

CLINICAL STUDY PROTOCOL

A PHASE 1, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SINGLE- AND MULTIPLE-ASCENDING SUBCUTANEOUS DOSES OF DR10624

PROTOCOL NO. DR10624-101

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The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Zhejiang Doer Biologics Co., Ltd.

The study will be conducted according to the International Council for Harmonisation Guideline E6(R2): Good Clinical Practice.

SIGNATURE PAGE

PROTOCOL TITLE: A Phase 1, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single- and Multiple-Ascending Subcutaneous Doses of DR10624

PROTOCOL NUMBER: DR10624-101

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INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol titled “A Phase 1, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single- and Multiple-Ascending Subcutaneous Doses of DR10624” in accordance with applicable standard operating procedures, International Council for Harmonisation (ICH) Good Clinical Practices, Good Laboratory Practices and all other applicable regulations, including the recommendations laid down in the most recent version of the Declaration of Helsinki. I have read and understand all sections of the protocol.

Signature of Principal Investigator

Date

Printed Name of Principal Investigator

TABLE OF CONTENTS

TITLE PAGE	1
SIGNATURE PAGE	2
INVESTIGATOR PROTOCOL AGREEMENT PAGE	3
TABLE OF CONTENTS.....	4
PROTOCOL SYNOPSIS	7
1. INTRODUCTION	24
1.1 BACKGROUND.....	24
1.1.1 Overview of DR10624	25
1.1.2 Non-Clinical Studies	27
1.1.3 Clinical Studies.....	28
1.2 RATIONALE FOR STUDY	28
1.2.1 Selection of Study Design	29
1.3 RATIONALE FOR SELECTED FIRST DOSE LEVEL OF DR10624	30
2. STUDY OBJECTIVES.....	31
2.1 PRIMARY OBJECTIVES.....	31
2.2 SECONDARY OBJECTIVES	32
2.3 EXPLORATORY OBJECTIVE	33
3. STUDY DESIGN.....	33
3.1 SCHEDULE OF EVENTS FOR PART 1	43
3.2 SCHEDULE OF EVENTS FOR PART 2	46
3.3 SCHEDULE OF EVENTS FOR PART 3	51
4. STUDY POPULATION.....	53
4.1 INCLUSION CRITERIA	53
4.2 EXCLUSION CRITERIA.....	55
4.3 LIFESTYLE CONSIDERATIONS	58
4.3.1 Caffeine, Alcohol, and Tobacco.....	58
4.3.2 Activity	59
4.4 WITHDRAWAL OF SUBJECTS FROM THE STUDY	59
4.4.1 Reasons for Withdrawal.....	59
4.4.2 Handling of Withdrawals.....	60
4.4.3 Replacements.....	60
5. STUDY TREATMENTS	60
5.1 TREATMENTS ADMINISTERED	60
5.1.1 Dose Escalation	62
5.1.2 Dose-Limiting Toxicities	63
5.1.3 Dose Escalation Stopping Criteria.....	63

5.2	INVESTIGATIONAL PRODUCTS	64
5.2.1	Study Drug Packaging and Storage	65
5.2.2	Study Drug Accountability	66
5.3	METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS.....	66
5.4	BLINDING.....	66
5.4.1	Blinding Procedures	66
5.4.2	Breaking the Blind.....	66
5.5	TREATMENT COMPLIANCE	67
5.5.1	Prior and Concomitant Medications	67
5.5.1.1	Prior Medications.....	68
5.5.1.2	Concomitant Medications.....	68
6.	STUDY PROCEDURES	68
6.1	PHARMACOKINETIC ASSESSMENTS AND ENDPOINTS	68
6.1.1	Pharmacokinetic Sample Collection.....	70
6.1.2	Pharmacokinetic Sample Analysis.....	70
6.2	PHARMACODYNAMIC ASSESSMENTS AND ENDPOINTS	70
6.2.1	Pharmacodynamic Sample Collection.....	71
6.2.2	Pharmacodynamic Sample Analysis.....	71
6.3	SAFETY ASSESSMENTS AND ENDPOINTS.....	72
6.3.1	Adverse Events	72
6.3.1.1	Adverse Event Definitions.....	72
6.3.1.2	Adverse Events of Special Interest	74
6.3.1.3	Eliciting and Documenting Adverse Events	75
6.3.1.4	Reporting Adverse Events	75
6.3.1.5	Reporting a Pregnancy	76
6.3.1.6	Assessment of Severity	76
6.3.1.7	Assessment of Causality	77
6.3.1.8	Follow-up of Adverse Events	78
6.3.2	Clinical Laboratory Testing	78
6.3.3	Vital Sign Measurements.....	79
6.3.4	12-Lead Electrocardiograms.....	79
6.3.5	Continuous Holter Electrocardiograms	80
6.3.6	Physical Examinations.....	80
6.3.7	Continuous Glucose Monitoring (Part 2 Only)	81
6.3.8	Glucometer Monitoring (Part 2 Only).....	81
6.3.9	MRI-PDFF (Part 2 Only).....	81
6.3.10	FibroScan (Part 2 Only).....	81
6.3.11	Satiety Test (Part 2 Only)	82

7.	STATISTICAL ANALYSIS PLANS	82
7.1	SAMPLE SIZE CALCULATIONS.....	82
7.2	ANALYSIS SETS	82
7.3	STATISTICAL ANALYSIS	82
7.3.1	Pharmacokinetic Analyses	83
7.3.2	Pharmacodynamic Analyses	84
7.3.3	Safety Analyses	86
7.4	HANDLING OF MISSING DATA	87
7.5	INTERIM ANALYSES	87
8.	REFERENCE LIST.....	88
9.	APPENDICES.....	89
9.1	APPENDIX 1: LIST OF ABBREVIATIONS	89
9.2	APPENDIX 2: STUDY GOVERNANCE	92
9.2.1	Data Quality Assurance	92
9.2.2	Investigator Obligations	92
9.2.2.1	Confidentiality	92
9.2.2.2	Institutional Review.....	93
9.2.2.3	Subject Consent	93
9.2.2.4	Study Reporting Requirements.....	93
9.2.2.5	Investigator Documentation.....	94
9.2.2.6	Study Conduct	94
9.2.2.7	Case Report Forms and Source Documents	94
9.2.2.8	Adherence to Protocol	95
9.2.2.9	Reporting Adverse Events	95
9.2.2.10	Investigator’s Final Report	95
9.2.2.11	Records Retention.....	95
9.2.2.12	Publications.....	96
9.2.3	Study Management.....	96
9.2.3.1	Monitoring	96
9.2.3.2	Management of Protocol Amendments and Deviations	97
9.2.3.3	Study Termination.....	97
9.2.3.4	Final Report	98

PROTOCOL SYNOPSIS

PROTOCOL NO.: DR10624-101

TITLE: A Phase 1, Randomized, Placebo-Controlled, Double-Blind Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single- and Multiple-Ascending Subcutaneous Doses of DR10624

STUDY PHASE: 1

STUDY SITE(S): The enrollment of subjects in this study may be across approximately 10 clinical sites worldwide, and enrollment for Part 3 (SAD) will be only from a single clinical site in China.

OBJECTIVES:

The primary objectives of this study are:

- **Part 1:** To assess the safety and tolerability of a single ascending subcutaneous (SubQ) dose of DR10624 in healthy adult subjects or overweight to obese adults but otherwise healthy subjects.
- **Part 2:** To assess the safety and tolerability of multiple ascending SubQ doses of DR10624 in obese adult subjects with modest hypertriglyceridemia.
- **Part 3:** To assess the safety and tolerability of a single ascending SubQ dose of DR10624 in Chinese healthy adult subjects or overweight or obese adults but otherwise healthy subjects in China.

The secondary objectives of this study are:

- **All Parts:** To determine the pharmacokinetic (PK) profiles of single and multiple SubQ doses of DR10624.
- **Part 2:** To assess the change from baseline in body weight, body mass index (BMI), and waist circumference in subjects receiving multiple SubQ doses of DR10624.
- **Part 2:** To assess the change from baseline in fasting lipid profile (total cholesterol, low density lipoprotein [LDL] cholesterol, high density lipoprotein [HDL] cholesterol, non-HDL cholesterol, lipoprotein (a) [Lp(a)], very low-density lipoprotein [VLDL] cholesterol, triglycerides, and free fatty acids) in subjects receiving multiple SubQ doses of DR10624.
- **Part 2:** To assess the pharmacodynamic (PD) response of DR10624 measured by the change from baseline value of partial areas under the curve in series biomarkers (glucose, C-peptide, insulin, and glucagon levels) following multiple SubQ doses of DR10624 using mixed meal tolerance test (MMTT).
- **Part 2:** To assess the change from baseline in fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), C-peptide, fasting insulin, glucagon, and adiponectin, as well as measures of insulin resistance (homeostatic model assessment index of insulin resistance, HOMA-IR) and beta-cell function (homeostatic model assessment index of beta-cell function, HOMA-B) in subjects receiving multiple SubQ doses of DR10624.

- **Part 2:** To assess the change of continuous glucose monitoring (CGM) outcome measures from baseline in subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes at screening:
 - Percentage of time spent in target range 3.9 to 10 mmol/L (Time in Range, TIR)
 - Time above target range (TAR)
 - Time below target range (TBR)
 - Average glucose
 - Glucose variability (coefficient of variation [CV])
- **All Parts:** To assess the safety of single and multiple SubQ doses of DR10624 as determined by the adverse event of special interest (AESI) of hypoglycemia.
- **Part 2:** To assess the change from baseline in Fibrosis 4 score (FIB-4) and non-alcoholic fatty liver disease fibrosis score (NFS) in subjects receiving multiple SubQ doses of DR10624.
- **Part 2:** To assess the change from baseline in hepatic fat fraction by magnetic resonance imaging - proton density fat fraction (MRI-PDFF) in subjects receiving multiple SubQ doses of DR10624 and in a prespecified subgroup of subjects with at least 8% baseline hepatic fat.
- **Part 2:** To assess the change in liver stiffness by FibroScan from baseline in subjects with baseline hepatic fat of at least 8% measured by MRI-PDFF.
- **Part 2:** To assess the change from baseline in liver function parameters in subjects receiving multiple SubQ doses of DR10624.
- **All Parts:** To assess the immunogenicity of DR10624.

The exploratory objective of this study is:

- **Part 2:** To assess the change from baseline in satiety measured by visual analogue scale (VAS) in subjects receiving multiple SubQ doses of DR10624.

STUDY DESIGN:

This is a Phase 1, first-in-human (FIH), randomized, double-blind, placebo-controlled study designed to assess the safety, tolerability, PK, and PD of single- and multiple-ascending SubQ doses of DR10624. The study will be conducted in 3 parts:

1. **Part 1:** An SAD part in healthy adult subjects or overweight to obese subjects but otherwise healthy adult subjects (Cohorts A, B, C, D, E, F, G, H, and P),
2. **Part 2:** A MAD part in obese adult subjects with modest hypertriglyceridemia (Cohorts I, J, K and L), and
3. **Part 3:** An SAD part in Chinese healthy adult subjects or overweight or obese but otherwise healthy adult subjects (Cohorts M, N and O).

In each study part, subjects who meet the criteria for study entry will be assigned to the planned dose cohort and will be randomly assigned in an x:y ratio to receive DR10624 or

placebo. All doses of DR10624 or placebo will be administered as a SubQ injection in the abdomen.

Safety data for each dose cohort will be reviewed in a blinded fashion by a safety review committee (SRC) before progression to the next higher dose cohort of all parts and/or before progression to Part 2. The sponsor will form an internal SRC for a blinded review of safety data for each subject and the entire cohort and will make a recommendation on whether to proceed to the next dose level and/or progression to Part 2. The SRC will be composed of the following individuals: the sponsor's medical officer or designee, the sponsor's clinical pharmacology representative or designee (if applicable), the sponsor's study statistician or designee (if applicable), the investigator, the treating physicians (if applicable), the medical monitor, and other applicable functions as nominated by the SRC chair, appointed by the Sponsor. A coordinator may organize and record decisions of the SRC (non-voting member).

Dosing in the next higher dose cohort of all parts and/or dosing in Part 2 will be permitted only after the blinded SRC confirms that it is safe to do so, and the sponsor or designee provide written/e-mail confirmation to the investigator. Study assessments (eg, adverse events [AEs], clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram [ECG], serum calcitonin results, and physical examination findings) will be used to evaluate safety and tolerability of a given dose level. Available blinded PK data will also be reviewed at the same time as blinded safety data for each cohort and PK sampling time points and other elements of the schedule of events for subsequent cohorts may be adjusted as needed based on SRC review.

In Part 3, eligible subjects will receive one of 3 dose levels of DR10624 or placebo in a 5:1 ratio. Provisional dose of these 3 cohorts (M, N, O) in Part 3 may repeat dose levels of Cohorts E, F, G, H, or P in Part 1. The tentative starting DR10624 dose (Cohort M) in Part 3 will be same as the dose in Cohort E (25mg) of the Part 1 (SAD). The following doses for each cohort in Part 3 will be determined by the SRC following an evaluation of available safety and PK data for subjects in Part 1 and the safety, tolerability, and available PK data obtained through Day 15 of preceding dose cohort in Part 3. The highest DR10624 dose in Part 3 will not exceed the maximum tolerated dose reached in Part 1.

Part 1 (Single-Ascending Dose)

Part 1 will have 9 cohorts and approximately 68 healthy adult subjects or overweight to obese adult subjects (obese subjects in Cohorts G, H, and P only) but otherwise healthy subjects: 4 subjects in Cohort A (all active), 8 subjects each (6 active: 2 placebo) in Cohorts B, C, D, E, F, G, H, and P. The starting DR10624 dose in Part 1 will be 0.5 mg SubQ. The provisional doses in Cohorts B, C, D, E, F, G, H, and P are planned to be 1.5, 4.5, 12.5, 25, 50, 65, 90, and 120 mg SubQ, respectively, with final doses for each cohort determined by the SRC following a full review of the data from the previous dosed cohort. The dose levels may be adjusted by the SRC.

Part 1 will consist of a screening period (Days -28 to -2), check-in (Day -1), an in-clinic period/follow-up period (Days 1 to 29), and an end-of-study (EOS) visit (Day 29).

DR10624 will be administered as a SubQ injection in the abdomen. Subjects in Cohort A will receive active study drug on Day 1. A single sentinel subject will be dosed with DR10624

first. At 72 hours after this subject has been dosed, if the sentinel subject shows no significant safety or tolerability concerns, the remaining 3 subjects in that cohort may be dosed.

Administration of the next higher dose level in Part 1 (Cohort B) will only proceed after the safety data obtained through Day 15 after dosing have been evaluated in a blinded fashion by the SRC for Cohort A. The safety evaluation interval (through Day 15) after dosing may be extended with the approval of the sponsor or sponsor's designee.

For SAD Cohorts B to P, subjects will receive active study drug or placebo on Day 1. The first 2 sentinel subjects from each dose cohort will receive either placebo or DR10624 (ie, both placebo and active must be represented). At 72 hours after these first 2 subjects have been dosed, if the sentinel group shows no clinically significant safety or tolerability concerns, the remaining subjects in that cohort may be dosed.

Administration of the next higher dose level in Part 1 will only proceed after the safety and tolerability data and available PK data obtained through Day 15 after dosing has been evaluated in a blinded fashion by the SRC for each dose cohort. The safety evaluation interval (through Day 15) after dosing may be extended with the approval of the sponsor or sponsor's designee.

Blood samples for PK assessments will be collected at: predose and 2, 4, 6, 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7), 168 (Day 8), 240 (Day 11), 336 (Day 15), 504 (Day 22), and 672 hours (Day 29) postdose.

Blood samples to assess fasting glucose and lipid profile will be collected from all subjects at screening, check-in, Day 3, Day 8, and Day 29/EOS.

Immunogenicity serum samples for status of subject's antidrug antibody (ADA) titer assessment (ie, ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer) will be collected from all subjects at:

- Predose on Day 1, or at early termination (ET; if applicable), and at follow-up visits on Days 8, 15, and 29/EOS.

The serum sampling time points for the ADA titer assessment will be the same for all subjects dosed with either placebo or DR10624.

In Part 1, subjects will reside within the clinic from Day -1 until discharge on Day 7 (144 hours after dosing) and return to the clinic on Days 8, 11, 15, 22, and 29/EOS for outpatient visits. The duration of the study in Part 1, excluding screening, is approximately 30 days.

Part 2 (Multiple-Ascending Dose)

Part 2 will have 4 cohorts, with 12 subjects each (10 active: 2 placebo) in Cohorts I, J, K and L, and a total of approximately 48 subjects. Obese subjects with modest hypertriglyceridemia will be enrolled.

Additional subjects per cohort and/or cohorts may be enrolled at the SRC's discretion. Any subject who is screened for Part 2 and is unable to be dosed but is otherwise eligible (eg, reserve subjects) will be permitted to be rescreened for subsequent cohorts. If rescreening

occurs, MRI-PDFF and FibroScan will not be required to be repeated if prior assessment occurred within 3 months of dosing.

DR10624 will be administered as a SubQ injection in the abdomen. The SRC will make the final recommendation on the starting dose, dosing frequency, and/or whether to proceed to Part 2. Dosing in Part 2 will be permitted only after the blinded safety data through Day 29/EOS after completing the dosing in the last subject in Cohort E in Part 1 have been evaluated and approved by the SRC. The MAD cohorts may run in parallel with the remaining SAD cohorts. The tentative starting DR10624 dose (Cohort I) in Part 2 will be the same as the dose in Cohort D of the SAD. Final doses for each cohort in Part 2 will be determined by the SRC following a blinded review of the data from the previous cohort. Cohorts J, K, and L may titrate to the target dose by assessing tolerance in subjects who have completed their dosing. The final decision on the titration plan will be made by the SRC. Dose cohorts in Part 2 will be enrolled sequentially. Subsequent MAD cohorts at higher dose levels can be initiated after the safety, tolerability, and PK data from at least 8 subjects, who have received at least 6 doses of DR10624 or placebo, from the preceding MAD cohort have been reviewed and deemed safe and well tolerated by the SRC.

Part 2 will consist of a screening period (Days -42 to -3), check-in (Day -2 to -1), a treatment/follow-up period (Days 1 to 106), and an EOS visit (Day 106).

Subjects will receive active study drug or placebo once every week, on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78. For the study drug administration on Days 1 and 78, subjects will reside within the clinic from the evening of Days -2 to 2 (24 hours after dosing) and from the evening of Day 77 to Day 79 (24 hours after dosing), respectively. For study drug administration on Days 8 to 71, subjects will be dosed during outpatient visits and will be domiciled in the clinic for a minimum of 30 minutes postdose for safety monitoring and observation of injection site reactions. A standard mixed meal (470 kcal, ~66% carbohydrate, 18% fat, and 16% protein) will be served to all subjects in the MAD cohorts on Day -1, Day 28, and after PK sample collection on Day 79.

Serial blood samples for analysis of the multiple-dose PK of DR10624 will be collected as follows:

- Day 1 (first dose): predose and 4, 6 (Day 1), 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 (Day 7) hours postdose
- Day 78 (last dose): predose and 4, 6 (Day 78), 24 (Day 79), 48 (Day 80), 72 (Day 81), 96 (Day 82), 120 (Day 83), 144 (Day 84), 168 (Day 85), 336 (Day 92), 504 (Day 99), and 672 (Day 106) hours postdose

Additional predose blood samples (trough) will be collected on Days 8 (168 hours postdose Day 1), 15, 22, 29, 36, 43, 50, 57, 64, and 71.

Blood samples will be collected at the following time points to assess the impact of DR10624 on postprandial PD response following a standard 4-hour MMTT:

- Baseline samples (-30, -15, and -5 minutes) for PD biomarkers (glucose, C-peptide, insulin, and glucagon levels) will be collected premeal on Day -1, Day 28 and Day 79.

- Serial samples for PD biomarkers (glucose, C-peptide, insulin, and glucagon levels) will be collected at 10, 15, and 30 minutes, and at 1, 1.5, 2, 3, and 4 hours from the start time of the meal on Day -1, Day 28, and Day 79.

For baseline CGM, subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes at screening will be fitted with a blinded sensor during the 14-day prerandomization phase prior to check-in and up to predose on Day 1. If the day of dosing changes or any subjects have completed their CGM earlier than check-in and are within the screening window, then the subjects will be considered for admission and dosing. The subjects with a history of diabetes will be required to continue the recommended 2 or more blood glucose meter checks per day that they perform as standard of care during the blinded CGM run-in period prior to check-in. Additional blinded sensors configured to record glucose concentrations will be fitted from Day 22 to Day 36 and Day 71 to Day 85.

A glucometer will be provided to all subjects in Part 2. Subjects will routinely monitor fasting blood glucose at least twice weekly throughout the study period and will be counseled on identification and management of hypoglycemia and hyperglycemia.

Blood samples to assess fasting glucose will be collected from all subjects at screening, Day -1, and Day 78 during the in-clinic period and on Days 4, 8, 15, 22, 28, 36, 43, 50, 57, 81, 85, and 106 at outpatient visits. Blood samples to assess fasting insulin, C-peptide, and glucagon will be collected from all subjects at screening and on Days -1, 8, 15, 22, 28, 57, 78, and 85.

Blood samples for assessment of fasting lipid profile will be collected from all subjects at screening and on Days -1, 8, 15, 29, 57, 85, and 106 (EOS or at ET).

Blood samples for assessment of adiponectin will be collected from all subjects on Days -1, 29, 57, and Day 85.

In addition, blood samples to assess HbA1c will be collected at screening and Days -1, 29, 57, and Day 85.

Blood samples to be collected on Day -1, Day 57, and Day 85 for safety assessments will be used to calculate NFS and FIB-4 based on the following formula:

$$\text{FIB-4} = \text{Age} \times \text{AST/platelet (PLT) count} \times \sqrt{\text{ALT}}$$

$$\text{NFS} = -1.675 + 0.037 \times \text{age} + 0.094 \times \text{body mass index (BMI, kg/m}^2\text{)} + 1.13 \times \text{Impaired glucose tolerance or diabetes (Yes 1, No 0)} + 0.99 \times \text{aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio} - 0.013 \times \text{platelets (10}^9\text{/L)} - 0.66 \times \text{albumin (g/dL)}.$$

Immunogenicity serum samples for status of subject's ADA assessment (ie, ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer) will be collected from all subjects at:

- Predose on Days 1, 8, 29, and 78 or at ET (if applicable) or Day 106/EOS.

MRI-PDFF measurements will be performed at screening and between Day 85 to 99 in subjects receiving multiple SubQ doses of DR10624 or placebo. In subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes, the MRI-PDFF at screening will be

performed prior to the 14-day predose CGM measurements. If applicable, MRI-PDFF will be conducted at ET only if the subject has received ≥ 6 weeks of treatment with study drug. For subjects that early terminate, MRI-PDFF measurement will be arranged as soon as possible.

FibroScan measurements will be performed at screening and on Day 85 (a window of ± 2 days is allowed), or if applicable, at ET visit (only if the subject has received ≥ 6 weeks of treatment with study drug) in subjects with baseline hepatic fat of at least 8% measured by MRI-PDFF.

In Part 2, subjects will reside within the clinic from the evening of Day -2 until discharge on Day 2 (24 hours after dosing) and will return to the clinic on the evening of Day 77 until discharge on Day 79 (24 hours after Day 78 dosing). Subjects will return to the clinic on Days 3, 4, 5, 6, 7, 8, 15, 22, 28, 29, 36, 43, 50, 57, 64, 71, 80, 81, 82, 83, 84, 85, 92, 99 and 106 for outpatient visits. The duration of the study in Part 2, excluding screening, is approximately 108 days.

If a subject, who has received at least one dose of the study drug, withdraws from the study, the subject may be asked to complete necessary assessments listed in the protocol within 4 weeks after the last dose this subject receives.

Based on the observed half-life of DR10624 in Part 1 of the study, the PK blood collection points and visit points in Part 2 may be adjusted subject to the SRC's discretion.

Part 3 (Single-Ascending Dose in China)

Part 3 will employ an adaptive study design with 3 cohorts and approximately 36 healthy adult subjects or overweight or obese adults but otherwise healthy subjects; 12 subjects (10 active: 2 placebo) will be enrolled in each cohort (Cohorts M, N, O).

Provisional dose of these 3 cohorts in Part 3 may repeat dose levels of Cohort E, F, G, H, or P in Part 1. The tentative starting DR10624 dose (Cohort M) in Part 3 will be the same as the dose in Cohort E (25 mg) of Part 1 (SAD). The following doses for each cohort in Part 3 will be determined by the SRC following an evaluation of available safety and PK data for subjects in Part 1 and the safety and tolerability, and available PK data obtained through Day 15 of the preceding dose cohort of Part 3.

Part 3 will consist of a screening period (Days -28 to -2), check-in (Day -1), an in-clinic period/follow-up period (Days 1 to 29), and end-of-study (EOS) visit (Day 29).

DR10624 will be administered as a SubQ injection in the abdomen. Eligible subjects will be divided into 2 subgroups based on BMIs obtained at screening, a BMI ≥ 28 kg/m² subgroup and a BMI < 28 kg/m² subgroup. The number of subjects in both subgroups in each cohort should be equal. In each subgroup, subjects will receive either DR10624 or placebo in a 5:1 ratio. The highest DR10624 dose in Part 3 will not exceed the maximum tolerated dose reached in Part 1.

Blood samples for PK assessments will be collected at: predose and at 4 and 6 (Day 1), 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7), 168 (Day 8), 240 (Day 11), 336 (Day 15), 504 (Day 22), and 672 hours (Day 29) postdose. The PK blood collection points and visit points may be adjusted based on the results of Part 1.

Blood samples to assess safety will be collected from all subjects at screening, check-in, and Days 3, 5, 7, 15, and 29/EOS.

Immunogenicity serum samples for status of subject's ADA titer assessment (ie, ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer) will be collected from all subjects at:

- Predose on Day 1 and at follow-up visits on Days 8, 15, and 29/EOS or at ET (if applicable).

The serum sampling time points for the ADA titer assessment will be the same for all subjects dosed with either placebo or DR10624.

In Part 3, subjects will reside within the clinic from Day -1 until discharge on Day 7 (144 hours after dosing) and return to the clinic on Days 8, 11, 15, 22, and 29/EOS for outpatient visits. The duration of Part 3, excluding screening, is approximately 30 days.

STUDY POPULATION:

Inclusion Criteria:

Each subject must meet all the following criteria to be enrolled in this study:

1. The subject is considered by the investigator to be in good general health as determined by medical history, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings at screening.
2. Female subjects (heterosexually active, of childbearing potential, not pregnant, not trying to become pregnant, and not lactating) are eligible to participate if they agree to total abstinence from heterosexual intercourse or use a highly effective method of birth control listed below, from screening through until at least 30 days after the last dose of the study drug. Highly effective methods of contraception acceptable for use in this study include:
 - Implant contraceptive (eg, Jadelle)
 - Intra-uterine device (IUD) containing either copper or levonorgestrel (eg, Mirena)
 - Male partner of the female subject should be sterilized (vasectomy)
 - Female sterilization (eg, by bilateral tubal ligation ['tying tubes'] or hysterectomy)

A second non-hormonal (barrier) method of contraception is required if a user dependent hormonal form of birth control is used:

- Injectable contraceptive (eg, Depo-Provera)
- Oral contraceptive pill (combined hormonal pill or progestogen-only pill)
- Vaginal contraceptive ring (eg, NuvaRing)

Barrier methods of birth control acceptable for this study include:

- Male condom
- Female condom
- Female diaphragm

Please note that barrier methods on their own are NOT highly effective methods of birth control. Females of childbearing potential must have negative pregnancy tests results at screening and check-in. Female subjects must refrain from egg donation throughout study and for 30 days after the last dose. Females who are postmenopausal (age-related amenorrhea for ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] ≥ 40 mIU/mL) or who have undergone permanent sterilization (hysterectomy, total bilateral salpingectomy, and bilateral oophorectomy [more than 3 months prior to check-in]) do not need to use any methods of contraception.

Male subjects with female partners of childbearing potential are eligible to participate if they are vasectomized, or agree to total abstinence from heterosexual intercourse, from screening through until at least 30 days after the last study dose, or use of an effective method of birth control listed above, from screening through until at least 30 days after the last study dose. Male subjects must refrain from sperm donation throughout the study and for 30 days after the last study dose.

3. The subject agrees to comply with all protocol requirements.
4. The subject is able to provide written informed consent.

Additional inclusion criteria for in Part 1, Cohorts A, B, C, D, E, F, G, H, and P:

1. The subject is male or female 18 to 55 years of age, inclusive.
2. The subject has a body weight ≥ 50 kg at screening and a BMI of 18 to 32 kg/m², inclusive, at screening in Cohort A, B, C, D, E, and F or

The subject has a BMI of 30 to 40 kg/m², inclusive, at screening in Cohorts G, H and P.

Additional inclusion criteria for Part 2 (Cohorts I, J, K, and L):

1. The subject is male or female 18 to 70 years of age, inclusive.
2. The subject has a BMI of 30 to 45 kg/m² at screening, inclusive.
3. Fasting triglyceride ≥ 150 mg/dL (1.7 mmol/L), and < 500 mg/dL (5.7 mmol/L), at screening. Fasting triglyceride may be repeated up to two times after 1 week if the initial results do not fall within the desired range.

Additional inclusion criteria for Part 3, Cohorts M, N, and O:

1. The subject is male or female 18 to 55 years of age, inclusive.
2. The subject has a body weight ≥ 50 kg for males and ≥ 45 kg for females at screening and a BMI of 19 to 40 kg/m², inclusive, at screening.

Exclusion Criteria:

Subjects meeting any of the following criteria will be excluded from the study:

1. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus types 1 or 2 antibodies at screening.
2. The subject has a personal or family history of medullary thyroid cancer, or multiple endocrine neoplasia syndrome Type 2, or a screening calcitonin ≥ 50 ng/L.
3. The subject has a history of chronic pancreatitis or episode of acute pancreatitis within 3 months of screening.
4. In Part 1 and Part 3, the subject has used any prescription medications (excluding oral contraceptives, paracetamol, and ibuprofen) within 14 days before the dose of study drug.

In Part 2 only, the subjects have been on stable lipid-lowering therapy or nutritional supplements that contains fish oil (or Omega-3 fatty acids) less than 8 weeks before the first dose of study drug.

5. The subject has consumed alcohol within 48 hours before dosing or during the confinement period.
6. The subject is a smoker or has used tobacco, nicotine, or nicotine-containing products (eg, snuff, nicotine patch, nicotine chewing gum, mock cigarettes, or inhalers) from start of the confinement period until after EOS. Subjects in Part 2 must be able to abstain from nicotine use during the inpatient periods of the study.
7. The subject has a history of alcohol abuse or drug addiction within the last year or excessive alcohol consumption (regular alcohol intake >21 units per week for male subjects and >14 units of alcohol per week for female subjects) (1 unit is equal to approximately ½ pint [200 mL] of beer, 1 small glass [100 mL] of wine, or 1 measure [25 mL] of spirits).
8. The subject has a positive test result for drugs of abuse and/or alcohol abuse at screening and check-in for the first inpatient period.
9. The subject is involved in strenuous activity or contact sports within 48 hours before admission.
10. The subject has donated blood or blood products >450 mL within 30 days before the first dose of study drug.
11. The subject has total cholesterol >10.3 mmol/L or triglycerides ≥5.7 mmol/L (500 mg/dL) at screening.
12. The subject has clinically significant history or presence of ECG findings as determined by the investigator at screening and check-in, including any of the following:
 - Abnormal sinus rhythm (heart rate <45 bpm and >100 bpm)
 - Risk factors for torsades de pointes (eg, heart failure, cardiomyopathy, or family history of long QT syndrome)
 - Sick sinus syndrome, second- or third-degree atrioventricular block myocardial infarction, pulmonary congestion, cardiac arrhythmia, prolonged QT interval, or conduction abnormalities
 - QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 msec (male subjects) or >470 msec (female subjects)
 - QRS interval >110 msec
 - PR interval <120 or >220 msec

In the event a value is outside of the reference range, this will be confirmed by 2 further repeat measurements, which will then be calculated as a mean of the original value and the 2 repeat measurements.

 - Repeated or frequent syncope or vasovagal episodes
 - Uncontrolled hypertension (defined as SBP ≥160mmHg, and/or DBP ≥100mmHg), angina, bradycardia (if assessed as clinically significant by the investigator), or severe peripheral arterial circulatory disorders

13. The subject has a history of relevant drug and/or food allergies (ie, allergy to DR10624 or excipients, or any significant food allergy that could preclude a standard diet in the clinical unit).
14. The subject has a history of severe allergic or anaphylactic reactions.
15. The subject has experienced a >5% loss in body weight within 2 months prior to screening.
16. Female subjects who are pregnant or lactating.
17. The subject has a positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A positive rapid antigen test (RAT), isothermal nucleic acid amplification, or polymerase chain reaction (PCR) coronavirus disease 2019 (COVID-19) test during screening or at admission is acceptable provided the subject has a known previous COVID-19 infection ≥ 3 weeks prior to dosing, has recovered, and is now asymptomatic.
18. The subject has received study drug in another investigational study within 30 days of dosing.
19. In the opinion of the investigator, the subject is not suitable for entry into the study.

Additional exclusion criteria for subjects in Part 2:

1. Subjects with coagulopathies
2. Poorly controlled diabetes, defined as HbA1c >8.5% at screening.
3. The subject has been treated with the following anti-diabetic agents, GLP-1Ra, dipeptidyl peptidase-4 inhibitors (DPP-4i), or insulin, within 30 days prior to screening until the follow-up visit.
4. The subjects with diagnosed diabetes have been on stable anti-diabetic therapies for less than 8 weeks prior to the first dose of study drug. The subjects have $>2 \times$ upper limit of normal (ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or $>1.5 \times$ ULN for bilirubin or alkaline phosphatase at screening.
5. Subjects with contraindications to MRI.

MRI contraindications include, but are not limited to:

- Brain aneurysm clip.
- Implanted neural stimulator.
- Implanted cardiac pacemaker or defibrillator, or presence of intracardiac wires.
- Prosthetic heart valves.
- Cochlear implant.
- Ocular foreign bodies that might be ferromagnetic (eg, metal shavings).
- Other implanted medical devices (eg, insulin pumps).
- Metal shrapnel or bullets still in the body.
- Severe claustrophobia.
- Subjects having difficulty tolerating prolonged positioning within the constraints of the MRI tube. Investigators should use their best judgment to assure that subjects' size will not interfere with MRI imaging at any of the specified time points.
- Tattoos (as determined by the investigator and imager).

STUDY TREATMENTS:

Part 1: DR10624; single SubQ doses. The starting DR10624 dose in Part 1 will be 0.5 mg SubQ (Cohort A). The provisional doses in Cohorts B, C, D, E, F, G, H, and P are planned to be 1.5, 4.5, 12.5, 25, 50, 65, 90, and 120 mg SubQ, respectively, with final doses for each cohort determined by the SRC following a full review of the safety, tolerability, and PK data from the previous cohort. The dose levels may be adjusted by the SRC.

Part 2: DR10624; multiple SubQ doses of once every week (Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78) for a total of 12 doses. The tentative starting DR10624 dose (Cohort I) in Part 2 will be the same as the dose in Cohort D of Part 1 (SAD). Final doses for each cohort will be determined by the SRC following a blinded review of the data from the previous cohort.

Part 3: DR10624; single SubQ doses. The provisional dose of 3 cohorts in this part may repeat dose levels of Cohort E, F, G, H, or P in Part 1. The tentative starting DR10624 dose (Cohort M) in Part 3 will be the same as the dose in Cohort E (25 mg) of Part 1 (SAD). The following doses for each cohort in Part 3 will be determined by the SRC following an evaluation of available safety, tolerability, and PK data for subjects in Part 1 and the safety data and available PK data obtained through Day 15 of the preceding dose cohort of Part 3. The highest DR10624 dose in Part 3 will not exceed the maximum tolerated dose reached in Part 1.

SubQ placebo vehicle will be used for placebo administration.

STUDY PROCEDURES:

Pharmacokinetic Assessments and Endpoints:

Blood samples for PK analysis of DR10624 will be collected in all parts of the study. The single- and multiple-dose PK parameters will be calculated as endpoints for DR10624 using actual sampling times rather than scheduled sampling times.

The following serum PK parameters will be calculated as primary PK endpoints, but are not limited to:

- Part 1, and Part 3:
 - Area under the serum concentration versus time curve (AUC) from time 0 to the last quantifiable concentration (AUC_{0-t})
 - AUC from time 0 extrapolated to infinity (AUC_{0-inf})
 - Maximum observed serum concentration (C_{max})
 - Time to reach maximum observed serum concentration (T_{max})
 - Terminal elimination half-life ($t_{1/2}$)
 - Mean residence time (MRT)
 - Apparent clearance after extravascular administration (CL/F)
 - Apparent volume of distribution during the terminal elimination phase after extravascular administration (V_z/F)
- Part 2, Day 1:

- AUC from time 0 to the time of the dosing interval (τ ; $AUC_{0-\tau}$)
- C_{max}
- T_{max}
- Part 2, Day 78:
 - $AUC_{0-\tau}$ at steady state ($AUC_{0-\tau,ss}$)
 - C_{max} at steady state ($C_{max,ss}$)
 - AUC_{0-t}
 - T_{max}
 - $t_{1/2}$
 - Accumulation ratio (AR), calculated as $AUC_{0-\tau}$ (Day 78) / $AUC_{0-\tau}$ (Day 1)
 - Predose concentrations on Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and concentration on Day 78 (C_{trough})
 - Systemic apparent clearance at steady state (CL/F_{ss})
 - Steady-state apparent volume of distribution (V_z/F_{ss})

Dose normalized AUCs and C_{max} and other additional PK parameters will be estimated to support the primary PK endpoints.

Pharmacodynamic Assessments and Endpoints:

Pharmacodynamic endpoints will be measured for Part 2 (MAD) cohorts only. The following PD endpoints will be assessed:

- Mean and percent change in body weight and adiponectin at protocol-specified time points from baseline through Day 85/end-of-treatment period (EOT)
- Mean change in BMI and, waist circumference at protocol-specified time points from baseline through Day 85/EOT
- Mean and percent change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, Lp(a), VLDL cholesterol, triglycerides, and free fatty acids) at protocol-specified time points from baseline through Day 85/EOT
- Mean and percent change in FPG from baseline through Day 85/EOT; mean change in HbA1c, C-peptide, fasting insulin, and glucagon; and HOMA-IR (calculated by $\text{fasting insulin } [\mu\text{U/mL}] \times \text{FPG } [\text{mmol/L}] / 22.5$) and HOMA-B (calculated by $20 \times \text{fasting insulin } [\mu\text{U/mL}] / (\text{FPG } [\text{mmol/L}] - 3.5)$) at protocol specified time points from baseline through Day 85/EOT
- The following PD response parameters will be calculated as endpoints using the standard 4-hour MMTT:
 - Partial area under the baseline-corrected glucose, C-peptide, insulin, and glucagon levels versus time curve from time 0 to 4 hours (ΔAUC_{0-4h}) post meal on Day -1, Day 28, and Day 79.

- Mean change in TIR, TAR, TBR, 24-hour mean glucose, and glucose variability (coefficient of variation [CV]) at protocol-specified time points from baseline through Day 85 in subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes at screening.
- Percent change from baseline in hepatic fat fraction measured by MRI-PDFF for the MAD cohorts and in a prespecified subgroup with MRI-PDFF $\geq 8\%$.
- Change from baseline in liver stiffness by FibroScan in subjects with baseline hepatic fat of at least 8% measured by MRI-PDFF.
- Change in the liver function parameters (ALT, AST, alkaline phosphatase [ALP], and gamma-glutamyl transferase [GGT]) at protocol-specified time points from baseline through Day 85
- Change in FIB-4 and NFS at protocol-specified time points from baseline through Day 85.

If relevant, population PK and PK/PD modeling will be used to evaluate drug exposure and exposure-response relationship for various PD endpoints.

Safety Assessments and Endpoints:

Safety and tolerability will be assessed by the following endpoints: monitoring and recording of AEs (including serious AEs [SAEs], AESIs), clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), serum calcitonin (Part 2 only), vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature), 12-lead ECG results, and physical examination findings.

Immunogenicity Assessments and Endpoints:

Blood samples for immunogenicity analysis of DR10624 will be collected in all parts of the study. Immunogenicity will be assessed as incidence of ADAs and titer of positive ADAs.

STATISTICAL ANALYSIS PLANS:

Sample Size:

The number of subjects at each part/cohort is based on clinical and practical considerations and not on statistical hypotheses. Approximately 152 subjects are planned for the study.

Analysis Sets:

The safety analysis set will include all subjects who receive at least 1 dose of DR10624 or placebo.

The PK analysis set will include subjects who receive at least 1 dose of DR10624 and have sufficient concentration data to support accurate estimation of at least 1 PK parameter.

The PD analysis set will include subjects who receive at least 1 dose of DR10624 or placebo and have baseline and at least 1 PD measurement at postbaseline.

The immunogenicity analysis set will consist of all subjects who receive at least 1 dose of DR10624 and have baseline and at least 1 postbaseline sample ADA assessment.

Data from subjects receiving placebo in each cohort of the same part will be pooled into 1 placebo group for analysis in each part.

Pharmacokinetic Analyses:

Serum concentration data will be listed and summarized by scheduled time point for each treatment and cohort within each part of the study separately using descriptive statistics (number of subjects, mean, standard deviation [SD], CV, median, minimum, and maximum). Serum concentration versus time profiles for each subject will be presented graphically. The mean serum concentrations versus scheduled time profiles will be presented graphically by treatment and cohort within each part of the study separately.

The PK parameters of DR10624 will be analyzed based on the actual sampling times. Pharmacokinetic parameters derived from serum samples using noncompartmental methods with Phoenix® WinNonlin® Version 8.3 or higher (Certara USA Inc., Princeton, New Jersey) or SAS® Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina). Geometric means and geometric mean CV will be reported for all PK parameters except for T_{max} .

For Part 3, the effect of BMI ($BMI \geq 28 \text{ kg/m}^2$ subgroup vs $BMI < 28 \text{ kg/m}^2$ subgroup) on DR10624 PK profiles may be explored.

Plots of dose-normalized AUCs and C_{max} versus dose will be presented for each of the 3 parts separately. Dose proportionality will be tested for each of the 3 parts separately using the power regression model for AUCs and C_{max} . The model is defined as:

$$\ln[\text{PK parameter}] = \beta_0 + \beta_1 \ln[\text{dose}]$$

where the PK parameter is AUC or C_{max} . The null hypothesis being tested is that the AUCs and C_{max} values are dose proportional, or slope (β_1) = 1 and within 90% CI of the slope.

Mean trough (predose) concentrations plots in Part 2 will be provided by treatment and cohort to visually assess steady state.

Steady state will be tested in Part 2 by regression analysis of trough level concentrations of individual subjects from samples collected on Days 8 through 78. The model to be used to estimate the slope and corresponding 90% CI is:

$$C_{\text{trough}} = \beta_0 + \beta_1(\text{day} + \text{error})$$

Statistical evidence that the subject has not achieved steady state will be found if the slope is positive and significantly different from 0 at the 5% level.

The relationship between immunogenicity status (ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer) and serum drug concentration and PK parameters may be explored. All data will be provided by subject listings.

Pharmacodynamic Analyses:

The pharmacodynamics variables in Part 2 (Weight, BMI, waist circumference, adiponectin, total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, Lp[a], VLDL cholesterol, triglycerides, free fatty acids, FPG, HbA1c, C-peptide, fasting insulin, glucagon, HOMA-IR, HOMA-B, NFS, FIB-4, liver enzymes [ALT, AST, ALP, and GGT], hepatic fat fraction, and liver stiffness) will be analyzed using the mixed model repeated measures (MMRM), with Least-squares (LS) mean difference provided for each dose vs placebo together with p-values. Details will be provided in the Statistical Analysis Plan (SAP). For PD response parameters calculated using a noncompartmental method (ΔAUC_{0-4h} in glucose,

C-peptide, insulin, and glucagon levels) on the original scale will be analyzed using statistical modeling for repeated measurements for MAD cohorts.

Baseline CGM-measured outcomes will be calculated for all obese subjects with modest hypertriglyceridemia, who have abnormal blood glucose, elevated HbA1c, or a history of diabetes at screening, using the blinded sensor data collected during the 14-day prerandomization phase prior to check-in and up to predose on Day 1. If the day of dosing changes or any subjects have completed their CGM earlier than check-in and are within the screening window, then the subjects will be considered for admission and dosing.

Multiple-dose CGM-measured outcomes will be calculated postdose on Days 22 to 36 and on Days 71 to 85/EOT. The CGM outcome measures will include percentage of time spent in target range 3.9 to 10.0 mmol/L, 24-hour mean glucose, glucose variability (CV), time in hyperglycemic (>10.0 mmol/L, >13.9 mmol/L, >16.7 mmol/L), and hypoglycemic (<3.9 mmol/L, <3.3 mmol/L, <3.0 mmol/L) ranges, and rate of hypoglycemic events per week (overall and nighttime event rates).

The percent change from baseline in hepatic fat fraction measured by MRI-PDFF and in a prespecified subgroup with MRI-PDFF $\geq 8\%$ will be listed and summarized by treatment for the MAD cohorts using descriptive statistics.

The actual values and changes from baseline in liver stiffness measured by FibroScan in subjects with baseline hepatic fat of at least $\geq 8\%$ measured by MRI-PDFF will be listed and summarized by treatment and time points for the Part 2 (MAD) cohorts using descriptive statistics.

Actual values and changes from baseline in ALT, AST, ALP and GGT will be listed and summarized by time point and treatment for the MAD cohorts using descriptive statistics.

Actual values and changes from baseline in FIB-4 and NFS will be listed and summarized by time point and treatment for the MAD cohorts using descriptive statistics.

Satiety in the VAS will be summarized by treatment and time at 0-hour (premeal), 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, and 6-hour from the start time of the meal during every MMTT.

Safety Analyses:

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by treatment, each part, and overall. All AE data will be presented in a data listing.

Treatment-emergent AEs will be summarized by treatment and overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to early discontinuation will also be presented in data listings.

Number of confirmed treatment-emergent hypoglycemic events will be summarized by treatment and overall. All AESIs will be presented in a data listing.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings will be presented in data listings.

The Holter results in Part 1, actual values and changes from baseline will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated and presented in data listings.

Proportion of subjects with positive or negative for ADAs will be summarized in a frequency table by treatment and by visit. For subjects with positive result for ADA, the titer values of ADAs will be summarized by treatment and by visit. Antidrug antibodies will be presented in data listings. Below ADAs categories will be summarized:

- Anti-DR10624 antibody
- Anti-DR10624 antibody with in vitro neutralizing effect (NADA)

DATE OF PROTOCOL: 01 Oct 2023

1. INTRODUCTION

1.1 BACKGROUND

Conventional chemicals (eg, sulfonylureas and thiazolidinediones) have been used to treat type 2 diabetes mellitus (T2D), with obvious hypoglycemic effects. However, one of the issues with the medications is they also cause weight gain. Several glucagon-like peptide-1 receptor (GLP-1R) agonists, such as exenatide (Byetta[®]), dulaglutide (Trulicity[®]), liraglutide (SAXENDA[®] and Victoza[®]), and semaglutide (Ozempic[®]), have a significant hypoglycemic effect and are widely used for the treatment of diabetes and obesity. Unlike insulin, the hypoglycemic effect of these GLP-1R agonists is strictly blood glucose-dependent, does not easily cause hypoglycemia, and reduces body weight (Nauck et al 2021). However, these drugs also cause side effects, mainly affecting the gastrointestinal tract (eg, nausea), and the weight loss is modest (ie, 5-10%) (Brandt et al 2018). Bariatric surgery is an alternative treatment that can significantly improve the metabolic outcomes of patients with obesity and diabetes. However, it is not widely used because most patients are unwilling to undergo such surgery due to surgical risks and long-term sequelae (Boettcher 2017). So far, both GLP-1R agonists and bariatric surgery rely on the physiological functions of important gastrointestinal hormones in the body (eg, glucagon-like peptide-1 [GLP-1], oxyntomodulin, fibroblast growth factor 19, and glucagon [GCG]), which regulate the secretion of pancreatic enzymes, insulin, and pancreatic polypeptide (Seeley et al 2015). Given the unmet medical need in the clinic, there is a great demand for safe, potent, and cost-effective therapeutics to treat metabolism diseases. The latest diabetes medications focusing on gut hormone poly-agonists are gradually showing superiority.

The analogs of GCG, GLP-1, and gastric inhibitory peptide (GIP) are commonly investigated incretins in preclinical or clinical studies for treating T2D. Glucagon and GLP-1 are enteric hormones derived from the processing of proglucagon in the body that oppose each other to control blood glucose. Glucagon has been demonstrated to increase blood glucose, whereas GLP-1 lowers blood glucose. Gastric inhibitory peptide is a physiological incretin hormone that lowers blood glucose by stimulating insulin secretion and suppressing gastric acid secretion (Brandt et al 2018). The GIP also protects bone marrow from bone hyperplasia. Besides, GCG can reduce body weight by increasing energy expenditure and inducing thermogenesis, while GLP-1 can lower body weight by reducing food intake and inhibiting appetite. Glucagon also has a lipid-lowering effect. Studies of poly-agonists are mainly focused on GLP-1R/glucagon receptor (GCGR), GLP-1R/GIP receptor (GIPR) dual agonists, and GLP-1R/GCGR/GIPR tri-agonists (Kleinert et al 2017). Studies have shown that these

agonists have synergistic physiological effects and have superior effects compared to any single agonist ([Finan et al 2015](#)).

Fibroblast growth factor 21 (FGF21) is an endocrine hormone that plays an important role in bile acid metabolism, energy consumption, and maintenance of glucose, lipid, vitamin D, and phosphate homeostasis. The FGF21 also reduces blood glucose and lipid content by improving insulin sensitivity and increasing energy consumption and fat decomposition. Although the hypoglycemic effect of FGF21 receptor (FGF21R) agonists has not been fully validated in clinical studies so far, these clinical studies confirmed the effect of recombinant FGF21 on improving lipid metabolism and reducing body weight. At least 7 different FGF21-class molecules have been tested in various stages of clinical studies, including Efruxifermin (AKR-001), BIO89-100, BMS-986036, BMS986171, RG7992, MK-3655, and NGM282. All these studies demonstrated that FGF21R agonists positively affect metabolic and cardiovascular diseases because of their strong lipid-lowering activity ([Sonoda et al 2017](#)).

In patients with T2D, hyperglycemia is often accompanied by dyslipidemia. In light of the potential lipid-lowering effects of FGF21, the sponsor proposes that by combining GLP-1R, GCGR, and FGF21R agonist activity, it will be possible to develop a multifunctional drug that is more effective at reducing blood glucose, weight, and fat compared to currently available options. DR10624, a GLP-1R/GCGR/FGF21R tri-agonist, has the potential to be such an agent.

1.1.1 Overview of DR10624

DR10624 is a GLP-1R/GCGR/FGF21R tri-agonist that has demonstrated in vivo efficacy in preclinical models of diet-induced obesity and T2D. It has a molecular weight of 101819.6 Daltons and is soluble in an aqueous solution. The development of DR10624 addresses an unmet medical need: regulating blood glucose homeostasis and lowering body weight in T2D patients. Additional indications, such as obesity and nonalcoholic steatohepatitis (NASH), are also being prospected.

Expressed by Chinese hamster ovary cells, DR10624 is a recombinant fusion protein consisting of a GLP-1/GCG chimeric peptide, which acts as a dual agonist on GLP-1R and GCGR, fused to the N-terminus of the fragment crystallizable of human immunoglobulin G subclass1 (hIgG1-Fc), and a recombinant human FGF21 mutant, which acts as an agonist on FGF21R, fused to the C-terminus. DR10624 is composed of 956 L-amino acids consisting of

2 identical single strands with each strand of 478 amino acids. The amino acid sequence is shown in [Figure 1-1](#).

Figure 1-1 Amino Acid Sequence of DR10624

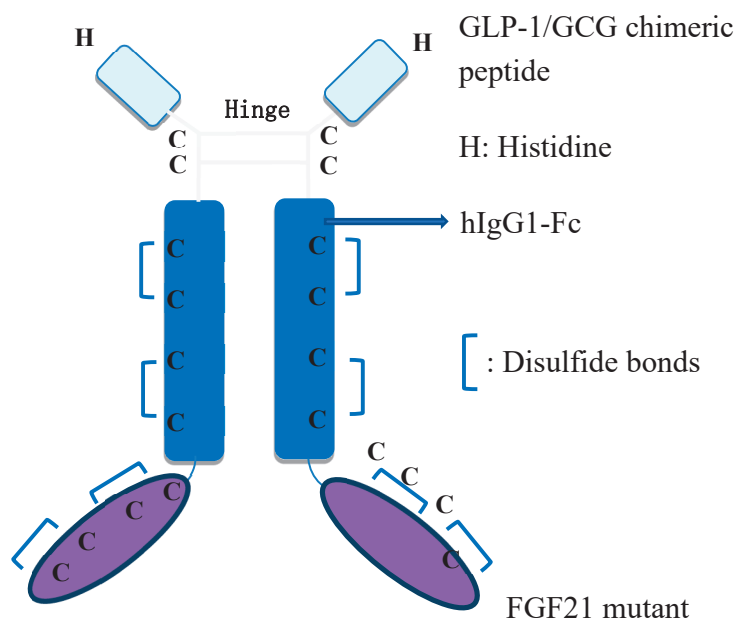
* Note: intra-chain disulfide bond pair sites are connected by lines

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HSQGTFTSDYSKYLDSQAAQDFVQWLLAGGPSSGAPPPSGGGGSGGGGSGGG
GSADKTHTC61PPC64PAPELLGGPSVFLFPPKPKDTLMISRTPEVTC96VVVDVSHE
DPEVKFNWYVDGVEVHNAKTKPREEQYASTYRVVSVLTVLHQDWLNGKEYK
C156KVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLT202LVKGF
YPSDIAVEWESNGQPENNYKTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFS2
60SVMHEALHNHYTQKSLSLSPGAGGGGAGGGGAGGGGAHPIPDSSPLLQFGGQ
VRQRYLYTDDAQQTEAHLEIREDTVGGAADQSPESLLQLKALKPGVIQILGV
KTSRFLC372QRPDGYGSLHFDPEAC390SFRERLLEDGYNVYQSEAHGLPLHC41
5PGNKSPHRDPAPRGPC431RFLPLPGLPPALPEPPGILAPQPPDVGSSDPLSMVGGG
QGRSPSYES
  
```

The higher-order structure is held together with 2 pairs of inter-chain and 8 pairs of intra-chain disulfide bonds. DR10624 consists of 3 regions: a GLP-1/GCG chimeric peptide, an aglycosylated hIgG1-Fc region, and an FGF21 mutant region ([Figure 1-2](#)).

Figure 1-2 Structure Chart of DR10624



Further information on DR10624 can be found in the investigator's brochure ([Zhejiang Doer Biologics Co., LTD. 2023](#)).

1.1.2 Non-Clinical Studies

Pharmacology studies have been conducted by Zhejiang Doer Biologics to examine the potential of DR10624 to activate the GLP-1R, GCGR, and FGF21R in vitro and regulate glucose homeostasis activity in vivo in rodent models with T2D or obesity. The results demonstrated that DR10624 showed comparable tri-agonist activities on the corresponding receptors in different species, such as human, mouse, rat, and cynomolgus monkey; dose-dependently reduced the blood glucose levels and area under the concentration-time curve (AUC)_{0-120min Glu} after a single subcutaneous (SubQ) injection of DR10624 following an oral glucose tolerance test (OGTT) in normal mice; significantly decreased the non-fasting and fasting blood glucose levels, and reduced the blood glucose levels and AUC_{0-120min Glu} after a single SC injection of DR10624 following an OGTT in T2D *db/db* mice; significantly decreased the non-fasting and fasting blood glucose and glycated hemoglobin (HbA1c) levels, reduced food intake, inhibited body weight gain, decreased fat mass and hepatic triglyceride content, improved the whole-body insulin sensitivity and islet β -cells function, and ameliorated the lipid metabolism disorders in T2D *ob/ob* mice; and significantly reduced body weight and fasting blood glucose, first causing a decrease and then an increase in food intake, and ameliorated lipid metabolism disorders and liver function damage in mice with high-fat-diet-induced obesity. Therefore, DR10624 showed a significant preclinical therapeutic effect on T2D, obesity, and hypertriglyceridemia.

Pharmacokinetics (PK) studies of DR10624 formulated as a solution for SubQ injection were conducted. Single-dose PK of DR10624 were evaluated at doses of 0.5 mg/kg, 1 mg/kg, and 3 mg/kg in Sprague-Dawley rats and at doses of 0.1 mg/kg, 0.3 mg/kg, and 1 mg/kg in cynomolgus monkeys. In Sprague-Dawley rats, $t_{1/2}$ of the dose groups ranged from 14.7 hours to 23.6 hours, time to reach maximum observed serum concentration (T_{max}) was 24.0 hours, and exposure levels were higher in females than males. In cynomolgus monkeys, $t_{1/2}$ of the dose groups ranged from 46.0 hours to 49.7 hours, T_{max} ranged from 40.0 hours to 48.0 hours, C_{max} generally increased in a dose proportional manner, and AUC_{0-504h} increased at a higher proportion than dose. Antidrug antibodies (ADAs) were detected in all dose groups in cynomolgus monkeys. There was no significant gender-specific difference in the major PK parameters for monkeys.

The toxicity profile of DR10624 was evaluated in GLP studies in rats and monkeys. A single dose of up to 30 mg/kg was generally well tolerated in rats or monkeys. Observed major

findings such as reduced body weight and food intake showed recovery and could be related to the pharmacological action of DR10624. Repeat-dose toxicology was evaluated by SubQ administration of DR10624 once weekly for 4 weeks at doses of 1, 3, and 10 mg/kg or for 13 weeks at doses of 0.5, 1, and 3 mg/kg in Sprague-Dawley rats and for 4 weeks at doses of 2, 6, and 20 mg/kg or for 13 weeks at 0.5, 1, and 3 mg/kg in cynomolgus monkeys. All animals survived until the planned necropsy. The observed changes in hematology, serum biochemistry, and histopathology showed a recovery or recovery trend during the 4-week or 13-week recovery period. In both species, dose levels were limited by pharmacologically mediated reductions in food intake and body weight. In the 13-week repeat-dose toxicology study, the no-observed-adverse-effect level (NOAEL) was determined to be 3 mg/kg in rats (on Day 85 for males, C_{max} was 5446 ± 883 ng/mL and AUC_{0-168h} was 298164 ± 70976 h·ng/mL; For females, C_{max} : 9546 ± 1534 ng/mL and AUC_{0-168h} was 648072 ± 118104 h·ng/mL); and the NOAEL was considered to be 3 mg/kg in monkeys (C_{max} was 23.0 ± 16.8 µg/mL, and AUC_{0-168h} was 2613 ± 1842 h·µg/mL on Day 85).

1.1.3 Clinical Studies

No clinical studies with DR10624 have been completed to date.

1.2 RATIONALE FOR STUDY

DR10624 is an Fc fusion protein tri-agonist with balanced GLP-1R/GCGR/FGF21R agonist activities that complement each other in regulating blood glucose and weight. The GLP-1R agonist activity lowers blood glucose, GCGR agonist activity reduces body weight by increasing energy consumption, and FGF21R agonist activity reduces blood glucose and lipid content. The development of DR10624 addresses an unmet medical need. Additional indications, such as obesity and NASH, are also being considered.

The objectives of the planned clinical investigation will be to evaluate the safety, tolerability, PK, and pharmacodynamics (PD) of single- and multiple-ascending SubQ doses of DR10624 via SubQ injection in a randomized, placebo-controlled, double-blind study. The design and choice of the study population of the planned first-in-human (FIH) clinical Phase 1 study is based on the need to provide initial safety, tolerability, PK, and PD outcomes of DR10624 for future clinical studies. Analysis of serum concentrations from this study will characterize the single- and multiple-dose PK of DR10624 and help to refine the dosing strategy for subsequent Phase 2 multiple-dose studies.

1.2.1 Selection of Study Design

This FIH study employs a seamless and integrated 3-part design, consisting of a single-ascending dose (SAD) part (Part 1) in healthy subjects or overweight to obese adults but otherwise healthy subjects, a multiple-ascending dose (MAD) part (Part 2) in obese adult subjects with modest hypertriglyceridemia, and an SAD part (Part 3) in Chinese healthy adult subjects or overweight or obese adults but otherwise healthy subjects.

This study design allows the safety, tolerability, PK, and PD data to be gathered in a stepwise fashion. The inclusion of obese subjects with modest hypertriglyceridemia will serve to determine target engagement by DR10624 by evaluating its effect on key biomarkers.

Sentinel dosing will be employed in all SAD cohorts (Part 1), except Cohort A, whereby the first 2 subjects (1 active and 1 placebo) will be dosed at least 72 hours before the remaining subjects at that level are dosed. Initiation of dosing of the remaining 6 subjects will depend on an initial safety review (eg, adverse events [AEs], clinical laboratory results, vital signs, electrocardiograms [ECGs], from the preceding 72 hours) by the investigator indicating that administration of the study drug was safe and well tolerated in the sentinel subjects. Cohort A will only have single sentinel subject on active and no placebo subjects and will have the remaining 3 active subjects dosed after 72 hours as above.

In Parts 1 and 2, a higher dose level will not be initiated until adequate information in the preceding dose level is available and reviewed. These parts will also employ strict dose escalation and cohort stopping criteria. Dosing in Part 2 will be permitted only after the blinded safety data through Day 29/end-of-study (EOS) after completing the dosing in the last subject in Cohort E in Part 1 have been evaluated and approved by the safety review committee (SRC).

An overlap of Part 1/SAD and Part 2/MAD is proposed to allow for the generation of safety, tolerability, PK, and PD data for multiple doses of DR10624 while the higher single dose cohorts generate the single-dose safety, tolerability, and PK data at higher dose levels. It is expected that the Part 1/SAD end of highest dose cohort review will have been completed or will coincide with the first Part 2/MAD cohort review, allowing for dose/regimen review and adjustment based on the single-dose data generated covering the anticipated therapeutic dose range.

Cohort management (recruitment, dose escalation, moving from SAD to MAD, stopping and expansion/modification rules) will be governed by an SRC consisting of the sponsor's medical officer or designee, the sponsor's clinical pharmacology representative or designee

(if applicable), the sponsor's study statistician or designee (if applicable), the investigator, the treating physicians (if applicable), the medical monitor, and other applicable functions as nominated by the SRC chair, appointed by the sponsor. ([Section 3](#)).

In Part 3, eligible subjects will receive either DR10624 or placebo in a 5:1 ratio. The tentative starting DR10624 dose (Cohort M) in Part 3 will be the same as the dose in Cohort E (25mg) of the Part 1 (SAD). The following doses for each cohort in Part 3 will be determined by the SRC following an evaluation of available safety, tolerability, and PK data for subjects in Part 1 and the safety and available PK data obtained through Day 15 of the preceding dose cohort of Part 3. The highest DR10624 dose in Part 3 will not exceed the maximum tolerated dose reached in Part 1.

This study design is in line with current regulatory guidance and is appropriate for the objectives of the study.

1.3 RATIONALE FOR SELECTED FIRST DOSE LEVEL OF DR10624

As DR10624 demonstrated tri-agonist activities on the corresponding receptors of humans, rats and cynomolgus monkeys, both animal models could be used to determine a human equivalent dose (HED). Human data using GLP-1, GCG and/or FGF21R agonist does not show high risk of hypoglycemia nor cytokine release, the starting dose for the initial Phase 1 studies in healthy subjects is generally established based on the results of toxicology studies in rodent and non-rodent species using a route and schedule of administration similar to those considered for Phase 1 studies.

The repeat-dose toxicology studies of DR10624 given once weekly by SC injection up for 13 weeks with 6-week recovery were carried on rats and cynomolgus monkeys. In the 4-week repeat-dose toxicology study, the no-observed-adverse-effect level was determined to be 1 mg/kg, and the maximum tolerated dose (MTD) to be 10 mg/kg in rats, and the NOAEL was determined to be 2 mg/kg and MTD to be 20 mg/kg in monkeys. In the 13-week repeat-dose toxicology study, the NOAEL was determined to be 3 mg/kg (on Day 85 for males, $C_{\max}$ was 5446 ± 883 ng/mL and AUC_{0-168h} was 298164 ± 70976 h·ng/mL; for females $C_{\max}$ was 9546 ± 1534 ng/mL and AUC_{0-168h} : 648072 ± 118104 h·ng/mL), and the NOAEL was considered to be 3 mg/kg in monkeys ($C_{\max}$ was 23.0 ± 16.8 µg/mL and AUC_{0-168h} was 2613 ± 1842 h·µg/mL on Day 85).

The following formula was used to predict the HED using animal dose and animal weight as described in the US Food and Drug Administration (FDA) Guidance for Industry and adjusted by the body surface area: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (DHHS 2005):

$$\text{HED} = \text{animal dose (mg/kg)} \times \left[\frac{\text{animal weight (kg)}}{\text{human weight (kg)}} \right]^{0.33}$$

The average weight for the 1 mg/kg group of rats was approximately 271 g and the average human weight assumed to be 60 kg.

$$\text{HED (mg/kg)} = 1 \text{ (mg/kg)} \times \left[\frac{0.271 \text{ (kg)}}{60 \text{ (kg)}} \right]^{0.33} = 0.1683 \text{ mg/kg}$$

The average weight for the 2 mg/kg group of cynomolgus monkeys was approximately 3.38 kg and the average human weight assumed to be 60 kg.

$$\text{HED (mg/kg)} = 2 \text{ (mg/kg)} \times \left[\frac{3.38 \text{ (kg)}}{60 \text{ (kg)}} \right]^{0.33} = 0.7741 \text{ mg/kg}$$

Since the HED value converted from rats is lower than the cynomolgus monkeys, the lower HED value (0.1683 mg/kg) is selected for starting dose calculation and adjusted by body surface area.

Although a 10-fold safety factor of the maximum recommended starting dose is acceptable for most biotherapeutics, a safety factor of 20 is applied for DR10624 as a precautionary measure. Therefore, the initial clinical dose of DR10624 will be 0.1683 mg/kg x 60 kg / 20 = 0.5 mg.

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objectives of this study are:

- **Part 1:** To assess the safety and tolerability of a single ascending SubQ dose of DR10624 in healthy subjects or overweight to obese but otherwise healthy adult subjects.
- **Part 2:** To assess the safety and tolerability of multiple ascending SubQ doses of DR10624 in obese adult subjects with modest hypertriglyceridemia.

- **Part 3:** To assess the safety and tolerability of a single-ascending SubQ dose of DR10624 in Chinese healthy subjects or overweight or obese but otherwise healthy adult subjects in China.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are:

- **All Parts:** To determine the PK profiles of single and multiple SubQ doses of DR10624.
- **Part 2:** To assess the change from baseline in body weight, body mass index (BMI), and waist circumference in subjects receiving multiple SubQ doses of DR10624.
- **Part 2:** To assess the change from baseline in fasting lipid profile (total cholesterol, low density lipoprotein [LDL] cholesterol, high density lipoprotein [HDL] cholesterol, non-HDL cholesterol, Lipoprotein (a) (Lp[a]), very low-density lipoprotein [VLDL] cholesterol, triglycerides, and free fatty acids) in subjects receiving multiple SubQ doses of DR10624.
- **Part 2:** To assess the PD response of DR10624 measured by the change from baseline value of partial areas under the curve in series biomarkers (glucose, C-peptide, insulin, and glucagon levels) following multiple SubQ doses of DR10624 using mixed meal tolerance test (MMTT).
- **Part 2:** To assess the change from baseline in fasting plasma glucose (FPG), HbA1c, C-peptide, fasting insulin, glucagon, and adiponectin; as well as measures of insulin resistance (homeostatic model assessment index of insulin resistance [HOMA-IR]) and beta-cell function (homeostatic model assessment index of beta-cell function [HOMA-B]) in subjects receiving multiple SubQ doses of DR10624.
- **Part 2:** To assess the change of continuous glucose monitoring (CGM) outcome measures from baseline in subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes at screening:
 - Percentage of time spent in target range 3.9 to 10 mmol/L (Time in Range, TIR)
 - Time above target range (TAR)
 - Time below target range (TBR)

- Average glucose
- Glucose variability (coefficient of variation [CV])
- **All Parts:** To assess the safety of single and multiple SubQ doses of DR10624 as determined by the adverse event of special interest (AESI) of hypoglycemia.
- **Part 2:** To assess the change from baseline in Fibrosis 4 score (FIB-4) and non-alcoholic fatty liver disease fibrosis score (NFS) in subjects receiving multiple SubQ doses of DR10624.
- **Part 2:** To assess the change from baseline in hepatic fat fraction by magnetic resonance imaging – proton density fat fraction (MRI-PDFF) in subjects receiving multiple SubQ doses of DR10624 and in a prespecified subgroup of subjects with at least 8% baseline hepatic fat.
- **Part 2:** To assess the change in liver stiffness by FibroScan from baseline in subjects with baseline hepatic fat of at least 8% measured by MRI-PDFF.
- **Part 2:** To assess the change from baseline in liver function parameters in subjects receiving multiple SubQ doses of DR10624.
- **Part 2:** To assess the immunogenicity of DR10624.

2.3 EXPLORATORY OBJECTIVE

The exploratory objective of this study is:

- **Part 2:** To assess the change from baseline in satiety measured by visual analogue scale (VAS) in subjects receiving multiple SubQ doses of DR10624.

3. STUDY DESIGN

This is a Phase 1, FIH, randomized, double-blind, placebo-controlled study designed to assess the safety, tolerability, PK, and PD of single- and multiple-ascending SubQ doses of DR10624. The study will be conducted in 3 parts:

1. **Part 1:** An SAD part in healthy adult subjects or overweight to obese adults but otherwise healthy subjects (Cohorts A, B, C, D, E, F, G, H, and P),

2. **Part 2:** A MAD part in obese adult subjects with modest hypertriglyceridemia (Cohorts I, J, K, and L), and
3. **Part 3:** An SAD part in Chinese healthy adult subjects or overweight or obese adults but otherwise healthy adult subjects (Cohorts M, N, and O).

In each study part, subjects who meet the criteria for study entry will be assigned to the planned dose cohort and will be randomly assigned in an x:y ratio to receive DR10624 or placebo. All doses of DR10624 or placebo will be administered as a SubQ injection in the abdomen.

Safety data for each dose cohort will be reviewed in a blinded fashion by an SRC before progression to the next higher dose cohort of all parts, and/or before progression to Part 2. The sponsor will form an internal SRC for a blinded review of safety data for each subject and the entire cohort and will make a recommendation on whether to proceed to the next dose level and/or progression to Part 2. Refer to [Section 5.1.1](#) for details on the composition of the SRC.

Dosing in the next higher dose cohort of all parts, and/or dosing in Part 2 will be permitted only after the blinded SRC confirms that it is safe to do so, and the sponsor or designee provides written/email confirmation to the investigator. Study assessments (eg AEs, clinical laboratory test results, vital sign measurements, 12-lead electrocardiogram [ECG], serum calcitonin results, and physical examination findings) will be used to evaluate safety and tolerability of a given dose level. Available blinded PK data will also be reviewed at the same time as blinded safety data for each cohort and PK sampling time points and other elements of the schedule of events for subsequent cohorts may be adjusted as needed based on SRC review.

In Part 3, eligible subjects will receive 1 of 3 dose levels of DR10624 or placebo in a 5:1 ratio. Provisional dose of these 3 cohorts (M, N, O) in Part 3 may repeat dose levels of Cohorts E, F, G, H, or P in Part 1. The tentative starting DR10624 dose (Cohort M) in Part 3 will be the same as the dose in Cohort E (25 mg) of Part 1 (SAD). The following doses for each cohort in Part 3 will be determined by the SRC following an evaluation of available safety and PK data for subjects in Part 1 and the available PK, safety, and tolerability data obtained through Day 15 of the preceding dose cohort in Part 3. The highest DR10624 dose in Part 3 will not exceed the maximum tolerated dose reached in Part 1.

Part 1 (Single-Ascending Dose)

Part 1 will have 9 cohorts and approximately 68 healthy adult subjects or overweight to obese adult subjects (obese subjects in Cohorts G, H, and P only) but otherwise healthy subjects: 4 subjects in Cohort A (all active), 8 subjects each (6 active: 2 placebo) in Cohorts B, C, D, E, F, G, H, and P. The starting DR10624 dose in Part 1 will be 0.5 mg SubQ. The provisional doses in Cohorts B, C, D, E, F, G, H, and P are planned to be 1.5, 4.5, 12.5, 25, 50, 65, 90, and 120 mg SubQ, respectively, with final doses for each cohort determined by the SRC following a full review of the data from the previous dose cohort. The dose levels may be adjusted by the SRC.

Part 1 will consist of a screening period (Days –28 to –2), check-in (Day –1), an in-clinic period/follow-up period (Days 1 to 29), and an EOS visit (Day 29).

DR10624 will be administered as a SubQ injection in the abdomen. Subjects in Cohort A will receive active study drug on Day 1. A single sentinel subject will be dosed with DR10624 first. At 72 hours after this subject has been dosed, if the sentinel subject shows no significant safety or tolerability concerns, as assessed by investigator, the remaining 3 subjects in that cohort may be dosed.

Administration of the next higher dose level in Part 1 (Cohort B) will only proceed after the safety data obtained through Day 15 after dosing have been evaluated in a blinded fashion by the SRC for Cohort A. The safety evaluation interval (through Day 15) after dosing may be extended with the approval of the sponsor or sponsor's designee.

For SAD Cohorts B to H, and P, subjects will receive active study drug or placebo on Day 1. The first 2 sentinel subjects from each dose cohort will receive either placebo or DR10624 (i.e., both placebo and active must be represented). At 72 hours after these first 2 subjects have been dosed, if the sentinel group shows no clinically significant safety or tolerability concerns, the remaining subjects in that cohort may be dosed.

Administration of the next higher dose level in Part 1 will only proceed after the safety and tolerability data and available PK data obtained through Day 15 after dosing have been evaluated in a blinded fashion by the SRC for each dose cohort. The safety evaluation interval (Day 15) after dosing for safety evaluation may be extended with the approval of the sponsor or sponsor's designee.

Blood samples for PK assessments will be collected at: predose and 2, 4, 6, 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7), 168 (Day 8), 240 (Day 11), 336 (Day 15), 504 (Day 22), and 672 hours (Day 29) postdose.

Blood samples to assess fasting glucose and lipid profile will be collected from all subjects at screening, check-in, Day 3, Day 8, and at Day 29/EOS.

Immunogenicity serum samples for status of subject's ADA titer assessment (i.e., ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer) will be collected from all subjects at:

- Predose on Day 1, or at early termination (ET; if applicable), and at follow-up visits on Days 8, 15, and 29/EOS.

The serum sampling time points for the ADA titer assessment will be the same for all subjects dosed with either placebo or DR10624.

In Part 1, subjects will reside within the clinic from Day -1 until discharge on Day 7 (144 hours after dosing) and return to the clinic on Days 8, 11, 15, 22, and 29/EOS for outpatient visits. The duration of the study in Part 1, excluding screening, is approximately 30 days.

Part 2 (Multiple-Ascending Dose)

Part 2 will have 4 cohorts, with 12 subjects each (10 active: 2 placebo) in Cohorts I, J, K and L, and a total of approximately 48 subjects. Obese subjects with modest hypertriglyceridemia will be enrolled in Part 2.

Additional subjects per cohort and/or cohorts may be enrolled at the SRC's discretion. Any subject who is screened for Part 2 and is unable to be dosed but is otherwise eligible (e.g., reserve subjects) will be permitted to be rescreened for subsequent cohorts. If rescreening occurs, MRI-PDFF and FibroScan will not be required to be repeated if prior assessment occurred within 3 months of dosing.

DR10624 will be administered as a SubQ injection in the abdomen. The SRC will make the final recommendation on the starting dose, dosing frequency, and/or whether to proceed to Part 2. Dosing in Part 2 will be permitted only after the blinded safety data through Day 29/EOS after completing the dosing in the last subject in Cohort E in Part 1 have been evaluated and approved by the SRC. The MAD cohorts may run in parallel with the remaining SAD cohorts. The tentative starting DR10624 dose (Cohort I) in Part 2 will be the same as the dose in Cohort D of the SAD. Final doses for each cohort in Part 2 will be determined by the SRC following a blinded review of the data from the previous cohort. Cohorts J, K, and L may titrate to the target dose by assessing tolerance in subjects who have completed their dosing. The final decision on the titration plan will be made by the SRC. Dose cohorts in Part 2 will be enrolled sequentially. Subsequent MAD cohorts at higher dose

levels can be initiated after the safety, tolerability, and PK data from at least 8 subjects, who have received at least 6 doses of DR10624 or placebo, from the preceding MAD cohort have been reviewed and deemed safe and well tolerated by the SRC.

Part 2 will consist of a screening period (Days -42 to -3), check-in (Day -2 to -1), a treatment/follow-up period (Days 1 to 106), and an EOS visit (Day 106). Any subject that is screened for part 2 and is unable to be dosed but is otherwise eligible (e.g. reserve subjects) will be permitted to be re-screened for subsequent cohorts. If rescreening occurs, MRI-PDFF and FibroScan will not be required to be repeated if prior assessment occurred within 3 months of dosing.

Subjects will receive active study drug or placebo once every week on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78. For the study drug administration on Days 1 and 78, subjects will reside within the clinic from the evening of Days -2 to 2 (24 hours after dosing) and from the evening of Day 77 to Day 79 (24 hours after dosing), respectively. For study drug administration on Days 8 to 71, subjects will be dosed during outpatient visits and will be domiciled in the clinic for a minimum of 30 minutes postdose for safety monitoring and observation of injection site reactions. A standard mixed meal (470 kcal, ~66% carbohydrate, 18% fat, and 16% protein) will be served to all subjects in the MAD cohorts on Day -1, Day 28, and after PK sample collection on Day 79.

Serial blood samples for analysis of the multiple-dose PK of DR10624 will be collected as follows:

- Day 1 (first dose): predose and 4, 6 (Day 1), 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 (Day 7) hours postdose
- Day 78 (last dose): predose and 4, 6 (Day 78), 24 (Day 79), 48 (Day 80), 72 (Day 81), 96 (Day 82), 120 (Day 83), 144 (Day 84), 168 (Day 85), 336 (Day 92), 504 (Day 99), and 672 (Day 106) hours postdose

Additional predose blood samples (trough) will be collected on Days 8 (168 hours postdose Day 1), 15, 22, 29, 36, 43, 50, 57, 64, and 71.

Blood samples will be collected at the following time points to assess the impact of DR10624 on postprandial PD response following a standard 4-hour MMTT:

- Baseline samples (-30, -15, and -5 minutes) for PD biomarkers (glucose, C-peptide, insulin, and glucagon levels) will be collected premeal on Day -1, Day 28, and Day 79.

- Serial samples for PD biomarkers (glucose, C-peptide, fasting insulin, and glucagon levels) will be collected at 10, 15, and 30 minutes, and at 1, 1.5, 2, 3, and 4 hours from the start time of the meal on Day -1, Day 28, and Day 79.

For baseline CGM, subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes at screening will be fitted with a blinded sensor during the 14-day prerandomization phase prior to check-in and up to predose on Day 1. If the day of dosing changes or any subjects have completed their CGM earlier than check-in and are within the screening window, then the subjects will be considered for admission and dosing. The subjects with a history of diabetes will be required to continue the recommended 2 or more blood glucose meter checks per day that they perform as standard of care during the blinded CGM run-in period prior to check-in. Additional blinded sensors configured to record glucose concentrations will be fitted from Day 22 to Day 36 and Day 71 to Day 85.

A glucometer will be provided to all subjects in Part 2. Subjects will routinely monitor fasting blood glucose at least twice weekly throughout the study period and will be counseled on identification and management of hypoglycemia and hyperglycemia.

Blood samples to assess fasting glucose will be collected from all subjects at screening, Day -1, and Day 78 during the in-clinic period and on Days 4, 8, 15, 22, 28, 36, 43, 50, 57, 81, 85, and 106 at outpatient visits. Blood samples to assess fasting insulin, C-peptide, and glucagon will be collected from all subjects at screening and on Days -1, 8, 15, 22, 28, 57, 78, and 85.

Blood samples for assessment of fasting lipid profile will be collected from all subjects at screening and on Days -1, 8, 15, 29, 57, 85, and 106 (EOS or at ET).

Blood samples for assessment of adiponectin will be collected from all subjects on Days -1, 29, 57, and Day 85.

In addition, blood samples to assess HbA1c will be collected at screening, on Days -1, 29, 57, and Day 85.

Blood samples to be collected on Day -1, Day 57, and Day 85 for safety assessments will be used to calculate NFS and FIB-4 based on following formula:

$$\text{FIB-4} = \text{Age} \times \text{AST/platelet (PLT) count} \times \sqrt{\text{ALT}}$$

$$\text{NFS} = -1.675 + 0.037 \times \text{age} + 0.094 \times \text{body mass index (BMI, kg/m}^2\text{)} + 1.13 \times \text{Impaired glucose tolerance or diabetes (Yes 1, No 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelets (10}^9\text{/L)} - 0.66 \times \text{albumin (g/dL)}.$$

Immunogenicity serum samples for status of subject's ADA assessment (ie, ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer) will be collected from all subjects at:

- Predose on Days 1, 8, 29, and 78 or at ET (if applicable) and Day 106/EOS.

MRI-PDFF measurements will be performed at screening and between Day 85 to 99 in subjects receiving multiple SubQ doses of DR10624 or placebo. In subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes, the MRI-PDFF at screening will be performed prior to the 14-day predose CGM measurements. If applicable, MRI-PDFF will be conducted at ET only if the subject has received ≥ 6 weeks of treatment with study drug. For subjects that early terminate, MRI-PDFF measurements will be arranged as soon as possible.

FibroScan measurements will be performed at screening and on Day 85 (a window of ± 2 days is allowed), or if applicable, at the ET visit (only if the subject has received ≥ 6 weeks of treatment with study drug) in subjects with baseline hepatic fat of at least 8% measured by MRI-PDFF.

In Part 2, subjects will reside within the clinic from the evening of Day -2 until discharge on Day 2 (24 hours after dosing) and will return to the clinic on the evening of Day 77 until discharge on Day 79 (24 hours after Day 78 dosing). Subjects will return to the clinic on Days 3, 4, 5, 6, 7, 8, 15, 22, 28, 29, 36, 43, 50, 57, 64, 71, 80, 81, 82, 83, 84, 85, 92, 99 and 106 for outpatient visits. The duration of the study in Part 2, excluding screening, is approximately 108 days.

If a subject, who has received at least one dose of the study drug, withdraws from the study, the subject may be asked to have necessary assessments listed in the protocol within 4 weeks after the last dose this subject receives.

Based on the observed half-life of DR10624 in Part 1 of the study, the PK blood collection points and visit points in Part 2 may be adjusted subject to the SRC's discretion.

Part 3 (Single-Ascending Dose in China)

Part 3 will employ an adaptive study design with 3 cohorts and approximately 36 healthy adult subjects or overweight or obese adults but otherwise healthy subjects; 12 subjects (10 active: 2 placebo) will be enrolled in each cohort (Cohorts M, N, O).

Provisional dose of these 3 cohorts in Part 3 may repeat dose levels of Cohort E, F, G, H, or P in Part 1. The tentative starting DR10624 dose (Cohort M) in Part 3 will be the same as the dose in Cohort E (25 mg) of Part 1 (SAD). The following doses for each cohort in Part 3 will

be determined by the SRC following an evaluation of available safety and PK data for subjects in Part 1 and the safety and tolerability, and available PK data obtained through Day 15 of the preceding dose cohort of Part 3.

Part 3 will consist of a screening period (Days –28 to –2), check-in (Day –1), an in-clinic period/follow-up period (Days 1 to 29), and an end-of-study (EOS) visit (Day 29).

DR10624 will be administered as a SubQ injection in the abdomen. Eligible subjects will be divided into 2 subgroups based on BMIs obtained at screening, a BMI ≥ 28 kg/m² subgroup and a BMI < 28 kg/m² subgroup. The number of subjects in both subgroups in each cohort should be equal. In each subgroup, subjects will receive either DR10624 or placebo in a 5: 1 ratio. The highest DR10624 dose in Part 3 will not exceed the maximum tolerated dose reached in Part 1.

Blood samples for PK assessments will be collected at: predose and at 4, 6 (Day 1), 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7), 168 (Day 8), 240 (Day 11), 336 (Day 15), 504 (Day 22), and 672 hours (Day 29) postdose. The PK blood collection points and visit points may be adjusted based on the results of Part 1.

Blood samples to assess safety will be collected from all subjects at screening, check-in, and Days 3, 5, 7, 15, and Day 29/EOS.

Immunogenicity serum samples for status of subject's ADA titer assessment (ie, ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer) will be collected from all subjects at:

- Predose on Day 1 and at follow-up visits on Days 8, 15, and 29/EOS or at ET (if applicable).

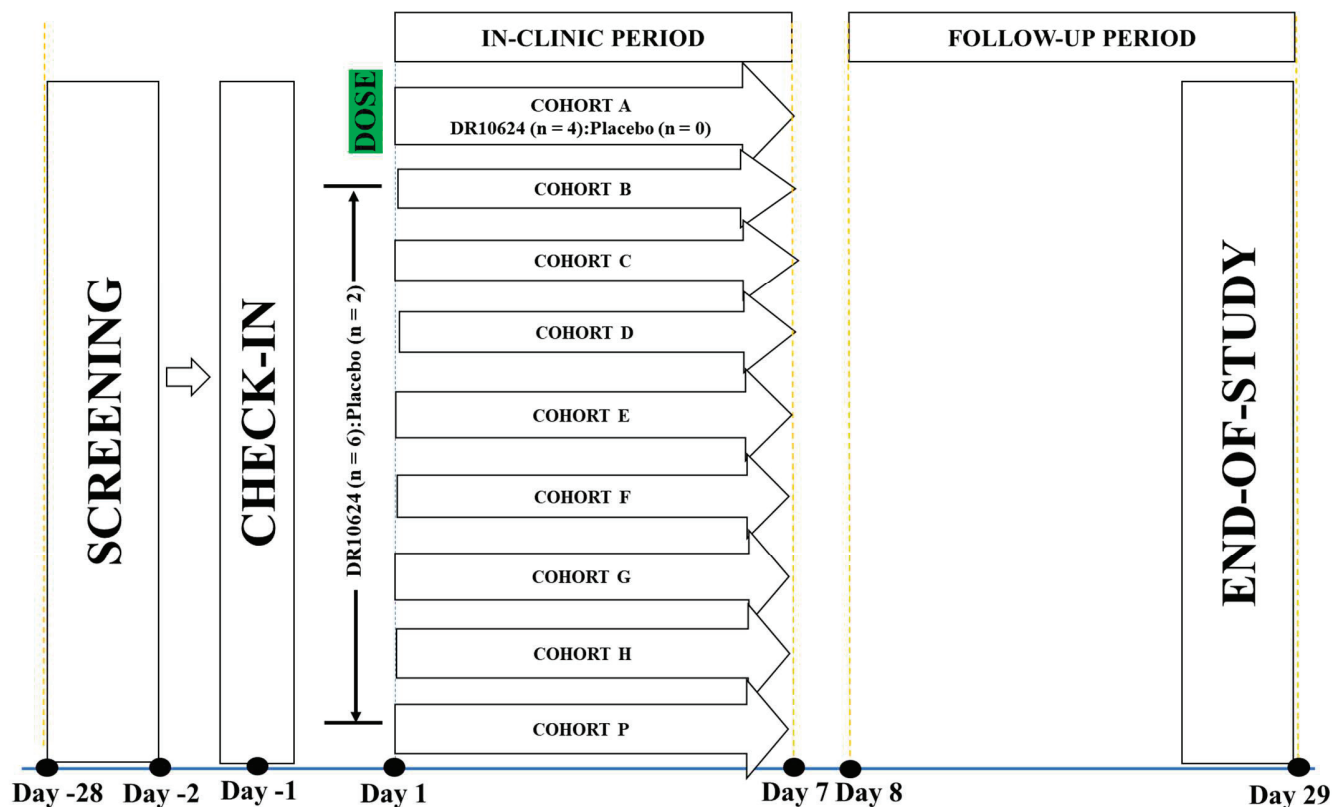
The serum sampling time points for the ADA titer assessment will be the same for all subjects dosed with either placebo or DR10624.

In Part 3, subjects will reside within the clinic from Day -1 until discharge on Day 7 (144 hours after dosing) and return to the clinic on Days 8, 11, 15, 22, and 29/EOS for outpatient visits. The duration of Part 3, excluding screening, is approximately 30 days.

An overview of the study design of Part 1, Part 2, and Part 3 are presented in [Figure 3-1](#), [Figure 3-2](#), and [Figure 3-3](#), respectively.

Figure 3-1

Overview of Study Design (Part 1)



Note: Subcutaneous doses of Cohort A: 0.5 mg; Cohort B: 1.5 mg; Cohort C: 4.5 mg; Cohort D: 12.5 mg; Cohort E: 25 mg; Cohort F: 50 mg; Cohort G: 65 mg; Cohort H: 90 mg; Cohort P: 120 mg

Figure 3-2 Overview of Study Design (Part 2)

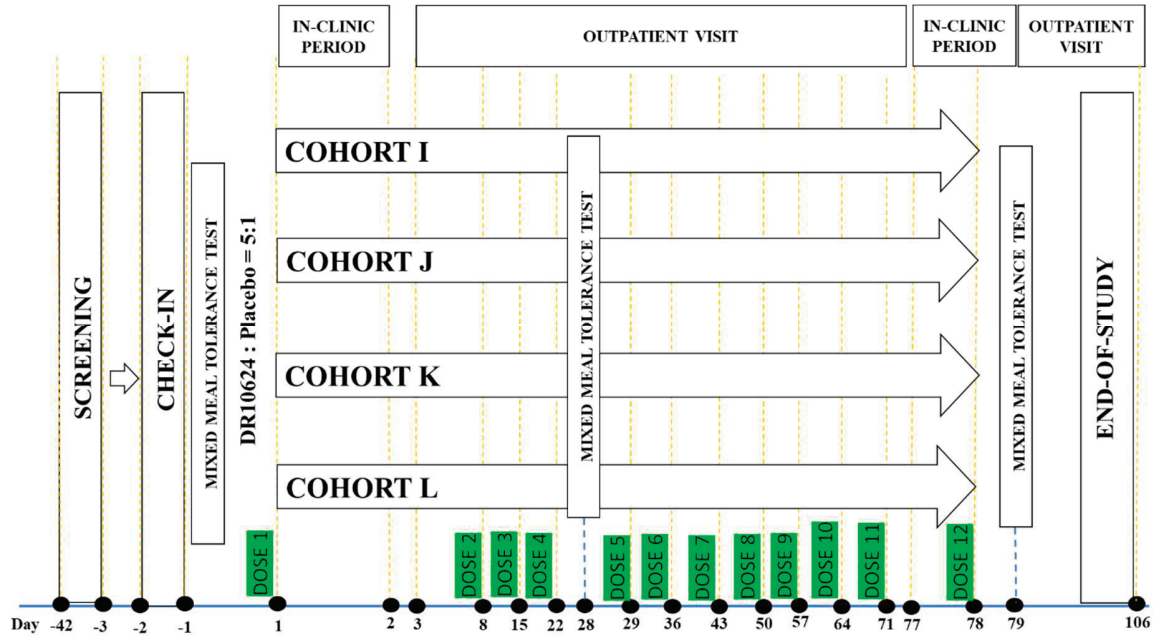
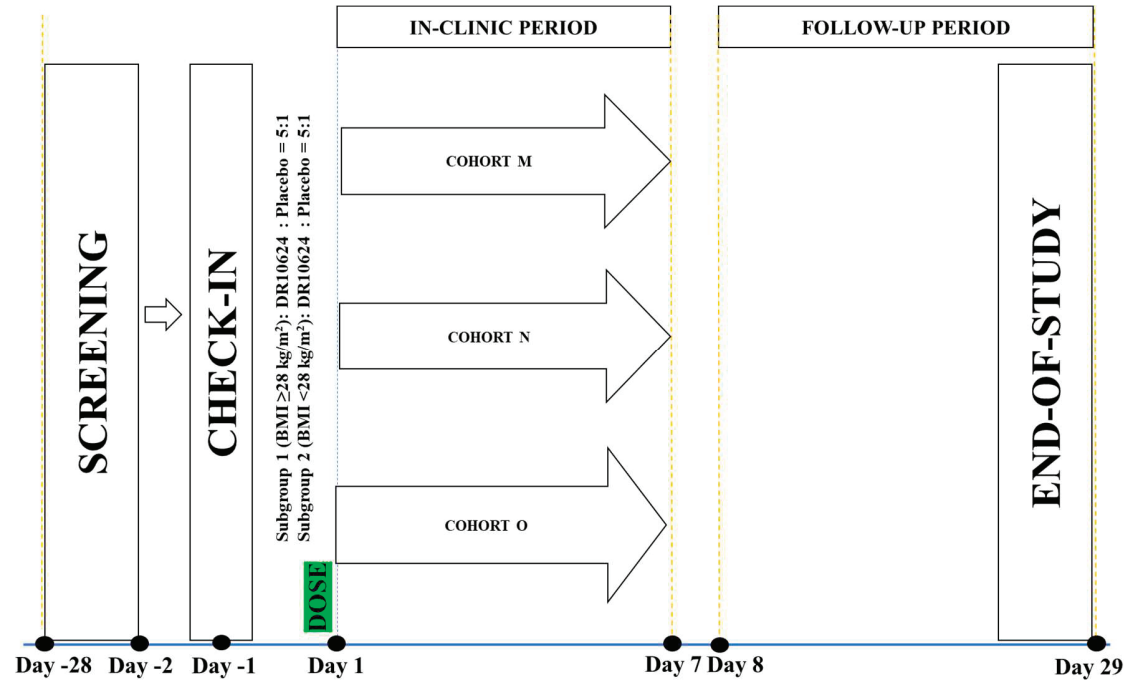


Figure 3-3 Overview of Study Design (Part 3)



3.1 SCHEDULE OF EVENTS FOR PART 1

Phase	Screening	Check-in (Baseline)	In-clinic Period								Follow-up Period			
			1	2	3	4	5	6	7	8	11	15	22	29/EOS/ ET ^(c)
Procedure ^(a)	Day	-1												
Admission to clinic		X												
Discharge from clinic ^(b)									X					
Outpatient visit										X	X	X	X	X
Informed consent	X													
Demographics	X													
Serology ^(c)	X													
Serum FSH ^(d)	X													
Inclusion/exclusion criteria	X	X												
Medical history	X	X												
Height, weight, and BMI ^(e)	X	X							X					X
Physical examination ^(f)	X	X							X					X
Vital sign measurements ^(g)	X	X	X	X	X	X	X	X	X			X		X
12-lead ECG ^(h)	X	X							X					X
12-lead Holter recording ⁽ⁱ⁾		X	X	X	X	X								
Clinical laboratory testing ^(j)	X	X			X		X		X			X		X
Fasting glucose and lipid profile ^(k)	X	X			X					X				X
Urine drug/alcohol screen ^(l)	X	X												
Pregnancy test ^(m)	X	X												X
Calcitonin	X													
Study drug administration ⁽ⁿ⁾			X											
PK blood sample collection ^(o)			X	X	X	X	X	X	X	X	X	X	X	X
ADA sample collection ^(p)			X							X		x		X
AEs ^(q)									X					
Prior/concomitant medications									X					
Abbreviations: ADA, antidrug antibody; AEs, adverse events; BMI, body mass index; ECG, electrocardiogram; EOS, end-of-study; ET, early termination; FSH, follicle-stimulating hormone; PK, pharmacokinetic; QTcF, QT interval corrected for heart rate using Fridericia's formula; SRC, safety review committee.														
Notes: Administration of the next higher dose level in Part 1 will only proceed after the safety and available PK data obtained through Day 15 after dosing have been evaluated in a blinded fashion by the SRC for each dose cohort.														

- (a) When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time window as possible. For blood draws, a window of ± 10 minutes is allowed for the 6-hour postdose sampling and a window of ± 60 minutes is allowed from 24 hours postdose (Day 2) up to 168 hours postdose (Day 8) sampling. On Days 11, 15, 22, and 29, a window of ± 1 day is allowed.
- (b) Discharge following scheduled safety assessments and the 144-hour (Day 7) PK sample collection.
- (c) Serology testing will include hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus types 1 and 2 antibodies.
- (d) Females only. A serum FSH test may be performed at screening to confirm postmenopausal status.
- (e) Height and weight will be measured, and BMI calculated at screening only. Only weight will be measured at check-in, Day 7, and Day 29/EOS/ET.
- (f) A full physical examination will be performed at screening. A brief physical examination will be performed at check-in, Day 7, and Day 29/EOS/ET. Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Further details are provided in [Section 6.3.6](#).
- (g) Vital signs will be measured at screening and check-in, within 30 minutes prior to study drug dosing on Day 1, 1 hour post drug dosing on Day 1, on Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 15, and Day 29/EOS/ET after the subject has been in the semi-supine position for at least 5 minutes. A window of ± 20 minutes from nominal time will be allowed for all vital sign measurements. Vital signs may be measured at additional time points at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Further details on vital sign measurements are provided in [Section 6.3.3](#).
- (h) Single 12-lead ECG recordings will be made at screening, check-in, Day 7, and Day 29/EOS/ET after the subject has been in the semi-supine or supine position for at least 5 minutes. A window of ± 120 minutes from nominal time will be allowed for all ECG recordings, if necessary. In the event a value is outside of the reference range, this will be confirmed by 2 further repeat measurements, which will then be calculated as a mean of the original value and the 2 repeat measurements. Further details on safety ECG recordings are provided in [Section 6.3.4](#).
- (i) The 12-lead Holter monitor will be started on Day -1 at least 12 hours before dosing on Day 1 and will continue until at least 72 hours after dosing on Day 1. Further details are included in [Section 6.3.5](#).
- (j) Clinical laboratory testing will occur at screening, check-in, Day 3, Day 5, Day 7, Day 15 and Day 29/EOS/ET. Blood samples will be collected and prepared per the clinic's standard procedures. Further details on clinical laboratory assessments, including a complete list of assessments, are provided in [Section 6.3.2](#).
- (k) Fasting glucose and fasting lipid profile will be assessed at screening, check-in, Day 3, Day 8, and Day 29/EOS/ET. If time points coincide with serum chemistry collection, analytes for fasting glucose and fasting lipid profile will be collected as part of the serum chemistry sample.
- (l) Urine drug and alcohol screen will occur at screening and check-in per the clinic's standard procedures.
- (m) Women of childbearing potential only. A serum pregnancy test will be performed at screening and on Day 29/EOS/ET. A urine pregnancy test will be performed at check-in.
- (n) The time of study drug dosing will be called "0" hour and is denoted with grey shading. The study drug will be administered SubQ in the abdomen. Subjects will fast overnight for at least 10 hours before dosing and will remain fasted for 2 hours after. Water is permitted as desired. Further details are provided in [Section 5.1](#).
- (o) Blood samples for PK analysis of DR10624 in serum will be collected at: predose and at 2, 4, 6 (Day 1), 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) following study drug dosing during the in-clinic period and at every scheduled outpatient visit until Day 29/EOS/ET (168 [Day 8], 240 [Day 11], 336 [Day 15], 504 [Day 22], and 672 hours [Day 29] following study drug dosing).
- (p) Blood samples for immunogenicity analysis of ADAs will be collected at: predose on Day 1 and following study drug dosing on Days 8, 15, and Day 29/EOS/ET.

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|---|
| <p>(g) Adverse events will be assessed from the time of study drug dosing until Day 29/EOS/ET and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. Further details on collection and reporting of AEs are provided in Section 6.3.1.</p> <p>(i) Follow-up/EOS visits will occur until Day 29/EOS/ET.</p> |
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3.2 SCHEDULE OF EVENTS FOR PART 2

Phase	Screening	Check- in (BL)	In-cli nic Perio d	Outpatient Visits																In-clinic Period	Outpatient Visits																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
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Abbreviations: ADA, antidrug antibody; AEs, adverse events; BL, baseline; BMI, body mass index; ECG, electrocardiogram; EOS, end-of-study; EOT, end-of-treatment period; ET, early termination; FSH, follicle-stimulating hormone; HbA1c, glycosylated hemoglobin; MAD, multiple-ascending dose; MMTT, mixed meal tolerance test; MRI-PDFF, magnetic resonance imaging-protein density fat fraction; PD, pharmacodynamic; PK, pharmacokinetic; QTcF, QT interval corrected for heart rate using Fridericia's formula; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SRC, safety review committee.

Notes: 1. Dose escalation in Part 2 will occur only after the available real time PK, safety, and tolerability data (including reported AEs, physical examinations, vital signs, 12-lead ECGs, and clinical laboratory results) from at least 8 subjects, who have received at least 6 doses of DR10624 or placebo in the preceding dose cohort are assessed and the study drug is deemed safe and well tolerated by the SRC.

2. If a subject, who has received at least one dose of the study drug, withdraws from the study, the subject may be asked to have necessary assessments listed in the protocol within 4 weeks after the last dose this subject receives.
- (a) When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time window as possible.
 - (b) Subjects will reside within the clinic from the evening of Day -2 until discharge on Day 2 (24 hours after dosing) and will return to the clinic on the evening of Day 77 until discharge on Day 79 (24 hours after Day 78 dosing). A window of ± 1 day is allowed for the second in-clinic period (Days 77, 78, and 79).
 - (c) Discharge following scheduled safety assessments and the 24-hour PK sample collection.
 - (d) Subjects will return to the clinic on Days 3, 4, 5, 6, 7, 8, 15, 22, 28, 29, 36, 43, 50, 57, 64, 71, 80, 81, 82, 83, 84, 85, 92, 99 and 106 for outpatient visits. EOS visit will occur on Day 106/EOS. A window of ± 1 day is allowed for all visits starting from Days 15.
 - (e) Serology testing will include hepatitis B surface antigen, hepatitis C virus antibody, human immunodeficiency virus types 1 and 2 antibodies, and SARS-CoV-2 (as per site practice).
 - (f) Females only. A serum FSH test may be performed at screening to confirm postmenopausal status.
 - (g) Height, waist circumference, and weight will be measured, and BMI will be calculated at screening. Additionally, weight and waist circumference will be measured, and BMI will be calculated on Days -1, 15, 29, 57, 85, and 106/EOS or at ET.
 - (h) A full physical examination will be performed at screening. A brief physical examination will be performed at Day -1, Day 4, Day 79, and Day 106/EOS or at ET. A symptom-directed physical examination will be performed at Day 85. Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Further details are provided in [Section 6.3.6](#).
 - (i) Vital signs will be measured at screening and Day -1; within 30 minutes prior to study drug dosing on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78; Day 4, Day 28, Day 81, Day 85, and Day 106/EOS or at ET after the subject has been in the semi-supine position for at least 5 minutes. A window of ± 20 minutes from nominal time will be allowed for all vital sign measurements. Vital signs may be measured at additional time points at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Further details on vital sign measurements are provided in [Section 6.3.3](#).
 - (j) Triplicate 12-lead ECG recordings will be made at screening, on Day -1, prior to study drug dosing on Days 1, 8, 15, 22, 43, 57, 71, and 78; on Day 4 (72 hours after the first dose), Day 28, Day 81 (72 hours after the last dose), Day 85, and Day 106/EOS or at ET after the subject has been in the semi-supine or supine position for at least 10 minutes. The triplicates will be performed at approximately 1-minute intervals. Each ECG recording (trace) will last 10 seconds. ECG should be collected immediately prior to PK sample collection. Further details on safety ECG recordings are provided in [Section 6.3.4](#).
 - (k) Clinical laboratory testing, including hematology, serum chemistry, urinalysis, and coagulation testing, will occur at screening, on Day -1, prior to study drug dosing on Days 15, 36, 43, and 57; and on Days 4, 7, 28, 77, 85, and 106/EOS or at ET. Blood samples will be collected and prepared per the clinic's standard procedures. Further details on clinical laboratory assessments, including a complete list of assessments, are provided in [Section 6.3.2](#). On Day -1, Day 57, and on Day 85, NFS and FIB-4 will be calculated using following formula: $FIB-4 = \text{Age} \times \text{AST/PLT count} \times \sqrt{\text{ALT}}$; $NFS = -1.675 + 0.037 \times \text{age} + 0.094 \times \text{body mass index (BMI, kg/m}^2\text{)} + 1.13 \times \text{Impaired glucose tolerance or diabetes (Yes 1, No 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelets (10}^9\text{/L)} - 0.66 \times \text{albumin (g/dl)}$.
 - (l) Fasting glucose will be assessed at screening, on Days -1, 4, 8, 15, 22, 28, 36, 43, 50, 57, 78, 81, 85, and Day 106/EOS or at ET. If both fasting glucose and clinical laboratory will be tested in a visit, the glucose level in clinical laboratory may be adopted, additional fasting glucose test is not required. A glucometer will be provided to all subjects in Part 2. Subjects will routinely monitor fasting blood glucose at least twice weekly throughout the study period and will be counseled on identification and management of hypoglycemia and hyperglycemia.
 - (m) Fasting insulin, C-peptide, and glucagon will be assessed at screening and on Days -1, 8, 15, 22, 28, 57, 78, and Day 85 or at ET.
 - (n) Urine drug and alcohol screen will occur on screening and Day -2 per the clinic's standard procedures.

- (o) Women of childbearing potential only. A serum pregnancy test will be performed at screening and Day 106/EOS or at ET and urine pregnancy test will be performed on Day -2, Day 29, Day 57, and Day 85.
- (p) Study drug dosing occurs on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 denoted with grey shading. All doses of study drug will be administered SubQ in the abdomen. Subjects will fast overnight for at least 10 hours before dosing and will remain fasted for 2 hours after. Water is permitted as desired. On Day 8 to Day 71 subjects will be domiciled in the clinic for a minimum of 30 minutes postdose for safety monitoring and observation of injection site reactions. Further details are provided in [Section 5.1](#).
- (q) For PK blood draws, all predose blood draws on Days 1 to 78 should be completed within 60 mins before dosing. For first and twelfth dose, a window of ± 10 minutes is allowed for the 4-and 6-hour postdose sampling and a window of ± 60 minutes is allowed for 24 hours postdose through the 168 hours postdose sampling. For twelfth dose, a window of ± 1 day is allowed for 336 hours postdose through the 672 hours postdose sampling. Further details are provided in [Table 3-1](#). The time of drug dosing on Day 1 and Day 78 will be called “0” hour respectively.
- (r) Blood samples for assessment of fasting lipid profile will be collected at screening and Days -1, 8, 15, 29, 57, 85, and Day 106 (EOS or at ET). Fasting triglyceride may be repeated up to two times 1 week later if the initial results do not fall within the desired range at screening. Baseline will be defined as the result of Day -1. Fasting triglyceride may be repeated once if the initial results do not fall within the desired range. If there are some repeat items in the lipid profile and clinical laboratory tests at a visit, a repeat test is not required.
- (s) Blood samples for immunogenicity analysis of ADAs will be collected at: predose on Days 1, 8, 29, and 78 and on Day 106/EOS or at ET.
- (t) A commercially available visual analogue scale will be used to assess satiety at 0 (premeal), 1 (± 5 min), 2 (± 5 min), 3 (± 10 min), 4 (± 10 min), 5 (± 10 min), and 6 hours (± 10 min) from the start time of the meal during every MMTT measurement.
- (u) Blood samples for adiponectin will be collected from all subjects on Days -1, 29, 57, and Day 85 or at ET.
- (v) Blood samples for calcitonin will be collected from all subjects at screening, on Day 57, and on Day 106/EOS or at ET.
- (w) Subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes at screening will be fitted for baseline continuous glucose monitoring with a blinded sensor during the 14-day pre-randomization phase prior to check-in and up to predose on Day 1. If the day of dosing changes or any subjects have completed their CGM earlier than check-in and are within the screening window then the subjects will be considered for admission and dosing. Additional blinded sensors configured to record glucose concentrations will be fitted from Day 22 to Day 36, and Day 71 to Day 85. Further details are provided in [Section 6.3.7](#).
- (x) On Day -1, Day 28 and Day 79, a standard mixed meal (470 kcal, ~66% carbohydrate, 18% fat, and 16% protein) will be served. Baseline sampling for biomarkers will be collected premeal at -30 (± 5 min), -15 (± 5 min), and -5 (within 5 min) minutes. A serial sampling for biomarkers will be collected at 10 (± 2 min), 15 (± 2 min), and 30 minutes (± 2 min), and at 1, 1.5, 2, 3, and 4 (± 5 min) hours from the start time of the meal.
- (y) Blood samples for assessment of HbA1c will be collected at screening, on Days -1, 29, 57, and Day 85 or at ET.
- (z) MRI-PDFF measurements will be performed at screening and between Day 85 to 99. In subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes, the MRI-PDFF at screening will be performed prior to the 14-day predose CGM measurements. If applicable, MRI-PDFF will be conducted at ET only if the subject has received ≥ 6 weeks of treatment with study drug. For subjects that early terminate, MRI-PDFF measurement will be arranged as soon as possible.
- (aa) FibroScan measurement will be performed at screening, and on Days 85 (a window of ± 2 days is allowed), or if applicable, at ET visit (only if subject has received ≥ 6 weeks of treatment with study drug) in subjects with baseline hepatic fat of at least 8% measured by MRI-PDFF.
- (bb) Adverse events will be assessed from the time of study drug dosing until Day 106/EOS and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. Note: Symptoms of hypoglycemia will be solicited during the in-clinic period and at all outpatient visits until Day 106/EOS. Confirmed hypoglycemic events are defined in [Section 6.3.1.2](#). Further details on collection and reporting of AEs are provided in [Section 6.3.1](#).

Table 3-1 Pharmacokinetic Sampling Schedule for Part 2

Study Week		1	2	3	4	5	6	7	8	9	10	11	12
Dosing Days		1	8	15	22	29	36	43	50	57	64	71	78
PK sampling time point	PK sampling time window												
Predose	-60 min	X	X	X	X	X	X	X	X	X	X	X	X
4h postdose	±10 min	X											X
6h postdose	±10 min	X											X
24h postdose	±60 min	X											X
48h postdose	±60 min	X											X
72h postdose	±60 min	X											X
96h postdose	±60 min	X											X
120h postdose	±60 min	X											X
144h postdose	±60 min	X											X
168h postdose	±60 min												X
336h postdose	±1 day												X
504h postdose	±1 day												X
672h postdose	±1 day												X

Note: Blood samples for PK analysis of DR10624 in serum will be collected on Day 1 at: predose and at 4, 6 (Day 1), 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 (Day 7) hours postdose and on Day 78 at: predose and 4, 6 (Day 78), 24 (Day 79), 48 (Day 80), 72 (Day81), 96 (Day 82), 120 (Day 83), 144 (Day 84), 168 (Day 85), 336 (Day92), 504 (Day 99), and 672 hours (Day 106) postdose. The time of drug dosing on Day 1 and Day 78 will be called “0” hour respectively. Additional predose blood samples (trough) will be collected on Days 8 (168 hours postdose Day 1), 15, 22, 29, 36, 43, 50, 57, 64, and 71.

3.3 SCHEDULE OF EVENTS FOR PART 3

Phase	Screening	Check-in (Baseline)	In-clinic Period							Follow-up Period				
Procedure ^(a)	Day	-1	1	2	3	4	5	6	7	8	11	15	22	29/EOS/ ET
Admission to clinic		X												
Discharge from clinic ^(b)									X					
Outpatient visit ^(c)										X	X	X	X	X
Informed consent	X													
Demographics	X													
Serology ^(d)	X													
Serum FSH ^(e)	X													
Inclusion/exclusion criteria	X	X												
Medical history	X	X												
Height, weight, and BMI ^(f)	X	X							X			X		X
Physical examination ^(g)	X	X							X					X
Vital sign measurements ^(h)	X	X	X	X	X	X	X	X	X			X		X
12-Lead ECG ⁽ⁱ⁾	X	X				X			X					X
Clinical laboratory testing ^(j)	X	X			X		X		X			X		X
Urine/Alcohol drug screen ^(k)	X	X												
Pregnancy test ^(l)	X	X												X
Calcitonin	X													
Study drug administration ^(m)			X											
PK blood sample collection ⁽ⁿ⁾			X	X	X	X	X	X	X	X	X	X	X	X
ADA sample collection ^(o)			X							X		X		X
AEs ^(p)														
Prior/concomitant medications									X					

Abbreviations: ADA, antidrug antibody; AEs, adverse events; BMI, body mass index; ECG, electrocardiogram; EOS, end-of-study; ET, early termination; FSH, follicle-stimulating hormone; PK, pharmacokinetic; QTcF, QT interval corrected for heart rate using Fridericia's formula; SARS-Co V-2, severe acute respiratory syndrome coronavirus 2; SRC, safety review committee.

Notes: Administration of the next higher dose level in Part 3 will be determined by the SRC following an evaluation of available safety, tolerability, and PK data for subjects in Part 1 and the safety and available PK data obtained through Day 15 of the preceding dose cohort of Part 3.

^(a) When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time window as possible. For blood draws, a window of ±10 minutes is allowed for the 6-hour postdose sampling and a

- window of ± 60 minutes is allowed from 24 hours postdose (Day 2) up to 168 hours postdose (Day 8) sampling. On Days 11, 15, 22, and 29, a window of ± 1 day is allowed.
- (b) Discharge following scheduled safety assessments and the 144-hour (Day 7) PK sample collection.
 - (c) Follow-up/EOS visits will be outpatient visits and will occur until Day 29/EOS.
 - (d) Serology testing will include hepatitis B surface antigen, hepatitis C virus antibody, human immunodeficiency virus types 1 and 2 antibodies, SARS-CoV-2 (as per site practice).
 - (e) Females only. A serum FSH test may be performed at screening to confirm postmenopausal status.
 - (f) Height and weight will be measured, and BMI calculated at screening only. Only weight will be measured at check-in, Day 7, Day 15 and Day 29/EOS.
 - (g) A full physical examination will be performed at screening. A brief physical examination will be performed at check-in, Day 7, and Day 29/EOS. Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Further details are provided in [Section 6.3.6](#).
 - (h) Vital signs will be measured at screening and check-in, within 30 minutes prior to study drug dosing on Day 1, 1 hour after drug dosing on Day 1, on Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 15, and Day 29/EOS after the subject has been in the semi-supine position for at least 5 minutes. A window of ± 20 minutes from nominal time will be allowed for all vital sign measurements. Vital signs may be measured at additional time points at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Further details on vital sign measurements are provided in [Section 6.3.3](#).
 - (i) Triplicate 12-lead ECG recordings will be made at screening, check-in, Day 4 (72 hours), Day 7, and Day 29/EOS after the subject has been in the semi-supine or supine position for at least 10 minutes. The triplicates will be performed at approximately 1-minute intervals. Each ECG recording (trace) will last 10 seconds. ECG should be collected immediately prior to PK sample collection. Further details on safety ECG recordings are provided in [Section 6.3.4](#).
 - (j) Clinical laboratory testing will occur at screening, check-in, Day 3, Day 5, Day 7, Day 15, and Day 29/EOS. Blood samples will be collected and prepared per the clinic's standard procedures. Further details on clinical laboratory assessments, including hematology, serum chemistry, urinalysis and coagulation in Part 3, are provided in [Section 6.3.2](#).
 - (k) Urine drug and alcohol screen will occur at screening and check-in per the clinic's standard procedures.
 - (l) Women of childbearing potential only. A serum pregnancy test will be performed at screening and on Day 29/EOS. A urine pregnancy test will be performed at check-in.
 - (m) The time of study drug dosing will be called "0" hour and is denoted with grey shading. The study drug will be administered SubQ in the abdomen. Subjects will fast overnight for at least 10 hours before dosing and will remain fasted for 2 hours after. Water is permitted as desired. Further details are provided in [Section 5.1](#).
 - (n) Blood samples for PK analysis of DR10624 in serum will be collected at: predose and at 4, 6, 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) following study drug dosing during the in-clinic period and at every scheduled outpatient visit until Day 29/EOS (168 [Day 8], 240 [Day 11], 336 [Day 15], 504 [Day 22], and 672 hours [Day 29] following study drug dosing).
 - (o) Blood samples for immunogenicity analysis of ADAs will be collected at predose on Day 1 and following study drug dosing on Days 8, 15, and Day 29/EOS.
 - (p) Adverse events will be assessed from the time of study drug dosing until Day 29/EOS and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. Further details on collection and reporting of AEs are provided in [Section 6.3.1](#).

4. STUDY POPULATION

Approximately 152 male and female subjects will be enrolled. The enrollment of subjects in this study may be across approximately 10 clinical sites worldwide, and the enrollment of SAD cohorts (Part 3) will be only from a single clinical site in China.

4.1 INCLUSION CRITERIA

Each subject must meet all the following criteria to be enrolled in this study:

1. The subject is considered by the investigator to be in good general health as determined by medical history, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings at screening.
2. Female subjects (heterosexually active, of childbearing potential, not pregnant, not trying to become pregnant, and not lactating) are eligible to participate if they agree to total abstinence from heterosexual intercourse or use a highly effective method of birth control listed below, from screening through until at least 30 days after the last dose of the study drug. Highly effective methods of contraception acceptable for use in this study include:

- Implant contraceptive (eg, Jadelle)
- Intra-uterine device (IUD) containing either copper or levonorgestrel (eg, Mirena)
- Male partner of the female subject should be sterilized (vasectomy)
- Female sterilization (eg, by bilateral tubal ligation [‘tying tubes’] or hysterectomy)

A second non-hormonal (barrier) method of contraception is required if a user dependent hormonal form of birth control is used:

- Injectable contraceptive (eg, Depo-Provera)
- Oral contraceptive pill (combined hormonal pill or progestogen-only pill)
- Vaginal contraceptive ring (eg, NuvaRing)

Barrier methods of birth control acceptable for this study include:

- Male condom

- Female condom
- Female diaphragm

Please note that barrier methods on their own are NOT highly effective methods of birth control. Females of childbearing potential must have negative pregnancy test results at screening and check-in. Female subjects must refrain from egg donation throughout study and for 30 days after the last dose. Females who are postmenopausal (age-related amenorrhea for ≥ 12 consecutive months and increased follicle-stimulating hormone [FSH] ≥ 40 mIU/mL) or who have undergone permanent sterilization (hysterectomy, total bilateral salpingectomy, and bilateral oophorectomy [more than 3 months prior to check-in]) do not need to use any methods of contraception.

Male subjects with female partners of childbearing potential are eligible to participate if they are vasectomized, or agree to total abstinence from heterosexual intercourse, from screening through until at least 30 days after the last study dose, or use of an effective method of birth control listed above, from screening through until at least 30 days after the last study dose. Male subjects must refrain from sperm donation throughout the study and for 30 days after the last study dose.

3. The subject agrees to comply with all protocol requirements.
4. The subject is able to provide written informed consent.

Additional inclusion criteria for Part 1, Cohorts A, B, C, D, E, F, G, H, and P:

1. The subject is male or female 18 to 55 years of age, inclusive.
2. The subject has a body weight ≥ 50 kg at screening and a BMI of 18 to 32 kg/m², inclusive, at screening in Cohort A, B, C, D, E, and F.
3. The subject has a BMI of 30 to 40 kg/m², inclusive, at screening in Cohorts G, H, and P.

Additional inclusion criteria for Part 2, Cohorts I, J, K, and L:

1. The subject is male or female 18 to 70 years of age, inclusive.
2. The subject has a BMI of 30 to 45 kg/m² at screening, inclusive.
3. Fasting triglyceride ≥ 150 mg/dL (1.7 mmol/L), and < 500 mg/dL (5.7 mmol/L), at screening. Fasting triglyceride may be repeated up to two times after 1 week if the initial results do not fall within the desired range.

Additional inclusion criteria for Part 3, Cohorts M, N, and O:

1. The subject is male or female 18 to 55 years of age, inclusive.
2. The subject has a body weight ≥ 50 kg for males and ≥ 45 kg for females at screening and a BMI of 19 to 40 kg/m², inclusive, at screening.

4.2 EXCLUSION CRITERIA

Subjects meeting any of the following criteria will be excluded from the study:

1. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus types 1 or 2 antibodies at screening.
2. The subject has a personal or family history of medullary thyroid cancer, or multiple endocrine neoplasia syndrome Type 2, or a screening calcitonin ≥ 50 ng/L.
3. The subject has a history of chronic pancreatitis or episode of acute pancreatitis within 3 months of screening.
4. In Part 1 and Part 3, the subject has used any prescription medications (excluding oral contraceptives, paracetamol, and ibuprofen) within 14 days before the dose of study drug. In Part 2 only, the subjects have been on stable lipid-lowering therapy or nutritional supplements that contains fish oil (or Omega-3 fatty acids) for less than 8 weeks before the first dose of study drug.
5. The subject has consumed alcohol within 48 hours before dosing or during the confinement period.
6. The subject is a smoker or has used tobacco, nicotine, or nicotine-containing products (eg, snuff, nicotine patch, nicotine chewing gum, mock cigarettes, or inhalers) from start

of the confinement period until after EOS. Subjects in Part 2 must be able to abstain from nicotine use during the inpatient periods of the study.

7. The subject has a history of alcohol abuse or drug addiction within the last year or excessive alcohol consumption (regular alcohol intake >21 units per week for male subjects and >14 units of alcohol per week for female subjects) (1 unit is equal to approximately ½ pint [200 mL] of beer, 1 small glass [100 mL] of wine, or 1 measure [25 mL] of spirits).
8. The subject has a positive test result for drugs of abuse and/or alcohol abuse at screening and check-in for the first inpatient period.
9. The subject is involved in strenuous activity or contact sports within 48 hours before admission.
10. The subject has donated blood or blood products >450 mL within 30 days before the first dose of study drug.
11. The subject has total cholesterol >10.3 mmol/L or triglycerides $\geq$ 5.7 mmol/L (500 mg/dL) at screening.
12. The subject has clinically significant history or presence of ECG findings as determined by the investigator at screening and check-in, including any of the following:
 - Abnormal sinus rhythm (heart rate <45 bpm and >100 bpm)
 - Risk factors for torsades de pointes (eg, heart failure, cardiomyopathy, or family history of long QT syndrome)
 - Sick sinus syndrome, second- or third-degree atrioventricular block myocardial infarction, pulmonary congestion, cardiac arrhythmia, prolonged QT interval, or conduction abnormalities
 - QT interval corrected for heart rate using Fridericia's formula (QTcF) >450 msec (male subjects) or >470 msec (female subjects)
 - QRS interval >110 msec
 - PR interval <120 or >220 msec

In the event a value is outside of the reference range, this will be confirmed by 2 further repeat measurements, which will then be calculated as a mean of the original value and the 2 repeat measurements.

- Repeated or frequent syncope or vasovagal episodes
 - Uncontrolled hypertension (defined as systolic blood pressure [SBP] ≥ 160 mmHg, and/or diastolic blood pressure [DBP] ≥ 100 mmHg), angina, bradycardia (if assessed as clinically significant by the investigator), or severe peripheral arterial circulatory disorders
13. The subject has a history of relevant drug and/or food allergies (ie, allergy to DR10624 or excipients, or any significant food allergy that could preclude a standard diet in the clinical unit).
14. The subject has a history of severe allergic or anaphylactic reactions.
15. The subject has experienced a $>5\%$ loss in body weight within 2 months prior to screening.
16. Female subjects who are pregnant or lactating.
17. The subject has a positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A positive rapid antigen test (RAT), isothermal nucleic acid amplification, or polymerase chain reaction (PCR) coronavirus disease-2019 (COVID-19) test during screening or at admission is acceptable provided the subject has a known previous COVID-19 infection ≥ 3 weeks prior to dosing, has recovered, and is now asymptomatic.
18. The subject has received study drug in another investigational study within 30 days of dosing.
19. In the opinion of the investigator, the subject is not suitable for entry into the study.

Additional exclusion criteria for subjects in Part 2:

1. Subjects with coagulopathies.
2. Poorly controlled diabetes, defined as HbA1c $>8.5\%$ at screening.

3. The subject has been treated with the following anti-diabetic agents, GLP-1Ra, dipeptidyl peptidase-4 inhibitors (DPP-4i), or insulin, within 30 days prior to screening until the follow-up visit.
4. The subjects with diagnosed diabetes have been on stable anti-diabetic therapies for less than 8 weeks prior to the first dose of study drug.
5. The subjects have $>2 \times$ upper limit of normal (ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or $>1.5 \times$ ULN for bilirubin or alkaline phosphatase at screening.
6. Subjects with contraindications to MRI.

MRI contraindications include, but are not limited to:

- Brain aneurysm clip.
- Implanted neural stimulator.
- Implanted cardiac pacemaker or defibrillator, or presence of intracardiac wires.
- Prosthetic heart valves.
- Cochlear implant.
- Ocular foreign bodies that might be ferromagnetic (eg, metal shavings).
- Other implanted medical devices (eg, insulin pumps).
- Metal shrapnel or bullets still in the body.
- Severe claustrophobia.
- Subjects having difficulty tolerating prolonged positioning within the constraints of the MRI tube. Investigators should use their best judgment to assure that subjects' size will not interfere with MRI imaging at any of the specified time points.
- Tattoos (as determined by the investigator and imager).

4.3 LIFESTYLE CONSIDERATIONS

4.3.1 Caffeine, Alcohol, and Tobacco

1. In Part 1 and Part 3: Subjects will abstain from ingesting alcohol-, caffeine-, or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate), and de-

caffeinated drinks for 48 hours before dosing and for the duration of the confinement period of the study.

2. Subjects will abstain from alcohol for 48 hours prior to study drug administration and during confinement at the study site until discharge.
3. In Part 1 and Part 3: Use of tobacco- or nicotine-containing products will not be allowed from the start of confinement at the study site until after the EOS visit. In Part 2: Use of tobacco- or nicotine-containing products will not be allowed during confinement at the study site until discharge.

4.3.2 Activity

1. Part 1 and Part 3: Subjects should refrain from strenuous exercise within 48 hours prior to admission to the study site and for the duration of the study. Subjects may participate in light recreational activities during the study (eg, watching television, reading).

Part 2: Subjects should maintain their normal physical exercise levels throughout the study.

2. Subjects will be advised not to donate blood or plasma donation for at least 3 months after the last dose administration.

4.4 WITHDRAWAL OF SUBJECTS FROM THE STUDY

4.4.1 Reasons for Withdrawal

Subjects can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment.

The investigator may withdraw a subject from the study if the subject meets any of the following criteria:

1. Is non-compliant with the protocol
2. Experiences a serious AE (SAE) or intolerable AE(s) that in the investigator's opinion requires withdrawal from the study
3. Has laboratory safety assessments that reveal clinically significant hematological or biochemical changes from baseline values

4. Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria
5. Requires a medication prohibited by the protocol
6. Requests an early discontinuation for any reason

The investigator can also withdraw a subject upon the request of the sponsor, or if the sponsor terminates the study. Upon occurrence of an SAE or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed until it is resolved, stable, or judged by the investigator to be not clinically significant.

4.4.2 Handling of Withdrawals

Subjects are free to withdraw from the study at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

When a subject withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, any subject who withdraws from the study prematurely will undergo all ET assessments. Any subject who fails to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

4.4.3 Replacements

At the discretion of the investigator, and after consultation with the medical monitor, any subject who withdraws before completing the study may be replaced to retain the target of 152 evaluable subjects. Any replacement subject will be assigned to receive the same treatment as the subject he or she is replacing.

5. STUDY TREATMENTS

5.1 TREATMENTS ADMINISTERED

Subjects will receive the study drug as described in [Section 3](#) and according to the schedule of events (SOE) for Part 1 ([Section 3.1](#)), Part 2 ([Section 3.2](#)), and Part 3 ([Section 3.3](#)). All study drug dosing will be performed at the clinical unit under the supervision of clinic staff. The study drug will be administered SubQ in the abdomen.

Part 1: The starting DR10624 dose in Part 1 will be 0.5 mg SubQ (Cohort A). The provisional doses in Cohorts B, C, D, E, F, G, H, and P are planned to be 1.5, 4.5, 12.5, 25, 50, 65, 90, and 120 mg SubQ, respectively, with final doses for each cohort determined by the SRC following a full review of the data from the previous cohort. The dose levels may be adjusted by the SRC.

Part 2: Dosing in Part 2 will be permitted only after the blinded safety data through Day 29/EOS after completing the dosing in the last subject in Cohort E in Part 1 has been evaluated and approved by the SRC. The MAD cohorts may run in parallel with the remaining SAD cohorts. The tentative starting DR10624 dose (Cohort I) in Part 2 will be same as the dose in Cohort D of Part 1 (SAD). Final doses for each cohort in Part 2 will be determined by the SRC following a blinded review of the data from the previous cohort. Cohorts J, K and L may titrate to the target dose by assessing tolerance in subjects who have completed their dosing. The final decision on the titration plan will be made by the SRC.

Part 3: The provisional dose of these 3 cohorts in Part 3 may repeat dose levels of Cohort E, F, G, H, or P in Part 1. The tentative starting DR10624 dose (Cohort M) in Part 3 will be same as the dose in Cohort E (25 mg) of Part 1 (SAD). The following doses for each cohort in Part 3 will be determined by the SRC following an evaluation of available safety, tolerability, and PK data for subjects in Part 1 and the safety data and available PK data obtained through Day 15 of the preceding dose cohort of Part 3. The highest DR10624 dose in Part 3 will not exceed the maximum tolerated dose reached in Part 1.

Subjects will be monitored for injection site reactions (eg, warmth, erythema, pruritus, pain, lipodystrophy, edema, ulceration, or necrosis) after the study drug administration, and will be graded for intensity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0 – November 2017. Injection site reactions will be evaluated and managed in accordance with the investigator's medical judgment. If an event is deemed as an immediate hypersensitivity reaction, symptomatic treatment (eg, antipyretics, antihistamines, beta-agonists, oxygen, intravenous fluid) may be administered and vital signs (temperature, blood pressure, heart rate, and respiratory rate) will be monitored every 5 minutes until stable and then every 15 minutes for 2 additional determinations. Study drug dosing will be permanently discontinued if the event is an anaphylactic reaction.

5.1.1 Dose Escalation

The sponsor will form an internal SRC for a blinded review of safety data for each subject and the entire cohort and will make a recommendation on whether to proceed to the next dose level. In Part 1 of the study, except for Cohort A, a sentinel cohort of 2 subjects will be used to mitigate the risk of unexpected AEs not predicted by preclinical pharmacology and toxicology studies for all cohorts. The sentinel subjects in Cohort B to H, and P will be dosed in a blinded fashion (1 active, 1 placebo) and monitored for at least 72 hours before the remaining subjects in that cohort are dosed. Initiation of dosing of the remaining subjects will depend on an initial safety review by the investigator indicating that administration of the study drug was safe and well tolerated in the sentinel subjects. Cohort A will have only a single sentinel subject on active study drug and no subjects on placebo and will have the remaining 3 active subjects dosed after 72 hours as above.

Dose escalation in Part 1 will occur only after the available real time PK, safety, and tolerability data (including reported AEs, vital signs, 12-lead ECGs, Holter ECGs, clinical laboratory results, and physical examination findings through Day 15) of the preceding dose cohort are assessed and the study drug is deemed safe and well tolerated by the SRC. The Day 15 interval after dosing for safety evaluation may be extended with the approval of the sponsor or sponsor's designee.

Dose escalation in Part 2 will occur after the safety, tolerability, and PK data from at least 8 subjects, who have received at least 6 doses of DR10624 or placebo, from the preceding MAD cohort have been reviewed and deemed safe and well tolerated by the SRC.

Dose escalation in Part 3 will occur only after available safety, and PK data for subjects in Part 1, and the available PK, safety, and tolerability data (including reported AEs, vital signs, 12-lead ECGs, clinical laboratory, results, and physical examination findings through Day 15) of the preceding dose cohort of Part 3 are assessed and the study drug is deemed safe and well tolerated by the SRC.

As new safety and/or PK data become available, the anticipated dose escalation scheme listed may change following a review of the data by the SRC. Preliminary PK data from subjects in this study will help guide dose escalation to higher doses.

The SRC member details will be provided in the safety committee charter. The SRC will be composed of the following individuals: the sponsor's medical officer or designee, the sponsor's clinical pharmacology representative or designee (if applicable), the sponsor's study statistician or designee (if applicable), the investigator, the treating physicians (if

applicable), the medical monitor, and other applicable functions as nominated by the SRC chair, appointed by the Sponsor. A coordinator may organize and record decisions of the SRC (non-voting member). A recommendation to stop dosing will be binding.

5.1.2 Dose-Limiting Toxicities

A dose-limiting toxicity (DLT) may be defined as any of the following:

1. A Grade 3 or worse treatment-related TEAE experienced by 2 or more subjects in a cohort, who, after unblinded safety review, are confirmed to have received study drug (DR10624).
2. An SAE or any other medically important AE that impacts subject safety experienced by 1 or more subjects in a cohort, who after unblinded safety review, are confirmed to have related to study drug (DR10624).
3. An AE or reaction judged by the investigator to be drug related during treatment that prevents continuation of treatment due to safety concerns.
4. Any AE judged by the investigator to be drug related (ie, causality rated as possible or greater) that is assessed as Grade 3 or worse according to the NCI-CTCAE, Version 5.0 – November 2017.
5. A DLT may be considered for a subject who withdraws because of intolerable treatment-related TEAE.

The investigator must use his or her judgment in determining whether any event is a DLT.

5.1.3 Dose Escalation Stopping Criteria

Dose escalation will be suspended if any of the following scenarios occur after confirmation of receipt of the study drug:

- Any preclinical or clinical events that, in the opinion of the SRC, contraindicate further dosing of additional subjects with study drug.
- In the opinion of the SRC, data from the previous dose cohort indicating safety concerns for the next cohort to be dosed at a higher level, such as unanticipated responses (e.g., clinically significant changes in clinical laboratory data, ECGs, vital signs, or physical examinations).

- In Part 1 or Part 3, two or more subjects in a dose cohort experience any DLT, or one subject experiences a Grade 3 or higher AE (DLT) that, in the opinion of the SRC, warrants suspension of dose escalation. In Part 2, 50% or more subjects in a dose cohort experience any DLT.
- In Part 1 or Part 3, two or more subjects, in each cohort, have $>3 \times \text{ULN}$ of either ALT or AST, or $>2 \times \text{ULN}$ for bilirubin or alkaline phosphatase where no other reason can be found to explain the increases. In Part 2, two or more subjects, in each cohort, have $>3 \times \text{ULN}$ (if baseline $<\text{ULN}$) or >2 times the baseline value (if baseline $>\text{ULN}$) of either ALT or AST; or $>2 \times \text{ULN}$ (if baseline $<\text{ULN}$) or >2 times the baseline value (if baseline $>\text{ULN}$) for bilirubin or alkaline phosphatase where no other reason can be found to explain the increases.
- In Part 1 or Part 3, one or more subjects, in each cohort, experience a Grade 3 or higher injection site reaction.
- In Part 1 or Part 3, one or more subjects, in each cohort, experience an allergic reaction that meets the criteria for a Grade 3 event (ie, anaphylaxis).

Dose escalation may also be suspended if, in the opinion of the investigator or sponsor, any other significant safety or tolerability issues are identified in the comprehensive review of available data that warrant further evaluation before additional subjects are dosed. This may include emerging nonclinical data, clinically relevant AEs, available PK and PD data, or relevant data from other sources indicating safety concerns even if the event(s) per se does not meet the protocol-specified definition of a DLT. Pharmacokinetics will be measured at every dose level. Exposure limits for escalation will be agreed by the SRC based on all safety, tolerability and PK data collected up until that point.

5.2 INVESTIGATIONAL PRODUCTS

The study drugs that will be used are as follows:

Product	Supplied Formulation
DR10624	Single-dose 2-mL glass vial containing 15.0 mg DR10624 lyophilized powder
	Single-dose 2-mL glass vial containing 40.0 mg DR10624 lyophilized powder
	Single-dose 2-mL glass vial containing 60.0 mg DR10624 injectable solution*

Product	Supplied Formulation
Matching placebo	0 mg solution

*The 60.0 mg (1 ml) /vial study drug will only be used in Part 2.

The 15 mg/vial drug product (DP) is supplied in a single-dose vial as a sterile, preservative-free, white to slightly yellow lyophilized powder for SubQ injection. Each single-dose vial of study drug contains 15.0 mg DR10624, L-histidine (2.33 mg), L-histidine HCl (1.05 mg), sucrose (80.00 mg), and polysorbate 80 (0.30 mg). After reconstitution with 1 mL of preservative-free Sterile Water for Injection, United States Pharmacopeia, the resulting concentration is 15.0 mg/mL DR10624, at a pH of approximately 6.5.

The 40.0 mg/vial study drug is supplied in a single-dose vial as a sterile, preservative-free, white to slightly yellow lyophilized powder for SubQ injection. Each single-dose vial of study drug contains 40.0 mg DR10624, L-histidine (2.33 mg), L-histidine HCl (1.05 mg), sucrose (80.00 mg) and polysorbate 80 (0.30 mg). After reconstitution with 1.1 mL of preservative-free Sterile Water for Injection, US Pharmacopeia, the resulting concentration is 40.0 mg/mL DR10624, at a pH of approximately 6.5.

The 60.0 mg (1 ml) /vial study drug is supplied in a single-dose vial as a sterile, preservative-free, colorless to slightly yellow solution for SubQ injection. Each single-dose vial of study drug contains 60.0 mg DR10624, L-histidine (2.52 mg), L-histidine HCl (0.79 mg), sucrose (80.00 mg) and polysorbate 80 (0.30 mg), a pH of approximately 6.5.

The placebo for DR10624 will be identical in appearance and will contain normal saline.

Further information on the study drug can be found in the investigator's brochure ([Zhejiang Doer Biologics Co., LTD. 2023](#)).

5.2.1 Study Drug Packaging and Storage

Zhejiang Doer Biologics will provide the investigator and clinical unit with adequate quantities of DR10624 and matching placebo. The clinical unit pharmacy will prepare the study drugs for each subject according to the SOE for Part 1 ([Section 3.1](#)), Part 2 ([Section 3.2](#)) and Part 3 ([Section 3.3](#)). Detailed instructions for the preparation of study drugs will be provided in a separate pharmacy manual.

All study drugs must be stored according to the labeled instructions in a secure cabinet or room with access restricted to necessary clinic personnel. The site will be required to keep a temperature log to establish a record of compliance with storage conditions.

5.2.2 Study Drug Accountability

The investigator will maintain accurate records of receipt of all study drugs, including dates of receipt. Accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, and to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained (except for dosing syringes that will be discarded per site standard procedure) or destroyed according to applicable regulations.

5.3 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

PPD will generate the randomization system. Eligible subjects will be randomly assigned as described in [Section 3](#) and after all entry criteria have been satisfied prior to dosing on Day 1. Within each cohort (except Cohort A), subjects will be randomly assigned to receive either DR10624 or placebo (Parts 1, 2 and 3). Randomization of subjects in each cohort will be carried out by an independent and qualified person, based on a manual randomization system, who is not directly involved in study conduct, data management, or data analysis.

5.4 BLINDING

5.4.1 Blinding Procedures

This study will employ a double-blind study design. The DR10624 and matching placebo will be identical in appearance. The unblinded pharmacist will be responsible for dispensing the study drug in a manner consistent with maintaining the blind. Neither the subjects nor the investigator will be aware of the treatment assignment. Access to the randomization code will be strictly controlled according to the standard operating procedures of the clinic.

5.4.2 Breaking the Blind

The medical monitor will be responsible for maintaining the blind throughout the study. A subject or subjects may be unblinded in the event of a DLT, SAE, or other event, or if there is a medical emergency where the identity of the drug must be known to properly treat a subject. A cohort may be unblinded to determine if dose escalation to the next dose level will terminate. If a subject becomes seriously ill or pregnant during the study, the blind will be broken only if knowledge of the administered study drug will affect that subject's available treatment options. In the event of a medical emergency requiring identification of the study

drug administered to an individual subject, the investigator will make every attempt to contact the medical monitor to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved. Unblinding will be handled via the manual randomization system.

5.5 TREATMENT COMPLIANCE

All doses of the study drug will be administered in the clinical unit under direct observation of clinic personnel and recorded in the eCRF. Clinic personnel will confirm that the subject has received the entire dose of study drug.

The date and time of study drug dosing will be recorded on the appropriate page of the eCRF. If a subject is not administered study drug, the reason for the missed dose will be recorded.

5.5.1 Prior and Concomitant Medications

Restrictions for prior and concomitant medications and therapies are provided in [Sections 4.1](#) and [4.2](#). Prior and concomitant medications and therapies will be coded using the latest version of the World Health Organization Drug Dictionary.

For Part 1 only, subjects may be pre-treated with medication for the prevention of nausea at the discretion of the Principal Investigator.

Medications required to treat any AEs that the subject experiences during the study are permitted.

Vaccinations will be allowed during the screening period but not be permitted from the start of dosing and to the end of the study.

For Part 2 only, subjects will be allowed to use nutritional supplements that contains fish oil (or Omega-3 fatty acids), lipid-lowering drugs, and anti-diabetic drugs (excluding GLP-1RA, DPP-4i, and insulin), as long as they have been on stable doses for more than 8 weeks before the first dose of study drug. Subjects will be allowed to use anti-hypertensive drugs and any other prescribed drugs to treat comorbidities, provided that the medication does not affect lipid metabolism.

For Part 2 only, subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes at screening, during the CGM measurement period, will not be allowed to use

substances that may interfere with CGM per the device manual and American Diabetes Association guidelines ([ElSayed et al 2023](#)).

5.5.1.1 Prior Medications

Information regarding prior medications taken by the subject within the 30 days before signing the informed consent form (ICF) will be recorded in the subject's eCRF.

5.5.1.2 Concomitant Medications

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the investigator. If a concomitant medication is taken, except for those specified in the protocol, a joint decision will be made by the investigator and the sponsor to continue or discontinue the subject based on the time the medication was administered, its pharmacology and PK, and whether the use of the medication will compromise the safety of the subject or the interpretation of the data. The investigator is responsible for ensuring that details regarding the medication are adequately recorded in the eCRF.

6. STUDY PROCEDURES

Before performing any study procedures, all potential subjects will sign an ICF as outlined in [Section 9.2.2.3](#). Subjects will undergo study procedures at the time points specified in the SOE for Part 1 ([Section 3.1](#)), Part 2 ([Section 3.2](#)), and Part 3 ([Section 3.3](#)).

The total amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL.

6.1 PHARMACOKINETIC ASSESSMENTS AND ENDPOINTS

Blood samples for PK analysis of DR10624 will be collected at the time points specified in the SOE for Part 1 ([Section 3.1](#)), Part 2 ([Section 3.2](#)), and Part 3 ([Section 3.3](#)). The single and multiple-ascending dose PK parameters will be calculated as endpoints for DR10624 using actual sampling times rather than scheduled sampling times.

The following serum PK parameters will be calculated as primary PK endpoints, but are not limited to:

- Part 1, and Part 3:
 - AUC from time 0 to the last quantifiable concentration (AUC_{0-t})
 - AUC from time 0 extrapolated to infinity (AUC_{0-inf})
 - C_{max}
 - T_{max}
 - Terminal elimination half-life ($t_{1/2}$)
 - Mean residence time (MRT)
 - Apparent clearance after extravascular administration (CL/F)
 - Apparent volume of distribution during the terminal elimination phase after extravascular administration (V_z/F)
- Part 2, Day 1:
 - AUC from time 0 to the time of the dosing interval (τ ; $AUC_{0-\tau}$)
 - C_{max}
 - T_{max}
- Part 2, Day 78:
 - $AUC_{0-\tau}$ at steady state ($AUC_{0-\tau,ss}$)
 - C_{max} at steady state ($C_{max,ss}$)
 - AUC_{0-t}
 - T_{max}
 - $t_{1/2}$

- Accumulation ratio (AR), calculated as $AUC_{0-\tau}$ (Day 78) / $AUC_{0-\tau}$ (Day 1)
- Predose concentrations on Days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and concentration on Day 78 (C_{trough})
- Systemic apparent clearance at steady state (CL/F_{ss})
- Steady-state apparent volume of distribution (V_z/F_{ss})

Dose-normalized AUCs and C_{max} and other additional PK parameters will be estimated to support the primary PK endpoints.

6.1.1 Pharmacokinetic Sample Collection

Details for the collection, processing, storage, and shipping of PK samples will be provided to the clinical unit in a separate PK manual.

6.1.2 Pharmacokinetic Sample Analysis

Pharmacokinetic samples will be analyzed using a validated assay for the PK assessments. Assay results and validation details will be provided in a separate bioanalytical report.

6.2 PHARMACODYNAMIC ASSESSMENTS AND ENDPOINTS

Blood samples for PD analysis of DR10624 will be collected at the time points specified in the SOE for Part 2 (MAD cohorts; [Section 3.2](#)). The following PD endpoints will be assessed:

- Mean and percent change in body weight and adiponectin at protocol-specified time points from baseline through Day 85/end-of-treatment period (EOT)
- Mean change in BMI and, waist circumference at protocol-specified time points from baseline through Day 85/EOT
- Mean and percent change in fasting lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, Lp(a), VLDL cholesterol, triglycerides, and free fatty acids) at protocol-specified time points from baseline through Day 85/EOT
- Mean and percent change in FPG from baseline through Day 85/EOT; mean change in HbA1c, C-peptide, fasting insulin, and glucagon; and HOMA-IR (calculated by $\text{fasting insulin } [\mu\text{U/mL}] \times \text{FPG } [\text{mmol/L}] / 22.5$) and HOMA-B (calculated by $20 \times \text{fasting insulin}$

$[\mu\text{U/mL}] / (\text{FPG} [\text{mmol/L}] - 3.5)$ at protocol-specified time points from baseline through Day 85/EOT

- The following PD response parameters will be calculated as endpoints using the standard 4-hour MMTT:
 - Partial area under the baseline-corrected glucose, C-peptide, insulin, and glucagon levels versus time curve from time 0 to 4 hours ($\Delta\text{AUC}_{0-4\text{h}}$) post meal on Day -1, Day 28, and Day 79.
- Mean change in TIR, TAR, TBR, 24-hour mean glucose, and glucose variability (coefficient of variation [CV]) at protocol-specified time points from baseline through Day 85/EOT in subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes at screening.
- Percent change from baseline in hepatic fat fraction measured by MRI-PDFF for the MAD cohorts, and in prespecified subgroup with MRI-PDFF $\geq 8\%$.
- Change from baseline in liver stiffness by FibroScan in subjects with baseline hepatic fat of at least 8% measured by MRI-PDFF.
- Change in the liver function parameters (ALT, AST, ALP, and GGT) at protocol-specified time points from baseline through Day 85/EOT.
- Change in FIB-4 and NFS at protocol specified time points from baseline through Day 85/EOT.

If relevant, population PK and PK/PD modeling will be used to evaluate drug exposure and exposure-response relationship for various PD endpoints.

6.2.1 Pharmacodynamic Sample Collection

Details for the collection, processing, storage, and shipping of PD samples will be provided to the clinical unit in a separate PD laboratory manual.

6.2.2 Pharmacodynamic Sample Analysis

Pharmacodynamic samples will be analyzed using a validated assay for the PD assessments. Assay results and validation details will be provided in a separate bioanalytical report.

6.3 SAFETY ASSESSMENTS AND ENDPOINTS

Safety and tolerability will be assessed by the following endpoints: monitoring and recording of AEs (including SAEs and AESIs), clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), serum calcitonin (Part 2 only), vital sign measurements (systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature), 12-lead ECG results, Holter results, and physical examination findings.

For all safety assessments, the investigator will determine whether results are clinically significant, which is defined as any variation in a result that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If clinical significance is noted, the result and reason for significance will be documented and an AE reported on the AE page of the subject's eCRF. The investigator will monitor the subject until the result has reached the reference range or the result at screening, or until the investigator determines that follow-up is no longer medically necessary.

Blood samples for immunogenicity analysis of DR10624 will be collected at the time points specified in the SOE for Part 1 ([Section 3.1](#)), Part 2 ([Section 3.2](#)), and Part 3 ([Section 3.3](#)). Immunogenicity will be assessed as incidence of ADAs and titer of positive ADAs.

6.3.1 Adverse Events

Adverse events will be assessed from the time of study drug dosing until EOS visit and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the sponsor, regardless of their relationship to study drug or clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

6.3.1.1 Adverse Event Definitions

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the study drug caused the AE. For the purposes of investigational new drug safety reporting, “reasonable possibility” means that there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

An adverse reaction is any AE caused by a study drug. Adverse reactions belong to a subset of all suspected adverse reactions and indicate that there are reasons to conclude that the study drug caused the event.

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator’s brochure or if it occurs with specificity or severity that has not been previously observed with the study drug being tested; or, if an investigator’s brochure is not required or available, the AE or suspected adverse reaction is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator’s brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator’s brochure listed only cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator’s brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

An AE or suspected adverse reaction is considered an SAE/suspected unexpected serious adverse reaction if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered “life threatening” if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that might have caused death if it had been more severe.

6.3.1.2 Adverse Events of Special Interest

All subjects enrolled in the study will be monitored for AESIs from enrollment through the EOS visit. Adverse events of special interest include confirmed hypoglycemia events, injection site reactions, and Grade 3 or higher anaphylaxis. Confirmed hypoglycemic events are defined as events requiring assistance from another person with carbohydrate, glucagon, or other resuscitative actions and/or confirmed by a plasma glucose value of <3.9 mmol/L (70 mg/dL) with or without symptoms in line with hypoglycemia in subjects with diagnosed T2D enrolled in Part 2, and/or confirmed by a plasma glucose value of <3.0 mmol/L (55 mg/dL) with or without symptoms in line with hypoglycemia in subjects without diagnosed T2D enrolled in Part 2 and subjects enrolled in Part 1, and/or confirmed by a plasma glucose value of <2.8 mmol/L (50 mg/dL) with or without symptoms in line with hypoglycemia in subjects enrolled in Part 3. A CGM-measured hypoglycemic event in Part 2 is defined as 15 consecutive minutes with a sensor glucose value <3.0 mmol/L (54 mg/dL); the hypoglycemic event will be considered as “ended” once at least 15 consecutive minutes have elapsed with a sensor glucose concentration ≥ 3.9 mmol/L (70 mg/dL); events must be separated by at least 30 minutes and presence or absence of symptoms during low excursions will be solicited.

All injection site reactions, including reports of pain and burning, and information regarding their time of day, time relative to injection, size, amount of erythema, induration, and pruritus, as well as severity and any medications taken to treat the conditions, will be recorded on subject’s eCRF. In addition, if the reaction is clinically significant, the site will attempt to contact the sponsor for potential follow-up procedures.

6.3.1.3 Eliciting and Documenting Adverse Events

Subjects will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to subject observations, AEs will be documented from any data collected on the AE page of the eCRF (e.g., laboratory values, physical examination findings, and ECG changes) or other documents that are relevant to subject safety.

6.3.1.4 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, dosage, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, any required treatment or evaluations, and outcome. Any AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition that is present at the time that the subject is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Any AE that is considered serious by the investigator or which meets SAE criteria ([Section 6.3.1.1](#)) must be reported to the sponsor immediately (after the investigator has confirmed the occurrence of the SAE) with an SAE report form within 24 hours. The investigator will assess whether there is a reasonable possibility that the study drug caused the SAE. The sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in current ICH Guideline for Good Clinical Practice and the National Regulatory Requirements. The investigator is responsible for notifying the institutional review board (IRB) directly. All AESIs will be reported as per local regulations.

For this study, the following contact information will be used for SAE reporting:

PPD Medical Monitor: Telephone (24 hour): 1-888-483-7729
e-mail: rtpsafety@ppd.com
Fax: 1-888-529-3580

Zhejiang Doer Biologics Medical Monitor: June (Junfang) Xu, M.D.
Chief Medical Officer, Huadong Medicine Co., Ltd
No. 866 Moganshan Road, Hangzhou, China
310011
Telephone: +86 17612101816

6.3.1.5 Reporting a Pregnancy

The sponsor must be notified immediately in the event of pregnancy occurring during the course of the study. Pregnancy is not considered as an AE and therefore should not be reported as an AE. All pregnancy events will be recorded with the pregnancy report form. If permission is granted by the mother, pregnancy will be followed until its completion or termination using the designated sections of the pregnancy report form. If an SAE occurs during pregnancy, either to the mother or fetus, it must be reported with the submission of an SAE report form.

6.3.1.6 Assessment of Severity

The severity (or intensity) of an AE refers to the extent to which it affects the subject's daily activities and will be graded according to the NCI-CTCAE Version 5.0 (November 2017). If an AE is not listed in the NCI-CTCAE, it should be graded on general guideline for Grade 1 through 5 according to the NCI-CTCAE Version 5.0 (November 2017; [Table 6-1](#)).

Table 6-1 Severity Grade of NCI-CTCAE Version 5.0

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL ^(a)
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL ^(b)
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

Abbreviation: ADL, Activities of Daily Living

^(a) Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

^(b) Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in the severity of an AE should be documented to allow the duration of the event at each level of intensity to be assessed. An AE characterized as intermittent does not require documentation of the onset and duration of each episode.

6.3.1.7 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (i.e., whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be classified as follows:

- Not related: There is not a reasonable possibility of relationship to study drug. The AE does not follow a reasonable temporal sequence from study drug administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).
- Related: There is a reasonable possibility of relationship to study drug. The AE follows a reasonable temporal sequence from study drug administration and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, or concomitant medications), represents a known reaction to the study drug or other drugs in its class, is consistent with the known pharmacological

properties of the study drug, and/or resolves with discontinuation of the study drug (and/or recurs with re-challenge, if applicable).

6.3.1.8 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

6.3.2 Clinical Laboratory Testing

Clinical laboratory testing will occur at the time points (and the allowable window) indicated in the SOE for Part 1 ([Section 3.1](#)), Part 2 ([Section 3.2](#)), and Part 3 ([Section 3.3](#)). Clinical laboratory tests will be performed by the clinical sites' local laboratories. Blood and urine samples will be collected under fasting conditions and will be prepared using standard procedures.

Repeat assessment for clinical laboratory tests may be performed once, if necessary, to evaluate inclusion and exclusion criteria or clinical laboratory abnormalities. The clinical laboratory that will perform the tests will provide the reference ranges for all clinical laboratory parameters. Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter.

The following clinical laboratory assessments will be performed:

Hematology	Absolute neutrophil count and leukocyte differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, and red blood cell distribution width
Serum Chemistry	ALT, albumin, alkaline phosphatase, amylase, AST, bilirubin (total), urea or urea nitrogen, calcium, bicarbonate or carbon dioxide binding force, chloride, cholesterol (total, HDL, LDL, VLDL), free fatty acids, creatinine, gamma-glutamyl transferase, glucose, lactate dehydrogenase, lipase, phosphorus, potassium, sodium, total protein, triglycerides, and uric acid <u>Subjects in Part 1: Fasting glucose and lipid profile.</u>
Coagulation	Activated partial thromboplastin time, international normalized ratio, and prothrombin time

Urinalysis	Appearance (if applicable), bilirubin, color (if applicable), glucose, ketones, leukocytes, reflex microscopy (performed if dipstick is positive for protein or the blood value is 1+ or greater; and includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, occult blood, pH, protein, specific gravity, and urobilinogen
Serology	Hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus antibody types 1 and 2 (screening only) SARS-CoV-2 (as per site practice)
Other Analyses	<u>All subjects:</u> Urine drug screen (alcohol [alcohol breath test or urine alcohol testing will be performed as per site's standard procedure], amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolites, methamphetamines, methylenedioxymethamphetamine, and opiates [including heroin, codeine, and oxycodone]), and ADA <u>Female subjects:</u> Follicle-stimulating hormone for confirming postmenopausal status, pregnancy test for women of childbearing potential (human chorionic gonadotropin); serum or urine, per SOE <u>Subject in Part 1 and Part 3:</u> Calcitonin <u>Subjects in Part 2:</u> Adiponectin and calcitonin <u>Subjects in Part 2:</u> Fasting glucose, fasting insulin, C-peptide, HbA1c, glucagon, and fasting lipid profile (total cholesterol, non-HDL cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, VLDL cholesterol, free fatty acids and Lp[a]).

6.3.3 Vital Sign Measurements

Vital signs will be measured after the subject has been in the semi-supine position for at least 5 minutes at the time points (and the allowable window) indicated in the SOE for Part 1 (Section 3.1), Part 2 (Section 3.2), and Part 3 (Section 3.3). Vital signs may be measured at additional time points at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature.

6.3.4 12-Lead Electrocardiograms

Single 12-lead ECG recordings will be made after the subject has been in the semi-supine or supine position for at least 5 minutes at the time points (and the allowable window) indicated in the SOE for Part 1 (Section 3.1). In the event a value is outside of the reference range for a subject in Part 1, this will be confirmed by 2 further repeat measurements, which will then be calculated as a mean of the original value and the 2 repeat measurements.

Triplicate 12-lead ECG recordings will be made after the subject has been in the semi-supine or supine position for at least 10 minutes at the time points (and the allowable window) indicated in the SOE for Part 2 ([Section 3.2](#)) and Part 3 ([Section 3.3](#)). The triplicates will be performed at approximately 1-minute intervals. Each ECG recording (trace) will last 10 seconds. In the event an average value is outside of the reference range for a subject in Part 2 and Part 3 at screening, this will be confirmed by 2 further single 12-lead ECG measurements, which will then be calculated as a mean of the original average value and the 2 repeat measurements.

Electrocardiogram assessments will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST-segment, T-wave, and U-wave abnormalities. In addition, measurements of the following intervals will be measured and reported: RR interval, PR interval, QRS width, QT interval, and QTcF.

6.3.5 Continuous Holter Electrocardiograms

The 12-lead Holter monitor will be started at the time points indicated in the SOE for Part 1 ([Section 3.1](#)). The continuous 12-lead digital ECG data will be stored on secured digital memory cards to be analyzed in the future. Twelve-lead ECGs will be extracted in replicates from the continuous ECG recording at predetermined time points matched to PK sampling and will be collected and analyzed. For the predose time points, extraction will occur at 60, 45, and 15 minutes prior to dosing. Holter recording time points may be adjusted as needed based on SRC review of available PK data.

6.3.6 Physical Examinations

A full physical examination will be performed at screening and will include, at minimum, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. A brief physical examination will be performed indicated in the SOE for Part 1 ([Section 3.1](#)), Part 2 ([Section 3.2](#)), and Part 3 ([Section 3.3](#)) and will include, at minimum, assessment of skin, lungs, cardiovascular system, and abdomen (liver and spleen). Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

6.3.7 Continuous Glucose Monitoring (Part 2 Only)

For baseline CGM, subjects with abnormal blood glucose, elevated HbA1c, or with a history of diabetes at screening will be fitted with a blinded sensor during the 14-day prerandomization phase prior to check-in and up to predose on Day 1. If the day of dosing changes or any subjects completing their CGM earlier than check-in and are within the screening window then the subjects will be considered for admission and dosing. The subjects with a history of diabetes will be required to continue the recommended 2 or more blood glucose meter checks per day that they perform as standard of care during the blinded CGM run-in period prior to check-in. Additional blinded sensors configured to record glucose concentrations will be fitted from Day 22 to Day 36, and Day 71 to Day 85.

Subjects will have an in-person session to review CGM insertion and blinded CGM use. The blinded receivers will be configured to record glucose concentrations not visible to the subjects, and there will be no alerts for out-of-range glucose excursions.

6.3.8 Glucometer Monitoring (Part 2 Only)

A glucometer will be provided to all subjects in Part 2. Subjects will routinely monitor fasting blood glucose at least twice weekly throughout the study period and will be counseled on identification and management of hypoglycemia and hyperglycemia.

6.3.9 MRI-PDFF (Part 2 Only)

MRI-PDFF measurements will be performed at screening and between Day 85 to 99 in subjects receiving multiple SubQ doses of DR10624 or placebo. In subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes, the MRI-PDFF at screening will be performed prior to the 14-day predose CGM measurements. If applicable, MRI-PDFF will be conducted at ET only if the subject has received ≥ 6 weeks of treatment with study drug. For subjects that early terminate, MRI-PDFF measurement will be arranged as soon as possible.

6.3.10 FibroScan (Part 2 Only)

FibroScan measurements will be performed at screening and on Day 85 (a window of ± 2 days is allowed), or if applicable, at ET visit (only if the subject has received ≥ 6 weeks of treatment with study drug) in subjects with baseline hepatic fat of at least 8% measured by MRI-PDFF.

6.3.11 Satiety Test (Part 2 Only)

For the MAD cohorts (Part 2), a commercially available visual analogue scale will be used by trained personnel to assess satiety at the time points indicated in the SOE ([Section 3.2](#)).

7. STATISTICAL ANALYSIS PLANS

7.1 SAMPLE SIZE CALCULATIONS

The number of subjects at each part/cohort is based on clinical and practical considerations and not on statistical hypotheses. Approximately 152 subjects are planned for the study.

7.2 ANALYSIS SETS

The analysis populations are as follows:

- The safety analysis set will include all subjects who receive at least 1 dose of DR10624 or placebo.
- The PK analysis set will include subjects who receive at least 1 dose of DR10624 and have sufficient concentration data to support accurate estimation of at least 1 PK parameter.
- The PD analysis set will include subjects who receive at least 1 dose of DR10624 or placebo and have at least 1 PD measurement at baseline and postbaseline.
- The immunogenicity analysis set will consist of all subjects who receive at least 1 dose of DR10624 and have the baseline sample and at least 1 postbaseline sample ADA assessment.

7.3 STATISTICAL ANALYSIS

Details of all statistical analyses will be described in a separate Statistical Analysis Plan. All data collected will be presented in data listings. For each part, data from subjects receiving placebo in each cohort will be pooled into 1 placebo group for analysis.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, SD, minimum, and maximum).

Baseline demographic and background variables will be summarized overall for all subjects. The number of subjects who enroll in the study and the number and percentage of subjects

who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

7.3.1 Pharmacokinetic Analyses

Serum concentration data will be listed and summarized by scheduled time point for each treatment and cohort within each part of the study separately using descriptive statistics (number of subjects, mean, standard deviation [SD], CV, median, minimum, and maximum). Serum concentration versus time profiles for each subject will be presented graphically. The mean serum concentrations versus scheduled time profiles will be presented graphically by treatment and cohort within each part of the study separately.

The PK parameters of DR10624 will be analyzed based on the actual sampling times. Pharmacokinetic parameters derived from serum samples using noncompartmental methods with Phoenix[®] WinNonlin[®] Version 8.3 or higher (Certara USA Inc., Princeton, New Jersey) or SAS[®] Version 9.4 or higher (SAS Institute Inc., Cary, North Carolina). Geometric means and geometric mean CV will be reported for all PK parameters except for T_{max} .

For part 3, the effect of BMI ($BMI \geq 28 \text{ kg/m}^2$ subgroup vs $BMI < 28 \text{ kg/m}^2$ subgroup) on DR10624 PK profiles may be explored.

Plots of dose-normalized AUCs and C_{max} versus dose will be presented for each of the 3 parts separately. Dose proportionality will be tested for each of the 3 parts using the power regression model for AUCs and C_{max} . The model is defined as:

$$\ln[\text{PK parameter}] = \beta_0 + \beta_1 \ln[\text{dose}]$$

where the PK parameter is AUC or C_{max} . The null hypothesis being tested is that the AUCs and C_{max} values are dose proportional, or slope (β_1) = 1 and within 90% CI of the slope.

Mean trough (predose) concentrations plots in Part 2 will be provided by treatment and cohort to visually assess steady state.

Steady state will be tested in Part 2 by regression analysis of trough level concentrations of individual subjects from samples collected on Days 8 through 78. The model to be used to estimate the slope and corresponding 90% CI is:

$$C_{\text{trough}} = \beta_0 + \beta_1(\text{day} + \text{error})$$

Statistical evidence that the subject has not achieved steady state will be found if the slope is positive and significantly different from 0 at the 5% level.

The relationship between immunogenicity status (ADA-negative or transiently and persistently ADA-positive, and low or high ADA titer) and serum drug concentration and PK parameters may be explored. All data will be provided by subject listings.

7.3.2 Pharmacodynamic Analyses

Mean and percent change from baseline through Day 85/EOT in body weight and mean change in BMI, waist circumference, adiponectin, and FPG will be analyzed by the standard mixed model for repeated measurements for MAD cohorts.

Mean and percent change from baseline through Day 85/EOT in total cholesterol, LDL cholesterol, HDL cholesterol, non-HDL cholesterol, Lp(a) cholesterol, VLDL cholesterol, triglycerides, and free fatty acids will be log transformed and analyzed by the standard mixed model for repeated measurements for MAD cohorts. The estimated differences and corresponding 95% CIs at Day 85 will be back transformed and presented as ratios.

Mean and percent change from baseline through Day 85/EOT in HbA1c, C-peptide, fasting insulin, and glucagon and HOMA-IR (calculated by $\text{fasting insulin } [\mu\text{U/mL}] \times \text{FPG } [\text{mmol/L}] / 22.5$) and HOMA-B (calculated by $20 \times \text{fasting insulin } [\mu\text{U/mL}] / (\text{FPG } [\text{mmol/L}] - 3.5)$) will be log-transformed and analyzed by the standard mixed model for repeated measurements in obese subjects with modest hypertriglyceridemia receiving multiple SubQ doses of DR10624. The estimated differences and corresponding 95% CIs will be back transformed and presented as ratios.

For PD response parameters calculated using a noncompartmental method ($\Delta\text{AUC}_{0-4\text{h}}$ in glucose, C-peptide, insulin, and glucagon levels), summary statistics (number of observations, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum) will be presented by time point and treatment for MAD cohorts.

Pharmacodynamics response parameters on the original scale will be analyzed using statistical modeling for repeated measurements. The difference between the least-squares means and the corresponding 95% CIs for the least-squares means will be presented. The primary comparison will be DR10624 to placebo. The comparison by treatment to placebo will also be performed.

The change from baseline in glucose, C-peptide, fasting insulin, and glucagon levels will be listed and summarized by time point and treatment for the MAD cohorts using descriptive

statistics (number of subjects, mean, SD, CV, median, minimum, and maximum). Glucose, C-peptide, fasting insulin, and glucagon levels versus time profiles for each subject of the MAD cohorts will be presented graphically. The mean glucose, C-peptide, fasting insulin, and glucagon levels versus scheduled time profiles will be presented graphically by dose for the MAD cohorts.

Baseline CGM-measured outcomes will be calculated for those obese subjects with modest hypertriglyceridemia, who have abnormal blood glucose, or elevated HbA1c, or a history of diabetes at screening, using the blinded sensor data collected during the 14-day prerandomization phase prior to check-in and up to predose on Day 1. If the day of dosing changes or any subjects have completed their CGM earlier than check-in and are within the screening window then the subjects will be considered for admission and dosing.

CGM-measured outcomes after multiple-doses of DR10624 or placebo will be calculated on Days 22 to 36 and on Day 71 to Day 85/EOT. The CGM outcome measures will include percentage of time spent in target range 3.9 to 10.0 mmol/L, 24-hour mean glucose, glucose variability (CV), time in hyperglycemic (>10.0 mmol/L, >13.9 mmol/L, >16.7 mmol/L), and hypoglycemic (<3.9 mmol/L, <3.3 mmol/L, <3.0 mmol/L) ranges, and rate of hypoglycemic events per week (overall and nighttime event rates).

In Part 2, the percent change from baseline in hepatic fat fraction measured by MRI-PDFF for the MAD cohorts and in a prespecified subgroup with MRI-PDFF $\geq 8\%$ will be listed and summarized by time point and treatment for the MAD cohorts using descriptive statistics.

In Part 2, actual values and changes from baseline in liver stiffness measured by FibroScan in subjects with baseline hepatic fat of at least $\geq 8\%$ measured by MRI-PDFF will be listed and summarized by treatment using descriptive statistics.

Actual values and changes from baseline in ALT, AST, ALP and GGT will be listed and summarized by time point and treatment for the MAD cohorts using descriptive statistics.

Actual values and changes from baseline in FIB-4 and NFS will be listed and summarized by time point and treatment for the MAD cohorts using descriptive statistics.

Satiety in the VAS will be summarized by treatment and time at 0-hour (premeal), 1-hour, 2-hour, 3-hour, 4-hour, 5-hour, and 6-hour from the start time of the meal during every mixed meal tolerance test (MMTT).

7.3.3 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of the MedDRA and summarized by treatment, each part, and overall. All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by treatment and overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will also be presented in data listings.

Number of confirmed treatment-emergent hypoglycemic events will be summarized by treatment and overall. All AESIs will be presented in a data listing.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings will be presented in data listings. In addition, the number and proportion of subjects with morphological and/or rhythm abnormalities on ECG, the number and proportion of subjects with clinically significant changes in ECG time intervals (PR, QRS, QT, and QTc intervals), and the number and proportion of subjects with ECG interval values meeting the criteria will be tabulated (e.g., QTc $\leq$ 450 ms, > 450 to $\leq$ 480 ms, > 480 ms to $\leq$ 500 ms, and > 500 ms).

The Holter results in Part 1, actual values and changes from baseline will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated and presented in data listings. In addition, the number and proportion of subjects with morphological and/or rhythm abnormalities on ECG, the number and proportion of subjects with clinically significant changes in ECG time intervals (PR, QRS, QT and QTc intervals), and the number and proportion of subjects with ECG interval values meeting the criteria will be tabulated (e.g., QTc $\leq$ 450 ms, > 450 to $\leq$ 480 ms, > 480 ms to $\leq$ 500 ms, and > 500 ms).

Proportion of subjects positive or negative for ADAs will be summarized in a frequency table by treatment and by visit. For subjects with positive result for ADA, the titer values of ADAs will be summarized by treatment and by visit. Antidrug antibodies will be presented in data listings. Below ADAs categories will be summarized:

- Anti-DR10624 antibody

- Anti-DR10624 antibody with in vitro neutralizing effect (NADA)

For all safety assessments, the investigator will determine whether the results are clinically significant.

7.4 HANDLING OF MISSING DATA

Serum concentrations that are below the limit of quantification (BLQ) will be treated as 0 for descriptive statistics. Mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable. Missing concentrations will be excluded from the calculations.

For the PK analysis, BLQ values will be treated as 0 with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing. Missing concentrations will be treated as missing from the PK parameter calculations.

7.5 INTERIM ANALYSES

No formal interim safety analyses will be performed in this study.

For each cohort, blinded safety data and available PK data will be reviewed before dosing in the next dose cohort and/or before dosing in Part 2 is allowed ([Section 3](#) and [Section 5.1.1](#)).

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9. APPENDICES

9.1 APPENDIX 1: LIST OF ABBREVIATIONS

Abbreviation	Term
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AR	accumulation ratio
AST	aspartate aminotransferase
AUC	area under the serum concentration versus time curve
AUC _{0-inf}	area under the serum concentration versus time curve from time 0 extrapolated to infinity
AUC _{0-t}	area under the serum concentration versus time curve from time 0 to the last quantifiable concentration
Δ AUC _{0-4h}	area under the baseline subtracted levels versus time curve from time 0 to 4 hours
AUC _{0-τ}	area under the serum concentration versus time curve from time 0 to the time of the dosing interval
AUC _{0-τ,ss}	area under the serum concentration versus time curve from time 0 to the time of the dosing interval at steady state
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
CGM	continuous glucose monitoring
CI	confidence interval
CL/F	apparent clearance after extravascular administration
CL/F _{ss}	systemic apparent clearance at steady state
C _{max}	maximum observed serum concentration
C _{max,ss}	maximum observed serum concentration at steady state
COVID-19	coronavirus disease 2019
C _{trough}	predose concentrations
CV	coefficient of variation
Da	Daltons
DBP	diastolic blood pressure
DLT	dose-limiting toxicity
DPP-4i	dipeptidyl peptidase-4 inhibitors
ECG	electrocardiogram
eCRF	electronic case report form
EOS	end-of-study
EOT	end-of-treatment period
ET	early termination

Abbreviation	Term
FDA	Food and Drug Administration
FGF21R	fibroblast growth factor 21 receptor
FIB-4	Fibrosis 4 score
FIH	first-in-human
FPG	fasting plasma glucose
FSH	follicle-stimulating hormone
GGT	gamma-glutamyl transferase
GIP	gastric inhibitory peptide
GIPR	gastric inhibitory peptide receptor
GLP-1	glucagon-like peptide-1
GLP-1R	glucagon-like peptide-1 receptor
GLP-1R/GCGR/FGF21R	glucagon-like peptide-1 receptor/glucagon receptor/fibroblast growth factor 21 receptor
GCG	glucagon
GCGR	glucagon receptor
HbA1c	glycated hemoglobin
HDL	high density lipoprotein
HED	human equivalent dose
hIgG1-Fc	fragment crystallizable of human immunoglobulin G subclass1
HOMA-B	homeostatic model assessment index of beta-cell function
HOMA-IR	homeostatic model assessment index of insulin resistance
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
IRT	interactive response technology
IUD	intra-uterine device
LDL	low density lipoprotein
LP(a)	lipoprotein (a)
LS	least-square
MAD	multiple-ascending dose
MTD	maximum tolerated dose
MedDRA	Medical Dictionary for Regulatory Activities
MetS	metabolic syndrome
MMTT	mixed meal tolerance test
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging – proton density fat fraction
MRT	mean residence time
NADA	antidrug antibody with in vitro neutralizing effect
NASH	nonalcoholic steatohepatitis
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NFS	non-alcoholic fatty liver disease fibrosis score
NOAEL	no-observed-adverse-effect level

Abbreviation	Term
Non-HDL	Non-high-density lipoprotein
OGTT	oral glucose tolerance test
PCR	polymerase chain reaction
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PLT	platelet
QTcF	QT interval corrected for heart rate using Fridericia's formula
RAT	rapid antigen test
RP2D	recommended Phase 2 dose
SAD	single-ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SD	standard deviation
SOE	schedule of events
SRC	safety review committee
SubQ	subcutaneous
$t_{1/2}$	terminal phase half-life
TAR	time above target range
TBR	time below target range
TEAE	treatment-emergent adverse event
TIR	time in range
T_{max}	time to reach maximum observed serum concentration
ULN	upper limit of normal
VAS	visual analogue scale
V_z/F_{ss}	steady-state apparent volume of distribution
VLDL	very low-density lipoprotein

9.2 APPENDIX 2: STUDY GOVERNANCE

9.2.1 Data Quality Assurance

This study will be conducted using the quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current ICH guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice, the protocol, and standard operating procedures. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with 21 Code of Federal Regulations 11. Each person involved with the study will have an individual identification code and password that allows for record traceability.

Important protocol deviations, should they occur during the study, will be presented in Section 10.2 of the clinical study report.

9.2.2 Investigator Obligations

The following administrative items are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

9.2.2.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the regulatory authorities, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

9.2.2.2 Institutional Review

Federal regulations and ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study that is to be provided to the subject or the subject's legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH 93 Harmonised Tripartite Guideline E6 (R2): Good Clinical Practice will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

9.2.2.3 Subject Consent

Written informed consent in compliance with ICH E6(R2) guidelines and applicable regulatory requirements shall be obtained from each subject before he or she enters the study or before performing any unusual or nonroutine procedure that involves risk to the subject. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject or his/her legal guardian will be given a full explanation of the study and will be allowed to read the approved ICF. Once the investigator is assured that the subject/legal guardian understands the implications of participating in the study, the subject/legal guardian will be asked to give his or her consent to participate in the study by signing the ICF. A copy of the ICF will be provided to the subject/legal guardian.

9.2.2.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate.

9.2.2.5 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 by providing essential documents, including but not limited to, the following:

- Institutional review board approval
- An original investigator-signed investigator agreement page of the protocol
- Curriculum vitae for the principal investigator and each sub-investigator. Current licensure must be noted on the curriculum vitae. Curriculum vitae will be signed and dated by the principal investigators and sub-investigators at study start-up, indicating that they are accurate and current.
- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the subject or legal guardians
- Laboratory certifications and reference ranges for any local laboratories used by the site

9.2.2.6 Study Conduct

The investigator agrees to perform all aspects of this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH E6(R2): Good Clinical Practice; the protocol; and all national, state, and local laws or regulations.

9.2.2.7 Case Report Forms and Source Documents

Site personnel will maintain source documentation, enter subject data into the eCRF as accurately as possible, and will rapidly respond to any reported discrepancies.

Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with 21 Code of Federal Regulations 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and any subsequent investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

9.2.2.8 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

9.2.2.9 Reporting Adverse Events

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. The investigator also agrees to provide the sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

9.2.2.10 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study's outcome and the sponsor and regulatory authorities with any reports required.

9.2.2.11 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor. The sponsor is responsible for informing the investigator/institution when these documents no longer need to be retained.

9.2.2.12 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and any other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without their prior authorization, but data and any publication thereof will not be unduly withheld.

9.2.3 Study Management

9.2.3.1 Monitoring

9.2.3.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

9.2.3.1.2 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, their representatives, or regulatory agencies access to all study records.

The investigator should promptly notify the sponsor and study site(s) of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

9.2.3.2 Management of Protocol Amendments and Deviations

9.2.3.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent immediate hazard to the subject, must be reviewed and approved by the sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator's IRB for approval before subjects are enrolled into an amended protocol.

9.2.3.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important deviation (sometimes referred to as a major or significant deviation) is a subset of protocol deviations that leads to a subject being discontinued from the study, or significantly affects the subject's rights, safety, or well-being and/or the completeness, accuracy, and reliability of the study data. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to local regulations or ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified in writing by the monitor of deviations. The IRB should be notified of all protocol deviations, if appropriate, in a timely manner.

9.2.3.3 Study Termination

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

End of the study is defined as the date on which the last subject completes the last visit (including the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

9.2.3.4 Final Report

Regardless of whether the study is completed or prematurely terminated, the sponsor will ensure that clinical study reports are prepared and provided to regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that clinical study reports in marketing applications meet the standards of the ICH Harmonised Tripartite Guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review complete study results.

Upon completion of the clinical study report, the investigator(s) will be provided with the final approved clinical study report, as appropriate.

Certificate Of Completion

Envelope Id: C4CB452D134F45DC9B838E931EE262ED			Status: Completed
Subject: Complete with DocuSign: DR10624-101_Clinical Study Protocol_Amendment 3_1October2023.pdf			
Source Envelope:			
Document Pages: 98	Signatures: 2	Envelope Originator:	
Certificate Pages: 3	Initials: 0	Nicole Anastos	
AutoNav: Enabled		929 N Front St	
Envelopeld Stamping: Disabled		Wilmington, NC 28401	
Time Zone: (UTC) Monrovia, Reykjavik		Nicole.Anastos@ppd.com	
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Yanshan Huang yanshanhuang@doerbio.com CEO Security Level: Email, Account Authentication (Required)		Sent: 09 October 2023 04:22 Viewed: 09 October 2023 05:16 Signed: 09 October 2023 05:19
	Signature Adoption: Pre-selected Style Signature ID: A506EF28-05D8-426A-A4A0-0D3F7420A034 Using IP Address: 207.140.241.131	
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Certified Delivery Events	Status	Timestamp
Carbon Copy Events	Status	Timestamp
Witness Events	Signature	Timestamp
Notary Events	Signature	Timestamp
Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	09 October 2023 04:22
Certified Delivered	Security Checked	09 October 2023 05:16
Signing Complete	Security Checked	09 October 2023 05:19
Completed	Security Checked	09 October 2023 05:19
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