Official Protocol Title:	A Phase 2a Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Different Dosing Regimens of Efinopegdutide (MK-6024) in Adults With Metabolic Dysfunction-Associated Steatotic Liver Disease
NCT number:	NCT06482112
Document Date:	04-Nov-2024

TITLE PAGE

THIS PROTOCOL AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

Protocol Title: A Phase 2a Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Different Dosing Regimens of Efinopegdutide (MK-6024) in Adults With Metabolic Dysfunction-Associated Steatotic Liver Disease

Study Number: 016-01

Compound Code(s): 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
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	NCT06482112
EU CT	Not Applicable
EudraCT	Not Applicable
jRCT	Not Applicable
WHO/UTN	Not Applicable
IND	153067

Approval Date: 04 November 2024

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
CCI [redacted]	[redacted]	[redacted]
Original Protocol	06-MAR-2024	Not Applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 01

Overall Rationale for the Amendment:

To reflect actual enrollment projections.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1.1, Synopsis	CCI [redacted]	CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Title Page	Added NCT number.	New information.
Section 1.1, Synopsis	CCI [redacted]	CCI [redacted].
Section 1.2, Schema	CCI [redacted]	CCI [redacted].
Section 2, Introduction	Revised paragraph describing treatment options for MASH (NASH).	Resmetirom was recently approved for the treatment of NASH.
Section 2.2.1, Pharmaceutical and Therapeutic Background	Revised paragraph describing treatment options for MASH (NASH).	Refer to rationale for Section 2.
	Added description of resmetirom.	Refer to rationale for Section 2.
CCI [redacted]	CCI [redacted]	CCI [redacted]
	CCI [redacted]	CCI [redacted]
Section 5.2, Exclusion Criteria	Criterion #25: moved resmetirom from the list of 'Other investigational agents' to the list of excluded treatment agents.	Refer to rationale for Section 2.
Section 6.5, Concomitant Therapy	Added resmetirom to the list of prohibited medications.	Refer to rationale for Section 2.

Section Number and Name	Description of Change	Brief Rationale
CCI [redacted]		
Throughout	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

TABLE OF CONTENTS

DOCUMENT HISTORY 3
PROTOCOL AMENDMENT SUMMARY OF CHANGES 3
1 PROTOCOL SUMMARY 13
1.1 Synopsis 13
1.2 Schema 15
CCI [redacted] **..... 17**
2 INTRODUCTION 24
2.1 Study Rationale 26
2.2 Background 27
2.2.1 Pharmaceutical and Therapeutic Background 27
2.2.2 Preclinical and Clinical Studies 28
2.2.2.1 Efinopegdutide Preclinical Overview 28
2.2.2.2 Efinopegdutide Clinical Overview 29
2.2.3 Ongoing Clinical Studies 31
2.3 Benefit/Risk Assessment 32
3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS 34
4 STUDY DESIGN 36
4.1 Overall Design 36
4.1.1 Management of Participants Before Randomization 36
CCI [redacted] 37
4.1.2 Management of Randomized Participants 37
4.2 Scientific Rationale for Study Design 39
4.2.1 Rationale for Endpoints 40
4.2.1.1 Efficacy Endpoints 40
CCI [redacted] 41
CCI [redacted] 41
CCI [redacted] 42
4.2.1.5 Planned Exploratory Biomarker Research 42
4.2.1.5.1 Planned Genetic Analysis 42
4.2.1.6 Future Biomedical Research 43
4.3 Justification for Dose 43
4.3.1 Starting Dose for This Study 43
CCI [redacted] 43
CCI [redacted] 44
4.4 Beginning and End-of-Study Definition 44
4.4.1 Clinical Criteria for Early Study Termination 45
5 STUDY POPULATION 46

5.1 Inclusion Criteria 46
5.2 Exclusion Criteria 48
5.3 Lifestyle Considerations 54
5.3.1 Diet and Activity Counseling 54
5.3.2 Caffeine, Alcohol, and Tobacco Restrictions 54
5.3.3 Activity Restrictions 54
5.4 Screen Failures 54
5.5 Participant Replacement Strategy 55
6 STUDY INTERVENTION 56
6.1 Study Intervention(s) Administered 56
6.1.1 Medical Devices 59
6.2 Preparation/Handling/Storage/Accountability 59
6.2.1 Dose Preparation 59
6.2.2 Handling, Storage, and Accountability 59
6.3 Measures to Minimize Bias: Randomization and Blinding 60
6.3.1 Intervention Assignment 60
6.3.2 Stratification 60
6.3.3 Blinding 60
6.4 Study Intervention Compliance 60
6.5 Concomitant Therapy 61
6.5.1 Rescue Medications and Supportive Care 62
CCI [redacted] **..... 63**
CCI [redacted] 63
CCI [redacted] 64
CCI [redacted] 64
CCI [redacted] 65
CCI [redacted] 65
6.7 Intervention After the End of the Study 66
6.8 Clinical Supplies Disclosure 66
6.9 Standard Policies 66
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL 67
7.1 Discontinuation of Study Intervention 67
7.2 Participant Withdrawal From the Study 69
7.3 Lost to Follow-up 70
8 STUDY ASSESSMENTS AND PROCEDURES 71
8.1 Administrative and General Procedures 71
8.1.1 Informed Consent 71

8.1.1.1 Full Informed Consent 72
8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research 72
8.1.2 Inclusion/Exclusion Criteria 72
8.1.3 Participant Identification Card 72
8.1.4 Medical History 73
8.1.5 Prior and Concomitant Medications Review 73
8.1.5.1 Prior Medications 73
8.1.5.2 Concomitant Medications 73
8.1.6 Assignment of Screening Number 73
8.1.7 Assignment of Randomization Number 73
CCI [redacted] 74
CCI [redacted] 74
CCI [redacted] 75
CCI [redacted] 75
CCI [redacted] 75
CCI [redacted] 76
CCI [redacted] 76
8.1.9.2 Alcohol Consumption Assessment and Counseling 76
8.1.9.3 Hypoglycemia and Hyperglycemia Counseling 76
CCI [redacted] 77
CCI [redacted] 77
8.1.10 Discontinuation and Withdrawal 77
8.1.10.1 Withdrawal From Future Biomedical Research 77
8.1.11 Participant Blinding/Unblinding 78
8.1.12 Calibration of Equipment 78
8.2 Efficacy Assessments 78
8.2.1 Liver Fat Content 78
8.2.2 Body Weight 79
CCI [redacted] 80
CCI [redacted] 80
8.3 Safety Assessments 80
8.3.1 Physical Examinations 80
8.3.1.1 Body Weight 80
8.3.1.2 Height 81
8.3.2 Vital Signs 81
8.3.3 Electrocardiograms 82
8.3.4 Glucose Metabolism 82

8.3.5 Clinical Safety Laboratory Assessments 82
8.3.6 Pregnancy Testing....83
8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events....83
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information 84
8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events....86
8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information...86
8.4.4 Regulatory Reporting Requirements for SAE 86
8.4.5 Pregnancy and Exposure During Breastfeeding 86
CCI [redacted] 87
CCI [redacted] 87
8.4.8 Drug–Device Combination Products/Combination Medicinal Products – Complaints, PQCs, and Malfunctions....88
8.5 Treatment of Overdose....88
CCI [redacted] **....88**
CCI [redacted] 88
CCI [redacted] **....89**
8.8 Pharmacodynamics....89
8.9 Biomarkers 89
8.9.1 Planned Genetic Analysis Sample Collection....89
8.10 Future Biomedical Research Sample Collection....90
8.11 Visit Requirements....90
CCI [redacted] 90
8.11.1.1 Visit Reminders 90
8.11.2 Fasting Before Scheduled Visits....91
CCI [redacted] 91
CCI [redacted] 91
8.11.3.2 Visit 1b/Imaging 92
8.11.3.3 Rescreening Visit....92
8.11.4 Randomization 93
8.11.5 Treatment Period Visits 93
CCI [redacted] 94
8.11.7 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study 94
8.11.8 End-of-Treatment Visit....95
CCI [redacted] 96
9 KEY STATISTICAL CONSIDERATIONS 97

9.1 Responsibility for Analyses/In-house Blinding 97
9.2 Hypotheses/Estimation 97
CCI [redacted] **.....97**
9.3.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints.....97
CCI [redacted] 97
CCI [redacted] 98
CCI [redacted] 98
CCI [redacted] 98
CCI [redacted] **.....98**
CCI [redacted] 98
CCI [redacted] 99
CCI [redacted] **.....99**
CCI [redacted] 99
9.5.2 Statistical Methods for Efficacy Analyses.....100
9.5.3 Statistical Methods for Safety Analyses 100
CCI [redacted] **.....101**
CCI [redacted] **.....101**
CCI [redacted] **.....101**
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 102
10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations 102
10.1.1 Code of Conduct for Interventional Clinical Trials 102
10.1.2 Financial Disclosure.....105
10.1.3 Data Protection.....106
10.1.3.1 Confidentiality of Data 106
10.1.3.2 Confidentiality of Participant Records.....106
10.1.3.3 Confidentiality of IRB/IEC Information.....107
10.1.4 Committees Structure.....107
10.1.4.1 Clinical Adjudication Committee (CAC) 107
10.1.5 Publication Policy 107
10.1.6 Compliance with Study Registration and Results Posting Requirements .108
10.1.7 Compliance with Law, Audit, and Debarment 108
10.1.8 Data Quality Assurance 109
10.1.9 Source Documents 110
10.1.10 Study and Site Closure.....110
10.2 Appendix 2: Clinical Laboratory Tests.....111
10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.....113
10.3.1 Definitions of Medication Error, Misuse, and Abuse.....113

10.3.2 Definition of AE 113
10.3.3 Definition of SAE 114
10.3.4 Additional Events Reported 115
10.3.5 Recording AE and SAE 116
10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor 119
10.4 Appendix 4: Combination Medicinal Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up 121
10.5 Appendix 5: Contraceptive Guidance 122
10.5.1 Definitions 122
10.5.2 Contraceptive Requirements 123
10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research 124
10.7 Appendix 7: Country-specific Requirements 128
10.8 Appendix 8: Other Medical Device: Complaints Including Product Quality Complaint, Malfunction, Serious Injury, Death, Fetal Distress/Fetal Death and Congenital Anomaly: Definitions and Reporting 129
CCI [redacted] **130**
10.10 Appendix 10: Common Terminology Criteria for Adverse Events Version 5.0 132
10.11 Appendix 11: eGFR Equations 133
10.12 Appendix 12: Abbreviations 134
11 REFERENCES 138

LIST OF TABLES

CCI [redacted] 53
Table 2 Study Interventions 57
Table 3 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events 85
CCI [redacted] 100
CCI [redacted] 112

LIST OF FIGURES

CCI [redacted] 16

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 2a Randomized, Open-Label Study to Evaluate the Efficacy and Safety of Different Dosing Regimens of Efinopegdutide (MK-6024) in Adults With Metabolic Dysfunction-Associated Steatotic Liver Disease

Short Title: Phase 2a Alternate Dosing Study of MK-6024 in Adults with Metabolic Dysfunction-Associated Steatotic Liver Disease

Acronym: Not applicable

Hypotheses, Objectives, and Endpoints:

In adults aged 18 to 80 years (inclusive) with MASLD:

Primary Objectives	**Primary Endpoints**
• To evaluate the effect of efinopegdutide administration once every 2 weeks versus once weekly on mean relative reduction from baseline in LFC after 28 weeks.	• LFC
• To evaluate the safety and tolerability of different efinopegdutide regimens.	• AEs • Discontinuation of study intervention due to AEs
Secondary Objective	**Secondary Endpoint**
• To evaluate the effect of efinopegdutide administration once every 2 weeks versus once weekly on mean percent change from baseline in body weight after 28 weeks.	• Body weight

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Non-alcoholic steatohepatitis
Population	Individuals of any sex/gender aged 18 to 80 years (inclusive) with MASLD
Study Type	Interventional

Intervention Model	Parallel This is a multisite study.
Type of Control	Different Dose or Regimen
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 11 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 CCI participants will be randomized.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use
Group 1	Efinopegdutide	2 mg	2 mg	Subcutaneous	Q1W for 4 weeks	Test Product
Group 1	Efinopegdutide	4 mg	4 mg	Subcutaneous	Q1W for 4 weeks	Test Product
Group 1	Efinopegdutide	7 mg	7 mg	Subcutaneous	Q1W for 4 weeks	Test Product
Group 1	Efinopegdutide	10 mg	10 mg	Subcutaneous	Q1W for 16 weeks	Test Product
Group 2	Efinopegdutide	2 mg	2 mg	Subcutaneous	Q2W for 4 weeks	Test Product
Group 2	Efinopegdutide	4 mg	4 mg	Subcutaneous	Q2W for 4 weeks	Test Product
Group 2	Efinopegdutide	7 mg	7 mg	Subcutaneous	Q2W for 4 weeks	Test Product
Group 2	Efinopegdutide	10 mg	10 mg	Subcutaneous	Q2W for 16 weeks	Test Product
Group 3	Efinopegdutide	2 mg	2 mg	Subcutaneous	Q2W for 4 weeks	Test Product
Group 3	Efinopegdutide	4 mg	4 mg	Subcutaneous	Q2W for 4 weeks	Test Product
Group 3	Efinopegdutide	7 mg	7 mg	Subcutaneous	Q2W for 4 weeks	Test Product
Group 3	Efinopegdutide	10 mg	10 mg	Subcutaneous	Q2W for 4 weeks	Test Product
Group 3	Efinopegdutide	15 mg	15 mg	Subcutaneous	Q2W for 12 weeks	Test Product

Q1W=once weekly; Q2W=once every 2 weeks.

Other current or former names or aliases for the study intervention are as follows: HM12525A, JNJ-64565111, and MK-6024.

Total Number of Intervention Groups/Arms	3
Duration of Participation	Each participant will take part in the study for approximately 37 weeks from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening period of up to 5 weeks, each participant will receive assigned study intervention for approximately 28 weeks. After the end of the treatment period, each participant will be followed for 4 weeks (approximately 5 weeks after the last dose of study intervention) for adverse event monitoring.

Study Governance Committees:

Executive Oversight Committee	No
External Data Monitoring Committee	No
Clinical Adjudication Committee	Yes
Standing Internal Data Monitoring Committee	No

Study governance considerations are outlined in Appendix 1.

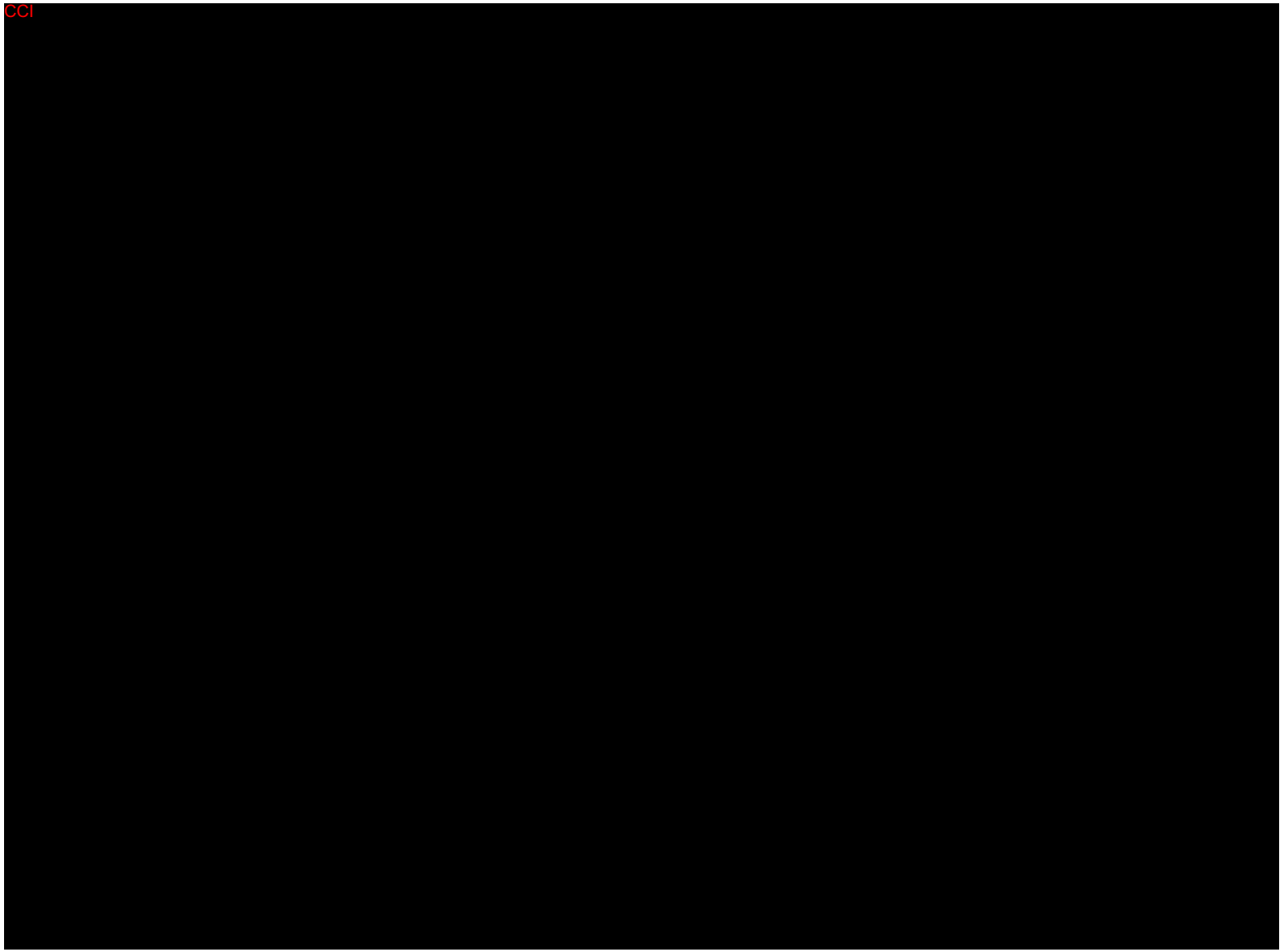
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 12.

1.2 Schema

The study design is depicted in Figure 1.

CCI



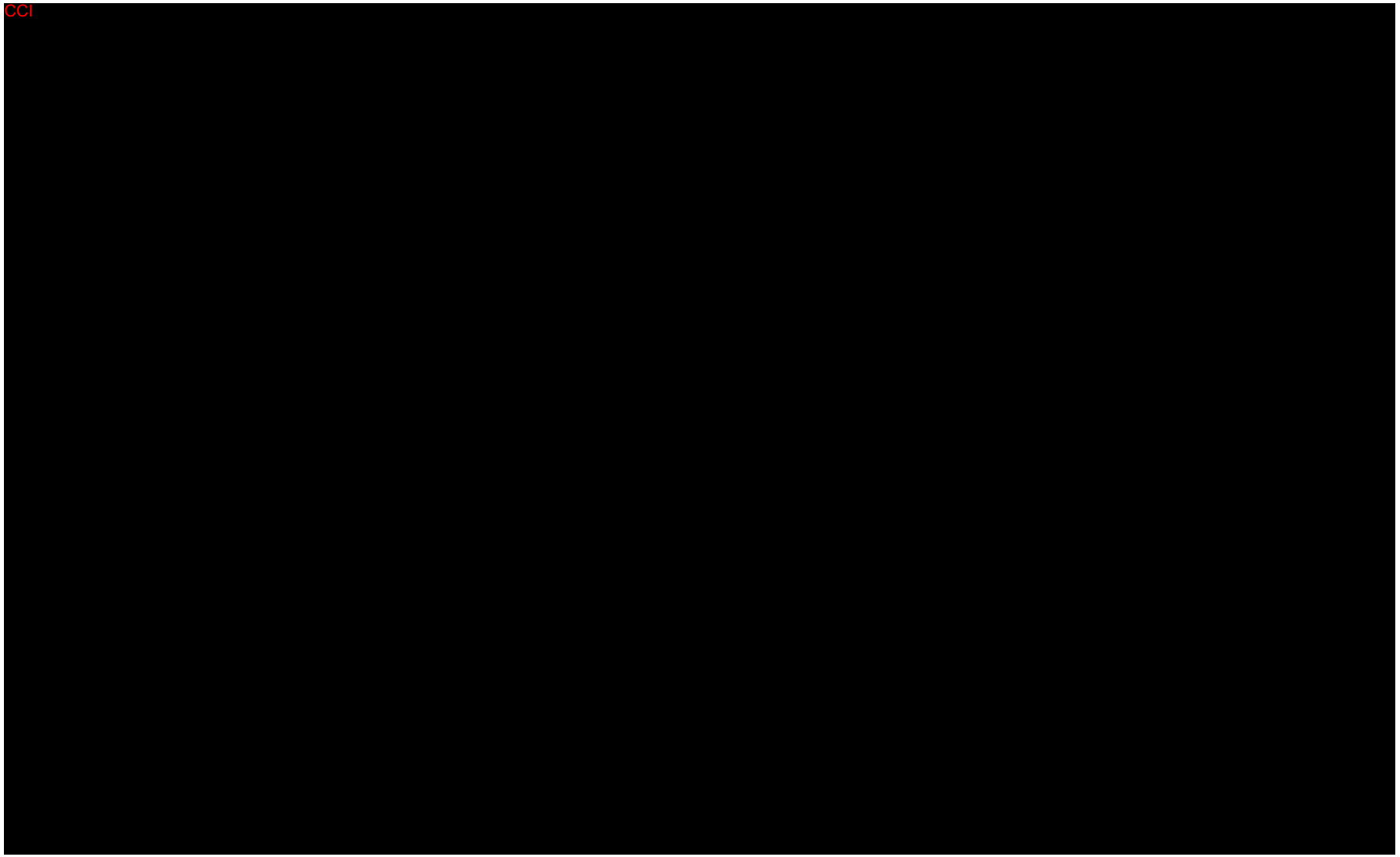
CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

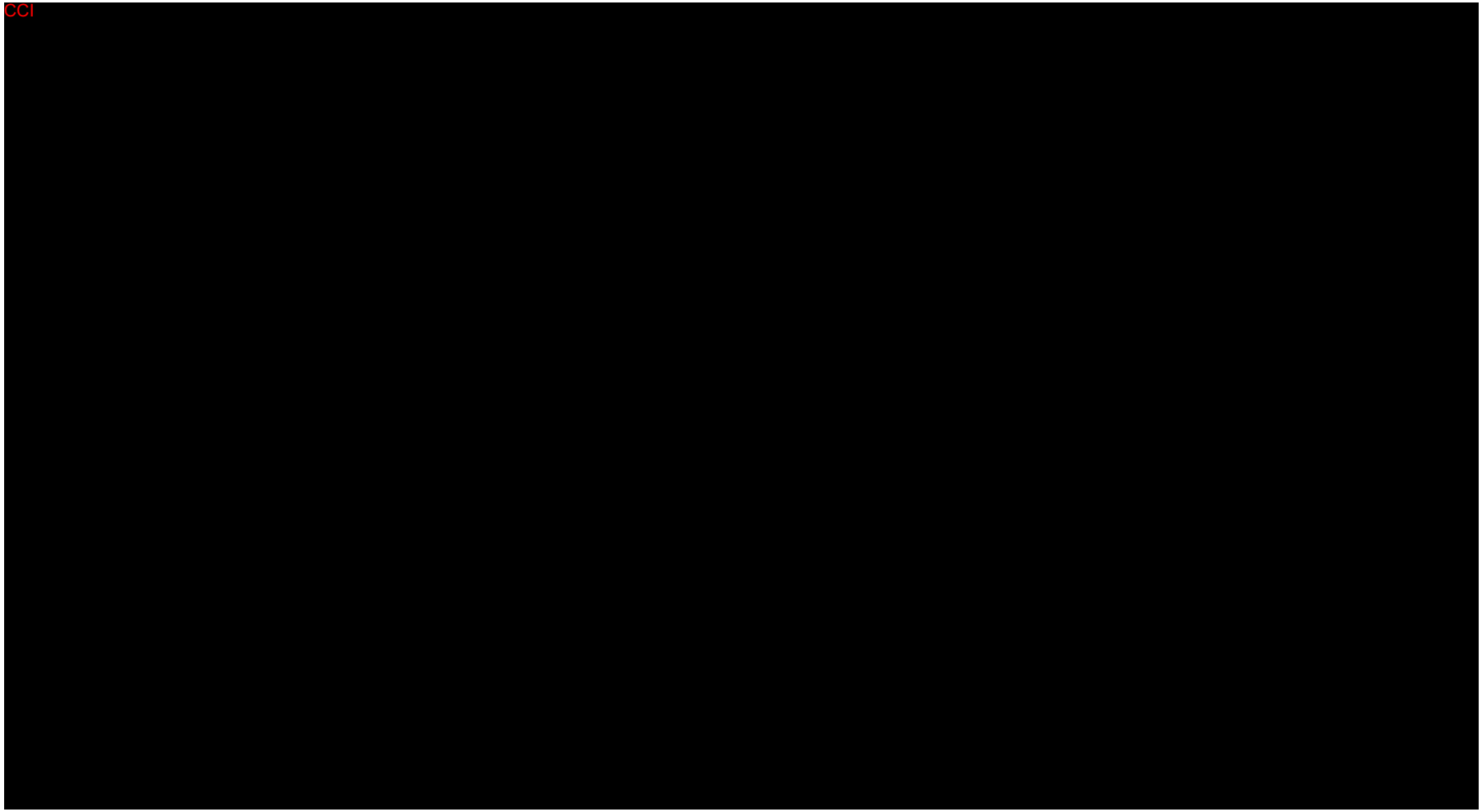



CCI

CCI

[redacted]

CCI



CCI

2 INTRODUCTION

The nomenclature for steatotic liver disease (SLD) has recently been updated [Rinella, M. E., et al 2023]. As such, the term NAFLD was replaced by MASLD, which encompasses hepatic steatosis accompanied by at least 1 of 5 cardiometabolic risk factors; the term NASH was replaced by MASH. The terms MASLD and NAFLD, as well as MASH and NASH, are used interchangeably in this document.

MASLD is a condition characterized by increased accumulation of fat in hepatocytes (steatosis) that is typically a consequence of obesity-associated insulin resistance and is strongly associated with metabolic syndrome [Younossi, Z. M., et al 2019].

MASH, the more serious form of MASLD, is a complex condition characterized by steatosis associated with inflammation and varying degrees of fibrosis. Only a subgroup of patients with steatosis will progress to MASH; however, currently there are no clear criteria to identify these patients [Cusi, K., et al 2022] [Food and Drug Administration 2018]. Progression to MASH can be viewed as the consequence of liver damage, due to the accumulation of FFAs that act as harmful agents in hepatocytes, leading to dysfunction and cell death [Friedman, S. L., et al 2018] [Mendez-Sanchez, N., et al 2018]. In addition to environmental factors leading to obesity, insulin resistance, and metabolic syndrome, genetics may play an important role [Friedman, S. L., et al 2018]. Genetic risk factors leading to MASLD, and progression to MASH, continue to be explored.

The treatment of SLD continues to evolve, as more details of the pathogenesis of the disease emerge. Presently, there are limited treatment options for MASH (NASH). Current treatment options involve targeting upstream pathological processes, such as weight gain and obesity, as well as directly targeting processes in the liver, such as abnormal lipid metabolism (eg, thyroid hormone receptor-beta agonism) and fibrosis.

GLP-1 receptor agonism is associated with reductions in serum glucose and weight loss. GLP-1 receptor agonists enhance glucose-stimulated insulin secretion and have become useful treatments for T2DM. There are several GLP-1 agonists approved for the treatment of T2DM and approved or in development for treatment of obesity. At the doses that have been developed for diabetes indications (eg, liraglutide 1.8 mg daily, semaglutide 1.0 mg weekly), GLP-1 receptor agonists are associated with weight loss of approximately 3% to 5%, generally attributed to reductions in food intake. More recently, higher dose administration of GLP-1 receptor agonists has been pursued for weight loss indications. At the approved doses for weight management, liraglutide 3.0 mg daily administration over 56 weeks resulted in weight loss of approximately 7.4% [U.S. Prescribing Information 2022], while semaglutide 2.4 mg once-weekly administration over 68 weeks resulted in approximately 15% weight loss [U.S. Prescribing Information 2023].

The weight loss associated with GLP-1 agonists is also associated with decreased inflammation within the liver of patients with MASH. The Liraglutide Efficacy and Action in NASH (LEAN) Phase 2 study showed that, of the participants who received liraglutide 1.8 mg daily and underwent an end-of-treatment liver biopsy after 48 weeks, 39% (9 of 23) had resolution of definite NASH, compared with 9% (2 of 22) in the placebo group

[Armstrong, M. J., et al 2016]. A Phase 2b study with once-daily semaglutide 0.1 mg, 0.2 mg, or 0.4 mg SC (0.7 mg to 2.8 mg weekly) showed histologic resolution of NASH without worsening of fibrosis in 40% to 59% of participants, relative to placebo (17%), after 72 weeks of treatment [Newsome, P. N., et al 2020]. Semaglutide is currently being evaluated for NASH treatment in a Phase 3 study.

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

Efinopegdutide (MK-6024) is a synthetic, modified oxyntomodulin peptide. It is the site-specific form of HMGLP/GCG25 (a GLP-1/glucagon dual agonist peptide) that is linked via a polyethylene glycol linker to a human IgG fragment, with agonist activity at both the GLP-1 and the glucagon receptors. Oxyntomodulin is a 37-amino acid peptide product of the proglucagon gene, released from the L-cells of the small intestine in response to food ingestion [Wynne, K., et al 2006]. Oxyntomodulin activates both the GLP-1 and glucagon receptors. Oxyntomodulin, administered 3 times daily before a meal, decreased appetite and reduced body weight by 2.3 kg during a 4-week period in healthy overweight and obese participants [Wynne, K., et al 2005]. In addition to the beneficial effects of weight loss on MASH, glucagon agonism may provide additional reduction in hepatic fat by stimulating fatty acid oxidation and reducing lipogenesis in the liver, relative to GLP-1 agonism alone [Boland, M. L., et al 2020].

Efinopegdutide was originally developed by Hanmi Pharmaceuticals. Phase 1 and 2 studies supported administration of a once-weekly SC injection. A 26-week, Phase 2b study in obese participants and a 12-week, Phase 2b study in obese participants with T2DM evaluated the weight loss and glycemic efficacy, and safety/tolerability of efinopegdutide at doses up to 10 mg once weekly. Dose-dependent reductions in body weight were observed with once-weekly administration of efinopegdutide in these Phase 2b studies in obese participants with and without T2DM (Section 2.2.2.2). The weight loss was greater or similar to that observed with liraglutide 3 mg daily, which is the dose approved for treatment of obesity [U.S. Prescribing Information 2022]. The absence of glucose lowering in the face of weight loss in these studies is attributable to glucagon receptor target engagement, but without deleterious effects on glycemia in nondiabetic or in T2DM participants. The increase in serum ketones (beta-hydroxybutyrate) and reduction in bicarbonate observed in these Phase 2b studies are consistent with glucagon-mediated enhancement of fatty acid oxidation in the liver. Events of ketoacidosis have not been observed in the efinopegdutide clinical studies to date.

Glucagon receptor agonism may provide greater reductions in hepatic fat and potentially on hepatic fibrosis than the reductions mediated by weight loss observed with GLP-1 receptor agonism alone.

In 2 mouse models of NASH, the GLP-1R/GCGR co-agonist cotadutide reduced fibrosis to a greater extent than the GLP-1 receptor agonist liraglutide, with similar degrees of weight loss [Boland, M. L., et al 2020]. In a mouse model of MCD diet-induced NASH, efinopegdutide completely prevented NASH development by eliminating steatosis as the primary effect and reduced the inflammatory cell infiltration and hepatic ballooning. In another study in the same mouse model, efinopegdutide was more effective in resolving NASH by improving liver function parameters and inhibiting oxidative stress compared with obeticholic acid or liraglutide (refer to the IB for details). In a 54-week, Phase 2 study with cotadutide, reductions in Pro-C3 levels, a marker of hepatic fibrogenic activity, were greater compared with liraglutide, albeit in conjunction with greater weight loss (5.02% versus 3.33%) [Dela Cruz, J. 2020].

As neither the GLP-1 receptor nor the glucagon receptor is expressed in human Kupffer or stellate cells, these findings suggest that antifibrotic effects may be mediated by upstream reductions in steatosis and inflammation.

2.1 Study Rationale

The purpose of this study is to evaluate the effects of different efinopegdutide regimens (Q1W 10 mg target dose, Q2W 10 mg target dose, and Q2W 15 mg target dose) on hepatic fat and body weight reduction and to assess the safety and tolerability of these efinopegdutide regimens in adults with MASLD. The conduct of this study is supported by preclinical data and by evidence from clinical studies in which efinopegdutide showed an acceptable safety and tolerability profile. In Phase 2b studies conducted by Janssen, efinopegdutide administration resulted in dose-dependent weight loss from baseline compared to placebo in obese participants, with and without T2DM. Furthermore, in Study MK-6024-001, 10 mg Q1W efinopegdutide significantly decreased LFC (%) from baseline, compared with semaglutide (1 mg Q1W), in participants with elevated liver fat (Section 2.2.2.2).

CCI

In this study, the efficacy and safety of the efinopegdutide dosing regimens will be compared when all participants have completed or prematurely discontinued the target stable-dose treatment period.

2.2 Background

Refer to the IB for detailed background information on efinopegdutide.

2.2.1 Pharmaceutical and Therapeutic Background

MASLD is a condition associated with an increased accumulation of TG in the liver that affects approximately 30% of the global adult population [Younossi, Z. M., et al 2023]. MASLD 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 liver and increased de novo hepatic lipogenesis [Fabbrini, E., et al 2010].

MASLD encompasses a spectrum of associated steatosis, ranging from simple steatosis to MASH that is accompanied by chronic inflammation within the liver, described histologically as steatohepatitis with or without fibrosis [Kechagias. S., et al 2020]. An increasing proportion of MASLD cases are expected to progress to MASH, rising from 20% to 27% between the years 2015 and 2030 [Friedman, S. L., et al 2018].

Patients with MASLD are usually asymptomatic. A diagnosis of MASLD is typically considered based on risk factors (obesity, dyslipidemia, T2DM, and metabolic syndrome), abnormal liver tests without alternate explanation, or when abdominal imaging incidentally detects hepatic fat. In patients with confirmed steatosis, the risk for MASH and advanced fibrosis can be further assessed through laboratory panels and imaging-based assessments of liver stiffness. These assessments cannot definitively diagnose MASH or fibrosis stage but are useful in evaluating the risk of advanced fibrosis.

Presently, there are limited treatment options for MASH (NASH). Lifestyle modifications directed at weight loss and exercise remain the most recommended treatment for MASLD and MASH; however, even in well-organized settings, only a minority of patients achieve and sustain weight loss. According to evidence-based practice guidelines for the treatment of patients with biopsy-proven MASH, 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 MASH, have been studied long-term to assess their impact on liver-related outcomes, or have fully characterized safety profiles in this patient population. Resmetirom, a thyroid hormone receptor-beta agonist, was recently approved in

the US for the treatment of noncirrhotic NASH with moderate-to-advanced liver fibrosis (consistent with stages F2 to F3 fibrosis) [U.S. Prescribing Information 2024], however, its long-term efficacy on liver-related outcomes has not been established. Given the growing global prevalence of MASH, the absence of well-characterized, safe, and highly effective MASH (NASH) treatments is a significant unmet medical need recognized by both medical societies and regulatory agencies [Friedman, S. L., et al 2018] [Chalasani, N., et al 2018].

2.2.2 Preclinical and Clinical Studies

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

2.2.2.1 Efinopegdutide Preclinical Overview

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

CCI [redacted]

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, in body weight gain, and in food consumption compared with controls. CCI [redacted]

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

2.2.2.2 Efinopegdutide Clinical Overview

In the completed clinical studies, at least 1 dose of efinopegdutide has been administered to a total of 870 participants across 8 Phase 1 studies, 1 Phase 2a study, and 2 Phase 2b studies. Refer to the IB for details. Key efficacy and safety data are summarized below.

In the completed Phase 1 studies, efinopegdutide in single doses between 0.25 nmol/kg and 4.0 nmol/kg (equivalent to 1.2 mg to 20 mg fixed dose, assuming a body weight of 90 kg) and in multiple doses between 0.5 nmol/kg and 3.0 nmol/kg (equivalent to 2.5 mg to 15 mg fixed doses, assuming a body weight of 90 kg) once weekly for 4 weeks was administered to healthy participants or participants with T2DM. CCI

[redacted]

Two randomized, double-blind, placebo-controlled Phase 2b studies (conducted by Janssen) evaluated weekly doses of efinopegdutide (5.0 mg, 7.4 mg, and 10 mg, ***not titrated***) in obese participants with and without T2DM: Study 64565111OBE2002 and Study 64565111OBE2001, respectively. Study 64565111OBE2001 also included an open-label active comparator, liraglutide, titrated to the target dose of 3.0 mg daily in 0.6 mg weekly increments. All doses of efinopegdutide significantly (p<0.001) reduced body weight from baseline when compared with placebo at Week 12 (Study 64565111OBE2002) and at Week 26 (Study 64565111OBE2001). In both studies, small changes from baseline in A1C and FPG were observed that were not clinically meaningful; fasting plasma insulin levels increased from baseline in the efinopegdutide dose groups compared with the placebo group.

In these Phase 2b studies, the overall incidence of TEAEs was higher in each efinopegdutide dose group compared with the placebo or liraglutide groups, with no apparent dose-relationship between the efinopegdutide 7.4 mg and 10.0 mg dose groups. Consistent with the safety profile of other GLP-1 receptor agonists, the most common TEAEs after treatment with efinopegdutide in both studies were nausea and vomiting, which were often observed within the first week of treatment. Nausea was the most frequent TEAE leading to discontinuation of study intervention; nearly all the AEs of nausea leading to discontinuation were deemed at least possibly related to the study drug by the investigator. In both studies, the incidence of SAEs was low and similar across all treatment groups. The incidences of AEs of clinical interest (ie, pancreatitis, injections site reactions, major adverse CV events, hypotension-related events, calcitonin elevation) were low and similar across all treatment groups. No thyroid neoplasms were reported.

In both studies, treatment with efinopegdutide was associated with non-dose-dependent reductions in SBP and DBP, along with elevations in pulse rate; however, the rate pressure product at the end of treatment was not meaningfully increased in the efinopegdutide groups

compared with baseline. The results of 24-hour assessments of vital signs, measured in a substudy of Study 64565111OBE2001, were consistent with the Week 26 results.

A Phase 2a randomized, active comparator-controlled (semaglutide; Ozempic®), open-label study, MK-6024-001, was conducted in adult participants with elevated liver fat (≥10%, as assessed by MRI-PDFF). One hundred forty-five participants were randomized in a 1:1 ratio to treatment with efinopegdutide 10.0 mg SC Q1W or semaglutide 1.0 mg SC Q1W, for a duration of 24 weeks. In both treatment groups, study intervention was titrated in 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.

The mean relative reduction from baseline in LFC (%) after 24 weeks of treatment was significantly greater in the efinopegdutide group compared with the semaglutide group, with a difference in LS means of 30.4% (90% CI: 22.1, 38.7; $p<0.001$). The mean absolute reduction from baseline in LFC (%) was also greater in the efinopegdutide group compared with the semaglutide group, with a 6.1% treatment difference in LS means (90% CI: 4.6, 7.7; $p<0.001$). The mean percent change from baseline in body weight after 24 weeks of treatment was similar in the efinopegdutide and semaglutide groups (LS mean change from baseline of -8.5 and -7.1, respectively), with a treatment difference in LS means of -1.4% (90% CI: -2.7, -0.1; $p=0.085$). Compared with semaglutide, treatment with efinopegdutide led to greater mean percent reductions from baseline in total cholesterol, non-HDL-C, LDL-C, HDL-C, triglycerides, and apoB.

Efinopegdutide showed an acceptable tolerability profile; the most frequently reported AEs were GI AEs, most often nausea, consistent with the safety profile of other GLP-1 receptor agonists [U.S. Prescribing Information 2023] [U.S. Prescribing Information 2022] [U.S. Prescribing Information 2022a]. The overall incidences of nausea and vomiting (approximately 28% and 17%, respectively) were lower than those observed in the previous

Phase 2b studies for the 10-mg dose, in which efinopegdutide was not titrated – approximately 67% and 55%, respectively, in Study 64565111OBE2001 and approximately 43% and 35%, respectively, in Study 64565111OBE2002 – presumably related to use of dose titration in the study. Two SAEs were reported (1 in each treatment group), none of which were deemed related to study intervention by the investigator (1 urinary calculus and 1 spinal osteoarthritis). Four participants in the efinopegdutide group discontinued study intervention due to AEs (3 due to GI AEs: nausea, vomiting, upper abdominal pain, and 1 due to hepatitis) compared with none in the semaglutide group; except for 1 AE of vomiting, these AEs were deemed related to study intervention by the investigator. These AEs were low toxicity grade and resolved after discontinuation of study intervention. Small changes from baseline in hemoglobin and hematocrit were noted in the efinopegdutide group at Week 24, consistent with observations in previous studies.

2.2.3 Ongoing Clinical Studies

MK-6024-013 is an ongoing Phase 2b, randomized, double-blind, placebo-controlled, study to evaluate the efficacy and safety of efinopegdutide in adult individuals with precirrhotic NASH. The study includes an open-label semaglutide (Wegovy®) arm to provide context for changes induced by weight loss that occur with efinopegdutide. CCI [redacted] The primary efficacy objective is to evaluate the effect of efinopegdutide versus placebo on the proportion of individuals with NASH resolution without worsening of fibrosis after 52 weeks of treatment.

MK-6024-014 is an ongoing Phase 1, nonrandomized, parallel-group, open-label study to compare the PK of efinopegdutide in participants with moderate and severe hepatic impairment and in healthy control participants reasonably matched to the demographics (age, weight, sex) of the group with hepatic impairment. The participants will receive a single dose of 7 mg efinopegdutide, CCI [redacted]. Safety will be monitored throughout the study by clinical and laboratory evaluations.

MK-6024-015 is an ongoing Phase 1, randomized, placebo-controlled, double-blind study of efinopegdutide in otherwise healthy, obese participants. Part 1 of the study evaluates the safety, tolerability, and PK of single SC efinopegdutide doses up to CCI [redacted]

MK-6024-017 is an ongoing Phase 2a, randomized, placebo-controlled, parallel-group, double-blind Phase 2a study to evaluate the effects of efinopegdutide treatment on noninvasive markers of hepatic steatosis CCI [redacted] fibroinflammatory

activity [redacted] and of fibrosis/fibrogenesis [redacted] and to assess the safety and tolerability of efinopegdutide in adults with compensated cirrhosis secondary to MASH.

2.3 Benefit/Risk Assessment

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

Based on available data from preclinical and clinical studies, efinopegdutide has an acceptable tolerability profile. [redacted]

The majority of TEAEs observed in studies to date have been related to the GI system, with nausea, vomiting, events concerning abdominal discomfort/distension/pain, eructation, and dyspepsia being the most frequently reported. [redacted]

[redacted]

CCI [redacted].

Preclinical observations have shown an increased incidence of thyroid C-cell tumors in rodents administered GLP-1 receptor agonists. While the risk in humans is unknown, the labels for approved GLP-1 receptor agonists contain a warning for possible development of thyroid C-cell tumors, including medullary thyroid carcinoma, in patients treated with the agents. Additionally, AEs of acute pancreatitis were reported in GLP-1 receptor agonist clinical trials [U.S. Prescribing Information 2023] [U.S. Prescribing Information 2022] [U.S. Prescribing Information 2022a]. Therefore, participants with personal or family histories of medullary thyroid carcinoma or MEN syndrome type 2, as well as with personal history of pancreatitis, will be excluded from participating in the study.

Given the current absence of available treatment options for patients with MASH, the serious potential health risks of progressive fibrosis and cirrhosis, and the available preclinical and clinical data that suggest efinopegdutide may be an effective treatment for MASH, the benefit-risk assessment for conducting this study is considered to be favorable.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

In adults aged 18 to 80 years (inclusive) with MASLD:

Primary Objectives	**Primary Endpoints**
• To evaluate the effect of efinopegdutide administration once every 2 weeks versus once weekly on mean relative reduction from baseline in LFC after 28 weeks.	• LFC
• To evaluate the safety and tolerability of different efinopegdutide regimens.	• AEs • Discontinuation of study intervention due to AEs
Secondary Objective	**Secondary Endpoint**
• To evaluate the effect of efinopegdutide administration once every 2 weeks versus once weekly on mean percent change from baseline in body weight after 28 weeks.	• Body weight

CCI

[redacted]


CCI

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, parallel-group, multisite, open-label Phase 2a study of 3 dosing regimens of efinopegdutide in participants with MASLD. This study will be conducted in conformance with GCP principles.

In this study, the efficacy and safety of the different dosing regimens of efinopegdutide will be assessed when all participants have either completed the treatment period or discontinued prematurely.

Participants in this Phase 2a study will be adults with MASLD. The MASLD diagnosis must be confirmed based on a LFC ≥10%, measured by MRI-PDFF (reviewed by BICR), at screening. Participants will not be eligible for the study if they have history or evidence of cirrhosis or chronic liver disease other than MASLD or MASH at screening.

4.1.1 Management of Participants Before Randomization

CCI

- If a participant has LFC ≥10%, as determined by BICR of the MRI-PDFF data, and all other eligibility criteria are satisfied, the participant will proceed to Visit 3/Randomization.
- If a participant does not satisfy the study eligibility criteria for LFC, the participant will be screen failed and will not proceed to Visit 3/Randomization.

CCI

4.1.2 Management of Randomized Participants

CCI

Participants or their caregivers will be instructed to inject 1 dose of study intervention SC to the abdomen, thigh, or upper arm (Section 8.1.8) either Q1W or Q2W. CCI

CCI [redacted]

CCI [redacted]

The participants should continue to receive their background standard of care per local clinical practice guidelines, unless specifically prohibited by the study protocol. If, based on assessment of a participant's clinical condition, the investigator or medically qualified designee or the non-study treating physician considers that additional assessments are indicated, these assessments may be performed at times other than the protocol-specified time points. Data resulting from these assessments should be made available to the investigator and recorded in the appropriate CRFs.

Throughout the study, changes in symptoms and biomarkers will be used to evaluate response to treatment. The safety and tolerability of the study intervention will be monitored by clinical assessment of AEs. AEs will be graded in severity according to the guidelines outlined in the current NCI CTCAE version (see Appendix 3, Appendix 10). CCI [redacted]

CCI

[redacted]

4.2 Scientific Rationale for Study Design

CCI

[redacted]

CCI [redacted]

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

Studies have shown that MASLD/MASH is more prevalent in certain racial and ethnic groups (eg, in Asians and Hispanics). In the US, the prevalence of MASLD varies among ethnic/racial groups, with the Hispanic population being affected disproportionately. The severity of MASLD may also be greater in this population. The increased prevalence and severity of MASLD in the Hispanic population is likely related to the interplay between issues such as genetic factors, access to health care, or the prevalence of chronic diseases such as metabolic syndrome or diabetes [Rich, N. E., et al 2018]. Few studies have evaluated racial/ethnic differences in MASLD/MASH prognosis, with inconsistent results, demonstrating the need for further research in this area [Rich, N. E., et al 2018] [Jaycox, S. H. 2016]. Moreover, when studying any new drug, especially early in the drug development process, it is important to collect race and ethnicity data along with other demographic data to ensure there is not a differential effect on safety or efficacy based on these parameters. Therefore, race and ethnicity data will be collected in this study.

CCI [redacted]

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

Liver Fat Content

LFC is central to the diagnosis of SLD/MASLD; resolution of steatosis may also correlate with histologic improvement in MASH. MRI-PDFF is an established, standardized, highly accurate, reproducible, noninvasive method of quantitative assessment of LFC that strongly correlates with histologic steatosis [Stine, J. G., et al 2021]. MRI-PDFF has been used to determine treatment efficacy in Phase 2 clinical development programs for NASH [Madrigal Pharmaceuticals, Inc. 2017] [Bautz, D. 2018] [Harrison, S. A., et al 2018] and in Study MK-6024-001 (Section 2.2.2.2). CCI [redacted]

Body Weight

Treatment with efinopegdutide, a dual GLP-1/glucagon agonist, results in body weight reduction. CCI [redacted]

Therefore, the mean percent change from baseline in body weight at Week 28 is a secondary endpoint for the study.

CCI [redacted]

4.2.1.5 Planned Exploratory Biomarker Research

The mechanism of action of many new therapeutics is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating participants. Thus, to aid future participants, it is important to investigate the determinants of response or resistance to the treatments administered. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapies. To identify novel biomarkers, biospecimens (eg, blood components, tissue material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include, but are not limited to, germline genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing) and biospecimen RNA analyses.

Germline Genetic Analyses

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. Genome and exome wide approaches may be used for this effort. In addition, epigenetic characterization techniques (ie, DNA methylation status, histone profiling) may also be explored. If genetic and/or epigenetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population.

Biospecimen RNA Analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in biospecimens may be performed to define gene signatures that correlate to clinical response to treatment with therapies. Specific gene sets (eg, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

4.2.1.5.1 Planned Genetic Analysis

Genetic variation may impact a participant's response to therapy, susceptibility to, severity, and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug ADME, mechanism of action of the drug, disease etiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to the study intervention(s), the disease under study, or related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases, and study intervention(s). Genetic research may consist of the analysis of 1 or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome. Analysis may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.1.6 Future Biomedical Research

The Sponsor will conduct FBR on DNA specimens for which consent was provided during this clinical study.

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

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

The initial efinopegdutide dose will be 2 mg for all study arms and will be escalated up to the highest target dose of either 10 mg (Q1W or Q2W) or 15 mg Q2W. CCI [redacted]

CCI [redacted]

CCI

[redacted]

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.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped as described in Appendix 1.10.

In the event of early termination, study procedures and/or planned analyses may be modified as necessary.

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

1. Has LFC ≥10%, as assessed by MRI-PDFF at Visit 1b/Imaging, reviewed by BICR.
2. Has BMI ≥25 kg/m^2 (≥23 kg/m^2 for Asian participants) at Visit 1a/Screening.

   AND

   Has stable weight (based on self-reporting), defined as ≤5% gain or loss of body weight for at least 3 months before Visit 1a/Screening.
3. Meets 1 of the following criteria:

- Has no history of T2DM

  OR

- Has a history of T2DM with an A1C ≤9% at Visit 1a/Screening **AND** the T2DM is controlled by diet or stable doses of oral AHAs (either as monotherapy or in combination) for at least 8 weeks before Visit 1a/Screening and through Randomization.

Demographics

4. Is an individual of any sex/gender, from 18 years to 80 years of age (inclusive), at the time of providing the informed consent.

Assigned Male Sex at Birth

Note: There are no contraception requirements for participants assigned male sex at birth.

Assigned Female Sex at Birth

5. A participant assigned female sex at birth is eligible to participate if not pregnant or breastfeeding, CCI

CCI

Informed Consent

6. The participant (or legally acceptable representative) has provided documented informed consent for the study. The participant (or legally acceptable representative) may also provide consent 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

1. Has a history or evidence of chronic liver disease other than MASLD or MASH, including but not limited to:

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

3. Has a history of pancreatitis.

4. Has a history of T1DM, diabetic ketoacidosis, or diabetes secondary to pancreatectomy.

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

6. Has a history of a bariatric surgical procedure ≤5 years before Visit 1a/Screening or a known clinically significant gastric emptying abnormality (eg, severe gastroparesis or gastric outlet obstruction).

CCI

14. Has significant systemic or major illnesses, including recent (≤6 months before Visit 1a/Screening) onset of events of congestive heart failure (NYHA functional class III to IV of the American Heart Association), unstable angina, myocardial infarction, arterial revascularization, stroke, or transient ischemic attack.

CCI

CCI

[redacted]

CCI

[redacted]

CCI

CCI

34. Is unable to have MRI-PDFF performed at Visit 1b/Imaging due to:

- Claustrophobia to a degree that prevents tolerance of an MRI-PDFF scanning procedure.
- **Note**: Sedation is permitted, at the discretion of the investigator.
- Metallic implants that prevent MRI-PDFF examination including, but not limited to, aneurysm clips, vascular grafts or cardiac implants, neural stimulators, cochlear implants, metallic contraceptive devices, metallic foreign bodies, metallic tattoos, body piercings that cannot be removed, or any other contraindication to MRI-PDFF examination.
- Exceeds the body habitus and/or weight limitations for the MRI scanner.

CCI

[redacted]

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Participants' alcohol consumption will be assessed as described in the SoA (Section 1.3). The participants will be counseled, as needed, to limit alcohol use to ≤1 standard drink per day or ≤7 standard drinks per week for females and ≤2 standard drinks per day or ≤14 standard drinks per week for males, on average. One standard drink is defined as any beverage containing 14 g of pure alcohol or as defined by local guidelines.

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

5.3.3 Activity Restrictions

Participants should not engage in strenuous exercise (eg, weightlifting, running, bicycling) for 48 hours before each blood collection for clinical laboratory tests for the duration of the study.

5.4 Screen Failures

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

Participants who fail screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

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

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Group 1	Active Comparator	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	2 mg	2 mg	Subcutaneous	Q1W for 4 weeks	Test Product	IMP	Central
Group 1	Active Comparator	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	4 mg	4 mg	Subcutaneous	Q1W for 4 weeks	Test Product	IMP	Central
Group 1	Active Comparator	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	7 mg	7 mg	Subcutaneous	Q1W for 4 weeks	Test Product	IMP	Central
Group 1	Active Comparator	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	10 mg	10 mg	Subcutaneous	Q1W for 16 weeks	Test Product	IMP	Central
Group 2	Experimental	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	2 mg	2 mg	Subcutaneous	Q2W for 4 weeks	Test Product	IMP	Central
Group 2	Experimental	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	4 mg	4 mg	Subcutaneous	Q2W for 4 weeks	Test Product	IMP	Central
Group 2	Experimental	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	7 mg	7 mg	Subcutaneous	Q2W for 4 weeks	Test Product	IMP	Central
Group 2	Experimental	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	10 mg	10 mg	Subcutaneous	Q2W for 16 weeks	Test Product	IMP	Central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period	Use	IMP or NIMP/ AxMP	Sourcing
Group 3	Experimental	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	2 mg	2 mg	Subcutaneous	Q2W for 4 weeks	Test Product	IMP	Central
Group 3	Experimental	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	4 mg	4 mg	Subcutaneous	Q2W for 4 weeks	Test Product	IMP	Central
Group 3	Experimental	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	7 mg	7 mg	Subcutaneous	Q2W for 4 weeks	Test Product	IMP	Central
Group 3	Experimental	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	10 mg	10 mg	Subcutaneous	Q2W for 4 weeks	Test Product	IMP	Central
Group 3	Experimental	Efinopegdutide	Combination Product	Solution for injection, pre-filled syringe	15 mg	15 mg	Subcutaneous	Q2W for 12 weeks	Test Product	IMP	Central

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q1W=once weekly; Q2W=once every 2 weeks.

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 2 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).

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

6.1.1 Medical Devices

Not applicable.

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

Intervention randomization will occur centrally using an IRT system. There are 3 study intervention arms. Participants will be assigned randomly to open-label efinopegdutide Q1W regimen (target dose of 10 mg) or to 1 of 2 efinopegdutide Q2W regimens (target dose of 10 mg or 15 mg, respectively), in a 1:1:1 ratio.

6.3.2 Stratification

Intervention randomization will be stratified according to concurrent diagnosis of T2DM at the time of randomization (Yes or No) as, in participants with T2DM, treatment may have a different efficacy profile than in participants without T2DM.

6.3.3 Blinding

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

CCI

CCI

[redacted]

6.5 Concomitant Therapy

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

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

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

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

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

CCI

[redacted]

CCI

[redacted]

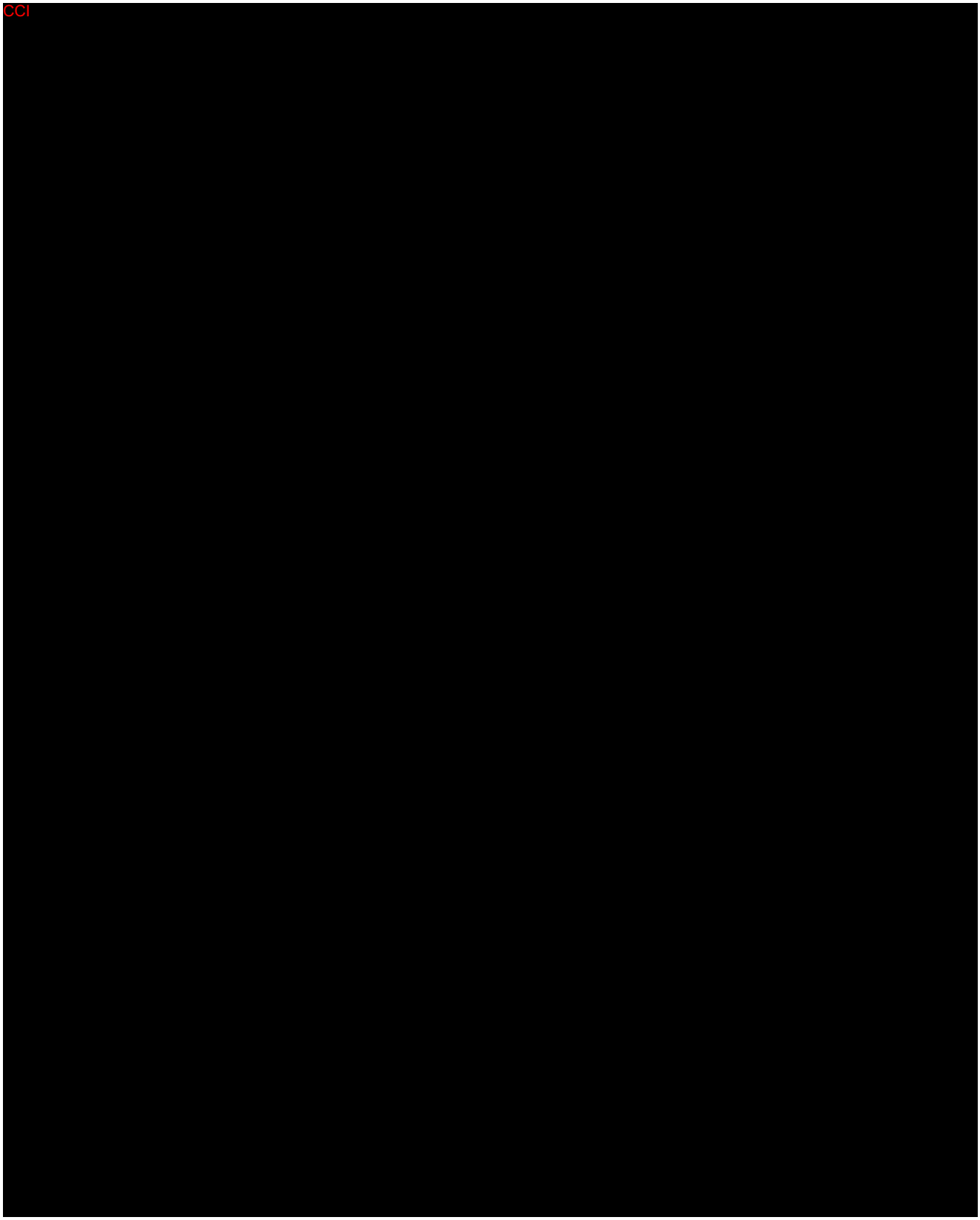
CCI

[redacted]

CCI

CCI

CCI



CCI

[redacted]

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.

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

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.7 unless the participant has withdrawn from the study (Section 7.2).

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

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

1. The participant or participant's legally acceptable representative requests to discontinue study intervention.
2. The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
3. The participant is unable to tolerate the lowest study intervention dose (2 mg) (Section 6.6.2).
4. The participant has a positive serum pregnancy test.

Clinical Events

5. The participant has a CTCAE Grade 3 (Appendix 10) clinical AE that is considered drug-related by the investigator.
6. The participant has any CTCAE Grade 4 (Appendix 10) clinical AE, unless the investigator and Sponsor concur that the AE is ***clearly not*** causally related to study intervention and that continuation/resumption of study intervention does not place the participant at unnecessary risk.

The following events are exceptions to #5 and #6; they may or may not be reported as AEs. For these events, CTCAE severity grading will not be used as a basis for a participant to be discontinued from study intervention. The requirements for a participant to be discontinued from study intervention are listed for each event.

CCI

[redacted]

CCI

[redacted]

Laboratory Abnormalities

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

The following laboratory abnormalities are exceptions to #7 and #8. For these events, CTCAE severity grading will not be used as a basis for a participant to be discontinued from study intervention. The requirements for a participant to be discontinued from study intervention are listed for each laboratory abnormality.

CCI

[redacted]

7.2 Participant Withdrawal From the Study

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

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

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

If a participant or their legally acceptable representative withdraws consent from further study follow-up, collection of vital status data may be completed by review of medical or public records in accordance with participant's informed consent and local regulations.

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.

If a participant or their legally acceptable representative withdraws consent from further study follow-up, collection of vital status data may be completed by review of medical or public records in accordance with participant's informed consent and local regulations.

Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- 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 providing documented informed consent 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 the Operations/Laboratory Manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

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 their legally acceptable representative) and of the person conducting the consent discussion.

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

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 Full Informed Consent

Specifics about the study and the study population are to be included in the ICF.

The participant (or their 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.

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 their 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. It is the responsibility of the investigator to determine all eligibility assessments and medical decisions regarding individuals considered for randomization.

8.1.3 Participant Identification Card

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

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

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee at Visit 1a/Screening; participant demographics will also be recorded.
At Visit 3/Randomization, the medical history record will be updated with any new conditions diagnosed during the screening period.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified requirements (Sections 5.1 and 5.2), and record prior medications taken by the participant before the first dose of study intervention. The site may rely on participant report for this information.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medications, if any, taken by the participant during the study on the appropriate eCRF. The investigator or qualified designee will confirm that the participant is not receiving any medications prohibited during the study as described in Section 6.5.

8.1.6 Assignment of Screening Number

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

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit (Visit 1a). Specific details on the screening/rescreening visit requirements are in Section 8.11.3. After all required screening procedures have been completed and the participant's eligibility has been confirmed, the study randomization visit (Visit 3) will be registered in IRT.

Pre-trial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.7 Assignment of Randomization Number

All eligible participants will be randomly allocated and will receive a randomization number. The randomization number identifies the participant for all procedures occurring after

randomization. Once a randomization number is assigned to a participant, it can never be reassigned to another participant.

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

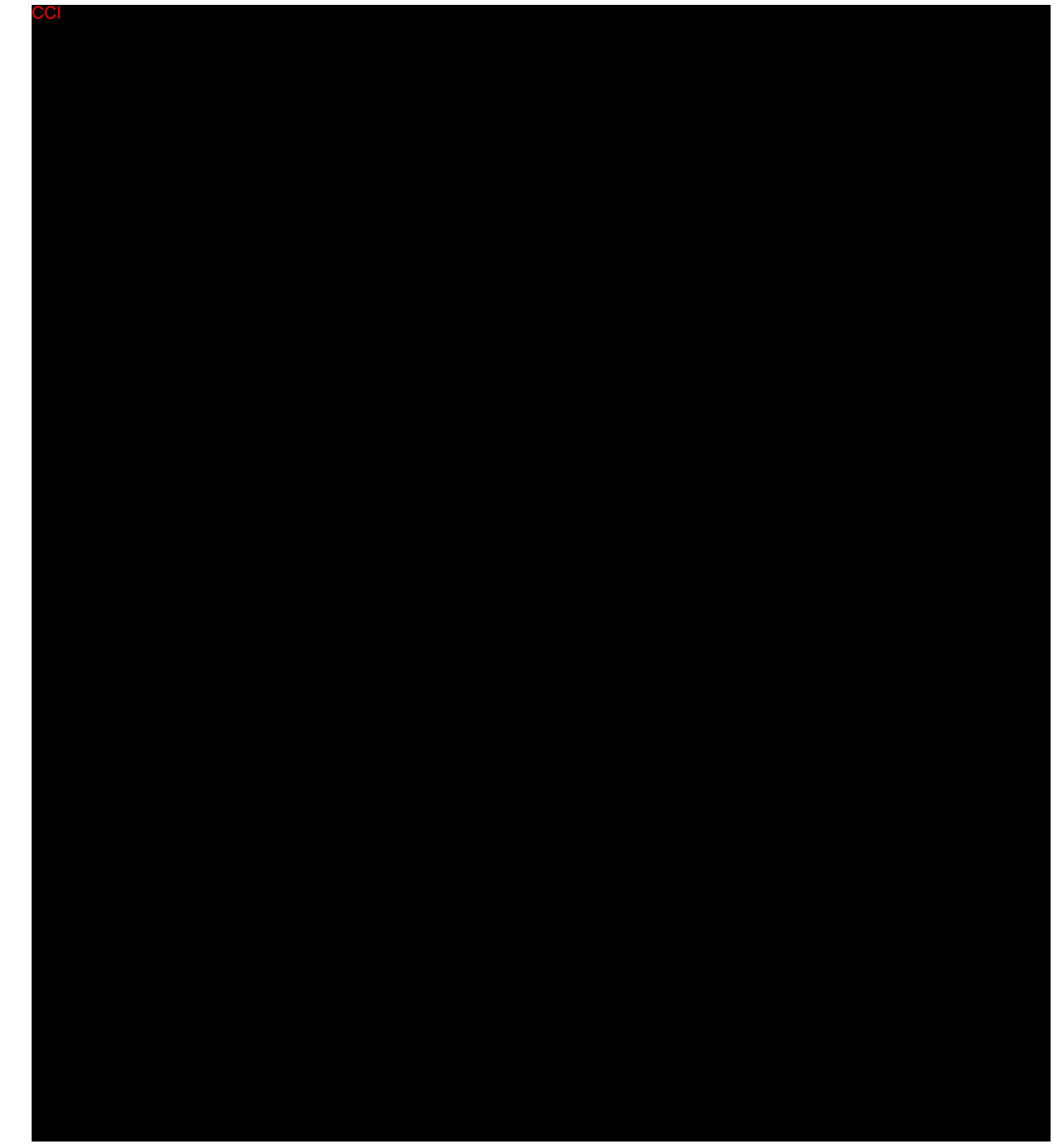
CCI

[redacted]

CCI

[redacted]

CCI



CCI

8.1.9.2 Alcohol Consumption Assessment and Counseling

At the site visits specified in the SoA (Section 1.3), the participants will report the average number of drinks consumed per week since the last visit and will be counseled by site staff to restrict alcohol consumption to the accepted number of alcoholic drinks per week (ie, no more than approximately 7 standard drinks per week for females or no more than approximately 14 standard drinks per week for males). If, at any visit, the participant is found to be noncompliant with alcohol use restrictions, the participant should be assessed and counseled more frequently. For participants who are noncompliant with the alcohol use restrictions for 4 or more weeks over the course of the study, consultation between the investigator and Sponsor is required for a collaborative decision on participant management.

For further details refer to Section 5.3.2.

8.1.9.3 Hypoglycemia and Hyperglycemia Counseling

The site staff will review the symptoms of hypoglycemia and hyperglycemia with the participants, as specified in the SoA (Section 1.3).

The site staff will counsel the participants with T2DM to self-monitor their fingerstick glucose concentrations at a frequency determined to be appropriate by the investigator and to report any occurrence of asymptomatic hypoglycemia.

Additionally, the site staff will counsel these participants to perform a fingerstick glucose measurement if any symptoms occur that may be related to ***hypoglycemia*** (eg, weakness, dizziness, shakiness, increased sweating, palpitations, or confusion) or ***hyperglycemia*** (eg, polyuria, polydipsia) and provide guidance on management. Furthermore, participants will be counseled to avoid delay in treating these symptoms and to contact the site at their earliest convenience.

The investigator should ensure that the participant's glucose meter is functioning accurately and that the test procedure is being correctly performed by the participant.

CCI

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should complete all applicable activities scheduled for the discontinuation visit at the time of study intervention discontinuation and should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.7.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the discontinuation visit, as outlined in Section 8.11.7, at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4. Participants who withdraw from the study while being monitored in the study following discontinuation of study intervention will not complete an additional discontinuation visit at the time of withdrawal.

8.1.10.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@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.

8.1.11 Participant Blinding/Unblinding

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

8.1.12 Calibration of Equipment

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

The MRI scanner must be calibrated according to the hospital standards and/or manufacturer's instructions. Additional details are provided in the MRI Site Imaging Manual. Critical equipment for this study includes a digital body weight scale. The study site is responsible for calibrating the scale per manufacturer's instructions, to ensure the scale used to measure body weight is working correctly. Additional details are provided in the Operations Manual.

8.2 Efficacy Assessments

8.2.1 Liver Fat Content

MRI-PDFF determines the percentage ratio of fat signal over the sum of fat and water signals in the tissue by separating the water and fat signals in the image using the difference in the magnetic resonance frequencies of protons in water and fat. MRI-PDFF can measure fat content over the entire liver and is usually reported as a single value averaged over the whole liver. CCI [redacted]

CCI [redacted]

To minimize variability, the same MRI-PDFF scanner and software should be used for an individual participant throughout the study.

CCI

[redacted]

8.2.2 Body Weight

The mean percent change from baseline in body weight at Week 28 is a secondary efficacy endpoint for the study. CCI [redacted]

Body weight (kg) will be measured in duplicate using a standardized digital scale, as outlined in the SoA (Section 1.3). Participant will be weighed wearing light clothing and no shoes. Body weight should be reported with precision to 1 decimal place (eg, 0.1 kg). The 2 measurements should be recorded in the source documents. If the 2 measurements differ by more than 0.2 kg or by 0.4 lb, proper positioning of the participant on the scale should be checked and/or an accuracy check of the scale should be conducted before obtaining a new set of duplicate measurements. The 2 new measurements should be recorded in the source documents. Only the final body weight measurement should be recorded in the eCRF.

Detailed information regarding the collection of body weight is in the Operations Manual.

CCI [redacted]

CCI [redacted]

Sample collection, storage, and shipment instructions are provided in the Laboratory Manual.

CCI [redacted]

CCI [redacted]

Detailed information regarding BP monitoring is included in the Operations Manual.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

Directed physical examinations will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard and as outlined in the SoA (Section 1.3).

The directed physical examinations will, at a minimum, include assessment of the heart, lungs, abdomen, skin, extremities, and a liver-focused assessment (liver, spleen, and ascites). Other body systems may be evaluated. Abnormalities considered clinically significant should be reported as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses. A physical examination (complete or directed) may be performed at any unscheduled visit if deemed necessary by the investigator or medically qualified designee.

8.3.1.1 Body Weight

Body weight (kg) will be measured at the study visits specified in the SoA (Section 1.3). For measurement details, refer to Section 8.2.2.

8.3.1.2 Height

Height will be measured at Visit 1a/Screening, using a calibrated stadiometer; the participant will wear no shoes. The height will be documented in meters, to the nearest 0.01 meter (0.01 meter = 1 cm).

8.3.2 Vital Signs

Vital signs (SBP, DBP, and HR) will be measured at the scheduled site visits specified in the SoA (Section 1.3). Vital signs will be measured before blood collection for laboratory tests.

Accurate measurement of BP is essential to detect potential treatment effects (see Section 8.2.4) as well as potential safety signals during the study. Several factors can cause significant deviations in the measured BP, including room temperature, exercise, alcohol consumption, nicotine-containing product use, positioning of the arm, muscle tension, bladder distension, talking, and background noise.

BP and HR should be measured under the following conditions:

- BP and HR measurements will be assessed in seated position, with a completely automated device. Manual techniques will be used only if an automated device is not available.
- No other procedures may be performed during the BP and HR measurements.
- Participants should avoid ingestion of caffeine and use of nicotine-containing products for at least 30 minutes before the BP and HR assessment.
- Measurements must be conducted after a 10-minute resting period with the participant comfortably seated in a chair with their legs uncrossed and the back and arm supported. The participant should be instructed to relax as much as possible and to not talk during the measurement procedure.
- The participant should be asked to remove all clothing that covers the location of cuff placement.
- Site personnel should ensure that the middle of the cuff on the upper arm is at the level of the right atrium (the midpoint of the sternum).
- Triplicate assessment of seated systolic and diastolic BP (mm Hg) and HR (bpm) will be collected at approximately 2-minute intervals. The time, positioning, and arm used should be recorded for each measurement. The mean value of the triplicate measurements will be recorded in the CRF.
- As much as possible, the site personnel should use the same BP measuring device and under the same external conditions throughout the study for each participant.

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

8.3.3 Electrocardiograms

A standard supine 12-lead ECG will be obtained and reviewed by the investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3) using an ECG instrument that automatically calculates the HR. The ECG recordings will be used to measure the PR, QRS, and QT intervals and to calculate the QTc intervals. Clinically significant abnormal findings at screening should be recorded as medical history. Assessments may be repeated during the study, as clinically indicated.

Participants should avoid ingestion of caffeine and use of nicotine-containing products for at least 30 minutes before the scheduled ECGs. ECGs should be performed after the participant has had their BP and HR assessed and before blood collection. Standard instrument calibration should be performed per manufacturer's instructions.

All ECGs performed should be reviewed at the investigative site for participant safety monitoring. The investigator is responsible for retaining all copies of the ECG reports. Refer to Section 10.3.2 for evaluation and potentially significant findings.

8.3.4 Glucose Metabolism

The laboratory safety endpoints for CCI [redacted] Participants should be fasted for at least 8 hours before the sample collection and should take their non-AHA concomitant medications as prescribed (see Section 8.11.2).

Sample collection, storage, and shipment instructions are provided in the Laboratory Manual.

8.3.5 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 Laboratory Manual and 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 5 weeks 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.
- Participants will be counseled to fast (ie, no food or drink [except water] and only non-AHA medications, as prescribed) for at least 8 hours before study visits requiring fasted blood collections or procedures (see Section 8.11.2).
- Serum hCG testing will be performed for POCBP when a pregnancy is suspected.

8.3.6 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 at monthly intervals during intervention.
  - Pregnancy testing (urine and/or serum) should be conducted as specified in the SoA for the time required to eliminate systemic exposure after the last dose of the 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 the study intervention is:
    - Efinopegdutide - 5 weeks after last dose
  - 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.

8.4 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

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

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

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

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and 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 3.

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

Table 3 Reporting 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
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
CCI [redacted]				
Cancer	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless serious)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

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

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

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

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

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. 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). The investigator will also make every attempt to follow nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities 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.

CCI

CCI

[redacted]

8.4.8 Drug–Device Combination Products/Combination Medicinal Products – Complaints, PQCs, and Malfunctions

Not applicable.

8.5 Treatment of Overdose

For all study arms, more than 1 dose of efinopegdutide, as defined in the protocol, administered within a 48-hour period will be considered an overdose.

No specific information is available on the treatment of efinopegdutide overdose. In case of overdose, the participant should be observed closely for signs of toxicity. Appropriate symptomatic medical treatment should be provided according to the clinical condition.

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

CCI

[redacted]

CCI

[redacted]

8.8 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

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

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the Operations/Laboratory Manual.

8.9.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be collected 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 FBR is approved and consent is given, 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 visit, 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

All sample collections for study-specific assessments shown in the SoA are described within the main Informed Consent.

If the participant has provided documented informed consent for FBR, leftover samples will be used for FBR. The following specimens will be included for FBR:

- Leftover samples listed in Section 8.9

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Sections 8.2 and 8.3.

CCI

8.11.1.1 Visit Reminders

Participants should be called at least 48 hours before each study visit and be reminded of:

- The date and time of the next appointment
- The visit requirements:
  - To not engage in physically strenuous exercise (ie, weightlifting, running, bicycling, etc) within 48 hours before their study visit.
  - To fast for at least 8 hours before the study visit (except Visit 1b/Imaging).

- To not take AHA medications at home the morning of the study visit. Non-study medications that are not AHA medications should be taken as directed by the prescribing physician.
- To bring any study intervention (used and unused prefilled syringes) to each site visit, starting with Visit 4/Week 4.
- To bring participant medication diaries to each site visit, starting with Visit 4/Week 4.

8.11.2 Fasting Before Scheduled Visits

Participants should be counseled to fast (ie, no food or drink except water, no AHA medications) for at least 8 hours before study visits requiring fasted blood collections or procedures (see Section 1.3). Participants who have not fasted for the Visit 1a/Screening should have all blood collections rescheduled and completed as soon as possible. After Visit 3/Randomization, participants who do not fast before a scheduled visit will be required to return fasted for a study visit within 3 days.

Note: Participants should take their non-AHA medications as prescribed before study visits requiring fasted blood collections or procedures (see Section 1.3).

CCI

At this visit, participants will also be assessed for the presence of metallic implants that can prevent MRI-PDFF examination including, but not limited to, aneurysm clips, vascular grafts or cardiac implants, neural stimulators, cochlear implants, metallic contraceptive devices, metallic foreign bodies, metallic tattoos, body piercings that cannot be removed, or any other contraindication to MRI-PDFF examination.

CCI

The investigator may retest a participant ***once*** during the 5-week Screening Period for not meeting study eligibility criteria (except MRI-PDFF). If possible, only the laboratory test not meeting an entry criterion should be retested (not the entire panel). The last laboratory draw/result should be used to assess the eligibility criterion. Participants who fail to meet the MRI-PDFF criterion will be screen failed and cannot be retested. Retested participants will be screen failed for not meeting study eligibility criteria after retesting.

8.11.3.2 Visit 1b/Imaging

The participants who satisfy all Visit 1a/Screening eligibility requirements will have their LFC measured by MRI-PDFF at this visit. [redacted]

8.11.3.3 Rescreening Visit

If the Screening Period is not sufficient to permit eligibility of a participant for any reason (eg, screen fail, time constraints), the investigator may initiate a Rescreening Period per Sections 1.3 and 5.4.

A participant may be rescreened if all of the following conditions apply:

- The participant is declared a screen fail in IRT
- The Sponsor is consulted before rescreening is initiated
- The participant provides documented informed consent
- The 5-week duration allowed for the Screening Period has ended
- The maximum interval between the screen fail and initiation of Rescreening is 90 days

Participants may only be rescreened ***once***. Rescreened participants will retain their original screening number assigned at Visit1a/Screening (Section 8.1.6).

Visit 2 applies only for the participants who are rescreened. For these participants, all procedures/tests/time frames planned for Visit 1a/Screening and Visit 1b/Imaging will be performed/assessed at Visit 2 and will follow the same staged approach as for the initial Screening Period.

Participants who have initially failed to meet the study eligibility criteria based on an evaluable MRI-PDFF scan may not be rescreened. If possible, only the laboratory test not meeting entry criterion should be repeated at rescreening (not the entire panel). The last laboratory draw/result should be used to assess the exclusion criterion. Rescreened participants will be screen failed for not meeting study eligibility criteria after retesting.

8.11.4 Randomization

At Visit 3/Randomization (Day 1), eligibility for study participation will be reassessed to determine whether the participants continue to meet the I/E criteria and if, between Screening and Randomization, they experienced events that would exclude them from participating in the study, for example, a new medical condition, major surgery, or changes in therapy.

Participants who continue to satisfy all study eligibility criteria will be randomized to either Q1W efinopegdutide (target dose 10 mg) or Q2W efinopegdutide (target dose of 10 mg or 15 mg) and assigned a unique randomization number (Section 6.3.1).

CCI

The site will dispense (supported by IRT) the appropriate number of devices (prefilled syringes) with the 2 mg dose of study intervention, for administration at home.

8.11.5 Treatment Period Visits

Visit timing and requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Sections 8.1 through 8.10.

CCI

CCI

If a participant reports a pregnancy at the time of telephone contact, an unscheduled site visit will be required to confirm participant's pregnancy with a serum pregnancy test (Section 8.3.6).

Unscheduled telephone contact between study visits may occur as needed.

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

It is intended that all randomized participants be followed through completion of the study, regardless of premature discontinuation of treatment, unless the participant withdraws consent from any study follow-up.

CCI

Notes:

For those participants who have discontinued study intervention early and who miss the remaining study visits, sites will be instructed to exert diligent efforts to continue to contact them. Sites must document the outcome of the telephone contact(s) to show diligent efforts have been made.

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

8.11.8 End-of-Treatment Visit

If applicable, participants will continue study intervention until Visit 9/Week 28. If necessary, the visit procedures may be performed over multiple days, not to exceed 1 week.

CCI

[redacted]

9 KEY STATISTICAL CONSIDERATIONS

This section outlines the principal statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to final database lock, will be documented in a subsequent version of the SAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

CCI [redacted]

9.1 Responsibility for Analyses/In-house Blinding

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

This study will be conducted as a randomized, open-label study, ie, the Sponsor, investigators, and participants will know the study interventions administered after randomization and treatment assignment.

The Clinical Biostatistics department of the Sponsor will generate the randomized allocation schedule for study intervention assignment. The randomized allocation will be implemented in an IRT by a study vendor.

9.2 Hypotheses/Estimation

Objectives of the study are stated in Section 3.

CCI [redacted]

9.3.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

9.3.1.1 Efficacy Endpoints

Primary Efficacy Endpoint

- Mean relative reduction from baseline in LFC at Week 28

Secondary Efficacy Endpoints

- Mean percent change from baseline in body weight at Week 28

CCI

[redacted]

CCI

[redacted]

9.5.2 Statistical Methods for Efficacy Analyses

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

The strategy to address multiplicity issues regarding the multiple comparisons is described in Section 9.7.

CCI [redacted]

The primary endpoint of mean relative reduction from baseline in LFC will be analyzed CCI [redacted]

CCI [redacted]

9.5.3 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of AEs and other relevant parameters, including glycemic responses (A1C and FPG), laboratory test results and vital signs measurements.

The overall safety endpoints include the number of participants with at least one AE, drug-related AE, serious AE, serious drug-related AE, Grade 3-5 AE, discontinuation from study intervention due to an AE, fatal AE, or with adjudicated AEs of malignancies and/or major adverse CV events. CCI [redacted],

CCI [redacted]

The safety evaluation will include a summary by treatment group of the number and percentage of participants with each type of AE. For overall safety endpoints, specific AEs and safety topics of special interest that meet predefined CI threshold rules, point estimates and 95% CIs for the differences between treatment groups in the percentages of participants with events will be provided using the Miettinen and Nurminen (M&N) method [Miettinen, O. and Nurminen, M. 1985].

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

CCI [redacted]

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 Committees Structure

10.1.4.1 Clinical Adjudication Committee (CAC)

A CAC will evaluate the following events during an individual's active participation in the study (28-week treatment period and approximately 5-week follow-up period after the last dose of study intervention) for the purposes of confirming them according to the criteria in the adjudication charters, as well as evaluating the presence of confounding factors:

1. Pancreatitis – GLP-1 RAs have been associated with AEs of pancreatitis.
2. Major CV events – Patients with MASH often have associated metabolic comorbidities that include obesity, dyslipidemia, T2DM, and MetS. Since CV disease is a major cause of mortality for individuals with these conditions, serious CV events will be adjudicated in this study (including events from participants who continue to be followed after discontinuation of study intervention).
3. Malignancy – Thorough evaluation of malignancies is important in the development program of all investigational medications; therefore, detailed information will be collected for participants who develop a malignancy.

All external personnel involved in the adjudication process will remain blinded to study intervention allocation throughout the study.

10.1.5 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.

10.1.6 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.

10.1.7 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.

10.1.8 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.

10.1.9 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.

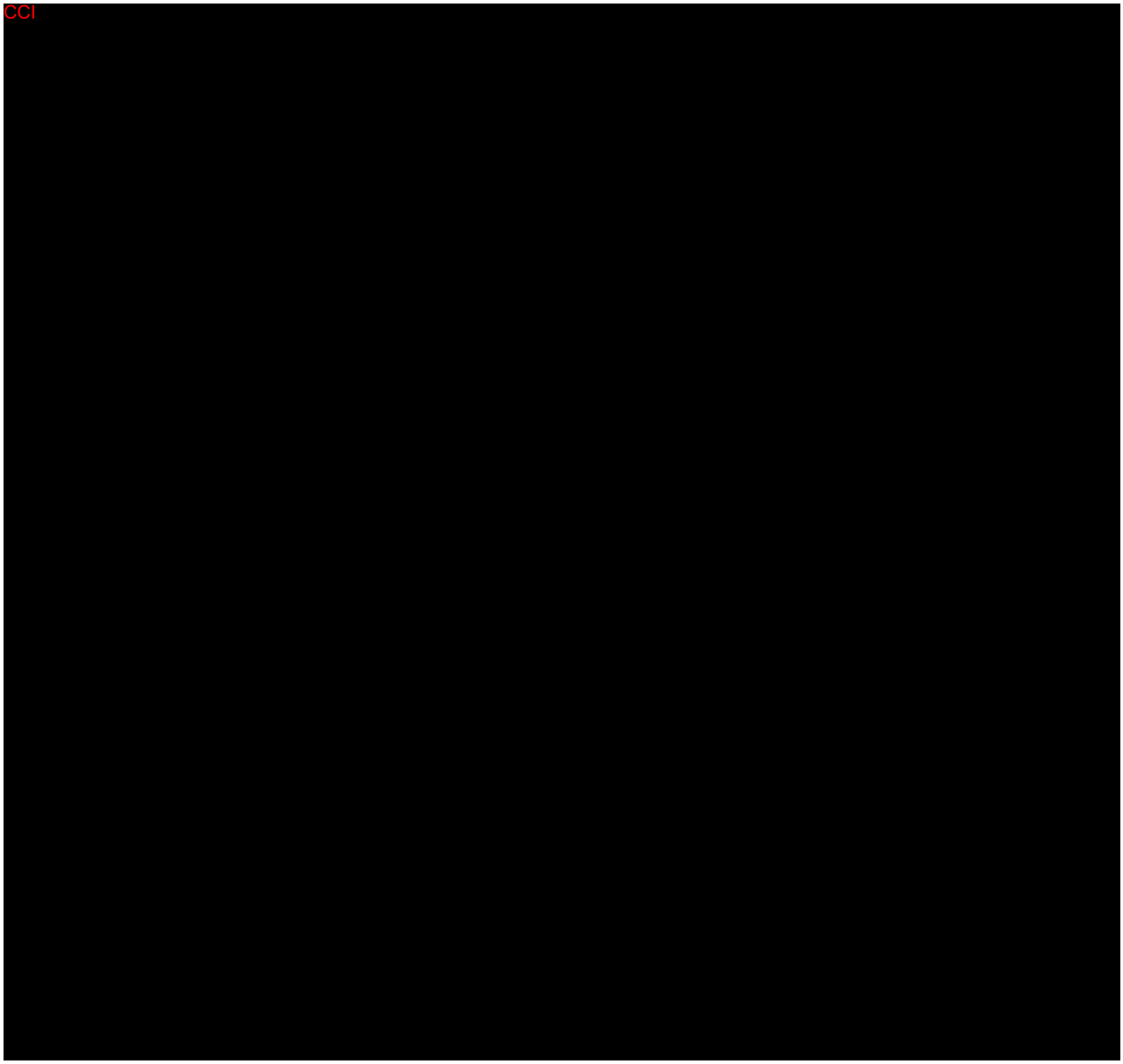
10.1.10 Study and Site Closure

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 5 will be performed by the central laboratory, except for the urine pregnancy testing, which will be performed by the local laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator.



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."
- Any new cancer or progression of existing cancer.

Events NOT meeting the AE definition

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

10.3.3 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) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
  - Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life-threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the 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: Combination Medicinal Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

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.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• IUS [a] • Progestogen-only subdermal contraceptive implant [b] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) – All sexual partner(s) of the POCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with partner(s) capable of producing sperm during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
[a] IUS is a progestin-releasing IUD. [b] If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. Note: • Tubal occlusion includes tubal ligation

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 8.9 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.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

Not applicable.

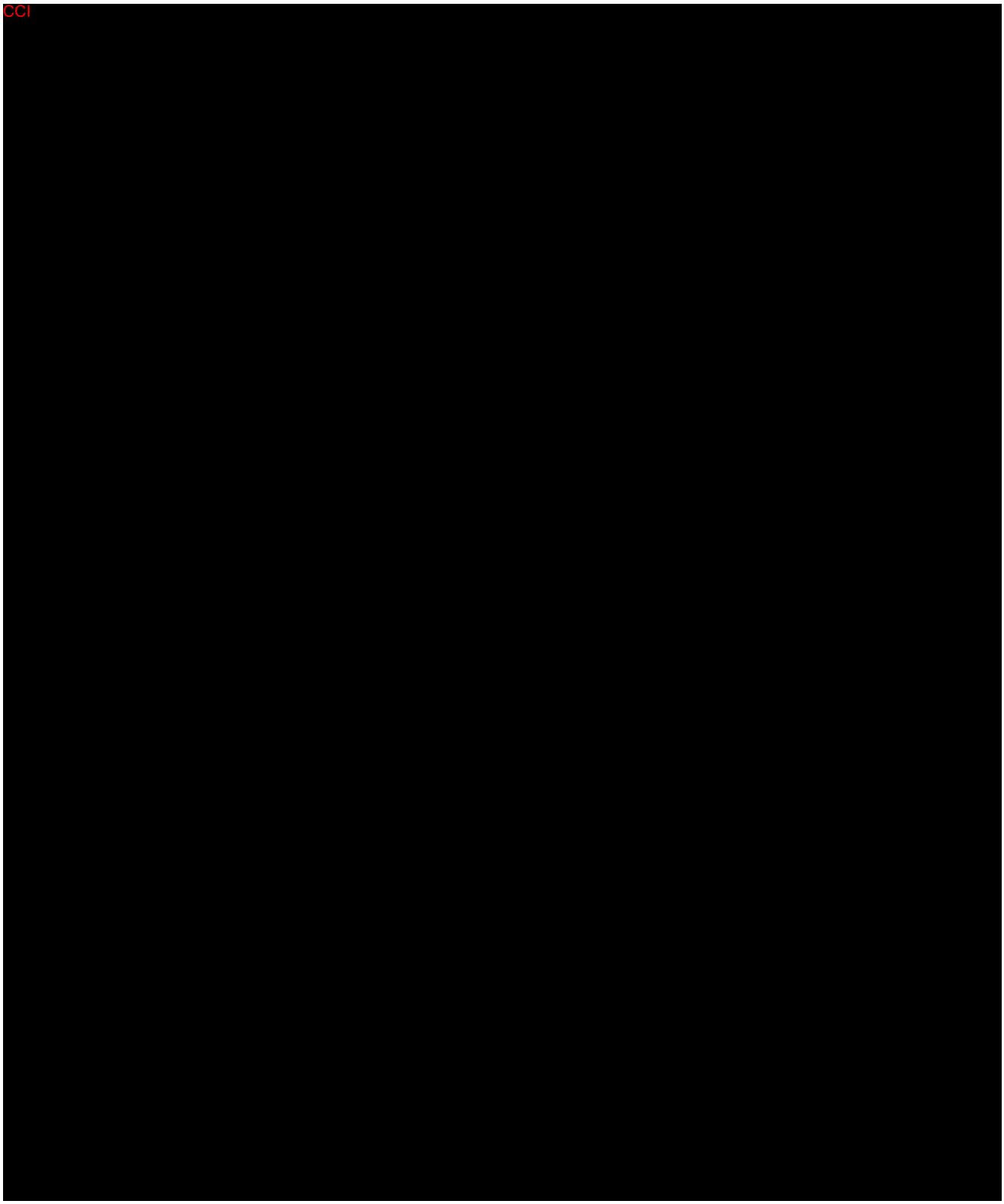
10.8 Appendix 8: Other Medical Device: Complaints Including Product Quality Complaint, Malfunction, Serious Injury, Death, Fetal Distress/Fetal Death and Congenital Anomaly: Definitions and Reporting

Not applicable.

CCI

[redacted]

CCI



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

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

10.11 Appendix 11: eGFR Equations

In this study, eGFR will be calculated using the CKD-EPIcr equation that does not use race [Inker, L. A., et al 2021], in accordance with recent recommendations from a joint NKF/ASN TaskForce [Delgado, C., et al 2021].

CKD-EPIcr equation:

$eGFRcr = 142 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.200} \times 0.9938^{Age} \times 1.012$ [if female]

where:

eGFR = estimated glomerular filtration rate (mL/min/1.73 $m^{2)}$

Scr = serum creatinine (mg/dL)

κ = 0.7 (females) or 0.9 (males)

α = -0.241 (females) or -0.302 (males)

min = indicates the minimum of Scr/κ or 1

max = indicates the maximum of Scr/κ or 1

Age = age (years)

10.12 Appendix 12: Abbreviations

Abbreviation	Expanded Term
A1C	glycated hemoglobin
ACC	acetyl-CoA carboxylase
ADA	anti-drug antibodies
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AHA	antihyperglycemic agent
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APaT	All-Participants-as-Treated
apoB	apolipoprotein B
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
BICR	blinded independent central review
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CAC	Clinical Adjudication Committee
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-EPIcr	CKD-EPI creatinine
C_{max}	maximum serum concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease caused by severe acute respiratory syndrome coronavirus 2
CRF	Case Report Form
CRN	Clinical Research Network
CSR	Clinical Study Report
CT	computed tomography
cT1	corrected T1 (MRI)
CTCAE	Common Terminology Criteria for Adverse Events
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
CTFG	Clinical Trial Facilitation Group
CTX	collagen type 1 cross-linked telopeptide
CV	cardiovascular
DBP	diastolic blood pressure
DC visit	discontinuation visit
DGAT2	diacylglycerol O-acyltransferase 2
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid

Abbreviation	Expanded Term
DPP-4	dipeptidyl peptidase-4
EC	exclusion criterion
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
ELF	enhanced liver fibrosis
EMA	European Medicines Agency
EQ-5D-5L	EuroQoL 5-Dimension 5-Level Questionnaire
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FAS	Full Analysis Set
FFA	free fatty acids
FGF21	fibroblast growth factor-21
FGFR1c	fibroblast growth factor receptor-1c
FPG	fasting plasma glucose
FIB-4	Fibrosis-4 index
FSH	follicle-stimulating hormone
FXa	activated coagulation factor X
FXR	farnesoid X receptor
GCGR	Glucagon Receptor
GCP	Good Clinical Practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP	Good Laboratory Practice
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
GLP-1 RA	glucagon-like peptide-1 receptor agonist
GnRH	gonadotropin-releasing hormone
HA	hyaluronic acid
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDL-C	high density lipoprotein-cholesterol
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure

Abbreviation	Expanded Term
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 Contract Research Organization
ID	identification
I/E	inclusion/exclusion
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IL-10	interleukin 10
IMP	investigational medicinal product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intention-to-treat
IU	International Units
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
JAPIC-CTI	Japan Pharmaceutical Information Center Clinical Trials Information
LDL-C	low density lipoprotein-cholesterol
LFC	liver fat content
LLN	lower limit of normal
LS	least squares
LSM	liver stiffness measurement
M&N	Miettinen and Nurminen
MAD	maximum administered dose
MASH	Metabolic dysfunction-associated steatohepatitis
MASLD	Metabolic dysfunction-associated steatotic liver disease
MCD	methionine choline-deficient
MEN	multiple endocrine neoplasia
MetS	metabolic syndrome
MRI	Magnetic Resonance Imaging
MRI-PDFF	MRI-Estimated Proton Density Fat Fraction
mRNA	messenger RNA
NAFL	nonalcoholic fatty liver
NAFLD	nonalcoholic fatty liver disease
NASH	nonalcoholic steatohepatitis
NCI	National Cancer Institute
NKF/ASN	National Kidney Foundation/American Society of Nephrology
NYHA	New York Heart Association
CCI	[redacted]
PCR	polymerase chain reaction

Abbreviation	Expanded Term
PD	pharmacodynamic
PDLC	predefined limits of change
PK	pharmacokinetic
POCBP	participant/participants of childbearing potential
PP	per protocol
PPAR	peroxisome proliferator-activated receptor
PQC	Product Quality Complaint
PRO	patient-reported outcome
CCI [redacted]	[redacted]
PTH	parathyroid hormone
Q1W	once weekly
Q2W	once every 2 weeks
QoL	quality of life
QTc	corrected QT interval
QTcR	QT interval corrected for heart rate changes
RBC	red blood cell
RNA	ribonucleic acid
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	subcutaneous(ly)
SD	standard deviation
SIM	Site Imaging Manual
SLAB	supplemental laboratory test(s)
SLD	steatotic liver disease
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
SU	sulfonylurea
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half life
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TA	therapeutic area
TEAE	treatment-emergent adverse event
TG	triglycerides
TQT	thorough QT
ULN	upper limit of normal
US	United States
VS	vital signs

11 REFERENCES

[Armstrong, M. J., et al 2016]	Armstrong MJ, Gaunt P, Aithal GP, Barton D, Hull D, Parker R, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. Lancet. 2016 Feb 13;387:679-90.	[05MCS6]
[Aronne, L. J., et al 2024]	Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin WY, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. JAMA. 2024 Jan 2;331(1):38-48.	[08HX6P]
[Bautz, D. 2018]	Bautz D. VKTX: positive results for phase 2 study of VK2809 in NAFLD. Chicago (IL): Zacks Investment Research; 2018 Sep 24. 7 p.	[0567BZ]
[Boland, M. L., et al 2020]	Boland ML, Laker RC, Mather K, Nawrocki A, Oldham S, Boland BB, et al. Resolution of NASH and hepatic fibrosis by the GLP-1R and GCGR dual-agonist cotadutide via modulating mitochondrial function and lipogenesis. Nat Metab. 2020 May;2:413-31. Extended data figures, life sciences reporting summary; 11 p.	[05MQMH]
[Chalasani, N., et al 2018]	Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology. 2018 Jan;67(1):328-57.	[056CWV]
[Cusi, K., et al 2022]	Cusi K, Isaacs S, Barb D, Basu R, Caprio S, Garvey WT, et al. American Association of Clinical Endocrinology clinical practice guideline for the diagnosis and management of nonalcoholic fatty liver disease in primary care and endocrinology clinical settings: co-sponsored by the American Association for the Study of Liver Diseases (AASLD). Endocr Pract. 2022;28:528-62.	[0875Z9]

[Dela Cruz, J. 2020]	Dela Cruz J. Cotadutide trims weight, improves liver markers in T2D patients with NAFLD [Internet]. Singapore: Monthly Index of Medical Specialities (MIMS) Pte Ltd.; 2020 Sep 4 [cited 2020 Nov 25]. Available from: https://specialty.mims.com/topic/cotadutide-trims-weight--improves-liver-markers-in-t2d-patients-with-nafld.	[05NF3B]
[Delgado, C., et al 2021]	Delgado C, Baweja M, Crews DC, Eneanya ND, Gadegbeku CA, Inker LA, et al. A unifying approach for GFR estimation: recommendations of the NKF-ASN Task Force on reassessing the inclusion of race in diagnosing kidney disease. J Am Soc Nephrol. 2021;32:2994–3015.	[07ZP4L]
[European Medicines Agency 2020]	European Medicines Agency. ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials: step 5. London (England): European Medicines Agency (EMA); 2020. 19 p. EMA/CHMP/ICH/436221/2017.	[05G4BV]
[Fabbrini, E., et al 2010]	Fabbrini E, Sullivan S, Klein S. Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications. Hepatology. 2010 Feb;51(2):679-89.	[0565MN]
[Food and Drug Administration 2018]	Food and Drug Administration. Noncirrhotic nonalcoholic steatohepatitis with liver fibrosis: developing drugs for treatment guidance for industry: draft guidance. Rockville, MD. Dec 2018.	[0565MP]
[Friedman, S. L., et al 2018]	Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med. 2018 Jul;24:908-22.	[05649M]

[Harrison, S. A., et al 2018]	Harrison SA, Rinella ME, Abdelmalek MF, Trotter JF, Paredes AH, Arnold HL, et al. NGM282 for treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. Lancet. 2018 Mar 24;391:1174-85. Erratum in: Lancet. 2018 Mar 24;391:e16.	[0568MV]
[Inker, L. A., et al 2021]	Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021 Nov 4;385(19):1737-49. Supplemental material; 87 p.	[07ZRQ6]
[Jaycox, S. H. 2016]	Jaycox SH. A fatty world: exploring racial disparity in NAFLD/NASH. J Hep. 2016 Dec 7;2(2):16.	[08D9BJ]
[Kechagias. S., et al 2020]	Kechagias S, Nasr P, Blomdahl J, Ekstedt M. Established and emerging factors affecting the progression of nonalcoholic fatty liver disease. Metabolism. 2020;111:154183.	[05MDML]
[Liang, K-Y and Zeger, S. L. 2000]	Liang K-Y, Zeger SL. Longitudinal data analysis of continuous and discrete responses for pre-post designs. Sankyha: The Indian Journal of Statistics 2000;62(Series B, Part 1):134-48.	[00V5V6]
[Loomba, R., et al 2023]	Loomba R, Sanyal AJ, Kowdley KV, Bhatt DL, Alkhouri N, Frias JP, et al. Randomized, controlled trial of the FGF21 analogue pegozafermin in NASH. N Engl J Med. 2023 Sep 14;389(11):998-1008.	[08HX4K]
[Madrigal Pharmaceuticals, Inc. 2017]	Madrigal Pharmaceuticals [Internet]. West Conshohocken (PA): Madrigal Pharmaceuticals, Inc.; c2019. Madrigal's MGL-3196 achieves primary endpoint in patients with biopsy-proven non-alcoholic steatohepatitis (NASH) in phase 2 clinical trial [press release]. 2017 Dec 6 [cited 2019 Mar 13]; 4 p. Available from: http://ir.madrigalpharma.com/news-releases/news-release-details/madrigals-mgl-3196-achieves-primary-endpoint-patients-biopsy.	[0567BY]

[Mendez-Sanchez, N., et al 2018]	Mendez-Sanchez N, Cruz-Ramon VC, Ramirez-Perez OL, Hwang JP, Barranco-Fragoso B, Cordova-Gallardo J. New aspects of lipotoxicity in nonalcoholic steatohepatitis. Int J Mol Sci. 2018 Jul 13;19:2034.	[06D957]
[Miettinen, O. and Nurminen, M. 1985]	Miettinen O and Nurminen M. Comparative Analysis of Two Rates. Stat Med 1985;4:213-26.	[03QCDT]
[Mohamadi, A. 2014]	Mohamadi A. Cross discipline team leader review: application number - 125431Orig1s00. Silver Spring (MD): Center for Drug Evaluation and Research (CDER); 2014 Mar 12. 67 p.	[082MZ9]
[Newsome, P. N., et al 2020]	Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med. In press 2020.	[05NMFV]
[Rich, N. E., et al 2018]	Rich NE, Oji S, Mufti AR, Browning JD, Parikh ND, Odewole M, et al. Racial and ethnic disparities in nonalcoholic fatty liver disease prevalence, severity, and outcomes in the United States: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2018 Feb;16(2):198-210, 210.e1-2.	[08B6TH]
[Rinella, M. E., et al 2023]	Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. Hepatology. 2023;78:1966-86.	[08GZTM]
[Rosenstock, M., et al 2023]	Rosenstock M, Tseng L, Pierce A, Offman E, Chen CY, Charlton RW, et al. The novel glycoPEGylated FGF21 analog pegozafermin activates human FGF receptors and improves metabolic and liver outcomes in diabetic monkeys and healthy human volunteers. J Pharmacol Exp Ther. 2023 Nov;387:204-13. Supplementary material; 11 p.	[08JJ05]

[Seghieri, M., et al 2018]	Seghieri M, Christensen AS, Andersen A, Solini A, Knop FK, Vilsboll T. Future perspectives on GLP-1 receptor agonists and GLP-1/glucagon receptor co-agonists in the treatment of NAFLD. Front Endocrinol. 2018 Nov 6;9:649.	[05MCY7]
[Stine, J. G., et al 2021]	Stine JG, Munaganuru N, Barnard A, Wang JL, Kaulback K, Argo CK, et al. Change in MRI-PDFF and histologic response in patients with nonalcoholic steatohepatitis: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2021 Nov;19(11):2274-83, 2283e1-5.	[089B9N]
[Sumida, Y. and Yoneda, M. 2018]	Sumida Y and Yoneda M. Current and future pharmacological therapies for NAFLD/NASH. J Gastroenterol. 2018;53:362-76.	[0565LQ]
[U.S. Prescribing Information 2022]	U.S. Prescribing Information: SAXENDA (liraglutide) injection, for subcutaneous use: Jun 2022.	[087S38]
[U.S. Prescribing Information 2022a]	U.S. Prescribing Information: TRULICITY (dulaglutide) injection, for subcutaneous use: Nov 2022.	[087S2V]
[U.S. Prescribing Information 2023]	U.S. Prescribing Information: WEGOVY (semaglutide) injection, for subcutaneous use: Jul 2023.	[08CQ0J]
[U.S. Prescribing Information 2024]	U.S. Prescribing Information: REZDIFFRA (resmetirom) tablets, for oral use: Mar 2024.	[08JVK7]
[Wynne, K., et al 2005]	Wynne K, Park AJ, Small CJ, Patterson M, Ellis SM, Murphy KG, et al. Subcutaneous oxyntomodulin reduces body weight in overweight and obese subjects: a double-blind, randomized, controlled trial. Diabetes 2005;54:2390-5.	[03RQ3W]
[Wynne, K., et al 2006]	Wynne K, Park AJ, Small CJ, Meeran K, Ghatei MA, Frost GS, et al. Oxyntomodulin increases energy expenditure in addition to decreasing energy intake in overweight and obese humans: a randomised controlled trial. Int J Obes 2006;30:1729-36.	[03RK8P]

[Younossi, Z. M., et al 2019]	Younossi ZM, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J Hepatol. 2019;71:793-801.	[05MCS2]
[Younossi, Z. M., et al 2023]	Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023;77:1335-47.	[08DC0N]