed in clinical trials of GLP-1R agonists so far. Survodutide could act on central GLP-1R (limited data on survodutide).	C-SSRS will be applied at every visit as required by regulatory agencies.

In this trial, the following safety measures will be additionally applied to minimise the risk for trial participants:

- Trial participants in all groups, including placebo group will receive standard of care that includes diet and physical activity counselling (if patient with overweight/obesity), as well as treatment of background medical conditions.
- There are no risks expected from stopping the IMP during the trial.
- Instructions are to be given to the trial participants to help improve the GI tolerability especially during the escalation phase. In addition, for trial participants who do not tolerate the assigned escalation schedule, the dose escalation schedule can be modified. Details are described in Section 4.1.4.1 and Appendix 10.2.
- Paediatric patients (less than 18 years old) are excluded from the trial.
- WOCBP who are pregnant, nursing, or intend to become pregnant, or are not using an adequate contraceptive method (Section 4.2.2.3 and Appendix 10.3) are excluded from the trial.
- To continue the assessment of the safety of survodutide, adjudication of predefined clinical events (Section 5.2.6.1.7) will be performed in this trial by a CEC. The progress of the trial will also be assessed at regular intervals by an independent DMC. Further details are described in Section 8.7, the CEC Charter, and the DMC Charter.

1.4.3 Discussion

Based on the currently available data, in trial participants with non-cirrhotic MASH, dual agonism at GLP-1R and GCGR is expected to resolve steatohepatitis, regress, stop or slow progression of fibrosis, prevent clinical decompensation and improve survival by targeting not only the disease of MASH, but also the underlying metabolic conditions. As with other

GLP-1R agonists, the most commonly occurring adverse events in patients receiving survodutide are gastrointestinal in nature (nausea, vomiting, and diarrhoea). There are no important identified risks defined for survodutide. Important potential risks for survodutide are MTC (C-cell carcinogenicity), pancreatic cancer, acute pancreatitis, and pre-renal acute kidney injury due to dehydration.

In the context of the anticipated benefit of survodutide, the benefit risk evaluation of the compound based on the available pre-clinical and clinical data, is favourable and support the conduct of this trial in a well-controlled clinical trial environment.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

Primary objectives

This Phase III trial is conducted to evaluate survodutide in adults with MASH and liver fibrosis stage 2 or 3 and consists of 2 parts: Part 1 and Part 2, with the following primary objectives:

Part 1
The primary objectives in Part 1 are to demonstrate superiority of survodutide compared with placebo on:

- The odds ratio (survodutide vs. placebo) for MASH resolution without worsening of liver fibrosis from baseline at Week 52
- The odds ratio (survodutide vs. placebo) for improvement in fibrosis with no worsening of MASH from baseline at Week 52

The primary treatment comparison (in Part 1) will be as randomised, including the effects of any early treatment discontinuation or change in background medication. Use of restricted medication and occurrence of any hepatic decompensation event, liver transplant or death will be counted as treatment failure (non-response).

Part 2
The primary objective in Part 2 is to demonstrate superiority of survodutide compared with placebo by means of the hazard ratio (survodutide vs. placebo) of a time to first occurrence of any of components of thecomposite endpoint that includes progression to cirrhosis, liver-related clinical outcome events, and all-cause mortality (at EoS).

The primary treatment comparison (in Part 2) will be as randomised, including the effects of any early treatment discontinuation or use of restricted medication or change in background medication.

Secondary objectives

Key secondary objectives of Part 1
To demonstrate the superiority of survodutide compared with placebo from baseline to Week 52 on:

- The difference of means for percentage change in body weight
- The difference of means for absolute change in haemoglobin A1c [HbA1c] (in participants with T2DM)
- The difference of means for absolute change in ELF score
- The difference of means for absolute change in liver stiffness assessed by VCTE
- The odds ratio (survodutide vs. placebo) for no progression of fibrosis at Week 52 assessed by central pathology

Key secondary objectives of Part 2
To demonstrate the superiority of survodutide from baseline to Week 114/EoT/EoS compared with placebo on:

- The difference of means for percentage change in body weight (at Week 114)
- The difference of means for absolute change in HbA1c (in participants with T2DM) (at Week 114)
- The difference of means for absolute change in ELF score (at Week 114)
- The difference of means for absolute change in liver stiffness assessed by VCTE (at Week 114)
- The odds ratio (survodutide vs. placebo) for no progression of fibrosis assessed by central pathology (at EoT)
- Occurrence of all-cause hospitalisation (first and recurrent) (at EoS)
- Time to first occurrence of any of the adjudicated components of the composite endpoint consisting of: CV death, non-fatal stroke, non-fatal MI, ischaemia related coronary revascularisation, or HFE (this includes HHF, emergency room visit, urgent care visit, or urgent outpatient HF visit) (5P-MACE) (at EoS)

Other secondary objectives of both Part 1 and Part 2 include different histological, imaging and biochemical test assessing disease regression in the liver together with overall metabolic conditions improvement and the long-term safety of survodutide.

2.1.2 Primary endpoints

The primary endpoints of the trial are summarised in Table 2.

Table 2 Primary endpoints of the trial

Measure	**Description**
Part 1: Primary efficacy endpoint (at Week 52) 1. Resolution of MASH without worsening of liver fibrosis on MASH Clinical Research Network (CRN) fibrosis score 2. At least a 1-point improvement in fibrosis stage with no worsening of MASH	- Binary dual endpoint derived from liver histology as compared to baseline liver histology - Trial is considered positive if at least 1 primary endpoint is positive - Resolution of steatohepatitis is defined by NASH CRN scores: for ballooning of 0 and inflammation of 0-1 - No worsening of MASH defined as no increase for **any of** the 3 NAS sub-scores (steatosis, inflammation, ballooning)
Part 2: Primary efficacy endpoints (at EoS) Time to first occurrence of any of components of the composite endpoint consisting of: • Progression to cirrhosis (defined as histological fibrosis score CRN F4), • All-cause mortality • Liver transplant • Hepatic decompensation event(s) (including ascites requiring treatment, hepatic encephalopathy [HE] requiring treatment, portal hypertension-related upper gastrointestinal [GI] bleeding, including events of bleeding from oesophageal varices, gastric varices, and portal hypertensive gastropathy) • Worsening of Model for End-stage Liver Disease (MELD) score to ≥15 • Progression to clinically significant portal hypertension (CSPH), defined as 'high-risk' GOVs confirmed in UGE	- Composite endpoint of listed clinical events adjudicated by Clinical Events Committee (except liver transplant) - Progression to F4 will be assessed by consensus reading of Pathology Review Committee (PRC) - The progression to CSPH based on high-risk GOV will be centrally read and adjudicated. The high-risk varices are defined as large varices) [P18-02639, R23-4358]

2.1.3 Secondary endpoints

Key secondary efficacy endpoints are:

In Part 1 (at Week 52)

- Percentage change from baseline in body weight
- Absolute change from baseline in HbA1c (in participants with T2DM)
- Absolute change from baseline in ELF score
- Absolute change from baseline in liver stiffness assessed by VCTE
- Achievement of no progression of fibrosis assessed by central pathology (yes/no)

In Part 2 (at Week 114/EoT/EoS)

- Percentage change from baseline in body weight (at Week 114)
- Absolute change from baseline in HbA1c (in participants with T2DM) (at Week 114)
- Absolute change from baseline in ELF score (at Week 114)
- Absolute change from baseline in liver stiffness assessed by VCTE (at Week 114)
- Achievement of no progression of fibrosis assessed by central pathology (yes/no) (at EoT)
- Occurrence of all-cause hospitalisation (first and recurrent) (at EoS)
- Time to first occurrence of any of the adjudicated components of the composite endpoint consisting of: CV death, non-fatal stroke, non-fatal MI, ischaemia related coronary revascularisation, or HFE (this includes HHF, emergency room visit, urgent care visit, or urgent outpatient HF visit) (5P-MACE) (at EoS)

Additional secondary objectives are related to following secondary endpoints:
In Part 1 (at Week 52) and
In Part 2 (at Week 114)

- Improvement of LFC defined as at least 30% relative reduction in LFC compared with baseline assessed by MRI-PDFF (subset of participants with MRI)
- Absolute change from baseline in LFC in MRI-PDFF (subset of participants with MRI)
- Absolute change from baseline in ALT [U/L]
- Absolute change from baseline in AST [U/L]
- Absolute change from baseline in systolic blood pressure (SBP) [mmHg]
- Absolute change from baseline in diastolic blood pressure (DBP) [mmHg]
- Absolute changes from baseline in lipids [mg/dL] (including but not limited to: total cholesterol, low-density lipoprotein [LDL] cholesterol, very low density lipoprotein [VLDL], high-density lipoprotein [HDL] cholesterol, TG)
- Absolute change from baseline in free fatty acids [mg/dL]
- Progression to cirrhosis (defined as histological fibrosis score CRN F4) (yes/no), only at Week 52

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

Further objectives include other histological, imaging and non-imaging features of MASH, clinical outcome assessments, assessment of biochemical and cellular biomarkers related to MASH, obesity disease and metabolic syndrome related comorbidities, evaluation of the effect of survodutide on standard of care medication, evaluation of safety and tolerability, investigation of the PK of survodutide (including steady state analysis) and the influence of covariates on the PK in the participant population using a population PK approach, and the exposure-response relationship with selected efficacy and safety endpoints PRO quality of life and immunogenicity assessment.

2.2.2 Further endpoints

Further endpoints are defined for Part 1 and Part 2 of the trial:
NOTE: any endpoint listed below previously defined as primary or secondary in Part 1 or Part 2 will not be tested as further endpoint again if already defined.

<u>Endpoints for the following histological features of MASH</u>
(in Part 1 – at Week 52)
(in Part 2 – at end of treatment [EoT])

NOTE: Week 52 histological assessments will be done only for first randomised 700 participants. All trial participants will have histological endpoints calculated based on EoT biopsy (except if progression to cirrhosis confirmed earlier, in this case the last available biopsy will be used for EoT).
AI - based algorithm for liver histology assessment will be performed at Week 52 only.

- Resolution of MASH associated at least 2-point reduction in NAS and no worsening of liver fibrosis
- Resolution of MASH and improvement of fibrosis (at least 1 stage of improvement)
- Resolution of MASH and no worsening of fibrosis
- Improvement of NAFLD activity score (NAS) by at least 2 points (at least a 1 point reduction in either lobular inflammation or hepatocellular ballooning) and no worsening of fibrosis
- Improvement of fibrosis of at least 1 stage and no worsening of MASH
- Improvement of fibrosis of at least 2 points MASH CRN
- Resolution of fibrosis, defined as MASH CRN fibrosis stage 0
- Improvement of each histological feature of MASH by at least 1 point (steatosis, lobular inflammation, and hepatocellular ballooning) and no worsening of fibrosis
- Improvement in histology-assessed ballooning (at least 1 point improvement in ballooning score)
- Improvement in histology-assessed inflammation (at least 1 point improvement in lobular inflammation score)
- Improvement in histology-assessed steatosis (at least 1 point improvement in steatosis score)

- Change from baseline in quantiative Fibrosis®
- Incidence of progression and incidence of regression on liver biopsy according to quantitative Fibrosis®
- Change from baseline in quantitative Steatosis®
- Incidence of progression and incidence of regression on liver biopsy according to quantitative Steatosis®
- Change from baseline in quantitative Ballooning®
- Incidence of progression and incidence of regression on liver biopsy according to quantitative Ballooning®
- Change from baseline in fibrosis in zones periportal, portal tract, peri-central, central vein and peri-sinusoidal, as determined by SHG-based digital pathology
- Change from baseline in septa width, length, and area
- Change from baseline in fibrosis in specific and distinct histological spatial zones and concomitant changes in steatosis in those zones, as measured by SHG-based digital pathology

Endpoints for the following, but not limited to, imaging features of MASH
(in Part 1 – at Week 52)
(in Part 2 – at Week 114)

- Improvement of LFC defined as at least 50% relative reduction in LFC compared with baseline assessed by MRI-PDFF (in the subset of participants with MRI)
- Improvement of LFC defined as at least 70% relative reduction in LFC compared with baseline assessed by MRI-PDFF (in the subset of participants with MRI)
- Achievement of normalising LFC (<5%) assessed by MRI-PDFF (in the subset of participants with MRI)
- Absolute and percentage change of LFC from baseline assessed by FibroScan® CAP (subset of participants using Fibroscan® SmartExam)
- Percentage change of liver stiffness from baseline assessed by FibroScan® VCTE
- Absolute changes in liver stiffness from baseline by MRE (subset of participants with MRI)
- Absolute change from baseline in cT1 (subset of participants with MRI)
- Achievement of cT1 with ≥80 ms reduction in cT1 (which is the threshold that relates to histological response) (subset of participants with MRI)
- Absolute and percentage change from baseline in liver volume assessed by MRI-PDFF (subset of participants in the MRI-substudy)
- Absolute and percentage change from baseline in spleen volume assessed by MRI-PDFF (subset of participants in the MRI-substudy)
- Absolute change from baseline in FAST[1] score
- Absolute change from baseline in MAST[2] score (subset of participants in the MRI-substudy)
- Absolute change from baseline in MEFIB[3] index (subset of participants in the MRI-substudy)

1 Combination of FibroScan® (VCTE, CAP) and aspartate aminotransferase (AST)
2 Combination of MRI (MRE, MRI-PDFF) and AST
3 Combination of MRE and Fibrosis-4 (FIB-4)

Endpoints for the following non-invasive tests (non-imaging)
(in Part 1 – Week 52)
(in Part 2 – Week 114)

- Absolute change from baseline in GGT [U/L], ALP [U/L], total bilirubin [mg/dL]
- Achievement of ALT/AST reduction >17 U/L
- Percentage change from baseline in ELF score
- Achievement of ELF score <7.7
- Absolute change from baseline in markers of liver function: MELD (see Section 5.1.4 for calculation), albumin, international normalised ratio (INR)
- Absolute change from baseline in NAFLD fibrosis score, FIB-4 score, APRI score (see Appendix 10.7 for calculation)

Liver outcomes
(in Part 2 – at EoS)

- Time to first occurrence of progression to cirrhosis (defined as histological fibrosis score CRN F4)
- Time to first occurrence of any of the hepatic decompensation events (ascites, HE, or portal hypertension-related upper GI bleeding), and increase of MELD score to ≥15 on at least 2 consecutive occasions at least 4 weeks apart (see Section 5.1.4 for calculation of MELD score)
- Time to first occurrence of liver transplant
- Time to first occurrence of progression to CSPH (defined as 'high-risk' GOVs confirmed in UGE)
- Time to event for all-cause mortality

Metabolic endpoints
(in Part 1 – at Week 52)
(in Part 2 – at Week 114)

- Absolute change from baseline in BMI [kg/m^2]
- Absolute change from baseline in body weight [kg]
- Absolute change from baseline in waist circumference [cm]
- Absolute change from baseline in waist-to-hip ratio (WHR, dimensionless ratio)
- Absolute changes from baseline in glycaemic parameters in participants with and without an established T2DM diagnosis at baseline:
    - HbA1c [%]
    - HbA1c [mmol/mol]
    - Fasting plasma glucose (FPG) [mg/dL]
    - Fasting plasma insulin (FPI) [mIU/L]
    - Fasting C-peptide [ng/mL]
    - HOMA-IR (units on a scale) (see Appendix 10.7 for calculation)
    - HOMA-β (percentage of normal beta cell function) (see Appendix 10.7 for calculation)
    - CPI (dimensionless ratio) (see Appendix 10.7 for calculation)
    - WHR (dimensionless ratio)

- For the trial participants with an established T2DM at baseline:
  - Achievement of HbA1c <7.0% (yes/no)
  - Achievement of HbA1c <6.5% (yes/no)
  - Achievement of HbA1c <5.7% (yes/no)

Further weight related endpoints:
(in Part 1 – at Week 52)
(in Part 2 – at Week 114)

- Achievement of body weight reduction ≥5% (yes/no)
- Achievement of body weight reduction ≥10% (yes/no)
- Achievement of body weight reduction ≥15% (yes/no)
- Achievement of body weight reduction ≥20% (yes/no)
- Achievement of body weight reduction ≥25% (yes/no)
- Achievement of body weight reduction ≥30% (yes/no)
- Achievement of BMI < 25 kg/m^2 or achievement of BMI reduction by at least 7 points (yes/no) in the following subgroups defined by baseline BMI:
  - 27 kg/m^2 – <30 kg/m^2
  - 30 kg/m^2 – <35 kg/m^2
  - 35 kg/m^2 – <40 kg/m^2
  - ≥40 kg/m^2

Kidney related endpoints
(in Part 1 – at Week 52)
(in Part 2 – at Week 114, EoS)

- Annual rate of change in $eGFR_{cr}$ from randomisation to last value on treatment (i.e. total slope)
- Annual rate of change in $eGFR_{cys}$ from randomisation to last-value on treatment (i.e. total slope)
- Absolute and relative change from baseline in $eGFR_{cr}$ to Week 52 and Week 114
- Absolute and relative change from baseline in $eGFR_{cys}$ to Week 52 and Week 114
- Absolute and relative change from baseline in UACR over time
- Progression and remission of UACR to higher/lower category (<30, ≥30 to ≤300, and >300 mg/g) from baseline to Week 24, Week 52, and Week 114.
- Absolute change from baseline in uric acid [µmol/L] to Week 52 and Week 114
- Percentage change from baseline in uric acid [%] to Week 52 and Week 114
- Time to first occurrence of kidney failure (defined by the need of chronic kidney replacement therapy [continuing for at least 30 days] or receipt of kidney transplant), sustained decline[1] of ≥40% eGFR ($CKD\text{-}EPI_{cr}$), or sustained decline of eGFR[1] ($CKD\text{-}EPI_{cr}$) to <15 mL/min/1.73 m^2, or renal death (5-component composite nephropathy endpoint) (at EoS)

1 A condition is considered sustained if it is determined by measurements of 2 consecutive visits. If the condition is met only at the last visit or once before the trial participant is discontinued or has died, then the respective condition is also considered sustained.

- Time to first occurrence of any of the components of the composite endpoint consisting of onset of sustained macroalbuminuria (UACR >300 mg/g [33.9 mg/mmol]), or sustained decline[1] of ≥40% eGFR ($CKD\text{-}EPI_{cr}$) compared with baseline (randomisation), or onset of sustained decline of eGFR[1] ($CKD\text{-}EPI_{cr}$) <15 mL/min/1.73 m^2, or initiation of chronic renal replacement therapy (dialysis[2] or transplantation), or renal death (5-component composite nephropathy endpoint) (at EoS)

Patient-reported outcome (PRO) related endpoints
Absolute change from baseline to:
(in Part 1 – at Week 52)
(in Part 2 – at Week 114)

- Chronic Liver Disease Questionnaire (CLDQ-NAFDL-NASH)
- NASH-CHECK Questionnaire

Effect of survodutide treatment on standard of care medications
Change of medication and dose, measured in 3 categories, assessed at baseline up:
(in Part 1 – at Week 52)
(in Part 2 – at Week 114)

- Antihypertensive medication (decrease, no change, increase)
- Lipid-lowering medication (decrease, no change, increase)
- Anti-hyperglycaemic medication (decrease, no change, increase)

Other clinical outcomes (at EoT/EoS)

- Time to first occurrence of any adjudicated composite endpoint consisting of: CV death, non-fatal MI, non-fatal stroke (3P-MACE)
- Time to first occurrence of any of the adjudicated components of the composite endpoint consisting of CV death, non-fatal stroke, non-fatal MI, or ischaemia related coronary revascularisation (4P-MACE)
- Time to first occurrence of fatal or non-fatal MI
- Time to first occurrence of fatal or non-fatal stroke
- Time to first occurrence of all-cause hospitalisation
- Time to first occurrence of HHF or CV death
- Occurrence of HHF (first and recurrent)
- Time to first occurrence of HCC
- Achievement of regression from T2DM to pre-diabetes (HbA1c ≥5.7% to <6.5% [≥39 to <48 mmol/mol]) or no diabetes (HbA1c<5.7%) in trial participants with T2DM at baseline (at EoT) (yes/no)

1 A condition is considered sustained if it is determined by measurements of 2 consecutive visits. If the condition is met only at the last visit or once before the trial participant is discontinued or has died, then the respective condition is also considered sustained.
2 Chronic dialysis is defined as dialysis with a frequency of twice per week or more for at least 90 days.

- For the trial participants with pre-diabetes status at baseline, defined as HbA1c ≥5.7% to <6.5% (≥39 to <48 mmol/mol) at baseline:
  - Achievement of normoglycemic status at EoT, defined as achievement of HbA1c <5.7% (<39 mmol/mol) at EoT (yes/no)
  - Prevention of pre-diabetes progressing to T2DM at EoT, defined as maintenance of HbA1c <6.5% (<48 mmol/mol) at EoT (yes/no)
- Number of clinically relevant hyperuricaemic events per trial participant. A clinically relevant hyperuricaemic event is defined to be either "acute gout", "gouty arthritis" or the initiation of treatment with serum uric acid lowering therapy (xanthine oxidase inhibitors, uricosuric agents or colchicine). The event "acute gout" (MedDRA/Preferred Term) or "gouty arthritis" (MedDRA/Preferred Term) will be determined in terms of a new onset or a deterioration of the baseline condition.

Safety
Absolute change from baseline in:
(in Part 1 – over time)
(in Part 2 – over time)

- Heart rate [bpm]
- Lipase [U/L]
- Amylase [U/L]
- Calcitonin [ng/L]

Pharmacokinetics
(in Part 1 – over time)
(in Part 2 – over time)

- Pre-dose concentration of survodutide in plasma immediately before dose N

Biomarkers
(in Part 1 – at Week 52: Pro -C3 only)
(in Part 2 – over time)

- Liver biomarkers:
  - Absolute and percentage change from baseline in Pro-C3 [ng/mL]
  - Absolute and percentage change from baseline in indirect target engagement biomarker:
    - Glucagon [pmol/L]
  - Absolute and percentage change from baseline in CV biomarkers:
    - NT-proBNP [pmol/L]
  - Absolute and percentage change from baseline in kidney biomarker:
    - Cystatin C [mg/L]

Immunogenicity assessment
(in Part 1 – over time)
(in Part 2 – over time)

- Occurrence of ADAs (including cross-reactive ADAs) to survodutide via a tiered approach by scheduled visits
- Occurrence of NAbs (including cross- NAbs) via a tiered approach by scheduled visits

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

Trial 1404-0044 is a randomised, double-blind, parallel-group, 2 arm, multi-centre placebo-controlled Phase III clinical trial evaluating the efficacy and safety of survodutide (target dose 6.0 mg, once weekly administered s.c.) versus placebo in approximately 1800 trial participants with MASH and F2 - F3 stage of liver fibrosis.

This trial consists of two parts: Part 1 which will evaluate the resolution of MASH and improvement of fibrosis in liver histology in the first approximately 700 randomised trial participants, and Part 2 which will assess the efficacy and safety of survodutide against placebo in long term liver related clinical outcomes for all randomised trial participants (N = 1800). The enrolment between both parts will be handled without interruption. The trial design is shown in Figure 1.

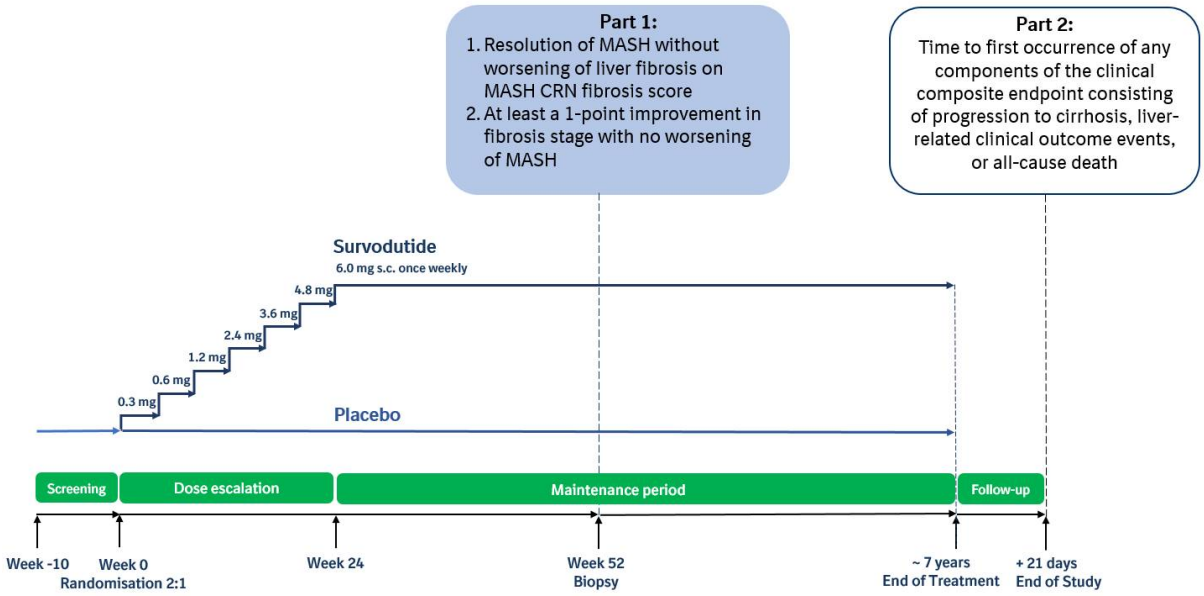

Figure 1 Trial design

CRN = clinical research network; MASH = metabolic dysfunction associated steatohepatitis

The trial has a screening period of up to 10 weeks to assess trial participant eligibility. Eligible trial participants will be randomised (2:1 ratio) to either survodutide or placebo. Randomisation will be stratified by region, the severity of fibrosis stage F2-F3 (determined by liver histology), by presence of T2DM at baseline as well as participation in MRI-substudy.

The trial is event-driven, and all randomised trial participants will remain in the trial until the defined number of primary endpoint events is projected to be reached (estimated EoS is about 7 years). A sufficient number of trial participants will be screened to randomise approximately 1800 trial participants. The estimated trial duration is about 7 years with a

recruitment period of approximately 36 months. The trial duration may be prolonged or shortened depending on when the required minimum number of 394 clinical events for the primary endpoint (of Part 2) has been reached. The estimated trial duration and length of double-blind treatment for each trial participant will vary accordingly. If the accumulated blinded data suggest a slower accrual of primary outcome events over calendar time than originally projected, then the number of randomised participants may be increased. Enrolment of these additional trial participants will be covered by a further protocol amendment. Recruitment period may also be extended accordingly. The number of confirmed primary outcome events will not be affected by this consideration.

Part 1 - when the first 700 randomised trial participants reach Week 52 of treatment (or terminated earlier) the statistical analysis of the liver biopsy histology-based primary efficacy endpoints will be conducted. The histological endpoints assessment is consistent with the FDA and EMA guidance document as reasonably likely to predict clinical benefit to support accelerated approval.

Part 2 will assess occurrence of composite clinical liver outcomes in all of the estimated 1800 trial participants. Each of the clinical outcome events (except liver transplantation) will require confirmation by a Clinical Events Committee (CEC) or for event assessed on liver histology (progression to cirrhosis) by PRC.

For all trial participants, site and remote (if allowed per local regulations) visits are scheduled at specified time intervals (SoA). The number of confirmed primary endpoint events will be continuously monitored during the trial. As soon as the event projection reliably suggests that the total number of trial participants with clinical liver outcomes confirmed by adjudication will be reached within an expected timeframe, respective actions will be initiated by the trial team to stop the trial. The trial can be also stopped earlier if the parallel trial 1404-0064 assessing clinical liver outcomes in trial participant population with cirrhotic MASH has reached required number of events to primary endpoint and demonstrated a positive benefit risk profile. From this point on, all trial participants are expected to perform their last visits (EoT and EoS visits) within the proposed time schedule communicated via an investigator letter.

Trial participants who complete the trial will return to the site for a follow-up EoS Visit 21 days after the EoT Visit. If trial participants discontinue IMP prematurely in the trial, they will return to the site for an Early Treatment Discontinuation (ETD) Visit within 7 days after last dose and will be asked to continue the trial visits as planned until EoS. If a trial participant is not willing to stay in the trial, the EoS Visit should be scheduled at least 28 days after the last IMP administration. All efforts should be made to follow-up on all trial participants until trial end. If a trial participant is not willing to return to the predefined trial visits, at minimum a phone call at trial end will be required to document the occurrence of outcome events, vital status, and adverse events (AEs). Please refer to Section 3.3.4.1

If a trial participant has experienced a CEC confirmed diagnosis of hepatic decompensation event (ascites or encephalopathy requiring treatment, portal hypertension-related upper GI bleeding) or liver transplant the IMP should be discontinued and ETD visit should be performed.

The End of Study (EoS) is defined as the date the last trial participant completes the last visit (including follow-up) as shown in the SoA.

A sub-population of up to 200 randomised trial participants will join an MRI-substudy where MRI-PDFF, MRE and cT1 liver assessments will be performed as per SoA. Participation in MRI-substudy is voluntary and not a prerequisite for participation in the trial. A separate informed consent is required for participation in MRI-substudy.

During the trial, participants should not initiate any restricted medication (please refer to Section 4.2.2.1). If a trial participant has experienced liver clinical outcome confirmed by PRC or CEC best standard of care should be followed (regular abdominal scan for HCC prevention, regular UGE for CSPH progression monitoring and treatment with non-selective beta blockers [NSBB] should be considered as per country guidelines). Best standard of care for anti-hyperglycaemia for participants with T2DM should be used according to their respective product labels and ADA/EASD guidelines [P22-05567]. Best standard of care medications should also be used to treat hypertension, dyslipidaemia, CVD, CKD, or any other co-existing medical conditions.

A blinded Clinical Events Committee (CEC) will review all clinical decompensation events (ascites, encephalopathy, or variceal hemorrhage) and events of worsening of MELD score to ≥15 (liver transplantation will not be adjudicated). Progression to CSPH will be adjudicated using central UGE recording. Safety events of all deaths, acute pancreatitis, pancreatic cancer, thyroid malignancy and C cell hyperplasia, DILI and HCC will also be adjudicated by CEC. CV events including CV death, MI, stroke, ischemia related coronary revascularisation and heart failure events (5P-MACE) will be adjudicated by CV experts within the CEC (list of all events in Section 5.2.6). The events for adjudication details on the composition of the committee, its procedures and interactions are defined in the CEC Charter.

A blinded Pathology Review Committee (PRC) will provide independent review of all liver biopsy samples that were collected during the trial according to the Pathology Review Charter. The analysis of the results will be reported in the respective Clinical Trial Reports (CTRs) and subsequent submission dossiers where applicable.

An unblinded Data Monitoring Committee (DMC) will serve to assess the progress of the clinical trial and monitor safety data including outcome events, in accordance with the DMC Charter. The DMC will recommend to the sponsor on a regular and ongoing basis whether to continue, modify, or stop the trial. The DMC is planned to meet at least quarterly.

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

This randomised, double-blind, placebo-controlled, Phase III trial is designed in accordance with regulatory guidelines related to products in clinical development for people with MASH and fibrosis stage F2-F3 [R20-2197, R24-1509]. This is a clinical outcomes driven trial where overall treatment duration is conditional to predefined event rates reduction in survodutide group comparing to placebo. A treatment duration of 52 weeks, for efficacy assessment based on liver histology in Part 1 is considered sufficient to assess efficacy and safety for Phase III clinical trials based on Phase II trial [c31864883] where efficacy and

safety of survodutide has been confirmed in 48 weeks of treatment. The inclusion of the placebo comparator helps to better characterise the nature of any dose response.

Trial participants should receive the best standard of care for the underlying conditions according to local or regional guidance for T2DM, hypertension, dyslipidaemia management, or any other co-existing medical conditions and the investigators should carefully monitor how the concomitant therapy should be adjusted during the trial. For all trial participants with complications, the sponsor will ask the investigators at each visit (through a separate field in the eCRF), if the participant is treated to the best standard of care for the management of complications (yes/no).

A Steering Committee, a DMC, and an independent (external) and blinded CEC will be established (see Section 8.7).

This trial will include an option for participants to complete questionnaires to provide feedback on their clinical trial experience. Providing this feedback is not required for trial participation, and information collected from these questionnaires will not be analysed as part of the clinical data for the trial (see Appendix 10.1). It will be implemented in countries where it is available and approved by the local authorities.

3.3 SELECTION OF TRIAL POPULATION

Boehringer Ingelheim is committed to ensuring that a representative patient population is recruited in its clinical trials. Regulatory authorities and/or Boehringer Ingelheim in some countries may impose certain population target(s) such as gender, race, ethnicity, and age for certain clinical trials. At the onset of the clinical trial, principal investigators and sites will be notified of the population target(s) for their specific country. To achieve the required population target(s), sites may be asked to focus their efforts on the recruitment of a certain sub-set of participants.

A sufficient number of subjects will be screened in approximately 450 sites and approximately up to 40 countries to randomise approximately 1800 trial participants.

In order to reduce screen failure rate during eligibility assessment process below are recommended pre-screening criteria (for initial participants' identification);
Potential non-cirrhotic MASH participants with F2-F3 fibrosis stage to be screened for this trial should have at least 3 out of 5 cardiometabolic risk factors using a slightly modified Delphi consensus criteria [R24-0157]:

- BMI ≥27 kg/m^2 (≥25 kg/m^2 for Asian trial participants) [R12-4298] OR Waist circumference in men >99 cm (40 in) and in women >85 cm (33.5 in) (for Asian trial participants as men ≥90 cm, women ≥80cm) [R23-4334]
- Fasting serum glucose ≥5.6 mmol/L [100 mg/dl] OR 2-hour post-load glucose levels ≥7.8 mmol/L [≥140 mg/dl] OR HbA1c ≥5.7% [39 mmol/L] OR T2DM OR treatment for T2DM
- Blood pressure ≥130/85 mmHg OR specific antihypertensive drug treatment
- Plasma triglycerides ≥1.70 mmol/L [150 mg/dL] OR lipid lowering treatment
- Plasma HDL-cholesterol <1.03 mmol/L [40 mg/dL] (men) and <1.29 mmol/L [50 mg/dL] (women) OR lipid lowering treatment.

Note: Determination of metabolic risk factors is based on investigator discretion and may be based on historic laboratory tests for dyslipidaemia or insulin resistance and/or concomitant medication usage for dyslipidaemia, T2DM, and/or hypertension.

Screening of participants for this trial is competitive. Investigators will be notified about screening completion and will then not be allowed to screen additional participants for this trial. Participants already in screening at this time will be allowed to continue to randomisation if eligible.

In case of logistical issues with the reporting of results by the central vendor(s) a patient who meets all inclusion criteria and does not meet any exclusion criteria should be considered for participation in the clinical trial even if he/ she exceeds the screening period of 10 weeks. Extension of the screening period requires a Sponsor approval.

Re-screening and/or re-testing (of assessments) is permitted. Whilst the information provided below is not an exhaustive list, it provides some guidance as to when such re-screening and/or re-testing would be considered appropriate.

Re-testing for eligibility criteria (within the defined screening window period):

- Is only to be performed once for ECG, vital signs, and a laboratory result which is obviously received beyond stability at the central laboratory or thought to be a spurious result based on previously available laboratory results.
- In the case a participant was in a non-fasted state at the screening visit and some laboratory values are exclusionary, retesting can occur during the screening period as per investigator judgment.
- The re-test should be carried out as soon as possible so that the test results can be available prior to the randomisation visit.

Re-screening

- Re-screening of the same trial participant is only allowed once and if approved by the sponsor or its representative.
- The trial participant should be declared a screening failure in the eCRF and IRT with their original trial participant number.
- Upon re-screening, the IRT system will allocate a new screening number for the trial participant.
- Trial participants who were considered ineligible because of uncontrolled hypertension or hyperglycaemia (see Section 3.3.3, exclusion criteria 12 and 22), can be re-screened at the discretion of the investigator after adequate blood pressure control and/or glycaemia level has been achieved.
- If a patient was a screening failure due to F4 stage of liver fibrosis in liver biopsy in this trial, patient can be re-screened to the sister trial 1404-0064 (compensated MASH cirrhosis patient population) within 1 month. The patient must sign ICF for this trial and will be allocated a new screening number. All safety laboratory assessments must

be repeated, but imaging assessments and liver biopsy can be carried over from screening from trial 1404-0044.

- If a patient was a screening failure due to F2 - F3 stage of liver fibrosis in liver biopsy in sister trial 1404-0064 (in compensated MASH cirrhosis patient population) screening for this trial can be re-started within 1 month. The participant must sign ICF for this trial and will be allocated a new screening number. All safety laboratory assessments must be repeated, but imaging assessments and liver biopsy can be carried over from screening for trial 1404-0064.

A log of all trial participants enrolled into the trial (i.e. who have signed informed consent) will be maintained in the ISF irrespective of whether they have been treated with IMP or not. Even for screen failure participants, a minimum of information will be collected: trial participant number, visit date, demographics, eligibility criteria, information on AEs (if applicable), and concomitant treatment relevant for the AE.

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

3.3.1 Main diagnosis for trial entry

The main diagnosis for trial entry is non-cirrhotic MASH and F2 - F3 stage of liver fibrosis.
At least 60% of all participants will be randomised with F3 stage fibrosis and the percentage of F3 fibrosis will be monitore[d] in 2nd part of enrolment, after the first 700 trial participants are randomised.
At least 35% of trial participants is expected to be males and same percentage of females, and the percentage will be monitored during enrolment.

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

For an eligible participant, all inclusion criteria must be answered “yes” at screening and re-confirmed at baseline (i.e. before randomisation), except for laboratory tests for which screening results are used for randomisation:

1. Male or female participants ≥18 years (or who are of legal age in countries where that is greater than 18 years) of age at time of consent.
2. Diagnosis of MASH (NAS ≥4, with at least 1 point in inflammation and ballooning each) and fibrosis stage F2–F3 proven by a biopsy conducted during the screening period or by a historical biopsy conducted within the last 6 months prior to randomisation.
3. Stable body weight defined as less than 5% self-reported change in body weight 3 months prior to the screening or during the period between the historical biopsy and randomisation, if a historical biopsy is used.
4. The participants will be randomised following screening parameters which needs to be met in consecutive order: AST >20 U/L, liver stiffness measured by FibroScan®

VCTE ≥7.5k Pa and FAST >0.36 at Visit 1 and liver fat fraction ≥8% measured by MRI-PDFF prior to scheduling the screening biopsy.

5. Be willing to maintain a stable diet and physical activity levels throughout the entire trial.
6. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
7. WOCBP[1] must be willing and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria and instructions on the duration of use is provided in the participant and Appendix 10.3.
8. In the investigator's opinion, are well-motivated, capable, and willing to:
    - Learn how to self-inject the IMP, as required for this protocol (persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the IMP)
    - Inject the IMP or accept injection from trained caregiver
    - Follow trial procedures for the duration of the trial, including, but not limited to: follow lifestyle advice (for example, dietary restrictions and exercise and exercise plan), maintain a diary, complete required questionnaires, and handle the IMP as described in the instruction for use (IFU)

3.3.3 Exclusion criteria

For an eligible participant, all the following exclusion criteria must be answered "no" at screening and re-confirmed at baseline (i.e. before randomisation), except for laboratory tests for which screening results are used for randomisation:

Liver related:

1. Any of the following liver laboratory test abnormalities at screening:
    - Serum AST and/or ALT elevation ≥5x ULN
    - Platelet count <140 000/mm^3 (<140 GI/L)
    - Alkaline phosphatase >2x ULN
    - Abnormal synthetic liver function as defined by screening central laboratory evaluation:
        - Albumin below <3.5 g/dL (35.0 g/L)
        - OR International normalised ratio (INR) of prothrombin time >1.3 (unless participant is on anticoagulants)
        - OR total serum bilirubin concentration ≥1.5x ULN (participants with a documented history of Gilbert's syndrome can be enrolled if the direct bilirubin is within normal reference range)
2. Any history or evidence of acute or chronic liver disease other than MASH including, but not restricted to:
    - Viral hepatitis, unless eradicated at least 3 years prior to screening (trial participants with the following laboratory findings are excluded:

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

  - HBV: Trial participants with positive HBsAg
  - HCV: Trial participants with positive HCV antibody and a positive HCV RNA (All trial participants with positive HCV antibody should be tested for HCV RNA. Trial participants with positive HCV antibody and no history of HCV treatment require a negative HCV RNA test at screening to be eligible for the trial. Trial participants treated for hepatitis C must also have a negative RNA test at least 3 years prior to screening to be eligible for the trial.)
- Evidence of drug-induced liver disease or alcoholic liver disease, as defined on the basis of typical exposure and history.
- Autoimmune hepatitis
- Wilson's disease
- Haemochromatosis
- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Alpha-1-antitrypsin deficiency

3. Histologically documented liver cirrhosis (fibrosis stage F4), either at screening or in a historical biopsy
4. History of or current diagnosis of hepatocellular carcinoma
5. History of or planned liver transplant
6. Inability or unwillingness to undergo a liver biopsy at screening (if a suitable historical biopsy is unavailable for central review), or during trial conduct.
7. History of portal hypertension or presence of decompensated liver disease (including hepatic encephalopathy, variceal bleeding, ascites, and spontaneous bacterial peritonitis)
8. MELD score ≥12 due to liver disease
   NOTE: MELD of ≥12 must be the result of liver disease to be exclusionary, NOT isolated laboratory abnormalities such as elevated creatinine due to chronic kidney disease, INR abnormality secondary to anticoagulants or laboratory error, and bilirubin elevation due to Gilbert's Syndrome.

Obesity

9. Treatment with any medication for the indication obesity within 3 months before screening biopsy or historical biopsy time point
10. Previous or planned (during the trial period) treatment for obesity with surgery or a weight loss device, or prior surgery of the GI tract which in the opinion of the investigator could interfere with body weight. The following are allowed:
    - >1 year before screening biopsy or historical biopsy time point: (1) liposuction and/or abdominoplasty, (2) lap banding, if the band has been removed, (3) intragastric balloon, if the balloon has been removed, (4) duodenal-jejunal bypass sleeve, if the sleeve has been removed
11. Have obesity induced by other endocrinologic disorders (i.e. Cushing Syndrome) or diagnosed monogenetic or syndromic forms of obesity (i.e. melanocortin 4 receptor deficiency, leptin deficiency, or Prader Willi Syndrome)

Glycaemia:

12. HbA1c >10% (>86 mmol/mol) as measured by the central laboratory at screening

- Trial participants with HbA1c >8% and ≤10% (>64 mmol/mol and ≤86 mmol/mol) should have documented efforts to control HbA1c to ≤8% (≤64 mmol/mol) to be eligible
- If screening HbA1c was >10% (>86 mmol/mol) the participant should be considered as screening failure and a new antidiabetic therapy should be initiated. HbA1c measurement can be then repeated and if HbA1c reduction <10% (>86 mmol/mol) is achieved the participant can be rescreened to the trial (rescreening can happen once only)

13. History of T1DM or any other type than type 2 (e.g. endocrinopathy and genetic syndromes)
14. In patients with T2DM uncontrolled and potentially unstable diabetic retinopathy or maculopathy, verified by an eye examination within 3 months before screening or in the period between screening and randomisation

Mental health:

15. Answered "yes" to any of the suicide-related behaviours (Actual attempt, Interrupted attempt, Aborted attempt, Preparatory act or behaviour) or to the non-suicidal self-injurious behaviour question on the "Suicidal Behaviour" section of the C-SSRS related to the past 2 years at Visit 1.
16. Answered "yes" to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" section of the C-SSRS related to the past 3 months prior to screening at Visit 1.
17. Reported a history of psychiatric inpatient hospitalisation (due to significant active or unstable major depressive disorder or other severe psychiatric disorder, e.g. schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the past year before screening OR are not stabilised on their psychiatric medications (i.e. change of medication type or dosage adjustment within 8 weeks prior to screening) OR major symptoms of depression defined as a PHQ-9 score of ≥15 at screening (based on investigator judgment this assessment can be repeated once within screening window).

    Patients with major depressive disorder or generalised anxiety disorder whose disease state is considered stable and expected to remain stable throughout the course of the trial, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.

Other medical:

18. Impaired renal function, defined as eGFR <30 mL/min/1.73 m^2 ($CKD\text{-}EPI_{cr}$) at screening or trial participants requiring dialysis
19. Known clinically significant gastric emptying abnormality (e.g. severe diabetic gastroparesis or gastric outlet obstruction)
20. Uncontrolled (as per investigators assessment) hypo- or hyperthyroidism at screening
21. History of either chronic or acute pancreatitis or elevation of serum lipase or amylase >2x ULN as measured by the central laboratory at screening
22. Uncontrolled hypertension (mean SBP ≥160 mmHg and/or mean DBP ≥100 mmHg) at screening (at least triplicate measurements each performed 5 minutes apart).

23. Trial participants who demonstrate recent evidence (within 6 months prior to screening) of acute or unstable cardiovascular events, e.g. hospitalisation for HF, acute coronary syndrome, unstable angina, MI, ischaemic or haemorrhagic stroke, transient ischaemic attack, and/or acute peripheral vascular event
24. HF with NYHA functional class IV
25. QTc (Fridericia) mean interval that is greater than 500 ms at screening (triplicate ECG) or personal or family history of long QT syndrome
26. History of infection with HIV or positive HIV test at screening
27. Major surgery (in the opinion of the investigator) performed within 3 months prior to screening or planned during the trial
28. Personal or family history of medullary thyroid carcinoma or MEN 2
29. Calcitonin ≥100 pg/mL (29.26 pmol/L) at screening
30. Confirmed diagnosis of malignancy (including remission) within 5 years prior to screening, except for basal- or squamous-cell carcinoma of the skin that has been treated successfully. Trial participants under evaluation for malignant disease currently are not eligible for trial participation.
31. History of active autoimmune disease, including actively treated lupus, rheumatoid arthritis, inflammatory bowel disease, requiring systemic treatment within the past 12 weeks or a documented history of clinically severe autoimmune disease, including autoimmune liver disease, or a syndrome that requires steroids or immunosuppressive agents.
    NOTE: Patients who require use of bronchodilators, topical, inhaled, or intranasal corticosteroids, or local steroid injections are not excluded from the trial. Trial participants with vitiligo or asthma/atopy would be an exception to this rule.
32. Current or history of significant alcohol consumption, defined as an average of ≥140 gram/week in female patients and >210 gram/week in male patients, for a period of >3 consecutive months, or an inability to reliably quantify alcohol consumption based upon judgment of the investigator.
33. History of organ transplantation (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant.
34. Women who are pregnant, nursing or who plan to become pregnant while in the trial
35. Known or suspected hypersensitivity to the IMP or related products

Other exclusions:

36. Participants 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 participant an unreliable trial participant)
37. Participants who must or wish to continue the intake of prohibited medication or any drug considered likely to interfere with the safe conduct of the trial, see Section 4.2.2.1
38. Participants who currently consider moving or relocating during the first year preventing them to attend the trial visits.
39. WOCBP who are using oral contraceptives during the screening visit and are:
    - Not willing to change to non-oral contraceptives at least 7 days prior to first dose of IMP
      or

- Not willing to add an additional barrier method of contraception during the entire treatment period with IMP and 28 days thereafter

40. Currently enrolled in another investigational device or drug trial, or less than 60 days or 5 half-lives, whichever is longer, since ending another investigational device or drug trial or receiving other investigational treatment(s); current or previous enrolment in strictly observational trials is allowed. If participant has taken part in previous clinical trial evaluating treatment for MASH, weight reduction and /or T2DM, there needs to be a window period of 6 months before screening biopsy or historical biopsy date.
41. Previous randomisation in this trial
42. Active, serious medical disease with a likely life expectancy <2 years
43. Any condition not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardise the participant's safety or compliance with the protocol or may interfere with the trial objectives

3.3.4 Discontinuation of trial participants from treatment or assessments

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

Participants may be discontinued at any time during the trial. A participant who discontinues treatment should undergo an ETD Visit 7 days after the last dose or, if more than 7 days passed, as soon as possible.

All efforts must be made to have participants who discontinue the IMP to continue in the trial with the scheduled visits and assessments. Visits may be converted to remote visits (if allowed per local regulations) or phone calls if the participant is not willing to attend the clinic visits. At minimum, a contact at the FU visit will be requested to obtain vital status. If IMP discontinuation occurred after Week 24 all effort to be made to encourage the participant to undergo liver biopsy assessment.

Trial participants should be informed of anticipated GI side effects (see Section 4.1.4.1), and investigators should provide guidance on how to avoid or overcome them (see Appendix 10.2).

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

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

3.3.4.1 Discontinuation of trial treatment

An individual trial participant must be discontinued from IMP if the following applies:

- The trial participant wants to discontinue trial IMP. The trial participant will be asked to explain the reasons but has the right to refuse to answer
- The trial participant has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, the safety of the trial participant cannot be guaranteed as the participant is not willing or able to adhere to the trial requirements in the future
- Pregnancy or intention of becoming pregnant of female trial participant. In case of pregnancy, the trial participant will be expected to attend the regularly scheduled trial visits as outlined above. She will be followed up during the trial and until birth or termination of the pregnancy (further details in Section 5.2.6.2.3)
- When pancreatitis is suspected, IMP should be stopped. If pancreatitis is confirmed, IMP should be discontinued (Section 5.2.6.1.7)
- In case of evidence of QTc (Fridericia) interval >500 ms or an increase in QTcF interval more than 60 ms AND QTcF interval above the ULN (470 ms for women, 450 ms for men) compared with the last ECG recording performed prior to the first IMP administration obtained from central ECG reading. If these changes are seen in a local ECG reading, IMP should be stopped and then discontinued, if this finding is confirmed by central ECG reading. If any local ECG is needed due to any acute symptom/event (e.g. syncope), QTcF should be measured.
- Suicidality (Section 5.2.5.1):
    - Answered “yes” to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) or to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the “Suicidal Ideation” section of the C-SSRS since last visit and/or
    - Answered “yes” to any of the suicide-related behaviours (Actual attempt, Interrupted attempt, Aborted attempt, Preparatory act or behaviour) or to the non-suicidal self-injurious behaviour question on the “Suicidal Behaviour” section of the C-SSRS since last visit
- PHQ-9 score ≥15
    - Trial participants should be referred to a mental health professional to assist with participants’ condition evaluation. If a trial participant’s psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy, then the participant, at the discretion of the investigator (in agreement with the mental health professional), may be continued in the trial on randomised therapy. If the trial participant refuses to be referred to an MHP, the investigator will decide if the participant can continue to receive IMP.
- Initiation of prohibited medications as per Section 4.2.2.1, if the trial participant will not or cannot discontinue them. If it is found that a trial participant took restricted medication, the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment, a decision will be made as to whether the trial participant can continue the IMP or should be discontinued.
- Bariatric surgery

- BMI ≤18.5 kg/m^2 is reached at any time during the trial. If a trial participant with BMI above 18.5 kg/m^2 wants to discontinue the IMP because the trial participant does not want to lose any more weight, the investigator should propose a dose reduction to prevent the discontinuation from IMP treatment. In such a case, the dose can be reduced by up to 3 dose steps but not lower than 2.4 mg.
- Diagnosis of T1DM
- Diagnosis of any malignancy after randomisation (exceptions are basal-cell or non-invasive squamous-cell carcinoma of the skin planned for curative treatment)
- Elevation of calcitonin ≥100 pg/mL (29.26 pmol/L)
- The trial participant develops a clinically significant elevation of liver enzymes. Refer to Section 5.2.6.1.4. If this criterion is met, the DILI Checklist provided in the ISF should be followed, IMP stopped and discontinued if DILI is confirmed.
- Trial participant has experienced a CEC confirmed diagnosis of hepatic decompensation event (ascites or encephalopathy requiring treatment, portal hypertension-related upper GI bleeding) or liver transplant.
- Development of any significant IMP-related hypersensitivity reaction, as per investigator's opinion
- Worsening of diabetic retinopathy or maculopathy
- Occurrence of any other treatment-emergent AE, SAE, or clinically significant finding for which the investigator believes that permanent IMP discontinuation is the appropriate measure to be taken.

For trial participants who prematurely discontinue IMP, every attempt must be made by the investigator to ensure that the trial participant continues participating in the trial. Trial participants that are not taking IMP may be less motivated to adhere to the scheduled trial visits. In potential cases where a participant is no longer willing to complete all follow-up measures, the following sequence of options should be considered and discussed if allowed by local regulations:

Option 1 Continue to attend regularly scheduled trial visits at the centre until the trial ends and allow for review of medical records (all assessments to be followed as per SoA except EoT biopsy and biomarkers)

Option 2 Conduct all remaining trial visits via remote visits (if allowed per local regulations) or over the phone and allow for review of medical records

Option 3 Conduct yearly trial visits and EoS Visit via remote visits (if allowed per local regulations) or over the phone, allow for review of medical records

Option 4 Conduct EoS Visit via a remote visit (if allowed per local regulations) or over the phone, allow for review of medical records

Option 5 No direct contact, medical records review only

Trial participants will be asked to choose the most rigorous form of follow-up that they are willing to comply with.

In case of a temporary treatment interruption only, the IMP should be restarted if medically justified (Section 4.1.4). Any planned temporary discontinuation due to a medical condition, requires discussion with the sponsor representative.

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

3.3.4.2 Withdrawal of consent to trial participation

A participant has the right to withdraw informed consent for participation at any time for any reason. However, withdrawal of consent from trial participation should be very rare and unusual. Because of this, the investigator must be involved in the discussions with the participant regarding a withdrawal of consent. Early discontinuation of IMP is not a criterion for withdrawal of consent for participation in the trial.

If the participant withdraws informed consent for participation in the trial, the trial will end for that participant. The participant should stop taking IMP and should be asked to complete the EOT Visit and follow-up procedures as described in the SoA and Section 3.3.4.1. Completing these procedures is strongly recommended for the participant's safety. Participants that withdraw informed consent will not be replaced.

The participant who withdraws informed consent for participation in the trial, will be asked if he/she agrees to provide data on vital status and body weight at the FU/EoS Visit, if allowed by local regulations.

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. Positive benefit risk profile demonstrated earlier by sister trial 1404-0064 assessing clinical liver outcomes in participants with cirrhotic MASH.
2. Failure to meet expected enrolment goals overall or at a particular trial site
3. New efficacy or safety information invalidating the earlier positive benefit-risk assessment; please see Section 3.3.4.1
4. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial
5. Termination of the development of the compound in this indication

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

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

3.3.4.4 Lost to follow-up

If a trial participant is lost to follow-up, every effort will be made by the investigator and site staff to contact and locate the participant before the participant is declared lost to follow-up. Investigators and site staff must use every possible allowable means, according to local regulations, to locate trial participants who have missed visits. Efforts to contact the trial participant may include but are not limited to:

- Calling all numbers for trial participant and listed contacts
- Calling primary care physician, referring specialist, and/or other listed physicians for more recent information, date of last office visit, or to determine vital status
- Sending an email and follow up with mailing certified letters (return receipt requested) to all known trial participant addresses and all listed contacts
- Reviewing trial participant's records and medical notes for any details of a hospitalisation doctor's visit or other procedure that may indicate location or status of the trial participant
- Use internet to search for possible contact information for the trial participant
- Try reverse directory for phone numbers to get possible addresses and/or new contact details
- Check local, regional, and national public records to locate the trial participant or search for vital status in accordance with local law
- Consider home visit
- Use third party vendor in compliance with local legislation

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 3 Test product

Substance:	Survodutide (BI 456906)
FDA Established Pharmacologic Class (EPC):	Not available
TRT/CURTRT/COMPTRT	TRT
Pharmaceutical formulation:	Solution for injection
Unit strength:	Filling volume: 0.5 mL Concentrations: 0.3 mg/0.5 mL, 0.6 mg/0.5 mL, 1.2 mg/ 0.5 mL, 2.4 mg/0.5 mL, 3.6 mg/0.5 mL, 4.8 mg/0.5 mL, and 6.0 mg/0.5 mL
Posology:	Once weekly (1 pre-filled syringe)
Mode of administration:	s.c. injections

Table 4 Comparator product

Substance:	Placebo
Pharmaceutical formulation:	Solution for injection
Unit strength:	Filling volume: 0.5 mL
Posology:	Once weekly (1 pre-filled syringe)
Mode of administration:	s.c. injections

4.1.2 Selection of doses in the trial and dose modifications

A single target dose of 6.0 mg once weekly was selected as maintenance dose for this trial based on the following two recently completed clinical trials:

- Phase II dose-finding 1404-0043 trial in a patient population with MASH (F1-F3) and
- Phase I/II 1404-0010 hybrid hepatic impairment trial, which included patients with compensated MASH cirrhosis.

Safety, tolerability, and efficacy data of survodutide evaluated in a dose-finding Phase II trial suggested that maximum therapeutic benefit, defined as histology-proven MASH resolution and fibrosis improvement, was achieved in participants treated with a survodutide dose of 6.0 mg with an acceptable safety and tolerability profile. The trial tested maintenance doses of 2.4 mg, 4.8 mg, and 6.0 mg of survodutide against placebo in 293 participants with MASH with F1-F3 fibrosis using once weekly injections [c31864883].

At Week 48, 44.2 % of participants in the survodutide 6.0 mg dose group achieved at least 1 stage decrease in fibrosis stage assessed from liver biopsy, compared with 21.5 % participants in the placebo group. This effect was dose dependent. The highest improvement

in additional efficacy parameters, such as at least 1 stage decrease in fibrosis with no worsening of MASH after 48 weeks (survodutide 6.0 mg dose group: 42.3% responders, placebo: 17.7% responders), and MASH resolution with the absence of increase in fibrosis and at least 2 point improvement in NAS, after 48 weeks (survodutide 6.0 mg dose group: 51.9% responders, placebo: 6.3% responders) was observed in the 6.0 mg dose group compared with other dose groups. The frequency of AEs in the 6.0 mg survodutide dose group was comparable with other dose groups, with GI events being the most frequently reported. Overall, no significant difference in the incidence of SAEs between survodutide treatment groups and the placebo group was noted, and no unexpected safety issues were identified.

The data from above-described Phase II dose-finding1404-0043 trial has been supported by the 1404-0010 hepatic impairment trial [c36158199] where safety and PK have been evaluated in participants with Child-Pugh A-B cirrhosis. During 28 weeks of treatment with survodutide 6.0 mg, 24 participants with cirrhosis Child-Pugh A-B (out of these participants more than 80% had cirrhosis due to MASH) were compared against 17 volunteers with normal liver function. No significant difference in PK and safety profile has been observed between participants with Child-Pugh A-B and participants with normal liver function. The most frequent AEs reported by trial participants were GI-related events. No unexpected safety issues were identified.

Below are other clinical trials contributing in dose selection assessment:

- Data from the dose-finding trial 1404-0036 in 387 participants with overweight or obesity (BMI ≥27 kg/m^2) without T2 DM using once weekly injections of 0.6, 2.4, 3.6, and 4.8 mg during 48 weeks of exposure [c31754142]
- Data from the dose-finding trial 1404-0002 in 411 participants with overweight or obesity with T2DM using bi-weekly or once-weekly injections of 0.3, 0.9, 1.8, 2.7 mg during 16 weeks [c36750061]
- Data from 125 participants with obesity or overweight up to 6 weeks for doses ranging from 0.7 to 3.15 mg/week (administered as daily dosing) and 0.3 to 3.0 mg/week (administered as weekly dosing), and later up to 16 weeks for doses ranging from 0.6 to 4.8 mg/week (administered as weekly or twice weekly dosing) from trial 1404-0003 [c26759941]

Current clinical experience with survodutide indicates an overall acceptable safety profile, and the most common AEs are GI-related and are expected to be mitigated by a gradual dose increase during up-titration period.
Overall, the selected dose levels are anticipated to support the safety and efficacy evaluation for survodutide in participants with pre-cirrhotic MASH.

4.1.3 Method of assigning trial participants to treatment groups

After the assessment of all inclusion and exclusion criteria, each eligible trial participant will be randomised in a 2:1 ratio at Visit 2 to a treatment group according to a randomisation plan (see Section 7.4). Randomisation codes will be generated through a validated software and kept blinded to the trial team, sites, and trial participants. Access to the codes will be controlled and documented. An Interactive Response Technology (IRT) system will be used

to screen participants, create a participant number, perform treatment assignment, manage initial/re-supply ordering of IMP supplies, and handle emergency unblinding.

Randomisation will be stratified according to the following stratification factors:

- Region (Europe, North America, Latin and South America, APAC, South Africa and Middle East)
- Fibrosis stage (F2/F3)
- Presence of T2DM at baseline (yes/no)
- Participation in MRI-substudy (yes/no)

4.1.4 Drug assignment and administration of doses for each trial participant

Dose escalation of survodutide/placebo takes place during the first 24 weeks after randomisation as displayed in Table 5 (approximately 4 weeks between each dose escalation).

Table 5 Dose escalation scheme

Treatment week	0 1 2 3	4 5 6 7	8 9 10 11	12 13 14 15	16 17 18 19	20 21 22 23	24[1]
Escalation	**Starting dose**	**1st**	**2nd**	**3rd**	**4th**	**5th**	**6th**
6.0 mg Survodutide group	0.3 mg	0.6 mg	1.2 mg	2.4 mg	3.6 mg	4.8 mg	6.0 mg (final)
Placebo group	Placebo						

1 Week 24 is the end of the escalation period and also the start of the maintenance period.

- Administration of survodutide/placebo at Week 24 marks the end of the dose escalation period and the start of the maintenance period. The end of dose escalation period can be prolonged to 32 weeks if the participant due to tolerability issues requires a longer period to reach the target dose
- Participants will be instructed to inject the IMP once weekly at the same day of the week to the extent possible (+/-1 day). The injection day need not match to the visit day. If the injection date is planned during the in-clinic site visit, the participant should not administer the IMP prior to the visit but after the actual visit to allow blood sampling to be done prior to the injection. The first IMP dose administered at Visit 2 should be injected at the site. Injections should be administered in the abdomen at any time of day irrespective of meals.
- Instructions and training will be given to the participants, and participants will receive IFU. Training will be repeated at time points specified in the SoA.
- Participants should record the date and time of the injections in their (e)Diary. If the participant does not feel comfortable giving self-injections, this may be organised locally, depending on country-specific regulatory, ethical, and site requirements.
- Participants should aim at reaching target dose of 6.0 mg once weekly:
    - If the participant does not tolerate the next dose during up-titration before reaching 2.4 mg, management of GI symptoms should be done by diet counselling, symptomatic medication, skipping a dose, or reducing dose with

the option to re-escalate. If symptoms persist despite the measures taken, the participant will be discontinued from IMP

- If the participant does not tolerate the next dose level during up-titration scheme after reaching 2.4 mg, management of GI symptoms should be done by diet counselling, symptomatic medication, skipping a dose, or reducing dose with the option to re-escalate. If despite the GI symptoms management the dose re-escalation has not been tolerated, participant may stay at achieved tolerated dose which will be consider as target dose (2.4 mg is a lowest accepted target dose; Table 7).

Also refer to Section 4.1.4.1 for further details

- In case, 1 or more IMP administrations are missed, the instruction in Table 6 should be followed. A missed dose should not affect the dose escalation scheme or scheduled dosing day of the next week. A minimum of 5 days between weekly doses is required.

Table 6 Instructions in case of missed IMP administration(s)

Number of missed doses	What to do
1 administration of IMP	• IMP administration as soon as noticed, but within 48 hours after original injection time-point • If noticed more than 2 days after originally scheduled injection time-point, no IMP administration until the next scheduled IMP injection
2 consecutive administrations of IMP	• Recommencement of IMP treatment if considered safe as per the investigator's discretion and if the participant does not meet any of the discontinuation criteria
3 consecutive administrations of IMP	• Consideration of treatment discontinuation. If the trial participant is willing to continue the treatment, the sponsor must be contacted to find an alternative option.
>3 consecutive administrations of IMP	• Treatment discontinuation • In some exceptional circumstances (e.g. COVID-19-like pandemic situation), the sponsor is to be contacted for an alternative option.

The REP of BI 456906 is 28 days (half-life 112 hours); therefore, a period of 28 days after last administration of the IMP will be assigned to the on-treatment period for evaluation.

In the event of force majeure or other disrupting circumstances (e.g. pandemic, war, please see Section 6), in-clinic visits may not be feasible or may need to be restricted to ensure participant safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue trial treatment. Only in very exceptional cases and after approval by sponsor, the IMP may be shipped directly to the participants' home, if legally acceptable according to local regulations. In agreement with the sponsor, a remote visit may assist the participant with IMP administration or may be organised locally, depending on country-specific regulatory, ethical, and site requirements.

4.1.4.1 Management of trial participants with gastrointestinal symptoms

For trial participants who experience intolerable GI symptoms, for example nausea, vomiting, or diarrhoea, the following steps shall be taken:

- First, the trial participant should be counselled on dietary behaviours that may help mitigate nausea and vomiting. This may include eating smaller meals, splitting 3 daily meals into 4 or more smaller ones, stopping eating when they feel full, reducing fat intake, and not eating for 2-3 hours before going to sleep. When a trial participant experiences vomiting or diarrhoea, the participant should be instructed to stay well hydrated.
- If symptoms persist, the trial participant should be prescribed symptomatic medication (antiemetic or antidiarrheal medication) at the discretion of the investigator and kept hydrated.
- A temporary interruption of the IMP for 1 dose is permitted.
- A temporary interruption of a second dose of the IMP may be allowed at the investigator's discretion.
- Trial treatment should be resumed at the assigned dose immediately, either alone or in combination with symptomatic medication, which can also be utilised to manage symptoms.
- If, between Weeks 16 and 32 of treatment, the symptoms persist in spite of these measures, down-titration and subsequent re-escalation is allowed (see Table 7) (after consultation with a sponsor representative). Down-titration in this case means either reducing the dose to the next lower dose for 2 – 4 weeks (see Appendix 10.2) or delaying a scheduled up-titration by 2 – 4 weeks; both with the intent of returning to the planned dose escalation scheme once the participant's GI symptoms have become tolerable, and with an overall delay to the dose escalation not exceeding 8 weeks beyond the regular dose escalation's end at Week 24.
- For any changes in dose outside of the regularly scheduled steps, IMP of the new dose is dispensed during an unscheduled visit, and the participant must return all kits of the old dose.
- If the symptoms become tolerable or are completely resolved, and as per investigator's discretion, it is recommended that the trial participant makes up to 2 attempts to re-escalate per dose escalation scheme to the assigned 6.0 mg dose level. In such cases, the entire dose escalation period must not be longer than 32 weeks.
- If the participant does not tolerate the next dose during up-titration scheme before reaching 2.4 mg, and the GI symptoms persist despite the measures taken (diet counselling, symptomatic medication, or skipping a dose) the participant will be discontinued from IMP.
- Continuing onto maintenance therapy at a lower dose of 2.4, 3.6, or 4.8 mg is only to be allowed if the trial participant would otherwise discontinue the IMP and if considered safe to continue the IMP, as per the investigator's discretion. For participants who are not able to attain or stay at the maintenance dose of 6.0 mg, a dose reduction from a non-tolerated dose to the next lower dose is possible after consultation with a sponsor representative. If, in conjunction with GI tolerability issues, 4.8 mg could be reached, this dose will be kept for the maintenance phase. For participants who are not able to attain or stay at the dose of 4.8 mg, a dose reduction to 3.6 mg would be possible in exceptional circumstances after consultation with a

sponsor representative. For participants who are not able to attain or stay at the dose of 3.6 mg, a dose reduction to 2.4 mg would be possible in exceptional circumstances after consultation with a sponsor representative.

- Thorough documentation of all measures taken to improve tolerability, including counselling on dietary behaviours, symptomatic medication (antiemetic or antidiarrheal), temporary interruption of IMP, and outcomes of the discussion with sponsor representative, is required in a specific eCRF page in case of a dose reduction. For further details, please refer to Appendix10.2.
- All participants who had any deviation from the scheduled up-titration – whether this was a down-titration or a delay in up-titration – must be invited back for an unscheduled visit for assignment of the maintenance dose. This unscheduled visit should take place at Week 32 at the latest. This visit can be scheduled at an earlier time point, as early as Week 25, if the investigator is confident that the participant's GI tolerability issues are resolved and no further dose up- or down-titrations are expected.

The management process for intolerable GI symptoms is graphically displayed in Appendix 10.2.

Table 7 Dose reduction scheme

Last dose of survodutide or placebo	**If not tolerated, the dose can be reduced to:**	**If not tolerated after re-escalation, the dose can be reduced to:**
2.4 mg or less	Discontinue IMP	Not applicable
3.6 mg	2.4 mg	2.4 mg (until EoT)
4.8 mg	3.6 mg	3.6 mg (until EoT)
6.0 mg	4.8 mg	4.8 mg (until EoT)

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Trial participants, investigators, central reviewers, and everyone involved (except as noted below) in the trial conduct or analysis or with any other interest in this double-blind trial will remain blinded regarding the randomised treatment assignments until the database is declared ready for analysis according to the sponsor's SOPs. Further details regarding the time point of unblinding the database for analysis are documented in the TSAP.

At the end of Part 1, an interim analysis will be conducted. The results will potentially be used for submission of marketing application. Access to comparative interim results will be limited to individuals who will be involved in the preparation work of the submission. From the end of Part 1, the trial conduct will be outsourced such that the personnel involved in conducting the trial are blinded regarding the treatment assignment until the database is

declared ready for Part 2 analysis. Logistical aspects related to preserving the blind will be described in the Logistics and Access Plan.

The DMC will be provided with unblinded data in order to allow them to review safety and to fulfil their tasks as outlined in the DMC charter. An independent team, not otherwise involved in the conduct of the trial, will provide the unblinded results to the DMC.

The access to the randomisation code will be kept restricted until its documented release per sponsor SOP.

The external (CRO) bioanalytical laboratory and respective external bioanalyst will receive the randomisation codes before the last trial participant completed the trial and prior to official unblinding to allow for the exclusion from the analyses of PK and ADA/NAb samples taken from placebo trial participants.

The TBA may receive unblinded data from the external bioanalytical laboratory after the last trial participant completed the last visit but prior to official unblinding of the analysis database at the EoS for preparation of data transfer e.g. check file structure prior to data upload and Study Data Tabulation Model transformation and bioanalytical report writing. Bioanalytics will not disclose the randomisation code or the results of their measurements until DBL.

4.1.5.2 Emergency unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency when the identity of the IMP must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The treatment allocation should not be disclosed to the sponsor unless this is explicitly requested. The reason for unblinding must be documented in the source documents and/or appropriate eCRF page.

Due to the requirements to report suspected unexpected serious adverse reactions (SUSARs), it may be necessary for a representative from Boehringer Ingelheim's Pharmacovigilance group to access the randomisation code for individual trial participants during trial conduct. The access to the code will only be given to authorised Patient Safety and Pharmacovigilance representatives for processing in the Pharmacovigilance database and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The IMP will be provided by Boehringer Ingelheim or a designated CRO. The IMP will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

- The investigator will be omitted due to the usage of an IRT system linking the investigator unequivocally to the medication number. Should local regulations outside EU require this particular, it will be added to the country specific label text.
- Since the labels are to be utilised across multiple trials in the BI 456906 development program, the trial number will be omitted and "1404-P03" will be printed as reference code instead, except for countries with exceptional regulatory requirements. The trial number will be captured via the IRT assignment and the trial participant identification card. In countries where this is not permitted or in other exceptional cases, the trial number will be printed in the label.

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

Only in very exceptional cases and after approval by sponsor, IMP may be shipped directly from the site to the participant's home. The IMP shipment will be initiated by the site and the product will be shipped via courier from the site to the participant's home, if legally acceptable according to local regulations.

4.1.7 Storage conditions

IMP supplies will be kept in their original packaging in order to protect them from light, in a secure limited access storage area, and refrigerated according to the recommended storage conditions on the IMP label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the CRA (as provided in the list of contacts) must be contacted immediately.
The IMP will be provided in pre-filled syringes at specific visits (see SoA). An IFU with step-by-step instructions on how to use the pre-filled syringe will be made available to the investigator. A copy will be placed in the ISF. The trial participant will also receive a copy of the IFU when pre-filled syringes are dispensed to the participant for self-administration. Moreover, the IFU will contain important safety information and storage instructions.

4.1.8 Drug accountability

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

- Approval of the clinical trial protocol by the IRB/IEC
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site
- Approval/notification of the RA, e.g. CA
- Availability of the *curriculum vitae* of the Principal Investigator
- Availability of a signed and dated CTP
- Availability of the proof of a medical license for the Principal Investigator
- Availability of FDA Form 1572 (if required by local regulations)

The IMPs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics, except if specifically authorised by the sponsor.

Trial participants should be instructed to bring all unused IMP, empty cartons, and sharps container with used syringes with them to their next in-clinic visit (scheduled and unscheduled). 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 trial participant, and the return to the sponsor or warehouse/drug distribution centre or alternative disposal of unused products using the IRT. If applicable, the sponsor or warehouse/drug distribution centre will maintain records of the disposal.

These records via IRT will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the IMP and trial participants. The investigator or designee will maintain records that document adequately that the trial participants were provided the doses specified by the CTP and reconcile all IMPs received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator or designee must verify that all unused or partially used IMP supplies have been returned by the trial participant 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

4.2.1.1 Concomitant medications

During the entire trial duration, the trial participant is expected to be treated according to the best standard of care for baseline medical conditions. Investigators will be asked to confirm in the eCRF during each visit if this condition is met.

As survodutide is expected to improve not only liver conditions related to MASH but also certain obesity related complications (e.g. lipid levels, blood pressure, HbA1c), the evaluation of existing lipid lowering, antihypertensive and anti-hyperglycaemic treatment should be done during in clinic visit and eventual adjustment of treatment should be recorded in eCRF. All concomitant medications, including anti-hyperglycaemia medications should be recorded on the appropriate pages of the eCRF. For the management of trial participants with GI symptoms, refer to Section 4.1.4.1.

Anti-hyperglycaemia medications are considered non-IMPs and should be used according to their respective labels. In case of persistent and unacceptable hyperglycaemia, glycaemic rescue treatment should be initiated as described in Section 4.2.1.1.2. Investigators can switch anti-hyperglycaemia treatment according to ADA/EASD guidelines [P22-05567] (excluding restricted medications stated in Section 4.2.2.1). Medication should preferably be weight-neutral and should first be based on intensification of background anti-hyperglycaemia treatment or addition of new background anti-hyperglycaemia medications according to local guidelines. The use of SGLT2i is encouraged in participants with T2DM and atherosclerotic CVD, HF, or CKD, and in participants with HF or CKD (regardless of T2DM).

If participants during the trial conduct progress to cirrhosis or later to CSPH, the standard of care should be followed (regular abdominal ultrasound for HCC surveillance, consider the

treatment with NSBBs if not contraindicated, and regular UGE assessment in those not on NSBBs) [R23-4358].

4.2.1.1.1 Home glucose monitoring

All participants with T2DM at baseline and participants who develop T2DM during the course of the trial, will be provided with a glucose monitoring device and supplies for use at home during the trial for self-measurement of blood glucose. Instruction on the use of the glucose monitoring device will be provided by the site staff. Trial participants may also use their own glucose monitoring device.

Weekly home measurements are recommended. Additionally, throughout the trial, blood glucose measurements should be performed at any time the trial participant is symptomatic, i.e. experiences signs/symptoms of hyper- or hypoglycaemia. More frequent testing may be done if deemed necessary by the investigator or required by local authorities.
Blood glucose measurements should be taken fasted (at least 8 hours) and prior to taking any diabetes medication.

At the time of signing consent, all trial participants with T2DM will be educated about signs and symptoms of both hyper- and hypoglycaemia, how to treat hypoglycaemia, and how to collect information for each episode of hyper- or hypoglycaemia and about the necessity to inform the investigator about such cases. This information will also be provided to trial participants who develop T2DM during the trial after diagnosis is confirmed. Trial participants will be instructed to record information about hyper- and hypoglycaemic episodes in the eDiary. Both conditions may be identified by spontaneous reporting of symptoms from trial participants, by plasma glucose samples collected during in-clinic visits, or by home glucose monitoring device.

4.2.1.1.2 Rescue medication for treatment of hyperglycaemia for trial participants with T2DM

If any trial participants develop T2DM while on trial, this information will be provided to them by the investigator at the on-site visit upon confirmation of the diagnosis.

In case of persistent and unacceptable hyperglycaemia, if any of the FPG values (including fasting SMBG values) exceeds 15 mmol/L (270 mg/dL) and no intercurrent cause of the hyperglycaemia can be identified, glycaemic rescue treatment should be initiated at the discretion of the investigator.

- If any of the FPG values (including fasting SMBG values) exceeds 15 mmol/L (270 mg/dL), a confirmatory FPG and HbA1c value (at the central laboratory) should be obtained by calling the trial participant for an unscheduled visit.
- If the confirmatory measurement exceeds 15 mmol/L (270 mg/dL), the trial participant should be offered rescue medication, at the discretion of the investigator, according to the ADA/EASD guidelines [P22-05567]; excluding prohibited medications and anti-obesity medications stated in Section 4.2.2.1.

The following scenarios can be foreseen within the rescue treatment start and should be documented in the eCRF as rescue medications:

1. Additional anti-hyperglycaemia medication used for 7 days or more or until treatment discontinuation
2. Increase in the dose of background medication other than insulin above the baseline dose for 7 days or more or until treatment discontinuation
3. Basal insulin background therapy dose increased by more than 10% from baseline level or addition of post-prandial insulin

If the trial participant does not have persistent and unacceptable hyperglycaemia >15 mmol/L (270 mg/dL) in any of the FPG values but the investigator deems necessary to adjust the anti-hyperglycaemia medications, these changes will not be considered as rescue therapy but as the therapy adjustment. Therapy adjustment has to be documented on the respective pages of the eCRF.

Trial participants that are started on rescue medication should continue to follow the protocol-specified visit schedule and stay on randomised treatment unless the investigator judges that it jeopardises safety.

Rescue medication should be documented in medical records and reported in the eCRF.

4.2.1.1.3 Hypoglycaemic episodes

When a trial participant experiences a hypoglycaemic episode, the participant should call the site and record the general information in relation to the hypoglycaemia (date, time, blood glucose measurements, and any symptoms) in the eDiary. Blood glucose should always be measured and recorded when a hypoglycaemic episode is suspected.

Hypoglycaemic events will be recorded in the eCRF using the definitions as stated in Section 5.2.6.1.4.

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

4.2.1.2 Dietary and physical activity counselling

Participants with baseline BMI ≥27 kg/m^2 at the randomisation visit, will receive diet and physical activity counselling done by a dietician or an equally qualified delegate according to local standards with an energy deficit of approximately 500 kcal/day compared with the trial participants' estimated total energy expenditure (TEE) [R20-2315].

The TEE is calculated at the randomisation visit by multiplying the estimated basal metabolic rate (BMR; Table 8) with a Physical Activity Level value of 1.3. The hypocaloric diet is recommended to be continued after randomisation and throughout the planned treatment period.

If a BMI of ≤22 kg/m^2 is reached, the recommended energy intake should be recalculated with no kcal deficit (maintenance diet) for the remainder of the trial.

Table 8 Equations for estimating the basal metabolic rate (BMR)

Sex	Age: years	BMR: kcal/day
Men	18-30	15.057 × actual weight in kg + 692.2
	31-60	11.472 × actual weight in kg + 873.1
	>60	11.711 × actual weight in kg + 587.7
Women	18-30	14.818 × actual weight in kg + 486.6
	31-60	8.126 × actual weight in kg + 845.6
	>60	9.082 × actual weight in kg + 658.5

An increase in physical activity, at least 150 to 300 minutes a week of moderate intensity combining aerobic and muscle strengthening exercises (or any other type of physical activity as deemed appropriate and necessary by the dietitian) will be encouraged and re-enforced.

All trial participants with BMI ≥27 kg/m^2 will receive diet and physical activity counselling at each trial visit as shown in the SoA.

Trial participants will be given a paper food and exercise Diary in which they will keep tracking their level of daily activity as well as their dietary compliance on a regular basis (weekly as a minimum) in order to assist and evaluate their lifestyle intervention.
The trial participants can also use their own tools (paper, applications) that they have been using prior to enrolment for tracking their diet and physical activity and present the tools at the on-site or remote (if allowed per local regulations) visit to the site personnel for analysis, as long as the site personnel agrees that these tools are fit for purpose.

The trial participant's dietary compliance and adherence to physical activity recommendations will be evaluated and registered in the eCRF every visit by the site staff.
The trial participants will receive dietary and physical activity guidance materials.

4.2.1.3 Severe and/or systemic hypersensitivity including injection reaction and anaphylactic reaction

In case of severe and/or systemic hypersensitivity including anaphylactic reaction emerging during or after injection(s) of the IMP, the investigator should consider in accordance with the severity of the reaction and local standard of care to

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

A blood sample should be drawn for immunoglobulin E, PK, ADA, and NAb assessment as detailed in the Laboratory Manual (ISF). In addition, the evaluation of histamine, serum tryptase, and complement components (C3 and C4) should be included.

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

In case of an anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA et al. [R11-4890] suspected to be caused by the IMP, the investigator should permanently discontinue treatment with survodutide.

Relevant data from trial participants with a severe and/or systemic hypersensitivity including injection reaction and anaphylactic reaction will be recorded in the eCRF as stated in Section 5.2.6.1.4.

4.2.1.4 Recommendations for elective surgery/procedures that require general anaesthesia or deep sedation, or planned UGE

For trial participants who undergo elective surgical procedures that require general anaesthesia or deep sedation, the following recommendations are made based on the American Society of Anesthesiologists Consensus-Based Guidance on Preoperative Management of Patients (Adults and Children) on GLP-1R agonists [R23-2688]:

- Consider holding the IMP 1 week prior to elective procedure/surgery that requires general anaesthesia or deep sedation
- On the day of the procedure, if GI symptoms such as severe nausea/vomiting/retching, abdominal bloating, or abdominal pain are present, consider delaying elective procedure.
- On the day of the procedure, if the participant has no GI symptoms, and the IMP has been held as advised, proceed as usual.

For trial participants undergoing planned / diagnostic UGE after randomisation, the following recommendations apply based on the American Gastroenterological Association Clinical Practice Update [R24-1423]:

- In participants who have followed standard perioperative procedures (typically an 8-hour solid food fast and a 2-hour liquid fast) and who do not have symptoms of nausea, vomiting, dyspepsia, or abdominal distention, UGE can be performed.
- In participants with symptoms suggesting possible retained gastric contents, transabdominal ultrasonography can be used to assess the stomach, and UGE should be delayed if the participant has retained stomach contents which could increase the risk of aspiration. Thereafter, a dose of the IMP can be skipped prior to the UGE.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

If such treatment is initiated during the trial, the participant should be instructed to discontinue the treatment, and if the treatment is discontinued, the participant should remain in the trial. If no discontinuation of such a drug is possible, the participant needs to stop IMP administration, all effort to be made to keep the participant in the trial.

GLP-1R agonists

- GLP-1R agonists including GLP-1R agonist/GIP combinations are not allowed 3 months before screening biopsy or historical biopsy time point and during the whole trial period until end of follow-up.

MASH medications

- Initiation of any dose of vitamin E higher then >400 IU/day or use of high dose vitamin E >800 IU/day is prohibited (dose up to 800 IU/day is allowed if the trial participant has been on stable dose for ≥6 months prior to screening biopsy or historical biopsy time point).
- Initiation of pioglitazone is not allowed (pioglitazone is allowed only if the trial participant has been on stable dose for ≥6 months prior to screening biopsy or historical biopsy time point).
- Any off label, or investigational or approved medications used for the purpose of treatment of MASLD/MASH are prohibited 6 months prior to screening biopsy or historical biopsy time point and during the entire duration of the trial until the end of the follow-up period. This include also saroglitazar used for anti-hyperlipidaemia treatment purpose.
- Treatment with drugs that may cause hepatic steatosis or steatohepatitis administered for at least 4 weeks within 6 months prior to screening biopsy or historical biopsy time point is prohibited (e.g. valproic acid, tamoxifen, methotrexate, amiodarone, chronic treatment with oral corticosteroids >5 mg/day of prednisone equivalent [one short, i.e. <2 weeks, course of oral corticosteroids more than 3 months before screening biopsy is allowed], or oestrogens at doses greater than those used for contraception or hormone replacement). Treatment with these drugs is also prohibited during the whole trial period until the end of the follow-up period.

Anti-obesity medications

- All anti-obesity medications including bupropion/naltrexone, orlistat, phentermine, and phentermine/topiramate are not allowed 3 months before screening biopsy or historical biopsy time point and during the whole trial period until the end of the follow-up period (including trial participants who discontinue the IMP).
- Anti-obesity supplements or participating in an organised weight loss program (e.g. Weight Watchers® or Noom®) or any medication (in the opinion of the investigator) that could provide weight change are not allowed 3 months before screening biopsy or historical biopsy time point and during the whole trial period until the end of the follow-up period.

Anti-hyperglycaemia medications

- Only trial participants who develop T2DM during the trial may initiate anti-hyperglycaemia medications for glucose control, with the exception of GLP-1R agonists, GLP-1R agonist/GIP combinations, amylin analogues (Table 9).
- During the trial the following medication for the treatment of diabetes is allowed as per local guideline: metformin, SGLT2i, thiazolidinediones (except pioglitazone), sulfonylurea, insulin, acarbose, or DPP-4 inhibitors (Table 9).
- Metformin should not be initiated during the trial for the treatment of other metabolic conditions (e.g. polycystic ovary syndrome, diabetes prevention).
- For participants on stable sulfonylurea or insulin treatment, it is recommended to lower the dose when starting the IMP treatment to avoid hypoglycaemic events.

All concomitant medications should be recorded on the appropriate pages of the eCRF.

Table 9 Anti-hyperglycaemia medications for the treatment of T2DM

Allowed medication	**Prohibited medication**[1]
Metformin	GLP-1R agonists
SGLT2i	GLP-1R agonist/GIP combinations
Thiazolidinediones[2]	Amylin analogues
Sulfonylureas[3]	
Insulin[4]	
Acarbose	
DPP-4 inhibitors	

1 Not allowed 3 months before screening biopsy or historical biopsy time point and during the whole trial period until end of follow-up.

2 Pioglitazone is allowed for participants on stable treatment (i.e. for ≥6 months prior to screening-biopsy or historical biopsy time point), but not allowed for treatment initiation during screening and the whole trial period

3 Allowed for participants on stable treatment (i.e. for ≥3months prior to screening), but not allowed for treatment initiation during screening and the whole trial period

4 HOMA-IR collection and evaluation should not be performed in participants on current insulin therapy.

Oral medications which have a narrow therapeutic index
Due to the effect of survodutide on gastric emptying which may affect the absorption of orally administered drugs, increased clinical or laboratory monitoring for orally administered co-medications that have a narrow therapeutic index is recommended, and if not possible, the drugs which have narrow therapeutic indices are not permitted during the IMP treatment period and at least 28 days after last dose.

CYP3A sensitive medications which have a narrow therapeutic index
As survodutide has the potential to down regulate CYP3A4 expression, which might affect safety and efficacy of CYP3A sensitive drug substances which have a narrow therapeutic index, all CYP3A sensitive medications which have narrow therapeutic indices (e.g. alfentanil, fentanyl, carbamazepine, cyclosporine, tacrolimus, sirolimus) are not permitted during the IMP treatment period and at least 28 days after last dose.

Oral contraceptives
Due to the effect of survodutide on gastric emptying which may affect the absorption of orally administered drugs and the effect of oral contraceptives may no longer be guaranteed, increased precautions are recommended (see Section 4.2.2.3). Women who use oral contraceptives at screening should be advised to change to non-oral contraceptives at least 7 days prior to first dose of IMP or to add additional barrier method of contraception during the entire treatment period with IMP and 28 days thereafter.

4.2.2.2 Restrictions on diet and lifestyle

Please refer to Section 4.2.1.2.

4.2.2.3 Contraception requirements

Contraception of male participants is not needed.

WOCBP (for the definition please refer to Section 3.3.2) must use a medically approved method of birth control throughout the trial and for a period of at least 28 days after last IMP intake.
A list of contraception methods meeting these criteria is provided in the trial participant information and Appendix 10.3.

4.3 TREATMENT COMPLIANCE

Trial participants will be provided with an eDiary to record all the injections of the IMP (at home or at the clinic during in-clinic visits). Trial participants who will not use the eDiary will be provided with a paper diary.

Trial participants should be encouraged to be fully compliant with the medication dosing schedule.

Trial participants should be compliant on clinic visits within the protocol allowed time window and on the dosing schedule when they self-administer the IMP at home with pre-filled syringes. An IFU with instructions on how to use the pre-filled syringes including important safety information and storage instructions will be provided to the investigators and trial participants.

A compliance check of the IMP administration will be performed at each clinic visit to ensure the weekly injection is being administered correctly at both the trial site and by the trial participant at home. In case of missed doses, the site should instruct the trial participant as indicated in Section 4.1.4. The investigator/site staff should explain to the trial participant the importance of treatment compliance and discuss with the trial participant any tolerability issue.

Trial participants will be provided with a medication bag to store empty cartons of the IMP and a sharp bin to store all used syringes. Unused IMP should be kept in the refrigerator. Trial participants are requested to bring all unused IMP, empty cartons, and sharps container with used syringes with them to their next in-clinic visit (scheduled and unscheduled) for the compliance check. The sharps container with used syringes should be returned to the site. Any discrepancies should be discussed with the investigator or the designee.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Efficacy assessments will be performed for time points defined in the SoA.

Participants must attend all site visits in a fasting state except at screening visit. Fasting is defined as at least 8 hours without food or liquids, except for water. Investigational medicinal product and any medication which should be taken with or after a meal should be withheld on the day of the visit until blood sampling has been performed. If the participant is not fasting as required, the participant must be called in for a retest within the visit window to have the fasting procedures done. Prior to FibroScan® measurements, 3 hours of fasting is required.

5.1.1 Liver biopsy

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

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

Table 10 Components of NAS and fibrosis staging

	NAS components						
	Steatosis		**Lobular inflammation**		**Ballooning**		**Total**
	Degree	Description	Degree	Description	Degree	Description	
	0	<5	0	No foci	0	0	
	1	5-33	1	<2 foci/200x	1	Few balloon cells	
	2	>33-66	2	2-4 foci/200x	2	Many cells/ prominent ballooning	
NAS	3	>66	3	>4 foci/200x			
	0-3		0-3		0-2		0-8

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

Source: [R23-4354]

In addition, the baseline and Week 52 liver biopsy specimens from patients that have provided Week 52 biopsy will be also read by computerised reading using AI-based algorithm.

5.1.2 VCTE and CAP (Liver Stiffness and Fat Content Assessments)

The liver will be evaluated using the FibroScan® device, an NIT using ultrasound technology. Evaluations will be performed at the time points specified in the SoA and the following measurements will be made:

- Fibrosis will be measured using VCTE which is an advanced ultrasound technique that measures liver stiffness.
- LFC will be measured using CAP, a measure of the ultrasound attenuation which corresponds to the decrease in amplitude of ultrasound waves as they propagate through the liver.

Sites must have the expertise in using the FibroScan® device, and the operator must be duly trained. Some sites will not have access to the novel acquisition technique known as SmartExam. If SmartExam is not available at a site, the participant can be scanned without but the site must continue to not use SmartExam on the participant for all exams within the entire trial duration. If SmartExam is available, SmartExam must be used on all participant exams. If possible, the same operator should perform the FibroScan® assessments on one

participant. If possible, the same operator should perform the FibroScan® assessments on one participant throughout the trial.

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

The FibroScan® assessment will be used initially during the screening to identify participants with MASH and F2-F3 fibrosis and during the trial to identify participants that may progress to cirrhosis and maybe required confirmatory biopsy. FibroScan® measurements of liver stiffness and fat contain will be performed about every 6 months, at the timepoints indicated in the SoA.

The FibroScan® - AST (FAST) score will be calculated for all subjects using the following equation:

$$FAST = \frac{e^{-1.65+1.07\times\ln(LSM)+2.66\times10^{-8}\times CAP^3-63.3\times AST^{-1}}}{1+e^{-1.65+1.07\times\ln(LSM)+2.66\times10^{-8}\times CAP^3-63.3\times AST^{-1}}}$$

FibroScan® should be performed under proper fasting (≥3 hours after food or liquids, except for water). FibroScan® results should be in good quality (at least 10 measurements, with a 60%-70% success rate, and results interquartile range <30% of the value of the median).

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

5.1.3 Magnetic resonance MRI assessments

Sites performing MRI assessments must be equipped, (or collaborating with a site equipped) with an MRI scanner from the following manufacturers: General Electric, Philips or Siemens. All imaging sites will undergo a technical qualification process prior to trial initiation based on a review of MRI/MRE equipment.
All MRI imaging data (liver volume, PDFF, MRE, cT1) will be reviewed and read centrally by a selected vendor to ensure consistent and standard approach. The same vendor will perform detailed sites assessment and respective team members training during trial start-up process. Other MR image sequences may be collected for additional exploratory analyses if required. MR image acquisition, including preparation time, is estimated approximately to 30 minutes. For time points, refer to the SoA.

All MRI techniques should be performed following fasting for at least 4 hours (other than sips of water for medication, or to ease thirst).

5.1.3.1 Magnetic resonance imaging (MRI-PDFF)

Magnetic resonance imaging to measure proton density fat fraction (MRI-PDFF) will be assessed at the time points specified in the SoA (as a part of screening procedure) and in the subset of participants (MRI-subset) for efficacy (liver fat reduction) assessment. Ideally, the site should have an MRI scanner from a major manufacture (GE, Philips, Siemens) which

should be equipped with a manufacturer specific MRI-PDFF package also known as multi-echo, multi-peak Dixon or chemical shift-based technique. MR images to compute the whole liver volume (by way of 3D image acquisition) will also be collected from each subject in the same MRI session in order to compute the liver fat volume.

5.1.3.2 Magnetic Resonance Elastography (MRE)

In the subset of participants (MRI-subset) MRE will be used to measure the liver stiffness [kPa] in addition to liver stiffness assess by FibroScan® as per SoA visit.

Sites must be equipped with a manufacture specific MRE acoustic passive driver and the specific software required to generate the MRE images. MRE is limited by the availability of the MRE hardware so MRI-subset of participants will be limited to sites with availability of MRE hardware. Liver stiffness is measured in kilopascals [kPa].

The MRE – AST (MAST) score will be calculated using the following equation:

$$MAST = -12.17 + 7.07 \log MRE + 0.037 PDFF + 3.55 \log AST$$

5.1.3.3 Magnetic resonance imaging (cT1)

Corrected T1 (cT1) is a non-invasive, MR-derived biomarker of fibro-inflammatory disease activity in the liver and corresponds to the longitudinal relaxation time (T1) of liver tissue. cT1 is part of a commercial product known as LiverMultiScan® and can be acquired using all MRI manufacturers. cT1 maps are provided in milliseconds [ms].
In the subset of participants (MRI-subset) the fibro-inflammatory disease activity will be measured through cT1 as per SoA.

5.1.4 Clinical Liver Assessments

Liver disease progression assessment will be recorded every 6 months starting from baseline till EoT. During the visit each participant will have the disease progression assessment done based on clinical conditions and available NITs (MRI-PDFF, MRE, liver stiffness (VCTE), ELF, platelets). MELD score, progression to CSPH, presence of ascites and HE will be assessed. Assessment will be entered into the eCRF.

The MELD score will be calculated from the central laboratory values attained at each visit. MELD will be calculated during screening to assess eligibility and will be monitored by site at each in-clinic visit as per SoA.

MELD will be calculated using the following formula:
MELD score = 10 X ([0.378 x ln total bilirubin mg/dL] + [1.12 x ln INR] + [0.957 x ln serum creatinine mg/dL] + 0.643).

- Serum creatinine in µmol/L will be converted to mg/dL by multiplying by 0.01131. The resulting value will be rounded to 2 decimal places.
    - If the serum creatinine is <1.00 mg/dL, use 1.00 as the serum creatinine value.

  - If the serum creatinine is >4.00 mg/dL or if the participant had 2 or more dialysis treatments within the preceding week, use 4.00 as the serum creatinine value.
- Total bilirubin in µmol/L will be converted to mg/dL by multiplying by 0.05848 and the resulting total bilirubin value to 1 decimal place.
  - If the total bilirubin is <1.0 mg/dL, use 1.0 as the total bilirubin value.
- If the INR is <1.0, use 1.0 as the INR value.

The online calculator [R24-1949] by selecting MELD score may also be used. To validate an initial MELD score increase from less than 12 at baseline to 15 or higher, the participant must be invited for unscheduled visit within 72 hours after receiving the elevated MELD score for re-assessment and central laboratory re-testing.

Triggered biopsy should be considered if in the opinion of the investigator (and with sponsor approval), the subject demonstrates clinical signs/symptoms consistent with conversion to cirrhosis.
If 1 of the following criteria is observed:

- LSM (VCTE) >25 kPa OR MRE ≥5kPa
- LSM (VCTE) >20 kPa with delta change from baseline ≥30%
  (if a participant has been enrolled into the trial with baseline LSM (VCTE) >20 kPa then platelet count <150 000/mm^3 (<150 GI/L) or ELF ≥11.3 to be added)
- LSM (VCTE) 15–20 kPa associated with a platelet count <150 000/mm^3 (150 GI/L) OR with ELF ≥11.3
- Cross sectional imaging (CT or MRI or Ultrasound) evidence of nodular liver contour, right hepatic lobe atrophy +/- left hepatic lobe hypertrophy and coarse liver parenchyma)

participant should be invited for an unscheduled visit 4 weeks later and VCTE and labs related results are to be repeated. If the results confirm a suspected diagnosis of cirrhosis the liver biopsy is to be scheduled after confirmation by sponsor medical monitor (no later than within 3 months from the liver disease progression assessment visit).

5.1.5 Upper gastrointestinal endoscopy

All trial participants who have progressed to cirrhosis during trial duration should be followed as per recommended standard of care (6-month abdominal ultrasound for HCC screening). All these participants should have UGE performed at the diagnosis of cirrhosis, then yearly, and at EoT or ETD visit for assessment of progression to CSPH with “high-risk” GOV, please refer to Section 4.2.1.4.

If GOV is diagnosed, UGE will be recorded and sent for adjudication by central reading. If ‘high-risk’ varices are observed (larges varices)) that event will be considered as clinical liver outcome event [R23-4358]. Guidelines for UGE acquisition and central reading procedures will be provided in an imaging manual.

For those participants who have developed GOVs, standard of care should be followed (considering treatment with NSBB in case of no contraindication, or endoscopic variceal ligation [if applicable] for those who cannot receive NSBB, as per AASLD guidance [R23-4358]).

5.1.6 Body measurements

5.1.6.1 Weight measurement

Weight scales will be provided to the trial sites and the same scale should be used to the extent possible for all measurements. Using the same scale will help to minimise the variability in body weight measurements. The equipment must be calibrated according to manufacturer's specifications. Weight should be recorded in kilograms up to 1 decimal.

The body weight must be measured in fasting state (except the screening visit). If the trial participant is not fasted, the participant should be called in for a new visit within the visit window. 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 consistently worn for all weight measurements in the trial. The trial participant should empty the bladder before weight is measured.

5.1.6.2 Height

Height should be measured without shoes, in centimetres.

5.1.6.3 Body mass index

BMI will be calculated by the eCRF from the height measured at Visit 2 and weight measured at the screening visit and all consecutive, in-clinic visits.

5.1.6.4 Waist and hip circumference measurement

Waist circumference measurements should be made around the bare midriff, i.e. the abdominal circumference located midway between the lower rib margin and the iliac crest. Hip circumference measurements should be taken around the widest portion of the buttocks without thick clothes (e.g. coats, jackets). Measures must be obtained in standing position with a non-stretchable measuring tape and to the nearest centimetre. The tape should touch the skin but not compress soft tissue and twists in the tape should be avoided. The trial participant should be asked to breath normally. The same measuring tape should be used throughout the trial to the extent possible. The measuring tape will be provided to the trial site by the sponsor.

5.1.7 Blood pressure measurements

For time points, refer to the SoA.

Initially, blood pressure should be taken in both arms. If the pressures differ by more than 10 mmHg (as in the presence of a subclavian stenosis), the arm with the highest pressure (either systolic or diastolic) should be used for all subsequent measurements.

Blood pressure measurements should be performed on the same arm. The same method and device should be used throughout the trial for a participant to the extent possible. After trial participants have rested quietly in the seated position for 5 minutes, 3 blood pressure

measurements will be taken 2 minutes apart at all visits with the exception of screening visit in which at least two triplicate measurements 5 minutes apart will be taken. All 3 results will be entered in the eCRF including time of measurements for calculation of mean blood pressure. The seated pulse rate will be taken during the 2-minute interval between the second and third blood pressure reading.

5.1.8 Efficacy laboratory parameters

Some of the laboratory parameters will be analysed as part of efficacy criteria (Sections 2.1 and 2.2)

5.1.9 Patient-reported outcomes

PRO measures will be administered to all trial participants (electronically; ePRO). Details to the (electronic) use can be found in the ISF. At sites where the PROs cannot be administered electronically or participant refusal of electronic version of questionnaires use, a paper back up will be available.

The following PROs will be used in this trial:

- NASH-CHECK Questionnaire:
  The NASH-CHECK is a 31-item disease-specific questionnaire, developed to evaluate symptoms and health-related quality of life (HRQoL) for patients living with NASH. It includes 10 items assessing symptoms and 21 items assessing HRQoL. The measure has a recall period of 7 days. The symptoms items use 11-point numerical rating scales, ranging from 0 (indicating no symptoms) to 10 (indicating worst possible or extreme symptoms). HRQoL items are grouped into activity limitations (8 items) and emotions and lifestyle (13 items).
- CLDQ NAFLD-NASH Questionnaire:
  The CLDQ NAFDL-NASH is a 36-item questionnaire, developed to assess patient-reported outcomes in individuals with chronic liver disease. Specifically tailored for NASH, this questionnaire collects data across 6 domains: abdominal symptoms, activity/energy, emotional health, fatigue, systemic symptoms, and worry.

The questionnaires must be completed by the trial participants at the site in a pre-specified order and before any other visit-related activities are performed (see Section 6.2.2). Enough time should be dedicated to give answers to all questions. Trial participants should be given the opportunity to complete the questionnaires without interruption in a calm and pleasant environment, e.g. in a private room/space for the trial participants and without being influenced by the investigator or other members of the trial team. Each time the questionnaires are completed, the approach for a participant should be consistent (i.e. in relation to the fasting status and other procedures).

PRO assessments are to be completed by the participant in the same language the participant provided written consent for the trial and without any help from or interpretation/translation by other people. All local language versions will be validated.

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

Whether the participant was able to complete the PRO assessment himself/herself and the mode of administration will be documented.

ePRO data will be electronically transferred to the ePRO vendor database. In case of technical malfunction data will be captured on paper back-up forms. The data flow for eCOA is described in the vendor data management plan.

5.2 ASSESSMENT OF SAFETY

The timing and frequency of safety assessments are described in SoA.

5.2.1 Physical examination

A complete physical examination will be performed at the screening visit. Further physical examinations during the trial should be followed as per SoA. The physical examination should be conducted according to the local medical practice. It includes at a minimum general appearance, neck (including thyroid gland), lungs, cardiovascular system, abdomen, extremities, and skin.

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

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the SoA, prior to blood sampling. This includes SBP and DBP pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. Please refer to Section 5.1.7 for instructions on blood pressure measurements.

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 11. For the sampling time points please see the SoA.

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

The central laboratory will send reports to the Investigator. It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator will be reported as AEs (please refer to Section 5.2.6.2).

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

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

Table 11 Laboratory parameters

Category	Test name
Safety laboratory test (clinical haematology)	Haematocrit Haemoglobin MCV (Mean Corpuscular Volume) MCH (Mean Corpuscular Haemoglobin) MCHC (Mean Cellular Haemoglobin Concentration) Red Blood Cell Distribution Width (RDW) Red Blood Cells (RBC) Count/ Erythrocytes (including morphology) WBC Count/ Leukocytes Platelet Count / Thrombocytes Differential Automatic (relative and absolute count): Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes
Safety laboratory test (clinical chemistry)	Albumin Alkaline phosphatase ALT Amylase AST Bicarbonate Bilirubin total, fractionated Calcium Calcitonin Chloride CK CK-MB (reflex test if CK is elevated) $eGFR_{cr}$ (CKD-EPI equation for adults) $eGFR_{cys}$ (CKD-EPI equation for adults) Enzymatic creatinine Gamma-glutamyl transferase hsCRP Lactate dehydrogenase Lipase Magnesium Phosphate Potassium Protein total Sodium Troponin I (reflex test if CK is elevated) Urea (blood urea nitrogen) Uric acid TSH
HCC surveillance	Alpha fetoprotein
Safety laboratory test (coagulation panel)	Activated Partial Thromboplastin Time (aPTT) Prothrombin Time (INR) Fibrinogen

Table 11 (cont.) Laboratory parameters

Category	Test name
Glucose metabolism	FPG FPI HbA1c C-peptide HOMA-IR HOMA-β
Lipids	Cholesterol HDL LDL VLDL Triglycerides Free fatty acids
Menopausal testing	FSH: for women age 40-55 years with amenorrhea for 12 months[1]
Pregnancy testing	• A urine pregnancy test will be done during screening for WOCBP. If it is negative, a serum pregnancy test will be done. • Urine pregnancy tests will be performed at all other in-clinic visits. If urine pregnancy test is positive, a confirmatory serum pregnancy test will be done. • Pregnancy tests can be done more frequently if required by local regulations.
Urinalysis	• Semiquantitative analyses: nitrite, protein, ketone, pH value, leukocyte esterase, erythrocytes • Quantitative analyses: urinary albumin, urinary creatinine, UACR
Severe and/or systemic hypersensitivity	• Histamine • IgE • Tryptase • Complement C3 • Complement C4 • PK[1] • ADA[1] • NAb[1]
Infectious serology	HBV surface antigen[2] HCV antibodies[2] HCV RNA[2, 3] HIV-1/2 combination[2]

1 Not to be analysed by central laboratory, not to be provided to the investigator
2 Only at screening
3 Only performed in case of HCV antibodies positivity or history of hepatitis C treatment

5.2.4 Electrocardiogram

12-lead ECGs should be collected prior to blood sampling at the time points specified in the SoA. At screening, a triplicate ECG (3 single ECGs recorded within 3 minutes) will be collected. Centralised ECG services will be provided by an external vendor. ECGs should be collected according to the trial-specific recommendations, using the standardised equipment provided by the vendor. ECGs may be repeated for quality or safety reasons. Trial participants must be supine for approximately 5 to 10 minutes before ECG collection. Trial participants should remain supine, but awake, during the ECG collection process.

The investigator has the responsibility to complete an initial review as soon as the ECG recordings are obtained at the site visit. At any time during the trial, the investigator may decide to place a hold on further dosing of the trial participant if there is an indication of significant abnormalities in the ECG and may prefer to wait until the results from the central reading are available.

The digital ECG recordings will be transmitted to the 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 reported to the site. The investigator must review the report. If the ECG is rated as abnormal, the investigator will have to determine if the abnormal findings are clinically significant. Clinically significant abnormal findings based on central reading will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate.

After the screening visit, the investigator must complete a review of the ECG results from central reading. Any pre-existing conditions should be recorded as baseline conditions.

ECGs recorded at the randomisation visit should be evaluated by the investigator before the trial participant receives the first dose. If abnormalities are observed by the investigator in the ECG reading at the randomisation visit, it is recommended that the investigator waits until the results from central reading are available, and the randomisation visit should be rescheduled. ECGs will be performed during the visits as outlined in the SoA. In addition, based on participant's symptoms (e.g. syncope, palpitations, etc) and investigator's judgement, ECGs can be performed adhoc.

The investigator will have the responsibility of following up with the trial participant if there are any clinically significant findings in the ECG report. It is recommended to repeat the 12-lead ECG recording and/or refer to a cardiologist and/or perform additional cardiac tests (i.e. cardiac enzymes) if there is an indication of significant abnormalities or in case of doubts.

QTcF will be applied as the QT correction method.
In case of evidence of:

- QTc (Fridericia) interval >500 ms,
- or an increase in QTcF interval more than 60 ms AND QTcF interval above the ULN (470 ms for women, 450 ms for men)

(compared to the last ECG recording performed prior to the first IMP administration obtained from central ECG reading) IMP should be stopped, and then discontinued if this finding is confirmed by central ECG reading.

If a clinically relevant increase (according to investigator judgement) in the QTcF interval or any other clinically significant quantitative or qualitative change from last ECG recording performed prior to the first IMP administration, is identified after the trial participant is randomised, the investigator will assess the symptoms (e.g. palpitations, near syncope, and syncope) and decide if the participant will continue taking the IMP.

Any clinically significant findings on the ECG will be recorded as AEs/SAEs and will be followed up and/or treated as medically appropriate.

All ECGs that are read in the central location will be stored in the vendor's database and transmitted to the sponsor periodically. If there is any clinically significant finding in an ECG performed locally due to presence of acute symptoms, this ECG will be transmitted to the vendor for central reading.

5.2.5 Other safety parameters

5.2.5.1 Mental health questionnaires

The mental health status of the trial participants will be assessed by the C-SSRS and PHQ-9 questionnaires. The C-SSRS will be provided to the sites in paper form. The PHQ-9 will be administered to all trial participants electronically where the digital approach is approved. At sites where it cannot be administered electronically, a paper back up will be available.

The C-SSRS is a semi-structured interview, developed by clinical experts in cooperation with the FDA and requested by regulatory agencies, assessing both suicidal behaviour and suicidal ideation. It does not give a global score but provides some categorical and some severity information specifically for behaviour and ideation.

The C-SSRS interview may be administered by any type of physician, psychologist, clinical social worker, mental health counsellor, nurse, or research coordinator with C-SSRS training. It has a typical duration of 5 minutes and causes only a low burden on trial participants. At a minimum, the interview consists of 2 screening questions related to suicidal ideation and 4 related to suicidal behaviour 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 trial participants with a history of SIB. After the baseline visit, the assessment "since last visit" will be performed at clinic and remote (if allowed per local regulations) visits as specified in the SoA.

The investigator has 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 an answer "yes" to either Question 4 (Active Suicidal Ideation with

Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS, or an answer "yes" to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS, or an answer "yes" to any of the suicide-related behaviours (Actual attempt, Interrupted attempt, Aborted attempt, Preparatory act or behaviour) on the "Suicidal Behaviour" portion of the C-SSRS, the investigator has to immediately interview the trial participant during the clinic visit and recommend the participant to consult with an MHP. Treatment with the IMP should be stopped, and the participant should be requested to continue in the trial. Additionally, all C SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behaviour must be reported as separate SAEs by the investigator. For 'Self-injurious behaviour, 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 has to decide based on clinical judgment whether it represents an AE as defined in this protocol, and if it is considered an AE then it must be reported accordingly.

PHQ-9 is the 9-item depression module of the patient health questionnaire, which is a self administered diagnostic tool used for assessment of mental disorders. It takes 5 to 10 minutes to complete the questionnaire and it should be completed together with the other PROs. If the PHQ-9 score is ≥15, the trial participants should be referred to an MHP to assist in deciding whether the participant may continue to receive the IMP.

5.2.5.1.1 Eye examination

Uncontrolled and potentially unstable diabetic retinopathy or maculopathy is defined as an exclusion criterion (Section 3.3.3, exclusion criterion 14) and a trial participant presenting these conditions during screening is not eligible to participate in the trial. Testing is required via one of these options prior to participant randomisation within the screening period or if such an examination has been performed within the past 3 months prior to screening, the results can be used for eligibility evaluation:

- The pharmacologically pupil-dilated fundus eye examination performed by an ophthalmologist or an equally qualified healthcare provider (e.g. optometrist) OR
- Other ophthalmologist examination of diabetic retinopathy (as recommended by country T2DM management guidelines)

During the trial conduct, a participant with T2D must have the eye examination performed at time points specified in the SoA or whenever the trial participant has experienced a worsening of vision. Respective findings have to be reported as AEs (please refer to Section 5.2.6.2).

5.2.6 Assessment of adverse events

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

5.2.6.1 Definitions of adverse events

5.2.6.1.1 Adverse event

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

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

The following should also be recorded on the appropriate eCRF(s):

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

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

5.2.6.1.2 Serious adverse event

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

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

5.2.6.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency (EMA) initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined in Section 5.2.6.1.2. A copy of the latest list of “Always Serious AEs” will be

provided in the ISF. These events should always be reported as SAEs as described in Section 5.2.6.2.

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

All C-SSRS reports of suicidal ideation Type 4 or 5 and all reports of suicidal behaviour must be reported as separate SAEs by the investigator.

5.2.6.1.4 Adverse events of special interest (AESIs)

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

The following AEs are considered as AESIs:

Potential severe Drug-Induced Liver Injury
A potential severe DILI that requires follow-up is defined by any of the following alerts (alterations) of hepatic laboratory parameters. Liver enzymes should be repeated or IMP interrupted as shown in Table 12 for non-cirrhotic participants. For participants who develop cirrhosis during the trials, Table 22 should be followed.

These laboratory findings constitute a hepatic injury alert, and trial participants showing any of these laboratory abnormalities need to be followed up according to the “DILI checklist” provided in the ISF.

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

Table 12 Algorithm for monitoring and management of possible hepatocellular DILI in non-cirrhotic trial participants with normal or elevated baseline ALT[1] (Adapted)

Treatment emergent ALT	**Treatment emergent total bilirubin**	**Liver related symptoms**	**Action [2, 3]**
Normal/near normal baseline [1]: ALT ≥5x ULN Elevated baseline [1]: ALT ≥3x baseline or ≥300 U/L (whichever occurred first)	Normal Participants with Gilbert's syndrome: no change in total bilirubin	None	Repeat ALT, AST, alkaline phosphatase, and total bilirubin in 2 – 3 days. Interrupt IMP if ALT remains elevated above triggered value on repeat testing. Initiate evaluation for other aetiologies of abnormal liver tests including PEth levels to rule out alcohol induced liver injury.
Normal/near normal baseline [1]: ALT ≥3x ULN Elevated baseline [1]: ALT ≥2x baseline or ≥300 U/L (whichever occurred first)	Normal Participants with Gilbert's syndrome: no change in total bilirubin	Severe fatigue, nausea, vomiting, right upper quadrant pain, rash, eosinophilia (>5%)	Repeat ALT, AST, alkaline phosphatase, and total bilirubin in 2 – 3 days. Interrupt IMP if ALT remains elevated above triggered value on repeat testing. Initiate evaluation for other aetiologies of abnormal liver tests including PEth levels to rule out alcohol induced liver injury.
Normal/near normal baseline [1]: ALT ≥8x ULN Elevated baseline [1]: ALT ≥5x baseline or ≥500 U/L (whichever occurred first)	Normal Participants with Gilbert's syndrome: no change in total bilirubin	None	Interrupt IMP. Initiate close monitoring and workup for competing aetiologies including PEth levels to rule out alcohol induced liver injury. IMP can be restarted only if another aetiology is identified and liver enzymes return to baseline.
Normal/near normal baseline [1]: ALT ≥3x ULN Elevated baseline [1]: ALT ≥2x baseline or ≥300 U/L (whichever occurred first)	Total bilirubin ≥2x ULN Participants with Gilbert's syndrome: doubling of direct bilirubin or increased INR to >1.5	None	Interrupt IMP. Initiate close monitoring and workup for competing aetiologies including PEth levels to rule out alcohol induced liver injury. IMP can be restarted only if another aetiology is identified and liver enzymes return to baseline.
Normal/near normal baseline [1]: ALT ≥5x ULN Elevated baseline[1]: ALT ≥3x baseline or ≥300 U/L (whichever occurred first)	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain, rash, eosinophilia (>5%)	Interrupt IMP. Initiate close monitoring and workup for competing aetiologies including PEth levels to rule out alcohol induced liver injury. IMP can be restarted only if another aetiology is identified and liver enzymes return to baseline.

1 Elevated baseline is defined as ALT ≥1.5x ULN.

2 The actions of close observation, monitoring, and IMP interruption often overlap. Occasionally, workup is initiated after IMP interruption.

3 Causality assessment should include obtaining a PK sample at time of potential DILI event for later analysis of excessive exposure. Causality assessment includes evaluation of PEth levels to rule out alcohol induced liver injury.

Source: [R20-1981]

For the trial participants who progressed to cirrhosis the Table 22 "Algorithm for monitoring and management of possible hepatocellular DILI in cirrhotic trial participants" should be used (please refer to Appendix 10.6).

Trial participants should be followed up until resolution of symptoms or signs in the above stated situations [P09-12413]. Treatment with the IMP may be restarted only if another aetiology is clearly identified, and the liver values have returned to baseline [R20-1981]. Otherwise, after resolution or stabilisation, the trial participant should complete the ETD procedures as outlined in the SoA.

Following completion of the DILI checklist, if the BI IMP cannot be excluded as a possible cause of DILI event, then discontinuation should be made permanent without rechallenge. If an alternate causality is confirmed by the DILI checklist evaluation, then BI IMP may be re-started, if warranted. Cases of DILI will be adjudicated.

Hepatocellular Carcinoma
Advanced liver fibrosis and cirrhosis are major risk factors for hepatocellular carcinoma (HCC). Trial participants will be screened for HCC every 6 months via measurement of α-fetoprotein. Confirmatory imaging via CT scan or MRI as per local clinical practice should be performed if there is suspicion of HCC on elevated α-fetoprotein. Standard of care workup should be applied in suspected cases of HCC, which may include biopsy [R24-0213]. Participants who have progressed during trial conduct to cirrhosis should have abdominal scan performed each 6 months. HCC events will be adjudicated.

Thyroid malignancies and C-cell hyperplasia
Individuals with personal or family history of MTC and/or MEN-2 will be excluded from the trial. Participants who are diagnosed with MTC during the trial will have IMP stopped.
The assessment of thyroid safety during the trial will include reporting of any case of thyroid malignancy (including MTC and papillary carcinoma) and measurements of calcitonin (for further details please refer to Section 5.2.6.2.5).

Trial participants with calcitonin levels ≥100 pg/mL or 29.26 pmol/L will be excluded from the trial. If an increased calcitonin value (≥100 pg/mL or 29.26 pmol/L) is observed during the course of the trial, IMP should be discontinued, and follow-up by an endocrinologist should be done.

This data will be captured in specific eCRFs. All cases of thyroid cancer will be adjudicated.

Systemic and serious cutaneous hypersensitivity or anaphylactic reactions
All systemic and serious cutaneous hypersensitivity or anaphylactic reactions will be reported as AESIs. Additional data should be recorded on the specific eCRF page. Further details are described in Section 4.2.1.3.

Acute gallbladder disease
All events of treatment-emergent biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as

needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Table 12 and Table 22. Additional data should be recorded on the specific eCRF page.

Severe hypoglycaemia requiring assistance (Level 3)
During screening visit all trial participants with T2DM will be educated about signs and symptoms of hypoglycaemia, how to treat hypoglycaemia, and how to collect information for each episode of hypoglycaemia. Hypoglycaemia may be identified by spontaneous reporting of symptoms from trial participants, by plasma glucose samples collected during in-clinic visits, or by home glucose monitoring device.

Upon onset of a hypoglycaemic episode, the trial participant is recommended:

- to measure and record plasma glucose every 15 minutes until the value is ≥3.9 mmol/L (70 mg/dL) and/or symptoms have been resolved in accordance with current guidelines.
- to record the general information in relation to the hypoglycaemia (date, time, plasma glucose measurements, and any symptoms in the eDiary).

The trial participants will be informed about the need to notify the investigator about all cases when they experience a hypoglycaemic episode. Hypoglycaemic events will be recorded in the eCRF using the definitions in Table 13 below.

Table 13 Classification of hypoglycaemia

Level	Glycaemic criteria/description
Level 1	Glucose <70 mg/dL (<3.9 mmol/L) and ≥54 mg/dL (≥3.0 mmol/L)
Level 2	Glucose <54 mg/dL (<3.0 mmol/L)
Level 3	A severe event characterised by altered mental and/or physical status requiring assistance for treatment of hypoglycaemia

Source: [R22-4277]

Hypoglycaemic events should be treated and additional glucose monitoring should be implemented per investigator discretion and medical judgement. All hypoglycaemic episodes will be recorded in a specific eCRF page. All symptomatic hypoglycaemic events should be reported as an AE. One AE entry can cover several hypoglycaemic episodes, if the trial participant has not recovered between the episodes. All Level 3 hypoglycaemic events (severe events characterised by altered mental and/or physical status requiring assistance) should be reported as an AESI.

If the hypoglycaemic episode fulfils the criteria for an SAE, then reporting should be done as described in Section 5.2.6.2.2.

5.2.6.1.5 Intensity (severity) of AEs

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

5.2.6.1.6 Causal relationship of AEs

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

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

Arguments that may suggest no reasonable possibility of a causal relationship could be:
- No plausible time to onset of the event relative to the time of IMP exposure is evident (e.g. pretreatment cases, diagnosis of cancer or chronic disease within days/weeks of IMP administration; an allergic reaction weeks after discontinuation of the IMP concerned)
- Continuation of the event despite the withdrawal of the IMP, considering the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger
- There is an alternative explanation, e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the IMP concerned
- Disappearance of the event even though trial IMP treatment continues or remains unchanged

5.2.6.1.7 Adverse events requiring additional data collection

Some pre-specified AEs critical for the assessment of the safety of survodutide will require additional data collection with a separate eCRF page, some of these events will be centrally adjudicated in a blinded fashion by an independent external CEC.

5.2.6.1.7.1 Events requiring adjudication

Definitions of the adjudicated events and the principles of standardised data collection in the centralised CEC adjudication process are outlined in the separate CEC Charter and process guideline. Below are the events which will be adjudicated by the CEC or confirmed by central reading.
- Liver related clinical events:
  - Progression to cirrhosis (defined as histological fibrosis score CRN F4),

  - Hepatic decompensation event(s), including
    - Ascites requiring treatment
    - Hepatic encephalopathy requiring treatment
    - Portal hypertension -related upper GI bleeding, including bleeding from oesophageal varices, gastric varices, and portal hypertensive gastropathy
  - Worsening of MELD score to ≥15
  - 'High-risk' GOVs (UGE central reading)
- Major adverse CV events (5P-MACE) including
  - Non-fatal MI
  - Non-fatal stroke
  - Ischaemia related coronary revascularisation
  - HFE (including HHF, emergency room visit, urgent care visit, or urgent outpatient HF visit)
  - CV death
- Non-CV death
- Acute pancreatitis
- Thyroid malignancies and C-cell hyperplasia
- Pancreatic cancer
- HCC
- DILI

Hepatic encephalopathy

HE is a serious complication of liver disease and portosystemic shunting that represents a continuum of neuropsychiatric changes and altered consciousness. It is classified as covert hepatic encephalopathy (CHE) in its mildest form and as overt hepatic encephalopathy (OHE) when clinically apparent.

During trial conduct any acute change in mental status, occurring without a differential diagnosis that could explain it (e.g. stroke, epilepsy), requires medical evaluation and treatment (ambulatory visit or hospitalisation) will be consider as HE event. The supporting documentation will be collected and send for adjudication.

In addition, during regular in-clinic visit if a participant presents, HE symptoms the neurological deficits will be assessed using West-Haven Criteria [R23-3923]. Each assessment will be recorded in eCRF including respective grading. If Grade ≥2 observed that event will be considered as clinical liver outcome event and case will be adjudicated.

Table 14 Classification of hepatic encephalopathy

Grade of hepatic encephalopathy	Description	Suggested operative criteria
Unimpaired	• No encephalopathy at all, no history of HE	Tested and proven to be normal
Minimal	• Psychometric or neuropsychlogical alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations
Grade I	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioural decay with respect to his or her standard on clinical examination or to the caregivers
Grade II	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behaviour • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms
Grade III	• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behaviour	Disoriented for space (at least three of the followings are wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms
Grade IV	• Coma	Does not respond even to painful stimuli

Source: [R23-3923]

Model for End-Stage Liver Disease (MELD) score to ≥15

Progression of disease will be assessed in MELD score at each in-clinic visit based on central laboratory results (refer to calculation in Section 5.1.4) If scores increase to 15 or above is recorded and confirmed during unscheduled visit event will be sent for adjudication. Clinically significant increases in MELD score should be recorded as AEs.

Ascites

Pathologic accumulation of fluid within the peritoneal cavity can occur with disease progression in cirrhosis.

The clinical presence of ascites will be assessed during each in-clinic visit by physical examination (as per SoA). In addition, abdominal ultrasound can be requested as per

investigator's judgment as only as ascites is suspected. If MRI or CT scan is performed for HCC diagnostic or other reason, ascites can also be detected and reported.

Each assessment will be recorded in the eCRF including respective grading, location (focal or free ascites) and all conditions related to ascites including paracenteses, ascitic fluid laboratory workup, diuretic use.

All ascites events should be reported as an AE and will be adjudicated. All Grade ≥2 ascites will be considered as clinical outcome event.

Table 15 Classification of ascites

Grade of ascites	Definition	Treatment
Grade 1	Mild ascites, only detectable by ultrasound	No treatment
Grade 2	Moderate ascites evident by moderate symmetrical distension of the abdomen	Restriction of sodium intake and diuretics
Grade 3	Large ascites with marked abdominal distension	Large volume paracentesis followed by restriction of sodium intake and diuretics (unless refractory ascites)

Source: [R23-3640]

Gastroesophageal varices

GOVs develop as a consequence of portal hypertension in patients who have progressed to cirrhosis.

UGE remain the gold standard procedure in the diagnosis of GOVs. Based on the endoscopic assessment, GOVs will be classified into small (<5 mm) and large varices (≥5 mm) [P18-02639]. If 'high-risk' varices are observed (larges varices) that event will be considered as clinical liver outcome event [R23-4358]. Each assessment will be recorded in eCRF as an AE including respective CTCAE grading. Each event will be recorded and sent for adjudication by central reading.

For those participants who has progressed to CSPH standard of care should be followed (considering treatment with NSBB in case of no contraindication, or endoscopic variceal ligation (if applicable) for those who cannot receive NSBB, as per AASLD guidance [R23-4358]).

Acute Varices Haemorrhage (initial bleed)

Acute varices haemorrhage (AVH) remains an emergent complication of cirrhosis with 6 week mortality ranges from 10% to 15 % and requires timely and effective management to prevent short-term mortality. Haemorrhage results from variceal wall rupture because of increased wall tension, itself related to elevated variceal transluminal pressure, increased variceal diameter, and decreased wall thickness. The incidence of AVH correlates with the magnitude of portal hypertension (HVPG measurement), severity of liver disease (e.g. CTP, class or MELD score), and varix characteristics (size, red wale signs).

The participants with AVH will be treated as per standard of care. Event will be recorded in eCRF and adjudicated.

Acute pancreatitis

Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems.

If acute pancreatitis is suspected, IMP should be stopped and appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the central laboratory (and locally, if needed). If there is evidence of increase in amylase or lipase (3x ULN) and suspicion of acute pancreatitis, an abdominal CT scan (or MRI) with contrast should be performed to confirm the diagnosis. If a CT scan with contrast is contraindicated, a CT without contrast or MRI should be performed. If imaging does not support the diagnosis of acute pancreatitis, the IMP can be restarted as per investigator's judgment. If abdominal imaging supports the diagnosis of acute pancreatitis, IMP should be discontinued, and the participant should be requested to continue in the trial. A review of the trial participant's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or amylase [total and/or pancreatic]) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to IMP(s).

Each trial participant will have measurements of amylase and lipase (assessed at the central laboratory) as shown in the SoA to assess the effects of the IMP on pancreatic enzyme levels. Relevant data from trial participants with acute or chronic pancreatitis will be entered into a specifically designed eCRF page. All cases of pancreatitis will be adjudicated.

Pancreatic cancer

Based on data from experimental studies in animal models, it has been speculated that the chronic over-stimulation of GLP-1R in exocrine pancreatic cells could induce pancreatitis, ultimately leading to an increased risk of pancreatic cancer. Cases of pancreatic cancer will be adjudicated. Additional data should be recorded on the specific eCRF page.

5.2.6.1.7.2 Events requiring additional data collection (these events will not be adjudicated)

Local tolerability and injection site reactions

Local tolerability at the administration site of survodutide will be assessed by the investigator during the IMP administration visit and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction, e.g. "swelling", "induration", "heat", or "redness" should be collected on the specific eCRF page and reported as AE if clinically significant.

Acute severe renal events

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute or worsening of chronic renal failure. Survodutide has not shown to be nephrotoxic, however, consistent with other GLP-1R agonists, GI AEs have been reported with survodutide, including nausea, diarrhoea, and vomiting. The events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure. Trial participants should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration. Adequate fluid substitution (oral or intravenous) and/or reduction in dose of concomitant diuretics should be initiated to prevent dehydration or exacerbation of dehydration. Renal function should be closely monitored in trial participants with GFR <60 mL/min/1.73 m^2 who develop severe vomiting and diarrhoea and when participants are dehydrated or at higher risk of dehydration. Additional data should be recorded on the specific eCRF page.

Persistent and unacceptable hyperglycaemia

Hyperglycaemia has to be identified and reported if any of the FPG values (including fasting SMBG values) exceeds 15 mmol/L (270 mg/dL) and no intercurrent cause of the hyperglycaemia can be confirmed. Please refer to Section 4.2.1.1.1 and 4.2.1.1.2 for details. Persistent and unacceptable episodes of hyperglycaemia should be recorded as AEs and in the specific eCRF page.

Worsening of diabetic retinopathy or maculopathy

Fast improvements in glucose levels may lead to a temporary worsening of diabetic eye disease. Trial participants with uncontrolled and potentially unstable diabetic retinopathy or maculopathy within the past 3 months before screening or in the period between screening and randomisation are excluded. All eye examinations including worsening of diabetic retinopathy should be recorded in the specific eCRF page. Please refer to Section 5.2.5.1.1 for further details.

Hypotension, orthostatic hypotension, and syncopal events

Clinically significant hypotension, orthostatic hypotension, and syncopal events should be recorded in the specific eCRF page.

Arrhythmias and cardiac conduction disorders

Treatment-emergent clinically significant cardiac conduction disorders will be recorded as AEs. Events that meet criteria for serious conditions as described in Section 5.2.6.1.2 must be reported as SAEs. All clinically significant arrhythmias and cardiac conduction disorders should be recorded in the specific eCRF page.

Major depressive disorder, requiring hospitalisation

Participants will be monitored for depression through AE collection and by using the PHQ-9. For further details, refer to Section 5.2.5.1.

Suicidal ideation and behaviour

Participants will be monitored for SIB through AE collection and by using the C-SSRS. For further details, refer to Section 5.2.5.1.

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

- All AEs (serious and non-serious) and all AESIs from signing the informed consent onwards until the individual trial participant's EoS (usually the FU/EoS Visit), please see Section 6.2.3).
- After the individual trial participant's EoS Visit the investigator does not need to actively monitor the trial participant for new AEs. The following events only should be reported:
    - Any occurrence of cancer of new histology
    - IMP related SAEs
    - IMP related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call.

Vital status data collection
Trial participants who discontinue trial treatment prematurely, and agree to be contacted further after ETD, should be followed up as described in Section 3.3.4.1. The above described AE reporting requirements apply as far as this is possible. If a trial participant only agrees to be contacted for vital status data collection, the investigator must report until the individual participant's EoS Visit any occurrence of cancer, all deaths/fatal AEs regardless of relationship, and trial drug related SAEs and trial drug related AESIs the investigator becomes aware of.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs that are relevant for the reported SAE or AESI, on the AE eCRF immediately (within 24 hours of becoming aware of the event) triggering a data transfer to the sponsor's unique entry point. On specific occasions, the investigator could inform the sponsor upfront via telephone in addition.

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

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

The country specific process will be described in the ISF.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a trial participant has been enrolled in the clinical trial and has taken IMP, the investigator must report any IMP 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.

It is not required to report the pregnancy of a partner of a male trial participant.

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

The ISF will contain the Pregnancy Monitoring Form (Part A and B) as well as specific process for reporting the pregnancy form to the sponsor's unique entry point.

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

5.2.6.2.4 Exemptions to SAE reporting

In accordance with the ICH guideline E2A and in order to maintain the integrity of this trial, the following primary endpoint events that are SAEs are exempted from expedited reporting to health authorities regardless of investigator causality. The medication code will not be broken for the purpose of expedited reporting to health authorities.

The following events are exempt from expedited reporting:

- Hepatic cirrhosis
- Hepatic decompensation event(s)
  - Ascites
  - Hepatic encephalopathy
  - Portal hypertension-related upper GI bleeding including events of bleeding from oesophageal varices, gastric varices, and portal hypertensive gastropathy
- Increase in MELD score
- Portal hypertension
- Gastric or oesophageal varices

Note to investigator: If a liver related event is suspected to be liver injury caused by the IMP, the event should be reported as drug-induced liver injury (DILI). DILI (related and unrelated to IMP) is not exempted from SAE reporting.

Protocol specified exempted events should be collected on the **appropriate eCRF page only**.

5.2.6.2.5 Other safety topics

Severe and serious gastrointestinal events

Survodutide may cause severe GI AEs, such as nausea, vomiting, and diarrhoea. Information about severe and serious GI AEs will be collected in the AE form, and information regarding antiemetic/antidiarrheal use will be collected in the Concomitant Medication form. For detailed information concerning the management of GI AEs, refer to Section 4.1.4.1 and Appendix 10.2.

Calcitonin monitoring

Trial participants with calcitonin levels ≥100 pg/mL or 29.26 pmol/L during the screening will be excluded from the trial. If an increased calcitonin value (≥100 pg/mL or 29.26 pmol/L) is observed during the course of the trial, IMP should be discontinued, and follow-up by an endocrinologist should be done.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of PK, blood samples will be collected at the time points indicated in the SoA and Appendix 10.5. Date and clock time of drug administration as well as actual date and clock time of PK sampling will be captured in the database.

For PK analysis, trough plasma concentration of survodutide will be used for the evaluation of the influence of intrinsic and extrinsic factors on survodutide.

A population PK analysis will be undertaken to analyse PK sampling data. The trough plasma concentrations will be used to refine an already existing population PK model. The results of the population PK analysis are not planned to be part of the trial report but will be reported in a separate pharmacometric report

5.3.2 Methods of sample collection

Detailed instructions on sampling, preparation, processing, shipment, and storage are provided in the laboratory manual.

For quantification of survodutide plasma concentrations, blood samples will be taken from a vein into a K2-EDTA-anticoagulant blood drawing tube at the time points described in the SoA. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

Until transfer on dry ice to the analytical laboratory, the aliquots will be stored upright at about -20°C or below at the trial site. At the analytical laboratory, the plasma sample will be stored at about -20°C or below until analysis.

At a minimum, the sample tube labels should list the following information: BI trial number, trial participant number, visit, and planned sampling time.

Plasma samples will be discarded at the latest 5 years after the final CTR has been signed. All laboratory kit supplies will be provided by the central laboratory vendor designated by the sponsor.

After completion of the trial, plasma samples may be used for further investigations into the metabolism of survodutide. The samples will be discarded after completion of the additional investigations but not later than 5 years after the final trial report has been signed.

5.3.3 Analytical determinations

Survodutide concentrations in plasma will be determined by a validated LC-MS/MS. All details of the analytical methods will be available prior to the start of sample analysis. From trial participants on active IMP, all samples will be analysed.The analysis will be performed under the responsibility of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany at a suitable CRO.

As described in Section 4.1.5.1, the external bioanalyst will be unblinded during sample analysis.

5.3.4 Pharmacokinetic - pharmacodynamic relationship

Exposure predictions based on the population PK model will be used for characterising the exposure-response relationships for selected efficacy and/or safety endpoints. The relationship between PK and biomarkers may also be investigated. These analyses will be documented in separate pharmacometrics reports.

5.4 ASSESSMENT OF BIOMARKERS

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in Sections 5.1 and 5.2.

Several exploratory and probable valid biomarkers will be determined as indirect response to IMP administration. Samples will be collected for biomarker analysis as shown in the SoA.

5.4.1 Biochemical and cellular biomarkers

Probable valid biomarker analyses of established biomarkers of disease activity may include, but not be limited to:

- ELF score: HA [ng/mL], PIIINP [ng/mL], and TIMP-1 [ng/mL]

Sampling for additional exploratory disease activity biomarkers may include but not be limited to:

- Liver fibrosis biomarker:
    - Pro-C3

- Indirect target engagement and metabolism biomarker:
  - Glucagon

- Cardiocvascular and renal biomarkers:
  - NT-proBNP
  - Cystatin C

5.4.1.1 Methods of sample collection

For the measurement of the probable valid and exploratory biomarkers, blood will be taken at the time points indicated in the SoA. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle.

Detailed instructions for biomarker blood sampling, preparation, processing, storage, and shipment of the different biofluids are provided in the laboratory manual. All laboratory kit supplies will be provided by the central laboratory vendor designated by the sponsor.

Samples can be analysed in a staged approach and decisions for further analysis may depend on the results of prior analyses. This may also imply that not all collected samples will be analysed, especially in case of termination of the project/trial or if biomarkers cannot be measured e.g. due to failure in assay validation. Sampling timepoints and periods may be adapted during the trial based on information obtained during trial conduct (e.g. as a result of preliminary PK/PD data), including addition or reduction of samples and visits.

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

The study samples will be discarded after completion of any investigations, but not later than 5 years after the final CTR has been signed as required by local regulations. Any leftover samples or derived material from pre-specified analyses (e.g. blood) may be used for further characterisation of metabolic diseases and their progress as well as method development/ validation but will be destroyed no later than 5 years after the final CTR has been signed.

Biomarker analyses will be performed by Boehringer Ingelheim or by a laboratory authorised by Boehringer Ingelheim.

Analytical results for the biomarker analyses will be described in the CTR or in a separate biomarker report.

5.4.2 Pharmacogenomic Biomarkers

All randomised participants will be asked for a blood sample for exploratory, pre-specified PGx analyses.

One blood sample for genotyping will be taken after randomisation at Visit 2. If not feasible at Visit 2, the sample may also be taken at a later visit.

Gene expression analysis will be conducted on RNA isolated from a small portion of liver tissue collected from a biopsy conducted within the trial (see SoA) if the total amount of tissue exceeds the amount that is necessary for the histological staging of MASH. Thus, tissue samples for gene expression analysis will only be collected once it has been established (by the person performing the biopsy) that sufficient material has been obtained for liver histology.

Detailed instructions for sampling, handling and shipment of samples are provided in the laboratory manual. All laboratory kit supplies will be provided by the central laboratory vendor designated by the sponsor. Remaining samples will be destroyed no later than 5 years after the final CTR has been signed. RNA and/or micro RNA will be extracted from liver tissue and DNA from whole blood using appropriate molecular genetics methods and analysed by appropriate technologies. All methods and assays will be validated for exploratory testing. The analyses will be performed either at Boehringer Ingelheim or a dedicated CRO.

Gene expression analysis will be performed only in countries where allowed by local regulations.

5.5 BIOBANKING

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

In order to be able to address future scientific questions, trial participants will be asked to voluntarily donate biospecimens for banking. If the trial participant agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an AE, or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies. Samples will be stored for testing for a period consistent with local regulations.

5.5.1 Methods and timing of sample collection

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

Blood will be drawn for DNA, plasma and serum banking purposes. Any analyses on DNA or plasma/serum samples will not be reported in the main CTR. Samples will be collected only in countries where all applicable local regulatory and ethics approvals have been obtained for biobanking.

5.6 OTHER ASSESSMENTS

5.6.1 Immunogenicity

5.6.1.1 Timing of immunogenicity measures

Blood samples will be obtained from trial participants receiving survodutide or placebo for the determination of ADAs and NAbs at the time points detailed in the SoA and in Appendix 10.5. Immunogenicity will be assessed via a tiered approach until FU/EoS Visit.

Serum samples will be analysed for the presence of ADAs (including cross-reactive ADAs to GLP-1 and Glucagon) and NAbs (including cross-NAbs to GLP-1 and Glucagon). Ad-hoc blood samples for ADA, NAb, and plasma concentration of survodutide assessment will be collected upon observation of severe or systemic hypersensitivity as described in Section 4.2.1.3.

5.6.1.2 Methods of sample collection

For both, ADA and NAb assessments, blood will be taken via venipuncture or indwelling catheter into a serum blood-drawing tube at the time points listed in the SoA, and additionally in the event of any severe or systemic hypersensitivity reaction as mentioned above. Sufficient volume of blood will be allocated for ADA and NAb analyses to ensure the numbers of assays needed to be run.

At a minimum, the sample tube labels should list the following information: BI trial number, trial participant number, visit, matrix, and analyte (ADA/NAb).

Serum samples will be kept on dry ice or stored in a freezer set to at least -20°C (preferably ≤-70°C) at the clinical site until shipment to the central laboratory. At the central laboratory and at the analytical laboratory, samples will be stored in a freezer set at -70°C (until and after analysis). The samples may be used for further ADA or NAb characterisation, methodological developments or investigations, e.g. for stability testing or characterise ADA response or to address Health Authority questions regarding the results/methodology, however only data related to the ADAs or NAbs will be generated by these additional investigations. The trial samples will be discarded after completion of the additional investigations but not later than 5 years after the final CTR has been signed.

Further details on sample collection, sample handling, and shipping are provided in the laboratory manual. All lab kit supplies will be provided by the central laboratory vendor designated by the sponsor.

5.6.1.3 Immunogenicity analysis

The presence of ADAs to survodutide will be assessed via a tiered approach using validated assays. All trial samples from participants randomised to survodutide will be tested in the screening assay and positive samples in the screening assay will be tested in the confirmatory assay. Trial samples that are confirmed positive will be further characterised for titer assessment, cross-reactivity to GLP-1, cross-reactivity to glucagon, neutralisation of survodutide activity on GLP-1R and neutralisation of survodutide activity on GCGR.

Samples that are positive for cross-reactivity to GLP-1 will be tested for cross-neutralisation of GLP-1. Samples that are positive for cross-reactivity to glucagon will be tested for cross-neutralisation of glucagon. The impact of the presence of ADAs on PK, clinical efficacy and safety will be evaluated.

The analysis will be performed under the responsibility of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT at a suitable contract research organisation.

5.6.2 Clinical staging of obesity

For participants with an BMI ≥30 kg/m^2 (≥25 kg/m^2 for Asian ethnicity), staging of obesity will be assessed by the investigator at screening and EoT/ETD as per SoA using the Edmonton obesity staging system (Appendix 10.4). The Edmonton obesity staging system is used for clinical prioritisation and management of obesity independent of BMI [R20-1982].

5.6.3 Evaluation of anti-hypertensive, lipid-lowering, and anti-hyperglycaemia medication

Any antihypertensive, lipid-lowering, and anti-hyperglycaemia medications must be recorded as concomitant medication. The regular evaluation of the treatment must be performed at the time points specified in the SoA. For any medication or dose changes from baseline in antihypertensive, lipid-lowering, and anti-hyperglycaemia treatment, the investigator must evaluate if the change should be considered as an increase, a decrease, or no change in treatment over time.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to evaluate efficacy and tolerability of BI 456906 and to determine PK and PD 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 the IMP. 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. The PK parameters and measurements outlined are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstance (e.g. pandemic, war), the execution of the investigational plan as per this clinical trial protocol may not be feasible. With the consent of the participant, the sponsor and investigator may agree on alternative, back-up, or rescue methodology which may include, but will not be limited to, virtual trial participant visits and assessments, direct-to-participant shipments of IMP, IMP administrations organised locally allowing local laboratories for safety assessments, providing options to either consider paper diaries or paper PROs for participants, and other measures that may be required to ensure trial continuity while maintaining participant safety and data integrity of primary endpoint. The implementation of these measures will depend on the participant's consent, operational feasibility, and local laws and regulations. Such alternative measures will be described in the participant information. If alternative methodology is implemented, the deviations from the original plan will be precisely documented.

6.1 VISIT SCHEDULE

For a detailed overview of the trial procedures, on-site and remote (if allowed per local regulations) visits scheduled at specified time intervals, and time windows for visits, please refer to the SoA.

The trial consists of a screening period (up to 10 weeks), followed by a dose escalation period of up to 24 weeks or up to a maximum of 32 weeks if 1 or 2 re-escalation attempts are needed due to occurrence of GI symptoms), a maintenance period after Week 24 until EoT/ETD, and a follow-up/EoS. The trial is event-driven, and all randomised trial participants will remain in the trial until the defined number of primary endpoint events has been reached. The trial will continue until the last trial participant has completed the last visit (including follow-up/EoS)

After giving his/her informed consent, the trial participant will be screened for inclusion and exclusion criteria for the trial at Visit 1. Visit 2 will be scheduled after results from the central laboratory, ECG central reading, and central pathology laboratory (liver biopsy assessment, if applicable) are obtained. The trial participant will be randomised at Visit 2 if all inclusion and none of the exclusion criteria are fulfilled.

The recommendations for pre-screening review criteria are provided in Section 3.3. A pre-screening log will be maintained at the participating sites. Trial sites may be compensated for their time and efforts for any pre-screening review activities. The pre-screening process can vary by sites, countries, or regions. Approval from local Ethics Committees and regulatory authorities will be obtained according to local requirements as applicable.

Windows of ±3 days (dose escalation period), ±7 days (maintenance period), +7 days (EoT and FU/EoS Visit) are allowed to accommodate trial participant's schedule. These time windows apply to scheduled visits, not to IMP administration. Time windows for IMP administration are outlined in Section 4.1.4. If any visit has to be rescheduled, subsequent visits should follow the original visit schedule (calculated always from the randomisation Visit 2). Additional visits for the purpose of re-testing laboratory parameters or AE monitoring may be included as deemed necessary by the investigator. If a visit is missed, the

trial participant should be instructed to contact the investigator as soon as possible. Handling of missed doses is described in Section 4.1.4. The investigator should contact the CRA to discuss the further schedule.

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

All trial participants will have a FU/EoS Visit at least 28 days after the last IMP administration which is 21 days after the EoT Visit.

In the event of disruptive circumstances (e.g. pandemic, war) the investigational plan as per this clinical trial protocol may not be feasible at a site. In this case, sponsor and investigator, with the informed consent of the participant, may agree on alternative, back-up methodology which may include but will not be limited to allowing local laboratories for safety assessments, virtual trial participant visits and assessments, direct-to-participant shipments of IMP, IMP administrations organised locally, providing options to either consider paper diaries or paper PROs for participants, and other measures that may be required to ensure trial continuity while maintaining participant safety and data integrity of primary endpoint.

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Please refer to Section 5 for explanations of procedures or assessments and to the SoA for corresponding time points.

An electronic secure online platform from an external vendor will be used in this trial (myMediData). This platform is the place where the trial site staff can communicate with the trial participant and combines telemedicine (including video conference), ePROs, and the eDiary. Trial participants will access the myMediData platform using a secure app on a smartphone or tablet or through any web-enabled device. The dashboard has a standardised design so that the participant only needs to log in once.

Electronic tools will be implemented only in participating countries where this is permitted based on applicable approvals from local regulatory authorities and ethics committees. Otherwise, traditional non-electronic approach (e.g. paper) will be used. In exceptional cases, if a trial participant is unable to use the electronic platforms or devices, a back-up solution with paper will be made available upon sponsor approval.

In this trial, defined visits should be conducted by telephone/videocall. The following assessments may be performed remotely at the timepoints indicated in the SoA:

- Collect and assess AEs and concomitant therapies, ePRO, and eDiary

- Assess IMP compliance
- Review safety laboratory results

If a participant is not able to come to the site for a trial visit, participant must be invited for an unscheduled visit to perform the corresponding tests/assessments.

Safety laboratory and other laboratory tests

The analysis will be performed by a central laboratory. If blood sampling for central laboratory at the trial site is not possible for any unpredictable reason, safety laboratory analyses may be performed at a local laboratory. The local laboratory tests would only be allowed to be documented in exceptional cases and should be discussed with the sponsor. Minimum required safety laboratory parameters are haematology (haematocrit, haemoglobin, erythrocytes, leukocytes, thrombocytes) and clinical chemistry (ALT, AST, bilirubin total, amylase, lipase). The results of the laboratory tests must be transferred to the investigator who ensures medical review and proper documentation in the eCRF.

6.2.1 Screening

Screening Period
Following informed consent, the trial participant will undergo Visit 1/screening assessments as indicated in the SoA. Once the trial participant has consented, the trial participant is considered to be enrolled in the trial. The trial participant should be recorded on the enrolment log and be registered in the IRT. The assessments must all fall within the acceptable screening visit window but do not need to be performed on the same day.

During the screening visit, demographics information will be collected. This includes:

- Age on the day of informed consent (in years)
- Sex (male, female in order to describe the trial participant`s sex at birth)
- Gender identity (male, female, non-binary, not answered, or other in order to describe how the trial participant self-identifies, regardless of their genotypic or phenotypic sex) if 1) locally accepted (i.e. based on HA/EC/IRB acceptance, independent of acceptance by investigators or participants), 2) investigators are willing to ask, and 3) trial participants are willing to reply
- For WOCBP, yes/no in order to characterise the patient population and as a basis for contraception requirements
- Ethnicity and race in order to sufficiently characterise the patient population, to support possible subgroup analyses if needed and to support the calculation of the kidney function via the CKD-EPI$_{cr}$ formula unless not acceptable according to local regulations

After all Visit 1 results are received and the patient is considered eligible, the liver biopsy should be performed in case a historical biopsy is not able to be used. When scheduling a liver biopsy as part of screening procedures sufficient time should be allowed to receive the results within given screening period.

If the trial participant meets the entry criteria, Visit 2 should occur as soon as possible once it has been confirmed that the trial participant is eligible. If the trial participant does not meet

the entry criteria (i.e. fails to meet one or more of the inclusion criteria, and/or meets one or more of the exclusion criteria) following Visit 1 procedures, they should be registered as a screen failure in the eCRF and IRT.

For detail regarding re-screening/re-testing for eligibility criteria, please refer to Section 3.3.

6.2.2 Treatment periods

Trial participants who meet all protocol criteria will be randomised at Visit 2. After randomisation, trial participants will start the treatment period which includes a dose escalation phase, followed by the dose maintenance phase as shown in Figure 1.

During the dose escalation period, on-site visits will be scheduled every 4 weeks. Remote visits (if allowed per local regulations) will be scheduled at Week 2 and 6.

During the maintenance period, on-site visits and remote visits will take place alternately as per SoA, thus, the participant has contact to the site every 6 weeks. The trial participant may choose to go to the trial site to complete the procedures required to be completed during the scheduled remote visits.

Procedures to be completed at each visit can be found in the SoA.

At visits specified in the SoA, trial participants should be instructed to come in the fasting state after at least 8 hours without food or liquid intake, except water, and without administering anti-hyperglycaemia medications (as applicable), which will be taken in the clinic. On days when fasting is required, the in-clinic visit should ideally be scheduled in the mornings, if this is convenient for the trial participant.

Sequence of assessments
For in-clinic visits after randomisation and review of inclusion/exclusion criteria, the suggested order of assessments (as applicable) is

1. Completion of questionnaires
2. Vital signs and other applicable assessments
3. Physical examination
4. ECG
5. Blood draws and urine collection
6. Dosing with IMP (when dosing performed at site during visit)

The questionnaires should be completed prior to any other assessment scheduled for the in-clinic visit and preferably in the following order:

1. NASH-CHECK Questionnaire
2. CLDQ NAFLD-NASH
3. PHQ-9
4. C-SSRS

At each visit, trial participants should be advised to follow the recommended diet and exercise plan and to record their compliance regularly (at least weekly) on the provided food and exercise Diary. The trial participants can also use their own tools (e.g. paper or local

applications) that they have been using prior to enrolment for tracking their diet, body weight, and physical activity. Diet and exercise counselling sessions are held at visits indicated in the SoA. When necessary, from a logistic point of view, it is possible to have the diet/exercise counselling on a different day than the actual in-clinic visit, but within the time window of the visit.

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.

During the remote visits (if allowed per local regulations), which are to be performed as video phone calls, the trial participants will be contacted by the site staff. They will be asked about their well-being, occurrence of AEs, intake of concomitant medications (including standard of care for the weight-related complications). Site staff will conduct the C-SSRS assessment, ask trial participants if they have performed the IMP administration and whether it was documented in the eDiary. During the remote Visits 3 and 5, site staff will also observe the IMP administration and if needed, perform retraining of the trial participants on the administration technique. If the remote Visits 3 and 5 are not performed as video calls but phone calls only, IMP administration may be observed by site staff during the next scheduled in-clinic visit. Trial participants will also be asked if they have followed the diet and physical activity recommendations and have documented it in the food and exercise Diary. When applicable, site staff will also ask trial participants if they experienced any hypo/hyperglycaemic episodes and if they documented the glucose measurements in the eDiary.

Remote visits should occur, by default, via video calls. In rare cases, the remote visits may be done by phone call. The trial participants will be trained by the study staff how to access the video conference application. All procedures to be performed during the remote visits are specified in the SoA. Remote visit responsibilities within the trial team will be defined in the study delegation log on site level (e.g. assessment of concomitant therapy and AEs by a physician).

If remote visits are not allowed per local regulations, they will be performed as in-clinic visits.

Exceptionally, and after consultation with the sponsor, a visit could be completed a few days in advance to accommodate for trial participant’s imperatives. The call to IRT and IMP allocation would be made, but the injection would occur as per the initial schedule and allowed time-window.

The trial participants will have the EoT Visit 1 week after last IMP injection. All trial participants will then enter the follow-up period and complete the observation period with the FU Visit – this visit should be performed 21 days after the EoT Visit, following the regular or premature completion of the treatment period.

A trial participant who discontinues IMP treatment will have an ETD Visit 1 week after the last dose.

6.2.3 Follow-up period and trial completion

All trial participants will have a FU Visit 21 days following the completion of the EoT Visit. Procedures to be completed at the FU Visit can be found in the SoA. The sequence of visit procedures will be the same as in the treatment period.

Trial participants who discontinue the IMP prematurely will have an ETD Visit up to 7 days after the last dose of IMP, FU Visit, and then continue with scheduled visits until the trial is stopped, and then complete the FU/EoS Visit once the trial has ended. All efforts should be made to follow-up on all trial participants until trial end (Section 3.3.4.1).

For trial participants who are not willing to return to predefined visits, refer to Section 3.3.4.1.

Trial participants who withdraw consent should stop taking IMP and should be asked to complete the EoT, and FU/EoS Visit procedures as described in the SoA and Section 3.3.4.2.

A trial participant is considered to have completed the trial in case any of the following applies:

- Completion of planned follow-up period (= FU/EoS Visit completed)
- Lost to follow-up
- Refusal to be followed-up
- Death

If needed in the opinion of the investigator, after EoS additional visits may be scheduled for continued safety monitoring.

Abnormal assessments or laboratory values judged clinically relevant by the investigator will be monitored until they returned to a medically acceptable level.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The trial consists of two parts. There are two planned analyses. At the end of Part 1 (i.e. at least 700 randomised participants have completed Week 52 visit or early terminated), an interim analysis is planned for the primary endpoint of Part 1, with an overall significance level of 0.01 (two-sided). And the end of Part 2, the final analysis is planned for the primary endpoint of Part 2, with an overall significance level of alpha (two-sided, an α of 0.04 + certain alpha propagated from the Part 1 analysis level, see Table 16 for values of alpha). TSAP will be finalised prior to the database lock for each part.

Table 16 α level in Part 2 analysis based on possible alpha propagated from Part 1 analysis

Outcome of Part 1 Analysis on Primary Endpoints	**Outcome of Part 1 on Key Secondary Endpoints**	**α Propagated from Part 1**	**Total α for Part 2 analysis**
Both primary endpoints significant	All significant	0.01	0.05
	At least one not significant	0	0.04
Only one primary endpoint significant	All significant	0.0025	0.0425
	At least one not significant	0	0.04
No primary endpoint significant	Exploratory	0	0.04

Part 1
The primary objectives in Part 1 are to demonstrate superiority of survodutide compared with placebo on:

- The odds ratio (survodutide vs. placebo) for MASH resolution without worsening of liver fibrosis from baseline at Week 52
- The odds ratio (survodutide vs. placebo) for Improvement in fibrosis with no worsening of MASH from baseline at Week 52

Part 2
The primary objective in Part 2 is to demonstrate superiority of survodutide compared with placebo by means of the hazard ratio (survodutide vs. placebo) of a time to first occurrence of any of components of composite endpoint that includes progression to cirrhosis, liver-related clinical outcome events, and all-cause mortality.

7.1 NULL AND ALTERNATIVE HYPOTHESES

Part 1
For the interim analysis at the end of Part 1, the null hypotheses and alternative hypotheses reflecting the primary and secondary objectives are as follows:

Let OR1_ survodutide 6.0 mg/placebo denote the true odds ratio of achievement of MASH resolution without worsening of liver fibrosis from baseline at Week 52 between survodutide 6.0 mg and placebo.

$H0_1$: OR1_ survodutide 6.0 mg/placebo=1 versus HA_1: OR1_ survodutide 6.0 mg/placebo≠1

Let OR2_ survodutide 6.0 mg/placebo denote the true odds ratio of achievement of at least a 1-point improvement in fibrosis stage with no worsening of MASH from baseline at Week 52 between survodutide 6.0 mg and placebo.

$H0_2$: OR2_ survodutide 6.0 mg/placebo=1 versus HA_2: OR2_ survodutide 6.0 mg/placebo ≠1

Let μ1_survodutide 6.0 mg and μ1_placebo denote the true mean of percentage change from baseline in body weight at Week 52 for survodutide 6.0 mg and placebo, respectively.

$H0_3$: μ1_survodutide 6.0 mg = μ1_placebo versus HA_3: μ1_survodutide 6.0 mg ≠ μ1_placebo

Let μ2_survodutide 6.0 mg and μ2_placebo denote the true mean of absolute change from baseline in HbA1c at Week 52 for participants with T2DM for survodutide 6.0 mg and placebo, respectively.

$H0_4$: μ2_survodutide 6.0 mg = μ2_placebo versus HA_4: μ2_survodutide 6.0 mg ≠ μ2_placebo

Let μ3_survodutide 6.0 mg and μ3_placebo denote the true mean of absolute change from baseline in ELF score at Week 52 for survodutide 6.0 mg and placebo, respectively.

$H0_5$: μ3_survodutide 6.0 mg =μ3_placebo versus HA_5: μ3_survodutide 6.0 mg ≠ μ3_placebo

Let μ4_survodutide 6.0 mg and μ4_placebo denote the true mean of absolute change from baseline in liver stiffness score at Week 52 for survodutide 6.0 mg and placebo, respectively.

$H0_6$: μ4_survodutide 6.0 mg =μ4_placebo versus HA_6: μ4_survodutide 6.0 mg ≠ μ4_placebo

Let OR3_ survodutide 6.0 mg/placebo denote the true odds ratio of achievement of no progression of fibrosis at Week 52 assessed by central pathology between survodutide 6.0 mg and placebo.

$H0_7$: OR3_ survodutide 6.0 mg/placebo=1 versus HA_7: OR3_ survodutide 6.0 mg/placebo≠1

To control the overall type I error rate of primary and key-secondary endpoints at the interim analysis ($\alpha = 0.01$), the following approach is used: The primary endpoints will be tested using truncated Hochberg procedure with truncation fraction of 0.5, i.e. the bigger p-value will be compared to 0.75α and the smaller p-value will be compared to 0.5α. If at least one primary endpoint is significant, it is considered success at the interim. α is passed to key secondary endpoints if both primary endpoints are significant, 0.25α is passed if only one primary endpoint is significant. The key secondary endpoints will be tested in hierarchical order.

Superiority will be declared if $H0_1$ is rejected in favour of HA_1 at the planned two-sided significance level and the estimated OR1_survodutide/placebo is greater than 1; Superiority will be declared if $H0_2$ is rejected in favour of HA_2 at the planned two-sided significance level and the estimated OR2_survodutide/placebo is greater than 1. The trial Part 1 will be

considered positive if superiority declared either for binary endpoint 'Resolution of MASH without worsening of liver fibrosis on MASH Clinical Research Network (CRN) fibrosis score' or 'At least a 1-point improvement in fibrosis stage with no worsening of MASH' based on Treatment-Regimen Estimand I of Part 1.

Part 2
For the final analysis, the null hypotheses and alternative hypotheses reflecting the primary and secondary objectives are as follows:

Let HR1_ survodutide 6.0 mg vs. placebo denote the true hazard ratio of delaying MASH disease progression (at EoS) between survodutide 6.0 mg and placebo.

$H0_1$: HR1_ survodutide 6.0 mg vs. placebo=1 versus HA_1: HR1_ survodutide 6.0 mg vs. placebo≠1

Let μ1_survodutide 6.0 mg and μ1_placebo denote the true mean of percentage change from baseline in body weight at Week 114 for survodutide 6.0 mg and placebo, respectively.

$H0_2$: μ1_survodutide 6.0 mg = μ1_placebo versus HA_2: μ1_survodutide 6.0 mg ≠ μ1_placebo

Let μ2_survodutide 6.0 mg and μ2_placebo denote the true mean of absolute change from baseline in HbA1c at Week 114 for participants with T2DM for survodutide 6.0 mg and placebo, respectively.

$H0_3$: μ2_survodutide 6.0 mg = μ2_placebo versus HA_3: μ2_survodutide 6.0 mg ≠ μ2_placebo

Let μ3_survodutide 6.0 mg and μ3_placebo denote the true mean of absolute change from baseline in ELF score at Week 114 for survodutide 6.0 mg and placebo, respectively.

$H0_4$: μ3_survodutide 6.0 mg = μ3_placebo versus HA_4: μ3_survodutide 6.0 mg ≠ μ3_placebo

Let μ4_survodutide 6.0 mg and μ4_placebo denote the true mean of absolute change from baseline in liver stiffness score at Week 114 assessed by VCTE for survodutide 6.0 mg and placebo, respectively.

$H0_5$: μ4_survodutide 6.0 mg = μ4_placebo versus HA_5: μ4_survodutide 6.0 mg ≠ μ4_placebo

Let OR1_ survodutide 6.0 mg/placebo denote the true odds ratio of achievement of no progression of fibrosis assessed by central pathology at EoT between survodutide 6.0 mg and placebo.

$H0_6$: OR1_ survodutide 6.0 mg/placebo=1 versus HA_6: OR1_ survodutide 6.0 mg/placebo≠1

Let HR2_ survodutide 6.0 mg vs. placebo denote the true hazard ratio of occurrence of all-cause hospitalisation (first and recurrent) between survodutide 6.0 mg and placebo.

$H0_7$: HR2_ survodutide 6.0 mg vs. placebo=1 versus HA_7: HR2_ survodutide 6.0 mg vs. placebo ≠1
Let HR3_ survodutide 6.0 mg vs. placebo denote the true hazard ratio of time to first occurrence of 5P-MACE (at EoS) between survodutide 6.0 mg and placebo.

$H0_8$: HR3_ survodutide 6.0 mg vs. placebo=1 versus HA_8: HR3_ survodutide 6.0 mg vs. placebo ≠1

To control the overall type I error rate of primary and key secondary endpoints at the final analysis (An α of 0.04 + certain alpha propagated from the Part 1 analysis level, see Table 16 for values of alpha), the primary endpoint will be tested first. If the primary endpoint is significant, the key secondary endpoints will be tested in hierarchical order.

Superiority will be declared if $H0_1$ is rejected in favour of HA_1 at the two-sided significance level (see Table 16 for value of alpha) and the estimated HR1_survodutide vs. placebo is less than 1. The trial Part 2 will be considered positive if superiority declared for primary endpoint based on Treatment-Regimen Estimand I of Part 2.

7.2 PLANNED ANALYSES

7.2.1 General considerations

Analysis sets

The statistical analysis will be based on the following analysis sets:

- Randomised set (RS): the RS includes all randomised trial participants.
- Treated set (TS): the TS is defined as all randomised trial participants who has at least one dose of IMP.

All efficacy and safety analyses will be based on the treated set. The primary efficacy analysis for Part 1 and Part 2 will be conducted using 'Treatment-Regimen' Estimand I of Part 1 and Part 2, respectively.

Important protocol deviations

IPD categories will be defined in the IPD specification document. IPDs will be identified no later than in the Report Planning Meeting.

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

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

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

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

7.2.2 Handling of Intercurrent Events

The expected intercurrent events of interest in this trial are premature treatment discontinuation, change in background medication, use of restricted medication, occurrence of hepatic decompensation event, occurrence of liver transplant and death from any cause.

There will be two estimands of interest addressing the primary objectives (for Part 1 and Part 2 each):

- Primary Estimand: Treatment-Regimen Estimand I
- Supplementary Estimand: Treatment-Regimen Estimand II.

For submission of the trial to support the registration of survodutide for MASH, the primary efficacy analysis will be conducted using 'Treatment Regimen' Estimand I.

Part 1 Primary Estimand: Treatment-Regimen Estimand I and Part 1 Supplementary Estimand: Treatment-Regimen Estimand II

- Treatment regimen under evaluation will be the randomised treatment taken for up to 52 weeks (with a dose escalation of survodutide vs. placebo during the first 24 weeks after randomisation).

- Target population: The treatment effect will be estimated for trial participants with biopsy confirmed MASH, fibrosis stage F2 and F3, with/without T2DM.

- Endpoint(s): Resolution of MASH without worsening of liver on MASH CRN fibrosis score; at least a 1-point improvement in fibrosis stage with no worsening of MASH

- Population level summary: the odds ratio (survodutide vs. placebo) for MASH resolution without worsening of liver fibrosis from baseline at Week 52; the odds ratio (survodutide /placebo) for improvement in fibrosis with no worsening of MASH from baseline at Week 52

- Intercurrent events and corresponding strategies are listed in Table 17:

Table 17 Handling of intercurrent events for Part 1 Estimand

Intercurrent event (ICE)	**Primary estimand: "Treatment-Regimen" Estimand I**	**Supplementary estimand: "Treatment-Regimen" Estimand II**
Premature treatment discontinuation	Include all available data ("Treatment policy" strategy)	Include all available data ("Treatment policy" strategy)
Change in background medication	Include all available data ("Treatment policy" strategy)	Include all available data ("Treatment policy" strategy)
Use of restricted medication	("Composite" strategy) Results in failure of meeting binary primary endpoints	Include all available data ("Treatment policy" strategy)
Hepatic decompensation event	("Composite" strategy) Results in failure of meeting binary primary endpoints	("Composite" strategy) Results in failure of meeting binary primary endpoints
Liver transplant	("Composite" strategy) Results in failure of meeting binary primary endpoints	("Composite" strategy) Results in failure of meeting binary primary endpoints
Death from any cause	("Composite" strategy) Results in failure of meeting binary primary endpoints	("Composite" strategy) Results in failure of meeting binary primary endpoints

Part 2 Primary Estimand: Treatment-Regimen Estimand I and Part 2 Supplementary Estimand: Treatment-Regimen Estimand II

- Treatment regimen under evaluation will be the randomised treatment (with a dose escalation of survodutide/placebo during the first 24 weeks after randomisation).

- Target population: The treatment effect will be estimated for trial participants with biopsy confirmed MASH, fibrosis stage F2 and F3, with/without T2DM.

- Endpoint: Time to first occurrence of any of components of the composite endpoint consisting of:
  - Progression to cirrhosis (defined as histological fibrosis score CRN F4),
  - All-cause mortality
  - Liver transplant
  - Hepatic decompensation event(s) (including ascites needing treatment, hepatic encephalopathy, variceal bleeding)
  - Worsening of Model for End-stage Liver Disease (MELD) score to ≥15
  - Progression to Clinically significant portal hypertension (CSPH), defined as high-risk GOVs confirmed in UGE

- Population level summary: Hazard ratio of survodutide vs. placebo for the time to event endpoint above

- Intercurrent events and corresponding strategies are listed in Table 18:

Table 18 Handling of intercurrent events for Part 2 Estimand

Intercurrent event (ICE)	**Primary estimand: "Treatment-Regimen" Estimand I**	**Supplementary estimand: "Treatment-Regimen" Estimand II**
Premature treatment discontinuation	Include all available data ("Treatment policy" strategy)	Include all available data ("Treatment policy" strategy)
Change in background medication	Include all available data ("Treatment policy" strategy)	Include all available data ("Treatment policy" strategy)
Use of restricted medication	Include all available data ("Treatment policy" strategy)	("Composite" strategy) Results in having an event for the time to event endpoint

Treatment-Regimen Estimand I of Part 1 will also be used for addressing secondary objectives of both Part 1 and Part 2 with binary endpoints; Treatment-Regimen Estimand I of Part 2 will also be used for addressing secondary objectives of Part 2 with time-to-event endpoints; Treatment-Regimen Estimand III will be used for addressing secondary objectives of both Part 1 and Part 2 with continuous endpoints. Handling of intercurrent events for Treatment-Regimen Estimand III are listed in Table 19. Treatment-Regimen Estimand IV will be used for addressing secondary objectives of Part 2 with recurrent event endpoint; Handling of intercurrent events for Treatment-Regimen Estimand IV are listed in Table 20.

Table 19 Handling of intercurrent events for Treatment-Regimen Estimand III

Intercurrent event (ICE)	"Treatment-Regimen" Estimand III
Premature treatment discontinuation	Include all available data ("Treatment policy" strategy)
Change in background medication	Include all available data ("Treatment policy" strategy)
Use of restricted medication	Include all available data ("Treatment policy" strategy)
Hepatic decompensation event	Include all available data ("Treatment policy" strategy)
Liver transplant	Include all available data ("Treatment policy" strategy)
Death from any cause	Include data prior to death ("Hypothetical" strategy)

Table 20 Handling of intercurrent events for Treatment-Regimen Estimand IV

Intercurrent event (ICE)	"Treatment-Regimen" Estimand IV
Premature treatment discontinuation	Include all available data ("Treatment policy" strategy)
Change in background medication	Include all available data ("Treatment policy" strategy)
Use of restricted medication	("Composite" strategy) Results in having an event for the recurrent event endpoint
Hepatic decompensation event	("Composite" strategy) Results in having an event for the recurrent event endpoint
Liver transplant	("Composite" strategy) Results in having an event for the recurrent event endpoint
Death from any cause	("Composite" strategy) Results in having an event for the recurrent event endpoint

7.2.3 Primary objective analyses

7.2.3.1 Main analyses

Primary endpoints are listed in Section 2.1.2. Primary analyses relative to the Estimands as defined above for Part 1:

Comparisons between treatment groups regarding the primary binary endpoints will be performed using a logistic regression adjusting fixed categorical effects of treatment, region, fibrosis stage and presence of T2DM at baseline. The likelihood-ratio test will be used to test for difference between treatments. Adjusted odds ratios together with 95% confidence intervals will be used to quantify the effect of treatment, comparing survodutide 6.0 mg to placebo as the reference. Missing data will be imputed using multiple imputation with full conditional specification approach by treatment, including baseline NAS score, fibrosis stage, ELF, and ProC3, and available post-baseline values of ELF and ProC3, as appropriate, in the imputation model.

Primary analyses relative to the Estimands as defined above for Part 2:

- Observation period: Each trial participant will be observed from randomisation until EoS
- Time-to-event: Time to first event will be derived as the time from randomisation to first occurrence of an event
- Time-to-censoring: Each trial participant without event will be censored either at the last day the participant was known to be free of the event irrespective of early treatment discontinuation, or at the end of the observation period, whichever comes first.

The primary endpoint of time to first occurrence of any of the components of the composite endpoint will be analysed using a Cox regression model including treatment, region, fibrosis stage, and presence of T2DM at baseline. Adjusted hazard ratio together with 95% confidence intervals will be used to quantify the effect of treatment, comparing survodutide 6.0 mg to placebo as the reference.

The time to the event of interest will be computed as (event date-randomisation date) + 1. All events observed after randomisation until individual day of trial completion will be included in the analysis.

Trial participants who do not have an event during the trial period will be censored at the individual day of trial completion or the last day that the trial participant was known to be free of the event, whichever is earlier. The time to censoring will be calculated as (individual day of trial completion or the last day known to be free of the event – randomisation date) + 1. For trial participants who have more than one primary endpoint event during the trial, the time to the first occurrence of the primary endpoint event will be considered for the primary analysis. Only the adjudicated and confirmed events will be used for the primary analysis.

In both parts, the statistical analyses will be based on the TS. Treatment groups will be compared as randomised.

7.2.3.2 Sensitivity Analyses

For the primary endpoints in Part 1, a sensitivity analysis will be performed to impute the participants without Week 52 biopsy data as non-responder. More details for sensitivity analyses will be specified in TSAP.

7.2.3.3 Subgroup Analyses

Subgroup analyses for all primary endpoints will include country, region, sex, BMI, age, the presence of T2DM at baseline and severity of fibrosis F2-F3 (determined by liver histology). Additional subgroup analyses will be pre-specified in the TSAP.

7.2.3.4 Supplementary Analyses

Two estimands for Part 1 and Part 2 have been defined in Section 7.2.2, where Treatment-Regimen Estimand II for each part are the supplementary estimands. Another supplementary estimand for Part 2 will be specified that the premature treatment discontinuation will be handled using a composite strategy.

Other supplementary estimands will be specified in the TSAP, if appropriate.

7.2.4 Secondary objective analyses

All secondary endpoints are listed in Section 2.1.3.

In the key secondary endpoints of Part 1 and Part 2, continuous endpoints will be analysed using analysis of covariance (ANCOVA) and evaluated based on Treatment-Regimen Estimand III as described in Section 7.2.2. Missing measurements at Week 52 for Part 1 or at Week 114 for Part 2 will be imputed within each treatment group based on MNAR assumption using “retrieved dropouts”, which is defined as participants who discontinued treatment but have endpoint measurement available. The ANCOVA model will be fitted using imputed data along with completers and retrieved dropouts to compare the treatment effect between survodutide 6.0 mg and placebo adjusting for covariates of region, fibrosis

stage, presence of T2DM at baseline and baseline corresponding measurements. Multiple imputation will be used to handle missing data and the results will be summarised using Rubin's method [R12-2378]. If there are not enough retrieved dropouts to provide a reliable imputation model, multiple imputation will be based on "follow the reference" strategy using the placebo arm.

In the key secondary endpoints of Part 1 and Part 2, binary endpoints will be analysed using similar logistic regression model as for the primary endpoints of Part 1 and evaluated based on Treatment-Regimen Estimand I of Part 1 as described in Section 7.2.3. In the key secondary endpoints of Part 2, recurrent event endpoint will be analysed using a semi-parametric regression model (LWYY model) adjusting for the categorical covariates region, fibrosis stage and presence of T2DM at baseline and evaluated based on Treatment-Regimen Estimand IV as described in Section 7.2.2 [P10-10083]. Hazard ratio together with 95% confidence intervals will be used to quantify the effect of treatment, comparing survodutide 6.0 mg to placebo as the reference.

In the key secondary endpoints of Part 2, time-to-event endpoint will be analysed using similar approach as the primary endpoint of Part 2.

In addition, other supplementary Estimands relative to key secondary endpoints in both Part 1 and Part 2 will be specified in the TSAP, if appropriate.

Other secondary endpoints will not be tested in a confirmatory way, details of the analyses will be provided in the TSAP.

7.2.5 Further objective analyses

Analyses as described above in Section 7.2.4 will be performed for further efficacy endpoints if appropriate. Details of analysis for further endpoints will be specified in TSAP.

A population PK analysis for survodutide will be performed using available plasma concentration data of survodutide. The trough plasma concentrations will be used to refine an already existing population PK model. The model may be supported by data and/or prior information from other clinical studies with survodutide. In a second step, exposure predictions based on the established population PK model will be used to characterise potential exposure-response relationships for selected efficacy and/or safety endpoints using exposure-response modelling. The population PK and PK-PD analyses are planned to be subject to a separate analysis plan(s) and report(s), and are not planned be a part of the CTR.

Immunogenicity of survodutide will be assessed via a tiered approach. Available serum samples will be analysed for the presence of ADAs (including cross-reactive ADAs to GLP-1 and glucagon) and NAbs (including cross-neutralising NAbs to GLP-1 and glucagon). Additionally, ad-hoc blood samples for ADA, NAb, and serum concentration of survodutide will be collected and assessed upon observation of severe or systemic hypersensitivity. The impact of the presence of ADAs on PK, clinical efficacy, and safety will be evaluated.

7.2.6 Safety analyses

Safety analysis will include all data through safety data collection and follow-up.

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard Boehringer Ingelheim summary tables and listings will be produced. All AEs with an onset between start of treatment and end of the REP, a period of 28 days after the last dose of trial IMP, will be assigned to the on-treatment period for evaluation.

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

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

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

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

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

Further details will be provided in the TSAP.

7.2.7 Other Analyses

Details on other analyses will be provided in the TSAP.

7.2.8 Interim Analyses

An interim analysis is planned at the end of Part 1, i.e. the first 700 participants have experienced 52 weeks of treatment. The results will potentially be used for submission of marketing application. Access to comparative interim results will be limited to individuals who will be involved in the preparation work of the submission. Logistical aspects related to preserving the blind will be described in the Logistics and Access Plan.

The interim analysis will be performed regarding the endpoints of Part 1 as described in Section 2. The analysis methods for the endpoints of Part 1 are mentioned in Section 7.2.3, 7.2.4, and 7.2.5. In order to control the family-wise error rate at the overall two-sided significance level α of 5% in the strong sense, for Part 1, with an overall significance level of 0.01 (two-sided) and for Part 2, with an overall significance level of alpha (two-sided, an α of 0.04 + certain alpha propagated from the Part 1 analysis level, see Table 16 for values of alpha).

The interim analysis will also involve PK and immunogenicity analyses described in Section 5.3.1 and 5.6.1. Further details will be provided in the TSAP.

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

7.3 HANDLING OF MISSING DATA

For trial participants who discontinue the IMP prematurely, all efforts will be made to follow participants for vital status and for any other endpoints including the primary endpoint until EOS.

For primary endpoints in Part 1, the missing data will be imputed using multiple imputation with full conditional specification approach as described in Section 7.2.3. Details on multiple imputation and methods for handling missing data for secondary and further endpoints will be provided in TSAP.

7.4 RANDOMISATION

Boehringer Ingelheim will arrange for the randomisation and the packaging and labelling of trial IMP. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. Specific parameters used for the creation of the randomisation schedule (e.g. block size or biasing coin probabilities will be documented in the CTR). Access to the codes will be controlled and documented.

Trial participants will be randomised in blocks with an allocation ratio 2:1 to one of the following target maintenance period treatments: survodutide 6.0 mg once weekly and placebo once weekly. Randomisation will be performed at the start of dose escalation period at Visit 2.

Randomisation will be stratified according to the following categories:

- Region (Europe/North America/Latin and South America/APAC/South Africa and Middle East)
- Severity of fibrosis (F2/F3)
- Presence of T2DM at baseline (yes/no)
- Participation in MRI-substudy (yes/no)

In addition, an adjustable screening cap will be implemented in the IRT system to ensure that enough trial participants with liver fibrosis stage F3 and also enough male/female trial participants are enrolled and randomised.

- Cap for number of trial participants participating in MRI-substudy: 200
- Cap for number of trial participants with liver fibrosis stage F2: 40% of all randomised trial participants

- Cap for number of male trial participants: 65% of all randomised trial participants for both Part 1 and Part 2 independently

- Cap for number of female trial participants: 65% of all randomised trial participants for both Part 1 and Part 2 independently

7.5 DETERMINATION OF SAMPLE SIZE

For the primary endpoints in Part 1, assuming response rate of 10% and 40% in resolution of MASH without worsening of fibrosis for placebo and survodutide, and response rate of 20% and 35% in at least 1-point improvement in fibrosis without worsening of MASH for placebo and survodutide respectively [data from 1404-0043 trial], a sample size of approximate 700 (675) with 2:1 allocation ratio will provide >90% power for endpoint 'Resolution of MASH without worsening of fibrosis' and approximately 90% power for endpoint 'At least a 1-point improvement in fibrosis stage with no worsening of MASH' at the significance level of 0.005, two-sided, considering an overall 0.01 alpha at Part 1.

For the primary endpoint in Part 2, assuming a yearly placebo event rate of 7% [R21-4177], HR of 0.7, 36 months of recruitment and around 48 months of follow up time, a sample size of 1452 with 2:1 allocation ratio will provide around 394 events and approximately 90% power at the significance level of 0.04 two-sided at the final analysis. As progression to cirrhosis based on biopsy is part of the composite, and participants that might prematurely discontinue from trial medication and will not have biopsy anymore, we add a drop-out rate of 20% for active and 10% for placebo every 24 months, resulting in an overall sample size for the final analysis of 1800 participants.

The event rate and recruitment progress will be assessed in a blinded manner during recruitment. If the accumulated blinded data suggest a slower accrual of primary outcome events over calendar time than originally projected, then the number of randomised participants may be increased. Enrolment of these additional trial participants will be covered by a further protocol amendment. Recruitment period may also be extended accordingly. The number of confirmed primary outcome events will not be affected by this consideration.

Based on the above considerations for both parts of the trial, it is planned to enrol 1800 participants for the trial.

Sample size was calculated using the R-package "rpact" in R software (version 4.2.2).

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

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

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

The investigator will inform the sponsor or delegate immediately of any urgent safety measures taken to protect the trial participants 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 CTR.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

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

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

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

The investigator or 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 be necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

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

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial participant protection and reliability of the results, as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH GCP E6, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management, and other processes focusing on areas of greatest risk. Continuous risk review and assessment may lead to adjustments in trial conduct, trial design, or monitoring approaches.

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

8.3 RECORDS

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

8.3.1 Source documents

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

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial participant. 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 trial participant may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the trial participant, documented in their medical records, would be acceptable.

Copies of source documents necessary for adjudication of events and ECG central reading will be provided to the corresponding vendors. Before sending or uploading those copies, the investigator must ensure that all trial participant identifiers (e.g. trial participant's name, initials, address, phone number, and social security number) have properly been removed or redacted from any copy of the trial participants' source documents.

Additional medical information will be sought for events requiring adjudication, additional data collection, SAEs and AESIs, and may include the collection of records held by the study site, other hospitals, or the trial participant's own doctors, or from electronic sources and registries. The electronic version of the ECG is regarded as source data. Dated and signed printouts will be stored in the trial participant's medical file. For the eDiary and eCOA data, the electronic record is the source document (or paper forms if used due to technical issues or participant refusal of electronic version).

If the trial participant is not compliant with the protocol, any corrective action e.g. re-training must be documented in the trial participant's medical record.

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

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

8.3.2 Direct access to source data and documents

The investigator/institution will allow site trial-related monitoring, audits, IRB/IEC review, and regulatory inspections. Direct access must be provided to the eCRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which

must always be available for review by the CRA, auditor, and regulatory inspector (e.g. FDA). They may review all eCRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor or delegate will also monitor compliance with the protocol and GCP.

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

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

Boehringer Ingelheim is responsible for fulfilling their legal and regulatory reporting obligation in accordance with regulatory requirements.

Exemptions from expedited reporting are described in Section 5.2.6.2.4.

8.5 STATEMENT OF CONFIDENTIALITY AND TRIAL PARTICIPANT PRIVACY

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred
- The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent
- The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, appropriate IRB/IEC members, and inspectors from regulatory authorities
- The sponsor has implemented privacy and security controls designed to help protect participants' personal data, including information security controls, firewalls, incident detection, and secure transfer measures
- In the event of an accidental or unlawful destruction, loss, alteration, unauthorised disclosure, or access to personal data ("breach"), the sponsor has implemented

procedures and measures to promptly address and mitigate any risk to the participant. In the event of a breach, the sponsor will notify the appropriate regulatory authorities and/or the participant(s) in accordance with applicable data protection law

- The contract between sponsor and trial sites specifies the responsibilities of the parties related to data protection, including the handling of data security breaches and respective communication and cooperation of the parties
- Information technology systems used to collect, process, and store trial-related data are secured by technical and organisational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorised disclosure or access

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

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

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

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last trial participant in the whole trial ("Last Participant Completed").The "**Last Participant Last Treatment"** (LPLT) date is defined as the date on which the last trial participant in the whole trial is administered the last dose of IMP (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the IMP 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 an HA request.

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

The IEC/CA 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 trial participants have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim.

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 Steering Committee consisting of independent experts and sponsor representatives forming Executive Committee and National Coordinators from all participating countries will be established to support the sponsor in designing the trial and successful execution. A separate Charter will describe the tasks and responsibilities of the Committee.

A DMC will be established. Members of the DMC are independent of BI, they are physicians experienced in the treatment of the disease under investigation and a statistician. The DMC will assess the progress of the trial, including an unblinded safety assessment at specified intervals. The DMC will receive urgent significant safety concerns for immediate evaluation. While DMC members are unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DMC meetings will be held at specified intervals. The DMC will recommend to the sponsor continuation, modification, or termination of the trial as detailed in the DMC charter. DMC recommendations as well as the final Boehringer Ingelheim decision will be reported to the appropriate RAs/HAs, IRBs/IECs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a DMC Charter.

An independent (external) and blinded CEC will be established for prospective adjudication of all clinical liver outcome events, cardiovascular (5P-MACE) events and safety events defined for adjudication (list of all events in Section 5.2.6.1.7). The events for adjudication details on the composition of the committee, its procedures and interactions are defined in the CEC Charter.

A blinded PRC will provide independent review of all liver biopsy samples that were collected during the trial according to the Pathology Review Charter. The analysis of the results will be reported in the respective CTRs and subsequent submission dossiers where applicable.

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

The trial will be managed by a CRO based on a contract which specifies the delegated responsibilities and duties. Boehringer Ingelheim has appointed a Clinical Trial Leader responsible for coordinating all required activities, in order to:

- Oversee and manage the trial in accordance with applicable regulations and SOPs
- Direct the clinical trial team and oversee the CRO in the preparation, conduct, and reporting of the trial
- Ensure appropriate training

The CRO will perform sites selection, start up, project management, clinical field monitoring, medical monitoring, and reporting trial progress and findings to sponsor.

Clinical Trial Supplies (IMP), Safety, Regulatory (CTA submission in US and China), Data Management and Statistical Evaluation will be done by Boehringer Ingelheim according to BI SOPs.

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

Central laboratory services (for laboratory parameters), central pathology laboratory services (for liver biopsy and histology reading), central imaging services (for MRI-PDFF, MRE, CT1, FibroScan® and UGE), a central ECG service, telemedicine and eCOA vendor (PROs and eDiary) and an IRT vendor will be used in this trial. Details will be provided in the IRT Quick Reference Document, Central and Pathology Laboratory Manuals, Imaging Manuals and specific instructions for the use of myMediData platform, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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10. APPENDICES

10.1 TRIAL PARTICIPANT FEEDBACK

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

10.2 MANAGEMENT OF GASTROINTESTINAL SYMPTOMS

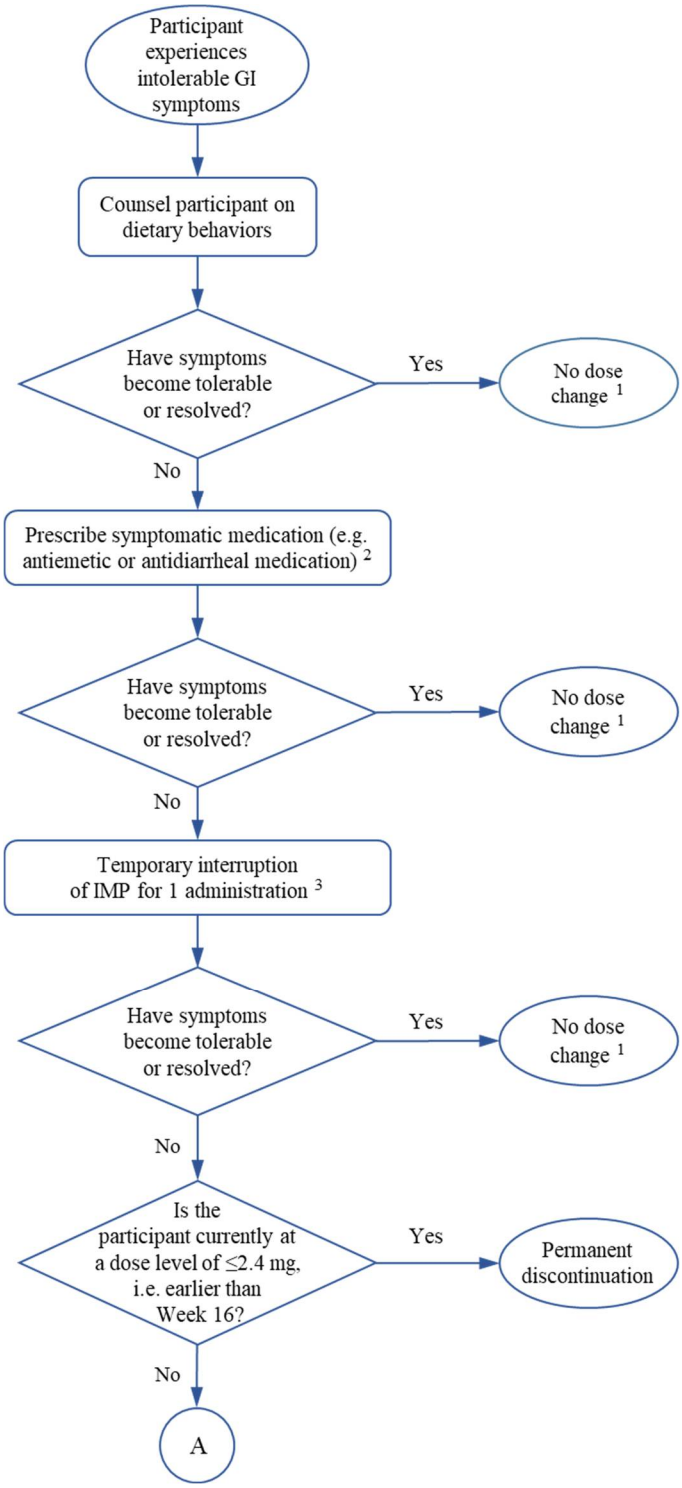

Figure 2 Management of gastrointestinal symptoms

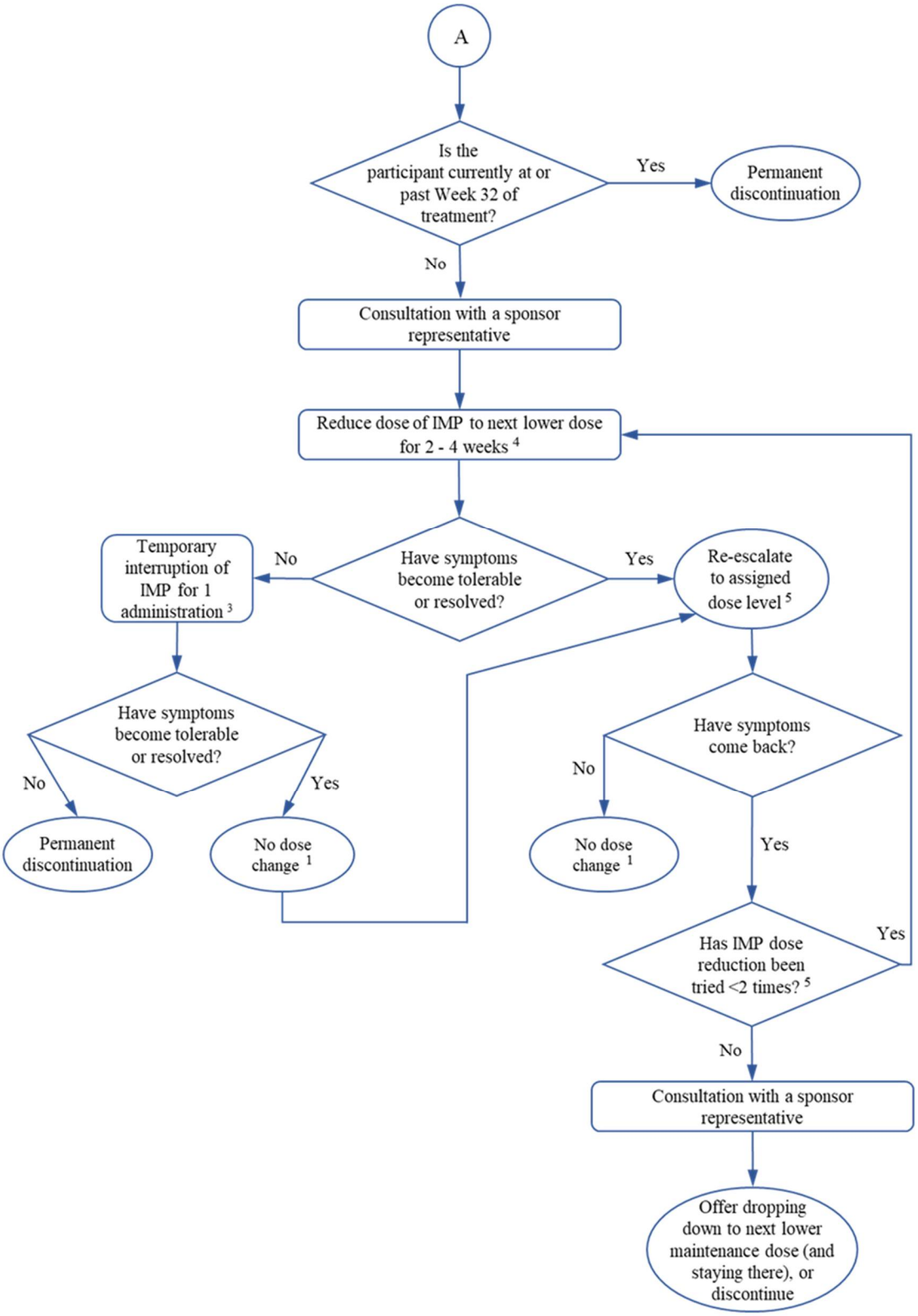

Figure 2 (cont'd) Management of gastrointestinal symptoms

1 Continue with dose escalation if in the escalation period or continue in the same dose if in the maintenance period.

2 Symptomatic medications (e.g. antiemetic or antidiarrheal medication) can be prescribed at any time point during escalation and maintenance period as deemed necessary by investigator.

3 A temporary interruption of a second administration of the IMP may be allowed at the investigator's discretion, i.e. 2 consecutive IMP administrations are skipped.

4 Alternatively to reducing the dose, a scheduled up-titration can be delayed by 2 – 4 weeks to support development of GI tolerability. The overall delay to the dose escalation must not exceed 8 weeks.
Continuing onto maintenance therapy at a lower dose than assigned at randomisation is only to be allowed if the trial participant would otherwise discontinue the IMP and if considered safe to continue the IMP, as per the investigator's discretion. Between Weeks 16 and 32 of treatment, for participants who are not able to attain or stay at the maintenance dose of 6.0 mg, a dose reduction from a non-tolerated dose to the next lower dose is possible after consultation with a sponsor representative. If, in conjunction with GI tolerability issues, 4.8 mg could be reached, this dose will be kept for the maintenance phase. For participants who are not able to attain or stay at the dose of 4.8 mg, a dose reduction to 3.6 mg would be possible in exceptional circumstances after consultation with a sponsor representative. For participants who are not able to attain or stay at the dose of 3.6 mg, a dose reduction to 2.4 mg would be possible in exceptional circumstances after consultation with a sponsor representative. A dose reduction below 2.4 mg once per week is not allowed. A participant at the 2.4 mg dose or lower who requires a dose reduction will be discontinued from treatment. Thorough documentation of all measures taken, including outcomes of the discussion with sponsor representative, is required in a specific eCRF page in case of a dose reduction or delay in up-titration. For any changes in dose outside of the regularly scheduled steps, IMP of the new dose is dispensed during an unscheduled visit, and the participant must return all kits of the old dose.

5 As per investigator's discretion, it is recommended that the trial participant makes up to 2 attempts to re-escalate per dose escalation scheme to his/her assigned dose level. In such cases, the entire dose escalation period should not be longer than 32 weeks.

10.3 CONTRACEPTION METHODS ALLOWED IN THIS TRIAL

Birth control methods (oral[1] and non-oral[2] contraceptives) which may be considered as highly effective and are allowed in this trial:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - Oral[3]
  - Intravaginal
  - Transdermal (only for trial participants weighing less than 90 kg or 198 pounds)
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral[3]
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner[4]
- Sexual abstinence[5]

1 Oral contraceptives include combined (oestrogen and progestogen containing) or progesterone-only hormonal contraceptive pills associated with inhibition of ovulation.
2 Non-oral contraceptives include combined hormonal contraception intravaginal or transdermal, progestogen-only hormonal contraception injectable or implantable, IUD, IUS, bilateral tubal occlusion, vasectomised partner, and sexual abstinence.
3 Women who use oral contraceptives at screening should be advised to change to non-oral contraceptives at least 7 days prior to first dose of IMP or to add a barrier method of contraception during entire treatment period with IMP and 28 days thereafter (preferably male condom). Women who initiate oral contraceptives at or after screening should be advised to continue using the previously applied contraception method for at least 7 days and use a barrier method of contraception in addition to the oral contraceptives during entire treatment period with IMP and 28 days thereafter (preferably male condom).
4 Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and there is documented absence of sperm.
5 Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the trial participant. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to IMP; and withdrawal are not acceptable.

10.4 CLINICAL STAGING OF OBESITY

Edmonton obesity staging system

Stage	Short description
Stage 0	No apparent risk factors
Stage 1	**Subclinical risk factors:** Presence of obesity-related subclinical risk factors (e.g. borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.), mild physical symptoms (e.g. dyspnoea on moderate exertion, occasional aches and pains, fatigue, etc.), mild psychopathology, mild functional limitations and/or mild impairment of well being
Stage 2	**Established complications:** Presence of established obesity-related chronic disease (e.g. hypertension, T2DM, sleep apnoea, osteoarthritis, reflux disease, polycystic ovary syndrome, anxiety disorder, etc.), moderate limitations in activities of daily living and/or well being
Stage 3	**End organ damage:** Presence of end organ damage such as MI, HF, diabetic complications, incapacitating osteoarthritis, significant psychopathology, significant functional limitations and/or impairment of well being
Stage 4	**End stage:** Having disabilities from obesity-related chronic diseases, severe disabling psychopathology, severe functional limitations and/or severe impairment of well being

10.5 TIME SCHEDULE FOR PHARMACOKINETIC (PK) AND ANTI-DRUG ANTIBODY (ADA) / NEUTRALISING ANTIBODY (NAB) BLOOD SAMPLING

Table 21 Time Schedule for PK and ADA/NAb Sampling

Visit	Day	Time Point [hh:min]	PK Sampling	ADA/NAb Sampling
2	1 (+/-0)	- 00:30 Within 30 min before IMP administration	X	X
4	29 (+/-3)		X	X
7	85 (+/-3)		X	X
10	169 (+/-3)		X	X
12	253 (+/-7)		X	X
15	365 (+/-14)		X	X
18	463 (+/-7)		X	X
V18 Rep	Every 24 weeks until EOT (+/-7)		X	X
EoT/ETD	(+7) for EoT	168:00 Approximately 168 h (1 week) after last IMP administration	X	X
Follow Up	(+7)	672:00 Approximately 672 h (4 weeks) after last IMP administration	X	X

10.6 MONITORING AND MANAGEMENT OF POSSIBLE HEPATOCELLULAR DILI IN CIRRHOTIC TRIAL PARTICIPANTS

Table 22 Algorithm for monitoring and management of possible hepatocellular DILI in cirrhotic trial participants with normal or elevated baseline liver tests

Baseline evaluation	**Treatment emergent ALT, AST**	**Treatment emergent AST:ALT**	**Treatment emergent TBL, DB, ALP**	**Treatment emergent INR**	**Decompensating events (VH, HE, ascites)**	**Action**
Normal baseline <1.5x ULN of ALT, AST (with normal TBL, DB, ALP, INR)	ALT or AST ≥2x baseline[1]	Rise in ALT out of proportion to AST, resulting in decreased ratio	Any increase ≥2x baseline TBL, ALP (with ≥50% DB) even without elevations of ALT	Any increase	None	Any of these changes should trigger increased monitoring with repeat testing within 1 week
	ALT or AST ≥2x baseline[1] or 3x ULN (whichever occurs first)		TBL ≥2x ULN ALP >2x baseline or 3x ULN	INR ≥1.5	None	Combination of changes in -AST or ALT or ALP and -TBL or INR: stop IMP and proceed with causality assessment[2]
	ALT or AST ≥5x ULN		No change	No change	None	Stop IMP and proceed with causality assessment[2]
	No change		ALP ≥3x ULN and DB ≥1 mg/dL over baseline[3]	No change	None	Stop IMP and proceed with causality assessment[2]
	Change or no change		Change or no change	Change or no change	Development of VH, HE, or ascites	Stop IMP and proceed with causality assessment[2]

Table 22 (cont'd) Algorithm for monitoring and management of possible hepatocellular DILI in cirrhotic trial participants with normal or elevated baseline liver tests

Baseline evaluation	**Treatment emergent ALT, AST**	**Treatment emergent AST:ALT**	**Treatment emergent TBL, DB, ALP**	**Treatment emergent INR**	**Decompensating events (VH, HE, ascites)**	**Action**
Abnormal baseline	ALT or AST ≥2x baseline[1] or 5x ULN (whichever occurs first)		TBL ≥2x ULN if normal at baseline (with ≥50% DB) TBL ≥1.5x ULN if abnormal at baseline, or DB ≥1 mg/dL over baseline ALP >2x baseline or 5x ULN	INR ≥1.5 or increased by 0.2 if baseline INR ≥1.5	None	Combination of changes in -AST or ALT or ALP and -TBL or INR: stop IMP and proceed with causality assessment[2]
Abnormal baseline	ALT or AST ≥3x baseline[1] or 8x ULN (whichever occurs first)		No change	No change	None	Stop IMP and proceed with causality assessment[2]
	No change		ALP ≥2x baseline and DB ≥1 mg/dL over baseline	No change	None	Stop IMP and proceed with causality assessment[2]
	Change or no change		Change or no change	Change or no change	Development of VH, HE, or ascites	Stop IMP and proceed with causality assessment[2]

1 Provided the values are also >ULN

2 Causality assessment should include obtaining a PK sample at time of potential DILI event for later analysis of excessive exposure.

3 Without an alternative aetiology

Source: [P21-10299]

10.7 CALCULATION OF SCORES AND PARAMETERS

NAFLD fibrosis score (units on a scale) [R17-3207]

Calculated as:
$-1.675 + 0.037 \cdot$ age [years] $+ 0.094 \cdot$ BMI [kg/m^2] $+ 1.13 \cdot$ (if T2DM) $+ 0.99 \cdot$ (AST [U/L]/ ALT [U/L]) $- 0.013 \cdot$ platelets [$\cdot 10^9$/L] $- 0.66 \cdot$ albumin [g/dL]

FIB-4 score (units on a scale) [R17-3206]

Calculated as:
(age [years] $\cdot$ AST [U/L])/(platelets [$\cdot 10^9$/L] $\cdot \sqrt{\text{ALT[U/L]}}$)

APRI score (units on a scale) [R17-3205]

Based on the ULN for AST, AST_{ULN}, provided by the central laboratory by sex and age group calculated as:
((AST [U/L]/AST_{ULN} [U/L])/platelets [$\cdot 10^9$/L]) $\cdot$ 100

HOMA-IR (units on a scale)

For FPG assessed in [mg/dL] calculated as:
(FPI [mIU/L] $\cdot$ FPG [mg/dL])/405

For FPG assessed in [mmol/L] calculated as:
(FPI [mIU/L] $\cdot$ FPG [mmol/L])/22.5

HOMA-β (percentage of normal beta cell function)

For FPG assessed in [mg/dL] calculated as:
(360 $\cdot$ FPI [mIU/L])/(FPG [mg/dL] - 63)

For FPG assessed in [mmol/L] calculated as:
(20 $\cdot$ FPI [mIU/L])/(FPG [mmol/L] - 3.5)

CPI (dimensionless ratio)
For FPG assessed in [mg/dL] calculated as:
fasting C-peptide [ng/mL]/(FPG [mg/dL] $\cdot$ 100

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

This is the original protocol.

APPROVAL / SIGNATURE PAGE

Document Number: c44205431 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-1

Title: A randomised, double-blind, placebo-controlled, multicentre, Phase III trial evaluating long-term efficacy and safety of survodutide weekly injections in adult participants with non-cirrhotic non-alcoholic steatohepatitis/metabolic associated steatohepatitis (NASH/MASH) and (F2) - (F3) stage of liver fibrosis

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval	Borowska,Dr.,Malgorzata_Luiza	29 May 2024 09:10 CEST
Author-Trial Statistician	Li,Xiyan	29 May 2024 10:36 CEST
Author-Clinical Trial Leader	Gomez,Lourdes	29 May 2024 10:44 CEST
Verification-Paper Signature Completion	Gomez,Lourdes	29 May 2024 10:49 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed