CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of RDX-002 on Postprandial Triglycerides in Patients Discontinuing the Glucagon-like Peptide-1 (GLP-1) Agonists, Semaglutide or Tirzepatide, for the Treatment of Obesity

Protocol Number:	RDX-002-024-011
IND Number:	75,151
Investigational Product:	RDX-002
Study Phase:	Phase 2
Sponsor:	Response Pharmaceuticals, Inc. 1104 West Broad St., #1064 Falls Church, VA 22046
Sponsor Contact:	William J Sasiela, PhD Chief Medical Officer Response Pharmaceuticals, Inc.
Principal Investigator:	Trisha Shamp, PhD, PA-C Nucleus Network 1000 Westgate Drive, Suite 149 St Paul, Minnesota 55114
Date of Protocol:	13 Dec 2024
Version of Protocol:	Amendment 2
Previous Date(s) and Version(s):	14 Nov 2024, Amendment 1 24 Jul 2024, Original Protocol

CONFIDENTIAL

All financial and nonfinancial support for this study will be provided by Response Pharmaceuticals, Inc. 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 Response Pharmaceuticals, Inc.

The study will be conducted according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) harmonised tripartite guideline E6(R3): Good Clinical Practice.

PROTOCOL APPROVAL

Study Title	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of RDX-002 on Postprandial Triglycerides in Patients Discontinuing the Glucagon-like Peptide-1 (GLP-1) Agonists, Semaglutide or Tirzepatide, for the Treatment of Obesity
Protocol Number	RDX-002-024-011
Protocol Date and Version	13 Dec 2024, Amendment 2

Protocol accepted and approved by:

Sponsor Signatory:

William J Sasiela, PhD
Chief Medical Officer
Response Pharmaceuticals, Inc.

Signature and Date

Biostatistician

Roman Ganzha, PhD
Director, Biostatistics
Clinical Data Services
Veranex Inc.

Signature and Date

INVESTIGATOR AGREEMENT

I have read and understood the protocol titled "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of RDX-002 on Postprandial Triglycerides in Patients Discontinuing the Glucagon-like Peptide-1 (GLP-1) Agonists, Semaglutide or Tirzepatide, for the Treatment of Obesity".

I agree to conduct and supervise this clinical study in accordance with this final protocol, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) harmonised tripartite guideline E6(R3): Good Clinical Practice, and all applicable government regulations. I will not make changes to the protocol before consulting with Response Pharmaceuticals, Inc or implement protocol changes without the Institutional Review Board (IRB) approval except to eliminate an immediate risk to subjects.

I will ensure that the rights, safety, and welfare, of subjects under my care are protected. I agree to ensure that the investigational product(s) is/are used in accordance with this final protocol.

I will ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

Principal Investigator

Trisha Shamp, PhD, PA-C
Nucleus Network
1000 Westgate Drive, Suite 149
St Paul, Minnesota 55114

Signature and Date

TABLE OF CONTENTS

PROTOCOL APPROVAL 2
INVESTIGATOR AGREEMENT 3
TABLE OF CONTENTS 4
LIST OF TABLES 9
LIST OF FIGURES 9
PROTOCOL SYNOPSIS 10
LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS 28
1. INTRODUCTION 31
1.1 Background: Obesity Treatments and Weight Regain 31
1.2 Microsomal Triglyceride Transfer Protein (MTP) Inhibition 32
1.3 Investigational Drug, RDX-002 33
2. STUDY OBJECTIVES AND ENDPOINTS 35
3. INVESTIGATIONAL PLAN 40
3.1 Study Design 40
3.2 Rationale for Study Design and Dose 43
4. SELECTION AND WITHDRAWAL OF PATIENTS 45
4.1 Study Population (Part A and Part B) 45
4.2 Inclusion Criteria (Part A) 45
4.3 Exclusion Criteria (Part A) 46
4.4 Eligibility Criteria (Part B) 49
4.5 Patient Withdrawal Criteria 49
4.4.1 Stopping Criteria 49
4.4.2 Reasons for Withdrawal/Discontinuation 50
4.4.3 Handling of Withdrawals 50
4.4.4 Replacements 51
5. STUDY TREATMENTS 52

5.1 Treatments Administered 52
5.2 Identity of Investigational Product(s) 52
5.3 Study Drug Receipt, Packaging and Labeling 53
5.4 Study Drug Storage 53
5.5 Study Drug Dispensing and Accountability 53
5.6 Method of Assigning Subjects to Treatment Groups 53
5.7 Blinding 54
5.8 Treatment Compliance 54
5.9 Prior and Concomitant Medications 55
5.9.1 Prohibited Medications 55
6. STUDY ASSESSMENTS AND PROCEDURES 57
6.1 Study Visits 57
6.1.1 Visit S1 (Day -42 to Day -14): Screening/Eligibility Assessments (Part A) 57
6.1.2 Visit G1 (Day -42 to Day -14): GLP-1 Therapy Assessments (Part A) 58
6.1.3 Timepoint G2 (Day -14 to Day -7): GLP-1 Treatment Discontinuation (Part A) 59
6.1.4 Visit T1 (Day 1): Baseline, Clinic Visit (Part A) 59
6.1.5 Visit T2 (Day 43): Clinic Visit (Part A) 61
6.1.6 Visit T3 (Day 85): End of Part A 62
6.1.7 Telephone Follow-up – Patient Reported Compliance (Part A) 63
6.1.8 Visit OT (Day 99): Off-treatment Follow-up Phone Call (Part A) 63
6.1.9 Visit B1 (Day 1)/Baseline (Clinic Visit): Initiation of Open-Label Extension (Part B) 63
6.1.10 Visit B2 (Day 43), Visit B3 (Day 85) and Visit B4 (Day 169-End of Part B and End of Study [EOS]) – Clinic Visit (Part B) 64
6.1.11 Telephone Follow-up – Patient Reported Compliance (Part B) 66
6.1.12 Visit OT (Day 183): Off-treatment Follow-up Phone Call (Part B) 66
6.2 Demographic and Other Baseline Characteristics 66
6.3 Efficacy Assessments 66

6.4 Pharmacokinetic Assessments 67
6.4.1 Pharmacokinetic Blood Sample Collection and Processing 67
6.4.2 Analytical Methodology 68
6.4.3 Pharmacokinetic Parameters 68
6.5 Pharmacodynamic Assessments 68
6.6 Safety Assessments 68
6.6.1 Adverse Events 68
6.6.1.1 Definition of Adverse Events 69
6.6.1.2 Serious Adverse Events 69
6.6.1.3 Documentation of Adverse Events 70
6.6.1.4 Assessment of Severity 70
6.6.1.5 Relationship to Study Medication 71
6.6.1.6 Reporting of Serious Adverse Events 71
6.6.1.7 Follow-up of Serious Adverse Events 72
6.6.2 Clinical Laboratory Assessments 72
6.6.3 Vital Signs 73
6.6.4 Electrocardiogram 74
6.6.5 Physical Examination 74
6.6.6 Stool Questionnaire 74
6.6.7 Pregnancy 74
7. STATISTICAL AND ANALYSIS METHODS 75
7.1 General Principles 75
7.2 Study Endpoints 75
7.3 Sample Size Calculations 75
7.4 Analysis Populations 76
7.5 Statistical Methods of Analysis 77
7.5.1 Patient Disposition 77

7.5.2 Demographic and Baseline Characteristics 77
7.5.3 Medical History 77
7.5.4 Prior and Concomitant Medication 77
7.5.5 Protocol Deviations 78
7.5.6 Efficacy Analyses 78
7.5.6.1 Analysis of the Primary Endpoint (Part A) 78
7.5.6.2 Analysis of the Secondary Endpoints (Part A) 78
7.5.6.3 Analysis of the Exploratory Endpoints (Part A) 78
7.5.6.4 Multiplicity Adjustment 78
7.5.6.5 Handling of Dropouts and Missing Data 79
7.5.6.6 Analyses of Pharmacokinetic Endpoints (Part A) 79
7.5.6.7 Analysis of the Efficacy Endpoints (Part B) 79
7.5.7 Safety Analyses (Part A and Part B) 79
8 DATA QUALITY ASSURANCE 81
8.1 Data Management 81
8.2 Study Monitoring, Audits, and Inspections 81
9 ETHICS 83
9.1 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) 83
9.2 Ethical Conduct of the Study 83
9.3 Informed Consent 83
9.4 Patient Confidentiality 84
10 ADMINISTRATIVE ASPECTS AND RECORD KEEPING 85
10.1 Study Administrative Structure 85
10.2 Primary Source Documentation 86
10.3 Maintenance and Retention of Records 86
10.4 Financial Disclosure and Obligations 87
10.5 Modifications to Protocol 87

10.6 Termination of Study 87
10.7 Publication Policy 88
11 REFERENCE LIST 89
12 APPENDICES 91
12.1 Appendix I: Schedule of Events (Part A) 91
12.2 Appendix II: Schedule of Events (Part B) 94
12.3 Appendix III: Blood Pressure, Body Weight, Waist Circumference and Total Body Fat Mass Measurements (Part A and Part B) 96
12.3.1 Blood Pressure Measurements 96
12.3.2 Body Weight and Waist Circumference Measurements 96
12.3.3 Total Body Fat Mass 97
12.4 Appendix IV: Pharmacokinetic and Postprandial Blood Sampling Schedule (Part A) 99
12.5 Appendix V: Composition of a High-Fat Meal (Part A) 100
12.6 Appendix VI: Patient Diary (Part A and Part B) 101
12.7 Appendix VII: Bristol Stool Form Scale (Part A and Part B) 104
12.8 Appendix VIII: Management Plan for Diarrhea (Part A and Part B) 105

LIST OF TABLES

Table 1 Key Study Administrative Information 85

LIST OF FIGURES

Figure 1 Study Design Schematic 43

PROTOCOL SYNOPSIS

Protocol Number: RDX-002-024-011

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of RDX-002 on Postprandial Triglycerides in Patients Discontinuing the Glucagon-like Peptide-1 (GLP-1) Agonists, Semaglutide or Tirzepatide, for the Treatment of Obesity

Sponsor:

Response Pharmaceuticals, Inc.

1104 West Broad St., #1064

Falls Church, VA 22046

Study Phase: Phase 2

Study Sites: One site in the United States (US)

Indication: Treatment of post - glucagon-like peptide-1 (GLP-1) agonist weight rebound

Rationale:

Obesity is a chronic, complex disease associated with increased risk for significant cardiovascular and metabolic comorbidities including hyperlipidemia, insulin resistance, type 2 diabetes, hypertension, and cardiovascular disease. Treatment of obesity has generally been challenging whether utilizing lifestyle modification (caloric restriction and/or increased calorie expenditure through exercise) or pharmacological therapies. The recent approval of potent GLP-1 agonists such as semaglutide and tirzepatide for obesity have greatly advanced the treatment of obesity by producing mean changes in body weight of 12 - 18%. However, cessation of this pharmacological treatment is frequently followed by weight regain, even with continued lifestyle intervention. Therefore, the perpetual challenge to maintain reduced body weight long-term following initial weight loss continues to remain.

The investigational drug, RDX-002, is a potent, selective, and gut-specific microsomal triglyceride transfer protein (MTP) inhibitor. MTP is critical in incorporating fats and cholesterol into lipoproteins in the gut and liver – the two primary sources of these compounds for production and delivery to the rest of the body. However, inhibition of hepatic MTP results in hepatic steatosis. RDX-002 inhibits MTP only in the absorptive cells lining the small intestine (enterocytes). Previous studies with RDX-002 have demonstrated the ability for weight loss as well as meaningful reductions in low-density lipoprotein cholesterol (LDL-C). Additionally, improvements in homeostatic model assessment for insulin resistance (HOMA-IR) and glycated hemoglobin (HbA1c) have been observed in patients with type 2 diabetes. The addition of a gut-specific MTP inhibitor after patients have discontinued treatment with the GLP-1 agonists, semaglutide or tirzepatide, could meaningfully reduce the weight regain (rebound).

This Phase 2 proof-of-concept study will be conducted in two parts. Part A will be randomized, double-blind, and placebo-controlled and will evaluate the effect of 12 weeks of treatment with RDX-002 on postprandial triglycerides (TGs) and body weight among patients who have recently discontinued

treatment with semaglutide or tirzepatide for obesity. Part B will be a 24-week open-label extension (OLE) and will demonstrate the long-term safety and durability of treatment effect of RDX-002 in eligible patients who have completed Part A.

Study Objectives and Endpoints: The objectives and associated endpoints for Part A and Part B of the study are as follows:

Part A

Objectives	Endpoints
Primary Objective	**Primary Efficacy Endpoint**
• To assess the efficacy of 12 weeks of treatment with 200 mg twice daily (BID) RDX-002 on the mean percentage change from baseline on postprandial TGs among patients who have recently discontinued treatment with semaglutide or tirzepatide for obesity.	• Difference in the mean percent change in the incremental postprandial TG area under the curve (AUC) in patients treated with RDX-002 as compared with placebo at Week 12. Note: Incremental postprandial TG AUC sets the pre-test meal (fasting) TG levels at zero and calculates the increased levels of TG that occur with consumption of the test meal. It measures only the incremental increase in TGs as the postprandial TGs and excludes the fasting, hepatic TGs.
Secondary Objectives	**Secondary Efficacy Endpoints**
• To evaluate the effect of 12 weeks of treatment with RDX-002 on mean percent change from baseline in body weight in patients who have recently discontinued semaglutide or tirzepatide obesity therapies;	• Difference in the mean percent change in the total postprandial TG AUC in patients treated with RDX-002 as compared with placebo at Week 12; Note: The total or absolute postprandial TG AUC measures the entire area under the curve that includes both the fasting (hepatic) TGs as well as the postprandial TGs; • Difference in the mean percent change from baseline in body weight in patients treated with RDX-002 as compared with placebo at Week 12; • Difference in the proportion of patients treated with RDX-002 exhibiting at least a 5% increase from baseline in body weight as

	compared with placebo at Week 12;
• To evaluate the effect of 12 weeks of treatment with RDX-002 on LDL-C in patients who have recently discontinued semaglutide or tirzepatide obesity therapies.	• Difference in the mean percent change from baseline in LDL-C in patients treated with RDX-002 as compared with placebo at Week 12.
Exploratory Objectives	**Exploratory Efficacy Endpoints**
• To explore the treatment effect of RDX-002 at Week 6 on body weight and LDL-C in patients who have recently discontinued GLP-1 treatment for weight loss;	• Difference in the mean percent change from baseline in body weight in patients treated with RDX-002 as compared with placebo at Week 6; • Difference in the mean percent change from baseline in LDL-C in patients treated with RDX-002 as compared with placebo at Week 6;
• To explore the treatment effect of RDX-002 at Weeks 6 and 12 on other fasting lipids (total cholesterol, non-high-density lipoprotein cholesterol [non-HDL-C]) and TGs in patients who have recently discontinued GLP-1 treatment for weight loss;	• Difference in the median percent change from baseline in fasting TGs in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Difference in the mean percent change from baseline in total cholesterol and non-HDL-C in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Relationship between changes in incremental postprandial TGs AUC and change in body weight for patients treated with RDX-002 as compared with placebo from baseline to Week 12; • Relationship between changes in incremental postprandial TGs AUC and change in body weight in patients pre- and post-discontinuation of GLP-1 treatment: o Relationship between percent change in incremental postprandial TGs AUC at Week 12 as compared to baseline and

	change in body weight at Week 12 as compared to baseline in patients treated with RDX-002; o Relationship between percent change in incremental postprandial TGs AUC at baseline compared to Visit G1 (pre-GLP-1 agonist discontinuation) and change in body weight from baseline to Week 12 in patients treated with placebo.
• To explore the treatment effect of RDX-002 at Weeks 6 and 12 on other obesity-linked risk factors; waist circumference, total body fat mass, HbA1c, HOMA-IR, high sensitivity C-reactive protein (hs-CRP), and fasting and postprandial glucose and insulin in patients who have recently discontinued GLP-1 treatment for weight loss;	• Difference in the mean change from baseline in waist circumference in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Difference in the mean percent change from baseline in total body fat mass as measured by Inbody H20N scale in patients treated with RDX-002 as compared to placebo at Weeks 6 and 12; • Difference in the mean change from baseline in HbA1c in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Difference in the mean change from baseline in HOMA-IR index in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Difference in the median percent change from baseline in hs-CRP levels in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Difference in the mean change from baseline in fasting glucose and insulin in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Difference in the mean change from baseline in postprandial glucose and insulin in patients

	treated with RDX-002 as compared with placebo at Weeks 6 and 12;
• To explore the effect of 12 weeks of treatment with RDX-002 on systolic blood pressure (SBP) and diastolic blood pressure (DBP) in patients who have recently discontinued GLP-1 treatment for weight loss;	• Difference in mean absolute change from baseline in SBP and DBP in patients treated with RDX-002 as compared with placebo at Week 12;
• To evaluate the effect of discontinuation of the GLP-1 agonists semaglutide or tirzepatide on changes in postprandial TGs.	• Difference in the mean percent change in incremental and absolute postprandial TGs AUCs from pre-GLP-1 discontinuation to baseline (1-2 weeks post-GLP-1 discontinuation).
Pharmacokinetic Objective	**Pharmacokinetic Endpoint**
• To evaluate the pharmacokinetics (PK) of RDX-002 in patients who have recently discontinued GLP-1 treatment for weight loss.	• PK parameters of RDX-002 and its main inactive metabolite at Week 12 in patients treated with RDX-002.
Safety Objective	**Safety Endpoints**
• To evaluate the safety of RDX-002 in patients who have recently discontinued semaglutide or tirzepatide obesity therapies.	• Incidence of treatment-emergent adverse events (TEAEs) including determination of serious adverse events (SAEs), TEAEs leading to discontinuation, and laboratory abnormalities as characterized by type, frequency, timing, severity (mild, moderate, severe), seriousness, and relationship to RDX-002; • Concomitant medications; • Clinical laboratory tests (hematology, chemistry, and urinalysis); • Vital sign measurements; • Electrocardiogram (ECG); • Physical examination findings; • Stool questionnaire.

Part B

Objectives	Endpoints
• To evaluate the safety and durability of efficacy of RDX-002 over 24 weeks of treatment.	**Efficacy Endpoints** • Difference in the mean percent change from original (Part A) baseline and Part B baseline in body weight, total body fat mass, and waist circumference at Weeks 6, 12, and 24; • Difference in the mean percent change from original (Part A) baseline and Part B baseline in fasting lipid panel, SBP, DBP, fasting glucose and insulin, HbA1c, HOMA-IR, and hs-CRP at Weeks 6, 12, and 24. **Safety Endpoints** • Incidence of TEAEs including determination of SAEs, TEAEs leading to discontinuation, and laboratory abnormalities as characterized by type, frequency, timing, severity (mild, moderate, severe), seriousness, and relationship to RDX-002; • Concomitant medications; • Clinical laboratory tests (hematology, chemistry, and urinalysis); • Vital sign measurements; • Electrocardiogram (ECG); • Physical examination findings; • Stool questionnaire.

Number of Patients: Approximately 64 patients with recent discontinuation of the GLP-1 agonists, semaglutide or tirzepatide, for the treatment of obesity, will be enrolled in Part A of the study. Patients who complete the study drug dosing in Part A of the study, have maintained a minimum of 80% compliance with study dosing and procedures from Part A, and are willing to participate in Part B of the study will be enrolled in Part B with agreement of the investigator.

Study Design and Methodology:

This Phase 2 study will be conducted in two parts at a single study site in the US. Part A will be a randomized, double-blind, placebo-controlled, parallel-group study and Part B will be an OLE to eligible patients who have completed Part A of the study. Patients who have a planned or willing discontinuation

of semaglutide or tirzepatide treatment for obesity, have lost ≥10% or 10 kg of their original (pre-GLP-1 baseline) body weight during treatment with the GLP-1 agonist and are aged 18 to 65 years (both inclusive) will be eligible for Screening.

Part A of the study will be conducted as follows with a visit window of ±3 days allowed for Visit T1, Visit T2 and Visit T3:

- **Visit S1 - Screening Visit (Day -42 to Day -14)**: The Screening Visit (Visit S1) will occur no more than 42 to 14 days prior to the Baseline and Randomization Visit (Visit T1) while patients are still on their current GLP-1 therapy.
- **Visit G1 - GLP-1 Therapy Assessments (Day -42 to Day -14)**: After completing all screening assessments, patients who meet the screening requirements will return to the clinic for the GLP-1 therapy assessment visit (Visit G1). This visit will be conducted prior to Timepoint G2, while patients are still on their current GLP-1 treatment. To allow for flexibility with patient scheduling and planning for the discontinuation of GLP-1 therapy, Visit S1 and Visit G1 should occur during the 28 days prior to Timepoint G2. At Visit G1, patients will undergo an assessment of postprandial TG levels. Patients will consume a standardized high-fat test meal and TG levels will be measured 30 minutes prior to the initiation of the test meal and at 1-, 2-, 3-, 4-, 6-, and 8-hours after the initiation of the test meal.

- **Timepoint G2 – Discontinuation of GLP-1 (Day -14 to Day -7)**: Patients will be instructed to commence the planned discontinuation of their current GLP-1 agonist treatment (semaglutide or tirzepatide) after Visit G1 and within 7 to 14 days prior to randomization to RDX-002 or matching placebo.
- **Visit T1 – Baseline and Randomization (Day 1)**: Eligible patients will be randomly assigned to receive RDX-002 or matching placebo for a 12-week treatment period. Only patients with recent discontinuation (7 to 14 days prior to randomization) of semaglutide or tirzepatide who lost ≥10% or 10 kg of body weight during their treatment with the above drugs and continue to satisfy the screening period study entrance criteria at Visit T1 (Day 1) will be randomized to treatment with RDX-002 or matching placebo. Patients will consume the standardized high-fat test meal at Visit T1 (Day 1). The TG levels will be measured 30 minutes prior to initiation of the test meal and at 1-, 2-, 3-, 4-, 6-, and 8-hours after the initiation of the test meal. Following the 8-hour blood draw, patients will take their first dose of either RDX-002 or placebo 30 minutes prior to dinner.

  Patients will take RDX-002 everyday BID; approximately 30 minutes prior to breakfast

(or the first meal of the day) and approximately 30 minutes prior to dinner.

- **Visit T2 - Clinic Visit (Day 43):** Patients will return to the clinic at Visit T2 (Day 43) for designated blood draws and study procedures. The TG levels will be measured 30 minutes prior to receiving their dose of either RDX-002 or placebo. Following the study procedures, patients will receive the dose of either RDX-002 or placebo 30 minutes prior to a standard clinic meal. At this visit, patients will also be offered the opportunity to participate in the Part B OLE study.
- **Visit T3 - Clinic Visit (Day 85) - End of Part A**: Patients will return to the clinic at Visit T3 (Day 85) for designated blood draws and study procedures. Following the study procedures, patients will receive their dose of either RDX-002 or placebo 30 minutes prior to beginning their standardized high-fat test meal. The TG levels will be measured 30 minutes prior to receiving the dose of either RDX-002 or placebo (and within 60 minutes prior to beginning of the standardized high-fat test meal) and post-dose at 1-, 2-, 3-, 4-, 6-, and 8-hours after the initiation of the test meal. End of study procedures will be conducted for patients not continuing in Part B of the study.

  Note: A follow-up telephone monitoring call will be conducted by the site staff every 2 weeks (±2 days) from the date of randomization up to Visit T3 (Day 85) to assess patient reported compliance to study treatment. During this telephone call, adherence to recording of dosing and bowel movement in patient diary, any adverse events (AEs) that occurred, and concomitant medications will be reviewed.
- **Visit OT - Off-treatment Follow-up Phone Call (Day 99)**: Patients who are not participating in the Part B OLE will receive an off-treatment (OT) follow-up phone call approximately 2 weeks after the last dose of RDX-002 or placebo for review of any AEs and concomitant medications.

  Notes:

  1. At Visit G1, Visit T1 (Day 1), and Visit T3 (Day 85), patients will be instructed to consume the standardized high-fat test meal entirely within 15 minutes. For patients who have difficulty consuming the meal within the initial allowable time, an additional window of up to 15 minutes will be provided to complete the meal;
  2. For Visit T1 (Day 1), Visit T2 (Day 43), and Visit T3 (Day 85), patients will be instructed to come for clinic visits without taking their scheduled doses of RDX-002 or placebo.

Part B of the study will be conducted as follows with a visit window of ±3 days allowed for all visits:

All eligible patients who have completed Part A and are willing to participate in the Part B OLE of the

study will receive open-label RDX-002 as a 200 mg BID dose for 24 weeks, regardless of their blinded treatment assignment (RDX-002 or placebo) in Part A.

- **Visit B1 (Day 1) – Part B Baseline and Initiation of OLE**: Patients participating in the Part B OLE will complete the study procedures of Visit T3 (Day 85, Part A) and receive the first dose of open-label RDX-002 as an evening dose 30 minutes prior to dinner.
- **Visit B2 (Day 43) and Visit B3 (Day 85):** Patients will return to the clinic for designated blood draws and study procedures. The fasting laboratory blood draws will be measured 30 minutes prior to receiving their dose of RDX-002. Following the study procedures, patients will receive their dose of RDX-002, 30 minutes prior to a standard clinic meal.
- **Visit B4 (Day 169-End of Part B and End of Study [EOS]) – Clinic Visit:** Patients will return to the clinic for designated blood draws and study procedures.
  Notes:
  1. Data from Visit B1 (Day 1, Part B) will serve as one of the baselines for Part B analyses;
  2. Visit T3 (Day 85, Part A) and Visit B1 (Day 1, Part B) can occur on the same day;
  3. For Visit B1 (Day 1), Visit B2 (Day 43), and Visit B3(Day 85), patients will be instructed to come for clinic visits without taking their scheduled doses of RDX-002;
  4. A follow-up telephone monitoring call will be conducted by the site staff every 2 weeks (±2 days) from Visit B1 (Day 1) up to Visit B4 (Day 169-End of Part B and EOS) to assess patient reported compliance to study treatment. During this telephone call, adherence to recording of dosing and bowel movement in patient diary, any AEs that occurred, and concomitant medications will be reviewed.
- **Visit OT - Off-treatment Follow-up Phone Call (Day 183)**: Patients will receive an OT follow-up phone call approximately 2 weeks after the last dose of RDX-002 for review of any AEs and concomitant medications.

Inclusion and Exclusion Criteria (Part A):

Inclusion Criteria: Each patient must meet all of the following criteria to be enrolled in Part A of the study:

1. Willing and able to provide written informed consent prior to the conduct of any study-specific procedures;
2. Planned or willing discontinuation of semaglutide or tirzepatide for the treatment of obesity prior to randomization (Visit T1/Day 1) through EOS;
3. Lost ≥10% or 10 kg of original (pre-GLP-1 baseline) body weight with semaglutide or tirzepatide;
4. Males and females aged 18 to 65 years (both inclusive) at Screening (Visit S1);
5. A HbA1c of <6.5% at Screening (Visit S1);
6. A 12-lead ECG at Screening (Visit S1) which, in the opinion of the investigator, had no abnormalities that compromised safety in this study;
7. Males and nonpregnant, nonlactating females. Females must be either:
   - Having negative pregnancy test at Screening (Visit S1);
   - Naturally postmenopausal, defined as ≥1 year without menses and follicle-stimulating hormone (FSH) ≥40.0 IU/L, or
   - Surgically sterile, including hysterectomy, bilateral oophorectomy, and/or tubal ligation, or females of childbearing potential willing to use 2 acceptable methods of birth control (unless they have agreed to follow the definition of true abstinence). The minimal requirement for adequate contraception should be started on Day 1, continuing during the study period, and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include:
     - oral, implantable, injectable, or topical birth control medications;
     - placement of an intrauterine device with or without hormones;
     - barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly;
     - vasectomized male partner who is the sole partner for this patient; or
     - True abstinence: when this is the preferred and usual lifestyle of the patient (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception).

Exclusion Criteria: Patients meeting any of the following criteria will be excluded from Part A of the study:

1. Type 1 or Type 2 diabetes;
2. Recent (within 3 months prior to the Screening visit [Visit S1]) myocardial infarction, unstable angina leading to hospitalization, uncontrolled symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of Screening), coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), carotid surgery or stenting, cerebrovascular accident, transient ischemic attack, endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (e.g., PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the investigator to be stable for the previous 3 months;
3. Uncontrolled hypertension, defined as SBP >160 mmHg and DBP >100 mmHg after being in supine position for 5 minutes;
4. Total fasting (minimum of 10 hours) TGs ≥400 mg/dL (4.5 mmol/L) at Screening (Visit S1);
5. Fasting glucose >126 mg/dL at Screening (Visit S1);
6. Uncontrolled hypothyroidism, including thyroid stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Screening (Visit S1); patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization (Visit T1/Day 1) are allowed;
7. Liver disease or dysfunction, including:
   - Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies at Screening (Visit S1); or
   - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥2 × ULN, and/or total bilirubin ≥2 × ULN at Screening (Visit S1). If total bilirubin ≥1.2 × ULN, a direct and indirect bilirubin will be obtained, and if consistent with Gilbert's disease or if the patient has a history of Gilbert's disease, the patient may be enrolled in the study;

     Note: At the discretion of the investigator, a single repeat of ALT and/or AST may be completed prior to randomization (Visit T1/Day 1); for those patients who have a repeat ALT and/or AST, the repeat value will be used to determine eligibility. Also, if test for hepatitis C antibody is positive, but optional reflexive test for hepatitis C ribonucleic acid is negative, the patient can be enrolled.
8. Renal dysfunction or glomerulonephritis, including estimated glomerular filtration rate (eGFR; using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] 2021 formula) <60 mL/min at Screening (Visit S1). Note, a single repeat qualifying eGFR,

performed at the discretion of the investigator, is acceptable;

9. Gastrointestinal conditions or procedures (including weight loss surgery; e.g., Lap-Band® or gastric bypass) except uncomplicated cholecystectomy and appendectomy that may affect drug absorption;
10. Known history of hematologic or coagulation disorders or a hemoglobin level <10.0 g/dL at Screening (Visit S1);
11. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed;
12. Unexplained creatine kinase (CK) >3 × ULN at any time prior to randomization (i.e., not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization;
13. History of drug or alcohol abuse within the last 2 years or reported current consumption of >14 alcoholic drinks/week, or any illicit drug use (checked positive for standard drug screening panel). Patients testing positive for tetrahydrocannabinol (THC) (whether prescribed or not) and for amphetamine derivatives prescribed by and under the care of a health care practitioner (except for weight management) can be enrolled after evaluation and at the discretion of the investigator;
14. Inability to follow the required minimum 2 meals a day, or unwillingness to consume meal on both study test occasions, or inability to fast, as required during the study;
15. Blood donation, participation in multiple blood draws, clinical study, major trauma, blood transfusion or surgery with or without blood loss within 30 days prior to randomization (Visit T1/Day 1);
16. Use of any experimental or investigational drugs except GLP-1 agonists within 30 days or 5 half-lives (whichever is longer) prior to Screening (Visit S1);
17. Use of any of the following prohibited diabetes or weight loss drugs prior to or during the study (as specified) unless meeting specific rescue criteria:
    - Other GLP-1 agonists such as Victoza/liraglutide, Byetta/exenatide, Trulicity/dulaglutide within 120 days prior to Screening (Visit S1);
    - Biguanides such as metformin within 60 days of Screening (Visit S1);
    - Sodium-glucose transport protein 2 (SGLT2) inhibitors such as Jardiance/empagliflozin, Invokana/canagliflozin, Farxiga/dapagliflozin within 60 days prior to Screening (Visit S1);
    - Dipeptidyl peptidase-4 (DPP-4) inhibitors such as Januvia/sitagliptin,

Tradjenta/linagliptin within 60 days prior to Screening (Visit S1);

- Thiazolidinediones (TZD/glitazones) such as Actos/pioglitazone, Avandia/rosiglitazone within 120 days prior to Screening (Visit S1);
- Sulfonylurea such as Amaryl/glimepiride, Glucotrol/glipizide XL/glipizide within 60 days prior to Screening (Visit S1);
- Injectable synthetic forms of amylin such as Pramlintide (symlin);
- Any other obesity medication or medications associated with weight loss within 90 days prior to Screening (Visit S1);
- Systemic corticosteroids within 60 days prior to Screening (Visit S1), use of topical and inhaled corticosteroids are allowed.

18. Recent (within 30 days unless otherwise specified) initiation or discontinuation of the following lipid-lowering medications:
    - Welchol/cholestagel/colesevelam hydrochloride; within 60 days prior to Screening (Visit S1);
    - Mipomersen; within 180 days prior to Screening (Visit S1);
    - Lomitapide; within 90 days prior to Screening (Visit S1);
    - Apheresis; within 90 days prior to Screening (Visit S1);
    - Statins;
    - Ezetimibe;
    - Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, within 60 days prior to Screening (Visit S1);
    - Red yeast rice extract - containing products;
    - Omega 3 fatty acids and derivatives such as Lovaza® and over-the-counter (OTC) fish oil supplements >2000 mg; within 60 days prior to Screening (Visit S1);
    - Niacin (>500 mg).
19. An employee or contractor of the facility conducting the study, or a family member of the principal investigator, co-investigator, or any Sponsor personnel;
20. Pregnant, breastfeeding, or intending to become pregnant within 30 days after study completion or last dose of study drug;
21. A medical or situational (i.e., geographical) finding that, in the investigator's opinion, may compromise the patient's safety or ability to complete the study.

Eligibility Criteria (Part B):

Patients who complete the study drug dosing in Part A of the study, have maintained a minimum of 80% compliance with study dosing and procedures from Part A, and are willing to participate in Part B of the study will be enrolled in Part B with agreement of the investigator.
Study Drug, Dosage, and Route of Administration: Investigational study drug: RDX-002 (4 × 50 mg tablets) and matching placebo **Part A**: At Visit T1 (Day 1), patients will be randomly assigned to receive RDX-002 or matching placebo for a 12-week treatment period. Patients will be dosed RDX-002 or matching placebo everyday BID; approximately 30 minutes prior to breakfast (or the first meal of the day) and approximately 30 minutes prior to dinner. Patients will orally take 4 tablets of RDX-002 or matching placebo BID. **Part B**: At Visit B1 (Day 1), all patients will receive RDX-002 for a 24-week treatment period. Patients will be dosed RDX-002 everyday BID; approximately 30 minutes prior to breakfast (or the first meal of the day) and approximately 30 minutes prior to dinner. Patients will orally take 4 tablets of RDX-002 BID.

Estimated Study Duration:

Part A: The expected study duration of Part A is approximately 120 to 140 days (20 weeks [with a visit window of ±3 days allowed for Visit T1, Visit T2 and Visit T3]), including an approximate 28-day Screening period and GLP-1 therapy assessment period, an approximate 14-day GLP-1 discontinuation period, a 12-week treatment period, and for patients who are not participating in Part B, an OT phone call 2 weeks post last dose of RDX-002 or placebo.

Part B: The expected study duration of Part B is approximately 182 days (with a visit window of ±3 days allowed for all visits) and includes a 168-day (24 week) open-label treatment period and an OT phone call 2 weeks post last dose of RDX-002.

Efficacy Assessments:

Part A: Efficacy assessments will include the evaluation of postprandial TGs, body weight, LDL-C, other fasting lipids (TGs, total cholesterol, and non-HDL-C), total body fat mass, waist circumference, HbA1c, glucose and insulin levels (fasting and postprandial), hs-CRP and HOMA-IR.

Part B: Efficacy assessments will include the evaluation of body weight, fasting lipid panel, total body fat mass, waist circumference, HbA1c, glucose and insulin levels (fasting only), hs-CRP and HOMA-IR.

Safety Assessments:

Part A and Part B: Safety assessments will include evaluation of TEAEs, concomitant medications, clinical laboratory tests (hematology, clinical chemistry, and urinalysis), vital signs, 12-lead ECG, physical examination findings, and stool questionnaire.

Sample Size:

Part A: Approximately 64 patients will be enrolled targeting 58 completers in this study, while accounting for 10% drop-out rate. This sample size was estimated based on the primary efficacy endpoint and one of the secondary efficacy endpoints (difference in the mean percent change from baseline in body weight in patients treated with RDX-002 as compared with placebo at Week 12):

- Primary efficacy endpoint with assumption of 60% difference in the mean percentage change in incremental postprandial TG AUC from baseline between RDX-002 and placebo and a pooled standard deviation (SD) of 50% observed in the previous clinical study, using two-sided test with 5% level of significance;
- Secondary efficacy endpoint with assumption of 3% absolute difference in the mean percent change in body weight between RDX-002 and placebo with a pooled SD of 4% using two-sided test with 5% level of significance.

A sample size of 64 patients results in at least 80% power (calculated using TWOSAMPLEMEANS in PROC POWER in Statistical Analysis System [SAS®]) and is considered to be sufficient to satisfy the above study objectives. Patients will be randomized into 1:1 allocation ratio (i.e., 32 patients in RDX-002 group and 32 patients in placebo group).

Part B: No formal sample size will be required for Part B. The number of patients will be determined by the number of eligible patients who have completed Part A and are willing to participate in Part B.

Statistical Methods:

Continuous data will be summarized using descriptive statistics such as mean, SD, median, first and third quartiles (Q1 and Q3), minimum, maximum, coefficient of variation (CV), geometric mean, and geometric CV. All statistical testing will be two-sided at significance level of 0.05 and no multiplicity adjustment will be made. Categorical data will be summarized using counts and percentages. Data will be summarized and listed by treatment group and visit/timepoint, where appropriate.

The following analysis sets will be used in the statistical analyses:

- **Safety Analysis Set**: The Safety Analysis Set will include all patients who receive at least one dose of RDX-002 or placebo.
- **Intent-to-Treat (ITT) Set**: The ITT Set will include all randomized patients. It will be the primary analysis set for the efficacy analyses.
- **Modified Intent-to-Treat (mITT) Set**: The mITT Set will include all randomized patients who have all key measurements (postprandial TGs, body weight and LDL-C) performed at Visit T1 (Day 1), Visit T2 (Day 43) and Visit T3 (Day 85). This population will be used for analysis of primary and secondary efficacy endpoints.
- **Per-Protocol (PP) Set**: The PP Set will include all patients who completed the study without major protocol deviations and satisfy any additional indication-specific requirements of the analysis population. The PP Set will be used for the secondary efficacy analyses.
- **Pharmacokinetic (PK) Analysis Set**: The PK Analysis set will consist of patients included in the Safety population who have at least one post-dose quantifiable plasma concentration for RDX-002. A quantifiable concentration is defined as a measurable value without any events or deviations that would compromise the integrity of the plasma concentration. It should be noted that due to the properties of RDX-002, which stays within the intestinal enterocyte with little to no absorption into the blood, some patients who correctly take the drug and have a PK blood sample taken may not show blood levels of RDX-002 or its main inactive metabolite.

Analysis of the Primary Endpoint (Part A)

The primary efficacy endpoint will be analyzed by an analysis of covariance (ANCOVA) model with terms for randomized treatment and baseline as a covariate. Summaries will include least squares (LS) means and associated standard errors (SEs) estimated from the ANCOVA. Differences in LS means and associated 95% confidence interval (CI) will be presented along with the p-value from the test of no difference in mean percent change from baseline between treatment groups. The primary analysis will be performed on the ITT Analysis Set with supportive analyses performed on the mITT Analysis Set and

PP Analysis Set.

Analyses of the Secondary Endpoints (Part A)

Continuous secondary efficacy endpoints will each be analyzed using the same methodology as specified for the primary efficacy endpoint.

The proportions of patients exhibiting a weight gain of at least 5% will be presented along with exact (Clopper-Pearson) 95% CIs. The difference between treatment groups in the proportion of patients exceeding this weight gain threshold will be presented along with exact (unconditional) 95% CIs for the difference. The difference in proportions will be calculated as RDX-002 minus placebo, such that a negative value favors RDX-002, i.e., a negative value indicates a reduction in the proportion of patients exceeding the weight gain threshold for patients randomized to RDX-002. Fisher's exact test will be used to compare the proportions between treatment groups.

Analyses of the Exploratory Endpoints (Part A)

Exploratory endpoints will be analyzed using descriptive statistics.

Analyses of the Pharmacokinetic Endpoints (Part A)

Unlike most pharmacological therapeutics, RDX-002, by design, acts in the intestinal enterocytes and little if any drug may be absorbed by patients. Therefore, in some patients no or only sporadic concentrations of RDX-002 or its main inactive metabolite, are detected in blood samples. The following PK parameters will be analyzed descriptively if and where possible depending upon the detection and quantification of parent and main inactive metabolite in blood samples; area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t, whichever occurs first (AUC_{0-t}), area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), maximum plasma concentration (C_{max}), terminal elimination rate constant (lambda [λ]), terminal elimination half-life ($t_{½}$), apparent total plasma clearance (CL/F), and apparent volume of distribution (Vz/F). Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is the time to maximum plasma concentration (T_{max}), where median, minimum, and maximum will be presented.

Analysis of Efficacy Endpoints (Part B)

Efficacy endpoints will be summarized using descriptive statistics. Changes from baseline will be analyzed for both the original (Part A) baseline as well as the Part B baseline. To avoid confounding of prior treatment assignment in Part A, patients treated with RDX-002 and placebo in Part A will be analyzed separately.

Safety Analyses (Part A and Part B)

All patients who receive at least one (1) dose of RDX-002 or placebo will be analyzed for safety. For Part A, the TEAEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) by treatment group overall and by severity and relationship to study drug. For Part B, the TEAEs will be summarized by MedDRA SOC and PT by

Part A treatment group separately and combined and also by severity and relationship to study drug. These summaries will include cumulative incidence (percent of patients experiencing at least one [1] AE), and exposure-adjusted incidence rates (in patient-years). Deaths, SAEs, withdrawal from study treatment due to TEAEs, and withdrawal from the study due to TEAEs will each be summarized by treatment group and provided in by-patient data listings.

Clinical laboratory assessments, including hematology, clinical chemistry, and urinalysis; physical examination findings; vital signs; and ECG results will be summarized by the value and by change from baseline in the value (where appropriate) at each post-baseline timepoint.

For Part B, patients will be analyzed both as separate groups based on the Part A treatment assignment (RDX-002 or placebo).

Date of Protocol: 13 Dec 2024

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{0-t}	area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t, whichever occurs first
$AUC_{0-\infty}$	area under the concentration-time curve from time zero to infinity
BID	twice daily
BMI	body mass index
CABG	coronary artery bypass graft
CFR	Code of Federal Regulations
CI	confidence interval
CL/F	apparent total plasma clearance
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DPP-4	dipeptidyl peptidase-4
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EDC	electronic data capture
EOS	end of study

Abbreviation	Definition
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	good clinical practices
GLP-1	glucagon-like peptide-1
HbA1c	glycated hemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment for insulin resistance
hs-CRP	high sensitivity C-reactive protein
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	intent-to-treat
kcal	kilo calories
λ	terminal elimination rate constant
LDL-C	low-density lipoprotein cholesterol
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MTP	Microsomal Triglyceride Transfer Protein
OLE	open-label extension
OT	off-treatment
OTC	over-the-counter
PCI	percutaneous coronary intervention

Abbreviation	Definition
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamic
PK	pharmacokinetic
PP	per-protocol
PT	preferred term
QD	once daily
RMR	resting metabolic rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	systolic blood pressure
SD	standard deviation
SGLT	sodium-glucose transport protein
SOC	system organ class
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TG	triglyceride
TID	three times a day
T_{max}	time to maximum plasma concentration
TSH	thyroid stimulating hormone
TZD	thiazolidinediones
ULN	upper limit of normal
US	United States
Vz/F	apparent volume of distribution
WHODD	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1 Background: Obesity Treatments and Weight Regain

Obesity is a chronic, complex disease associated with increased risk for significant cardiovascular and metabolic comorbidities including hyperlipidemia, insulin resistance, type 2 diabetes, hypertension, and cardiovascular disease (Guh et al 2009). The worldwide prevalence of obesity has increased significantly and more than doubled during the last decade (World Health Organization, Fact Sheet, March 2024). In the United States (US), more than 2 in 5 adults (42.4%) are obese (body mass index [BMI] of >30 kg/m^2) and about 1 in 11 adults (9.2%) are severely obese (BMI of >40 kg/m^2) (NIDDK, Overweight & Obesity Statistics, 2021).

Treatment of obesity has generally been challenging whether utilizing lifestyle modification (caloric restriction and/or increased calorie expenditure through exercise) or pharmacological therapies. The recent approval of potent glucagon-like peptide-1 (GLP-1) agonists such as semaglutide and tirzepatide for obesity have greatly advanced the treatment of obesity. In the STEP-1 Phase 3 trial, 68 weeks of treatment with once-weekly subcutaneous semaglutide (at a dose of 2.4 mg) plus lifestyle intervention was associated with sustained, clinically relevant reduction in body weight (12.4%) (Wilding et al 2021). In the SURMOUNT-1 Phase 3 trial, 72 weeks of treatment with once-weekly subcutaneous tirzepatide at 5 mg, 10 mg, or 15 mg resulted in substantial and sustained reductions in body weight (11.9%, 16.4%, and 17.8%, respectively) (Jastreboff et al 2022). Treatment of obesity by either lifestyle modification or drug therapy has been shown to reduce the risk of type 2 diabetes (Diabetes Prevention Program 2002) and major cardiovascular events (Lincoff et al, SELECT Trial 2023).

Maintaining reduced body weight on a long-term following initial weight loss continues to remain a perpetual challenge in obese patients. Cessation of pharmacological treatment is frequently followed by weight regain, even with continued lifestyle intervention. Weight regain following withdrawal of treatment also results in the return and/or increases in cardiometabolic risk factors. In the STEP 1 trial extension, patients regained two-thirds of their prior weight loss (mean of 11.6% body weight regained from mean 17.3% lost with semaglutide treatment) one year after treatment withdrawal of semaglutide (including lifestyle intervention). Similar changes were observed in cardiometabolic variables. Increases in mean levels of glycated hemoglobin (HbA1c) (5.2 to 5.6%), C-reactive protein (CRP) (1.28 to 1.83 mg/L), lipid levels (total cholesterol: 184.6 to 191.4 mg/dL, triglycerides [TGs]: 95.7 to 122.4 mg/dL), systolic blood pressure (SBP) (121 to 131 mmHg), and diastolic blood pressure (DBP) (78 to 82 mmHg) were observed during the semaglutide off-treatment (OT) phase from Week 68 to Week 120

(Wilding et al 2022). A dietary intervention trial that investigated the effect of rate of weight loss showed a similar effect. In this study, patients were assigned to lose weight at a gradual rate or rapid rate via two levels of caloric restriction. Among the patients that achieved a 12.5% or more weight loss in both diet groups (15% mean reduction in body weight), similar and relatively rapid body weight regain was seen in both groups of patients following the cessation of the lifestyle intervention – even with the intervention of a 400-500 kilo calories (kcal)/day calorie restriction once weight regain was observed. Overall, patients in the rapid and gradual weight loss groups saw 10.3 and 10.4 kg regain of the 14.6 and 14.3 kg of body weight lost, respectively (Purcell et al 2014). These data suggest that regardless of the mechanism of weight loss, rapid and near complete regain of body weight is a common feature in the treatment of obesity among patients losing significant body weight during a treatment period. It is likely that this will be more frequently observed among patients taking GLP-1 agonists given the initial success of weight loss with these treatments.

Numerous peripheral and central mechanisms regulate weight regain (Busetto et al 2021) and include a return to higher calories consumption as well as reduced resting calorie expenditure. The phenomenon of "metabolic adaptation" or "adaptive thermogenesis" acts to counterweight loss and is thought to contribute to weight regain. Resting metabolic rate (RMR) and body composition changes were measured in 14 of the 16 originally studied "Biggest Loser" competitors 6 years after the end of the weight loss competition. Most subjects regained a significant amount of the weight lost during the televised competition. After 6 years, 41.0 ± 31.3 kg of the lost weight was regained ($p = 0.0002$), while RMR was 704 ± 427 kcal/day below baseline ($p < 0.0001$) and metabolic adaptation was -499 ± 207 kcal/day ($p < 0.0001$) (Fothergill et al 2016).

Studies examining the effect of GLP-1 agonists on lipid metabolism have also demonstrated a significant reduction in chylomicron production with these agents (Taskinen et al 2021). Therefore, a reduction in intestinal fat calorie uptake from dietary sources may play a role in GLP-1-induced weight loss and a subsequent increase following cessation of GLP-1 therapy may play a role in the body weight regain.

1.2 Microsomal Triglyceride Transfer Protein (MTP) Inhibition

Microsomal Triglyceride Transfer Protein (MTP) is critical in incorporating fats and cholesterol into lipoproteins in the gut and liver-the two primary sources of these compounds-for production and delivery to the rest of the body. It plays a crucial role in the assembly of TGs, cholesterol esters, and phospholipids into ApoB-containing lipoproteins and is integral in the assembly of very low-density lipoprotein cholesterol (VLDL-C) in liver. MTP is also found in the intestine and is critical in the transfer of TGs onto apolipoprotein B48 (ApoB48) for subsequent transfer

to the systemic circulation. Impaired lipid metabolism (dyslipidemia) is considered a major contributor to the etiology of metabolic and cardiovascular disease. Dyslipidemia, broadly characterized by elevated circulating levels of low-density lipoprotein-cholesterol (LDL-C) and TGs, is commonly treated by therapeutic intervention at the level of hepatic lipoprotein metabolism (statins, fibrates, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) though there are successful and complementary drugs that reduce hyperlipidemia through intestinal lipoprotein metabolism including the cholesterol absorption inhibitor, ezetimibe and bile acid sequestrants (Kim et al 2011). However, these intestinally-acting drugs only impact LDL-C levels and have no effect on postprandial TGs or body weight.

Inhibition of hepatic MTP results in hepatic steatosis. First generation MTP-inhibitors were designed to inhibit both hepatic and intestinal MTP in order to maximize the reductions in lipids. However, these programs ran into the issue of significant hepatic fat accumulation that severely limited their use in broader patient populations (Cuchel et al 2013, Cuchel et al 2007). The only approved hepatically and intestinally acting MTP-inhibitor is indicated for the severe, rare genetic disease, homozygous familial hypercholesterolemia. The development of agents that affect postprandial lipid levels by inhibiting only intestinal MTP (no impact on the liver) may serve as the next generation of agents for the treatment of metabolic disorders. The ability to inhibit enterocytic, but not hepatic MTP, make it possible for such agents to pharmacologically isolate the intestine to better understand the postprandial state and its impact on the etiology of metabolic disease while avoiding the fat accumulation issues of the liver. Inhibition of intestinal enterocyte MTP would be expected to reduce dietary fat absorption (and therefore reduced dietary calories from fat) as well as reduce uptake of dietary cholesterol and fatty acids. Therefore, the addition of a gut-specific MTP-inhibitor after patients have discontinued treatment with the GLP-1 agonists, semaglutide or tirzepatide, could meaningfully reduce the weight regain (rebound).

1.3 Investigational Drug, RDX-002

The investigational drug, RDX-002, is a potent, selective, and gut-specific MTP inhibitor. It inhibits MTP only in the absorptive cells lining the small intestine (enterocytes). Therefore, RDX-002 avoids the hepatotoxic effects observed with systemically available MTP inhibitors, such as lomitapide. Through this gut-specific MTP-inhibition, RDX-002 reduces the formation of chylomicrons that carry dietary fat/calories, TGs, and cholesterol into circulation.

The safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of orally administered RDX-002 have been evaluated in five completed Phase 1 and four completed Phase 2 clinical studies in 565 volunteers or patient participants. In each of these studies, with the exception of SLX-07-04 (which evaluated a new formulation of RDX-002 that was not

investigated further), RDX-002 dose-dependently decreased the AUC_{0-24} of postprandial plasma levels of TGs to a $p < 0.05$ level. This decrease was sustained for the duration measured in each of these studies (up to 24 hours) (Investigator's Brochure RDX-002 [Formerly SLx-4090; KD026]).

In Study SLx-4090-07-03, RDX-002 (200 mg three times a day [TID] or 200 mg once daily [QD]) given to patients with elevated TGs levels for 14 days, significantly decreased fasting total serum cholesterol (-29 mg/dL) and LDL-C (-31 mg/dL). In combination with a statin in hyperlipidemic patients, RDX-002 decreased LDL-C levels compared to placebo and increased the number of patients achieving a target level of <100 mg/dL. Mean body weight progressively decreased over the 12-week course of the study (-1.1 kg with RDX-002 plus statin versus -0.2 kg with placebo) (Study SLx-4090-08-06). In patients with uncontrolled Type 2 diabetes, in combination with metformin, RDX-002 significantly reduced HbA1c (-0.44%) after 12 weeks of treatment (Study SLx-4090-09-07). The reduction in HbA1c levels was accompanied by weight loss (1.1 kg with RDX-002 versus -0.4 kg with placebo). In a 2-week open-label study examining the effects of RDX-002 in antipsychotic-induced weight gain in antipsychotic naïve, healthy volunteers with no meaningful metabolic dysregulation, RDX-002 (200 mg, twice daily [BID], 30 minutes prior to breakfast and dinner) was associated with a significant decrease in postprandial TGs in subjects treated with olanzapine (10 mg, QD, with breakfast). This contrasted with an increase in postprandial TGs during the first week in subjects treated with olanzapine alone. Treatment with olanzapine alone was associated with a significant weight gain in subjects (mean increase 1.7 kg), which was blunted when co-administered with RDX-002 treatment (mean increase 0.4 kg) (Study RDX-002-22-09)
(Investigator's Brochure RDX-002 [Formerly SLx-4090; KD026]).

Based on these results, RDX-002, a small molecule inhibitor selective for intestinal MTP (iMTP) could offer a novel treatment approach for weight management and metabolic disease. In particular, in patients that have recently discontinued GLP-1 agonists for the treatment of obesity, the prior data indicate that RDX-002 could blunt the rapid weight gain seen upon cessation as well as reduce the accompanying increased rates of insulin resistance (and the subsequent drift to prediabetes and type 2 diabetes) and dyslipidemia.

Thus, this Phase 2, proof-of-concept study (RDX-002-024-011) will be conducted in two parts. Part A will evaluate the effect of 12 weeks of treatment with RDX-002 on postprandial TGs and body weight among patients who have recently discontinued treatment with the GLP-1 agonists, semaglutide or tirzepatide, for obesity. Part B will be a 24-week open-label extension (OLE) and will further evaluate the long-term safety and durability of treatment effect of RDX-002 in eligible patients who have completed Part A.

2. STUDY OBJECTIVES AND ENDPOINTS

The objectives and associated endpoints for Part A and Part B of the study are as follows:

Part A	
Objectives	**Endpoints**
Primary Objective • To assess the efficacy of 12 weeks of treatment with 200 mg BID RDX-002 on the mean percentage change from baseline on postprandial TGs among patients who have recently discontinued treatment with semaglutide or tirzepatide for obesity.	**Primary Efficacy Endpoint** • Difference in the mean percent change in the incremental postprandial TG area under the curve (AUC) in patients treated with RDX-002 as compared with placebo at Week 12. Note: Incremental postprandial TG AUC sets the pre-test meal (fasting) TG levels at zero and calculates the increased levels of TG that occur with consumption of the test meal. It measures only the incremental increase in TGs as the postprandial TGs and excludes the fasting, hepatic TGs.
Secondary Objectives • To evaluate the effect of 12 weeks of treatment with RDX-002 on mean percent change from baseline in body weight in patients who have recently discontinued semaglutide or tirzepatide obesity therapies;	**Secondary Efficacy Endpoints** • Difference in the mean percent change in the total postprandial TG AUC in patients treated with RDX-002 as compared with placebo at Week 12; Note: The total or absolute postprandial TG AUC measures the entire area under the curve that includes both the fasting (hepatic) TGs as well as the postprandial TGs; • Difference in the mean percent change from baseline in body weight in patients treated with RDX--002 as compared with placebo at Week 12; • Difference in the proportion of patients treated with RDX-002 exhibiting at least a 5% increase from baseline in body weight as compared with placebo at Week 12;

• To evaluate the effect of 12 weeks of treatment with RDX-002 on LDL-C in patients who have recently discontinued semaglutide or tirzepatide obesity therapies.	• Difference in the mean percent change from baseline in LDL-C in patients treated with RDX-002 as compared with placebo at Week 12;
Exploratory Objectives	**Exploratory Efficacy Endpoints**
• To explore the treatment effect of RDX-002 at Week 6 on body weight and LDL-C in patients who have recently discontinued GLP-1 treatment for weight loss;	• Difference in the mean percent change from baseline in body weight in patients treated with RDX-002 as compared with placebo at Week 6; • Difference in the mean percent change from baseline in LDL-C in patients treated with RDX-002 as compared with placebo at Week 6;
• To explore the treatment effect of RDX-002 at Weeks 6 and 12 on other fasting lipids (total cholesterol, non-high-density lipoprotein cholesterol [non-HDL-C]) and TGs in patients who have recently discontinued GLP-1 treatment for weight loss;	• Difference in the median percent change from baseline in fasting TGs in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Difference in the mean percent change from baseline in total cholesterol and non-HDL-C in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Relationship between changes in incremental postprandial TGs AUC and change in body weight for patients treated with RDX-002 as compared with placebo from baseline to Week 12; • Relationship between changes in incremental postprandial TGs AUC and change in body weight in patients pre- and post-discontinuation of GLP-1 treatment: o Relationship between percent change in incremental postprandial TGs AUC at Week 12 as compared to baseline and change in body weight at Week 12 as

	compared to baseline in patients treated with RDX-002; o Relationship between percent change in incremental postprandial TGs AUC at baseline compared to Visit G1 (pre-GLP-1 agonist discontinuation) and change in body weight from baseline to Week 12 in patients treated with placebo.
• To explore the treatment effect of RDX-002 at Weeks 6 and 12 on other obesity-linked risk factors; waist circumference, total body fat mass, HbA1c, homeostatic model assessment for insulin resistance (HOMA-IR), high sensitivity C-reactive protein (hs-CRP), and fasting and postprandial glucose and insulin in patients who have recently discontinued GLP-1 treatment for weight loss;	• Difference in the mean change from baseline in waist circumference in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Difference in the mean percent change from baseline in total body fat mass as measured by Inbody H20N scale in patients treated with RDX-002 as compared to placebo at Weeks 6 and 12; • Difference in the mean change from baseline in HbA1c in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Difference in the mean change from baseline in HOMA-IR index in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Difference in the median percent change from baseline in hs-CRP levels in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12; • Difference in the mean change from baseline in fasting glucose and insulin in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12;
	• Difference in the mean change from baseline

	in postprandial glucose and insulin in patients treated with RDX-002 as compared with placebo at Weeks 6 and 12;
• To explore the effect of 12 weeks of treatment with RDX-002 on SBP and DBP in patients who have recently discontinued GLP-1 treatment for weight loss;	• Difference in mean absolute change from baseline in SBP and DBP in patients treated with RDX-002 as compared with placebo at Week 12;
• To evaluate the effect of discontinuation of the GLP-1 agonists semaglutide or tirzepatide on changes in postprandial TGs.	• Difference in the mean percent change in incremental and absolute postprandial TGs AUCs from pre-GLP-1 discontinuation to baseline (1-2 weeks post-GLP-1 discontinuation).
Pharmacokinetic Objective	**Pharmacokinetic Endpoint**
• To evaluate the PK of RDX-002 in patients who have recently discontinued GLP-1 treatment for weight loss.	• PK parameters of RDX-002 and its main inactive metabolite at Week 12 in patients treated with RDX-002.
Safety Objective	**Safety Endpoints**
• To evaluate the safety of RDX-002 in patients who have recently discontinued semaglutide or tirzepatide obesity therapies.	• Incidence of treatment-emergent adverse events (TEAEs) including determination of serious adverse events (SAEs), TEAEs leading to discontinuation, and laboratory abnormalities as characterized by type, frequency, timing, severity (mild, moderate, severe), seriousness, and relationship to RDX-002; • Concomitant medications; • Clinical laboratory tests (hematology, chemistry, and urinalysis); • Vital sign measurements; • Electrocardiogram (ECG); • Physical examination findings; • Stool questionnaire.

Part B

Objectives	Endpoints
• To evaluate the safety and durability of efficacy of RDX-002 over 24 weeks of treatment.	**Efficacy Endpoints** • Difference in the mean percent change from original (Part A) baseline and Part B baseline in body weight, total body fat mass, and waist circumference at Weeks 6, 12, and 24; • Difference in the mean percent change from original (Part A) baseline and Part B baseline in fasting lipid panel, SBP, DBP, fasting glucose and insulin, HbA1c, HOMA-IR, and hs-CRP at Weeks 6, 12, and 24. **Safety Endpoints** • Incidence of TEAEs including determination of SAEs, TEAEs leading to discontinuation, and laboratory abnormalities as characterized by type, frequency, timing, severity (mild, moderate, severe), seriousness, and relationship to RDX-002; • Concomitant medications; • Clinical laboratory tests (hematology, chemistry, and urinalysis); • Vital sign measurements; • Electrocardiogram (ECG); • Physical examination findings; • Stool questionnaire.

3. INVESTIGATIONAL PLAN

3.1 Study Design

This Phase 2 study will be conducted in two parts at a single study site in the US. Part A will be a randomized, double-blind, placebo-controlled, parallel-group study and Part B will be an OLE to eligible patients who have completed Part A of the study. Patients who have a planned or willing discontinuation of semaglutide or tirzepatide treatment for obesity, have lost ≥10% or 10 kg of their original (pre-GLP-1 baseline) body weight during treatment with the GLP-1 agonist and are aged 18 to 65 years (both inclusive) will be eligible for Screening.

Part A of the study will be conducted as follows with a visit window of ±3 days allowed for Visit T1, Visit T2 and Visit T3:

- **Visit S1 - Screening Visit (Day -42 to Day -14)**: The Screening Visit (Visit S1) will occur no more than 42 to 14 days prior to the Baseline and Randomization Visit (Visit T1) while patients are still on their current GLP-1 therapy.
- **Visit G1 - GLP-1 Therapy Assessments (Day -42 to Day -14)**: After completing all screening assessments, patients who meet the screening requirements will return to the clinic for the GLP-1 therapy assessment visit (Visit G1). This visit will be conducted prior to Timepoint G2, while patients are still on their current GLP-1 treatment. To allow for flexibility with patient scheduling and planning for the discontinuation of GLP-1 therapy, Visit S1 and Visit G1 should occur during the 28 days prior to Timepoint G2. At Visit G1, patients will undergo an assessment of postprandial TG levels. Patients will consume a standardized high-fat test meal (Appendix V) and TG levels will be measured 30 minutes prior to the initiation of the test meal and at 1-, 2-, 3-, 4-, 6-, and 8-hours after the initiation of the test meal.
- **Timepoint G2 – Discontinuation of GLP-1 (Day -14 to Day -7)**: Patients will be instructed to commence the planned discontinuation of their current GLP-1 agonist treatment (semaglutide or tirzepatide) after Visit G1 and within 7 to 14 days prior to randomization to RDX-002 or matching placebo.
- **Visit T1 – Baseline and Randomization (Day 1)**: Eligible patients will be randomly assigned to receive RDX-002 or matching placebo for a 12-week treatment period. Only patients with recent discontinuation (7 to 14 days prior to randomization) of semaglutide or tirzepatide who lost ≥10% or 10 kg of body weight during their treatment with the above drugs and continue to satisfy the screening period study entrance criteria at Visit T1 (Day 1) will be randomized to treatment with RDX-002 or matching placebo.

Patients will consume the standardized high-fat test meal at Visit T1 (Day 1). The TG levels will be measured 30 minutes prior to initiation of the test meal and at 1-, 2-, 3-, 4-, 6-, and 8-hours after the initiation of the test meal. Following the 8-hour blood draw, patients will take their first dose of either RDX-002 or placebo 30 minutes prior to dinner.

Patients will take RDX-002 everyday BID; approximately 30 minutes prior to breakfast (or the first meal of the day) and approximately 30 minutes prior to dinner.

- **Visit T2 - Clinic Visit (Day 43)**: Patients will return to the clinic at Visit T2 (Day 43) for designated blood draws and study procedures. The TG levels will be measured 30 minutes prior to receiving their dose of either RDX-002 or placebo. Following the study procedures, patients will receive the dose of either RDX-002 or placebo 30 minutes prior to a standard clinic meal. At this visit, patients will also be offered the opportunity to participate in the Part B OLE study.
- **Visit T3 - Clinic Visit (Day 85) - End of Part A**: Patients will return to the clinic at Visit T3 (Day 85) for designated blood draws and study procedures. Following the study procedures, patients will receive their dose of either RDX-002 or placebo 30 minutes prior to beginning their standardized high-fat test meal. The TG levels will be measured 30 minutes prior to receiving the dose of either RDX-002 or placebo (and within 60 minutes prior to beginning of the standardized high-fat test meal) and post-dose at 1-, 2-, 3-, 4-, 6-, and 8-hours after the initiation of the test meal. End of study procedures will be conducted for patients not continuing in Part B of the study.

  Note: A follow-up telephone monitoring call will be conducted by the site staff every 2 weeks (±2 days) from the date of randomization up to Visit T3 (Day 85) to assess patient reported compliance to study treatment. During this telephone call, adherence to recording of dosing and bowel movement in patient diary, any adverse events (AEs) that occurred, and concomitant medications will be reviewed.
- **Visit OT - Off-treatment Follow-up Phone Call (Day 99)**: Patients who are not participating in the Part B OLE will receive an OT follow-up phone call approximately 2 weeks after the last dose of RDX-002 or placebo for review of any AEs and concomitant medications.

Notes:

1. At Visit G1, Visit T1 (Day 1), and Visit T3 (Day 85), patients will be instructed to consume the standardized high-fat test meal (Appendix V) entirely within 15 minutes.

For patients who have difficulty consuming the meal within the initial allowable time, an additional window of up to 15 minutes will be provided to complete the meal;

2. For Visit T1 (Day 1), Visit T2 (Day 43), and Visit T3 (Day 85), patients will be instructed to come for clinic visits without taking their scheduled doses of RDX-002 or placebo.

Part B of the study will be conducted as follows with a visit window of ±3 days allowed for all visits:

All eligible patients who have completed Part A and are willing to participate in the Part B OLE of the study will receive open-label RDX-002 as a 200 mg BID dose for 24 weeks, regardless of their blinded treatment assignment (RDX-002 or placebo) in Part A.

- **Visit B1 (Day 1) – Part B Baseline and Initiation of OLE**: Patients participating in the Part B OLE will complete the study procedures of Visit T3 (Day 85, Part A) and receive the first dose of open-label RDX-002 as an evening dose 30 minutes prior to dinner.
- **Visit B2 (Day 43) and Visit B3 (Day 85):** Patients will return to the clinic for designated blood draws and study procedures. The fasting laboratory blood draws will be measured 30 minutes prior to receiving their dose of RDX-002. Following the study procedures, patients will receive their dose of RDX-002, 30 minutes prior to a standard clinic meal.
- **Visit B4 (Day 169-End of Part B and End of Study [EOS]) – Clinic Visit**: Patients will return to the clinic for designated blood draws and study procedures.

  Notes:

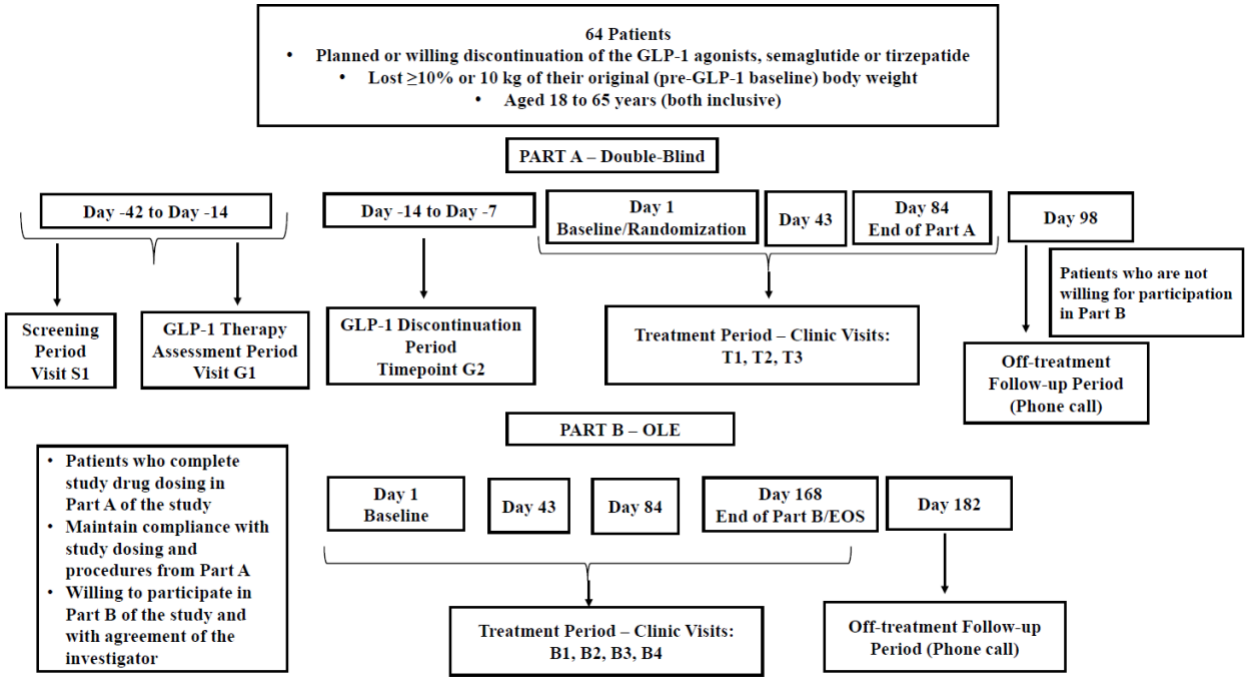
  1. Data from Visit B1 (Day 1, Part B) will serve as one of the baselines for Part B analyses;
  2. Visit T3 (Day 85, Part A) and Visit B1 (Day 1, Part B) can occur on the same day;
  3. For Visit B1 (Day 1), Visit B2 (Day 43), and Visit B3 (Day 85), patients will be instructed to come for clinic visits without taking their scheduled doses of RDX-002;
  4. A follow-up telephone monitoring call will be conducted by the site staff every 2 weeks (±2 days) from Visit B1 (Day 1) up to Visit B4 (Day 169-End of Part B and EOS) to assess patient reported compliance to study treatment. During this telephone call, adherence to recording of dosing and bowel movement in patient diary, any AEs that occurred, and concomitant medications will be reviewed.

- **Visit OT - Off-treatment Follow-up Phone Call (Day 183)**: Patients will receive an OT

follow-up phone call approximately 2 weeks after the last dose of RDX-002 for review of any AEs and concomitant medications.

The study design for Part A and Part B is illustrated in Figure 1.

Figure 1 Study Design Schematic



Abbreviations: EOS = end of study; GLP-1 = glucagon-like peptide-1; OLE = open-label extension.

3.2 Rationale for Study Design and Dose

The study design for Part A of this Phase 2, randomized, double-blind, placebo-controlled, parallel group study is appropriate to evaluate the effect of RDX-002 on postprandial TGs and body weight in patients discontinuing the GLP-1 agonists, semaglutide or tirzepatide, for the treatment of obesity. Part B will be a 24-week OLE to demonstrate the long-term safety and durability of treatment effect of RDX-002 in eligible patients who have completed Part A.

Dose selection for this study is based upon results from 9 previous clinical studies with RDX-002 (five Phase 1 and four Phase 2 studies). To date, the safety, tolerability, PK, and PD of RDX-002 have been evaluated in 565 participants (203 normal healthy participants and 362 patients with dyslipidemia, Type 2 diabetes). A total number of 404 participants have been exposed to RDX-002 (158 healthy participants; 246 patients with dyslipidemia and/or Type 2 diabetes). In healthy participants, RDX-002 has been evaluated at increasing single doses ranging up to 800 mg and at multiple doses up to 200 mg TID (600 mg daily) for up to 14 days. Repeat doses of RDX-002 reduced serum postprandial TG levels and decreased both total

cholesterol and LDL-C after 14 days. The dose of 200 mg BID has been selected for this clinical trial and patient population as it is felt to be a dose that will effectively inhibit postprandial TGs in a meaningful portion of patients (>50%) while reducing potential issues of tolerability and compliance. The data from previous studies indicate that RDX-002 could blunt the rapid weight gain in patients that have recently discontinued GLP-1 agonists for the treatment of obesity.

RDX-002 has been well tolerated and there were no clinically significant AEs or SAEs and, because of the gut-selective nature of RDX-002, plasma levels of RDX-002, if present at all, were very low (≤5 ng/mL). The safety profile of RDX-002 was similar to that of placebo, in the studies where placebo was used.

Based on the safety and PK results of these previous studies, the dose of 200 mg BID is expected to be safe and well tolerated.

4. SELECTION AND WITHDRAWAL OF PATIENTS

4.1 Study Population (Part A and Part B)

Approximately 64 patients with recent discontinuation of the GLP-1 agonists, semaglutide or tirzepatide, for the treatment of obesity, will be enrolled in Part A of the study. Patients who complete the study drug dosing in Part A of the study, have maintained a minimum of 80% compliance with study dosing and procedures from Part A, and are willing to participate in Part B of the study will be enrolled in Part B with agreement of the investigator.

4.2 Inclusion Criteria (Part A)

Each patient must meet all of the following criteria to be enrolled in Part A of the study:

1. Willing and able to provide written informed consent prior to the conduct of any study-specific procedures;
2. Planned or willing discontinuation of semaglutide or tirzepatide for the treatment of obesity prior to randomization (Visit T1/Day 1) through EOS;
3. Lost ≥10% or 10 kg of original (pre-GLP-1 baseline) body weight with semaglutide or tirzepatide;
4. Males and females aged 18 to 65 years (both inclusive) at Screening (Visit S1);
5. A HbA1c of <6.5% at Screening (Visit S1);
6. A 12-lead ECG at Screening (Visit S1) which, in the opinion of the investigator, had no abnormalities that compromised safety in this study;
7. Males and nonpregnant, nonlactating females. Females must be either:
    - Having negative pregnancy test at Screening (Visit S1);
    - Naturally postmenopausal, defined as ≥1 year without menses and follicle-stimulating hormone (FSH) ≥40.0 IU/L, or
    - Surgically sterile, including hysterectomy, bilateral oophorectomy, and/or tubal ligation, or females of childbearing potential willing to use 2 acceptable methods of birth control (unless they have agreed to follow the definition of true abstinence). The minimal requirement for adequate contraception should be started on Day 1, continuing during the study period, and for at least 30 days after the last dose of study drug. Acceptable methods of birth control include:
        - oral, implantable, injectable, or topical birth control medications;

- placement of an intrauterine device with or without hormones;
- barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly;
- vasectomized male partner who is the sole partner for this patient; or
- True abstinence: when this is the preferred and usual lifestyle of the patient (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods], declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception).

4.3 Exclusion Criteria (Part A)

Patients meeting any of the following criteria will be excluded from Part A of the study:

1. Type 1 or Type 2 diabetes;
2. Recent (within 3 months prior to the Screening visit [Visit S1]) myocardial infarction, unstable angina leading to hospitalization, uncontrolled symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of Screening), coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), carotid surgery or stenting, cerebrovascular accident, transient ischemic attack, endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (e.g., PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may be considered if deemed by the investigator to be stable for the previous 3 months;
3. Uncontrolled hypertension, defined as SBP >160 mmHg and DBP >100 mmHg after being in supine position for 5 minutes;
4. Total fasting (minimum of 10 hours) TGs ≥400 mg/dL (4.5 mmol/L) at Screening (Visit S1);
5. Fasting glucose >126 mg/dL at Screening (Visit S1);
6. Uncontrolled hypothyroidism, including thyroid stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Screening (Visit S1); patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization (Visit T1/Day 1) are allowed;
7. Liver disease or dysfunction, including:
    - Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies at Screening (Visit S1); or
    - Alanine aminotransferase (ALT), aspartate aminotransferase (AST) ≥2 × ULN,

and/or total bilirubin ≥2 × ULN at Screening (Visit S1). If total bilirubin ≥1.2 × ULN, a direct and indirect bilirubin will be obtained, and if consistent with Gilbert's disease or if the patient has a history of Gilbert's disease, the patient may be enrolled in the study;

Note: At the discretion of the investigator, a single repeat of ALT and/or AST may be completed prior to randomization (Visit T1/Day 1); for those patients who have a repeat ALT and/or AST, the repeat value will be used to determine eligibility. Also, if test for hepatitis C antibody is positive, but optional reflexive test for hepatitis C ribonucleic acid is negative, the patient can be enrolled.

8. Renal dysfunction or glomerulonephritis, including estimated glomerular filtration rate (eGFR; using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] 2021 formula) <60 mL/min at Screening (Visit S1). Note, a single repeat qualifying eGFR, performed at the discretion of the investigator, is acceptable;
9. Gastrointestinal conditions or procedures (including weight loss surgery; e.g., Lap-Band® or gastric bypass) except uncomplicated cholecystectomy and appendectomy that may affect drug absorption;
10. Known history of hematologic or coagulation disorders or a hemoglobin level <10.0 g/dL at Screening (Visit S1);
11. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ are allowed;
12. Unexplained creatine kinase (CK) >3 × ULN at any time prior to randomization (i.e., not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have single repeat CK ≤3 × ULN prior to randomization;
13. History of drug or alcohol abuse within the last 2 years or reported current consumption of >14 alcoholic drinks/week, or any illicit drug use (checked positive for standard drug screening panel). Patients testing positive for tetrahydrocannabinol (THC) (whether prescribed or not) and for amphetamine derivatives prescribed by and under the care of a health care practitioner (except for weight management) can be enrolled after evaluation and at the discretion of the investigator;
14. Inability to follow the required minimum 2 meals a day, or unwillingness to consume meal on both study test occasions, or inability to fast, as required during the study;

15. Blood donation, participation in multiple blood draws, clinical study, major trauma, blood transfusion or surgery with or without blood loss within 30 days prior to randomization (Visit T1/Day 1);
16. Use of any experimental or investigational drugs except GLP-1 agonists within 30 days or 5 half-lives (whichever is longer) prior to Screening (Visit S1);
17. Use of any of the following prohibited diabetes or weight loss drugs prior to or during the study (as specified) unless meeting specific rescue criteria:
    - Other GLP-1 agonists such as Victoza/liraglutide, Byetta/exenatide, Trulicity/dulaglutide within 120 days prior to Screening (Visit S1);
    - Biguanides such as metformin within 60 days of Screening (Visit S1);
    - Sodium-glucose transport protein 2 (SGLT2) inhibitors such as Jardiance/empagliflozin, Invokana/canagliflozin, Farxiga/dapagliflozin within 60 days prior to Screening (Visit S1);
    - Dipeptidyl peptidase-4 (DPP-4) inhibitors such as Januvia/sitagliptin, Tradjenta/linagliptin within 60 days prior to Screening (Visit S1);
    - Thiazolidinediones (TZD/glitazones) such as Actos/pioglitazone, Avandia/rosiglitazone within 120 days prior to Screening (Visit S1);
    - Sulfonylurea such as Amaryl/glimepiride, Glucotrol/glipizide XL/glipizide within 60 days prior to Screening (Visit S1);
    - Injectable synthetic forms of amylin such as Pramlintide (symlin);
    - Any other obesity medication or medications associated with weight loss within 90 days prior to Screening (Visit S1);
    - Systemic corticosteroids within 60 days prior to Screening (Visit S1), use of topical and inhaled corticosteroids are allowed.
18. Recent (within 30 days unless otherwise specified) initiation or discontinuation of the following lipid-lowering medications:
    - Welchol/cholestagel/colesevelam hydrochloride; within 60 days prior to Screening (Visit S1);
    - Mipomersen; within 180 days prior to Screening (Visit S1);
    - Lomitapide; within 90 days prior to Screening (Visit S1);
    - Apheresis; within 90 days prior to Screening (Visit S1);

- Statins;
- Ezetimibe;
- PCSK9 inhibitors, within 60 days prior to Screening (Visit S1);
- Red yeast rice extract - containing products;
- Omega 3 fatty acids and derivatives such as Lovaza® and over-the-counter (OTC) fish oil supplements >2000 mg; within 60 days prior to Screening (Visit S1);
- Niacin (>500 mg).

19. An employee or contractor of the facility conducting the study, or a family member of the principal investigator, co-investigator, or any Sponsor personnel;
20. Pregnant, breastfeeding, or intending to become pregnant within 30 days after study completion or last dose of study drug;
21. A medical or situational (i.e., geographical) finding that, in the investigator's opinion, may compromise the patient's safety or ability to complete the study.

4.4 Eligibility Criteria (Part B)

Patients who complete the study drug dosing in Part A of the study, have maintained a minimum of 80% compliance with study dosing and procedures from Part A, and are willing to participate in Part B of the study will be enrolled in Part B with agreement of the investigator.

4.5 Patient Withdrawal Criteria

4.4.1 Stopping Criteria

Patients will be discontinued from the study if they experience unacceptable AEs, as determined by the investigator. Liver enzymes will be measured at all clinic visits. For patients that experience ALT and/or AST elevations >3 × ULN, repeat measures of ALT, AST, ALP and bilirubin should be conducted 48 to 72 hours following the initial elevation and patients will be more closely observed for signs of more significant liver disease (including additional blood tests of liver enzymes as needed) including investigation of alternative causes of liver dysfunction (e.g., viral hepatitis, alcoholic or autoimmune hepatitis, nonalcoholic steatohepatitis or other concomitant therapies). De-challenge and re-challenge of study drug will be considered.

Discontinuation of study drug should be considered if patients meet one of the following criteria:

- ALT or AST >8 ×ULN;
- ALT or AST >5 × ULN for >2 weeks;

- ALT or AST >3 × ULN and total bilirubin >2 × ULN or INR >1.5;
- ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and or eosinophilia (>5%).

Permanent or temporary discontinuation or reduction in the dosage of the study drug for Grade 3 TEAEs will be at the discretion of the investigator.

4.4.2 Reasons for Withdrawal/Discontinuation

Patients may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or at the study site. A patient may be withdrawn from the study for any of the following reasons:

- The patient withdraws consent or the investigator or sponsor decide to discontinue the patient's participation in the study;
- Does not meet the protocol inclusion or exclusion criteria;
- Noncompliance with the protocol;
- A serious or severe AE that in the investigator's opinion requires withdrawal from the study;
- Laboratory safety assessments that reveal clinically significant changes from the baseline values;
- Symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies withdrawal;
- Lost to follow-up;
- Study terminated by Sponsor;
- Other (e.g., pregnancy, development of contraindications of use of study drug).

Every effort should be made to keep patients in the study. The reasons for patients not completing the study will be recorded. Upon occurrence of a serious or severe AE, the investigator will confer with the Sponsor. If a patient is discontinued because of an AE, the event will be followed until it is resolved.

4.4.3 Handling of Withdrawals

Patients are free to withdraw from the study or study treatment at any time upon request. Patient participation in the study may be stopped at any time at the discretion of the investigator or at the request of the Sponsor.

Patients who discontinue study treatment or active participation in the study will no longer receive study drug. When a patient 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, all patients who discontinue study treatment or withdraw from the study prematurely will undergo all EOS assessments. Patients who fail to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol.

It is vital to obtain follow-up data on any patient withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

4.4.4 Replacements

Withdrawn patients may be replaced at the Sponsor's discretion.

5. STUDY TREATMENTS

5.1 Treatments Administered

Part A: At Visit T1 (Day 1), approximately 64 patients will be randomly assigned to receive RDX-002 or matching placebo for a 12-week treatment period in a 1:1 allocation ratio. The expected study duration is approximately 120 to 140 days (20 weeks), including an approximate 28-day Screening period and GLP-1 therapy assessment period, an approximate 14-day GLP-1 discontinuation period, a 12-week treatment period, and for patients who are not participating in Part B, an OT phone call 2 weeks post last dose of RDX-002 or placebo.

Investigational study drug: RDX-002 (4 × 50 mg tablets) and matching placebo

Patients will be dosed with RDX-002 or matching placebo everyday BID; approximately 30 minutes prior to breakfast (or the first meal of the day) and approximately 30 minutes prior to dinner. Patients will orally take 4 tablets of RDX-002 or matching placebo BID.

Part B: At Visit B1 (Day 1), all eligible patients who have completed Part A and willing to participate in Part B will receive RDX-002 for a 24-week treatment period. Patients will be dosed RDX-002 everyday BID; approximately 30 minutes prior to breakfast (or the first meal of the day) and approximately 30 minutes prior to dinner. Patients will orally take 4 tablets of RDX-002 BID.

5.2 Identity of Investigational Product(s)

The investigational study drug, RDX-002 tablets (50 mg) are a formulation containing RDX-002 drug substance and excipients.

A brief description of RDX-002 is provided below:

- Response Pharmaceutical Code: RDX-002
- Chemical Name (IUPAC): phenyl 6-[[3-methoxy-2-[4-(trifluoromethyl)phenyl]benzoyl]amino]-3,4-dihydro-1H-isoquinoline-2-carboxylate
- Appearance: Off-white to pale yellow solid
- Melting Point Range: 166 to 172°C
- Molecular Weight: 546.5
- Crystallinity: Crystalline material; no known polymorph
- Solubility: <8 µg/mL at pH 7.4

5.3 Study Drug Receipt, Packaging and Labeling

The investigator will maintain accurate records of receipt of all study drug, including dates of receipt. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded.

The study drugs will be labeled with trial-specific labels, and the content on the labels will be in accordance with Good Manufacturing Practices (GMP) and local requirements.

5.4 Study Drug Storage

The study drugs will be stored with appropriate labeling under storage conditions specified in the Pharmacy manual and in accordance with Good Clinical Practice (GCP). All investigational products will be stored in a secure temperature-controlled area with access limited to the authorized site staff and under physical conditions that are consistent with investigational product-specific requirements.

5.5 Study Drug Dispensing and Accountability

The site will acknowledge receipt of the study drugs and document this in the respective log. The investigator, site pharmacist, or investigator's designated personnel will maintain a record of the inventory and disposition of all study drugs received for the study. Sufficient quantity of study drugs will be dispensed to patients to allow for BID dosing until their next scheduled site visit. A drug accountability record of the study drugs dispensed, dosed, returned, and unused will be maintained at the study site and will become part of the study file.

All the study drugs shall be issued and used in accordance with the protocol, and it is the investigator's responsibility to ensure that an accurate record is maintained of the study drug issued and returned. Under no circumstances will the investigator supply the study drug to a third party, allow the study drug to be used other than as directed by this clinical study protocol, or dispose of the study drug in any other manner without prior permission from the Sponsor. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, study drug will be reconciled, verified by the monitor, and signed off by the investigator. Destruction of study drug will take place only on receipt of Sponsor's written authorization.

5.6 Method of Assigning Subjects to Treatment Groups

The study randomization schedule for Part A, inclusive of the treatment assignment and unique randomization number, will be generated or produced using a validated plan.

Part B is an OLE and therefore all patients participating in Part B will receive RDX-002 and will maintain the same unique identification number they received in Part A

5.7 Blinding

Part A will be a randomized, double-blind, study. Patients and investigator (or designee) will remain blinded to the study treatment assignment during the study.

In case of an emergency, SAE (see Section 6.6.1.2), or in cases when knowledge of the study treatment assignment is needed in order to make treatment decisions, the investigator (or designee) may unblind the patient's study treatment assignment. The investigator (or designee) should make every attempt to contact the Sponsor prior to initiating any unblinding procedures.

When a blind is broken for safety reasons, the patient will be withdrawn from the study treatment and the event will be recorded on the eCRF. The patient will be encouraged to continue safety follow-up per study schedule. The circumstances leading to the breaking of the treatment code should be fully documented in the investigator's study files and in the patient's source documentation. Assignment of study treatment should not be recorded in any study documents or source document.

Part B will be an OLE to Part A of the study.

5.8 Treatment Compliance

The administration of the study drugs during clinic visits will be supervised by the investigator (or designee) and documented in the eCRF. The study drug will be self-administered by the patient on non-clinic visit days. Upon dispensing study drug to the patient, the investigator or designee will instruct the patient on the protocol-specified instructions for administering the study drug to ensure consistent treatment adherence throughout the study.

In Part A of the study at Visit T1 (Day 1) and Visit T2 (Day 43) and in Part B of the study at Visit B1 (Day 1), Visit B2 (Day 43) and Visit B3 (Day 85), patients will be dispensed a sufficient supply of study drug for self-administration until the next scheduled visit. Patients will be counseled to document treatment compliance by recording their dosing on the patient diary (Appendix VI) which will be completed every day. Site staff will also telephone the patient every 2 weeks from the date of randomization to assess patient reported compliance to study treatment (Section 6.1.7).

Patients will be instructed to return all bottles of study medication (used and unused) to the site at each subsequent visit. The study site will perform a pill count (compliance assessment) each time the bottles are returned. Study drug accountability and reconciliation will be performed by the study staff and the study monitor(s) by checking the used and unused study drug in Part A of the study at Visit T2 (Day 43) and Visit T3 (Day 85) and in Part B of the study at Visit B1 (Day 1), Visit B2 (Day 43), Visit B3 (Day 85) and Visit B4 (Day 169) to ensure that the patient has taken the assigned study drug.

5.9 Prior and Concomitant Medications

Prior medication is any medication taken before initiation of study treatment (used in the 30 days before Screening). Concomitant medications (used from Day 1 onwards for both Part A and Part B of the study) will include all prescription drugs, herbal products, vitamins, minerals, and OTC medications taken on or after initiation of study treatment.

Patients taking regular (or a course of) diabetes drugs, or OTC health food supplements/prescription drugs for weight loss immediately prior to or during the study will be excluded from the study. Use of hormonal or oral birth control medications will be allowed. Use of paracetamol at doses of up to 3 g per day for the relief of pain will be allowed at the discretion of the investigator.

The use of background lipid-modifying drugs (see Section 5.9.1 for list) or any antihypertensive drugs are allowed as long as they have been initiated within the prescribed time limits prior to Screening and remain constant in terms of dose and dose frequency during the course of the study.

The investigator is to be informed as soon as possible about any new medication or changes in dose of medication taken between the time of Screening until the end of the study. Initiation of any new anti-hypertensive medications during the study treatment period are discouraged unless the patient's blood pressure exceeds 160/90 mm Hg and/or is deemed necessary by the investigator. Any use of medication taken during the study will be recorded in the appropriate section of the eCRF with indication, dose information, and dates of administration.

5.9.1 Prohibited Medications

In addition to the prescription medications, the use of any of the following medications/treatments prior to or during the study will be prohibited:

- Use of any of the following prohibited diabetes or weight loss drugs prior to or during the study (as specified) unless meeting specific rescue criteria:
    - Other GLP-1 agonists such as Victoza/liraglutide, Byetta/exenatide, Trulicity/dulaglutide within 120 days prior to Screening (Visit S1);
    - Biguanides such as metformin within 60 days of Screening (Visit S1);
    - Sodium-glucose transport protein 2 (SGLT2) inhibitors such as Jardiance/empagliflozin, Invokana/canagliflozin, Farxiga/dapagliflozin within 60 days prior to Screening (Visit S1);
    - Dipeptidyl peptidase-4 (DPP-4) inhibitors such as Januvia/sitagliptin, Tradjenta/linagliptin within 60 days prior to Screening (Visit S1);

- Thiazolidinediones (TZD/glitazones) such as Actos/pioglitazone, Avandia/rosiglitazone within 120 days prior to Screening (Visit S1);
- Sulfonylurea such as Amaryl/glimepiride, Glucotrol/glipizide XL/glipizide within 60 days prior to Screening (Visit S1);
- Injectable synthetic forms of amylin such as Pramlintide (symlin);
- Any other obesity medication or medications associated with weight loss within 90 days prior to Screening (Visit S1);
- Systemic corticosteroids within 60 days prior to Screening (Visit S1), use of topical and inhaled corticosteroids are allowed.

- Recent (within 30 days unless otherwise specified) initiation or discontinuation of the following lipid-lowering medications:
  - Welchol/cholestagel/colesevelam hydrochloride; within 60 days prior to Screening (Visit S1);
  - Mipomersen; within 180 days prior to Screening (Visit S1);
  - Lomitapide; within 90 days prior to Screening (Visit S1);
  - Apheresis; within 90 days prior to Screening (Visit S1);
  - Statins;
  - Ezetimibe;
  - PCSK9 inhibitors, within 60 days prior to Screening (Visit S1);
  - Red yeast rice extract - containing products;
  - Omega 3 fatty acids and derivatives such as Lovaza® and OTC fish oil supplements >2000 mg; within 60 days prior to Screening (Visit S1);
  - Niacin (>500 mg).

6. STUDY ASSESSMENTS AND PROCEDURES

The procedures to be performed during the study for Part A and Part B are described below and summarized in the schedule of events presented in Appendix I and Appendix II, respectively. A visit window of ±3 days will be allowed for Visit T1, Visit T2 and Visit T3 for Part A and all visits for Part B of the study.

6.1 Study Visits

6.1.1 Visit S1 (Day -42 to Day -14): Screening/Eligibility Assessments (Part A)

Before performing any study procedures, all potential patients will sign and date an informed consent form (ICF). Patients will have the opportunity to have any questions answered before signing the ICF. The investigator or a qualified designee must address all questions raised by the patient. The investigator/designee will also sign and date the ICF. Patients who have a planned or willing discontinuation of semaglutide or tirzepatide for the treatment of obesity, have lost ≥10% or 10 kg of their original (pre-GLP-1 baseline) body weight during treatment with the GLP-1 agonist and are aged 18 to 65 years (both inclusive) will be eligible for Screening. Details of body weight lost will be verified from the medical history/records collected during Screening and the initiation of GLP-1 treatment.

The following procedures and assessments will be performed/completed during Screening (Appendix I):

- Informed consent
- Assignment of patient identification (screening) number
- Review of inclusion and exclusion criteria
- Demographic information (e.g., age, gender, race, ethnicity)
- Medical history
- Prior medications
- Physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature)
- 12-lead ECG
- Height
- Body weight and BMI

- Total body fat mass
- Waist circumference
- Clinical laboratory tests
  - Hematology
  - Clinical chemistry, including fasting glucose
  - Urinalysis (microscopic)
  - Serum pregnancy test for all females of childbearing potential
  - Serology test: hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV) tests
- Urine drug test
- Breath alcohol test
- eGFR using CKD-EPI formula
- Fasting lipid panel includes LDL-C, total cholesterol, non-HDL-C, and TGs
- HbA1c
- hs-CRP

Screening assessments may be repeated once per patient at the investigator/designee's discretion. The last assessment performed for any of the efficacy/safety measurements will be considered as the Screening assessment.

6.1.2 Visit G1 (Day -42 to Day -14): GLP-1 Therapy Assessments (Part A)

The following procedures and assessments will be performed during GLP-1 therapy assessments (Appendix I):

- Physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature)
- Clinical laboratory tests
  - Hematology
  - Clinical chemistry, including fasting glucose
  - Urinalysis (microscopic)
- eGFR using CKD-EPI formula

- High-fat test meal (Appendix V)
- Body weight and BMI
- Total body fat mass
- Waist circumference
- Fasting lipid panel includes LDL-C, total cholesterol, non-HDL-C, and TGs
- Fasting TGs
- Fasting insulin
- HbA1c
- hs-CRP
- HOMA-IR
- Postprandial TGs, insulin, and glucose
- Adverse event monitoring and recording
- Review of concomitant medications.

6.1.3 Timepoint G2 (Day -14 to Day -7): GLP-1 Treatment Discontinuation (Part A)

- Discontinuation of current GLP-1 treatment
- Adverse event monitoring and recording
- Review of concomitant medications

6.1.4 Visit T1 (Day 1): Baseline, Clinic Visit (Part A)

After completion of the high-fat test meal on Day 1, approximately 64 eligible patients will be randomized in a 1:1 ratio to receive either RDX-002 (n = 32) or matching placebo (n = 32). The following baseline procedures and assessments will be performed/completed at Visit T1 (Day 1) (Appendix I):

- Review of inclusion and exclusion criteria
- Physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature)
- 12-Lead ECG
- Clinical laboratory tests

  - Hematology
  - Clinical chemistry, including fasting glucose
  - Urinalysis (microscopic)
  - Urine pregnancy test for all females of childbearing potential
- Urine drug test
- Breath alcohol test
- eGFR using CKD-EPI formula
- Body weight and BMI
- Total body fat mass
- Waist circumference
- Randomization
- High-fat test meal (Appendix V)
- RDX-002 or matching placebo dosing
- Fasting lipid panel includes LDL-C, total cholesterol, non-HDL-C, and TGs
- Fasting TGs
- Fasting insulin
- HbA1c
- hs-CRP
- HOMA-IR
- Postprandial TGs, insulin, and glucose
- Patient diary dispensing (Appendix VI)
- Study drug dispensing
- Adverse event monitoring and recording
- Review of concomitant medications
- Stool questionnaire.

6.1.5 Visit T2 (Day 43): Clinic Visit (Part A)

The following procedures and assessments will be performed/completed at Visit T2 (Day 43) (Appendix I):

- Physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature)
- Clinical laboratory tests
  - Hematology
  - Clinical chemistry, including fasting glucose
  - Urinalysis (microscopic)
- eGFR using CKD-EPI formula
- Body weight and BMI
- Total body fat mass
- Waist circumference
- Standard clinic meal
- RDX-002 or placebo dosing
- Fasting lipid panel includes LDL-C, total cholesterol, non-HDL-C, and TGs
- Fasting TGs
- Fasting insulin
- HbA1c
- HOMA-IR
- hs-CRP
- Patient diary dispensing (Appendix VI)
- Collection and review of patient diary
- Study drug dispensing
- Collection and review of used and unused study drug
- Adverse event monitoring and recording
- Review of concomitant medications

- Stool questionnaire
- Patients will be offered an opportunity to participate in Part B OLE.

6.1.6 Visit T3 (Day 85): End of Part A

The following procedures and assessments will be performed/completed at Visit T3 (Day 85) for patients not continuing in Part B (Appendix I):

- Physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature)
- 12-Lead ECG
- Clinical laboratory tests
  - Hematology
  - Clinical chemistry, including fasting glucose
  - Urinalysis (microscopic)
- eGFR using CKD-EPI formula
- Body weight and BMI
- Total body fat mass
- Waist circumference
- High-fat test meal (Appendix V)
- RDX-002 or placebo dosing
- Fasting lipid panel includes LDL-C, total cholesterol, non-HDL-C, and TGs
- Fasting TGs
- Fasting insulin
- HbA1c
- hs-CRP
- HOMA-IR
- Postprandial TGs, insulin, and glucose
- PK sampling
- Collection and review of patient diary

- Collection and review of used and unused study drug
- Adverse event monitoring and recording
- Review of concomitant medications
- Stool questionnaire.

6.1.7 Telephone Follow-up – Patient Reported Compliance (Part A)

A follow-up telephone monitoring call will be conducted by the site staff every 2 weeks (±2 days) from the date of randomization up to Visit T3 (Day 85) to assess patient reported compliance to study treatment. During this telephone call, adherence to recording of dosing and bowel movement in patient diary, any AEs that occurred, and concomitant medications will be reviewed.

6.1.8 Visit OT (Day 99): Off-treatment Follow-up Phone Call (Part A)

Patients who are not participating in the Part B OLE will receive an OT follow-up phone call approximately 2 weeks after the last dose of RDX-002 or placebo for review of any AEs and concomitant medications.

6.1.9 Visit B1 (Day 1)/Baseline (Clinic Visit): Initiation of Open-Label Extension (Part B)

Patients who complete the study drug dosing in Part A of the study, have maintained a minimum of 80% compliance with study dosing and procedures from Part A, and are willing to participate in Part B of the study will be enrolled in Part B with agreement of the investigator.

Before performing any study procedures, all potential patients will sign and date an ICF. Patients will have the opportunity to have any questions answered before signing the ICF. The investigator or a qualified designee must address all questions raised by the patient. The investigator/designee will also sign and date the ICF.

Note: Visit T3 (Day 85, Part A) and Visit B1 (Day 1, Part B) can occur on the same day.

The following baseline procedures and assessments will be performed/completed at Visit B1 (Day 1) (Appendix II):

- Informed consent
- Physical examination
- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature)
- 12-lead ECG

- Body weight and BMI
- Total body fat mass
- Waist circumference
- Clinical laboratory tests
  - Hematology
  - Clinical chemistry, including fasting glucose
  - Urinalysis (microscopic)
- eGFR using CKD-EPI formula
- RDX-002 dosing
- Standard clinic meal
- Fasting lipid panel includes LDL-C, total cholesterol, non-HDL-C, and TGs
- Fasting insulin
- HbA1c
- HOMA-IR
- hs-CRP
- Patient diary dispensing (Appendix VI)
- Collection and review of patient diary from Part A
- Study drug dispensing
- Collection and review of used and unused study drug from Part A
- Adverse event monitoring and recording
- Review of concomitant medications
- Stool questionnaire.

6.1.10 Visit B2 (Day 43), Visit B3 (Day 85) and Visit B4 (Day 169-End of Part B and End of Study [EOS]) – Clinic Visit (Part B)

The following procedures and assessments will be performed/completed at Visit B2 (Day 43), Visit B3 (Day 85) and Visit B4 (Day 169-End of Part B and EOS) (Appendix II):

- Physical examination

- Vital signs (blood pressure, heart rate, respiratory rate, and body temperature)
- 12-lead ECG
- Clinical laboratory tests
  - Hematology
  - Clinical chemistry, including fasting glucose
  - Urinalysis (microscopic)
- eGFR using CKD-EPI formula
- Body weight and BMI
- Total body fat mass
- Waist circumference
- RDX-002 dosing (BID) (only at Visit B2 [Day 43] and Visit B3 [Day 85])
- Standard clinic meal (only at Visit B2 [Day 43] and Visit B3 [Day 85])
- Fasting lipid panel includes LDL-C, total cholesterol, non-HDL-C, and TGs
- Fasting insulin
- HbA1c
- HOMA-IR
- hs-CRP
- Patient diary dispensing (only at Visit B2 [Day 43] and Visit B3 [Day 85]) (Appendix VI)
- Collection and review of patient diary
- Study drug dispensing (only at Visit B2 [Day 43] and Visit B3 [Day 85])
- Collection and review of used and unused study drug
- Adverse event monitoring and recording
- Review of concomitant medications
- Stool questionnaire.

6.1.11 Telephone Follow-up – Patient Reported Compliance (Part B)

A follow-up telephone monitoring call will be conducted by the site staff every 2 weeks (±2 days) from Visit B1 (Day 1) up to Visit B4 (Day 169-End of Part B and EOS) to assess patient reported compliance to study treatment. During this telephone call, adherence to recording of dosing and bowel movement in patient diary, any AEs that occurred, and concomitant medications will be reviewed.

6.1.12 Visit OT (Day 183): Off-treatment Follow-up Phone Call (Part B)

Patients will receive an OT follow-up phone call approximately 2 weeks after the last dose of RDX-002 for review of any AEs and concomitant medications.

6.2 Demographic and Other Baseline Characteristics

Demographics and other baseline characteristics, including age, body weight (kg), height (cm), BMI, race, ethnicity, gender, and full medical and medication history will be collected at Visit S1 (Screening).

6.3 Efficacy Assessments

Part A: Efficacy assessments will include the evaluation of postprandial TGs, body weight, LDL-C, other fasting lipids (TGs, total cholesterol, and non-HDL-C), total body fat mass, waist circumference, HbA1c, glucose and insulin levels (fasting and postprandial), hs-CRP, and HOMA-IR.

At Visit G1, Visit T1 (Day 1), and Visit T3 (Day 85), after an overnight fast of at least 10 hours, blood samples for the determination of glucose and insulin, fasting lipids panel, HbA1c, HOMA-IR, and hs-CRP will be collected prior to the high-fat test meal. Postprandial samples for TGs, glucose and insulin will be collected at 1-, 2-, 3-, 4-, 6-, 8-hours after the initiation of the test meal with a ±5 minutes collection window for each sample (Appendix I, Appendix IV).

Two blood samples will be collected approximately 30 minutes apart at fasting for TGs, glucose and insulin, any time prior to the high-fat test meal.

All lipid panel tests on Visit T1 (Day 1), Visit T2 (Day 43), and Visit T3 (Day 85) and postprandial assessments for TGs on Visit T1 (Day 1) and Visit T3/End of Part A will be analyzed by a local laboratory and the results will be blinded. HbA1c, glucose, insulin, hs-CRP, and HOMA-IR will be analyzed by local unblinded laboratory that will report as per the standard practices.

As a part of secondary and exploratory objectives, treatment effects of RDX-002 will be evaluated on body weight, total body fat mass, waist circumference and blood pressure,

respectively. Body weight and total body fat mass results are blinded and therefore will be measured by unblinded study staff at Visit T2 (Day 43) and Visit T3 (Day 85).

Part B: Efficacy assessments will include the evaluation of body weight, fasting lipid panel, total body fat mass, waist circumference, HbA1c, glucose and insulin levels (fasting only), hs-CRP, and HOMA-IR.

At Visit B1 (Day 1), Visit B2 (Day 43), Visit B3 (Day 85), and Visit B4 (Day 169), after an overnight fast of at least 10 hours, blood samples for the determination of glucose and insulin, fasting lipids panel, HbA1c, HOMA-IR, and hs-CRP will be collected.

All lipid panel tests on Visit B1 (Day 1), Visit B2 (Day 43), Visit B3 (Day 85), and Visit B4 (Day 169) will be analyzed by a local laboratory and the results for only Visit B1 (Day 1) will be blinded. HbA1c, glucose, insulin, hs-CRP, and HOMA-IR will be analyzed by local unblinded laboratory that will report as per the standard practices.

Body weight and total body fat mass results are blinded and only for Visit B1 (Day 1) these will be measured by unblinded study staff.

Body weight and BMI along with waist circumference will be measured at the time points indicated in the schedule of events (Appendix I, Appendix II). The standardized procedures for measuring blood pressure, body weight, total body fat mass, and waist circumference for all patients are provided in Appendix II.

6.4 Pharmacokinetic Assessments

The PK assessments are only applicable for Part A of the study.

6.4.1 Pharmacokinetic Blood Sample Collection and Processing

Blood samples for the determination of plasma concentrations of RDX-002 and its main inactive metabolite will be collected prior to the morning dosing (at least 30 minutes prior to receiving study drug) and at 1-, 2-, 3-, 4-, 6-, 8-hours after the initiation of the high-fat test meal only at Visit T3 (Day 85) with a ±5 minutes collection window for each sample (Appendix IV). The PK samples at Visit T3 (Day 85) will be collected at the same timepoints as postprandial TGs (Section 6.3).

Procedures for collection, processing, and shipping of PK blood samples will be detailed in the Laboratory Manual.

6.4.2 Analytical Methodology

Plasma concentrations of RDX-002 and its main inactive metabolite will be measured using a fully validated analytical procedure. Specifics of the analytical method will be provided in the Laboratory Manual.

6.4.3 Pharmacokinetic Parameters

The following PK parameters will be analyzed where possible due to the relative lack of absorption of RDX-002 or its main inactive metabolite:

- AUC_{0-t} Area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t, whichever occurs first.
- $AUC_{0-\infty}$ Area under the concentration-time curve from time zero to infinity
- C_{max} Maximum measured plasma concentration
- T_{max} Time to maximum plasma concentration.
- $t_{½}$ Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$
- λ Terminal elimination rate constant
- CL/F Apparent total plasma clearance
- Vz/F Apparent volume of distribution

6.5 Pharmacodynamic Assessments

Not applicable.

6.6 Safety Assessments

For Part A and Part B of the study, safety will be assessed by the following parameters as shown in the schedule of events (Appendix I, Appendix II):

- The TEAEs and concomitant medications will be evaluated throughout the course of the study;
- Clinical laboratory tests, vital signs, 12-lead ECG, physical examination findings, and stool questionnaire.

6.6.1 Adverse Events

The investigator or designee is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to the study drug or their clinical significance.

6.6.1.1 Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug.

6.6.1.2 Serious Adverse Events

A SAE is any AE, occurring at any dose and regardless of causality that:

- Results in death;
- Is life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form;
- Requires in subject hospitalization or prolongation of existing hospitalization. Hospital admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., surgery performed earlier than planned);
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions;
- Is a congenital anomaly/birth defect;
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in the definitions for SAEs. 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 in-subject hospitalization, or the development of drug dependency or drug abuse.

6.6.1.3 Documentation of Adverse Events

Each patient will be monitored by the investigator or a qualified designee for any AEs occurring throughout the study period.

All AEs and SAEs occurring after the start of the study will be reported and followed until resolution or permanent outcome of the event.

At every study visit, patients will be asked a standard nonleading 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 OTC medications).

All AEs, whether or not caused by the study drug, will be recorded on the AE page in the eCRF. The information to be collected will include: event term, drug treatment, dose, date/time of onset of AE or the worsening of a previously observed AE or worsening of any previously existing disease, date of resolution of the AE, relationship of the AE to the study drug(s), severity of the AE, and description of action taken in treating the AE and/or change in study drug administration or dose.

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

The intensity/severity assessment for patients experiencing persistent or complicated diarrhea will be done based on the management plan for diarrhea and Common Terminology Criteria for Adverse Events (CTCAE) definitions provided in Appendix VIII.

6.6.1.4 Assessment of Severity

For both serious and nonserious AEs, the investigator will determine both the intensity of the event and the relationship of the event to study drug administration.

The intensity of each AE will be determined according to the following criteria:

Mild	an AE that is easily tolerated, causing no limitation of usual activities
Moderate	an AE causing some limitation of usual activities
Severe	an AE causing inability to carry out usual activities

6.6.1.5 Relationship to Study Medication

Relationship to study drug administration will be determined as follows:

Not Related	the experience can be readily explained by the patient's underlying medical condition or concomitant medications and no relationship exists between the study medication and the experience.
Unlikely Related	the temporal relationship between the AE and the administration of the study medication is uncertain and it is likely that the AE can be explained by the patient's medical condition or other therapies.
Possibly Related	there is some logical temporal relationship between the AE and the administration of the study medication, and the experience is unlikely to be explained by the patient's medical condition or other therapies.
Probably Related	the temporal relationship is compelling between the administration of the study medication and the AE cannot be explained by the patient's medical condition or other therapies.

6.6.1.6 Reporting of Serious Adverse Events

In addition to standard documentation of AEs in the source and case report form, all SAEs (as defined Section 6.6.1.1) must be reported to the contract research organization (CRO)/Sponsor immediately (i.e., within 24 hours) after the time site personnel first learns about the event.

All SAEs and deaths will be reported whether or not considered causally related to the study drug. All SAEs including deaths will continue to be documented through the 30 days following the last dose of study drug and will be monitored until they are resolved or permanent outcome of the event or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illnesses. The SAE forms will be provided to each clinical study site. The information to be collected will include a minimum of the following: subject number, a narrative description of the event and an assessment by the investigator as to the intensity of the event and relatedness to study drug. Follow-up information on the SAE can be requested by Sponsor.

In the event of unexpected serious adverse drug reactions associated with the use of the study drug, Sponsor will notify the appropriate regulatory agency(ies) and all participating investigators on an expedited basis. It is the responsibility of the investigator to promptly notify the Institutional Review Board (IRB) / Independent Ethics Committee (IEC) of all suspected unexpected serious adverse drug reactions involving risk to human patients.

6.6.1.7 Follow-up of Serious Adverse Events

Follow-up information to a SAE report shall be submitted to the Sponsor by the investigator as soon as the relevant information is available and reviewed by the investigator.

All AEs will be followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

The investigator is responsible for submitting the completed SAE Report Form with the fullest possible details within 3 calendar days of his/her knowledge of the SAE.

6.6.2 Clinical Laboratory Assessments

After an overnight fast of at least 10 hours, the following clinical laboratory assessments will be performed at the time points indicated in the schedule of events (Appendix I, Appendix II):

Hematology:

- Hematocrit
- Hemoglobin
- Red blood cell (RBC) count
- Mean corpuscular hemoglobin concentration (MCHC)
- Glycated hemoglobin (HbA1c)
- White blood cell (WBC) count with differential
- Platelet count
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular volume (MCV)

Clinical Chemistry:

- Blood urea nitrogen (BUN)
- Serum creatinine
- Uric acid
- Calcium
- Glucose
- Magnesium
- Alkaline phosphatase
- Bilirubin (total, direct and indirect)
- Creatinine
- Lactate dehydrogenase (LDH)
- Total Protein
- FSH (as needed)
- AST (SGOT)
- ALT (SGPT)
- Amylase
- Albumin
- Sodium
- Chloride
- Potassium
- Carbon dioxide
- Creatine Kinase
- Phosphorus
- Uric Acid
- TSH (at Screening only)

Insulin and HOMA-IR will be collected at time points indicated in the schedule of events (Appendix I, Appendix II).

The eGFR will be calculated using the CKD-EPI formula.

Standard Fasting Lipid Panel:

- Low-density lipoprotein cholesterol (LDL-C)
- High-density lipoprotein cholesterol (HDL-C)
- Total cholesterol
- Non-high density lipoprotein cholesterol (non-HDL-C)
- Triglycerides

Urinalysis:

- Specific gravity
- pH
- Glucose
- Protein
- Esterase
- Blood ketones
- Bilirubin
- Urobilinogen
- Leukocyte
- Nitrite

Reflex to microscopic examination will be collected as per standard laboratory procedures.

Serum and urine pregnancy testing: will be performed for all females of childbearing potential. Serum pregnancy test will be performed at Visit S1 (Day -42 to Day -14), and urine pregnancy test will be performed at Visit T1 (Day 1).

Serology: HBV, HCV, HIV tests.

Urine drug test and breath alcohol test: will be conducted according to the local laboratory standard practices.

Note: Coronavirus disease-19 (COVID-19) testing will be done as per study site practice and local regulations.

6.6.3 Vital Signs

Vital signs measurements including blood pressure, heart rate, respiratory rate, and body temperature will be collected pre-dose at the time points indicated in the schedule of events (Appendix I, Appendix II). Patients must be in a supine position for at least 5 minutes before each measurement. Standardized procedure for measuring blood pressure for all patients is provided in Appendix II.

6.6.4 Electrocardiogram

A 12-lead ECG will be obtained pre-dose at the time points indicated in the schedule of events (Appendix I, Appendix II). Patients must be in a supine position for at least 5 minutes before each measurement.

6.6.5 Physical Examination

A complete physical examination will be performed for all patients at the time points indicated in the schedule of events (Appendix I, Appendix II). The examination will include an assessment of the patient's general appearance (including evaluation of extremities, eyes, nose, mouth/throat/neck, and thyroid) and body systems (dermatologic, lymphatic, respiratory, cardiovascular, gastrointestinal, musculoskeletal, and neurologic). Height will be measured only at Screening.

6.6.6 Stool Questionnaire

Patients will be provided with the Patient Diary (Appendix VI) and Bristol Stool Form Scale (Appendix VII) to self-assess and document their bowel movements. During clinic visits, reporting on the Patient Diary and Bristol Stool Form Scale will be done by the patient/designated site staff at the time points indicated in the schedule of events (Appendix I, Appendix II). During non-clinic visits, patients will be instructed to complete the form on a daily basis, as applicable.

A diarrhea management plan for patients who experience persistent or complicated diarrhea is provided in Appendix VIII.

6.6.7 Pregnancy

Any pregnancy occurring while the patient is on study drug or by study completion must be reported to CRO/Sponsor within 24 hours of awareness.

While pregnancy itself (or positive pregnancy test) is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons (e.g. medical or surgical management of ectopic pregnancy) will be recorded as an AE or SAE.

The pregnancy must be followed up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study.

7. STATISTICAL AND ANALYSIS METHODS

Detailed methodology of summary and statistical analysis of the data collected in this study will be documented in the Statistical Analysis Plan (SAP). The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition or its analysis will be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed, if deemed appropriate.

If differences occur between analyses of data described in the SAP and the current protocol, the analyses described in the SAP will assume primacy.

The SAP will be developed and finalized before database lock. All analyses will be performed using Statistical Analysis System (SAS®) Version 9.4 or higher, unless otherwise specified in the SAP.

Analysis and reporting of Part A and Part B data will be performed separately. Part B data will be reported by the Part A treatment assignments.

7.1 General Principles

Detailed descriptions for the handling of missing data, patient eligibility criteria for the analysis will be provided in the SAP. Data and results will be presented separately for RDX-002 and placebo group.

All safety data will be summarized for the patients who receive at least one treatment of the study drug.

All statistical testing will be two-sided at significance level of 0.05 and no multiplicity adjustment will be made.

7.2 Study Endpoints

The primary, secondary, exploratory, PK, efficacy and safety endpoints are aligned with the study objectives for Part A and Part B of the study and are presented in Section 2.

7.3 Sample Size Calculations

Part A: Approximately 64 patients will be enrolled targeting 58 completers in this study, while accounting for 10% drop-out rate. This sample size was estimated based on primary efficacy endpoint and one of the secondary efficacy endpoints (difference in the mean percent change from baseline in body weight in patients treated with RDX-002 as compared with placebo at Week 12):

- Primary efficacy endpoint with assumption of 60% difference in the mean percentage

change in incremental postprandial TG AUC from baseline between RDX-002 and placebo and a pooled standard deviation (SD) of 50% observed in the previous clinical study, using two-sided test with 5% level of significance;

- Secondary efficacy endpoint with assumption of 3% absolute difference in the mean percent change in body weight between RDX-002 and placebo with a pooled SD of 4% using two-sided test with 5% level of significance.

A sample of 64 patients results in at least 80% power (calculated using TWOSAMPLEMEANS in PROC POWER in SAS®) and is considered to be sufficient to satisfy the above study objectives. Patients will be randomized into 1:1 allocation ratio (i.e., 32 patients in RDX-002 group and 32 patients in placebo group).

Part B: No formal sample size will be required for Part B. The number of patients will be determined by the number of eligible patients who have completed Part A and are willing to participate in Part B.

7.4 Analysis Populations

The following analysis sets will be used in the statistical analyses:

- **Safety Analysis Set**: The Safety Analysis Set will include all patients who receive at least one dose of RDX-002 or placebo.
- **Intent-to-Treat (ITT) Set**: The ITT Set will include all randomized patients. It will be the primary analysis set for the efficacy analyses.
- **Modified Intent-to-Treat (mITT) Set:** The mITT Set will include all randomized patients who have all key measurements (postprandial TGs, body weight and LDL-C) performed at Visit T1 (Day 1), Visit T2 (Day 43) and Visit T3 (Day 85). This population will be used for analysis of primary and secondary efficacy endpoints.
- **Per-Protocol (PP) Set**: The PP Set will include all patients who completed the study without major protocol deviations and satisfy any additional indication-specific requirements of the analysis population. The PP Set will be used for the secondary efficacy analyses.
- **Pharmacokinetic (PK) Analysis Set**: The PK Analysis set will consist of patients included in the Safety population who have at least one post-dose quantifiable plasma concentration for RDX-002. A quantifiable concentration is defined as a measurable value without any events or deviations that would compromise the integrity of the plasma concentration. It should be noted that due to the properties of RDX-002, which stays within the intestinal enterocyte with little to no absorption into the blood, some patients

who correctly take the drug and have a PK blood sample taken may not show blood levels of RDX-002 or its main inactive metabolite.

7.5 Statistical Methods of Analysis

Continuous data will be summarized using descriptive statistics such as mean, SD, median, first and third quartiles (Q1 and Q3), minimum, maximum, coefficient of variation (CV), geometric mean, and geometric CV. Categorical data will be summarized using counts and percentages. Tables will have columns corresponding to treatment groups. Data will be summarized and listed by treatment group and visit/timepoint, where appropriate. Full details of the statistical methods are outlined in the final SAP.

7.5.1 Patient Disposition

Number and percentage of patients enrolled, included in the Safety Analysis Set, completing the study and discontinuing early from the study will be presented. Patients who discontinued early from the study are further presented by the primary reason for discontinuation.

7.5.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively. Demographic characteristics include age, gender, race, and ethnicity. Baseline characteristics include height, body weight, and BMI.

7.5.3 Medical History

Medical history events will be classified by system organ class (SOC) and preferred term (PT), according to Medical Dictionary for Regulatory Activities (MedDRA). Medical history events will be summarized by SOC and PT by treatment group for patients in the Safety Analysis Set. The summaries will display the number and percentage of patients experiencing any medical history event as well as the number and percentage of patients with at least one medical history event in each SOC and PT. Medical history data will also be listed for the Safety Analysis Set.

7.5.4 Prior and Concomitant Medication

Prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODD) and summarized by Anatomical Therapeutic Chemical (ATC) class and PT.

7.5.5 Protocol Deviations

Protocol deviations will be summarized descriptively with counts and percentages in overall, by classification, and by category for the Safety Analysis Set. Protocol deviations will also be listed.

7.5.6 Efficacy Analyses

7.5.6.1 Analysis of the Primary Endpoint (Part A)

The primary efficacy endpoint will be analyzed by an analysis of covariance (ANCOVA) model with terms for randomized treatment and baseline as a covariate. Summaries will include least squares (LS) means and associated standard errors (SEs) estimated from the ANCOVA. Differences in LS means and associated 95% confidence interval (CI) will be presented along with the p-value from the test of no difference in mean percent change from baseline between treatment groups. The primary analysis will be performed on the ITT Analysis Set with supportive analyses performed on the mITT Analysis Set and PP Analysis Set.

7.5.6.2 Analysis of the Secondary Endpoints (Part A)

Continuous secondary efficacy endpoints will each be analyzed using the same methodology as specified for the primary efficacy endpoint.

The proportions of patients exhibiting a weight gain of at least 5% will be presented along with exact (Clopper-Pearson) 95% CIs. The difference between treatment groups in the proportion of patients exceeding this weight gain threshold will be presented along with exact (unconditional) 95% CIs for the difference. The difference in proportions will be calculated as RDX-002 minus placebo, such that a negative value favors RDX-002, i.e., a negative value indicates a reduction in the proportion of patients exceeding the weight gain threshold for patients randomized to RDX-002. Fisher's exact test will be used to compare the proportions between treatment groups.

7.5.6.3 Analysis of the Exploratory Endpoints (Part A)

Exploratory endpoints will be analyzed using descriptive statistics.

7.5.6.4 Multiplicity Adjustment

No adjustments for multiplicity will be done for the analyses.

7.5.6.5 Handling of Dropouts and Missing Data

Any missing data will be reported.

Handling of missing data will be outlined in the SAP.

7.5.6.6 Analyses of Pharmacokinetic Endpoints (Part A)

Unlike most pharmacological therapeutics, RDX-002, by design, acts in the intestinal enterocytes and little if any drug may be absorbed by patients. Therefore, in some patients no or only sporadic concentrations of RDX-002 or its main inactive metabolite, are detected in blood samples. The following PK parameters will be analyzed descriptively if and where possible depending upon the detection and quantification of parent and main inactive metabolite in blood samples; AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, lambda (λ), $t_{½}$, CL/F, and Vz/F. Descriptive summary statistics will include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is the T_{max}, where median, minimum, and maximum will be presented.

7.5.6.7 Analysis of the Efficacy Endpoints (Part B)

Efficacy endpoints will be summarized using descriptive statistics. Changes from baseline will be analyzed for both the original (Part A) baseline as well as the baseline visit for Part B. To avoid confounding of prior treatment assignment in Part A, patients treated with RDX-002 and placebo in Part A will be analyzed separately.

7.5.7 Safety Analyses (Part A and Part B)

The safety analyses will be based on the Safety Analysis Set. Safety will be evaluated by presenting summaries of AEs, clinical laboratory assessments, vital signs, ECG results, and physical examination findings by treatment group. Descriptive summaries and listings of individual patient safety data will be presented by treatment groups.

For Part A, the TEAEs will be summarized by MedDRA SOC and PT by treatment group overall and by severity and relationship to study drug. For Part B, the TEAEs will be summarized by MedDRA SOC and PT by Part A treatment group separately and combined and also by severity and relationship to study drug. These summaries will include cumulative incidence (percent of patients experiencing at least one [1] AE), and exposure-adjusted incidence rates (in patient-years). Deaths, SAEs, withdrawal from study treatment due to TEAEs, and withdrawal from the study due to TEAEs will each be summarized by treatment group and provided in by-patient data listings.

Clinical laboratory assessments, including hematology, clinical chemistry, and urinalysis; physical examination findings; vital signs; and ECG results will be summarized by the value and by change from baseline in the value (where appropriate) at each post-baseline timepoint.

For safety analyses in Part B, patients will be analyzed both as separate groups based on the Part A treatment assignment (RDX-002 or placebo).

A complete description of the safety analysis variables will be presented in the SAP.

8 DATA QUALITY ASSURANCE

8.1 Data Management

Clinical data management will be performed in accordance with CRO applicable standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data and documented in the Data Management Plan.

Data management personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the electronic data capture (EDC) system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to data.

Medical history, current medical conditions, and AEs will be coded using the current version of MedDRA and WHODD.

Clinical laboratory data results will be sent to the CRO responsible for data management and will be incorporated into the clinical statistical database.

The database will be declared locked once the data have been verified for completeness and accuracy, and after instruction from the Sponsor. Authorization is required prior to making any database changes to locked data by written agreement from Sponsor.

For EDC studies, after database lock, the investigator will receive paper copies or electronic copies of the patient data for archiving at the investigational site.

A separate data management plan will be prepared to describe the data management process.

8.2 Study Monitoring, Audits, and Inspections

Steps to ensure the accuracy and reliability of the data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator, and associated personnel before the study, periodic monitoring visits by Sponsor or its representatives, and transmission of clinical laboratory data into the clinical study database. The eCRFs will be reviewed for accuracy and completeness by the clinical monitor during onsite monitoring visits; any discrepancies will be resolved with the investigator or designees, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

Quality assurance personnel from the Sponsor or its representatives may visit the study center to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection

and comparison with the eCRFs. Patient privacy must, however, be respected. Sufficient prior notice will be provided to allow the investigator to properly prepare for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a licensing application or by an IRB/IEC to ensure patient rights, safety, and well-being. The investigator should immediately notify the Sponsor or its representatives if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

9 ETHICS

9.1 Institutional Review Board (IRB) or Independent Ethics Committee (IEC)

Approval should be obtained from IRB/IEC before participation of human patients in research studies as per the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) harmonized tripartite guideline E6(R3): GCP. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH E6(R3) will be maintained by the study center and will be available for review by the Sponsor or its designee.

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

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must promptly supply the Sponsor or its designee, the IRB/IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

9.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH Good Clinical Practice, and all applicable local regulations.

9.3 Informed Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient before entering the study or performing any unusual or non-routine procedure that involves risk to the patient. The informed consent template will be provided by the study center. If any institution-specific modifications to study related procedures are proposed or made by the study center, the consent should be reviewed by the Sponsor or its designee or both before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

The ICF will include information on sample biobanking which will be stored for up to 5 years to be used by the Sponsor for further research and testing.

Before recruitment and enrollment, each prospective patient will be given a full explanation of the study and be allowed to read the IRB/IEC-approved ICF. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed and dated original ICFs and give a copy of the signed and dated original ICF to the patient or legal guardian.

9.4 Patient Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient 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 patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the Sponsor or designee, the Food and Drug Administration (FDA), or other local regulatory agencies, or the IRB/IEC.

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.

10 ADMINISTRATIVE ASPECTS AND RECORD KEEPING

10.1 Study Administrative Structure

Table 1 presents the study administrative details.

Table 1 Key Study Administrative Information

Role	Name/Address
Sponsor	Response Pharmaceuticals, Inc. 1104 West Broad Street #1064 Falls Church, VA 22046
Sponsor Contact	William J Sasiela, PhD Chief Medical Officer Response Pharmaceuticals, Inc.
Principal Investigator	Trisha Shamp PhD, PA-C Nucleus Network 1000 Westgate Drive, Suite 149 St Paul, Minnesota 55114
Regulatory Affairs	Craig Audet, PhD Independent Consultant WRS Regulatory Consultants, LLC
Contract Research Organizations (CROs)/Vendors:	
Clinical Study Site	Nucleus Network 1000 Westgate Drive, Suite 149 St Paul, Minnesota 55114
Central Laboratory	Hennepin County Medical Center 701 Park Ave, Minneapolis, MN 55415
Local Laboratory (blinded for postprandial TGs)	MCBD-SDSC Dock Mayo Clinic Laboratories 3050 Superior Drive NW Rochester, MN 55905
Pharmacokinetic Analyses	Inotiv 27012 Kent Ave West Lafayette, IN 47906
Drug Packaging and Labeling	Catalent Clinical Development & Supply 10381 Decatur Road Philadelphia, PA 19154

Role	Name/Address
Drug Distribution	Catalent Clinical Development & Supply 3031 Red Lion Road Philadelphia, PA 19114
Data Management, Study Management and Monitoring, Statistics, Medical Monitoring, and Medical Writing	Veranex, Inc. 3 Independence Way, Suite 106 Princeton, NJ 08540

10.2 Primary Source Documentation

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary to reconstruct and evaluate the study. Source data are contained in source documents. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient's memory aid (diaries) or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, and patient files and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical study.

Site will maintain appropriate medical and research records for this study, in compliance with ICH-GCP E6(R3) guidelines and local regulatory guidelines, in addition to regulatory and institutional requirements for protection of patient confidentiality. The Sponsor or the Sponsor's representatives and the IRB/IEC will have access to medical and research records. The site will permit the Sponsor or Sponsor's representatives, study monitors, IRB/IEC, and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of study safety and progress.

10.3 Maintenance and Retention of Records

Essential documents should be retained until at least 5 years after the completion of the study or submission of the data to the regulatory authority (or authorities), whichever is later, or 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 the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained. The investigator will notify the Sponsor prior to discarding study documentation.

10.4 Financial Disclosure and Obligations

The investigator agrees that the study will be conducted according to the principles of ICH E6(R3). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

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

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

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

10.5 Modifications to Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before patients can be enrolled into an amended protocol. If the protocol amendment substantially alters the study design or potential risk to the patient, a new written ICF for continued participation in the study must be signed by each patient affected by the change.

10.6 Termination of Study

The Sponsor reserves the right to terminate the investigational site or this clinical study at any time for clinical or administrative reasons.

The EOS is defined as the date on which the last patient completes the last clinic visit. An OT follow-up phone call will be conducted approximately 2 weeks after the last dose of RDX-002 or placebo for Part A and after the last dose of RDX-002 for Part B of the study.

10.7 Publication Policy

After completion of the study, a clinical study report will be prepared, based on the statistical and clinical evaluation of the results. 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 other related issues. The Sponsor has final approval authority over all such issues.

Study results may not be published without prior written approval from the Sponsor.

11 REFERENCE LIST

Busetto L, Bettini S, Makaronidis J, et al. Mechanisms of weight regain. Eur J Intern Med. 2021; 93:3-7.

Cuchel M, Bloedon LT, Szapary PO, et al. Inhibition of microsomal triglyceride transfer protein in familial hypercholesterolemia. N Engl J Med. 2007;356(2):148-56.

Cuchel M, Meagher EA, du Toit Theron H, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet. 2013;381(9860):40-6.

Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403.

Fothergill E, Guo J, Howard L, et al. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. Obesity (Silver Spring). 2016;24(8):1612-9.

Guh DP, Zhang W, Bansback N, et al. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health. 2009;9:88.

Investigator's Brochure RDX-002 (Formerly SLx-4090; KD026). Response Pharmaceuticals, Inc. Version: 10, Release Date: Final, 17 Jun 2024.

Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. SURMOUNT-1 Trial. N Engl J Med. 2022;387(3):205-16.

Kim E, Campbell S, Schueller O, et al. A small-molecule inhibitor of enterocytic microsomal triglyceride transfer protein, SLx-4090: biochemical, pharmacodynamic, pharmacokinetic, and safety profile. J Pharmacol Exp Ther. 2011; 337(3):775-85.

Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. N Engl J Med. 2023;389(24):2221-32. SELECT Trial: Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK): Overweight & Obesity Statistics. Sep 2021. Accessed from: https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity

Purcell K, Sumithran P, Prendergast LA, et al. The effect of rate of weight loss on long-term weight management: a randomised controlled trial. Lancet Diabetes Endocrinol. 2014;2(12):954-62.

Taskinen MR, Björnson E, Matikainen N, et al. Effects of liraglutide on the metabolism of triglyceride-rich lipoproteins in type 2 diabetes. Diabetes Obes Metab. 2021;23(5):1191–1201.

Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. Semaglutide Treatment Effect in People with Obesity (STEP) Program. N Engl J Med. 2021;384(11):989-1002.

Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Diabetes Obes Metab. 2022;24(8):1553-64.

World Health Organization Fact Sheet: Obesity and overweight. 01 Mar 2024. Accessed from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.

12 APPENDICES

12.1 Appendix I: Schedule of Events (Part A)

	Screening Period	GLP-1 Therapy Assessment Period	GLP-1 Discontinuation Period	Treatment Period – Clinic Visit			Off-treatment Follow-up Period (Phone call)
Study Visits/Days	**Visit S1 (Day -42 to Day -14)**	**Visit G1 (Day -42 to Day -14)**	**Timepoint G2 (Day -14 to Day -7)**	**Visit T1 (Day 1) Baseline and Randomization**	**Visit T2 (Day 43)**	**Visit T3 (Day 85) End of Part A**	**Visit OT (Day 99)**
Window Period (Days)	**NA**	**NA**	**NA**	**±3**	**±3**	**±3**	**±3**
Informed consent	X						
Assignment of patient identification (screening) number	X						
Inclusion and exclusion criteria	X			X			
Demographics	X						
Medical history	X						
Prior medications	X						
Physical examination	X	X		X	X	X	
Height	X						
Vital signs	X	X		X	X	X	
12-Lead ECG	X			X		X	
Hematology	X	X		X	X	X	
Clinical chemistry, including fasting glucose	X	X		X	X	X	
Urinalysis (microscopic)	X	X		X	X	X	
Serology test	X						
Breath alcohol test	X			X			
Urine drug test	X			X			

	Screening Period	GLP-1 Therapy Assessment Period	GLP-1 Discontinuation Period	Treatment Period – Clinic Visit			Off-treatment Follow-up Period (Phone call)
Study Visits/Days	**Visit S1 (Day -42 to Day -14)**	**Visit G1 (Day -42 to Day -14)**	**Timepoint G2 (Day -14 to Day -7)**	**Visit T1 (Day 1) Baseline and Randomization**	**Visit T2 (Day 43)**	**Visit T3 (Day 85) End of Part A**	**Visit OT (Day 99)**
Window Period (Days)	**NA**	**NA**	**NA**	**±3**	**±3**	**±3**	**±3**
Serum pregnancy test	X						
Urine pregnancy test				X			
eGFR using CKD-EPI formula	X	X		X	X	X	
Instruction for discontinuing current GLP-1 agonist treatment			X				
Randomization				X			
High-fat test meal		X		X		X	
Standard clinic meal					X		
RDX-002 or matching placebo dosing (BID)				X	X	X	
Body weight and BMI	X	X		X	X	X	
Total body fat mass	X	X		X	X	X	
Waist circumference	X	X		X	X	X	
Fasting TGs		X		X	X	X	
Fasting lipid panel	X	X		X	X	X	
Fasting insulin		X		X	X	X	
Postprandial glucose, insulin, TGs		X		X		X	
HbA1c	X	X		X	X	X	
hs-CRP	X	X		X	X	X	
HOMA-IR-		X		X	X	X	
PK sampling						X	
Dispensing of patient diary				X	X		

	Screening Period	GLP-1 Therapy Assessment Period	GLP-1 Discontinuation Period	Treatment Period – Clinic Visit			Off-treatment Follow-up Period (Phone call)
Study Visits/Days	**Visit S1 (Day -42 to Day -14)**	**Visit G1 (Day -42 to Day -14)**	**Timepoint G2 (Day -14 to Day -7)**	**Visit T1 (Day 1) Baseline and Randomization**	**Visit T2 (Day 43)**	**Visit T3 (Day 85) End of Part A**	**Visit OT (Day 99)**
Window Period (Days)	**NA**	**NA**	**NA**	**±3**	**±3**	**±3**	**±3**
Collection and review of patient diary					X	X	
Dispensing of study drug				X	X		
Collection and review of used and unused study drug					X	X	
AE monitoring and recording		X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X
Stool questionnaire				X	X	X	
Offer an opportunity to participate in Part B					X		
Telephonic follow-up monitoring call				X (every 2 weeks ±2 days)			

Abbreviations: AE = adverse event; BID = twice daily; BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; GLP-1 = glucagon-like peptide-1; HbA1C = glycated hemoglobin; HOMA-IR = homeostatic model assessment for insulin resistance; hs-CRP = high sensitivity C-reactive protein; NA = not applicable; OT = off-treatment; PK = pharmacokinetic; TG = triglycerides.

12.2 Appendix II: Schedule of Events (Part B)

	Treatment Period – Clinic Visit				Off-treatment Follow-up Period (Phone call)
Study Visits/Days	**Visit B1 (Day 1) Baseline**	**Visit B2 (Day 43)**	**Visit B3 (Day 85)**	**Visit B4 (Day 169) End of Part B and EOS**	**Visit OT (Day 183)**
Window Period (Days)	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X				
Physical examination	X	X	X	X	
Vital signs	X	X	X	X	
12-Lead ECG	X	X	X	X	
Hematology	X	X	X	X	
Clinical chemistry, including fasting glucose	X	X	X	X	
Urinalysis (microscopic)	X	X	X	X	
eGFR using CKD-EPI formula	X	X	X	X	
Standard clinic meal	X	X	X		
RDX-002 dosing (BID)	X	X	X		
Body weight and BMI	X	X	X	X	
Total body fat mass	X	X	X	X	
Waist circumference	X	X	X	X	
Fasting lipid panel	X	X	X	X	
Fasting insulin	X	X	X	X	
HbA1c	X	X	X	X	
hs-CRP	X	X	X	X	
HOMA-IR	X	X	X	X	
Dispensing of patient diary	X	X	X		

	Treatment Period – Clinic Visit				Off-treatment Follow-up Period (Phone call)
Study Visits/Days	**Visit B1 (Day 1) Baseline**	**Visit B2 (Day 43)**	**Visit B3 (Day 85)**	**Visit B4 (Day 169) End of Part B and EOS**	**Visit OT (Day 183)**
Window Period (Days)	**±3**	**±3**	**±3**	**±3**	**±3**
Collection and review of patient diary	X (from Part A)	X	X	X	
Dispensing of study drug	X	X	X		
Collection and review of used and unused study drug	X (from Part A)	X	X	X	
AE monitoring and recording	X	X	X	X	X
Concomitant medications	X	X	X	X	X
Stool questionnaire	X	X	X	X	
Telephonic follow-up monitoring call	X (every 2 weeks ±2 days)				

Abbreviations: AE = adverse event; BID = twice daily; BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = end of study; HbA1C = glycated hemoglobin; HOMA-IR = homeostatic model assessment for insulin resistance; hs-CRP = high sensitivity C-reactive protein; OT = off-treatment.

12.3 Appendix III: Blood Pressure, Body Weight, Waist Circumference and Total Body Fat Mass Measurements (Part A and Part B)

12.3.1 Blood Pressure Measurements

Blood pressure (BP) will be collected pre-dose at the time points indicated in the schedule of events (Appendix I, Appendix II).

- Patients should not exercise, smoke or consume caffeine 30 minutes prior to BP measurement;
- Blood pressure measurements should be done prior to ECG recordings;
- Below listed standardized procedure for measuring BP should be followed:
    - Patient should be in supine position for at least 5 minutes and the measurement arm supported so that the midpoint of the BP cuff is at heart level;
    - A BP monitor (preferably of the same make and model) should be used for all patient measurements;
    - An appropriate-sized cuff should be used with the bladder centered over the brachial artery;
    - The arm used for BP measurement should be recorded and maintained for all measurements;
    - All BP measurements should be preferably at approximately the same time of day unless not possible;
    - At each visit, 3 BP measurements (each measurement 1 - 2 minutes apart at supine position) should be obtained using the same arm. Mean supine BP is defined as the average of 3 supine BP measurements for any single clinic visit;
    - If the lowest and highest SBP measurements are >15 mm Hg apart, additional readings should be performed to achieve 3 readings within 15 mm Hg SBP are obtained. Up to six readings may be obtained, if needed. The visit BP measurement will be determined from the 3 readings with SBP within 15 mm Hg.

12.3.2 Body Weight and Waist Circumference Measurements

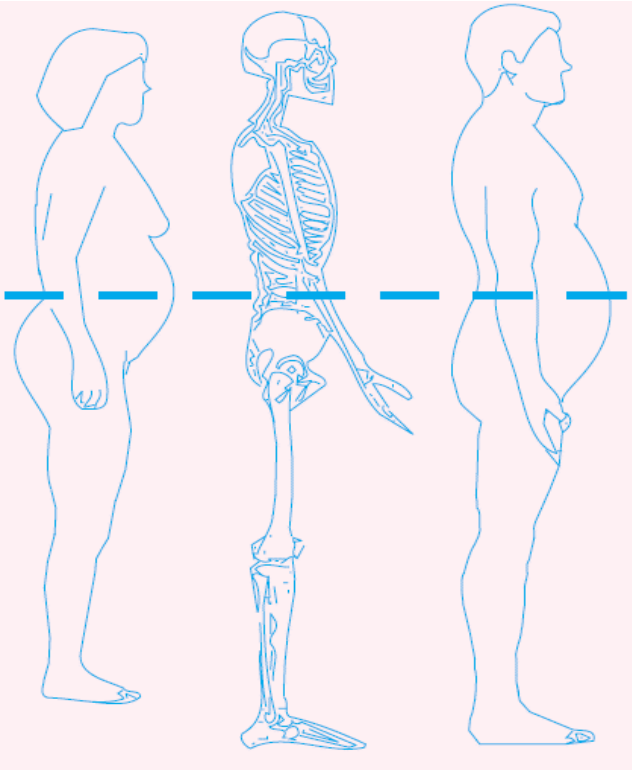
Body weight and waist circumference will be taken for all patients according to the schedule of events (Appendix I, Appendix II). The BMI will be calculated based on the patients' height measurement taken at Visit S1.

To obtain the most valid and reliable measurement, patients will be encouraged to weigh first thing in the morning, while wearing minimal clothing (e.g., hospital gown), before eating/drinking and after voiding their bladder/bowels.

To measure waist circumference, study site staff should follow the following steps:

- Locate the upper hip bone and the top of the right iliac crest;
- Place a measuring tape in a horizontal plane around the abdomen at the level of the iliac crest;
- Before reading the tape measure, ensure that the tape is snug, but does not compress the skin, and is parallel to the floor;
- Measure at the end of a normal expiration.

Measuring – Tape Position for Waist Circumference in Adults



12.3.3 Total Body Fat Mass

InBody H20N device will be used to obtain total body fat mass for all patients according to the schedule of events (Appendix I, Appendix II).

InBody H20N device is a smart weight analyzer that measures whole-body composition with advanced technology and ease of use. It comes with handlebar electrodes as well as footplate electrodes, so the entire body composition is measured, not estimated. The device has an auto-calibration functionality that is completed each time the device is turned on.

Below is an image of the InBody H20N Scale:



12.4 Appendix IV: Pharmacokinetic and Postprandial Blood Sampling Schedule (Part A)

Visit	Analyte	Onboard Drug	# Patients	# Timepoints	Timepoints	Total Samples
Visit G1	TG, glucose, insulin	RDX-002:Placebo	32:32	8	0 (×2), 1, 2, 3, 4, 6, 8	512
Visit T1	TG, glucose, insulin	RDX-002:Placebo	32:32	8	0 (×2), 1, 2, 3, 4, 6, 8	512
Visit T3	TG, glucose, insulin	RDX-002:Placebo	32:32	8	0 (×2), 1, 2, 3, 4, 6, 8	512
Visit T3	RDX-002, main inactive metabolite	RDX-002:Placebo	32:32	7	0, 1, 2, 3, 4, 6, 8	448
					TOTAL	1,984
					TOTAL TGs	1,536

Abbreviations: PK = pharmacokinetic, TG(s) = triglycerides.
Notes:
1. The PK samples at Visit T3 will be collected at same timepoints as postprandial TGs.
2. Postprandial samples for TGs, glucose and insulin and PK samples will be collected with a ±5 minutes collection window.

12.5 Appendix V: Composition of a High-Fat Meal (Part A)

An example of a high-fat meal	• Two eggs fried in butter • Two strips of bacon • Two slices of toast with butter • Four ounces of hash brown potatoes • Eight ounces of whole milk
Total calories	800-1000
Calories from protein	150
Calories from carbohydrates	250
Calories from fat	500-600
Percent calories from fat	≥50

Note: 50 percent of calories are derived from fat. Substitutions can be made to this meal if the total and fat calorie content, volume, and viscosity are maintained.
Source: Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations Guidance for Industry. US Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER), Clinical Pharmacology, June 2022.

Picture of a High-Fat Meal



12.6 Appendix VI: Patient Diary (Part A and Part B)

To be Completed by Clinic Staff			
Patient Initials:		Date Diary Provided to Patient	
Patient ID:		Date Diary Returned to Clinic:	

Instructions: This diary is used to collect information that will help us better understand the results of this study. Please complete this diary each day starting with the day and date you first received your study medication. Enter the information in each column by hand. Starting with the day/date you first received your study medication, write the time you took your first dose of the study medication, the time you ate your first meal of the day, the time you took your second (evening) dose of study medication, and the time you ate your evening meal. If you missed a dose of your study medication, please put an X in the shaded box "I did not take my study medication" for that day/time.

The clinic staff will call you every 2 weeks to talk with you briefly about the information you enter on this diary.

Please bring this completed diary to your next clinic visit, for clinic staff to review.

To be Completed by Clinic Staff			
Patient Initials:		Date Diary Provided to Patient	
Patient ID:		Date Diary Returned to Clinic:	

Date (DD/MMM/YYYY i.e. 25 Dec 2024)	**First Dose of Study Medication TIME (hh:mm) AM/PM-circle one**	**I did not take my study medication**	**First Meal of the Day TIME (hh:mm) AM/PM-circle one**	**Second Dose of Study Medication TIME (hh:mm) AM/PM-circle one**	**I did not take my study medication**	**Dinner/Evening Meal TIME (hh:mm) AM/PM-circle one**
	AM/PM		AM/PM	AM/PM		AM/PM
	AM/PM		AM/PM	AM/PM		AM/PM
	AM/PM		AM/PM	AM/PM		AM/PM
	AM/PM		AM/PM	AM/PM		AM/PM
	AM/PM		AM/PM	AM/PM		AM/PM
	AM/PM		AM/PM	AM/PM		AM/PM
	AM/PM		AM/PM	AM/PM		AM/PM

To be Completed by Clinic Staff			
Patient Initials:		Date Diary Provided to Patient	
Patient ID:		Date Diary Returned to Clinic:	

On this diary, please write down each time (written as HH:MM and circle AM or PM) you had a bowel movement and provide the type (1-7) of bowel movement you had by comparing it to the description and picture on the Bristol Stool Form Scale that your clinic staff provided you. If you had more than one bowel movement on any day, please enter a description for each on a separate line.

Date (DD/MMM/YYYY i.e. 25 Dec 2024)	**Time of Bowel Movement**	**Stool Description**	**Time of Bowel Movement**	**Stool Description**	**Time of Bowel Movement**	**Stool Description**	**Time of Bowel Movement**	**Stool Description**	**Time of Bowel Movement**	**Stool Description**	**Time of Bowel Movement**	**Stool Description**	**Time of Bowel Movement**	**Stool Description**
	AM/PM		AM/PM		AM/PM		AM/PM		AM/PM		AM/PM		AM/PM	
	AM/PM		AM /PM		AM/PM		AM/PM		AM/PM		AM/PM		AM/PM	
	AM/PM		AM /PM		AM/PM		AM/PM		AM/PM		AM/PM		AM/PM	
	AM/PM		AM /PM		AM/PM		AM/PM		AM/PM		AM/PM		AM/PM	
	AM/PM		AM /PM		AM/PM		AM/PM		AM/PM		AM/PM		AM/PM	
	AM/PM		AM /PM		AM/PM		AM/PM		AM/PM		AM/PM		AM/PM	
	AM/PM		AM /PM		AM/PM		AM/PM		AM/PM		AM/PM		AM/PM	

If you experience a severe change in your physical condition, please seek immediate medical attention at the nearest Emergency Room and notify the study site (Nucleus Network) as soon as possible @ 651-641-2900 (24 Hour).

12.7 Appendix VII: Bristol Stool Form Scale (Part A and Part B)

Bristol Stool Form Scale		
Type	**Description**	**Image**
Type 1	Separate hard lumps, like nuts	
Type 2	Sausage-shaped but lumpy	
Type 3	Like a sausage or snake but with cracks on its surface	
Type 4	Like a sausage or snake, smooth and soft	
Type 5	Soft blobs with clear-cut edges	
Type 6	Fluffy pieces with ragged edges, a mushy stool	
Type 7	Watery, no solid pieces	

12.8 Appendix VIII: Management Plan for Diarrhea (Part A and Part B)

Given the intestinal mechanism of action for RDX-002, gastrointestinal side effects including diarrhea, can sometimes be observed with treatment. Diarrhea from RDX-002 typically occurs during the first 2 weeks after initiation of treatment and is often-self-limiting after a few days of treatment. Patients with uncomplicated Grade 1 or Grade 2 diarrhea should discontinue any lactose-containing food products, alcohol, or high-osmolar supplements (beverages with high sugar content [juices, nectars, energy drinks, colas], beverages containing high amounts of caffeine etc.,). Patients should temporarily decrease consumption of high-fat foods and increase consumption of clear liquids (8 - 10 glasses per day). Loperamide can also be administered and a decrease in the RDX-002 dosing from 200 mg BID to 100 mg BID can also be considered. Patients with persistent or complicated diarrhea (see definition below) should consider temporary de-challenge or discontinuation of RDX-002 as well as more intensive treatment of the diarrhea.

The Common Terminology Criteria for Adverse Events (CTCAE) definitions for diarrhea intensity are as follows:

Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental activities of daily living	Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated	Death

Complicated diarrhea is defined as CTCAE Grade 3 or 4 diarrhea or Grade 1 or 2 diarrhea with 1 or more of the following signs or symptoms:

- Cramping;
- Nausea/vomiting (≥ Grade 2);
- Decreased performance status;
- Fever;
- Sepsis;
- Neutropenia;
- Frank bleeding;
- Dehydration.