Official Protocol Title:	An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of Efinopegdutide (MK-6024) in Participants with Moderate and Severe Hepatic Impairment
NCT number:	NCT06052566
Document Date:	31-Jul-2023

TITLE PAGE

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Protocol Title:

An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of Efinopegdutide (MK-6024) in Participants with Moderate and Severe Hepatic Impairment

Protocol Number: 014-00

Compound Number: MK-6024

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
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Regulatory Agency Identifying Number(s):

IND	153,067

Approval Date: 31 July 2023

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
Original Protocol	31-JUL-2023	Not applicable

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: An Open-Label, Single-Dose Study to Evaluate the Pharmacokinetics of Efinopegdutide (MK-6024) in Participants with Moderate and Severe Hepatic Impairment

Short Title: Efinopegdutide (MK-6024) Hepatic Impairment Study

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

The study population includes male and female participants with moderate and severe hepatic impairment between the ages of 18 and 75 years (inclusive) and healthy mean-matched controls.

Primary Objective	**Primary Endpoint**
To evaluate the serum pharmacokinetics of efinopegdutide after a single dose in participants with moderate hepatic impairment compared to matched healthy control participants Estimation: The serum PK (AUC0-inf and Cmax) of efinopegdutide following a single 7 mg dose of efinopegdutide in participants with moderate hepatic impairment will be estimated and compared to those in healthy matched control participants.	AUC0- ∞, AUC0-last, Cmax, Tmax, apparent terminal t1/2, CL/F, and Vz/F
To evaluate the serum pharmacokinetics of efinopegdutide after a single dose in participants with severe hepatic impairment compared to healthy matched control participants Estimation: The serum PK (AUC0-inf and Cmax) of efinopegdutide following a single 7 mg dose of efinopegdutide in participants with severe hepatic impairment will be estimated and compared to those in healthy matched control participants	AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t1/2, CL/F, and Vz/F

Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of efinopegdutide in participants with hepatic impairment	Adverse experiences and discontinuations due to adverse events.

Overall Design:

Study Phase	Phase 1
Primary Purpose	Treatment
Indication	Non-alcoholic steatohepatitis
Population	Participants with moderate or severe hepatic impairment, Healthy participants
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	No Treatment Control
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 8 months 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 24 participants will be allocated as described in Section 9.8.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Moderate HI	Efinopegdutide	14 mg/mL	7 mg	SC	Single dose, Day 1	Test Product
Severe HI	Efinopegdutide	14 mg/mL	7 mg	SC	Single dose, Day 1	Test Product
Healthy Matched Control	Efinopegdutide	14 mg/mL	7 mg	SC	Single dose, Day 1	Test Product

HI=hepatic impairment; SC=subcutaneous

Other current or former name(s) or alias(es) for study intervention(s) are as follows: MK-6024, HM1252A, JNJ-64565111, and efinopegdutide.

Total Number of Intervention Groups/Arms	3
Duration of Participation	Each participant will participate in the study for approximately 9 weeks from the time the participant provides documented informed consent through the final contact.

Study Governance Committees:

Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No

Study governance considerations are outlined in Appendix 1.

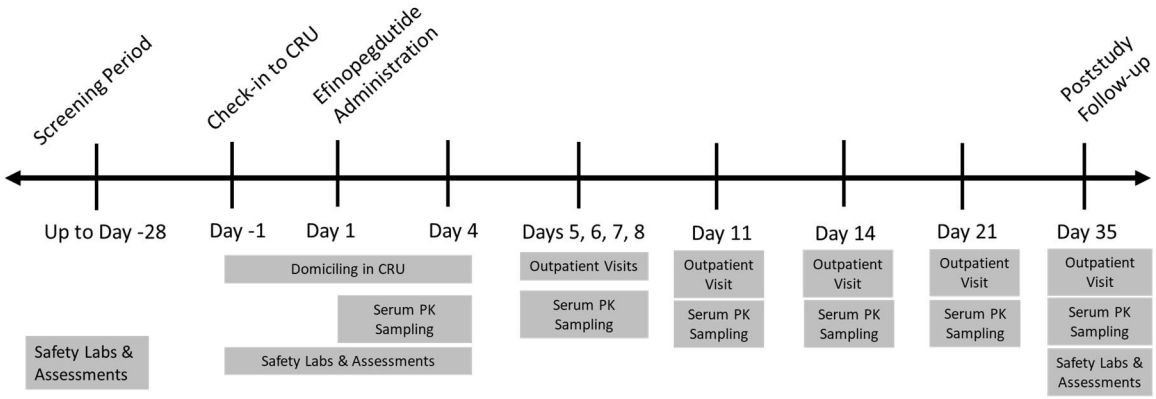
Study Accepts Healthy Participants: Yes

A list of abbreviations is in Appendix 11.

1.2 Schema

The study design is depicted in Figure 1.

Figure 1 Study Schema



CRU=clinical research unit; PK=pharmacokinetic

1.3 Schedule of Activities

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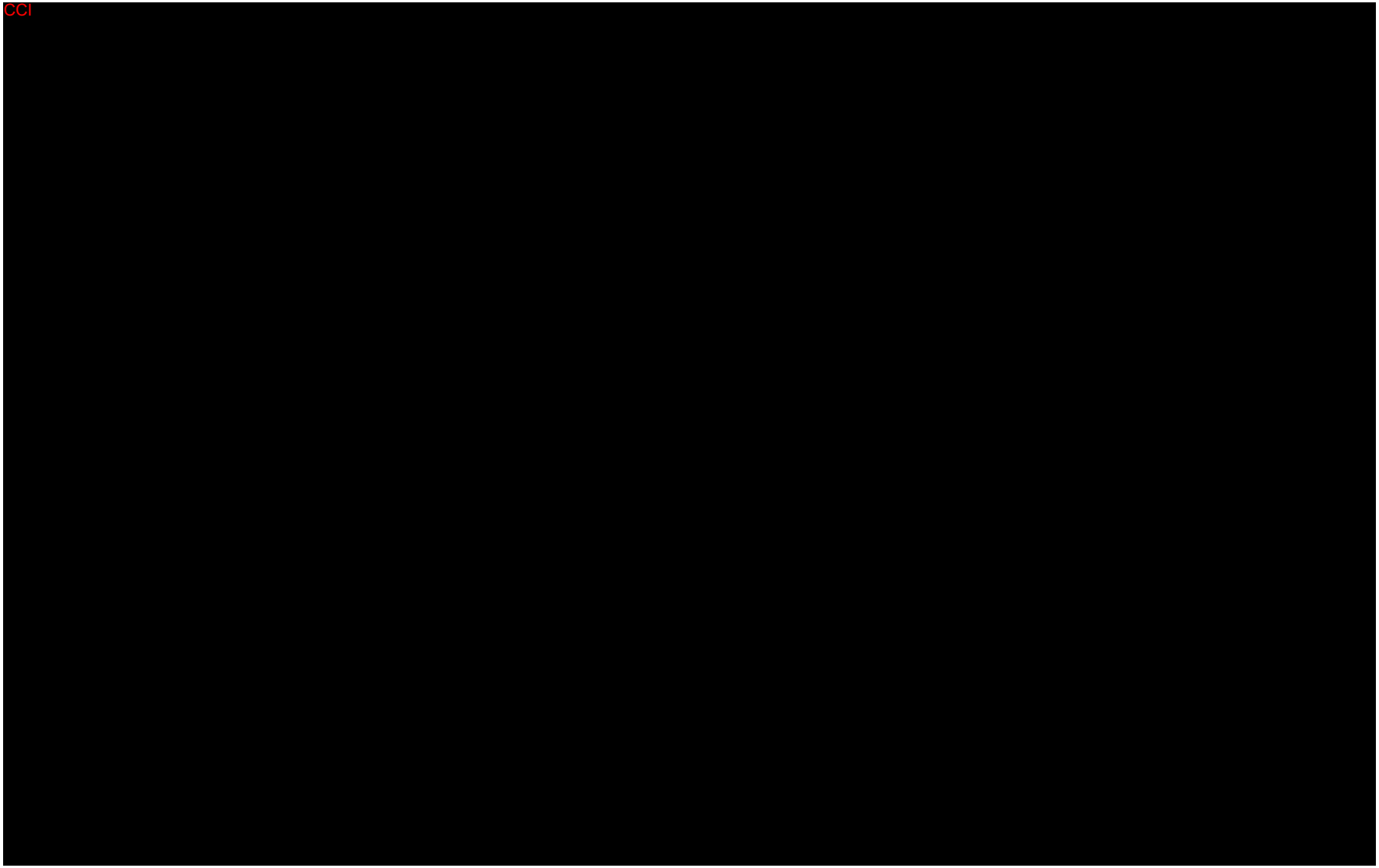

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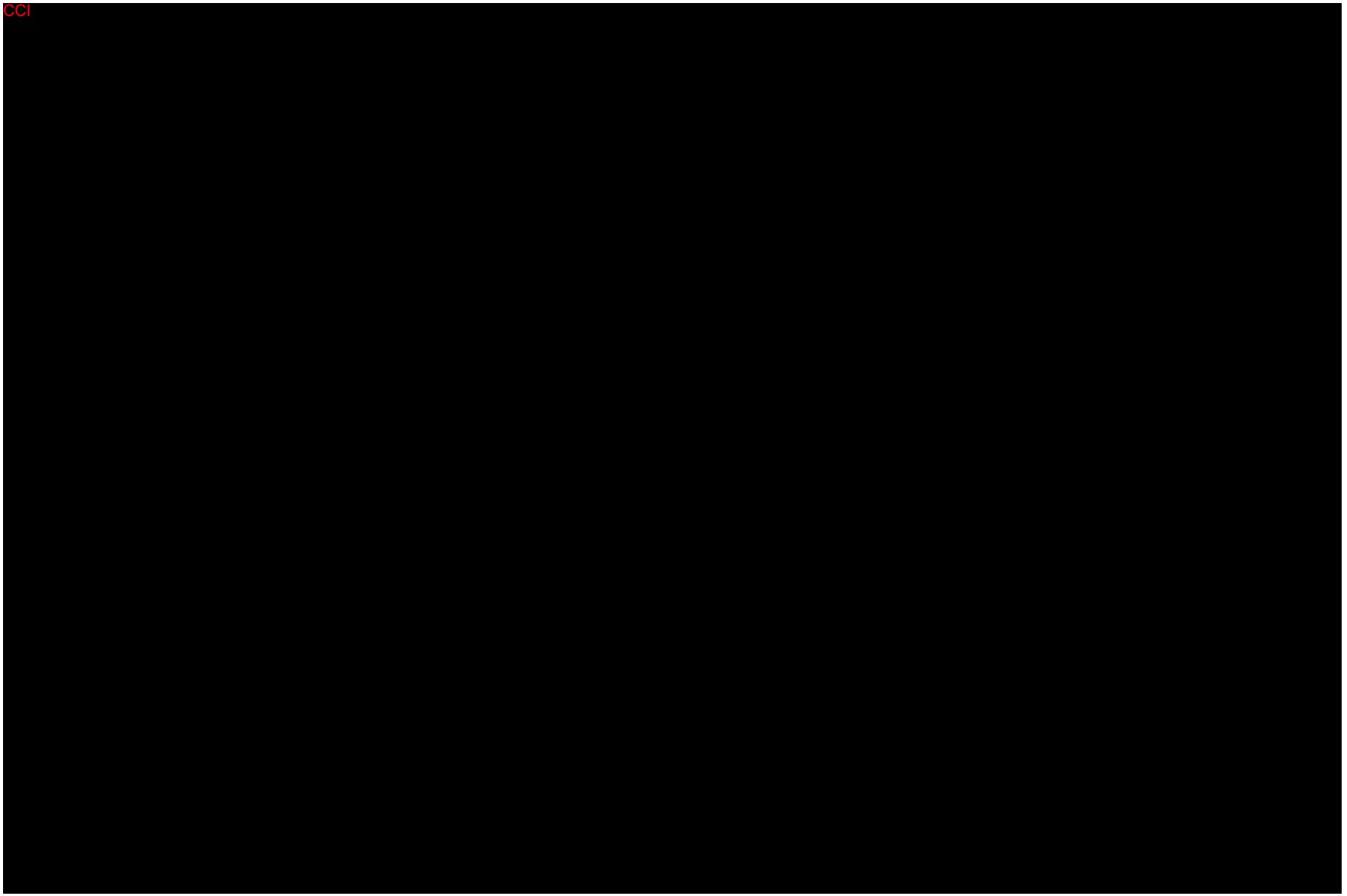

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2 INTRODUCTION

2.1 Study Rationale

Efinopegdutide is a dual GLP-1/glucagon receptor agonist being developed for treatment of NASH.

The liver is involved in drug clearance through multiple oxidative and conjugative metabolic pathways and through biliary excretion. Hepatic insufficiency from acute or chronic liver disease may affect excretion and metabolism, leading to accumulation of drug and metabolites. Hepatic disease can therefore alter the levels of drugs, potentially leading to an effect on efficacy and/or safety. In accordance with FDA hepatic impairment guidance, a Sponsor should evaluate the PK of its investigational drug in hepatic impaired participants when hepatic metabolism and/or excretion accounts for a substantial portion (>20% of the absorbed drug) of the elimination of the parent or active metabolite. It is not yet known how hepatic impairment will affect the PK of efinopegdutide. Previous studies evaluating the effect of hepatic impairment in the setting of the GLP-1 agonist semaglutide, demonstrated no effect on exposure and concluded that no dose modification would be required [Jensen, L., et al 2018][Baekdal, T. A., et al 2018].

This Phase 1 study will evaluate the general PK, safety, and tolerability of a single dose of efinopegdutide in participants with moderate and severe hepatic impairment, compared to participants in good health.

2.2 Background

Refer to the IB for detailed background information on efinopegdutide.

2.2.1 Pharmaceutical and Therapeutic Background

NAFLD is a condition associated with an increased accumulation of triglycerides in the liver that affects approximately 25% of the global adult population. 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 the adipose tissue to the liver and increased de novo hepatic lipogenesis [Fabbrini, E., et al 2010].

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 are expected to progress to NASH, rising from 20% to 27% between the years 2015 and 2030 [Friedman, S. L., et al 2018].

Patients with NASH are usually asymptomatic. A diagnosis of NASH is typically considered when patients have abnormal liver tests without alternate explanation or when abdominal imaging incidentally detects hepatic fat. 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 assessments cannot definitively diagnose NASH

or fibrosis stage but are useful in evaluating the risk of advanced fibrosis. A definitive diagnosis of NASH requires liver biopsy [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 metabolic syndrome [Younossi, Z. M., et al 2016][Younossi, Z., et al 2018][Chalasani, N., et al 2018]. Approximately 20% of the patients with NASH 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].

Lifestyle modifications directed at weight loss and exercise remain the most recommended treatment for NAFLD and NASH; however, even in well-organized settings, only a minority of patients achieve and sustain weight loss. Presently, there are no approved medications for the treatment of NASH. According to evidence-based practice guidelines for the treatment of patients with biopsy-proven NASH, pioglitazone and GLP-1 receptor agonists are recommended as pharmacotherapies for patients with T2DM and high-dose vitamin E (800 IU/day) is recommended for nondiabetic patients [Cusi, K., et al 2022][Sumida, Y. and Yoneda, M. 2018]. However, neither pioglitazone nor vitamin E have demonstrated a robust histologic efficacy in patients with NASH, have been studied long-term to assess their impact on liver-related outcomes, or have fully characterized safety profiles in this patient population. Given the growing global prevalence of NASH, 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

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.

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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 [redacted]

Findings in the 26-week rat study were consistent with those in the shorter term 4-week rat study. [redacted]

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 [redacted]

Key safety data are summarized below.

In the [redacted] studies, efinopegdutide was generally well tolerated at doses up to [redacted] The most common AEs were GI-related, primarily nausea and vomiting, and appeared to be dose-related. [redacted] in the same individual were considered treatment related. [redacted]

In the Phase 2b studies, the most common AEs were also GI-related (nausea and vomiting). P009 (Study 64565111OBE2001) was a randomized, double-blind placebo-controlled and open-label active-controlled, parallel-group, 5-arm, multicenter Phase 2b study. Nondiabetic, obese participants 18 to 70 years of age (inclusive) were assessed. A total of 474 participants were randomized to placebo, efinopegdutide at 5.0 mg, 7.4 mg, and 10.0 mg; or open-label liraglutide 3.0 mg. P010 (Study 64565111OBE2002) was a randomized, double-blind, placebo-controlled, parallel-group, 4-arm, multicenter study that evaluated efinopegdutide in obese, 18 to 70-year-old participants with T2DM. A total of 196 participants were randomized to placebo, and efinopegdutide at 5.0 mg, 7.4 mg, and 10.0 mg. In both studies there was significantly reduced body weight at all dose levels of efinopegdutide compared to placebo. In both Phase 2b studies, the overall incidence of TEAEs was higher in each efinopegdutide dose group compared with the placebo or liraglutide groups. There were a total of 24 SAEs in the Phase 2b studies, of which 3 were considered treatment related in efinopegdutide groups and 2 in the liraglutide group.

P001 was a Phase 2a, randomized, active-comparator-controlled, open-label study to evaluate the efficacy and safety of efinopegdutide in adult individuals with NAFLD. Approximately 145 participants have been randomized in a 1:1 ratio to treatment with efinopegdutide 10.0 mg SC once weekly or semaglutide 1.0 mg SC once weekly, for a duration of 24 weeks. In both treatment groups, study intervention was titrated 3 steps over a period of 8 weeks. The primary efficacy objective was to evaluate the effect of efinopegdutide versus semaglutide on the mean relative reduction (%) from baseline in LFC, measured by MRI-PDFF, after 24 weeks of treatment. Treatment with efinopegdutide 10 mg SC once weekly resulted in a mean relative reduction in LFC from baseline superior by 30% to that observed with semaglutide 1 mg SC weekly. Most AEs were nonserious and of low toxicity grade. Gastrointestinal AEs were reported in over half of the participants in the efinopegdutide and semaglutide groups, most commonly nausea, diarrhea, and vomiting. Efinopegdutide 10 mg SC weekly had an acceptable AE profile that was similar to that of semaglutide 1 mg once weekly. Treatment with efinopegdutide SC once weekly for 24 weeks was associated with small decreases in hemoglobin and hematocrit.

Refer to the IB for a more extensive summary of the preclinical and clinical data available for efinopegdutide.

2.2.3 Ongoing Clinical Studies

P011 is a randomized, placebo -controlled, sequential, single-site, double-blind study of MK-6024 in healthy Chinese participants. CCI

[redacted]

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[redacted]

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[redacted]

2.2.4 Information on Other Study-related Therapy

There are no other study-related therapies in this protocol.

2.3 Benefit/Risk Assessment

Participants in clinical studies will not receive direct benefit from treatment during participation as clinical studies are designed to provide information about the safety and properties of an investigational medicine.

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

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

The study population includes male and female participants with moderate and severe hepatic impairment between the ages of 18 and 75 years (inclusive) and healthy mean-matched controls.

Primary Objective	**Primary Endpoint**
To evaluate the serum pharmacokinetics of efinopegdutide after a single dose in participants with moderate hepatic impairment compared to matched healthy control participants Estimation: The serum PK (AUC0-inf and Cmax) of efinopegdutide following a single 7 mg dose of efinopegdutide in participants with moderate hepatic impairment will be estimated and compared to those in healthy matched control participants.	AUC0- ∞, AUC0-last, Cmax, Tmax, apparent terminal t1/2, CL/F, and Vz/F
To evaluate the serum pharmacokinetics of efinopegdutide after a single dose in participants with severe hepatic impairment compared to healthy matched control participants Estimation: The serum PK (AUC0-inf and Cmax) of efinopegdutide following a single 7 mg dose of efinopegdutide in participants with severe hepatic impairment will be estimated and compared to those in healthy matched control participants	AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t1/2, CL/F, and Vz/F
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of efinopegdutide in participants with hepatic impairment	Adverse experiences and discontinuations due to adverse events.

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
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4 STUDY DESIGN

4.1 Overall Design

This is a non-randomized, parallel-group, multi-center, open-label study to compare the PK of efinopegdutide in participants with moderate and severe hepatic impairment (based on the Child-Pugh (CP) classification) to healthy control participants reasonably matched to the demographics (age, weight, sex) of the group with hepatic impairment.

Screening of participants will occur within 28 days prior to the first dose. Up to 16 adult male and female participants with HI, and up to 8 matched healthy control male and female participants will be enrolled. Participants with moderate hepatic impairment (Panel A) will enroll first. Enrollment of severe hepatic impairment participants (Panel B) will occur after a review of safety data of 3 participants from Panel A. Enrollment in Panels A and B will then continue until at least 6 PK-evaluable participants are enrolled in each panel. Participants will be considered PK-evaluable if sufficient serum concentration data were collected to determine the PK parameters of interest (e.g. AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t1/2, CL/F, Vz/F). Enrollment of healthy matching control participants (Panel C) shall commence following the completion of enrollment of either Panel A or B, whichever is completed first. Each healthy control participant will be matched to the mean age (±15 years) and BMI (±3.5 kg/m^2) of the participants in the first HI panel to complete enrollment. A total of 6 healthy participants shall be enrolled into Panel C at this stage, and the number of males and females shall generally be matched to the numbers of hepatic impairment participants within ±1; i.e. if there are 4 males and 4 females in the hepatic insufficient group, every effort will be made to ensure a 4:4 ratio in the healthy participants, but 3:5 or 5:3 would be acceptable as well.

Following completion of enrollment of the second HI panel, the matching characteristics (age, BMI, sex) of the already-enrolled healthy participants in Panel C will be compared against the mean values of the HI panel that is completed second. If any of the participants already enrolled in Panel C do not also meet the matching criteria for the second completed HI panel, additional healthy participants will be enrolled into Panel C in order to provide 6 healthy control participants who match the mean age (±15 years) and BMI (±3.5 kg/m^2) of the subjects in the second HI panel. The sex of the additional healthy participant(s) will be selected to ensure that there is a minimum of 2 participants of each sex in the group of participants within Panel C who match with the second HI panel. The PK comparisons between each hepatically impaired panel (A and B) and healthy controls (Panel C) will include only control participants who meet the matching criteria for the respective HI panel. Assignment to a group will be as per Table 1.

Table 1 Group Assignment

Panel	Impairment Stage	n	Child-Pugh Score[a]
A	Moderate	8	7 to 9
B	Severe	8	10 to 15
C	Healthy	8	0

[a] Child-Pugh (CP) score based on standard scoring. Baseline CP will be obtained by taking the mean of the CP score obtained from screening and from the most recent historical values within a 6-month period prior to screening. If no historical measurement is available, a second baseline CP will be assessed during the screening period (>72 hours apart) and the mean of the 2 values will be used for group assignment.

On Day 1, participants will receive a single dose of 7 mg efinopegdutide, followed by PK sampling until 72 hours postdose in the clinic. There will be additional visits on Days 5, 6, 7, 8,11, 14, 21, and 35 for the collection of PK. Safety will be monitored throughout the study be repeated clinical and laboratory evaluations.

As noted, the CP classification will be used to categorize hepatic impairment. The CP scale is used by clinicians to categorize chronic liver disease and cirrhosis and is also used to categorize participants with hepatic impairment for PK studies. In the current study, patients with chronic, stable hepatic impairment with features of cirrhosis due to any etiology will be enrolled, and the CP scale will be used to classify the severity of liver disease (Table 2). The points from each row are summed, leading to the final CP score. Scores of 5 to 6, 7 to 9, and 10 to 15 are classified as having mild, moderate, or severe hepatic impairment, respectively. To ensure an adequate number of study participants with laboratory abnormalities consistent with hepatic dysfunction, at least 50% of the participants with hepatic impairment will be required to have a score of at least 2 on one of the laboratory parameters (reduced serum albumin, increased serum bilirubin, or increased INR), and every effort will be made to enroll at least 2 participants with a CP score of >13. Note that the CP score is intended for application in individuals who have been diagnosed with liver disease and has a minimum starting score of 5. Thus, it is not appropriate to apply this score in participants without liver disease, and healthy participants will be assigned a “score” of 0 based on lack of liver disease and lab values within normal population limits for albumin, bilirubin, and INR.

Table 2 Child-Pugh Score for Severity of Liver Disease Classification

	Points Score for Increasing Abnormality		
Assessment	**1**	**2**	**3**
Encephalopathy[a]	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
INR	<1.7	1.7 to 2.3	>2.3
Bilirubin (mg/dL) – not PBC[b] Bilirubin (mg/dL) – only for PBC[b]	<2 <4	2 to 3 4 to 10	>3 >10

INR = international normalized ratio; PBC = primary biliary cirrhosis
[a] Portal-system encephalopathy is Staged 0 to 4.
[b] Select only one dependent on type of cirrhosis.

The CP classification will be used due to its widespread use and acceptance by regulatory agencies, including the U.S. FDA. This study design is supported by FDA guidelines for drugs which undergo substantial hepatic metabolism and for which an indication is sought for patients with hepatic impairment.

Because this is a Phase 1 assessment of efinopegdutide in humans, the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is therefore written with flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Refer to Section 8.11.6 for examples of modifications permitted within the protocol parameters.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

An open-label, single-dose study design has been deemed optimal to evaluate the effect of hepatic impairment on the PK of efinopegdutide. PK of efinopegdutide have been established in previous studies in healthy participants and indicate that steady state is reached after 5 weeks. Based on preclinical studies, it is anticipated that in humans, efinopegdutide will undergo elimination via multiple pathways. It remains unclear how hepatic impairment will affect the PK and metabolism of efinopegdutide, and thus the study design will include a cohort of individuals with moderate hepatic impairment as well as a cohort of individuals with severe hepatic impairment, which will provide important data as the compound advances into further clinical development. The study will evaluate and compare efinopegdutide PK in participants with moderate HI and severe HI to healthy control participants that are reasonably matched to the mean demographic parameters (sex, age, BMI) of participants with varying degrees of HI to control for the influence of covariates.

Patients with hepatic impairment often develop elevated circulating glucagon levels [Silva, G., et al 1990]. The mechanism of this increase in glucagon is incompletely understood, however a potential cause may be an increase in secretion by the pancreas and reduced metabolism by the liver. A study evaluating the effects of exogenously administered glucagon revealed a mild but significant increase in hepatic portal pressures in patients with cirrhosis, but not in control individuals. Exogenous glucagon also caused an increase in heart rate and blood pressure, but these changes were significantly attenuated in cirrhotic patients compared to healthy controls and the dosage of glucagon used in this study is [redacted] above the estimated increase in glucagon concentrations with a 7 mg dose of efinopegdutide. Given these observations and the vulnerability of the hepatically impaired population, recruitment of participants will begin with moderate HI. Enrollment of severe HI participants will only begin following review of safety and tolerability data from at least 3 moderate HI participants.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

There are no efficacy endpoints in this trial.

4.2.1.2 Safety Endpoints

The safety data for MK-6024 to date has been described in detail in the IB and summarized in Section 2.2.2.

The general safety and tolerability of efinopegdutide will be assessed by clinical evaluation of AEs and monitoring of physical examinations, vital signs (HR and BP), 12-lead ECGs, glycemic responses (fasting glucose and HbA1c), and standard laboratory safety tests (hematology, serum chemistry, and urinalysis).

All procedures will be conducted at the time points specified in the SoA. AEs will be recorded throughout the study.

4.2.1.3 Pharmacokinetic Endpoints

The primary endpoints for this study will include the PK parameters of AUC0- ∞, AUC0-last, and Cmax of efinopegdutide. Serum PK parameters included in this primary endpoint will be evaluated and compared between participants with moderate hepatic impairment with CP classification 7-9 compared to healthy matched control participants using GMR and CI to assess differences between two groups. Similarly, the serum PK parameters will be evaluated and compared between participants with severe hepatic impairment with CP classification 10-15 compared to healthy matched control participants.

For each PK parameter (AUC0- ∞, AUC0-last, Cmax, Tmax, apparent terminal t1/2, CL/F, and Vz/F of serum efinopegdutide), descriptive statistics will be provided.

4.2.1.4 Pharmacodynamic Endpoints

Previous clinical studies demonstrate that weekly dosing of efinopegdutide may lead to decreases in body weight. While clinically meaningful changes in body weight are not expected following a single efinopegdutide dose in this study, to better understand this potential impact of efinopegdutide in hepatic impairment participants, the body weight will be measured throughout the study. All procedures will be conducted at the time points specified in the SoA.

Efinopegdutide is intended to deliver therapeutic benefit through a mechanism of action via dual agonism of the GLP-1 and glucagon receptors. However, the mechanisms through which these effects are achieved are not completely understood. Therefore, much remains to be learned regarding how efinopegdutide works and how it may best be used to treat patients with NASH. To aid in these efforts, exploratory assessments of known and/or unknown biomarkers may be performed. CCI [redacted]

4.2.1.5 Immunogenicity Endpoints

Immunogenicity to efinopegdutide will be described as the results of the ADA assay from samples taken as described in the SoA (see Section 1.3). ADA samples will be collected from all participants. The incidence and magnitude (titer) of ADA positive participants and potential effects of ADA on PK and safety will be reported, as appropriate.

4.2.1.6 Planned Exploratory Biomarker Research

4.2.1.6.1 Planned Genetic Analysis

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[redacted]

4.2.1.7 Future Biomedical Research

CCI

[redacted]

4.2.2 Rationale for the Use of Comparator/Placebo

Not applicable.

4.3 Justification for Dose

The methods used in calculating doses and estimated exposures are detailed in Section 4.3.1 and Section 4.3.2.

In previous Phase 1 studies of efinopegdutide, single doses of up to 4.0 nmol/kg (approximately 20 mg) have been generally well-tolerated. The most common AEs were gastrointestinal-related, and most consistently included nausea, vomiting, abdominal discomfort/distention/pain and decreased appetite. Dose-dependent increases in GI AEs, particularly nausea and vomiting, were observed across the single dose studies and the multiple dose studies that did not include titration steps from lower to higher doses. Thus, while 10 mg may be the eventual clinical dose, a single dose of 7 mg is selected based on better tolerability of this dose compared to a 10 mg dose, as is consistent with FDA guidelines [U.S.Department of Health and Human Services - Food and Drug Admi 2003]. Based on the sensitivity of the PK assay, single doses lower than 7 mg may fall below the LLOQ at earlier postdose time points than would be optimal for the PK analysis.

As this is a Phase 1 assessment of efinopegdutide in humans, and the PK, pharmacodynamic and safety profiles of the compound are still being evaluated, modifications to the dose or dosing regimen may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. Details of allowed modifications are provided in Section 8.11.6.

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 (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

A study may be paused during review of newly available preclinical/clinical safety, PK, pharmacodynamic, efficacy, or biologic data or other items of interest, prior to a final decision on continuation or termination of the study. It may be necessary to keep the study open for gathering/reviewing of additional supportive data to optimally complete the objective(s) of the study. If necessary, the appropriate amendment(s) to the protocol and/or appropriate communication(s) will be generated. If the decision has been made to end the study following this review period, the study end will be defined as the date of the Sponsor decision, and this end of study date supersedes the definitions outlined above. The Competent Authority(ies) and IRB(s)/IEC(s) will be apprised of the maximum duration of the study beyond the last participant out and the justification for keeping the study open.

4.4.1 Clinical Criteria for Early Study Termination

There are no prespecified criteria for terminating the study early.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

Moderate or Severe HI

1. Has a diagnosis of chronic (>6 months), stable, hepatic impairment with features of cirrhosis due to any etiology (stability of hepatic disease should correspond to no acute episodes of illness within the previous 2 months due to deterioration in hepatic function). For the purposes of this study, diagnosis of cirrhosis based on assessment on imaging features (ultrasound, transient elastography, or magnetic resonance elastography) indicative of cirrhosis in combination with clinical features of cirrhosis or biopsy-confirmed cirrhosis will be acceptable.

   Note: Individuals who have undergone a TIPS (transjugular intrahepatic portosystemic shunt) procedure may be considered for inclusion upon consultation with the Sponsor.
2. **Moderate HI:** Has a score on the CP scale ranging from 7 to 9 at screening.
3. **Severe HI:** Has a score on the CP scale ranging from 10 to 15 at screening.

   Note: Baseline CP will be obtained by taking the mean of the CP score obtained from screening and from historical values within a 6-month period prior to screening. If no historical measurement is available, a second baseline CP will be taken during the screening period (>72 hours apart) and the mean of the 2 values will be used for group assignment; the second CP score may be obtained at the time of check in.
4. With the exception of hepatic impairment, the participant is in generally good health based on medical history, physical examination, VS measurements and ECGs performed prior to randomization. Participants with stable, chronic medical or psychiatric conditions may be included at the discretion of the investigator and the Sponsor.
5. With the exception of hepatic impairment, baseline health is judged to be stable based on laboratory safety tests obtained at the screening visit and prior to study drug administration. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out of range laboratory values.

Note: The laboratory safety test parameter values for CCI [redacted]

Healthy Participants

6. Is in good health based on medical history, physical examination, VS measurements, and ECGs performed before randomization. Appendix 9 provides a table of the 12-lead Electrocardiogram Abnormality Criteria.
7. Is in good health based on laboratory safety tests obtained at the screening visit and before administration of the of study drug. Appendix 2 provides a table of laboratory safety tests to be performed. Appendix 10 provides an algorithm for the assessment of out-of-range laboratory values.

All Participants (Panels A, B, and C)

Demographics

8. CCI [redacted] See Section 8.3.1 for criteria on rounding to the nearest whole number. BMI= weight (kg)/height $(m)^2$.
9. Is an individual of any sex/gender, from 18 years to 75 years of age inclusive, at the time of providing the informed consent.

Participants Assigned Male at Birth

CCI [redacted]

Participants Assigned Female at Birth

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

- Is not a POCBP
  OR
- Is a POCBP and:

CCI [redacted]

CCI

[redacted]

Informed Consent

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

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

<u>Moderate or Severe HI</u>

1. Has a history of any illness that, in the opinion of the investigator, might confound the results of the study or poses an additional risk to the participant by their participation in the study.

CCI

[redacted]

4. Is positive for HIV-1 or HIV-2 at the prestudy (screening) visit.
5. Has received antiviral and/or immune modulating therapy for HBV or HCV within 90 days prior to study start.

CCI

[redacted]

.

2021 CKD-EPI Equation:

$$eGFR = 142 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.200} \times 0.994^{Age} \times 1.012 \text{ if female}$$

where Scr is serum creatinine, k is 0.7 for females and 0.9 males, α is -0.241 for females and -0.302 for males, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1.

CCI

[redacted]

Healthy Participants

CCI

[redacted]

10. Positive test(s) for HBsAg, hepatitis C antibodies or HIV.Note: Participants with a documented cure and/or a positive serologic test for HCV with a negative HCV viral load may be included upon consultation with the Sponsor.

All Participants (Panels A, B, and C)

11. History of cancer (malignancy). Participants with adequately treated disease deemed as "cured," or who, in the opinion of the study investigator, are highly unlikely to sustain a recurrence for the duration of the study may be enrolled at the discretion of the investigator.

CCI

[redacted]

13. The participant had a major surgery and/or donated or lost 1 unit of blood (approximately 500 mL) within 4 weeks prior to the prestudy (screening) visit.

Prior/Concomitant Therapy

Moderate or Severe HI

CCI

Healthy Participants

15. Unable to refrain from or anticipates the use of any medication, including prescription and nonprescription drugs or herbal remedies beginning approximately 2 weeks (or 5 half-lives) prior to administration of the initial dose of study intervention, throughout the study (including washout intervals between treatment periods), until the poststudy visit. There may be certain medications that are permitted (see Section 6.5).

Prior/Concurrent Clinical Study Experience

16. Participated in another investigational study within 4 weeks (or 5 half-lives, whichever is greater) prior to the prestudy (screening) visit. The window will be derived from the date of the last visit in the previous study.

Diagnostic Assessments

All Participants

17. **Participants with HI:** The participant meets the following criteria for ECG:

CCI

Other Exclusions

All Participants

CCI

[redacted]

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

5.3.1.1 Diet Restrictions

Fasting requirements for study procedures, such as but not limited to laboratory safety evaluations are specified in Appendix 2.

Participants will fast from all food and drinks, except water, for at least 8 hours prior to study drug administration. Participants will fast from all food and drinks except water until completing 4-hour postdose procedures. After the 4-hour postdose procedures have been completed, subsequent meals and snacks will be unrestricted. Meals will be provided to the participants by the site while domiciling.

Water will be restricted 1 hour prior to and 1 hours after study drug administration.

5.3.1.2 Fruit Juice Restrictions

There are no specific restrictions for fruit and fruit juice consumption.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

5.3.2.1 Caffeine Restrictions

Participants are advised to refrain from consumption of caffeinated beverages or xanthine-containing products from 12 hours prior to the screening visit, admission, post-dose visits, poststudy visit, and during the domiciled period.

At all other times, caffeinated beverages or xanthine-containing products will be limited to no more than 6 units per day (1 unit = 120 mg of caffeine).

5.3.2.2 Alcohol Restrictions

Participants are advised to refrain from consumption of alcohol 24 hours prior to the screening visit, admission, post-study visits, poststudy visit, and during the domiciled period.

At all other times, alcohol consumption is limited to no more than approximately 3 alcoholic beverages or equivalent servings (1 serving is approximately equivalent to: beer <354 mL/12 ounces>, wine <118 mL/4 ounces>, or distilled spirits <29.5 mL/1 ounce>) per day.

5.3.2.3 Tobacco Restrictions

Participants will follow the smoking restrictions (and if applicable, the use of nicotine/nicotine-containing products) defined by the CRU.

5.3.3 Activity Restrictions

Participants will avoid unaccustomed strenuous physical activity (ie, weightlifting, running, bicycling, etc) from the prestudy (screening) visit until administration of the initial dose of study intervention, throughout the study (including washout intervals between treatment periods), and until the poststudy visit.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information may be included, as outlined in the eCRF entry guidelines. Minimal information may include demography, screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

5.5 Participant Replacement Strategy

If a participant withdraws from the study a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention or intervention sequence (as appropriate) as the participant being replaced. The replacement participant will be assigned a unique allocation number.

The study site should contact the Sponsor for the replacement participant's allocation number.

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 will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in Table 3.

Table 3 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Treatment Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Moderate HI	Experimental	Efinopegdutide	Combination Product	Injection, Solution	14 mg/mL	7 mg	SC	Single dose, Day 1	Test Product	IMP	Provided centrally by the Sponsor
Severe HI	Experimental	Efinopegdutide	Combination Product	Injection, Solution	14 mg/mL	7 mg	SC	Single dose, Day 1	Test Product	IMP	Provided centrally by the Sponsor
Healthy Matched Control	Experimental	Efinopegdutide	Combination Product	Injection, Solution	14 mg/mL	7 mg	SC	Single dose, Day 1	Test Product	IMP	Provided centrally by the Sponsor

EEA=European Economic Area; HI=hepatic impairment; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; SC=subcutaneous

The classification of IMP and NIMP/AxMP 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 and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All supplies indicated in Table 3 will be provided per the "Sourcing" column depending on local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.1.1 Medical Devices

The drug-device combination product/combination medicinal product provided for use in this study is an efinopegdutide prefilled syringe for SC injection. Refer to Section 8.4.8 and Appendix 4 for instructions on reporting events associated with the combination product.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is in Section 4.3.

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

Participants in this study will be allocated by nonrandom assignment. A sample allocation schedule is shown in Table 4.

Table 4 Allocation of Participants to Treatment

Hepatic Impairment Stage	n	Treatment
Moderate[a]	8	Efinopegdutide 7.0 mg
Severe[a]	8	Efinopegdutide 7.0 mg
Healthy[b]	8	Efinopegdutide 7.0 mg

[a] The participants in the groups defined by hepatic function should be reasonably similar to one another with respect to age, gender, and weight. However, participants with normal hepatic function should be matched at the group level. In order to make this matching possible, participants with normal hepatic function need to be enrolled after the participants with hepatic impairment have been recruited.

b Participants with normal hepatic function are within ±15 years of the mean age and within ± 3.5 kg/m^2 of the mean BMI for the severe hepatic function group. In addition, the numbers of males and females of the healthy participants will be generally matched to the numbers of hepatic insufficient participants within ±1; i.e. if there are 4 males and 4 females in the hepatic insufficient group, every effort will be made to ensure a 4:4 ratio in the healthy participants, but 3:5 or 5:3 would be acceptable as well.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Participants will be dosed at the site; they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of administration will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

If a participant does not discontinue all prior medications within 14 days or 5 half-lives of starting the study, they may be included in the study if the investigator can rationalize that the specific use of a prior medication is not clinically relevant within the context of the study.

Concurrent use of any prescription or nonprescription medication, or concurrent vaccination, during the ongoing study (ie, after intervention allocation) must first be discussed between the investigator and Sponsor before administration, unless appropriate medical care necessitates that therapy or vaccination should begin before the investigator and Sponsor can consult. The participant will be allowed to continue in the study if both the Sponsor and the investigator agree.

Paracetamol/acetaminophen may be used for minor ailments without prior consultation with the Sponsor.

In addition, the following concomitant medications/vaccinations are permitted:

- COVID-19 vaccine may be administered. Study intervention must be given at least 72 hours following or at least 48 hours prior to any COVID-19 vaccination.

For Participants with Moderate or Severe Hepatic Impairment:

Participants who are taking medication to treat general medical conditions and/or conditions associated with hepatic disease (e.g., hypertension, non-insulin dependent diabetes mellitus, hypercholesterolemia, hypo- or hyperthyroidism, gout, depression) will be allowed to participate in the study at the discretion of the Investigator and following consultation with the Sponsor Clinical Monitor. Participants must be on a stable regimen for at least 1 month prior to study drug administration and able to withhold the use within 4 hours prior to and 8 hours after study drug administration. Any exceptions to this must first be discussed between the Investigator and Sponsor.

Certain prescription medications used to treat manifestations of hepatic disease (e.g., lactulose, neomycin, etc.) will be allowed during the study, but the patient must be on a steady dose, drug, and regimen for ~ 1 month prior to dosing on Day 1. Lactulose should be restricted at least 6 hours prior to and 6 hours after dosing on Day 1 since it may potentially affect absorption.

Example of types of medications that would be used for chronic medical conditions that would be allowed include (but are not limited to) the following:

- Angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, diuretics
- Beta blockers
- Metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors, alpha-glucosidase inhibitors, incretin mimetics

- Statins
- Levothyroxine
- Colchicine, allopurinol
- Selective serotonin uptake inhibitors (SSRIs), tricyclic antidepressants
- Proton pump inhibitors

Participants with a valid medical marijuana card will be allowed to participate in the study at the discretion of the Investigator, however use of medical marijuana should be restricted at least 24 hours prior to, and 24 hours after, study intervention administration.

Any medication (including over-the-counter) that, by the determination of the Investigator, might interfere with the study (e.g., cimetidine) must be discontinued at least 2 weeks (or 5 half-lives of the compound, whichever is longer) prior to the dosing of study drug.

Medications with known effect on QT/QTc prolongation may be allowed following discussion with the Sponsor.

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification

Dose modifications are not applicable to this study.

6.6.1 Stopping Rules The following stopping rules will be used during the conduct of this study.

If any of the below stopping rules are met, the study will be paused, and no further dosing will occur until the Sponsor has reviewed the totality of data available. In the case a stopping rule is met by adverse drug reactions identified in the MK-6024 IB, the study may be continued by addressing an individual participant (e.g. discontinuing the participant based on Section 7.1) instead of stopping the entire study. To continue the study, joint agreement with the Sponsor and investigator will be needed.

1. An individual participant reports an SAE considered related to the study intervention by the investigator

2. Two (2) or more participants within a Panel (at the same dose level) report Severe Nonserious AEs considered related to the study intervention by the investigator.

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 are not provided.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

In clinical studies with a single intervention, discontinuation of study intervention can only occur before the intervention. Therefore, participants who receive a single-dose intervention cannot discontinue 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 8.1.9. 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.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, 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 procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- 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 each participant over the duration of the study will not exceed the volume mentioned in Appendix 8. If additional pharmacokinetic and/or safety analysis is necessary, additional blood (no more than 50 mL in total) may be obtained.

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.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

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.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, 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 allocation, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification 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 before medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 14 days before starting the study.

8.1.5.2 Concomitant Medications

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

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 intervention allocation. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

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

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

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or an appropriately qualified designee.

8.1.8.1 Timing of Dose Administration

After it is confirmed that the participant meets eligibility, study intervention administration will occur after the completion of Day 1 predose procedures Study intervention should be administered SC to the abdomen. The time of the dose will be designated as time "0" hr and the exact time of administration will be recorded.

8.1.9 Discontinuation and Withdrawal

The investigator or study coordinator must notify the Sponsor when a participant has been discontinued/withdrawn from the study. If a participant discontinues for any reason at any time during the course of the study, the participant may be asked to return to the clinic (or be contacted) for a poststudy visit as per the number of days described in Section 1.3 to have the applicable procedures conducted. However, the investigator may decide to perform the poststudy procedures at the time of discontinuation or as soon as possible after discontinuation. If the poststudy visit occurs prior to the safety follow-up time frame as specified in Section 8.4.1, the investigator should perform a follow-up telephone call at the end of the follow-up period (Section 8.4.1) to confirm if any AEs have occurred since the poststudy clinic visit. Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 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@MSD.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.

8.1.10 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.

8.1.11 Domiciling

Participants will report to the CRU on Day -1 before the scheduled day of study intervention administration on Day 1 and remain in the unit until after completion of the postdose procedures on Day 4. At the discretion of the investigator, participants may be requested to remain in the CRU longer.

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.

8.2 Efficacy/Immunogenicity Assessments

There are no direct efficacy assessments in this study.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Appendix 8.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded at the timepoints listed in the SoA (Sec. 1.3).

Symptom driven physical examinations may be performed at other times at the Investigator's discretion.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

BMI

BMI equals a person's weight in kilograms divided by height in meters squared ($BMI = kg/m^2$). BMI will be rounded to the nearest whole number according to the standard convention of 0.1 to 0.4 round down and 0.5 to 0.9 round up.

Body weight and height will be obtained with the participant's shoes off and jacket or coat removed.

8.3.2 Vital Signs

- Body temperature, HR, RR, and BP will be assessed.
- BP and HR will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available. The same arm should be used for all measurements for each individual participant if possible. The correct size of the BP cuff and the correct positioning of the participant's arm is essential to increase the accuracy of BP measurements.

8.3.2.1 Resting Vital Signs

Vital Sign Measurements (Heart Rate and Blood Pressure)

Participants should be resting in a quiet setting without distractions in a semirecumbent position for at least 10 minutes before having VS measurements obtained. Semirecumbent VS will include HR, systolic and diastolic BP, RR, and body temperature at timepoints indicated in the SoA.

The predose (baseline) HR and BP will be triplicate measurements, obtained at least 1 to 2 minutes apart within 3 hours of dosing efinopegdutide. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Screening and all postdose VS measurements will be single measurements.

Respiratory Rate and Body Temperature

RR and body temperature will be single measurements per timepoint at all timepoints. The same method must be used for all measurements for each individual participant and should be the same for all participants at a given site.

8.3.2.2 Orthostatic Vital Signs

Orthostatic VS (HR and systolic and diastolic BP) will be obtained as single measurements per timepoint at all timepoints. Participants should be semirecumbent for at least 10 minutes and then stand upright for approximately 2 minutes before measurement of orthostatic VS.

8.3.3 Electrocardiograms

- 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. The correction formula to be used for QTc is Fridericia. Refer to Appendix 9 for evaluation and potentially significant findings.

Special care must be taken for proper lead placement by qualified personnel. Skin should be clean and dry before lead placement. Participants may need to be shaved to ensure proper lead placement. Female participants may need to remove interfering garments.

Participants should be resting in the semirecumbent position for at least 10 minutes before each ECG measurement. At each time point when triplicate ECG are required, 3 individual ECG tracings should be obtained at least 1 minute apart. The full set of triplicates should be completed in no more than 6 minutes.

If repeat ECGs are required, the clinical site will decide whether to leave the electrodes in place or mark the position of the electrodes for subsequent ECGs. To mark the position of the electrodes, 12-lead electrode sites will be marked on the skin of each participant with an ECG skin-marker pen to ensure reproducible electrode placement.

Day 1 predose ECGs will be obtained in triplicate at least 1 minute apart within 3 hours before dosing efinopegdutide. The median of these measurements will be used as the baseline to calculate change from baseline for safety evaluations (and for rechecks, if needed). Screening and all postdose ECG measurements (including poststudy visit) will be single measurements.

During the treatment period, if a participant demonstrates an increase in QTc interval ≥60 msec compared with median predose baseline measurement, the participant will continue to be monitored by at least single repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QTc is within 60 msec of baseline. If prolongation of the QTc interval ≥60 msec persists, a consultation with a cardiologist may be appropriate and the Sponsor should be notified.

If a participant demonstrates a QTc interval ≥500 msec on a postdose ECG, the Sponsor should be notified, and the ECGs should be reviewed by a cardiologist. The participant should be telemetry monitored (until the QTc interval is <500 msec) or should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If the QRS interval from any postdose ECG is 20% greater than the median baseline QRS interval and is >120 msec (and change is not considered rate related or pacing induced) or there appears to be new onset intermittent bundle branch block, then the ECG will be immediately repeated twice within 5 minutes. The median value of the QRS interval from the 3 ECGs will represent the value at that time point. If the median QRS interval increase from baseline for any postdose time point is >20%, the participant will continue to be monitored by repeat 12-lead ECGs every 15 minutes for at least 1 hour or until the QRS interval is within 20% of baseline. If a >20% prolongation of the QRS interval persists, a consultation with a cardiologist may be appropriate and the Sponsor should be notified.

If at any time the QRS interval is prolonged ≥200 msec (and change is not considered rate related or pacing induced), then the Sponsor should be notified. The ECGs should be reviewed by a cardiologist and the participant should be considered for transfer to a location where closer monitoring and definitive care (eg, a CCU or ICU) is available.

If the participant has unstable hemodynamics, or has any clinically significant dysrhythmias noted on telemetry, the participant should be immediately transferred to an acute care setting for definitive therapy.

If prolongation of the QTc interval is noted, concomitant medications that prolong QTc interval should be held until the QTc interval is within 60 msec of baseline and the QTc interval is <500 msec.

A cardiologist will be consulted by the investigator as needed to review ECG tracings with significant abnormalities.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- 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, as defined in Appendix 2, must be conducted in accordance with the SoA.
- 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 or within 14 days after the last dose of study intervention, 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.

8.3.5 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine and/or serum) should be conducted as per SoA for the time required to eliminate systemic exposure after the last dose of each study intervention and should correspond with the time frame for participant's contraception as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is:Efinopegdutide: 35 days

- 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.

8.3.6 Photograph of Rash

Photographs of the rash are highly recommended to be taken immediately, along with any additional information that may assist the investigator to evaluate the skin reaction, skin eruption, or rash occurrence in determining etiology and study intervention relationship.

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 need to document if an SAE was associated with a medication error, misuse, or abuse.

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

AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation, must be reported by the investigator under any of the following circumstances:

- if the participant is receiving placebo run-in or other run-in treatment,
- if the event causes the participant to be excluded from the study,
- if it is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, placebo, or a procedure.

From the time of intervention allocation through 14 days after cessation of 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 any time outside the period specified in the previous paragraph also 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 the investigator 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 5.

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

Table 5 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting 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
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

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
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 24 hours 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 allocated 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 toward 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 SAEs) 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 (spontaneously reported to the investigator or their designee) that occurs in a participant 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

Not applicable.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.
2. Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*
   *Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this study.

8.4.8 Medical Device and Drug–Device Combination Products – PQCs/Malfunctions

The method of documenting and reporting of such events [complaints associated with medical devices including PQCs/malfunctions] will occur as below and in Appendix 4.

To fulfill regulatory reporting obligations worldwide, medical device information associated with AEs will be collected and reported to the Sponsor in the same time frame as AEs per Section 8.4.1 via CRF (paper or electronic) and as per data entry guidelines.

PQCs/malfunctions, including those that involve a participant or any user/associated person, must be reported to the Sponsor. Sponsor shall review reported events by the investigator to fulfill the legal responsibility of notifying appropriate regulatory authorities and other entities about certain safety information relating to medical devices and drug-device combination products being used in clinical studies.

The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality between the AE and the medical device or device constituent of combination product.

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose of any drug administered as part of the study exceeding the dose prescribed by the protocol. It is up to the investigator or the reporting physician to decide whether a dose is to be considered an overdose, in consultation with the Sponsor.

Sponsor does not recommend specific treatment for an overdose. 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.

8.6 Pharmacokinetics

The decision as to which serum samples will be measured for evaluation of PK will be collaboratively determined by the Sponsor. If indicated, these samples may also be measured and/or pooled for assay in an exploratory manner for metabolites and/or additional pharmacodynamic markers. Blood samples collected may be stored and further analysis may be performed, if required.

8.6.1 Blood Collection for Serum Efinopegdutide

Sample collection, storage, and shipment instructions for serum samples will be provided in the Operations Manual.

8.7 Pharmacodynamics

Pharmacodynamic assessments will be conducted as outlined in the SoA (Section 1.3), including for endogenous glucagon. Blood samples collected may be stored and further analysis may be performed, if required.

8.8 Immunogenicity Assessment

Serum samples for ADA assessment will be collected to evaluate the incidence and magnitude of anti-efinopegdutide antibodies. ADA samples will be collected from all participants according to the ADA sampling scheme outlined in the SoA (Section 1.3). Throughout the study, the date and time of each ADA sample will be recorded. Sample collection, storage, and shipment instructions for serum samples will be provided in the Operations manual.

8.9 Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research will be collected from all participants as specified in the SoA:

- Blood for Genetic Analysis

8.9.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the participant provides documented informed consent for FBR. If the planned genetic analysis is not approved, but future biomedical research is approved, this sample will be collected for the purpose of FBR.

The planned genetic analysis sample should be obtained pre-dose on Day 1, but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

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 samples listed in Section 8.9

8.11 Medical Resource Utilization and Health Economics

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

8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.12.1 Screening

Within approximately 28 days before intervention allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.

Participants may be rescreened after consultation with the Sponsor. Rescreening should include all screening procedures listed in the SoA, including consent review. Rescreen procedures cannot be conducted the day prior to intervention allocation if there are Day −1 procedures planned per protocol.

8.12.2 Treatment Period

Refer to the SoA (Section 1.3) and Administrative and General Procedures (Section 8.1)

8.12.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

At any point if a participant discontinues from treatment but continues to be monitored in the study, a subset of study procedures specified in the SoA may be completed at the discretion of the investigator and with Sponsor agreement. The subset of study procedures completed will be communicated in a PCL.

8.12.4 Poststudy

Participants will be required to return to clinic approximately 35 days after the last dose of study intervention for the poststudy visit.

8.12.5 Critical Procedures Based on Study Objectives: Timing of Procedure

For this study, the blood sample for efinopegdutide is the critical procedure.

At any postdose timepoint, the blood sample for efinopegdutide needs to be collected as close to the exact time as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible. Study procedures can be performed before or after the prescribed/scheduled time.

The order of priority can be changed during the study with joint agreement of the Investigator and the Sponsor Clinical Director.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

The following variance in procedure collection times will be permitted.

- PK and ADA Collection as outlined in Table 6.

Table 6 PK and ADA Collection Windows

Scheduled Sampling Point	**Sample Collection Window**
Predose	Within 3 hr prior to dosing
0 to < 48 hr post-dose	± 1 hr
48 hr post-dose to Day 8	± 2 hr
Day 11 to Day 21	± 1 day
Poststudy Visit	± 2 day

- Pre-dose standard safety evaluations: VS and ECG up to 3 hours prior to dosing; laboratory safety tests and physical exam up to 24 hours prior to dosing.
- Postdose standard safety evaluations: VS, ECG, laboratory safety tests, and physical exam
  - Prior to 24-hours post dose may be obtained within 15 minutes of the theoretical sampling time
  - Between 24-hours and 48-hours postdose may be obtained within 1 hour of the theoretical sampling time
  - From 48-hours postdose to Day 8 may be obtained within 2 hours of the theoretical sampling time
  - From Day 11 to Day 21 may be obtained within 24 hours of the theoretical sampling time
  - Poststudy visit samples may be obtained within 2 days of the theoretical sampling time

8.12.6 Study Design/Dosing/Procedures Modifications Permitted Within Protocol Parameters

This is a Phase 1 assessment of efinopegdutide in humans, and the PK, pharmacodynamic, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen, and/or clinical or laboratory procedures currently outlined may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants.

As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol.

- Instructions to take study intervention with or without food or drink may also be modified based on newly available data
- Modification of the PK sample processing and shipping details based on newly available data

The PK/pharmacodynamic sampling scheme currently outlined in the protocol may be modified during the study based on newly available PK or pharmacodynamic data (eg, to obtain data closer to the time of peak serum concentrations). If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional pharmacodynamic markers.

Up to additional 50 mL of blood may be drawn for safety, PK, and/or pharmacodynamic analyses. The total blood volume withdrawn from any single participant will not exceed the maximum allowable volume during his/her participation in the entire study (Appendix 8).

The timing of procedures for assessment of safety procedures (eg, vital signs, ECG, safety laboratory tests, etc) may be modified during the study based on newly available data. Additional laboratory safety tests may be added to blood samples previously drawn to obtain additional safety information. These changes will not increase the number of study procedures for a given participant during his/her participation in the entire study.

It is understood that the current study may use some or none of the alterations described above. Any alteration made to this protocol to meet the study objectives must be detailed by the Sponsor in a letter to the Study File and forwarded to the investigator for retention. The letter may be forwarded to the IRB/IEC at the discretion of the investigator.

9 KEY STATISTICAL CONSIDERATIONS

This section details the principal statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

9.1 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be conducted by, or under the direct auspices of, the Early Clinical Development Statistics Department in collaboration with the Quantitative Pharmacology and Pharmacometrics Department and Translational Medicine Department of the Sponsor.

9.2 Hypotheses/Estimation

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

(Primary Estimation) The serum PK (AUC0-inf, AUC0-last and Cmax) of efinopegdutide following a single 7 mg dose of efinopegdutide in participants with hepatic impairment (moderate HI and severe HI) will be estimated and compare to those in healthy matched control participants.

9.3 Analysis Endpoints

9.3.1 Primary Endpoints

Pharmacokinetics: The pharmacokinetic variables of serum efinopegdutide AUC0-inf, AUC0-last, Cmax, Tmax, apparent terminal t1/2, CL/F and Vz/F are of primary interest.

9.3.2 Secondary Endpoints

Safety: The safety endpoints will include all types of adverse events and discontinuation of study intervention due to adverse event(s), in addition to laboratory safety tests, ECGs, and vital signs. Baseline is defined as measurements obtained pre-dose Day 1.

9.3.3 Exploratory Endpoints

CCI

9.4 Analysis Populations

The following populations are defined for the analysis and reporting of data. All participants will be reported, and their data analyzed, according to the study intervention(s) they actually received.

9.4.1 Safety Analysis Populations

The All Participants as Treatment population consists of all participants who received the study intervention. This population will be used for assessments of safety and tolerability.

9.4.2 PK Analysis Populations

The Per-Protocol Population consists of the subset of participants who comply with the protocol sufficiently to ensure that generated data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of important protocol deviations. Important protocol deviations will be identified to the extent possible prior to unblinding by individuals responsible for data collection/compliance, and its analysis and interpretation. Any participants or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all participants who are compliant with the study procedure as aforementioned and have available data considered sufficient to exhibit the effect of treatment will be included in the Per-Protocol dataset. This population will be used for the PK analyses.

9.5 Statistical Methods

9.5.1 Statistical Methods for PK Analyses

Separately for each pharmacokinetic parameter, individual values of AUC0-∞, AUC0-last, and Cmax of serum efinopegdutide will be natural log-transformed and evaluated with a linear fixed effects model containing a categorical effect for populations (moderate hepatic impairment group, severe hepatic impairment group and healthy matched control group). An unstructured covariance matrix will be used to allow for unequal population variances via the REPEATED statement with the GROUP=Population in SAS PROC MIXED. The Kenward and Roger adjustment will be used to calculate the denominator degrees of freedom for the fixed-effect (DDFM=KR). Ninety-five percent (95%) confidence intervals for the least squares means for each population will be constructed on the natural log scale and will reference the t-distribution. Exponentiating the least-squares means and their corresponding 95% confidence intervals will yield estimates for the population geometric means and confidence intervals about the geometric means on the original scale. Sample SAS code is given below:

```
proc mixed data=data;
class population;
model lnpk = population /ddfm=kr;
repeated/ group= population;
lsmeans population /cl alpha=0.05;
run;
```

To compare subjects with HI in each of the hepatic insufficient categories (moderate HI and severe HI) to matching subjects with normal hepatic function, a two sided 90% confidence interval for the true difference in means (HI – normal hepatic function) will be calculated for each PK parameters (AUC0-∞, AUC0-last and Cmax) using the mean square error from the model and referencing a t-distribution. These confidence limits will be exponentiated to obtain the 90% confidence interval for the true ratio of geometric means (HI/normal hepatic function) for each of the insufficient categories.

Figures showing summary concentration-time profiles by hepatic impairment category (linear plot with arithmetic mean (±SD) for concentration and semi-log plot with arithmetic mean) will be provided.

Individual values will be listed for each PK parameter (AUC0-∞, AUC0-last, Cmax, Tmax, apparent terminal t1/2, CL/F, and Vz/F) by population, and the following (non model based) descriptive statistics will be provided: N (number of subjects with non-missing data), arithmetic mean, standard deviation, arithmetic percent CV (calculated as 100 x standard deviation/arithmetic mean), median, minimum, maximum, geometric mean, and geometric percent CV (calculated as 100 x sqrt(exp(s2) - 1), where s2 is the observed variance on the natural log-scale).

9.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including laboratory test results, vital signs, and ECG measurements.

The overall safety endpoints include the number of participants with at least one AE, drug-related AE, serious AE, serious, drug-related AE, who discontinue from study intervention due to an AE, or with an AE resulting in death.

The safety evaluation will include a summary by population group of the number and percentage of participants with each type of AE.

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

9.5.3 Statistical Methods for Pharmacodynamic Analyses

The concentration profile of endogenous glucagon will be plotted across time by group. The change from baseline endogenous glucagon will be summarized by group. Similarly, the change from baseline body weight will be summarized by group.

9.5.4 Statistical Methods for Immunogenicity Endpoints

The incidence and magnitude (titer) of ADA positive participants will be summarized.

9.6 Interim Analyses

Not applicable

9.7 Multiplicity

Not applicable

9.8 Sample Size and Power Calculations

The sample size selected for each population to evaluate the effect of hepatic impairment on the PK of efinopegdutide was not chosen to satisfy any a priori statistical requirement. This sample size (N=6 evaluable per group) has historically been shown to be sufficient for studies of this type and should provide adequate data to support the planned analyses. Nevertheless, estimates of the expected precision of the estimates, based on these sample sizes and the known variability obtained from a hepatic PK study presented below. The precision of the estimated GMRs (hepatic impairment / normal hepatic function) of PK parameters obtained from this study can be assessed by calculating the half-width of the 90% CIs expected for the given sample size and assumed variability. The observed between-participant coefficients of variation were CCI standard deviation on the log scale) for AUC0-inf from a SAD study in Healthy Overweight/Obese Adults (Protocol MK-6024-005). Assuming a sample size of 6 participants per population and observed between-participant SD is CCI on the log scale, then the half width of the 90% CI of GMR for MK-6024 AUC0-inf on the log scale will be CCI. The lower and upper 90% confidence limits for the GMR will be given by OBS/CCI and OBS*CCI for AUC0-inf, where OBS is the observed GMR. Thus, for example, if the observed GMR for AUC0-inf was CCI then the approximate 90% CI for the GMR would be CCI

Similarly, the observed between-participant coefficients of variation were CCI standard deviation on the log scale) for Cmax from Protocol MK-6024-005. Assuming a sample size of 6 evaluable participants per population and observed between-participant SD is CCI on the log scale, then the half width of the 90% CI of GMR for MK-6024 Cmax on the log scale will be CCI The lower and upper 90% confidence limits for the GMR will be given by OBS/CCI and OBS*CCI for Cmax. Thus, for example, if the observed GMR for Cmax was 1.50, then the approximate 90% CI for the GMR would be [CCI].

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Interventional Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and healthcare providers to ensure operational feasibility. Trial design also includes

proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial. Individuals involved in trial conduct receive training commensurate with their role prior to their becoming involved in the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations and ICH Guidelines. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for

financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.5 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.6 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.7 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.9 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 will be performed by the local laboratory.
- Blood for laboratory tests are to be obtained following at least an 8-hour fasting (except water).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 7 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH Reticulocytes (Absolute count)		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry	BUN	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate	Chloride	Phosphorous
	Creatinine	Sodium	ALT/SGPT	Total Protein
	Fasting plasma glucose	Calcium	Alkaline phosphatase	
Other safety Tests	HbA1c			
Coagulation	• PT/INR (International normalized ratio, for hepatic impaired participants only)			
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum OR urine hCG pregnancy test (as needed for POCBP)			
Other Screening Tests	• FSH (as needed in postmenopausal PONCBP only) • Serum or urine alcohol and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids, and benzodiazepines) per site SOP • Serology (HIV-1 and HIV-2 antibodies in all participants; HBsAg and hepatitis C virus antibody) in healthy participants only)			
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; POCBP=people of childbearing potential; PONCBP=people of nonchildbearing potential; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; Notes: Laboratory safety tests will be performed after approximately an 8-hour fast. Predose Day 1 laboratory procedures can be conducted up to 24 hours prior to study intervention administration.				

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 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 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."

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.

10.3.3 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:

a. Results in death
b. 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.
c. 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.

d. 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.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. 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.

10.3.4 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.

10.3.5 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/toxicity

- 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) reported during the study and assign it to 1 of the following categories:
  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).
  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).
  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

Assessment of causality

- Did the study intervention cause the AE?
- The determination of the likelihood that the study intervention 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 study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention 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 study intervention? 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 study intervention 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 study intervention; (3) the study is a single-dose drug study; or (4) study intervention (s) is/are only used 1 time.)
  - **Rechallenge:** Was the participant reexposed to the study intervention 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; (2) the study is a single-dose drug study; or (3) study intervention (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 STUDY INTERVENTION, OR IF REEXPOSURE TO THE STUDY INTERVENTION POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the study intervention or drug class pharmacology or toxicology?
- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their 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 study intervention relationship).
  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)
- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.
- 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 their 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.

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.

10.3.6 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 email 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

The recording and follow-up procedures described in this protocol apply to all medical devices as described below. For purposes of this section, medical devices in scope for device information collection include devices intended to be used by a study participant according to the study protocol that are manufactured by the Sponsor or for the Sponsor by a third party, licensed by the Sponsor for human use and/or drug-device combination products as listed in Section 6.1.1. Product Quality Complaints/Malfunctions must be reported to the Sponsor.

10.4.1 Definitions

Combination Product – A product comprised of 2 or more regulated components (ie, a drug and a device; a biologic and device; a biologic and a drug; or a drug, a device, and a biologic). Combination products can be single entity, copackaged, or colabeled.

Complaint – Any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a device after it is released for distribution. This would include PQC, AE, and customer feedback.

A complaint does not necessarily need to involve a user or any other person.

Constituent Part – A drug, device, or biological product that is part of a combination product.

Customer Feedback – A report that does not allege a PQC or defect and has no relevant safety information/untoward event associated with it (eg, goodwill or courtesy replacement, consumer preference or suggestion, remark that may suggest an improvement in the functionality or quality of a medical device, or device like features of a drug delivery system).

Malfunction – The failure of a device to meet its performance specifications or otherwise perform as intended.

Medical Device – Any instrument, apparatus, appliance, material, or other article, whether used alone or in combination, including the software necessary for its proper application intended by the MANUFACTURER to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment, or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for an injury or handicap,
- investigation, replacement, or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological, or metabolic means, but which may be assisted in its function by such means.

PQC – Any communication that describes a potential defect related to the identity, strength, quality, purity, or performance of a product identified by external customers. This includes potential device or device component malfunctions. Note: A report of Lack or Limited Efficacy is considered an AE rather than a PQC.

Serious Injury – An injury or illness that:

1. Is life-threatening,
2. Results in permanent impairment of a body function or permanent damage to a body structure, or
3. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.

10.4.2 Recording, Assessing Causality, and Follow-up of PQCs/Malfunctions

Recording

When a complaint including PQC/malfunction occurs it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

Events occurring during the study will be recorded in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate CRF (paper or electronic) as per instructions provided in the data entry guidelines. Medical device/device constituent part of drug-device combination product information will be collected and reported to the Sponsor in the same time frame as SAEs as per Section 8.4.1 via CRF (paper or electronic). PQCs/malfunctions must be reported to the Sponsor.

Assessing Causality

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship.

The investigator will use clinical judgment to determine the relationship.

Alternative causes such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration should be considered and investigated.

Follow-up

The investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the event as complete as possible.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Participants of Childbearing Potential (POCBP)

A participant assigned female sex at birth is considered fertile following menarche and capable of becoming pregnant until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, not considered POCBP:

- Premenarchal
- Premenopausal with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth who are not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth who are on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Participants of Nonchildbearing Potential (PONCBP)

Participants assigned female sex at birth who are in the following categories are not capable of becoming pregnant and, therefore, are considered PONCBP:

- Premenopausal with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Müllerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in participants assigned female sex at birth not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Participants assigned female sex at birth on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:

CCI

[redacted]

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.10 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used 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@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction 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 withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

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10.7 Appendix 7: Country-specific Requirements

Not applicable.

10.8 Appendix 8: Blood Volume Table

CCI

ADA=antidrug antibodies; FSH=follicle stimulating hormone; HbA1c=hemoglobin A1c; HIV=human immunodeficiency virus; INR=international normalized ratio; POCBP= people of childbearing potential; PT=prothrombin time; SoA= schedule of activities; SOP= standard operating procedures;

a Laboratory safety tests will include serum pregnancy tests at the specified timepoints in the SoA with no additional blood volume is required. Serum pregnancy testing will only occur in POCBP, if applicable

b Serum FSH will be completed for postmenopausal females only

c To be completed per SOP. HIV-1 and HIV-2 screening will occur for all panels. Hepatitis B/C screening will only be conducted for healthy-match control participants

d Will only be collected for participants in hepatic impairment participants

e If additional pharmacokinetic/pharmacodynamic and/or safety analysis is necessary, additional blood (no more than 50 mL in total) may be obtained.

f Blood volumes represent the maximum volume to be collected per participant in the study. Certain sites might have a lower overall total blood volume per participant based on laboratory blood volumes required to run assays.

10.9 Appendix 9: 12-Lead Electrocardiogram Evaluation Criteria

	Screen Failure Criteria	**Potentially Significant Postrandomization Findings**
RHYTHM		
Sinus Tachycardia	>110 bpm	HR >110 bpm and HR increase of ≥25 bpm from baseline
Sinus Bradycardia	<40 bpm	HR <40 bpm and HR decrease of ≥5 bpm from baseline
Sinus Pause/Arrest	>2.0 seconds	>2.0 seconds
Atrial Premature Complex	>1 beat	≥3 beats
Ventricular Premature Complex	All	≥3 beats
Ectopic Atrial Rhythm	None	None
Junctional Rhythm	Junctional Rhythm with HR <40 bpm	Junctional Rhythm with HR <40 bpm
Idioventricular Rhythm	All	All
Atrial Fibrillation	All	All
Atrial Flutter	All	All
Supraventricular Tachycardia	All	All
Ventricular Tachycardia	All	All
AXIS		
Left Axis Deviation	RBBB With LAHB	New Onset LAHB
Right Axis Deviation	RBBB With LPHB	New Onset LPHB
CONDUCTION		
1st Degree AV Block	PR ≥230 ms	PR ≥230 ms + Increase of >15 ms; or PR Increase of >25%
2nd Degree AV Block	Mobitz Type II	Mobitz Type II
3rd Degree AV Block	All	All
LBBB	All	All
RBBB	RBBB With LAHB/LPHB as Defined Above	New Onset RBBB (Not Including Rate-related)
ICRBBB (QRS <120 ms)	No Exclusion	Nothing
Short PR/Preexcitation Syndrome	Delta Wave + PR <120 ms	Delta Wave + PR <120 ms
Other Intraventricular Conduction Delay	QRS ≥130 ms	QRS ≥130 ms + Increase of ≥10 ms
QTc (B or F)		
Male	QTc ≥470 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline

	Screen Failure Criteria	**Potentially Significant Postrandomization Findings**
Female	QTc ≥480 ms	QTc ≥500 ms or Increase of ≥60 ms From Baseline
HYPERTROPHY		
Atrial Abnormalities	Definite Evidence of P Mitrale or P Pulmonale	Definite Evidence of P. Mitrale or P. Pulmonale
Ventricular Abnormalities	Voltage Criteria for LVH Plus Strain Pattern	Voltage Criteria for LVH Plus Strain Pattern
MYOCARDIAL INFARCTION		
Acute or Recent	All	All
Old	All	All
ST/T MORPHOLOGY		
ST Elevation Suggestive of Myocardial Injury	In 2 or more contiguous leads	In 2 or more contiguous leads
ST Depression Suggestive of Myocardial Ischemia	In 2 or more contiguous leads	In 2 or more contiguous leads
T-wave Inversions Suggestive of Myocardial Ischemia	In 2 or more contiguous leads	In 2 or more contiguous leads
Nonspecific ST-T Changes (In 2 or More Leads)	No exclusion	In 2 or more contiguous leads
PACEMAKER	**All**	**All**

AV=atrioventricular; bpm=beats per minute; HR=heart rate: ICRBBB=incomplete right bundle branch block; LAHB=left anterior hemiblock; LPHB=left posterior hemiblock; LVH=left ventricular hypertrophy; mm=millimeter; ms=milliseconds, PR=pulse rate; QTcB=QT correction using Bazett's formula; QTcF=QT correction using Fredericia formula; RBBB=right bundle branch block; ST/T=ST-segment/T wave.

Baseline is defined as Predose Day 1.

10.10 Appendix 10: Algorithm for Assessing Out of Range Laboratory Values

For all laboratory values obtained at prestudy (screening) visit and/or predose evaluation:

A. If all protocol-specified laboratory values are normal, the participant may enter the study.
B. If a protocol-specified laboratory value is outside the parameter(s) outlined in the inclusion/exclusion criteria (including repeats if performed), the participant will be excluded from the study.
C. If ≥1 protocol-specified laboratory value not specified in the inclusion/exclusion criteria is outside the normal range, the following choices are available:
   - The participant may be excluded from the study.
   - The participant may be included in the study if the abnormal value(s) is NCS (the investigator must annotate the laboratory value "NCS" on the laboratory safety test source document).
   - The participant may be included in the study if the abnormality is consistent with a pre-existing medical condition which is not excluded per protocol (eg, elevated eosinophil count in a participant with asthma or seasonal allergies), the medical condition should be annotated on the laboratory report.

   OR

   - The abnormal test may be repeated (refer to items below for continuation of algorithm for repeated values).
     - If the repeat test value is within the normal range, the participant may enter the study.
     - If the repeat test value is still abnormal, the study investigator will evaluate the potential participant with a complete history and physical examination, looking especially for diseases that could result in the abnormal laboratory value in question. If such diseases can be ruled out, and if the abnormal laboratory value is not clinically relevant, then the participant may enter the study.
D. If there is any clinical uncertainty regarding the significance of an abnormal value, the participant will be excluded from the study.

10.11 Appendix 11: Abbreviations

Abbreviation	Expanded Term
ACCP	American College of Chest Physicians
ADA	antidrug antibodies
ADL	activities of daily living
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
AR	adverse reaction
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATD	accelerated titration design
ATP	adenosine triphosphate
AUC	area under the curve
AUC0-inf	area under the curve from 0 to infinity
BCG	Bacillus Calmette–Guérin
BDS	blood drug screen
BICR	blinded independent central review
bid	twice daily
BMI	body mass index
BP	blood pressure
CAC	Clinical Adjudication Committee
CCU	Cardiac care unit
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CF	compact flash
CG	Cockcroft-Gault
CHS	cough hypersensitivity syndrome
CI	confidence interval

Abbreviation	Expanded Term
C_{max}	maximum serum concentration
CL/F	apparent clearance
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CP	Child-Pugh
CrCl	creatinine clearance
CR	complete response
CRF	Case Report Form
CRU	clinical research unit
CSD	Cough Severity Diary
C-SSRS	Columbia-Suicide Severity Rating Scale
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CTMS	Clinical Trial Management System
CYP	cytochrome P450
DAIDS	Division of AIDS
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
ECI	event of clinical interest

Abbreviation	Expanded Term
eCRF	electronic Case Report Form
eCTA	exploratory Clinical Trial Application
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	Executive Oversight Committee
ePROs	electronic patient-reported outcomes
E-R	exposure response
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FEV1	forced expiratory volume in 1 second
FAS	Full Analysis Set
FFPE	formalin-fixed, paraffin embedded
FIH	first in human
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCGR	glucagon receptor
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony-Stimulating Factor
GERD	gastroesophageal reflux disease
GI	gastrointestinal
GLP	glucagon-like peptide
GM-CSF	Granulocyte Macrophage Colony-Stimulating Factor
GMR	geometric mean ratio
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen

Abbreviation	Expanded Term
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HI	hepatic impairment
HIV	human immunodeficiency virus
HR	heart rate
HRQoL	health-related quality of life
HRT	hormone replacement therapy
HSSB	Hepatic-specific Safety Board
IA(s)	interim analysis(ses)
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
ICU	intensive care unit
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IND	Investigational New Drug
IO	Immune oncology
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ITP	idiopathic thrombocytopenic purpura
IUD	intrauterine device

Abbreviation	Expanded Term
IUS	intrauterine hormone-releasing system
IV	intravenous
IVD	in vitro diagnostic
IVRS	interactive voice response system
IWG	International Working Group
IWRS	integrated web response system
JRCT	Japan Registry of Clinical Trials
KPS	Karnofsky performance status
LAM	lactational amenorrhea method
LCQ	Leicester Cough Questionnaire
LFC	liver fat content
LLN	lower limit of normal
LLOQ	lower limit of quantitation
mAb	monoclonal antibody
MAD	maximum administered dose
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified Toxicity Probability Interval
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NCI	National Cancer Institute
NCS	not clinically significant
NEAB	noneosinophilic bronchitis
NDA	New Drug Application
NOAEL	no observed adverse effect level
OR	objective response

Abbreviation	Expanded Term
ORR	objective response rate
OS	overall survival
OSF	on-site formulation
OTC	over the counter
PBO	placebo
PBPK	physiologically based PK
PCL	Protocol Clarification Letter
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PET	positron emission tomography
PFS	progression free survival
PGIC	Patient Global Impression Change
PK	pharmacokinetic
PKCθ	protein kinase C-theta
po	orally
PP	per-protocol
PQC	product quality complaint
PR	partial response
PRO	patient-reported outcome
QW	once weekly
Q2W	every 2 weeks
Q3W	every 3 weeks
QoL	quality of life
QP2	Department of Quantitative Pharmacology and Pharmacometrics
RCC	refractory chronic cough
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid
rP2D	recommended Phase 2 dose
RR	respiratory rate

Abbreviation	Expanded Term
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SCr	Serum Creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transminase
SIM	Site Imaging Manual
SLAB	Supplemental laboratory test(s)
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
STING	stimulator of interferon genes
SUSAR	suspected unexpected serious adverse reaction
SVR12	sustained viral response
T2DM	type 2 diabetes mellitus
TEA	Treatment Eligibility Assessment (form)
TEAE	treatment-emergent adverse event
T_{max}	time to maximum serum concentration
TMDD	target-mediated drug disposition
$t_{½}$	half life
UACS	upper airway cough syndrome
UCC	unexplained chronic cough
UDS	urine drug screen
ULN	upper limit of normal
URTI	upper respiratory tract infection
UTN	Universal Trial Number
Vd	volume of distribution

Abbreviation	Expanded Term
VAS	Visual Analog Scale
VS	vital signs
Vz/F	apparent volume of distribution
WBC	white blood cell
WPAI	Work Productivity and Activity Impairment
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential
ZAP70	zeta-chain-associated protein kinase

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