Official Protocol Title:	A Phase 2a, Randomized, Active-Comparator-Controlled, Open-Label Study to Evaluate the Efficacy and Safety of Efinopegdutide (MK-6024) in Individuals With Nonalcoholic Fatty Liver Disease.
NCT number:	NCT04944992
Document Date:	26-Aug-2021

Title Page

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Protocol Title: A Phase 2a, Randomized, Active-Comparator-Controlled, Open-Label Study to Evaluate the Efficacy and Safety of Efinopegdutide (MK-6024) in Individuals With Nonalcoholic Fatty Liver Disease.

Protocol Number: 001-02

Compound Number: MK-6024

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter called the Sponsor or MSD)

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

IND	153067
EudraCT	2020-005136-30

Approval Date: 26 August 2021

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 02	26-AUG-2021	This amendment was created primarily to add an IA.
Amendment 01	17-FEB-2021	This amendment was created primarily to add the Sponsor's siDMC to supplement the safety data monitoring conducted in this study. Additional changes included corrections and clarifications to the protocol language.
Original Protocol	07-DEC-2020	Not applicable.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 02

Overall Rationale for the Amendments:

This amendment was created primarily to add an IA.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
Primary Change		
4.1 Overall Design 4.2 Scientific Rationale for Study Design 4.4.1 Clinical Criteria for Early Study Termination 9.1 Statistical Analysis Plan Summary 9.7 Interim Analyses	Incorporation of an IA.	To inform on administrative decisions regarding other aspects of the efinopegdutide program. In addition, to support potential termination of the study for futility based on poor LFC (MRI-PDFF) response and/or safety and tolerability issues.

Section # and Name	Description of Change	Brief Rationale
Additional Changes		
1.1 Synopsis 1.2 Schema CCI [redacted] 4.1 Overall Design 4.2 Scientific Rationale for Study Design CCI [redacted] 8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 8.12.6 Post-Treatment Follow-up Visit	Revised the following: • Changed timing of V13 (post-treatment follow-up) from 5 weeks after *the last visit of the treatment period* (V12 /Week 24) to 5 weeks after *the last dose of study intervention*. • Reduced duration of participant participation from 33 to 32 weeks. • Reduced overall estimated study duration from 73 to 72 weeks.	Based on the half-life of the study intervention, post-treatment follow-up (V13) should occur 5 weeks after the last dose of study intervention. Due to weekly dosing, the last dose of study intervention occurs at Week 23; therefore, V13 should be 5 weeks after Week 23 instead of 5 weeks after V12 (Week 24). Since the protocol was amended to clarify V13 should be 5 weeks after the last dose of study intervention, the duration between V12 and V13, and thereby the overall estimated study duration, was decreased by 1 week.
1.1 Synopsis 1.2 Schema 3 Hypotheses, Objectives, and Endpoints 4.1 Overall Design 5 Study Population 5.1 Inclusion Criteria CCI [redacted]	Added South Korea-specific age requirements.	Clarification

Section # and Name	Description of Change	Brief Rationale
1.2 Schema CCI [redacted] 4.1 Overall Design 8.1.10 Discontinuation and Withdrawal 8.12.5 Discontinued Participants Continuing to be Monitored in the Study	Removed reference to V12 as the EOT visit and added a DC visit for participants who prematurely discontinue study intervention.	These changes are to ensure participants who prematurely discontinue study intervention can be monitored throughout the protocol-specified treatment period (ie, 24 weeks) and potentially minimize the risk of having missing data.
CCI [redacted]		

Section # and Name	Description of Change	Brief Rationale
2 Introduction 2.2.3 Information on Other Study-related Therapy 2.3 Benefit/Risk Assessment 4.2.2 Rationale for the Use of Active Comparator 4.3.3 Rationale for Dose Interval and Study Design	Added available semaglutide development program information as well as updated reference documents.	Revised to align with newly available information.
4.3.1 Starting Dose for This Study 6.1 Study Interventions Administered	Revised the dosage levels of semaglutide per injection from *0.1875 mL* to *0.19 mL*, from *0.375 mL* to *0.37 mL*, and from *0.75 mL* to *0.74 mL*.	Revised to match the information in the semaglutide Summary of Product Characteristics.
4.4.1 Clinical Criteria for Early Study Termination 9.7 Interim Analyses 10.1.4.2 Executive Oversight Committee 10.1.4.3 Internal Data Monitoring Committee	Clarified that the EOC is comprised of senior management in the TA (Diabetes, Endocrinology, and Metabolism) with programmatic oversight, who are not directly associated with study conduct.	Clarification

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Updated Inclusion Criterion #1 to allow for historical MRI-PDFF imaging of the liver if performed ≤2 months before V1/Screening and if obtained from the same study-qualified imaging center(s) and imaged per the Site Imaging Manual for this study to be considered as potentially acceptable to determine LFC % as part of eligibility after consultation with the Sponsor.	To potentially reduce participant burden.
5.2 Exclusion Criteria 6.5 Concomitant Therapy	Updated Exclusion Criterion #36 to remove restrictions on vitamin E dose, and to only exclude participants on vitamin E if their dose is >100 IU/day and has not been stable for at least 3 months before V1/Screening. Removed high dose vitamin E (>400 IU/day) from the list of prohibited medications.	Since use of high dose vitamin E (>400 IU/day) is common in the target study population, these changes will allow participants on high dose vitamin E to participate in the study while the dose stability requirement will mitigate the potential confounding factor caused by high dose vitamin E.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Clarified Exclusion Criterion #41: • Participation in an interventional clinical study is defined as having received an investigational compound or used an investigational device. • Participants enrolled in COVID-19 vaccine trials may be included in this study and will be reviewed on a case-by-case basis for approval by the Sponsor.	Clarification
5.2 Exclusion Criteria	Revised the platelet count study limit for exclusion in Table 1 Laboratory Exclusion Criteria from $<150 \times 10^9/L$ to $<140 \times 10^9/L$.	To align with the central laboratory lower limit of normal.
5.2 Exclusion Criteria	Removed the reference to the operations/laboratory manual from footnote *b* in Table 1 Laboratory Exclusion Criteria.	Clarification
7.1 Discontinuation of Study Intervention	Corrected Note (1) under the tachycardia bullet to state that participants with a minimally symptomatic event that is not sustained or recurrent, and who do *not* meet other discontinuation criteria may continue in the study.	Typographical error

Section # and Name	Description of Change	Brief Rationale
8.1.9.1 Timing of Dose Administration	Revised the length of time between which 2 doses of study intervention may be administered from *at least 2 days (>48 hours)* to *at least 48 hours*.	Clarification
8.2.1 Liver Fat Content by Magnetic Resonance Imaging-Estimated Proton Density Fat Fraction	Clarified that clinically significant findings should be reported by the investigator and recorded appropriately.	Clarification
8.5 Treatment of Overdose	Revised the definition of overdose from any dose higher than the prescribed maximum dose of efinopegdutide or semaglutide as defined in the protocol to any total dose within 48 hours that is higher than the prescribed maximum dose of efinopegdutide or semaglutide as defined in the protocol.	Overdose (Section 8.5) is defined as any dose greater than the maximum dose of study intervention Q1W (10 mg efinopegdutide or 1 mg semaglutide). According to the dosing instructions (Section 8.1.9.1), if a participant misses a dose of study intervention, the missed dose can be administered if noticed within 5 days and then the next dose taken as regularly scheduled. Consequently, a participant could possibly exceed the maximum dose of study intervention allowed per week. Therefore, the additional text clarified that an overdose only occurs if the total dose of study intervention within 48 hours is greater than the maximum dose.
CCI [redacted]		

Section # and Name	Description of Change	Brief Rationale
8.12.5 Discontinued Participants Continuing to be Monitored in the Study	Increased the number of study site visits (from 11 to 12) that should be completed by participants who discontinue early from study intervention.	To enable participants who prematurely discontinue study intervention (unless the participant withdraws consent from any study follow-up) to be monitored for the protocol-specified treatment period (ie, 24 weeks).
CCI [redacted]		
8.12.6 Post-Treatment Follow-up Visit	Changed section heading from *Post-Treatment Period*.	Clarification
9.1 Statistical Analysis Plan Summary 9.6.2 Analysis Methods for Safety Analyses 9.9.2 Safety	Added references for the M&N method.	Clarification
9.7 Interim Analyses CCI [redacted]	CCI [redacted]	

Section # and Name	Description of Change	Brief Rationale
9.7 Interim Analyses	Clarified that the criteria required to trigger the siDMC for events of tachycardia apply only if the events are considered related to study intervention by the investigator.	Clarification
9.11 Compliance (Medication Adherence) 9.12 Extent of Exposure	Revised the basis for evaluation of compliance, adherence, and extent of exposure from days to weeks.	Based on dose administration; compliance, adherence, and extent of exposure are calculated based on weeks rather than days.
CCI [redacted]		

Section # and Name	Description of Change	Brief Rationale
10.11 Appendix 11: Abbreviations	Corrected the expanded term for MRI-PDFF from Magnetic Resonance Imaging-Estimated Proton Density Fat *Fracture* to Magnetic Resonance Imaging-Estimated Proton Density Fat *Fraction*.	Typographical error
Throughout the document	Editorial and formatting changes	Completed for emphasis, clarity, or consistency

Note: Minor edits such as the renumbering of tables or relettering of footnotes are not listed.

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LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2a, Randomized, Active-Comparator-Controlled, Open-Label Study to Evaluate the Efficacy and Safety of Efinopegdutide (MK-6024) in Individuals With Nonalcoholic Fatty Liver Disease.

Short Title: Phase 2a Study of Efinopegdutide (MK-6024) in Individuals With NAFLD

Acronym: Not applicable.

Hypotheses, Objectives, and Endpoints:

In males and females aged 18 to 70 years (in Taiwan, aged 20 to 70 years; in South Korea, aged 19 to 70 years [Appendix 7]) with NAFLD:

Objectives	Endpoints
Primary	
• To evaluate the effect of efinopegdutide versus semaglutide on mean relative reduction from baseline in LFC after 24 weeks. • Hypothesis (H1): Efinopegdutide is superior to semaglutide with respect to mean relative reduction from baseline in LFC after 24 weeks. • Hypothesis (H2): Efinopegdutide is superior to semaglutide by 10% or more with respect to mean relative reduction from baseline in LFC after 24 weeks.	• LFC (%) measured by MRI-PDFF (evaluated by BICR)
• To evaluate the safety and tolerability of efinopegdutide compared with semaglutide.	• AEs • Discontinuation of study intervention due to AEs
Secondary	
• To evaluate the effect of efinopegdutide versus semaglutide on mean absolute reduction from baseline in LFC after 24 weeks.	• LFC (%) measured by MRI-PDFF (evaluated by BICR)

Objectives	Endpoints
• To evaluate the effect of efinopegdutide versus semaglutide on mean percent change from baseline in body weight at 24 weeks.	• Weight (kg)
• To evaluate the effect of efinopegdutide versus semaglutide on change from baseline in fasting lipid levels over 24 weeks.	• Lipid profile: cholesterol (total, non-HDL-C, HDL-C, LDL-C), TG, and apoB

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Treatment of individuals with NAFLD
Population	Males and females aged 18 to 70 years (in Taiwan, aged 20 to 70 years; in South Korea, aged 19 to 70 years [Appendix 7]) with NAFLD and LFC ≥10% by MRI-PDFF
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active-comparator-control
Study Blinding	Unblinded Open-label
Blinding Roles	No Blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 72 weeks from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 130 participants will be randomized.

Intervention Groups and Duration:

<table>
<tr><td>Intervention Groups</td><td>Participants will be randomized in a 1:1 ratio and dosed Q1W.
<table>
<tr><th>Intervention Group Name</th><th>Drug</th><th>Dose Strength</th><th>Dose Frequency</th><th>Route of Admin</th><th>Treatment Period (24 Weeks)</th><th>Use</th></tr>
<tr><td rowspan="3">Group 1</td><td>Efinopegdutide</td><td>2.4 mg</td><td>Q1W</td><td>SC</td><td>V3 up to V7</td><td>Experimental</td></tr>
<tr><td>Efinopegdutide</td><td>5.0 mg</td><td>Q1W</td><td>SC</td><td>V7 up to V8</td><td>Experimental</td></tr>
<tr><td>Efinopegdutide</td><td>10.0 mg</td><td>Q1W</td><td>SC</td><td>V8 up to V12</td><td>Experimental</td></tr>
<tr><td rowspan="3">Group 2</td><td>Semaglutide</td><td>0.25 mg</td><td>Q1W</td><td>SC</td><td>V3 up to V7</td><td>Experimental</td></tr>
<tr><td>Semaglutide</td><td>0.5 mg</td><td>Q1W</td><td>SC</td><td>V7 up to V8</td><td>Experimental</td></tr>
<tr><td>Semaglutide</td><td>1.0 mg</td><td>Q1W</td><td>SC</td><td>V8 up to V12</td><td>Experimental</td></tr>
<tr><td colspan="7">Admin administration; Q1W once every week; SC subcutaneous; V visit.</td></tr>
</table>
Current or former names or aliases for the study intervention are as follows: HM12525A, JNJ-64565111, MK-6024, and efinopegdutide.</td></tr>
<tr><td>Total Number of Intervention Groups/ Arms</td><td>2</td></tr>
<tr><td>Duration of Participation</td><td>Each participant will participate in the study for approximately 32 weeks from the time the participant provides documented informed consent through the final contact.

After a staged screening period (V1 up to V3) of approximately 4 weeks, each eligible participant will be randomized to receive open-label efinopegdutide or semaglutide for approximately 24 weeks (V3 up to V12). A follow-up visit (V13) will occur approximately 5 weeks after the last dose of study intervention.</td></tr>
</table>

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	Yes
Study governance considerations are outlined in Appendix 1. The Data Monitoring Committee for this study is the MRL siDMC.	

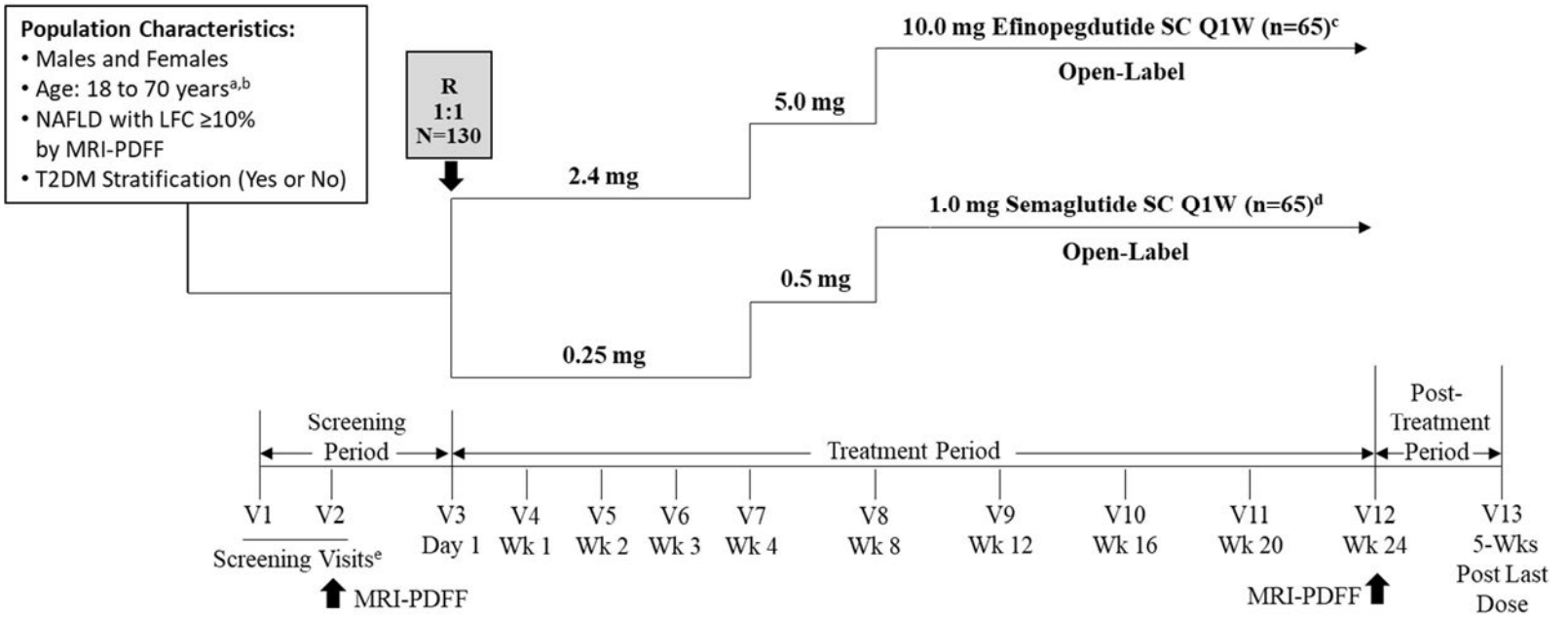
Study Accepts Healthy Volunteers: No

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Design



EOT=end of treatment; LFC=liver fat content; MRI-PDFF=magnetic resonance imaging-proton density fat fraction; NAFLD=nonalcoholic fatty liver disease; R=randomization; Q1W=once every week; SC=subcutaneous; T2DM=type 2 diabetes mellitus; V=visit; Wk=week.

[a] For participants in Taiwan, the population age will be from 20 to 70 years.
[b] For participants in South Korea, the population age will be from 19 to 70 years.
[c] If the 10.0 mg target dose is not tolerated, then down-titration should be considered at subsequent study visits.
[d] If the 1.0 mg target dose is not tolerated, then down-titration should be considered at subsequent study visits.
[e] The interval between V1 and V3 will be approximately 4 weeks.

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2 INTRODUCTION

NAFLD is characterized by steatosis within the liver. It is increasingly recognized as the hepatic manifestation of overall metabolic dysfunction and is closely associated with obesity, insulin resistance, and T2DM [Younossi, Z. M., et al 2016]. In a meta-analysis conducted by Younossi et al, the global prevalence of NAFLD among T2DM patients was 55.5% and the global prevalence of NASH among patients with T2DM was 37.3% [Younossi, Z. M., et al 2019].

GLP-1 agonism is associated with reductions in serum glucose and weight loss. There are several GLP-1 agonists approved for the treatment of T2DM and approved or in development for obesity. GLP-1 receptor agonists enhance glucose-stimulated insulin secretion and have become useful treatments for T2DM. At the doses that have been developed for diabetes indications (eg, liraglutide 1.8 mg daily, semaglutide 1.0 mg weekly), GLP-1 receptor agonists are associated with weight loss of approximately 3% to 5%, generally attributed to reductions in food intake. More recently, higher dose administration of GLP-1 receptor agonists has been pursued for weight loss indications. Liraglutide 3.0 mg daily and semaglutide 2.4 mg once weekly are approved for weight loss in the United States and European Union and in the United States, respectively.

The weight loss associated with GLP-1 agonists is also associated with decreased inflammation within the liver of patients with NASH. The Liraglutide Efficacy and Action in NASH (LEAN) Phase 2 study showed 39% (9/23) of participants who received liraglutide 1.8 mg daily and underwent an end of treatment liver biopsy after 48 weeks had resolution of definite NASH compared with 9% (2/22) in the placebo group [Armstrong, M. J., et al 2016]. Semaglutide is currently being evaluated for NASH in late stage studies. A Phase 2b study with semaglutide at 0.1 mg, 0.2 mg, or 0.4 mg SC once daily (0.7 mg to 2.8 mg weekly) showed histologic resolution of NASH without worsening of fibrosis in 40.4% to 58.9% of participants relative to placebo (17.2%) after 72 weeks of dosing [Newsome, P. N., et al 2020].

Glucagon receptor activation has direct effects on lipolysis, basal energy expenditure, and liver lipid metabolism, and may complement the effects of GLP-1 receptor agonism for the treatment of NASH [Seghieri, M., et al 2018]. Glucagon has been shown to cause reductions in food intake and increases in energy expenditure. However, the metabolic effects of glucagon, particularly the hyperglycemic effects, limit the utility of glucagon as a weight loss agent. The combination of GLP-1 receptor agonism with glucagon receptor agonism thus offers the potential for complementary effects on weight loss, while attenuating the hyperglycemia that would be associated with pure glucagon activity.

Efinopegdutide (MK-6024) is a synthetic modified oxyntomodulin peptide. It is the site-specific form of HMGLP/GCG25 (a GLP-1/glucagon dual agonist peptide) that is linked via a polyethylene glycol linker to a human IgG fragment with agonist activity at both the GLP-1 and the glucagon receptors. Oxyntomodulin is a 37 amino acid peptide product of the proglucagon gene released from the L-cells of the small intestine in response to food ingestion [Wynne, K., et al 2006]. Oxyntomodulin activates both the GLP-1 and glucagon

receptors. Oxyntomodulin, administered 3 times daily before a meal, decreased appetite and reduced body weight by 2.3 kg during a 4-week period in healthy overweight and obese participants [Wynne, K., et al 2005]. In addition to the beneficial effects of weight loss on NAFLD, glucagon agonism may provide additional reduction in hepatic fat by stimulating fatty acid oxidation and reducing lipogenesis in the liver relative to GLP-1 agonism alone [Boland, M. L., et al 2020].

Efinopegdutide was originally developed by Hanmi Pharmaceuticals. Phase 1 and 2 studies supported administration of a Q1W SC injection. A 26-week Phase 2b study in obese participants and a 12-week Phase 2b study in obese participants with T2DM, evaluated the weight loss and glycemic efficacy, and safety/tolerability of efinopegdutide at doses up to 10 mg Q1W. Dose-dependent reductions in body weight with Q1W administration of efinopegdutide were observed in these Phase 2b studies in obese participants with and without T2DM. Weight loss was greater or similar to liraglutide 3 mg daily, which is the dose approved for obesity. The absence of glucose-lowering in the face of weight loss in these studies is attributable to glucagon receptor target engagement, but without deleterious effects on glycemia in nondiabetic or in T2DM participants. The increase in serum ketones (beta-hydroxybutyrate) and reduction in bicarbonate observed in these Phase 2b studies are consistent with enhancement of fatty acid oxidation and glucagon activation in the liver (MSD; data on file).

In 2 mouse models of NASH, the GLP-1R/GCGR co-agonist cotadutide reduced fibrosis to a greater extent than the GLP-1 receptor agonist liraglutide with similar degrees of weight loss [Boland, M. L., et al 2020]. In another mouse model of NASH, the co-agonist ALT-801 suppressed hepatic stellate cell pathway pro-fibrosis genes more than the GLP-1 receptor agonist semaglutide [Nestor, J. J., et al 2020]. In a 54-week Phase 2 study with cotadutide, reductions in Pro-C3 levels, a marker of hepatic fibrogenic activity, were greater compared with liraglutide, albeit in conjunction with greater weight loss (5% versus 3.3%) [Nahra, R., et al 2020] [Dela Cruz, J. 2020].

As neither the GLP-1 receptor nor the glucagon receptor are expressed in human Kupffer or stellate cells, these findings suggest that anti-fibrotic effects may be mediated by upstream reductions in steatosis and inflammation. In summary, glucagon receptor agonism may provide additional reductions in hepatic fat and potentially on hepatic fibrosis than the reductions mediated by weight loss observed with GLP-1 agonism.

2.1 Study Rationale

The principal goals of this Phase 2a study are to assess the effects on hepatic fat reduction and fibrosis biomarkers of GLP-1 and glucagon receptor co-agonism with efinopegdutide relative to GLP-1 agonism alone with the use of semaglutide, and inform on the role of efinopegdutide as a potential novel therapy for NASH.

The study will also expand the safety and tolerability characterization of efinopegdutide.

2.2 Background

Refer to the IB for detailed background information on efinopegdutide.

2.2.1 Pharmaceutical and Therapeutic Background

NAFLD affects approximately 25% of the global adult population and is a condition associated with an increased accumulation of TG in the liver. NAFLD encompasses a spectrum of disease, ranging from simple steatosis to NASH that is associated with chronic inflammation within the liver described histologically as steatohepatitis with or without fibrosis[Kechagias. S., et al 2020]. An increasing proportion of NAFLD cases will progress to NASH, rising from 20% to 27% between the years 2015 and 2030 [Friedman, S. L., et al 2018].

In general, patients with NASH are diagnosed between the ages of 40 and 60 years, and have associated metabolic comorbidities that include obesity, dyslipidemia, T2DM, and MetS [Younossi, Z. M., et al 2016] [Younossi, Z., et al 2018] [Chalasani, N., et al 2018]. Approximately 20% of the NASH population will progress to cirrhosis with increases in all cause and liver-related mortality including increased rates of hepatocellular carcinoma [Sheka, A. C., et al 2020]. Additionally, some patients develop hepatocellular carcinoma without cirrhosis [Stine, J. G., et al 2018] [Perumpail, R. B., et al 2015]. NASH remains an area of unmet need with no approved therapies and a growing global prevalence.

NAFLD has been recognized as the hepatic manifestation of overarching metabolic dysregulation and is considered a consequence of obesity-related insulin resistance resulting in increased trafficking of fatty acids from adipose to liver and de novo hepatic lipogenesis [Fabbrini, E., et al 2010].

NAFLD patients are typically asymptomatic; therefore, more likely to initially be identified based on risk factors (obesity, MetS, T2DM) and/or abnormal liver tests without alternate explanation. The presence of steatosis may be assessed through imaging (ultrasound, magnetic resonance imaging). In patients with confirmed steatosis, the risk for NASH and advanced fibrosis can be further assessed through laboratory panels and imaging-based assessments of liver stiffness. These diagnostics cannot definitively diagnose NASH or fibrosis stage but are useful in assessing risk of advanced fibrosis.

Lifestyle modification directed at weight loss and exercise remain the most recommended treatment for NAFLD; however, even in well-organized settings, only a minority of patients achieve and sustain weight loss. Presently, there are no agency-approved medications for the treatment of NASH. According to evidence-based practice guidelines, pioglitazone and high dose vitamin E (800 IU/day) are now recommended as pharmacotherapies for biopsy-proven NASH patients with and without diabetes, respectively [Sumida, Y. 2018]. However, neither pioglitazone nor vitamin E have demonstrated in the NASH population a robust histological efficacy, been studied long-term to assess impact on liver-related outcomes or have fully characterized safety. The absence of well-characterized, safe, and highly effective NASH treatments is a significant unmet medical need recognized by both medical societies and regulatory agencies [Friedman, S. L., et al 2018] [Chalasani, N., et al 2018].

2.2.2 Preclinical and Clinical Studies

Toxicology and clinical data are briefly summarized below. Refer to the efinopegdutide IB for a more extensive summary of the preclinical and clinical data available for efinopegdutide.

2.2.2.1 Efinopegdutide Preclinical Overview

The preclinical safety profile of efinopegdutide has been assessed in safety pharmacology studies, single-dose toxicity studies, 2 repeat-dose toxicology studies in rats for 4- and 26-weeks duration, and 2 repeat-dose toxicology studies in monkeys for 4- and 16-weeks duration.

In GLP safety pharmacology studies in male rats, single-dose injections of efinopegdutide caused no notable effects on respiratory parameters but caused neurobehavioral changes that were secondary to the expected pharmacological effect of large body weight loss. In GLP cardiovascular safety studies in cynomolgus monkeys, efinopegdutide caused non-dose-dependent relatively higher nocturnal HR as well as dose-dependent increased body temperature and slight QTcR interval prolongation; however, parameters were not considered adverse. No other notable effects on cardiovascular parameters were observed.

The predominant treatment-related effects of efinopegdutide in 4-week repeat-dose toxicity studies in rats and monkeys are attributable to exaggerated pharmacological actions of efinopegdutide on GLP-1R and GCGR receptors that caused pronounced dose-related decreases in body weight, body weight gain, and food consumption compared with controls. In turn, these effects led to several dose-related secondary findings on hematology, clinical chemistry, urinalysis, and gross and microscopic pathology parameters that were considered to result from the pronounced adverse effects on body weight and food consumption and associated metabolic stress. These effects are consistent with findings associated with feed restriction and stress responses. In the monkey, there was an additional effect of increased cellularity of endocrine islet cells in the pancreas. Similar effects of increased cellularity of the pancreas with no increase in cell proliferation have been observed in monkeys during development of other GLP-1 agonists (eg, albiglutide, exenatide) and were considered to be pharmacologically mediated.

Findings in the 26-week rat study were consistent with those in the shorter term 4-week rat study. The chronic monkey study was initiated as a 26-week study, but the study duration was shortened to 16 weeks because it was not possible to maintain systemic exposure due to ADA formation. The ADAs were neutralizing against GLP-1R activity and to a lesser extent against GCGR activity.

2.2.2.2 Efinopegdutide Clinical Overview

Based on completed clinical studies, at least 1 dose of efinopegdutide has been administered to a total of 783 participants across 7 Phase 1 studies and 2 Phase 2b studies. Key safety data are summarized below.

In a first-in-human, 2-part, Phase 1 study (HM-OXM-101), healthy male and female participants 18 to 65 years of age were randomized to receive single doses of efinopegdutide 0.25 nmol/kg to 4.0 nmol/kg (n 30) or placebo (n 10) and in Part 2, 48 male and female participants 18 to 70 years of age with T2DM were randomized to receive efinopegdutide 0.5 nmol/kg to 2.0 nmol/kg (n 36) or placebo (n 12) dosed Q1W for 4 weeks. CCI

CCI

Two Phase 2b studies were conducted with efinopegdutide (not titrated) in obese participants with and without T2DM. Study 64565111OBE2002 was a randomized, double-blind, placebo-controlled, parallel-group, 4-arm, multicenter study that evaluated efinopegdutide in obese (BMI: ≥35 kg/m^2 to ≤50 kg/m^2), 18 to 70-year-old participants with T2DM. A total of 196 participants were randomized to placebo (n 50), and efinopegdutide at 5.0 mg (n 48), 7.4 mg (n 49), and 10.0 mg (n 49). At Week 12, all 3 doses of efinopegdutide significantly reduced body weight from baseline when compared with placebo (after adjustment for

multiplicity). Corresponding placebo-subtracted percent changes were -4.56%, -5.85%, and -7.23% for the 5.0 mg, 7.4 mg, and 10.0 mg efinopegdutide dose groups, respectively ($p<0.001$), thereby meeting the primary efficacy objective. Clinically meaningful weight reduction was observed in all 3 doses of efinopegdutide as early as Week 2 and generally increased through Week 12. Treatment with efinopegdutide was associated with non-dose-dependent reductions in SBP and DBP along with elevations in pulse rate. The rate pressure product at Week 12 was not meaningfully increased compared with baseline (MSD; data on file).

At Week 12, there was a nominal 0.13% increase in the level of HbA1c (A1C) from baseline in the efinopegdutide 5.0 mg dose group compared with small reductions of -0.03% and -0.07% in the 7.4 mg and 10.0 mg efinopegdutide dose groups along with a -0.19% reduction in the placebo group. Consistent with the A1C data, there was little change in FPG; an increase of 2.5 mg/dL and 1.1 mg/dL was observed in the 5.0 mg and 7.4 mg efinopegdutide dose groups compared with reductions of -11.7 mg/dL and -5.8 mg/dL in the efinopegdutide 10.0 mg and placebo dose groups, respectively. Fasting plasma insulin levels increased from baseline by 22%, 25%, and 6% in the 5.0 mg, 7.4 mg, and 10.0 mg efinopegdutide dose groups, respectively, compared with a 5% increase in the placebo group (MSD; data on file).

Study 64565111OBE2001 was a randomized, double-blind placebo-controlled and open-label active-controlled, parallel-group, 5-arm, multicenter Phase 2b study. Nondiabetic, obese (BMI: ≥35 kg/m^2 to ≤50 kg/m^2) participants 18 to 70 years of age (inclusive) were assessed. A total of 474 participants were randomized to placebo (n 60), efinopegdutide at 5.0 mg (n 59), 7.4 mg (n 118), and 10.0 mg (n 118); or open-label liraglutide 3.0 mg (n 119). At Week 26, all 3 doses of efinopegdutide significantly reduced body weight from baseline compared with placebo (after adjustment for multiplicity) with corresponding placebo-subtracted percent changes of -6.8%, -8.1%, and -10.0% for the efinopegdutide 5.0 mg, 7.4 mg, and 10.0 mg dose groups, respectively, thereby successfully meeting the primary objective. At Week 26, the liraglutide group showed a placebo-subtracted reduction in body weight of -5.8% (MSD; data on file).

At Week 26, there was no change in the levels of A1C in the efinopegdutide and placebo groups compared with a -0.2% reduction in the liraglutide group. Consistent with the A1C data, there was little change in FPG in the efinopegdutide and placebo groups compared with an approximate -6 mg/dL reduction in the liraglutide group. Fasting plasma insulin levels compared with baseline were unchanged in the liraglutide group, increased by 30% across the efinopegdutide dose groups, and decreased by 17% in the placebo group (MSD; data on file).

The 24-hour assessments of vital signs measured in a substudy showed treatment and non-dose-dependent related effects. There was a decrease in 24-hour mean SBP from baseline to the last measurement in the efinopegdutide dose groups relative to placebo. The placebo-subtracted mean reduction in SBP was -4.6 mm Hg, -4.4 mm Hg, and -9.8 mm Hg for the 5.0 mg, 7.4 mg, and 10.0 mg dose groups, respectively. Similarly, there efinopegdutide was a decrease in 24-hour mean DBP from baseline to the last measurement in the efinopegdutide dose groups relative to placebo. The placebo-subtracted mean reduction in DBP

was -5.1 mm Hg, -2.9 mm Hg, and -4.8 mm Hg for the efinopegdutide 5.0 mg, 7.4 mg, and 10.0 mg dose groups, respectively. Regarding HR, there was an increase in the placebo-subtracted mean 24-hour value from baseline to the last measurement of 4.6 bpm and 5.4 bpm in the efinopegdutide 7.4 mg and 10.0 mg dose groups, respectively (MSD; data on file).

In both Phase 2b studies, the overall incidence of TEAEs was higher in each efinopegdutide dose group compared with the placebo or liraglutide groups, with no apparent dose-relationship between the efinopegdutide 7.4 mg and 10.0 mg dose groups. Consistent with the safety profile of other GLP-1 receptor agonists, the most common TEAEs after treatment with efinopegdutide in both studies were nausea and vomiting, which were often observed within the first week of treatment. In study 64565111OBE2001, the incidence of nausea was 64.1% for the combined efinopegdutide groups compared with 6.7% for placebo and 40.3% for liraglutide. Similarly, the incidence of vomiting was 42.0% in the combined efinopegdutide groups compared with 0% for placebo and 16.8% for liraglutide. Approximately 53% of participants treated with efinopegdutide experienced an AE of nausea within the first week of treatment (compared with approximately 3% and 20% in the placebo and the titrated liraglutide groups, respectively). In study 64565111OBE2002, the AE of nausea occurred in 27.1%, 34.7%, and 42.9% of participants in the efinopegdutide 5.0 mg, 7.4 mg, and 10.0 mg dose groups, respectively, compared with 10.2% in the placebo group. Approximately 21.9% and 15.1% of participants experienced an AE of nausea or vomiting, respectively, within the first week of treatment (compared with 2.0% and 0% in the placebo group) (MSD; data on file).

In study 64565111OBE2001, there was a total of 17 SAEs with a similar incidence reported across treatment groups. Three SAEs in the efinopegdutide 10.0 mg dose group and 2 SAEs in the liraglutide group were considered related to study intervention by the investigator. There were 6 discontinuations due to SAEs with a single event each in the efinopegdutide 5.0 mg and 7.4 mg dose groups, and 2 events each in the efinopegdutide 10.0 mg dose group and liraglutide group. There was a single death (myocardial infarction) in the liraglutide group. The incidence of AEs of clinical interest (ie, hypoglycemia, pancreatitis, injections site reactions, major adverse cardiovascular events, hypotension-related events, calcitonin elevation, and thyroid neoplasm) were low and similar across all treatment groups. In study 64565111OBE2002, there was an incidence of 7 SAEs reported (1 event in the placebo group; 2, 1, and 3 events in the efinopegdutide 5.0 mg, 7.4 mg, and 10.0 mg dose groups, respectively), none of which were deemed related to study intervention by the investigator (MSD; data on file).

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2.2.3 Information on Other Study-related Therapy

Semaglutide is a GLP-1 receptor agonist that is resistant to degradation via DPP-4. GLP analogs, including semaglutide, have been shown to improve liver enzymes, oxidative stress, and hepatic steatosis [Li, Q., et al 2020] [Newsome, P. N., et al 2020] [Newsome, P., et al 2019]. Semaglutide is more resistant than other GLP-1 agonists to degradation via DPP-4 and has an increased affinity to albumin. As a result, semaglutide has a t½ of approximately 1 week, rendering it appropriate for Q1W SC administration [Lau, J., et al 2015].

Semaglutide is currently approved as an up to 1.0 mg Q1W SC injection in adults with T2DM to improve blood sugar, and in adults with T2DM with known heart disease to reduce the risk of major cardiovascular events (ie, heart attack, stroke, or death) [U.S. Prescribing Information 2020].

Semaglutide SC 2.4 mg once weekly is approved as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial BMI 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least 1 weight-related comorbid condition (eg, hypertension, T2DM, dyslipidemia) [U.S. Prescribing Information 2021]. In adults without diabetes who were treated with SC semaglutide 2.4 mg once weekly, the average body weight loss after 68 weeks was 14.9% of the initial body weight compared to 2.4% in individuals who received placebo [Wilding, J. P. H., et al 2021]. In another study that enrolled adults with T2DM, treatment with SC semaglutide 2.4 mg once weekly for 68 weeks showed an average body weight loss of 9.6% from the initial body weight compared to 3.4% in individuals who received placebo [Davies, M., et al 2021].

Additionally, semaglutide is currently being evaluated for NASH in Phase 2 and 3 studies. A Phase 2 study in individuals with NASH treated with once daily semaglutide (0.1 mg, 0.2 mg, or 0.4 mg) compared with placebo showed resolution of NASH and no worsening of liver fibrosis after 72 weeks. At the semaglutide 0.4 mg daily dose, 33 of 56 participants (59%) achieved NASH resolution compared with 10 of 58 participants (17%) on placebo [Newsome, P. N., et al 2021].

Semaglutide is generally well tolerated. In clinical studies, the most common adverse reactions reported in ≥5% of patients treated with semaglutide include nausea, vomiting, diarrhea, abdominal pain, and constipation. In general, these reactions were mild or moderate in severity and of short duration.

Semaglutide is contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with MEN 2, and patients with a history of a serious hypersensitivity reaction to semaglutide, such as anaphylaxis or angioedema.

For further information regarding semaglutide refer to the approved product labels [U.S. Prescribing Information 2020] [U.S. Prescribing Information 2021].

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Semaglutide 1.0 mg SC Q1W is an approved dose for T2DM and is associated with weight loss that is expected to reduce LFC. Notably, higher doses of semaglutide are approved for obesity and in late stage development for NASH. Although semaglutide is not currently indicated in the broad NAFLD population, there is experience from ongoing clinical studies and no unanticipated safety issues have been reported. This was the rationale to consider semaglutide as an active comparator at the dose of 1.0 mg Q1W. Furthermore, the study population will contain a large proportion of participants with T2DM for which semaglutide is indicated; based on a recent large meta-analysis the global prevalence of NAFLD among T2DM patients was 55.5% [Younossi, Z. M., et al 2019].

Based on available data to date from preclinical and clinical findings, efinopegdutide was found to be generally well tolerated. Potential adverse effects that have developed in clinical testing to date include gastrointestinal intolerance and increases in HR. Both appear to be generally consistent with effects reported for other agents in the GLP-1 receptor agonist class.

The majority of TEAEs were related to the gastrointestinal system, with nausea, vomiting, events concerning abdominal discomfort/distension/pain, eructation, and dyspepsia being the most frequently reported. To improve gastrointestinal tolerability, this study will use a 8-week dose-escalation regimen as gradual dose-escalation of GLP-1 agonists have been shown to successfully reduce the proportion of participants experiencing dose-limiting nausea and vomiting.

The increases in HR associated with administration of efinopegdutide have generally increased with dose. Therefore, in addition to routine monitoring of HR at each study visit, participants that experience an increase in HR >100 bpm (tachycardia) of any duration associated with symptoms the study investigator considers potentially related to cardiac ischemia, congestive heart failure and/or hemodynamic compromise will be discontinued from study intervention (see Section 7.1).

Also observed, and specific to participants with T2DM treated with efinopegdutide, were isolated increases in FPG. While glucagon and GLP-1 agonism have counteracting effects on glucose control, dual agonism of GLP-1 and GCGR generally leads to improved glucose control in participants with T2DM as the effects of GLP-1 to increase insulin secretion appear to overcome the effects of glucagon agonism to increase endogenous glucose production. However, it is possible that some participants may be more sensitive to the glucagon agonism induced by efinopegdutide than to the GLP-1 agonism, and these participants may have plasma glucose concentrations increased by treatment with efinopegdutide. As participants with severe obesity, such as those enrolled in this study, are at risk to develop prediabetes and diabetes over time, the glycemic status of all participants enrolled will be monitored throughout the duration of study.

Given the partial similarities in the mode of action with other approved GLP-1 receptor agonists, other potential adverse human effects include pancreatitis and elevations in calcitonin. Therefore, in addition to the routine assessment of AEs, the following safety measures are included to monitor and address these potential effects: participants with personal or family histories of medullary thyroid carcinoma or multiple endocrine neoplasm type-2 syndrome as well as personal history of pancreatitis will be excluded from participating in the study, and those enrolled will undergo periodic monitoring of calcitonin, and amylase/lipase.

Given the lack of available treatment options for patients with NASH, the serious potential health risks of progressive fibrosis and cirrhosis, and the available preclinical and clinical data summarized above and in the IB that indicate efinopegdutide may be an effective treatment for NASH, the benefit-to-risk assessment for conducting this study is considered to be favorable.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In males and females aged 18 to 70 years (in Taiwan, aged 20 to 70 years; in South Korea, aged 19 to 70 years [Appendix 7]) with NAFLD:

Objectives	Endpoints
Primary	
• To evaluate the effect of efinopegdutide versus semaglutide on mean relative reduction from baseline in LFC after 24 weeks. • Hypothesis (H1): Efinopegdutide is superior to semaglutide with respect to mean relative reduction from baseline in LFC after 24 weeks. • Hypothesis (H2): Efinopegdutide is superior to semaglutide by 10% or more with respect to mean relative reduction from baseline in LFC after 24 weeks.	• LFC (%) measured by MRI-PDFF (evaluated by BICR)
• To evaluate the safety and tolerability of efinopegdutide compared with semaglutide.	• AEs • Discontinuation of study intervention due to AEs

Objectives	Endpoints
Secondary	
• To evaluate the effect of efinopegdutide versus semaglutide on mean absolute reduction from baseline in LFC after 24 weeks.	• LFC (%) measured by MRI-PDFF (evaluated by BICR)
• To evaluate the effect of efinopegdutide versus semaglutide on mean percent change from baseline in body weight at 24 weeks.	• Weight (kg)
• To evaluate the effect of efinopegdutide versus semaglutide on change from baseline in fasting lipid levels over 24 weeks.	• Lipid profile: cholesterol (total, non-HDL-C, HDL-C, LDL-C), TG, and apoB
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4 STUDY DESIGN

4.1 Overall Design

This is a Phase 2a, randomized, active-comparator-controlled (semaglutide; Ozempic®), parallel-group, multi-site, open-label study of efinopegdutide in participants with NAFLD. This study will be conducted in conformance with GCP.

The duration of the study will be approximately 32 weeks (with up to 13 clinic visits) for each participant. This will include a staged screening period (V1 up to V3) of approximately 4 weeks; a 24-week active-comparator-controlled treatment period (V3 through V12); and a post-treatment period with a follow-up visit (V13) at approximately 5 weeks after the last dose of study intervention.

Approximately 12 participants in the efinopegdutide arm who elect to participate in the PK substudy will have 4 additional blood samples collected (ie, V3.1/D3, V3.2/D5, V6, and V9) during the study.

Approximately 130 males and females aged 18 to 70 years (in Taiwan, aged 20 to 70 years; in South Korea, aged 19 to 70 years [Appendix 7]) with NAFLD based on a LFC of ≥10% as assessed by MRI-PDFF, and who meet all eligibility criteria will be randomized in this study.

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4.2 Scientific Rationale for Study Design

The study was designed in general accordance with the US FDA and EMA guidance on the development of drugs for the treatment of noncirrhotic NASH [Food and Drug Administration 2018] [European Medicines Agency 2018].

The study will not be blinded since semaglutide is currently available only as a single-patient-use pen and cannot easily be blinded in the context of a clinical study. Efinopegdutide and semaglutide will therefore be dispensed as open-label medications.

Randomization will be used to minimize bias in the assignment of participants to treatment groups, to increase the likelihood that known and unknown participant attributes (eg, demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups.

The stratification for T2DM (Yes or No) will be used for randomization to ensure balance in the treatment groups within each stratum.

The currently approved dose of semaglutide is 1.0 mg SC Q1W for T2DM. Based on multiple epidemiologic studies, the NAFLD population contains a large proportion of individuals with T2DM, thus we anticipate the T2DM population will be well represented in this study with an enrollment cap of approximately 60% in each of the arms. As a higher dose of semaglutide is in late stage development for the treatment of NAFLD/NASH, the results from this study of semaglutide 1.0 mg Q1W will be used to model anticipated changes in LFC with higher doses to inform on the relative efficacy of efinopegdutide 10.0 mg Q1W.

The approximate 4-week screening period will allow time before randomization to obtain laboratory results that are needed to determine the participant's eligibility for the study. Participants enrolled in this study will likely have no prior experience with injection of medication; therefore, injection training of participants/caregivers by the study staff on the use of the prefilled syringes/pens for injection will be performed on Day 1 and V7/Week 4. Injection training will be provided at other visits as needed. The duration of the treatment period in this study is 24 weeks, which should be sufficient to capture the maximal or near-maximal relative reductions of LFC in the active doses. The 5-week post-treatment follow-up visit is designed to assess safety by collecting data on SAEs or resolution of ongoing SAEs that occurred since the last dose of study intervention.

The incorporation of an IA will inform on administrative decisions regarding other aspects of the efinopegdutide program. In addition, the IA may be used to support potential termination of the study for futility based on poor LFC (MRI-PDFF) response and/or safety and tolerability issues.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

One of the key goals of this study is to demonstrate the efficacy of efinopegdutide in the treatment of individuals with NAFLD. Participants will have images of the liver obtained by MRI-PDFF which will be centrally analyzed by BICR. The primary efficacy endpoint is the effect of efinopegdutide versus semaglutide on mean relative reduction (%) from baseline in LFC measured by MRI-PDFF after 24 weeks of treatment with the image analysis performed by BICR. MRI-PDFF is a highly accurate noninvasive measure of the proportion of fat content of a tissue. This technique separates the water and fat signals in the image using the difference in magnetic resonance frequencies of protons in water and fat. It represents the percentage ratio of fat signal over the sum of fat and water signal. MRI-PDFF can be used for measuring LFC over the entire liver and is usually reported as a single value averaged over the whole liver. MRI-PDFF is an established methodology for quantitative assessment of LFC that has been assessed as a primary or secondary endpoint in Phase 2 clinical development programs for NASH [Madrigal Pharmaceuticals, Inc. 2017] [Bautz, D. 2018] [Harrison, S. A., et al 2018].

The secondary efficacy endpoints that will be assessed include the effect of efinopegdutide versus semaglutide on mean absolute reduction from baseline in LFC measured by MRI-PDFF (evaluated by BICR) after 24 weeks of treatment, and the changes from baseline after 24 weeks in body weight and lipid metabolism. Body weight reduction is an anticipated

outcome of co-activation of GLP-1R and GCGR and its measurement over 24 weeks of treatment will provide insight into the effects of efinopegdutide on this endpoint. Lipid metabolism endpoints will include changes in baseline over 24 weeks of treatment in cholesterol (total, non-HDL-C, HDL-C, LDL-C), TG, and apoB. These parameters provide insight into the effects of efinopegdutide on this endpoint and characterize the time course of lipid metabolism in this study.

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4.2.1.2 Safety Endpoints

The safety data for efinopegdutide to date has been described in detail in the IB and summarized in Section 2.2.2.

In support of the safety objective to evaluate the safety and tolerability profile of efinopegdutide, the safety and tolerability endpoints will be assessed by clinical evaluation of AEs and inspection of other study parameters including physical examinations, 12-lead ECGs, vital signs (ie, HR, BP), glycemic responses, serum ketone levels, and other laboratory safety tests.

All procedures will be conducted at the time points CCI [redacted] AEs will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE, Version 5.0 (see Appendix 10). Note: For AEs that are an exception to the NCI CTCAE grading, see Section 7.1.

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4.2.1.4 Pharmacodynamic Endpoints

PD endpoints that will be assessed include changes from baseline through Week 24 in biomarkers reflecting liver inflammation and fibrosis.

Since fibrosis stage is a major predictor of liver-related mortality, the evaluation of liver inflammation and fibrosis is critical in the management of patients with NAFLD. The following biomarkers or composite scores will be assessed as potential metrics for estimation of baseline severity of liver inflammation and fibrosis and/or response to treatment: ELF, CK-18 M30, and Pro-C3. These noninvasive biomarkers or composite scores will be used to

supplement information obtained from the primary and secondary efficacy endpoints (see Section 8.7.1).

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4.2.1.7 Future Biomedical Research

The Sponsor will conduct FBR on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for FBR.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for FBR is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of FBR research are presented in Appendix 6.

4.2.2 Rationale for the Use of Active Comparator

Semaglutide is a GLP-1 receptor agonist indicated as an adjunct to a reduced-calorie diet and increased physical activity to improve glycemic control in adults with T2DM and reduce the risk of major adverse cardiovascular events in adults with T2DM and established cardiovascular disease, as indicated in the product labeling [U.S. Prescribing Information 2020]. Semaglutide has shown beneficial effects on glucose control and weight loss compared with placebo and other antidiabetic drugs in patients with T2DM [O'Neil, P. M., et al 2018]. It is currently approved as a treatment option for patients with obesity and under investigation for its potential as a treatment option for patients with NASH [U.S. Prescribing Information 2021] [Newsome, P. N., et al 2021]. Given the partially common mechanism of action, a direct comparison between semaglutide and efinopegdutide will facilitate the interpretation of efficacy findings and of possible differences in efficacy measures observed between the 2 drugs on LFC and fibrosis biomarkers. Importantly, the use of semaglutide will provide an essential reference arm for the assessment of the safety and tolerability profile of efinopegdutide, as it is expected that both agents are associated with an increased incidence of GI AEs and hemodynamic effects such as increases in HR. Further, the same administration route, SC, reduces the possible confounding effect of treatment compliance that would exist if the comparator was an oral agent.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

The initial efinopegdutide dose will begin at 2.4 mg Q1W (0.12 mL Q1W) and will be escalated up to the full dose of 10.0 mg Q1W (0.5 mL Q1W).

The initial semaglutide dose will begin at 0.25 mg Q1W (0.19 mL Q1W) and will be escalated up to the full dose of 1.0 mg Q1W (0.74 mL Q1W).

See Section 6.6.1 for further information on the dose-escalation of efinopegdutide and semaglutide and Section 6.6.2 for allowable modifications to the titration schedule based on individual participant tolerance.

4.3.2 Maximum Dose/Exposure for This Study

The maximum doses for participants on efinopegdutide or semaglutide will be 10.0 mg Q1W and 1.0 mg Q1W, respectively. Participants will be exposed to efinopegdutide or semaglutide for approximately 24 weeks. For more information, see Section 6.1 and Section 8.1.9.

4.3.3 Rationale for Dose Interval and Study Design

The selection of doses and regimens to be administered in this study are based on available preclinical and clinical safety, PK, PD, and efficacy data to date. Dose-dependent GI tolerability (predominantly nausea and vomiting) issues have been previously observed in the efinopegdutide clinical development program and are also well-described for GLP-1R agonists and GLP-1R/GCGR co-agonists. The use of titration regimens to mitigate the prevalence of GI AEs has been successfully implemented for marketed GLP-1 agonists, and thus will be applied in the current study. The t½ of approximately 7 days allows for a weekly dosing frequency for efinopegdutide, and, therefore, near steady-state concentrations should be reached in approximately 4 weeks. Based on PK data from the completed Phase 1 multiple-dose studies, near steady-state exposures are achieved by Week 4 of dosing. Efinopegdutide demonstrates linear pharmacokinetics. Therefore, a dose-titration strategy using 4-week intervals will enable efinopegdutide to gradually accumulate to steady-state levels before increasing to the next dose level.

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This study population will contain a large proportion of participants with T2DM for which semaglutide is indicated as an antihyperglycemic agent. Based on a recent large meta-analysis, the global prevalence of NAFLD among T2DM patients was 55.5% [Younossi, Z. M., et al 2019]. Semaglutide SC 1.0 mg Q1W is approved for T2DM. However, higher doses of semaglutide are approved for obesity (2.4 mg SC Q1W) and in late stage development for NASH. Semaglutide is anticipated to be the best in class GLP-1 agonist for NASH and therefore considered as an active comparator at the dose of 1.0 mg Q1W. Changes in LFC at the end of therapy with the semaglutide 1.0 mg Q1W dose will be used to model responses

expected at higher doses of semaglutide that may be approved in the future for NASH and will inform on the relative efficacy of efinopegdutide.

The basis for the 24-week duration of study intervention in this study was informed first, by the 12 week period to reach steady-state exposures using a dose-titration approach, and second, by the need to allow sufficient time for GLP-1 and glucagon receptor agonism mediated weight loss to occur to obtain a robust assessment of the reduction in LFC in both active treatment arms. The rationale for a 24-week study duration is supported by the lack of significant reductions in LFC observed in 12-week studies with other GLP-1 agonists in individuals with T2DM and overweight patients with T2DM [Tang, A., et al 2015] [Smits, M. M., et al 2016] while significant reductions observed with longer durations of treatment. In a study where participants were treated with exenatide (n 19) and liraglutide (n 6) for 24 weeks, a significant relative reduction of 42% in LFC was observed, with parallel reductions in body weight (5.0 kg) and in A1C (1.6%) [Cuthbertson, D. J., et al 2012]. More recently, the results of the Lira-NAFLD study (N 68) showed participants with inadequately controlled T2DM treated with liraglutide for 24 weeks experience a significant 31% reduction in LFC (MRI-PDFF) compared with participants with intensification of their antidiabetic treatment with insulin. This study also showed that the effect of liraglutide treatment on liver fat was mainly driven by body weight loss [Petit, J. M., et al 2017].

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

This study may be terminated early for safety concerns or futility by the TA-EOC (see Section 9.7).

5 STUDY POPULATION

Male and female participants with NAFLD between the ages of 18 and 70 years (inclusive) (in Taiwan, between the ages of 20 and 70 years; in South Korea, aged 19 to 70 years [inclusive] [Appendix 7]) will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Has an LFC ≥10% as assessed by MRI-PDFF at V2/MRI-PDFF.

   Note: Prior MRI-PDFF imaging of the liver performed ≤2 months of V1/Screening, obtained from the same study qualified imaging center(s), and imaged per the Site Imaging Manual for this study may be acceptable to determine LFC % as part of eligibility.

2. Has a BMI ≥25 kg/m^2 and ≤50 kg/m^2 at the time of V1/Screening.

3. Has stable weight (based on self-reporting) defined as ≤5% gain or loss of body weight for at least 3 months before V1/Screening.

4. Meets 1 of the following criteria:

   - Has no history of T2DM

     OR

   - Has a history of T2DM with an A1C ≤8.5% at V1/Screening **AND** controlled by diet or a stable dose of metformin for the 3 months before V1/Screening.

     Note: Antihyperglycemic agents, other than metformin, are not permitted.

Demographics

5. Is male or female, from 18 years to 70 years of age (inclusive) (in Taiwan, from 20 years to 70 years of age [inclusive]; in South Korea, from 19 years to 70 years [inclusive] [Appendix 7]), at the time of signing the informed consent.

Female Participants

6. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a WOCBP

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least 5 weeks

after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.7.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Informed Consent

7. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant may also provide consent for FBR and/or the PK substudy. However, the participant may participate in the main study without participating in FBR and/or the PK substudy.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

Metabolic/Endocrine

1. Has a history of T1DM, diabetic ketoacidosis, or diabetes secondary to pancreatitis or pancreatectomy.
2. Has a history of obesity with a known secondary cause (eg, Cushing's disease/syndrome).
3. Has an ongoing, inadequately controlled hypothyroidism or hyperthyroidism.

   Note: Participants taking thyroid hormone replacement therapy must be on stable doses for at least 6 weeks before V1/Screening.
4. Has a history of glucagonoma.

5. Has a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasm type-2 syndrome.

6. Has a calcitonin value of ≥50 pg/mL (≥50 ng/L) at V1/Screening.

7. Has symptomatic hyperglycemia that, in the investigator's opinion, requires immediate initiation, adjustment, or addition of antihyperglycemic therapy.

Cardiovascular

8. Has significant systemic or major illnesses including recent events (≤6 months before V1/Screening) of congestive heart failure (NYHA functional class III to IV of the American Heart Association), unstable angina, myocardial infarction, arterial revascularization, stroke, or transient ischemic attack.

9. Has a history of pathologic, symptomatic, or sustained tachyarrhythmia (eg, atrial fibrillation, sustained supraventricular tachycardia, symptomatic non-sustained supraventricular tachycardia, ventricular tachycardia, or ventricular fibrillation).

10. Has a history of Wolff-Parkinson-White syndrome or congenital long QT syndrome.

11. Has an average triplicate seated BP reading of SBP ≥160 mm Hg and/or DBP ≥100 mm Hg at V1/Screening.

    Note: If the participant meets this exclusion criterion **AND** the investigator believes that the value can be explained by reversible cause (eg, anxiety, recent exertion, etc.), the BP measurements can be repeated (ie, in triplicate with at least 2 minutes between measurements) after the participant has rested for at least 10 minutes **OR** BPs can be retested at an unscheduled screening visit. If repeat measurements still meet this exclusion criterion, the participant must be excluded.

12. Has an average triplicate seated HR reading of <50 bpm or >100 bpm.

    Note: If the participant meets this exclusion criterion **AND** the investigator believes that the value can be explained by reversible cause (eg, anxiety, recent exertion, etc.), the HR measurements should be repeated (ie, in triplicate with 2 minutes between measurements) after the participant has rested for at least 10 minutes. If the participant has a resting sitting HR <50 bpm or >100 bpm on repeat (ie, average of 3 consecutive measurements), the participant must be excluded.

Gastrointestinal and Hepatic

13. Has a history or evidence of chronic liver disease other than NAFLD or NASH, including but not limited to, hepatitis B as defined by the presence of HBsAg, hepatitis C as defined by the presence of HCV RNA or positive hepatitis C antibody (anti-HCV), drug-induced liver disease, autoimmune liver disease, primary biliary cholangitis, primary sclerosing cholangitis, Reye Syndrome, Wilson's disease, alpha-1-antitrypsin deficiency, hemochromatosis, or known bile duct obstruction.

14. Has a known history of cirrhosis:

    - Fibrosis score >3 based on a historical liver biopsy or a liver stiffness score >14 kPa based on a historical FibroScan®.

      Note: Participants with a historical diagnosis of NASH (F0 to F3) by liver biopsy (local reading) within 6 months of V1/Screening could be eligible to enroll in the study.

    - Evidence of decompensated liver disease including but not limited to ascites, esophageal or gastric variceal bleeding, hepatocellular carcinoma, hepatic encephalopathy, splenomegaly, or spontaneous bacterial peritonitis.

15. Has a history of acute or chronic pancreatitis.

16. Has a history of a bariatric surgical procedure or a known clinically significant gastric emptying abnormality (eg, severe gastroparesis or gastric outlet obstruction).

Psychiatric-Related

17. Has a previous or current history of a clinically significant eating disorder (eg, anorexia nervosa, bulimia, or binge-eating).

18. Has a history of severe psychiatric disorders (eg, schizophrenia, bipolar disorder, etc.), major depressive disorder, or any lifetime history of suicide attempt.

Other Medical Conditions

19. Has a history of malignancy ≤5 years before providing documented informed consent for the study except for squamous or basal cell carcinomas of the skin and carcinomas in situ of the cervix.

20. Has a clinically active hematologic disorder (eg, aplastic anemia, symptomatic anemia, myeloproliferative or myelodysplastic syndromes, proliferative bone marrow disorder, thrombocytopenia) and/or hemostasis disorder (eg, Von Willebrand disease, hemophilia, Factor V Leiden thrombophilia, sickle-cell disease, polycythemia, leukemia).

21. Has HIV as assessed by medical history or current use of antiretroviral therapy.

22. Has undergone a major surgery (eg, requiring general anesthesia) within 3 months before providing documented informed consent for the study, or has not fully recovered from surgery, or has major surgery planned during the participation of the current study.

    Note: Participants with planned surgical procedures to be conducted under local anesthesia may participate.

23. Has a history of organ transplantation, except for corneal transplant.

24. Has received blood products ≤2 months before V1/Screening, and/or donated blood products ≤1 month before V1/Screening, and/or plans to donate blood products throughout the duration of the study.

25. Has active diabetic proliferative retinopathy or a history of maculopathy.

    Note: Participants with non-proliferative diabetic retinopathy may participate in the study.

26. Has untreated obstructive sleep apnea.

Prior/Concomitant Therapy

27. Has known allergies, hypersensitivity, contraindication, or intolerance to the active ingredients and/or excipients of efinopegdutide or semaglutide.

28. Has been treated with any GLP-1 receptor agonist or investigational GLP-1/GCGR co-agonist within the 6 months before V1/Screening.

29. Has been treated with thiazolidinediones (ie, pioglitazone, rosiglitazone) within the 6 months before V1/Screening.

30. Has previous or current use of prescription weight-management medications (including but not limited to orlistat, topiramate and/or phentermine, lorcaserin, naltrexone and/or bupropion), or over-the-counter weight-loss medications or therapies within the 3 months before V1/Screening.

31. Has been treated with systemic corticosteroid medication within the 3 months before V1/Screening or is likely to require treatment with systemic corticosteroid medication during the study treatment period (for longer than 2 consecutive weeks in duration).

    Note: Participants using inhaled, intranasal, intra-articular, or topical corticosteroids or corticosteroids in therapeutic replacement doses may participate.

32. Has been treated with any of the following medications within the 3 months before V1/Screening or is likely to require treatment with the following medications during the study treatment period:

    - Antipsychotic drugs
    - Anticonvulsants (eg, barbiturates, gamma-aminobutyric acid analogs, hydantoins, phenyltriazines, succinimides, valproic acid and its derivatives, carbamazepine, zonisamide, and felbamate)
    - Tricyclic antidepressants, lithium, levodopa, and dopamine receptor agonists

33. Is currently on treatment with selective serotonin reuptake inhibitors (eg, fluoxetine, sertraline, paroxetine, escitalopram, citalopram, dapoxetine, seproxetine, zimelidine, mesembrine, reboxetine) and/or serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine, duloxetine, desvenlafaxine, milnacipran, fluvoxamine) that is not a stable dose for at least 3 months before V1/Screening.

34. Is currently on treatment with an antihypertensive therapy that is not a stable dose for at least 3 months before V1/Screening.

    Note: Beta blockers (systemic and ophthalmic) or medications with sympathomimetic activity (eg, pseudoephedrine, phenylpropanolamine, inhaled albuterol, methylphenidate) are prohibited.

35. Is currently on treatment with an antihyperlipidemic therapy that is not a stable dose for at least 1 month before V1/Screening.

36. Is currently on treatment with >100 IU/day of vitamin E **AND** the dose has not been stable for at least 3 months before V1/Screening.

37. Is on treatment with anticoagulants (eg, warfarin, heparin).

38. Is on treatment with or has used drugs associated with NAFLD (eg, amiodarone, anabolic steroids, chemotherapeutic agents [ie, 5-fluorouracil, tamoxifen, irinotecan, cisplatin, and asparaginase], cocaine, dronedarone, estrogens at doses greater than those used for hormone replacement or contraception, methotrexate, tetracycline [intravenous administration at high doses], valproic acid, and other known hepatotoxins [ie, drugs with a warning of hepatotoxicity in the package insert]) ≤6 months before V1/Screening.

39. Has a recent history of drug abuse (defined as within 3 years of V1/Screening) or is a current user of recreational or illicit drugs at the time of V1/Screening.

40. Is currently on treatment with or is likely to require treatment with a prohibited medication listed in Section 6.5.

Prior/Concurrent Clinical Study Experience

41. Is currently participating in or has participated in an interventional clinical study and received an investigational compound or used an investigational device ≤3 months (≤6 months for a NAFLD or NASH interventional clinical study with an investigational compound or device) before participating in this current study. Participants enrolled in observational studies or COVID-19 vaccine trials may be included and will be reviewed on a case-by-case basis for approval by the Sponsor.

Diagnostic Assessments

42. Has a clinically significant ECG abnormality that requires further diagnostic evaluation or intervention (eg, new arrhythmia, conduction disturbance) at V1/Screening.

43. Has an inability to have an MRI-PDFF performed due to:

    - Claustrophobia to a degree that prevents tolerance of an MRI-PDFF scanning procedure.

      Note: Sedation is permitted at the discretion of the investigator.

    - Metallic implant of any sort that prevents MRI-PDFF examination including, but not limited to, aneurysm clips, metallic foreign body, vascular grafts or cardiac implants, neural stimulator, metallic contraceptive device, metallic tattoo, body piercing that cannot be removed, cochlear implant, or any other contraindication to MRI-PDFF examination.

44. Has poor venous access that precludes the routine peripheral blood sampling required for this study.

45. Has exclusionary laboratory values as listed in Table 1.

    Note: If any of the laboratory exclusion criteria in Table 1 are met at the V1/Screening, the site may have the abnormal value retested 1 time.

Table 1 Laboratory Exclusion Criteria

Parameter[a]	Population (if applicable)	Study Limit for Exclusion
eGFR[b]	-	<45 mL/min/1.73 m^2
ALT	-	>5 × ULN
AST	-	>5 × ULN
ALP	-	>2 × ULN
Albumin	-	<3.5 g/dL
Total bilirubin[c]	-	≥1.3 mg/dL
INR	-	>ULN
Lipase	-	>ULN
Triglycerides	-	≥600 mg/dL (≥6.77 mmol/L)
Hemoglobin	Male Female	<12.0 g/dL (120 g/L) <11.0 g/dL (110 g/L)
Platelet count	-	<140 × 10^9/L
Bicarbonate	-	<20 mEq/L
Thyroid-stimulating hormone	-	Outside the central laboratory normal range

ALP alkaline phosphatase; ALT alanine aminotransferase; AST aspartate aminotransferase; CKD Epi Chronic Kidney Disease Epidemiology Collaboration; eGFR estimated glomerular filtration rate; INR international normalized ratio; ULN upper limit of normal; V visit.

[a] Participants with an exclusionary laboratory value may have 1 repeat determination performed if the investigator considers the V1/Screening result to be inconsistent with prior determinations. Only the laboratory test not meeting entry criterion should be repeated (not the entire panel). The last laboratory draw/result should be used to assess the exclusion criterion.

[b] Calculated by the central laboratory using the CKD Epi formula.

[c] Participants with an elevated total bilirubin but with a direct bilirubin within normal limits are eligible.

Other Exclusions

46. Routinely consumes ≥480 mg of caffeine in caffeinated beverages per day.

    Note: One cup of coffee contains approximately 120 mg of caffeine. Refer to the label of the caffeinated product for individual caffeine content.

47. Has a previous or current history of significant alcohol consumption for a period of more than 3 consecutive months within the 24 months before V1/Screening.

    Note: Significant alcohol consumption is defined as approximately 7 standard drinks per week in females and approximately 14 standard drinks per week in males, on average. One standard drink is defined as any beverage containing 14 g of pure alcohol or as defined by local guidelines.

48. In the opinion of the investigator the participant has a condition(s) (eg, medical, psychiatric, cognitive disorder) that would impede the ability to comply with scheduled visits, treatment plan, laboratory tests, and/or other study procedures.

49. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

5.3 Lifestyle Considerations

5.3.1 Diet and Activity Counseling

Participants will receive dietary and activity counseling at V3/Randomization by a qualified health care professional. At subsequent visits CCI the site staff will review the diet and activity guidance sheets with the participant. All participants will receive dietary and activity counseling uniformly across the sites. Detailed dietary and activity information will not be captured.

Participants will be counseled to maintain a medically appropriate, routine exercise program and consistent physical activity level during the study. Participants should not engage in strenuous exercise (ie, weightlifting, running, bicycling, etc.) for 48 hours before each blood collection for clinical laboratory tests for the duration of the study.

5.3.2 Alcohol, Caffeine, and Tobacco Restrictions

Participants will be assessed for alcohol consumption CCI and counseled as needed to limit alcohol use to ≤1 standard drink per day or less than approximately 7 standard drinks per week in females, and ≤2 standard drinks per day or less than approximately 14 standard drinks per week in males, on average. One standard drink is defined as any beverage containing 14 g of pure alcohol or as defined by local guidelines.

Participants will be instructed to avoid the ingestion of caffeine and nicotine-containing products for at least 30 minutes before scheduled ECGs, HR, and BP procedures/assessments.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws from the study will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies (study interventions provided by the Sponsor) will be packaged to support enrollment as required. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study interventions to be used in this study are outlined in Table 2.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strengths	Dosage Levels	Route of Admin	Treatment Period	Use	IMP/ NIMP	Sourcing
Group 1	Experi-mental	Efinopegdutide 20 mg/mL	Drug	Sterile Solution	2.4 mg	1 x 0.12 mL Injection Q1W	SC	V3 up to V7	Experi-mental	IMP	Provided Centrally by the Sponsor
Group 1	Experi-mental	Efinopegdutide 20 mg/mL	Drug	Sterile Solution	5.0 mg	1 x 0.25 mL Injection Q1W	SC	V7 up to V8	Experi-mental	IMP	Provided Centrally by the Sponsor
Group 1	Experi-mental	Efinopegdutide 20 mg/mL	Drug	Sterile Solution	10.0 mg	1 x 0.5 mL Injection Q1W	SC	V8 up to V12	Experi-mental	IMP	Provided Centrally by the Sponsor
Group 2	Active Compa-rator	Semaglutide 1.34 mg/mL	Drug	Sterile Solution	0.25 mg	1 x 0.19 mL Injection Q1W	SC	V3 up to V7	Experi-mental	IMP	Provided Centrally by the Sponsor
Group 2	Active Compa-rator	Semaglutide 1.34 mg/mL	Drug	Sterile Solution	0.5 mg	1 x 0.37 mL Injection Q1W	SC	V7 up to V8	Experi-mental	IMP	Provided Centrally by the Sponsor
Group 2	Active Compa-rator	Semaglutide 1.34 mg/mL	Drug	Sterile Solution	1.0 mg	1 x 0.74 mL Injection Q1W	SC	V8 up to V12	Experi-mental	IMP	Provided Centrally by the Sponsor

Admin administration; EEA European Economic Area; IMP investigational medicinal product; NIMP noninvestigational medicinal product; Q1W once every week; SC subcutaneous; V visit.

Notes:

- The classification of IMP and NIMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP/NIMP may exist. In these circumstances, local legislation is followed.
- For the efinopegdutide 2.4 mg dose, site personnel must expel the contents of the efinopegdutide 10.0 mg prefilled syringe into a sterile empty vial. Only the equivalent efinopegdutide 2.4 mg dose will be drawn up into a sterile syringe and administered at the site.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending on local country operational requirements.

Refer to Section 8.1.9 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Specific calculations or evaluations required to be performed to administer the proper dose to each participant are outlined in a separate document provided by the Sponsor. The rationale for selection of doses to be used in this study is in Section 4.3.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to open-label efinopegdutide 10.0 mg Q1W SC or semaglutide 1.0 mg Q1W SC.

6.3.2 Stratification

Intervention randomization will be stratified according to concurrent diagnosis of T2DM at the time of randomization (Yes or No). If either proportion of participants, those with T2DM or those without T2DM, exceeds approximately 60% of the total targeted sample size, the remaining participants enrolled will be restricted to the other stratum within this stratification factor.

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the interventions administered.

6.4 Study Intervention Compliance

When participants/caregivers administer study intervention at the site, compliance with study intervention will be assessed by site personnel observation. The date and time of each dose administered in the clinic will be recorded in the source documents, the CRF, and the participant diary. At all protocol-specified site visits, the investigator or qualified designee is to record whether treatment is taken per protocol. If not, the date(s) and reason for each dosing noncompliance must be recorded.

When participants/caregivers administer study intervention at home, compliance with study intervention will be assessed at the next site visit. Compliance will be assessed using participant diaries. Also, a visual inspection of the prefilled syringes/pens returned (used and unused) will be performed (when available). Deviation(s) from the prescribed dosage regimen will be recorded in the CRF.

If a discrepancy is noted when comparing entries in the participant's diary with the amounts of returned study intervention, the investigator or qualified designee must discuss the discrepancy with the participant and the explanation must be documented. Only the participant shall make any changes to the diary entries. The investigator or qualified designee will be responsible for transferring the appropriate information from the diary onto the appropriate CRF.

A record of the number of prefilled syringes/pens dispensed to and returned by each participant must be maintained and reconciled with study intervention and compliance records at the sites, by qualified site staff. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Sponsor Clinical Director or appropriate designee should be contacted if there are any questions regarding concomitant or prior therapy.

Both efinopegdutide and semaglutide have the potential to delay gastric emptying based on GLP-1 receptor agonism. A delay in gastric emptying can potentially impact the absorption of concomitantly administered oral medications. Therefore, caution should be exercised when oral medications are concomitantly administered with efinopegdutide or semaglutide.

Prohibited Medications

Medications listed below are prohibited during the treatment and post-treatment follow-up periods:

- Antihyperglycemic agents: Except metformin or open-label study intervention (efinopegdutide or semaglutide)

  Note: Sulfonylureas are prohibited unless needed for additional therapy for T2DM management.

- Prescription weight-management medications or over-the-counter weight-loss medications or therapies

- Corticosteroids: Treatment with oral, intravenous, or intramuscular corticosteroids for longer than 2 consecutive weeks in duration or repeated courses of pharmacologic doses of corticosteroids are prohibited. Inhaled, intranasal, intra-articular, or topical corticosteroids, or corticosteroids in therapeutic replacement doses are allowed

- Antipsychotic drugs
- Anticonvulsants
- Tricycle antidepressants, lithium, levodopa, and dopamine receptor agonists
- Beta blockers (systemic and ophthalmic) or medications with sympathomimetic activity
- Anticoagulants (eg, warfarin, heparin)
- Drugs associated with NAFLD (eg, amiodarone, anabolic steroids, chemotherapeutic agents [ie, 5-fluorouracil, tamoxifen, irinotecan, cisplatin, and asparaginase], cocaine, dronedarone, estrogens at doses greater than those used for hormone replacement or contraception, methotrexate, tetracycline [intravenous administration at high doses], valproic acid, and other known hepatotoxins [ie, drugs with a warning of hepatotoxicity in the package insert])

  Note: Investigators are encouraged to review each medication for potential hepatotoxicity by searching https://ncbi.nlm.nih.gov/books/n/livertox
- Antiretroviral therapies
- Any other investigational agent

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified to be used in this study.

6.6 Dose Modification (Escalation/Titration)

6.6.1 Dose-Escalation (Up-Titration)

Efinopegdutide

Efinopegdutide will be supplied as a sterile solution for injection at a concentration of 20.0 mg/mL. Efinopegdutide will be provided in syringes with an attached 29-gauge needle and prefilled with nominal volumes of 0.25 mL or 0.5 mL of efinopegdutide (5.0 mg or 10.0 mg, respectively). For the efinopegdutide 2.4 mg Q1W dose, the contents of a efinopegdutide 10 mg (0.5 mL) prefilled syringe will be dispensed into a sterile empty vial and 0.12 mL (2.4 mg) will be drawn into a new empty 0.3 mL syringe with 0.01 mL gradations.

Participants randomized to efinopegdutide will start the study (V3/Day 1) on a dose of 2.4 mg Q1W (0.12 mL/injection). The efinopegdutide 2.4 mg Q1W dose will be prepared as described above and will be repeated at V4, V5, and V6. **Note**: These doses will be administered at the study site.

At V7/Week 4 dose-escalation of efinopegdutide will proceed to 5.0 mg (0.25 mL) Q1W. From V8/Week 8 dose-escalation of efinopegdutide will proceed to 10.0 mg (0.5 mL) Q1W.

For participants who in the opinion of the investigator cannot tolerate the efinopegdutide 10.0 mg Q1W dose, see Section 6.6.2.

Semaglutide

Semaglutide will be supplied as a sterile solution in a prefilled, disposable, single-patient-use pen that contains either 2 mg of semaglutide in 1.5 mL (1.34 mg/mL) or 4 mg of semaglutide in 3 mL (1.34 mg/mL) in the following package configurations: (1) delivers 0.25 mg per injection, (2) delivers 0.5 mg per injection, or (3) delivers 1 mg per injection.

Participants randomized to semaglutide will start the study (V3/Day 1) on a 0.25 mg Q1W dose. Dose-escalation of semaglutide will proceed to 0.5 mg Q1W after 4 weeks of dosing (V7/Week 4) followed by a dose-escalation to 1.0 mg Q1W after another 4 weeks of dosing (V8/Week 8). **Note**: Study intervention will be administered at the study site at V3/Day1 through V7/Week 4.

For participants who in the opinion of the investigator cannot tolerate the semaglutide 1.0 mg Q1W dose, see Section 6.6.2.

The rationale for the dose-escalation regimens can be found in Section 4.3.

6.6.2 Down-Titration

The intention of the protocol is to maintain participants on the target dose of study intervention for as long as possible after randomization.

If a participant experiences intolerance **AND** has reached the target dose of efinopegdutide 10 mg Q1W or semaglutide 1.0 mg Q1W, the participant's efinopegdutide or semaglutide can be down-titrated to 5.0 mg Q1W or 0.5 mg Q1W, respectively, as considered appropriate by the investigator. Down-titration below 5.0 mg Q1W for efinopegdutide or 0.5 mg Q1W for semaglutide will not be permitted.

If a participant has had efinopegdutide/semaglutide down-titrated from the target dose, then up-titration should be considered when clinical tolerance of the study intervention has been achieved.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists will not be provided.

The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available (see Section 8.1.11).

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.12.5 unless the participant has withdrawn from the study Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

1. The participant or participant's legally acceptable representative requests to discontinue study intervention.
2. The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
3. For participants randomized to efinopegdutide, the participant is unable to tolerate at least the 5.0 mg Q1W dose. For participants randomized to semaglutide, the participant is unable to tolerate at least the 0.5 mg Q1W dose.
4. After a prolonged study intervention interruption (defined as 2 consecutive missed doses) and after consultation with the Sponsor.
5. The participant has a confirmed positive serum pregnancy test.
6. The participant/caregiver is unable to administer study intervention by V6.

Clinical Events

7. The participant has a CTCAE Grade 3 clinical AE that is considered drug-related by the investigator.
8. The participant has any CTCAE Grade 4 clinical AE, unless the investigator and Sponsor concur that the AE is ***clearly not*** causally related to study intervention and that continuation/resumption of study intervention does not place the participant at unnecessary risk.

The following AE is an exception to #7 and #8. For this event, CTCAE severity grading will not be used as a basis for a participant to be discontinued from study intervention. The requirement for a participant to be discontinued from study intervention is listed for the AE.

- **Tachycardia:** A participant with tachycardia (mean sitting HR >100 bpm) of any duration associated with symptoms that the study investigator considers potentially related to cardiac ischemia, congestive heart failure, and/or hemodynamic compromise will be discontinued from study intervention. Concerning symptoms might potentially include chest discomfort, chest pain, shortness of breath, and/or lightheadedness.

  Note (1): Participants with a minimally symptomatic event that is not sustained or recurrent, and who do not meet other discontinuation criteria may continue in the study.

  Note (2): HR assessments are based on the mean of 3 consecutive values. HR monitoring and assessment instructions are detailed in Section 8.3.5.

Laboratory Test Abnormalities

9. The participant has a CTCAE Grade 3 laboratory abnormality considered drug-related by the investigator, if clinically significant medical intervention is required to treat the event ***and/or*** the abnormality leads to hospitalization.
10. The participant has any CTCAE Grade 4 laboratory abnormality that requires clinically significant medical intervention to treat the event ***and/or*** the abnormality leads to hospitalization. Continuation/resumption of study medication may be considered if the investigator and Sponsor concur that the abnormality is ***clearly not*** causally related to study medication and that this does not place the participant at unnecessary risk.

The following laboratory abnormalities are exceptions to #9 and #10. For these events, CTCAE severity grading will not be used as a basis for a participant to be discontinued from study intervention. The requirements for a participant to be discontinued from study intervention are listed for each laboratory abnormality.

- **Abnormalities of ALT and/or AST:** If the participant has abnormal ALT and/or AST meeting criteria specified in Appendix 9 and no other cause for the combination

of laboratory abnormalities is immediately apparent (eg, prolonged INR with warfarin use), study intervention will be discontinued.

Note: See Appendix 9 for additional details on management of study intervention for participants with elevated liver enzymes.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, [redacted] should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.10. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.
- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

[redacted]

- Adherence to the study design requirements [redacted] is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedure met the protocol-specified criteria [redacted]

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from most participants over the duration of the study is not anticipated to exceed approximately 450 mL (see operations manual). For participants in the PK substudy, the maximum amount of blood collected over the duration of the study is not anticipated to exceed approximately 500 mL (see operations manual).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

8.1.1.3 Consent and Collection of Specimens for the PK Substudy

The investigator or medically qualified designee will explain the PK substudy consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to the PK substudy. A copy of the informed consent will be given to the participant before performing any procedure related to the PK substudy.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician (or a qualified designee), to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization (V3/Week 0), site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified requirements (see Sections 5.1 and 5.2), and record prior medication taken by the participant within 3 months before V1/Screening. The site may rely on participant report for this information.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study on the appropriate eCRF.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

After all required screening procedures have been completed and a participant's eligibility has been confirmed, the study randomization visit will be registered in IVRS.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Compliance

8.1.8.1 Diet and Activity Counseling/Monitoring

Participants will receive diet and activity guidance sheets (see Section 5.3.1). At site visits CCI [redacted] site staff will reinforce the information on the diet and activity guidance sheets.

8.1.8.2 Assessment of Alcohol Consumption

Participants will report the average number of drinks consumed per week since the last visit.

Participants who consume more than the recommended amount of alcoholic drinks per week (ie, more than approximately 7 standard drinks per week in females or more than approximately 14 standard drinks per week in males) must be counseled by the site. If a participant is noncompliant with the alcohol use restrictions for 3 or more visits over the course of the study, consultation between the investigator and Sponsor is required for a collaborative decision on participant management.

For further details see Section 5.3.2.

8.1.8.3 Hypoglycemia and Hyperglycemia Counseling

The site will review the symptoms of hypoglycemia and hyperglycemia with the participant CCI [redacted]

The site will counsel participants with T2DM to monitor their fingerstick glucose concentrations at a frequency determined to be appropriate by the investigator. Additionally, the site will counsel these participants to perform a fingerstick glucose measurement if any symptoms occur that may be related to hypoglycemia (eg, weakness, dizziness, shakiness, increased sweating, palpitations, or confusion) and provide guidance on management. Furthermore, participants will be counseled to avoid delay in treating these symptoms.

8.1.8.4 Dehydration and Postural Hypotension Counseling

The site will review the signs and symptoms of dehydration and postural hypotension with the participant CCI [redacted] Participants should contact a medical professional promptly if these symptoms occur.

8.1.8.5 Injection Training (Participant and/or Caregiver)

At V3/Week 0 (Day 1/Randomization) and V7/Week 4:

1. Participants/caregivers will receive training from the site staff on the proper method for SC injection and will review written instructions for injection. Participants/caregivers

will take home the written instructions (V3 only) and will be instructed to review these materials at home.

2. Participants/caregivers will be expected to administer the study intervention (efinopegdutide or semaglutide) under the guidance of the site staff.

    - Administration of study intervention should occur after completion of all study procedures including the collection of all fasting blood samples.

8.1.8.6 Dispense Open-Label Study Intervention

Participants will be dispensed open-label study intervention (efinopegdutide or semaglutide) at scheduled study visits from V3/Week 0 (Day 1) through V7/Week 4.

At study visits V7/Week 4 through V11/Week 20, study intervention kits will be dispensed to participants to self-administer study intervention at home.

Refer to Section 8.1.9 for further details.

8.1.8.7 Witnessed Dosing

Administration of study intervention will be witnessed by the investigator and/or qualified study staff at V3/Week 0 through V7/Week 4. Dosing should occur after completion of all study procedures including the collection of all fasting blood samples.

During the treatment period:

1. Retraining on the administration of study intervention will be provided as needed during the study and documented by site staff as appropriate.

2. Participants/caregivers should be instructed to refer to the written instructions when administering injections of the study intervention at home.

Notes:

- No coaching by site staff will be provided to the participant/caregiver during study intervention administration unless deemed necessary.

- If a participant/caregiver is unable to administer study intervention, the site staff may administer the dose of study intervention to the participant through V5/Week 2.

- If a participant/caregiver is unable to administer study intervention by V6/Week 3, they will be discontinued from study intervention.

8.1.8.8 Dispense/Review Participant Diary

Participants will receive diaries [redacted] to document their experience with injections; specifically, to collect the date, time, and who administered the injection, as well as any comments related to the injection experience.

Participants should bring their completed diary to all study visits [redacted] and be reminded to do so (eg, by phone or text) before each visit. Site personnel will review the diaries at each study visit to monitor compliance and review for any potential AEs from the comments entered.

See Section 6.4 for details on study intervention compliance.

8.1.8.9 Study Intervention Accountability

When participants/caregivers administer study intervention at home (ie, Week 5 through Week 23), accountability for the administration of study intervention will be assessed at the next site visit. Compliance will be assessed using participant diaries. A visual inspection of the prefilled syringes/pens returned (used and unused) will also be performed (when available) to ensure accurate drug accountability.

Refer to Section 6.4 for further details on study intervention compliance.

8.1.9 Study Intervention Administration

Administration of study intervention will be witnessed by the investigator and/or study staff at V3/Week 0 through V7/Week 4. Dosing after V7/Week 4 and through Week 23 should be administered Q1W by the participant/caregiver unsupervised at home.

Beginning at V3/Week 0, participants/caregivers will be instructed to administer Q1W a single injection of study intervention (ie, efinopegdutide or semaglutide). Study intervention should be administered SC to the abdomen, thigh, or upper arm. Participants/caregivers should be instructed to use a different injection site each week when injecting into the same body region.

8.1.9.1 Timing of Dose Administration

Study intervention should begin on the day of randomization (V3/Week 0/Day 1) and administered at the study site as a witnessed dose. This first dose of study intervention (efinopegdutide or semaglutide) should be administered after completion of all study procedures including the collection of all fasting blood samples.

Administration of study intervention at V4/Week 1 through V7/Week 4 should also be performed as a witnessed dose at the study site after completion of all study procedures including the collection of all fasting blood samples.

Dosing after V7/Week 4 and through Week 23 should be administered Q1W by the participant/caregiver unsupervised at home on the same day each week, at any time of the day, with or without meals.

The day of weekly administration can be changed, if necessary, as long as the time between 2 doses is at least 48 hours. If a dose of study intervention is missed, administer study intervention as soon as possible within 5 days after the missed dose. If more than 5 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, participants can then resume their regular Q1W dosing schedule.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period (V3 through V12) should be encouraged to complete all applicable activities scheduled for the DC visit at the time of study intervention withdrawal and to continue to be followed for all remaining study visits as outlined in [redacted] Section 8.12.5.

For participants who withdraw from the study, any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.10.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

Critical equipment for this study includes a digital body weight scale. The study site is responsible for conducting accuracy checks to ensure the scale to measure body weight is working correctly. Additional details are provided in the operations manual.

8.2 Efficacy Assessments

8.2.1 Liver Fat Content by Magnetic Resonance Imaging-Estimated Proton Density Fat Fraction

LFC will be assessed by MRI-PDFF during screening (V2/MRI-PDFF) and at V12/Week 24. The process for image collection and transmission to the iCRO is in the Site Imaging Manual. The same imaging technique and MRI-PDFF scanner should be used for a participant throughout the study to minimize variability.

The screening MRI-PDFF must be performed at V2 and all participants must have satisfied all V1/Screening eligibility criteria before imaging can be performed.

For participants who discontinue study intervention before V12/Week 24, an MRI-PDFF should be performed at the time of study intervention discontinuation if at least 4 weeks have passed since the first dose of study intervention (see Section 8.12.5).

All scheduled MRI-PDFF images/data for all participants will be submitted to the iCRO for LFC assessment by BICR (see Section 8.12.3.2). The iCRO will communicate to the site whether a participant has met the MRI-PDFF entry criterion (ie, LFC ≥10%). A specific LFC score will not be communicated to the sites or participants during the study.

Clinically significant findings in the local interpretation of the MRI-PDFF images at baseline and during the treatment period should be reported by the site investigator and recorded appropriately.

For further information see Section 8.12.3.2.

8.2.2 Body Weight Assessment and Monitoring

Body weight (kg) will be measured in duplicate using a standardized, digital scale CCI [redacted] CCI [redacted] The 2 measurements should be recorded in the source documents. If the 2 measurements differ by more than 0.2 kg or by 0.4 lb, (1) check the participant to ensure proper positioning and/or conduct an accuracy check on the scale and (2) a different set of duplicate measurements must be obtained, and the 2 new measurements should be

recorded in the source documents. Only the final body weight measurement should be recorded in the eCRF.

Detailed information regarding the collection of body weight can be found in the operations manual.

8.2.3 Lipid Metabolism

The laboratory efficacy endpoints for lipid metabolism (cholesterol [total, HDL-C, LDL-C], TG, and apoB) should be collected CCI Participants should be fasted for at least 8 hours before collection and should take their concomitant medications as prescribed (see Section 8.12.1).

Sample collection, storage, and shipment instructions for samples will be provided in the laboratory manual.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided in subsequent sections. The anticipated maximum amount of blood to be drawn over the duration of the study (from prestudy to poststudy visits) can be found in Section 8. The approximate blood volumes drawn by visit and by sample type per participant can be found in the operations manual.

CCI

8.3.1 Physical Examinations

Complete and directed physical examinations will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard CCI The complete physical examinations will at minimum include assessments of general appearance, skin, lymphatic system, eyes, ears, nose, throat, cardiovascular system, respiratory system, abdomen/gastrointestinal system, urological system, musculoskeletal system, and neurological system. Unless the study investigator feels there is a specific need, genitourinary, rectal, and breast examination should be omitted from the complete physical examination.

The directed physical examinations will at a minimum include assessment of the heart, lungs, abdomen, skin, and extremities. Other body systems may be evaluated with either type of examination. Abnormalities considered clinically significant should be reported as AEs.

A physical examination (complete or directed) may be performed at any unscheduled visit if deemed necessary by the investigator or medically qualified designee.

8.3.2 Height

Height will be measured without shoes using a calibrated stadiometer at V1/Screening. Document height in meters to the nearest 0.01 meter (0.01 meter 1 cm).

8.3.3 Body Mass Index

BMI will be calculated (weight/height^2 in kg/m^2) by the investigator or qualified designee based on participant's height and weight at V1/Screening to ensure the participant meets study inclusion criteria (see Section 5.1). Document BMI to the nearest 0.1 kg/m^2.

See Section 8.2.2 for details on body weight assessment and monitoring.

8.3.4 12-Lead Electrocardiogram

A standard supine 12-lead ECG will be obtained and reviewed locally by an investigator or medically qualified designee (consistent with local requirements) CCI CCI Clinically significant abnormal ECG findings observed during the 4-week screening period should be recorded as medical history. Assessments may be repeated during the study, as clinically indicated.

- Participants should avoid the ingestion of caffeine and nicotine-containing products for at least 30 minutes before the scheduled ECGs.

- ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position and before the assessment of BP and HR as well as before blood collection.

All ECGs performed should be reviewed at the investigative site for participant safety monitoring. The investigator is responsible for retaining all copies of the ECG reports.

8.3.5 Vital Signs

Vital signs will be measured at all scheduled site visits except V2/MRI-PDFF CCI CCI At all scheduled visits, HR and BP should be measured under the following conditions:

- Triplicate assessment of sitting systolic and diastolic BP (mm Hg) and HR (bpm) will be collected at approximate 2-minute intervals using automated devices. The time, positioning, and arm used should be recorded for each measurement.

- Measurements must be conducted after a 10-minute resting period with the participant comfortably seated in a chair with the legs uncrossed and the back and arm supported. Measurements should not be made while the participant is on an examination table. The participant should be instructed to relax as much as possible and to not talk during the measurement procedure.

- Site personnel should ensure that the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum).

- The participant should be asked to remove all clothing that covers the location of cuff placement.

- Site personnel should use the same BP measuring device and under the same external conditions throughout the study for each participant.

- Other procedures should not be performed during the time of the BP and HR measurements.

Detailed information regarding BP and HR monitoring is contained in the operations manual. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.6 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed CCI [redacted] CCI [redacted]

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, CCI [redacted] must be conducted in accordance with the laboratory manual and the SoA (see Section 1.3).

- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

- Participants will be counseled to fast (ie, no food, study intervention, or drink except water and concomitant medications as prescribed) for at least 8 hours before study visits requiring fasted blood collections or procedures (see Section 8.12.1).

- Serum hCG testing will be performed in female participants where a pregnancy is suspected.

8.3.7 Pregnancy Testing

- Pregnancy testing:

  - Pregnancy testing requirements for study inclusion are described in Section 5.1.

- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1.

- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.8 Adverse Event Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs CCI and more frequently if clinically indicated. AEs will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE, Version 5.0 (see Appendix 10). **Note**: For AEs that are an exception to the NCI CTCAE grading, see Section 7.1.

The criteria for the discontinuation of study intervention for individual participants are described in Section 7.1.

Please refer to Section 8.4 for detailed information regarding assessing and reporting AEs, SAEs, and other reportable safety events.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the event causes the participant to be excluded from the study or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention randomization through 5 weeks after the last dose of study intervention, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside the period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 3.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 3 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
SAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/termination ; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential DILI - Require regulatory reporting	Not required	Within 24 hours of learning of event
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

DILI drug induced liver injury; ECI event of clinical interest; NSAE nonserious adverse event; SAE serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

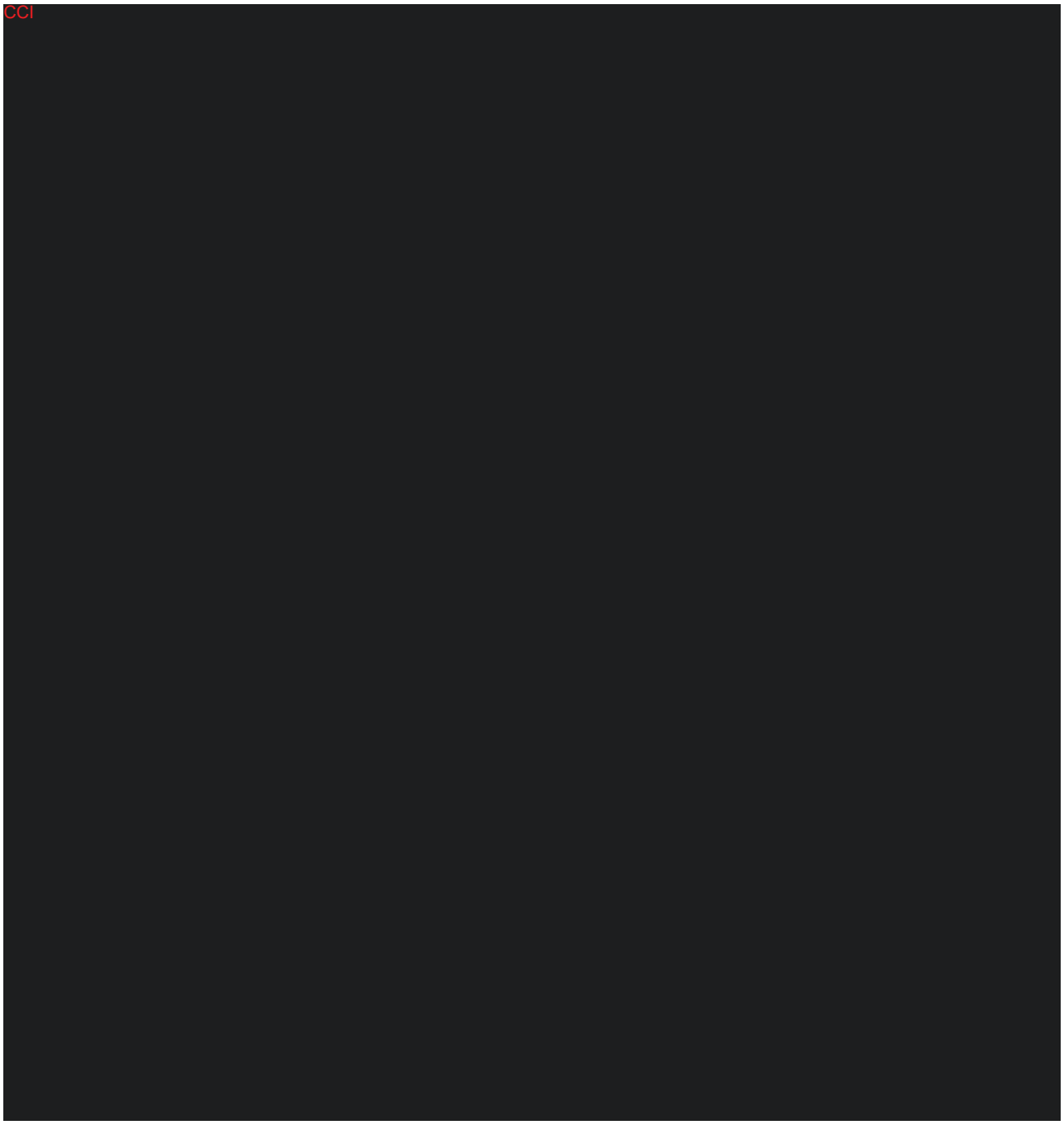
The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

There are no disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs.

CCI



CCI

[redacted]

8.5 Treatment of Overdose

In this study, an overdose is any total dose within 48 hours that is higher than the prescribed maximum dose of efinopegdutide or semaglutide as defined in the protocol.

No specific information is available on the treatment of overdose. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

CCI

[redacted]

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[redacted]

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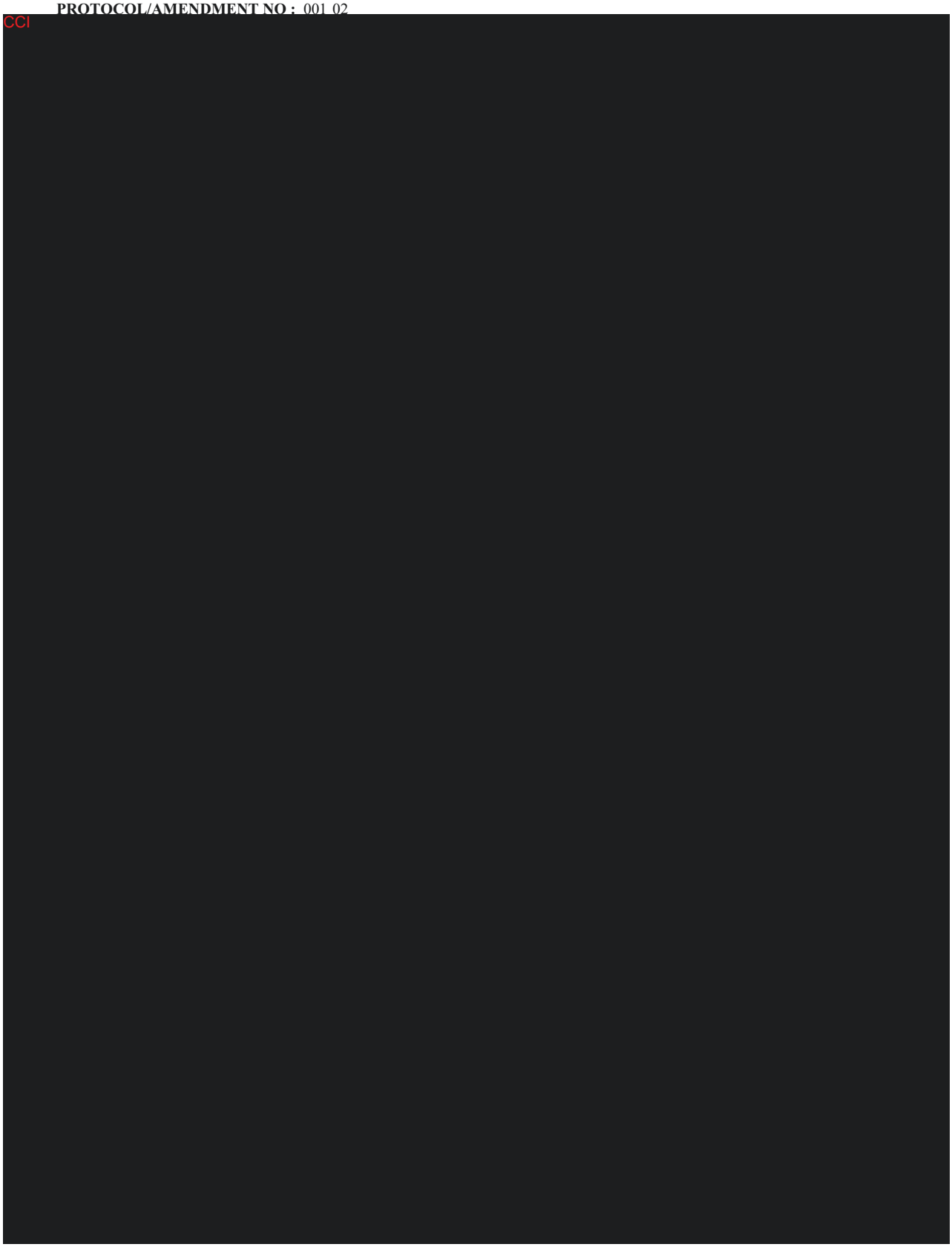

CCI

[redacted]

8.9 Biomarkers

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Blood for genetic analysis
- Blood for serum biomarkers
- Blood for plasma biomarkers
- Blood for plasma peptide biomarkers (eg, endogenous glucagon)

Note: Participants should be fasted for the collection of serum, plasma, and plasma peptide biomarkers.

CCI

[redacted]

8.10 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for FBR, the following specimens will be obtained as part of FBR:

- Leftover DNA for future research
- Leftover main study serum biomarkers for future research
- Leftover main study plasma biomarkers for future research
- Leftover main study plasma peptide biomarkers for future research

8.11 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics are not evaluated in this study.

8.12 Visit Requirements

CCI [redacted] Specific procedure-related details are provided in Section 8.

8.12.1 Fasting Before Scheduled Visits

Participants should be counseled to fast (ie, no food or drink except water, and concomitant medications as prescribed) for at least 8 hours before study visits requiring fasted blood collections or procedures CCI [redacted] Participants who have not fasted for the V1/Screening should have all blood collections rescheduled and completed before the V2/MRI-PDFF. After randomization (V3/Week 0), participants who do not fast before a scheduled visit will be required to return fasted for a study visit within 3 days.

Note: Participants should take their concomitant medications as prescribed before study visits requiring fasted blood collections or procedures CCI [redacted]

8.12.2 Scheduling Visits

The V2/MRI-PDFF should be scheduled at V1/Screening.

During the treatment period, at the end of each study visit the next study visit should be scheduled. Every effort should be made to adhere to the visit schedule CCI [redacted] Visits during the treatment period should be scheduled within ±3 days (V3 through V7) and ±5 days (V8 through V12). If unavoidable and after consultation with the Sponsor, a visit may be scheduled at a time outside this recommended range, but the schedule for subsequent visits must be adjusted so that the total duration of the treatment period is as close as possible to 24 weeks. Visits should be scheduled relative to the date of randomization V3/Week 0 (Day 1). If a visit is scheduled at a time other than the protocol designated time, careful consideration must be given to the amount of study intervention the participant has available.

Study sites should phone the IVRS at each of the scheduled study visits (except V2 and V13) for purposes of enrollment tracking.

8.12.2.1 Visit Reminders

Before each study visit, participants should be called and be reminded of:

- The date and time of their next appointment.
- The requirement:

  To not engage in physically strenuous exercise (ie, weightlifting, running, bicycling, etc.) within 48 hours before their study visit.

  To fast for at least 8 hours before all study visits requiring fasting laboratory collections.

  To take non-study medications as directed by the prescribing physician.

  That administration of study intervention will be witnessed by the investigator and/or study staff at the study visit (V3/Week 0 through V7/Week 4 only).

  To bring study intervention (used and unused prefilled syringes/pens) to site visits V8 through V13.

  To bring participant diaries to site visits V4 through V12.

8.12.3 Screening

The interval from V1 up to V3 will constitute a screening period of approximately 4 weeks. The screening period may be extended under special circumstances (eg, scheduling issues, delays in obtaining MRI-PDFF results) with the explicit approval of the Sponsor Clinical Director.

8.12.3.1 V1/Screening

Potential participants will be evaluated at V1/Screening to determine if they fulfill the entry requirements as described in Sections 5.1 and 5.2. For participants assessed as eligible to participate in the study, blood and urine samples will be obtained CCI [redacted] CCI [redacted] Participants who have not fasted for the V1/Screening should have all blood collections rescheduled and completed before V2/MRI-PDFF.

Note: All participants at study sites in Argentina must be tested for hepatitis B, hepatitis C, and HIV at V1/Screening (see Appendix 7).

If any participant fails to meet the V1/Screening study entry criteria, rescreening is permitted only once **AND** if the investigator believes that the results of the V1/Screening procedures/assessments were inconsistent with the participant's medical history and/or clinical status.

8.12.3.2 V2/MRI-PDFF

LFC will be measured by MRI-PDFF once the participant has been found to meet all study eligibility criteria assessed at V1/Screening. All MRI-PDFF images/data will be evaluated by BICR. The appointed iCRO will review all baseline images/data and confirm participants meet the MRI-PDFF entry criteria (see Section 5.1) before V3/Randomization.

Note: A second MRI-PDFF will be performed at 24 weeks after V3/Randomization. If a participant discontinues study intervention early, see Section 8.12.5.

8.12.4 Treatment Period

At V3/Randomization (Day 1), participants who meet all study entry criteria will enter the treatment period of approximately 24 weeks. Participants will be randomized in a 1:1 ratio to efinopegdutide 10 mg Q1W or semaglutide 1.0 mg Q1W. Participants will be assigned a unique treatment/randomization number.

After completion of all V3/Randomization (Day 1) procedures/assessments (including the collection of fasting blood samples)[CCI] study eligible participants will be provided instruction on the administration of study intervention. Study intervention will be administered by participants/caregivers as a witnessed dose at the study site. Participants will record in their diary the date, time, and who administered the injection as well as any comments related to the injection experience.

At scheduled site visits from V4/Week 1 through V7/Week 4, study intervention will be dispensed, and participants/caregivers will administer study intervention as a witnessed dose at the study site after all study procedures have been performed [CCI] [CCI] Participants will record in their diary the date, time, and who administered the injection as well as any comments related to the injection experience.

After V7/Week 4 and up to V12/Week 24, participants/caregivers will be expected to administer study intervention at home[CCI] Therefore, at all scheduled site visits from V7/Week 4 through V11/Week 20, the site will dispense (supported by IRT) study intervention kits for administration of study intervention at home.

Beginning after V7/Week 4 and continuing through the end of the treatment period, participants will record in their diary the date, time, and who administered the injection as well as any comments related to the injection experience. Participants will return their diary, used and unused prefilled syringes/pens, and the study intervention kit packaging at their next scheduled site visit.

Note: Participants will be re-instructed on appropriate injection technique at V7/Week 4 and as needed based on observed injection experience. See Section 8.1.8.3 for further details.

See Section 8.1.9.1 for timing of dose administration.

8.12.5 Discontinued Participants Continuing to be Monitored in the Study

Procedure for all participants who discontinue from study intervention:

- All applicable activities scheduled for the DC visit should be completed CCI [redacted] except as noted below:

  For participants where at least 4 weeks have passed since the first dose of study intervention, the end of study MRI-PDFF should be performed as part of the DC visit procedures. Note, MRI-PDFF assessed in these participants will potentially be used for further evaluation of the kinetics of LFC reduction from the onset of treatment. For participants where less than 4 weeks have passed since the first dose of study intervention, an end of study MRI-PDFF should not be performed at the time of withdrawal.

It is intended that all randomized participants should be followed through completion of the study, regardless of premature discontinuation of treatment, unless the participant withdraws consent from any study follow-up. Thus, participants who discontinue from study intervention before completion of the study should continue to be monitored after the DC visit procedures are completed to obtain relevant information through the end of the study.

Procedure for participants who discontinue from study intervention **AND** continue to be monitored after discontinuation:

- All applicable activities should be completed at scheduled study visits through V12/Week 24 CCI [redacted] **except as noted below**:

  CCI [redacted]

  MRI-PDFF should not be performed at V12/Week24.

For those participants who have discontinued study intervention early and who miss the remaining study visits, sites will be instructed to exert diligent efforts to continue to contact them. To enable sites to reach participants, the participants should provide primary and secondary contact information (eg, home telephone, work telephone, mobile telephone). Sites must document the outcome of the telephone contact(s) to show diligent efforts have been made.

Additionally, the ICF will explain the importance of continued data collection from participants, including the use of continued contact by telephone.

8.12.6 Post-Treatment Follow-up Visit

Participants will be required to return to the study site for a post-treatment follow-up visit (V13) approximately 5 weeks after the last dose of study intervention.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If after the study has begun changes are made to primary and/or key secondary hypotheses or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but before database lock, will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

Other planned analyses (ie, those specific to the analysis of PK data and FBR) will be documented in separate analysis plans.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized here. The comprehensive plan is provided in Sections 9.2 through 9.12.

Study Design Overview	A Phase 2a, Randomized, Active-Comparator-Controlled, Open-Label Study to Evaluate the Efficacy and Safety of Efinopegdutide (MK-6024) in Individuals With Nonalcoholic Fatty Liver Disease
Treatment Assignment	Participants (approximately 130) will be randomized in a 1:1 ratio between 2 treatment groups: (1) efinopegdutide 10.0 mg Q1W or (2) semaglutide 1.0 mg Q1W. Randomization will be stratified by T2DM status (Yes or No).
Analysis Populations	Efficacy: FAS Safety: APaT
Primary Endpoint	Relative reduction (%) from baseline in LFC at Week 24.
Key Secondary Endpoint	Not applicable.
Statistical Methods for Key Efficacy Analyses	The primary efficacy analysis will compare the efficacy of efinopegdutide to semaglutide in relative reduction (%) from baseline in LFC at Week 24. The difference (efinopegdutide minus semaglutide) in means and the associated 90% CI and *p*-value will be provided based on a cLDA model. For the primary hypotheses, efinopegdutide will be considered superior to semaglutide if the 1-sided *p*-value is <0.05 (ie, lower bound of the 2-sided 90% CI excludes zero). If the test of superiority is successful, and if the lower bound of the 2-sided 90% CI is at least 10%, efinopegdutide will be considered superior to semaglutide by 10% or more.
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for the between-treatment difference (efinopegdutide minus semaglutide) in the percentage of participants with events, these analyses will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985].

Interim Analyses	An IA is planned for administrative purposes. In addition, the IA may be used to assess futility. The IA is planned to be performed once ≥25 participants in the efinopegdutide group have had LFC measured by MRI-PDFF at the Week 24 assessment. The study may stop for futility if the posterior probability is <5% that the true mean relative reduction from baseline in LFC is ≥30% for the efinopegdutide group.
Multiplicity	The Type-I error rate will be controlled at 1-sided α=0.05 using an ordered testing procedure. H1 (superiority) will be tested first. H2 (superiority by 10% or more) will be tested only if the success criterion of H1 is met.
Sample Size and Power	The planned sample size is approximately 130 participants. The sample size was chosen based on the primary endpoint, relative reduction (%) from baseline in LFC at Week 24, assuming a true treatment difference of approximately 19.4%, a common SD of 20%, and 10% dropouts. (H1) A sample size of 65 participants per arm provides approximately 99% power to establish that efinopegdutide is superior to semaglutide, with a 1-sided α=0.05. (H2) A sample size of 65 participants per arm provides approximately 80% power to establish that efinopegdutide is superior to semaglutide by at least 10%, with a 1-sided α=0.05.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This study is being conducted as a randomized, open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented by the IRT vendor.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for within- and/or between-treatment differences are listed below.

For analysis purposes, the baseline assessment is considered the one closest to but before or on the day of randomization (Day 1).

9.4.1 Efficacy Endpoints

Primary Efficacy Endpoint

- Mean relative reduction (%) from baseline in LFC measured by MRI-PDFF (evaluated by BICR) after 24 weeks.

Secondary Efficacy Endpoints

- Mean absolute reduction (%) from baseline in LFC measured by MRI-PDFF (evaluated by BICR) after 24 weeks.
- Mean percent change from baseline in body weight after 24 weeks.
- Mean change from baseline in fasting lipid levels over 24 weeks.

Efficacy endpoints are further described in Section 4.2.1.1.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory safety tests, and vital signs.

Safety parameters are described in Section 4.2.1.2.

9.4.3 Pharmacokinetic Endpoint

The key PK endpoint for efinopegdutide is Ctrough.

Additional details are in Section 4.2.1.3.

9.4.4 Pharmacodynamic Endpoints

PD endpoints are biomarkers and/or composite scores reflecting liver inflammation and fibrosis including ELF, CK-18 M30, and Pro-C3.

Additional details are in Section 4.2.1.4.

9.4.5 Immunogenicity Endpoints

Immunogenicity endpoints are the incidence and magnitude (titer) of ADA to efinopegdutide.

Additional details are in Section 4.2.1.5.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

The FAS population will serve as the primary population for all efficacy analyses. All randomized participants who have at least 1 injection (including only partial) of study intervention and have at least 1 assessment will be included in this population. Participants will be included in the treatment group to which they are randomized.

For analyses that require a baseline value, participants with a missing baseline value will be excluded.

9.5.2 Safety Analysis Population

Analyses of safety will be performed in the APaT population, consisting of all randomized participants who received at least 1 injection (including only partial) of study intervention. Participants will be included in the treatment group corresponding to the study treatment they received for the analysis of safety data. This will be the randomized treatment group for all participants except for those who take incorrect study intervention for the entire treatment period. Such participants will be included in the treatment group corresponding to the study intervention actually received. Any participant who receives both correct and incorrect study intervention injections will be analyzed according to the randomized treatment group and a narrative will be provided for any events that occur during the injection period for which the participant was incorrectly dosed.

At least 1 laboratory or vital sign measurement obtained after at least 1 dose of study intervention is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Safety analysis will be based on observed data only. No imputation will be performed for missing data.

9.5.3 Pharmacokinetic Analysis Population

The population for PK data analysis will include all participants with at least 1 measurable PK sample after treatment with efinopegdutide.

9.5.4 Pharmacodynamic Analysis Population

The population for the PD endpoints will be the FAS population. All randomized participants who have at least 1 injection (including only partial) of study intervention and have at least 1 assessment for those analyses for which this is required will be included in this population.

9.5.5 Immunogenicity Analysis Population

The population for immunogenicity analysis will include all participants with at least 1 ADA assay result after treatment with efinopegdutide.

9.6 Statistical Methods

Efficacy results that will be deemed to be statistically significant after consideration of the Type-I error control strategy are described in Section 9.8. Nominal *p*-values (ie, unadjusted for multiplicity) may be computed for other efficacy analyses for descriptive purposes rather than for assessing statistical significance. All statistical tests will be conducted at the α 0.05 (1-sided) level.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the exploratory objectives will be described in the sSAP.

The primary efficacy estimand (treatment policy) used for this study, following the guidance in ICH E9 (R1) [European Medicines Agency 2020], has the following 5 attributes:

1. The **treatment** condition of interest and, as appropriate, the alternative treatment condition to which the comparison will be made: intervention with efinopegdutide or semaglutide.

2. The **population** of patients targeted by the clinical question: individuals with NAFLD.

3. The **variable** (or endpoint) to be obtained for each participant that is required to address the clinical question: relative reduction (%) from baseline in LFC.

4. The specification of how to account for **other intercurrent events** to reflect the scientific question of interest: Discontinuation of study treatment, down-titration of study treatment, and taking additional medication are intercurrent events of interest. A treatment policy approach will be taken for intercurrent events. Thus, responses following intercurrent events are of interest for the estimand.

5. The **population-level summary** for the endpoint which provides the basis for a comparison between-treatment conditions: difference in the mean relative reduction (%) from baseline at Week 24.

9.6.1.1 Primary Efficacy Endpoint

The primary approach for addressing the primary hypotheses will use a cLDA method proposed by Liang and Zeger [Liang, K-Y. and Zeger, S. L. 2000]. This model assumes a common baseline mean across treatment groups within strata and a different mean for each treatment group at the Week 24 post-baseline time point. In this model, the response vector consists of the baseline value and the calculated relative reduction (%) from baseline at the Week 24 post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will also adjust for treatment, time, stratum (Section 6.3.2), treatment by stratum interaction, time by treatment, and time by stratum interaction. The treatment difference (efinopegdutide versus semaglutide) in terms of mean relative reduction (%) from baseline in LFC after 24 weeks

will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

A *p*-value for the comparison of efinopegdutide versus semaglutide <0.05 (1-sided) will be considered statistically significant. If this is significant, and if the lower bound of the 2-sided 90% CI is at least 10%, efinopegdutide will be considered superior to semaglutide by 10% or more.

Although the baseline measurement is included in the response vector, it is independent of treatment, and hence, the baseline means are constrained to be the same for different treatment groups within each stratum. Of note, if there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal ANCOVA model which uses the baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and CIs for individual treatment effects. Moreover, this model allows the inclusion of participants who are missing either the baseline or the Week 24 post-baseline measurement, thereby increasing efficiency.

The model-based least squares mean change from baseline for each treatment group and difference (with CI) between-treatment groups at the Week 24 post-baseline time point will be summarized.

Some participants who discontinue from the study before their Week 24 assessment may have a post-randomization LFC measurement before discontinuation. For the primary analysis at the Week 24 timepoint, the Week 24 assessment used in the analysis will be the assessment that is closest to the Week 24 nominal visit (Day 168) that is on or after relative Day 28.

The primary analysis approach is based on an assumption that the mechanism for missing data is ‘missing at random’. If significance is achieved in the first hypothesis test (H1), sensitivity analyses of relative reduction (%) from baseline in LFC will be performed to assess the robustness of the primary analysis results to violations of the ‘missing at random’ assumption. The sensitivity analyses will be described in the sSAP.

9.6.1.2 Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analyzed using the same cLDA model as described for the primary endpoint in Section 9.6.1.1. For analysis of absolute reduction from baseline in LFC, the response vector will consist of observed baseline and post-baseline values. For other endpoints except TG, the response vector will consist of the baseline value and the calculated percent changes from baseline. For analyses of TG, the response vector will consist of log-transformed baseline and post-baseline values. The treatment difference in terms of mean percent changes from baseline to a given time point will be estimated from this model through back-transformations.

Table 6 summarizes the analysis strategies for the primary and secondary efficacy endpoints.

Table 6 Analysis Strategy for Key Efficacy Variables

Endpoint	Approach	Statistical Method	Missing Data Approach
Primary Endpoint			
Mean relative reduction (%) from baseline in LFC	Primary	cLDA	Model-based
Secondary Endpoints			
Mean absolute reduction from baseline in LFC	Primary	cLDA	Model-based
Mean percent change from baseline in body weight	Primary	cLDA	Model-based
Mean percent change from baseline in lipid profile (Total cholesterol, HDL-C, LDL-C, Non-HDL-C, TG, and apoB)	Primary	cLDA	Model-based
apoB apolipoprotein B; cLDA constrained longitudinal data analysis method; HDL C high density lipoprotein cholesterol; LDL C low density lipoprotein cholesterol; LFC liver fat content; TG triglycerides.			

9.6.2 Analysis Methods for Safety Analyses

Safety and tolerability will be assessed, comparing efinopegdutide to semaglutide, by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs. The primary approach to analysis of safety will include all data through 24 weeks on treatment including the 5-week follow-up assessment (data out to the follow-up assessment will be considered as on treatment based on a 35-day relative day cutoff post last dose).

Adverse Events

AEs will be coded using the standard MedDRA and grouped according to SOC.

The analysis of safety results will follow a tiered approach (Table 7). The tiers differ with respect to the analyses that will be performed.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be subject to inferential testing for statistical significance. No AEs have been designated as Tier 1 for this study.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between-treatment differences in the proportion of participants with events.

Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event. All other AEs and PDLCs will belong to Tier 3. The threshold of at least 4 events was chosen because the 95% CI for the between-group difference in percent incidence will

always include zero when the treatment groups each have fewer than 4 events and thus would add little to the interpretation of potentially meaningful differences.

In addition, adjudication-confirmed AEs (ie, pancreatitis), summary measures of AEs consisting of the percentage of participants with any AE, with a drug-related AE, with a SAE, with an AE which is both drug-related and serious, who discontinued due to an AE, and who died will be considered Tier 2 endpoints.

The 95% CIs will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985].

Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in AEs and PDLCs.

Tier 3 Events

Safety endpoints that are not Tier 2 events will be considered Tier 3 events. Only point estimates by treatment group will be provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory and vital signs parameters, summary statistics for baseline, on treatment, and change from baseline values will be provided by treatment group.

Adjudicated Adverse Experiences

For AEs prespecified for adjudication (see Section 10.1.4.1), results of adjudication will also be provided as a listing in the CSR for this study. Further details may be provided in the sSAP.

Table 7 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any serious AE	X	X
	Any drug-related AE	X	X
	Any serious and drug-related AE	X	X
	Discontinuation due to AE	X	X
	Death	X	X
	Specific AEs, SOCs, or PDLCs (incidence ≥4 of participants in 1 of the treatment groups)	X	X
	Adjudicated AEs	X	X
Tier 3	Specific AEs, SOCs, or PDLCs (incidence <4 of participants in all the treatment groups)		X
	Change from baseline results (laboratory tests, ECGs, vital signs)		X

AE adverse event; CI confidence interval; ECG electrocardiogram; PDLC predefined limit of change; SOC system organ class; X results will be provided.

9.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed using tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.6.4 Analysis Methods for Pharmacokinetic Analyses

The details of PK analyses will be provided in a pharmacometric analysis plan.

9.7 Interim Analyses

An IA is planned for administrative purposes. In addition, the IA may be used to assess futility. The IA is planned to be performed once ≥25 participants in the efinopegdutide treatment group have had LFC measured at the V12/Week 24 assessment. Key endpoints to be evaluated include LFC, body weight, AEs, and laboratory PDLC.

The IA will be performed by an internal independent statistician and scientific programmer who will have no other responsibilities associated with the study, and results will be reviewed by the TA-EOC.

The administrative purposes served by the IA are to enable the TA-EOC to assess whether the interim results are favorable enough to merit initiation of additional programmatic activities.

Study enrollment is expected to be complete at the time of the IA. If at least 10 participants are still actively participating in the study and have not reached V11/Week 20 at the time of the IA, the TA-EOC will assess the LFC results for futility. CCI

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Safety Data Review

In addition to the IA described above, a review of safety data by the Sponsor's siDMC will be triggered if any of following criteria are met:

- Three participants in the same treatment group develop the same Grade 3 or higher AE (CTCAE grading) that is considered drug-related by the investigator
- Two participants in the same treatment group develop any CTCAE Grade 4 AE that is considered drug-related by the investigator

- One participant develops a CTCAE Grade 5 AE that is considered drug-related by the investigator

Note: As described in Section 7.1, discontinuation for tachycardia does not use CTCAE grading. If 3 participants in the same treatment group meet the tachycardia discontinuation criterion **AND** the events are considered drug-related by the investigator, the siDMC will be triggered.

The results of the IA and the safety data review (if conducted) will not be shared with the investigators before the completion of the study. The processes by which recommendations and decisions are reached and communicated for the safety data review will be documented in a protocol-specific siDMC charter.

9.8 Multiplicity

The Type-I error rate will be controlled at 1-sided α 0.05 using an ordered testing procedure. H1 (superiority) will be tested first. H2 (superiority by 10% or more) will be tested only if the success criterion for H1 is met.

9.9 Sample Size and Power Calculations

9.9.1 Efficacy

The planned sample size is approximately 130 participants (65 participants per arm). The sample size was chosen based on the mean relative reduction (%) from baseline in LFC measured by MRI-PDFF at Week 24, assuming a treatment difference of approximately 19.4% and a dropout rate (without a Week 24 value) of 10% in each treatment group. The value of 19.4% is derived based on the following additional assumptions: 20% treatment difference among participants who complete 24 weeks of treatment (approximately 80% of the study population) and 10% to 15% treatment difference among participants who discontinue treatment prematurely but have a measurement in the range for Week 24 (approximately 10% of the study population). The half-width of the 90% CI is expected to be 6.1%.

Based on the above assumptions, the study has approximately 99% power to demonstrate that efinopegdutide is superior to semaglutide (H1) and approximately 80% power to demonstrate that efinopegdutide is superior to semaglutide by at least 10% (H2), at a 1-sided α 0.05 for each hypothesis.

Table 10 displays the power for H1 and H2 under various assumptions for the difference and SD.

Table 10 Power (%) for Hypothesis 1/Hypothesis 2 Under Various Assumptions

True SD of Relative Reduction (%) From Baseline in LFC at Week 24	True Difference in Mean Relative Reduction (%) From Baseline		
	15	20	25
15	>99/55.9	>99/97.4	>99/>99
20	>99/38.3	>99/85.2	>99/>99
25	94.3/28.8	>99/69.4	>99/94.3

LFC liver fat content; SD standard deviation.
The power is calculated based on a sample size of 65 participants per arm, a dropout rate of 10% (ie, 10% missing values at Week 24), and a 1 sided α 0.05.

9.9.2 Safety

Given the sample size of 65 participants per arm, Table 11 provides examples of differences in proportions in AEs between efinopegdutide and semaglutide that would have a 95% CI that excludes zero.

Table 11 Examples of Adverse Event Incidences for Which the 95% Confidence Interval for the Difference Would Exclude Zero

Efinopegdutide n/N (%)	Semaglutide n/N (%)	Difference in % Versus Semaglutide Estimate (95% CI)[a]
4/65 (6.2%)	0/65 (0.0%)	6.2 (0.4, 14.8)
7/65 (10.8%)	1/65 (1.5%)	9.2 (1.2, 19.3)
9/65 (13.8%)	2/65 (3.1%)	10.8 (1.4, 21.7)

AE adverse event; CI confidence interval; M&N Miettinen and Nurminen; n number of participants with an AE; N population size.
[a] Based on the M&N method [Miettinen, O. and Nurminen, M. 1985].

9.10 Subgroup Analyses

The primary efficacy endpoint will be summarized for each of the following baseline defined subgroups:

- Concurrent diagnosis of T2DM at the time of randomization (Yes or No)
- Age (≥65 years or <65 years)
- BMI (>30 kg/m^2 or ≤30 kg/m^2)
- LFC (>median or ≤median)
- Sex (male or female)

9.11 Compliance (Medication Adherence)

Compliance data for study intervention will be collected during the study. Any deviation from protocol-directed administration will be reported.

For each participant, percent compliance (reflecting the percent of time on study intervention from the first dose until study intervention discontinuation) and percent adherence (reflecting the percent of time on study intervention from the first dose until study discontinuation) will be calculated using the following formulas:

$$\textit{Compliance (\%)} \quad \frac{\textit{Number of Compliant Weeks}}{\textit{Number of Weeks in the Treatment Period}} \times 100\%$$

$$\textit{Adherence (\%)} \quad \frac{\textit{Number of Compliant Weeks}}{\textit{Number of Weeks in the Study Period}} \times 100\%$$

As the study intervention is a weekly injection, the week that the participant received an injection of the study intervention following the time of dose administration (Section 8.1.9) will be considered compliant weeks. However, participants will be considered noncompliant for those weeks that the study intervention CRF indicates general compliance problems.

The number of weeks in the treatment period is defined as the number of weeks from the week of the first dose of study intervention to the week of the last dose of study intervention. For percent adherence, the number of weeks in the study is the total number of weeks from the week of the first dose to the week of study completion (Week 24) or withdrawal from the study (up to Week 24), excluding the 5 weeks of follow-up post last dose.

Summary statistics will be provided on percent compliance and percent adherence by treatment group.

9.12 Extent of Exposure

The extent of exposure to study intervention will be evaluated by summary statistics and frequencies for the “Number of Weeks on Study Intervention” by treatment group.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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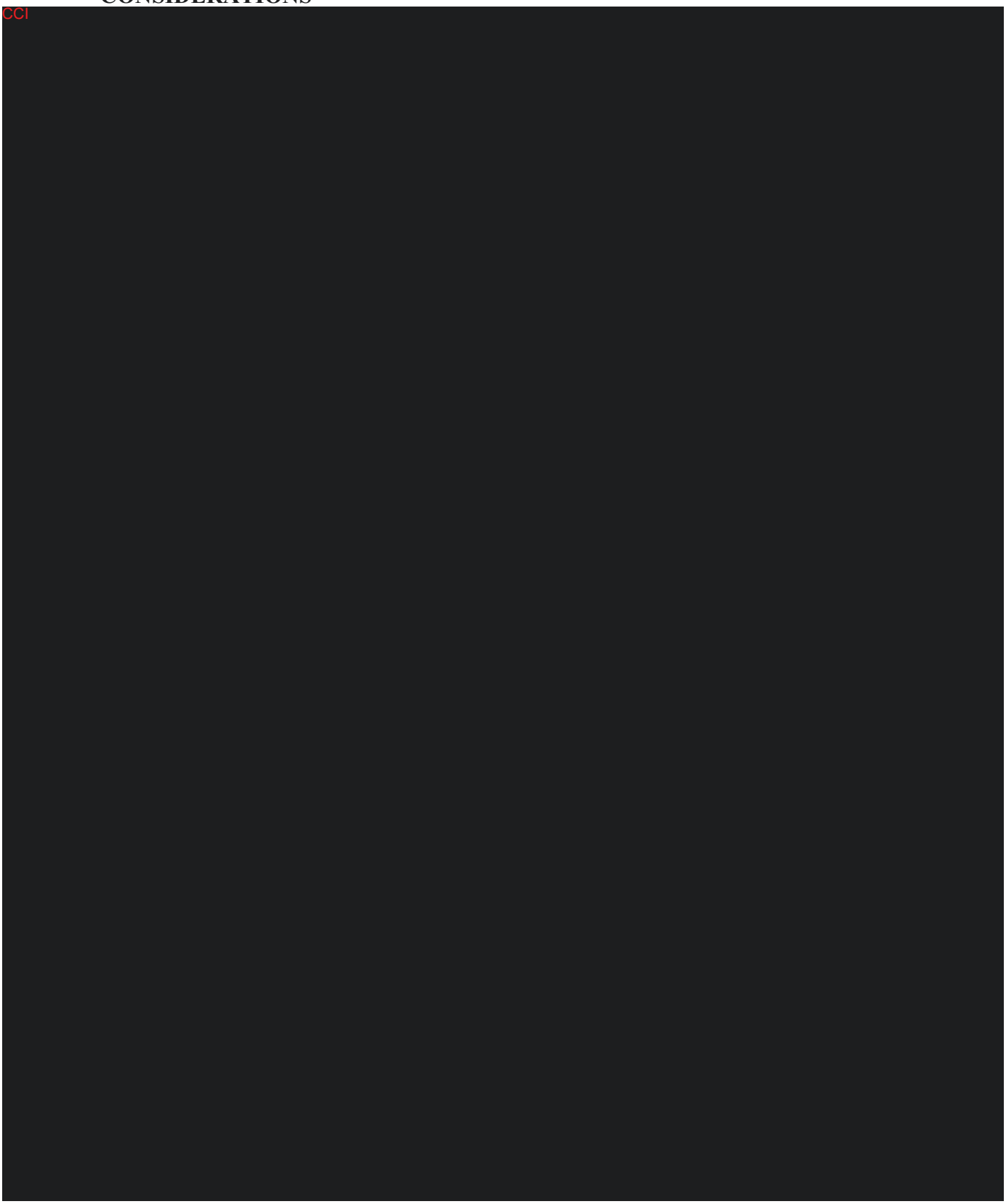

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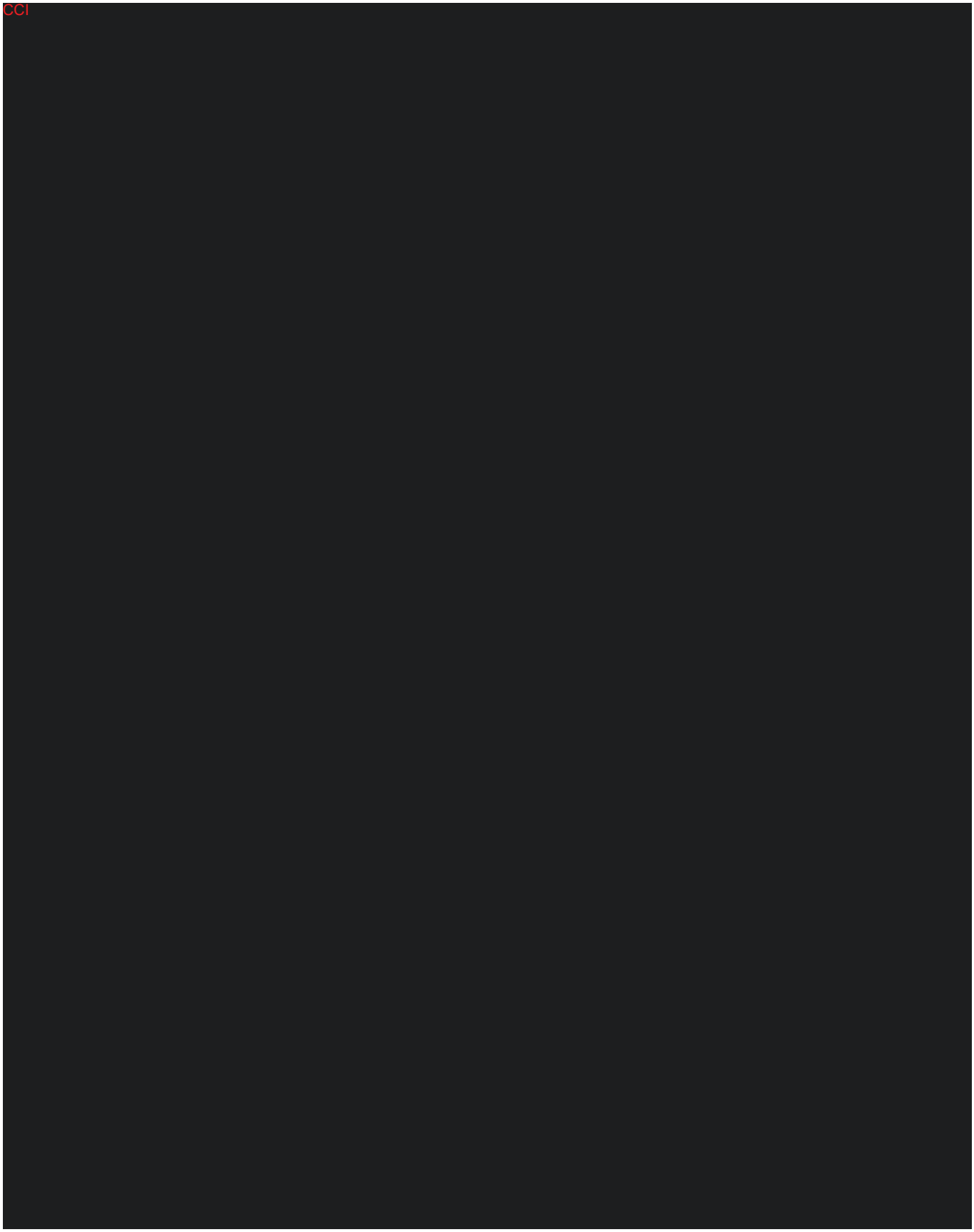

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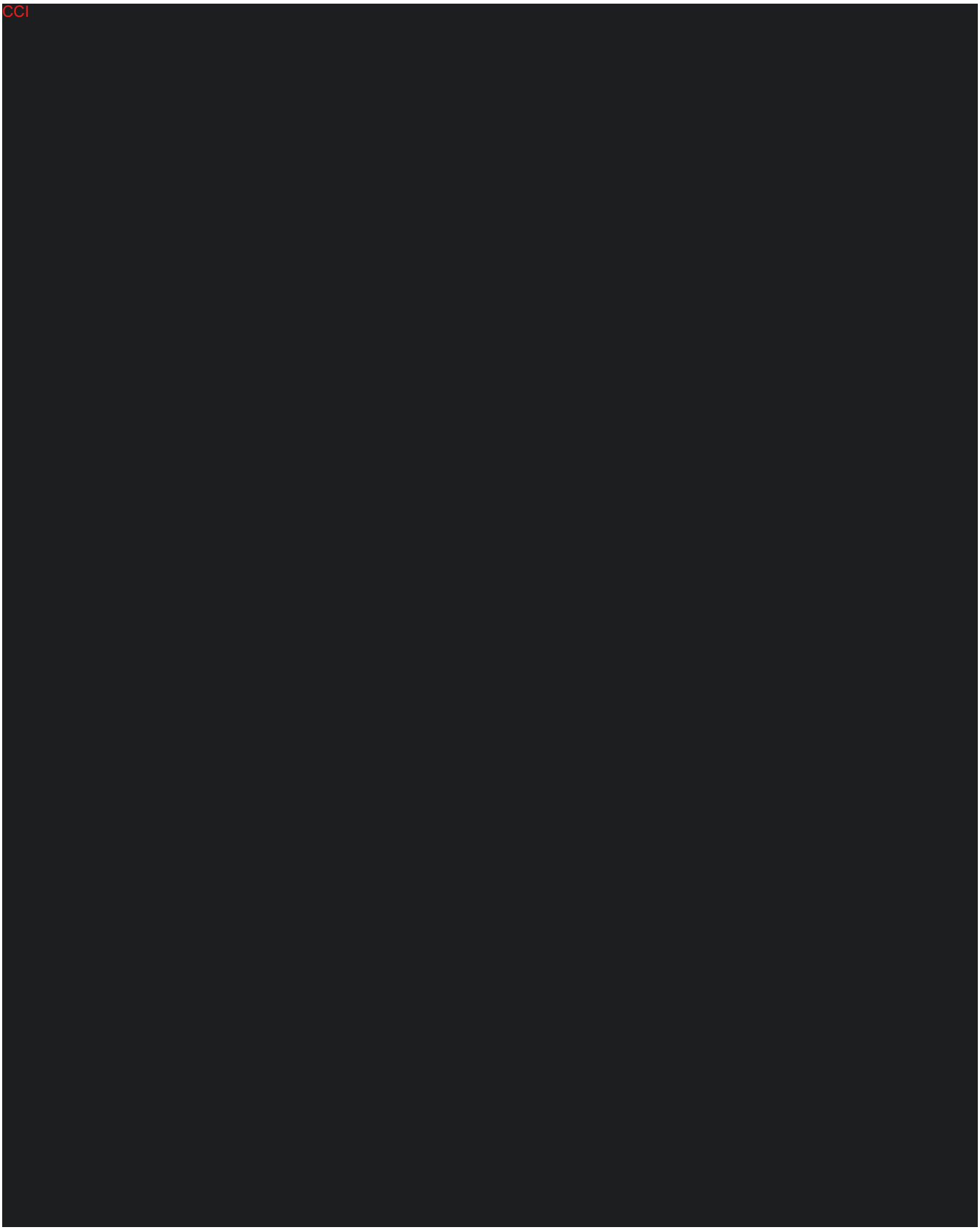

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

- **Results in death**
- **Is life-threatening**
  - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**
  - In offspring of participant taking the product regardless of time to diagnosis.
- **Other important medical events**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer
- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

    - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

    - Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

    - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

    - Grade 4: Life threatening consequences; urgent intervention indicated.

    - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**

    - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill

count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

- **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

  (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

  (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

    - Yes, there is a reasonable possibility of Sponsor's product relationship:

        - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

    - No, there is not a reasonable possibility of Sponsor's product relationship:

        - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug-device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

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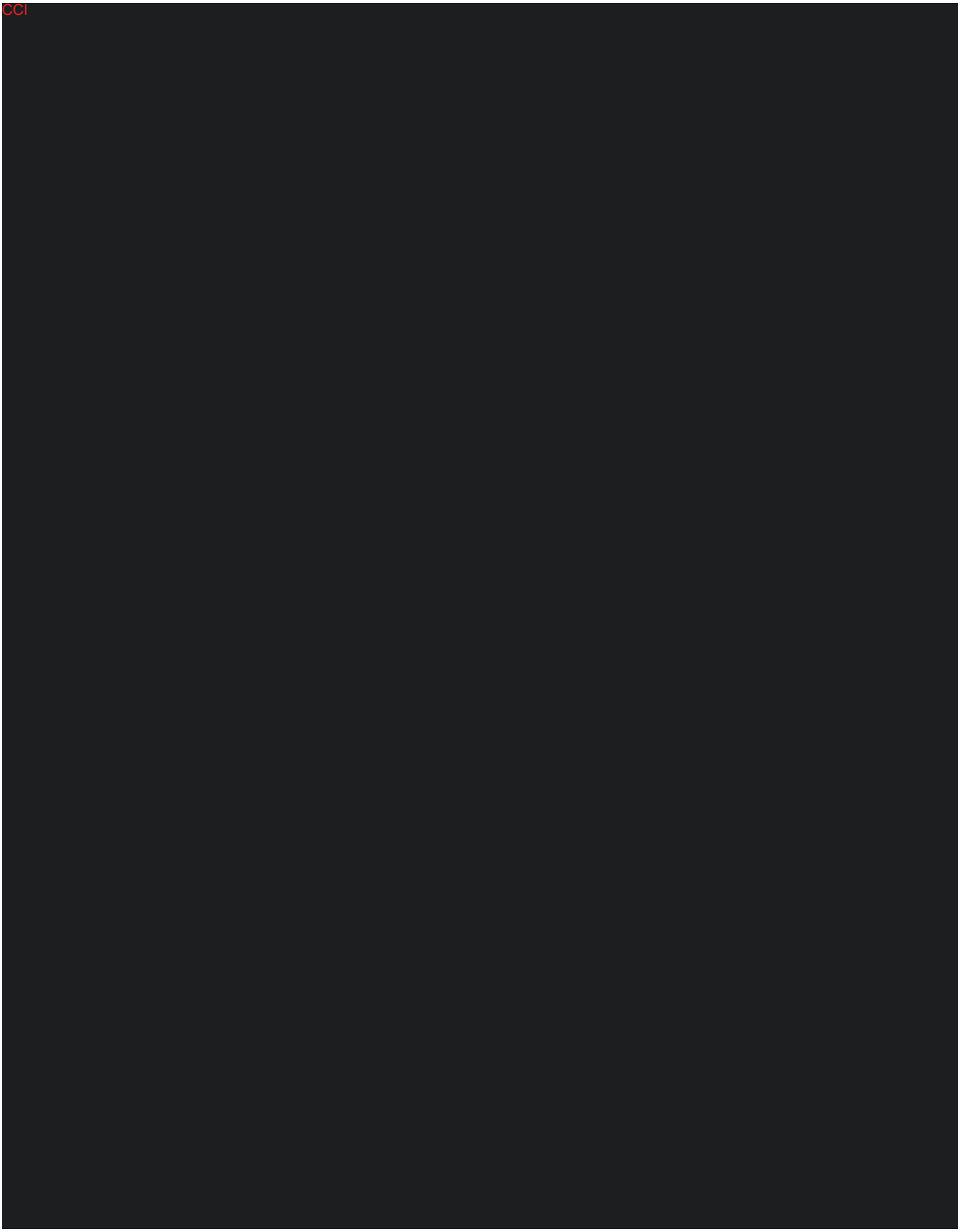

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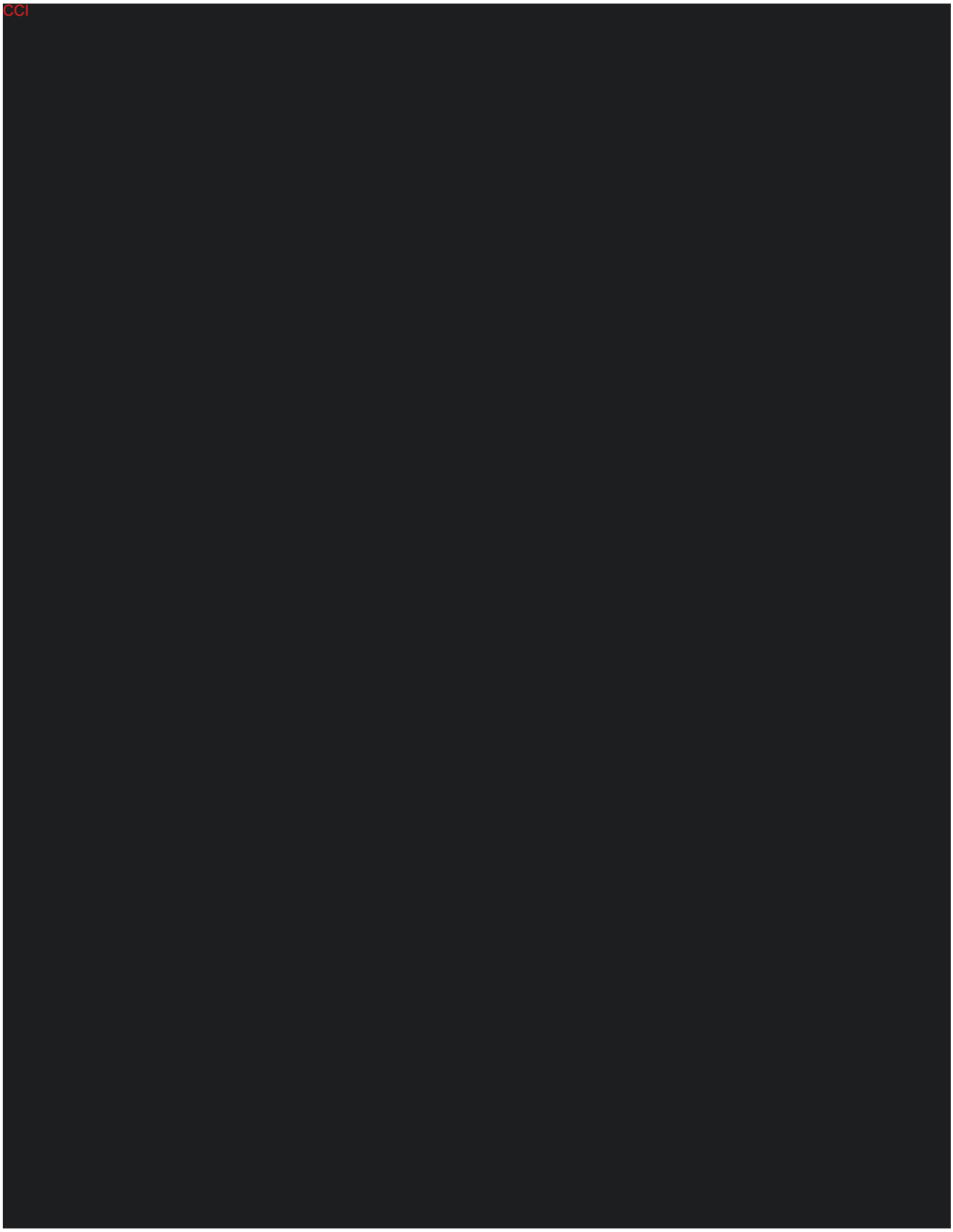

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10.8 Appendix 8: Other Medical Device: Complaints Including Product Quality Complaint, Malfunction, Serious Injury, Death, Fetal Distress/Fetal Death and Congenital Anomaly: Definitions and Reporting

Not applicable.

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10.10 Appendix 10: Common Terminology Criteria for Adverse Events Version 5.0

The descriptions and grading scales found in the NCI CTCAE, Version 5.0 (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf) will be used for AE reporting except as noted in Section 7.1.

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
A1C	Glycated Hemoglobin
ABPM	Ambulatory Blood Pressure Monitoring
ADA	Anti-Drug Antibodies
ADL	Activities of Daily Living
ADME	Absorption, Distribution, Metabolism, and Excretion
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
APaT	All Participants as Treated
apoB	Apolipoprotein B
AST	Aspartate Aminotransferase
BICR	Blinded Independent Central Review
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats Per Minute
CAC	Clinical Adjudication Committee
CI	Confidence Interval
CK-18 M30	Cytokeratin 18 Antibody M30
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cLDA	constrained Longitudinal Data Analysis Method
Cmax	maximum Plasma Concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSR	Clinical Study Report
Ctrough	trough Concentration
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
D	Day
DBP	Diastolic Blood Pressure
DC	Discontinuation
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic Acid
DPP-4	Dipeptidyl Peptidase-4
ECG	Electrocardiogram
ECI	Event of Clinical Interest
eCRF	electronic Case Report Form
EDC	Electronic Data Collection
eGFR	estimated Glomerular Filtration Rate
ELF	Enhanced Liver Fibrosis
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EOT	End of Treatment
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FPG	Fasting Plasma Glucose
FSH	Follicle Stimulating Hormone

Abbreviation	Expanded Term
GCGR	G-protein Coupled Glucagon Receptor
GCP	Good Clinical Practice
GI	Gastrointestinal
GCKR	Glucokinase Regulatory Protein
GLP	Good Laboratory Practice
GLP-1	Glucagon-like Peptide-1
GLP-1R	Glucagon-like Peptide-1 Receptor
H1, H2	Hypothesis 1, Hypothesis 2
HA	Hyaluronic Acid
HbA1C	Glycated Hemoglobin
HBsAg	Hepatitis B Surface Antigen
hCG	human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HDL-C	High Density Lipoprotein-Cholesterol
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HRT	Hormone Replacement Therapy
HSD17B13	Hydroxysteroid 17-Beta Dehydrogenase 13
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
iCRO	imaging CRO
IgG	Immunoglobulin G
ID	Identification
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IVRS	Interactive Voice Response System
LDL-C	Low Density Lipoprotein-Cholesterol
LFC	Liver Fat Content
LS	Least Squares
LYPLAL1	Lysophospholipase-like Protein 1
M&N	Miettinen and Nurminen
MBOAT7	Membrane Bound O-Acyltransferase Domain-Containing 7
MedDRA	Medical Dictionary for Regulatory Activities
MEN 2	Multiple Endocrine Neoplasia Syndrome Type 2
MetS	Metabolic Syndrome
MRI-PDFF	Magnetic Resonance Imaging-Estimated Proton Density Fat Fraction
MRL	Merck Research Laboratories
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
NAFLD	Nonalcoholic Fatty Liver Disease
NASH	Nonalcoholic Steatohepatitis
NCI	National Cancer Institute
NYHA	New York Heart Association
PD	Pharmacodynamic

Abbreviation	Expanded Term
PDLC	Predefined Limits of Change
PIIINP	Collagen Type III Amino-Terminal Propeptide
PK	Pharmacokinetic
PNPLA3	Patatin-like Phospholipase Domain-Containing Protein 3
PP	Per Protocol
PPP1R3B	Protein Phosphatase 1 Regulatory Subunit 3B
PQC	Product Quality Complaint
Q1W	Once Every Week
QP2	Department of Quantitative Pharmacology and Pharmacometrics
QTcR	QT Interval Corrected for Heart Rate Changes
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SC	Subcutaneous
SD	Standard Deviation
siDMC	Standing Internal Data Monitoring Committee
SLAB	Supplemental Laboratory Test(s)
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SOC	System Organ Class
sSAP	supplemental Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction
t1/2	Half-Life
TA	Therapeutic Area
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TEAE	Treatment Emergent Adverse Event
TG	Triglycerides
TIMP1	Tissue Inhibitor of Metalloproteinase-1
TM6SF2	Transmembrane 6 Superfamily Member 2
ULN	Upper Limit of Normal
V	Visit
WOCBP	Woman/Women of Childbearing Potential
WONCBP	Woman/Women of Nonchildbearing Potential

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