

Zhejiang Doer Biologics Co., Ltd.

DR10624-101

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

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Final Statistical Analysis Plan

Version 1.0

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List of Abbreviations

λ_z	apparent terminal elimination rate constant
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARAUC	accumulation ratio based on AUC
AST	aspartate aminotransferase
AUC	area under the curve
AUC _{0-inf}	area under the curve from time 0 extrapolated to infinity
Δ AUC _{0-4h}	area under the curve from time 0 to 4 hours
AUC _t	area under the curve from time 0 to the last measurable observed concentration
AUC _{0-tau}	AUC within a dosing interval
%AUC _{ext}	percentage of AUC _{0-inf} due to extrapolation
AUMC	area under the first moment curve
BLQ	below the limit of quantification
BMI	body mass index
CAP	controlled attenuation parameter
CGM	continuous glucose monitoring
CI	confidence interval
CL/F	apparent total body clearance
C _{max}	maximum observed concentration
C _{trough}	trough concentration (predose)
CS	compound symmetry
CSR	clinical study report
CV	coefficient of variation
D	dose
ECG	electrocardiogram
eCRF	electronic case report form
EOT	end of treatment
EOS	end of study

FIB-4	Fibrosis 4 index
FIH	first-in-human
FPG	fasting plasma glucose
GGT	gamma-glutamyltransferase
GLSM	geometric least squares mean ratio
HbA1c	glycated hemoglobin
HCS	heterogeneous compound symmetry
HDL	high density lipoprotein
HOMA-B	homeostatic model assessment index of beta-cell function
HOMA-IR	homeostatic model assessment index of insulin resistance
ICH	International Council for Harmonisation
LDL	low density lipoprotein
LP(a)	lipoprotein (a)
LSM	least-squares means
MAD	multiple-ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MMTT	mixed meal tolerance test
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging-proton density fat fraction
MRT _{0-t}	mean residence time from time zero to the last observed measurable concentration
MRT _{0-inf}	mean residence time from time zero extrapolated to infinity
NADA	antidrug antibody with in vitro neutralizing effect
NCA	non-compartmental analysis
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NFS	non-alcoholic fatty liver disease fibrosis score
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PLT	platelet
PT	preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
Rsqr	r ² , coefficient of determination

SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SOA	schedule of assessments
SOC	system organ class
SRC	safety review committee
ss	steady state
SubQ	subcutaneous
$t_{1/2}$	apparent terminal elimination half-life
TAR	time above target range
TBR	time below target range
TEAE	treatment-emergent adverse event
TIR	time in range
TLFs	tables, listings and figures
T_{max}	time of maximum observed concentration
V_z/F	apparent volume of distribution during the terminal phase
VAS	visual analogue scale
VLDL	very low-density lipoprotein
WHODrug	World Health Organization Drug Dictionary

1. Introduction

The objectives of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single- and multiple-ascending subcutaneous (SubQ) doses of DR10624. The purpose of this statistical analysis plan (SAP) is to define the planned statistical analysis of the study data consistent with the study objectives. This SAP is written based on protocol DR10624-101, amendment 3 version 4.0, dated 1 October 2023.

2. Objectives and Endpoints

2.1 Primary Objectives and Endpoints

The primary objective is to assess the safety and tolerability of single- and multiple-ascending SubQ dose of DR10624 in all 3 parts of the study. The primary endpoints are listed below:

- Adverse event (AE)
- Serious adverse event (SAE)
- Adverse event of special interest (AESI)
- Clinical laboratory tests (hematology, coagulation, serum chemistry, and urinalysis)
- Calcitonin (Part 2)
- Vital sign measurements
- 12-lead electrocardiogram (ECG)
- Continuous Holter ECG (Part 1 if data permit)
- Physical examination findings

2.2 Secondary Objectives and Endpoints

The secondary objectives are to determine the PK profiles of single and multiple SubQ doses of DR10624 in all parts of the study. PK endpoints are detailed in [Section 8](#) of this SAP. Immunogenicity of DR10624, including the incidence of antidrug antibody (ADA) and titer of positive ADAs will be assessed in all parts of the study. Safety of single and multiple SubQ doses of DR10624 as determined by the adverse event of special interest (AESI) of hypoglycemia will be assess in all parts.

Change from baseline in the following secondary endpoints are also assessed for Part 2:

- Physical measurements:
 - Body weight
 - Body mass index (BMI)
 - Waist circumference
- Fasting lipid profile:

- Total cholesterol
 - Low density lipoprotein (LDL) cholesterol
 - High density lipoprotein (HDL) cholesterol
 - Non-HDL cholesterol (calculated as total cholesterol – HDL cholesterol)
 - Lipoprotein (a) (Lp[a])
 - Very low-density lipoprotein (VLDL) cholesterol
 - Triglycerides
 - Free fatty acids
- Partial areas under the curve for the following PD biomarkers levels using mixed meal tolerance test (MMTT):
 - Glucose
 - C-peptide
 - Insulin
 - Glucagon
- PD endpoints including:
 - Fasting plasma glucose (FPG)
 - Glycated hemoglobin (HbA1c)
 - Fasting insulin, C-peptide, glucagon
 - Adiponectin
 - Homeostatic model assessment index of insulin resistance (HOMA-IR)
 - Homeostatic model assessment index of beta-cell function (HOMA-B)
- Continuous glucose monitoring (CGM) endpoints (subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes at screening):
 - Time in range (TIR) calculated as the percentage of times or readings in the target range of 3.9 to 10 mmol/L
 - Time above range (TAR)
 - Time below range (TBR)
 - Average glucose
 - Glucose variability (coefficient of variation [CV])
- Rate of hypoglycemic events per week (if applicable):
 - Overall rate of hypoglycemic events per week
 - Nighttime rate of hypoglycemic events per week
- Hepatic fat fraction by magnetic resonance imaging-proton density fat fraction (MRI-PDFF) in subjects receiving multiple SubQ doses of DR10624 and in a prespecified subgroup of subjects with at least 8% baseline hepatic fat.
- Liver stiffness measured by FibroScan (subjects with at least 8% baseline hepatic fat measured by MRI-PDFF)
- Liver function parameters and endpoints:

- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Alkaline phosphatase (ALP)
- Gamma-glutamyl transferase (GGT)
- Fibrosis 4 score (FIB-4)
- Non-alcoholic fatty liver disease fibrosis score (NFS)

2.3 Exploratory Objective and Endpoint (Part 2 Only)

The exploratory objective is to assess the change from time-matched baseline in satiety measured by visual analogue scale (VAS).

3. Study Design

The detailed study designs are included in [protocol Section 3](#). Schedule of assessments (SOA) are specified in [Table 16.1](#) (Part 1), [Table 16.2](#) (Part 2) and [Table 16.4](#) (Part 3).

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 or higher (SAS Institute, Cary, NC).

Descriptive statistics for continuous variables will include number of observations, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. For categorical variables, frequencies and percentages will be presented.

All tables, listings, and figures (TLFs) will be presented by study part and treatment. The final doses for DR10624 SubQ injection in each study part is indicated in [protocol Section 3](#) and will be confirmed by safety review committee (SRC).

Unless otherwise indicated, outputs which are summarized by treatment will be summarized by the actual dose level for subjects on DR10624; subjects who receive placebo will be pooled into a single group. Subjects who receive DR10624 in Cohort L (Part 2) will be pooled into a titration dose group.

All data listings will be sorted by study part (if applicable), treatment and subject number.

No algorithm for imputation of missing data will be employed. If there are partial dates in AE or medication taken, conservative judgement will be used to determine if the AE or medication occurred before or after the first dose of study drug.

Study days are calculated with respect to the first dose date as below:

- If the assessment/observation date is on or after the first dose date, then Study Day = Assessment/Observation Date – First Dose Date + 1;

- Otherwise, Study Day = Assessment/Observation Date – First Dose Date

Baseline will be defined as the last non-missing assessment (including repeated and unscheduled assessments) before the first dose of study drug, unless otherwise specified.

For summary of safety assessments, if there are repeated at a time point, the first non-missing assessment at that time point will be used in the summary tables. For 12-lead and Holter ECG, average of any triplicate or replicated numeric measurements at each time point will be derived and included in the summary of actual values and change from baseline.

Unscheduled results will not be included in the summary tables, except for determining baseline, but will be presented in data listings.

For the calculation of descriptive statistics, missing data will be excluded from the calculations if not otherwise specified. If a measurement is reported with “<” or “<=” before a result, the value will be imputed with half the result. If a measurement is reported with “>” or “>=” before a result, the value will be imputed with 1.1 times the result.

The methodology and data handling specifications for PK data are detailed in [Section 8](#).

4.1. Sample Size

The number of subjects is based on clinical and practical considerations and not on a formal statistical power calculation. Approximately 152 subjects are planned for the study.

4.2. Randomization and Blinding

Eligible subjects will be randomized to DR10624 or placebo in accordance with study design as described in [protocol Section 3](#). The detailed randomization methods and blinding procedures are described in [protocol Section 5.3](#) and [Section 5.4](#), respectively.

4.3. Analysis Sets

The following analysis sets are defined:

- The safety analysis set includes subjects who receive at least 1 dose of DR10624 or placebo.
- The PK analysis set includes subjects who receive at least 1 dose of DR10624 and have sufficient concentration data to support accurate estimation of at least 1 PK parameter. Where subjects experience issues which may affect exposure to DR10624 (eg, emesis, dosing errors, etc), data will be reviewed by the study pharmacokineticist and evaluated for exclusion from the PK analysis set on a

case-by-case basis. All subjects excluded from the PK analysis set will be documented in the data listings.

- The PD analysis set includes subjects who receive at least 1 dose of DR10624 or placebo and have at least 1 PD measurement at baseline and postbaseline.
- The immunogenicity analysis set includes subjects who receive at least 1 dose of DR10624 and have baseline and at least 1 postbaseline sample ADA assessment.

5. Subject Disposition

5.1 Disposition

The following will be summarized by study part, treatment and overall for all enrolled subjects:

- The number of subjects enrolled (screened)
- The number of screen failure (according to reasons for screen failure)
- The number of subjects randomized
- The number of subjects received treatment
- The number of subjects completed treatment
- The number of subjects did not complete treatment (according to reasons for discontinuation from treatment)
- The number of subjects completed study
- The number of subjects did not complete study (according to reasons for discontinuation from study)
- The number of subjects in each analysis population

Subject disposition data will be presented in a data listing.

5.2 Protocol Deviations

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

All and important protocol deviations will be summarized by study part and overall for the safety analysis set. All protocol deviations will be presented in a data listing.

5.3 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria deviations will be presented in a data listing for all randomized subjects.

6. Demographics and Baseline Characteristics

6.1 Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics:

- Age at consent (years)
- Height (cm)
- Weight (kg)
- Derived body mass index (BMI) (kg/m^2)

Body Mass Index (BMI) = (body weight in kilograms)/(height in meters)².

Frequency counts and percentages will be tabulated for the categorical variables:

- Sex
- Race
- Ethnicity
- History of type 2 diabetes at screening (Part 2 only)

The summaries will be presented by study part, treatment and overall for the safety analysis set. Demographic and baseline information will be presented in a data listing.

6.2 Medical History

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 25.0 or above). Medical history will be summarized by study part, treatment, system organ class (SOC), preferred term (PT) and presented in a data listing.

7. Treatments and Medications

7.1 Prior and Concomitant Medications

Medications that stop prior to the first dose of study drug will be classified as prior medication. Medications that start on or after the first dose of study drug will be classified as concomitant. If a medication starts before the first dose of study drug and stops on or after the first dose of study drug, then the medication will be classified as both prior and concomitant. Partial start and end dates in medication will be used to classify the

medication as prior, concomitant or both. If partial or complete missing start and end dates cannot be used to classify the medication, then the corresponding medication will be assumed to be concomitant.

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODrug Global B3-March 2022 or above) and presented in a data listing.

7.2 Medical or Surgical Treatment Procedures

All medical or surgical procedures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 25.0 or above) and will be presented in a data listing.

7.3 Study Treatment

Exposure to study drug including duration of exposure (days), total dose (mg) administered and dosing compliance $[(\text{administered total doses}/\text{expected total doses}) \times 100]$ will be summarized by treatment for Part 2. The study drug administration data as collected on electronic case report form (eCRF) will be presented in a data listing.

7.4 Meal (Part 2)

Meal data for MMTT will be presented in a listing for subjects in Part 2.

8. Pharmacokinetics

All PK listings will be presented using the safety population, and subjects not included in the PK population will be highlighted. Individual PK concentration-time profiles will be presented graphically using the safety population (subjects receiving placebo will not be presented). Subjects without any estimable PK parameters will not be presented in the listing of PK parameters (eg, placebo subjects). PK tables, mean figures and all statistical analyses will be presented using the PK analysis set.

8.1 Data Handling

Data rounding specifications for PK data are documented in the TLFs shells.

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

For PK analysis, all BLQ values will be treated as zero, with the exception of BLQ values observed between 2 quantifiable concentrations which will be set to missing. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing. Missing concentrations will be treated as missing from the PK parameter calculations.

8.2 Serum Concentrations

The collection time points are presented in the below tables:

Part 1

Pharmacokinetic Time Points
Predose
2, 4, 6 hours
24, 48, 72, 96, 120, 144, 168 hours
240, 336, 504, and 672 hours

Part 2

Pharmacokinetic Time Points
Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78: Predose
Day 1 and Day 78: 4, 6 hours
Day 1 and Day 78: 24, 48, 72, 96, 120, 144, 168 hours (Day 8 predose/Day 85)
Day 78: 336, 504, 672 hours

Part 3

Pharmacokinetic time points

Predose
4, 6 hours
24, 48, 72, 96, 120, 144, 168 hours
240, 336, 504, and 672 hours

Postdose PK collections with actual sampling time that deviates from the predefined collection time by more than 5% will be flagged in the data listings and excluded in the calculation of concentration summary statistics.

Individual serum concentrations will be presented in data listings and summarized separately using descriptive statistics (number of observations, number of BLQs, arithmetic mean, SD, CV, median, minimum, and maximum) by study part, cohort, study day (where applicable), and nominal time.

Individual serum concentrations will be plotted by study part, cohort, study day and actual time on both linear and semi-logarithmic scales. Mean serum concentrations will be plotted by study part, cohort, study day (where applicable), and nominal time on both linear and semi-logarithmic scales with all dose levels overlaid on the same plots.

For Part 2, individual and mean serum trough concentrations versus study day (Day 8 to 78) will be plotted by cohort on both linear and semi-logarithmic scales to visually assess steady state.

8.3 Serum Pharmacokinetic Parameters

Pharmacokinetic parameters will be derived using non-compartmental analysis (NCA) with Phoenix[®] WinNonlin[®] Version 8.3 or higher (Certara USA, Inc., Princeton, NJ). The following serum PK parameters will be calculated for DR10624 using actual sampling times (where data permit) and all concentrations including concentrations collected outside the predefined collection windows will be included in the analysis:

Part 1 and 3:

C_{max}	Maximum observed concentration.
C_{max}/D	Dose normalized C_{max} .
T_{max}	Time of maximum observed concentration.
AUC_{0-t}	AUC from time 0 to t hours postdose, calculated using the linear trapezoidal rule.

AUC _{0-t} /D	Dose normalized AUC _{0-t}
AUC _{0-inf}	AUC from time 0 extrapolated to infinity, calculated as $[AUC_{0-t} + (C_{last}/\lambda_z)]$ where C_{last} is the last observed measurable concentration.
AUC _{0-inf} /D	Dose normalized AUC _{0-inf}
t _{1/2}	Apparent terminal elimination half-life, calculated as: $\ln(2)/\lambda_z$.
CL/F	Apparent total body clearance, calculated as: Dose/AUC _{0-inf} .
V _z /F	Apparent volume of distribution during the terminal phase, calculated as: Dose/ $[\lambda_z * AUC_{0-inf}]$.
MRT _{0-t}	Mean residence time from time zero to the last observed measurable concentration, calculated as: AUMC _{0-t} /AUC _{0-t} , where AUMC is the area under the first moment curve.
MRT _{0-inf}	Mean residence time from time zero extrapolated to infinity, calculated as: AUMC _{0-inf} /AUC _{0-inf} , where AUMC is the area under the first moment curve.

In addition to the above PK parameters, which will be listed and summarized, the following parameters will also be listed for Part 1 and Part 3 to document the selection of data points used to estimate t_{1/2} using non-compartmental procedures:

λ_z	Apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase.
Number points	Number of data points used to estimate λ_z ; a minimum of 3 data points must be used, and C _{max} must not be included.
λ_z lower	Lower bound used for the estimation of λ_z .
λ_z upper	Upper bound used for the estimation of λ_z .
Rsq	r ² , the coefficient of determination (goodness of fit statistic); λ_z and all associated parameters will only be reported where $r^2 \geq 0.80$.
%AUC _{ext}	Percentage of AUC _{0-inf} due to extrapolation; AUC _{0-inf} , AUC _{0-inf} /D, CL/F, V _z /F and MRT _{0-inf} values will be flagged and excluded from summary statistics where %AUC _{ext} > 20%.

Part 2:

C _{max}	Maximum observed concentration on Day 1.
C _{max} /D	Dose normalized C _{max} on Day 1.

$C_{\max,ss}$	$C_{\max}$ at steady state on Day 78.
$C_{\max,ss}/D$	Dose normalized $C_{\max,ss}$ on Day 78.
$AUC_{0-\tau}$	AUC within a dosing interval on Day 1, calculated using the linear trapezoidal rule.
$AUC_{0-\tau}/D$	Dose normalized $AUC_{0-\tau}$ on Day 1.
$AUC_{0-\tau,ss}$	$AUC_{0-\tau}$ at steady state on Day 78.
$AUC_{0-\tau,ss}/D$	Dose normalized $AUC_{0-\tau}$ at steady state on Day 78.
AUC_{0-t}	AUC from time 0 to the last measurable observed concentration (C_{last}) on Day 78, calculated using the linear trapezoidal rule.
AUC_{0-t}/D	Dose normalized AUC from time 0 to the last measurable observed concentration (C_{last}) on Day 78, calculated using the linear trapezoidal rule.
$T_{\max}$	Time of maximum observed concentration on Day 1 and Day 78.
ARAUC	Accumulation ratio based on AUC, calculated as: $AUC_{0-\tau,ss}(\text{Day } 78)/AUC_{0-\tau}(\text{Day } 1)$.
C_{trough}	Predose concentrations on Days 8 to 78.
$t_{1/2}$	Apparent terminal elimination half-life on Day 78, calculated as: $\ln(2)/\lambda_z$.
CL/F_{ss}	Apparent total body clearance at steady state on Day 78, calculated as: $\text{Dose}/AUC_{0-\tau,ss}$.
V_z/F_{ss}	Apparent volume of distribution during the terminal phase at steady state on Day 78, calculated as: $\text{Dose}/(\lambda_z * AUC_{0-\tau,ss})$.

In addition to the above PK parameters, which will be listed and summarized, the following parameters will also be listed for Part 2 Day 78 to document the selection of data points used to estimate $t_{1/2}$ using non-compartmental procedures:

λ_z	Apparent terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase.
Number points	Number of data points used to estimate λ_z ; a minimum of 3 data points must be used, and $C_{\max}$ must not be included.
λ_z lower	Lower bound used for the estimation of λ_z .
λ_z upper	Upper bound used for the estimation of λ_z .

Rsq	r^2 , the coefficient of determination (goodness of fit statistic); λ_z and all associated parameters will only be reported where $r^2 \geq 0.80$.
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Serum PK parameters will be presented in data listings and summarized separately using descriptive statistics (number of observations, arithmetic mean, SD, CV, geometric mean, geometric CV, median, minimum, and maximum) by study part, cohort, and study day (where applicable). T_{max} will be summarized using number of observations, median, minimum, and maximum only.

8.4 Pharmacokinetic Statistical Analyses

8.4.1 Dose Proportionality (Power Model)

A non-linear Power Model will be used to assess dose-proportionality for AUCs and C_{max} in each study part. Dose proportionality for Part 1 will be assessed separately for Cohort A to F (0.5 - 50 mg) and Cohort G, H, P (65 - 120 mg). The proportional relationship between the expected value of each parameter $E(y)$ and dose is written as a power function:

$$E(y) = \alpha \text{ dose}^\beta \text{ [Equation 1]}$$

where ' α ' is a constant, ' β ' is the proportionality constant and ' y ' is the parameter of interest. The exponent, β , will be estimated by performing a linear regression of $\ln(\text{parameter})$ (AUCs and C_{max}) versus $\ln(\text{dose})$. The exponent, β , is the estimated slope of the resulting regression line, since taking logs of Equation 1 gives the linear relationship:

$$\ln(y) = \ln(\alpha) + \beta \ln(\text{dose}) + \varepsilon \text{ [Equation 2]}$$

The point estimate of the exponent β and its corresponding 90% confidence interval (CI) will be used to determine the degree of dose proportionality in each study part. Dose proportionality may be established if the 90% CI around the slope includes 1.

Linear regression plots of systemic exposure (AUCs and C_{max}) versus dose will be presented using log-log scales with the power model overlaid. Plots of mean dose normalized AUCs and C_{max} versus dose will also be presented by study part.

8.4.2 Steady State (Part 2)

A stepwise process will be used for testing of steady state with an increasing start timepoint until only 3 time points are left. A linear mixed model with study day as fixed effect and subject as random effect within each dose level will be used to assess steady state.

The following statistical model for each step is defined:

$$\ln(C_{\text{trough}}) = \beta_0 + \beta_1 (\text{study day}) + \varepsilon$$

where β_1 is the regression slope within each dose level. The linear mixed model will include $\ln(C_{\text{trough}})$ from start timepoint (study days 8 for first step, continues with increasing start timepoint until day 64) to day 78 as dependent variable, study day as fixed effect and random effects on the subject. The estimate of the overall slope β_1 , its corresponding 90% CI and p-values obtained from the linear mixed model will be presented to assess steady state for each dose level.

9. Pharmacodynamics (Part 2)

All PD analysis will be performed using the PD analysis set. Descriptive statistics for PD endpoints include number of observations, SD, CV (if applicable), geometric mean (if applicable), geometric CV (if applicable), median, minimum, and maximum.

9.1 Mixed Model Repeated Measures (MMRM) for Physical Measurements and PD endpoints

Mixed model repeated measures will be fitted for the following untransformed endpoints if data permit:

- Body weight
- BMI
- Waist circumference
- Adiponectin
- FPG

Change and percent change (only for weight) from baseline will be included in the MMRM as dependent variables. This model will also include baseline as covariate, treatment, time point, and treatment by time point interaction as fixed effects and a repeated statement of time points within subjects with an unstructured covariance structure. The Kenward and Roger method will be used for the denominator degrees of freedom in the model. In case of convergence issues, the following alternative structures will be used for fitting in order: Heterogeneous Toeplitz, heterogeneous AR(1), Heterogeneous CS, Homogeneous CS. Difference of the least-squares means (LSM) with the corresponding 95% CIs between each dose level of DR10624 and placebo will be presented at each time point in the table.

Actual values, change and percent change from baseline in the above endpoints at each time point will be summarized by treatment using descriptive statistics. Mean and individual plots of body weight, BMI, waist circumference, adiponectin and FPG

(including analysis value, change from baseline and percent change from baseline) versus time point will be presented by treatment. All data for the above endpoints will be presented in a listing.

9.2 MMRM for Fasting Lipid Profile

Mixed model repeated measures will also be fitted for the following natural logarithm transformed endpoints in fasting lipid profile if data permit:

- Total cholesterol
- LDL cholesterol
- HDL cholesterol
- Non-HDL cholesterol (calculated as total cholesterol – HDL cholesterol)
- Lp(a) cholesterol
- VLDL cholesterol
- Triglycerides
- Free fatty acids

The above endpoints will be natural logarithm transformed and included in the MMRM as dependent variables. This model will also include natural logarithm transformed baseline as covariate, treatment, time point, and treatment by time point interaction as fixed effects and a repeated statement of time points within subjects with an unstructured covariance structure. The Kenward and Roger method will be used for the denominator degrees of freedom in the model. In case of convergence issues, the following alternative structures will be used for fitting in order: Heterogeneous Toeplitz, heterogeneous AR(1), Heterogeneous CS, Homogeneous CS. The geometric least squares mean ratio (GLSM) with the corresponding 95% CIs between each dose level of DR10624 and placebo will be presented at each time point in the table.

Actual values, change and percent change from baseline in the above endpoints at each time point will be summarized using descriptive statistics and listed by treatment. Mean and individual plots of fasting lipid profile (including analysis value, change from baseline and percent change from baseline) versus time point will be presented by treatment.

9.3 MMRM for HbA1c, Fasting Insulin, C-peptide, Glucagon and Insulin Resistance Measures

A similar approach of MMRM as detailed in [Section 9.2](#) will be used for the following PD endpoints if data permit:

- HbA1c
- Fasting insulin, C-peptide, glucagon
- HOMA-IR (calculated by fasting insulin [$\mu\text{U/mL}$] $\times$ FPG [mmol/L]/22.5)

- HOMA-B (calculated by $20 \times \text{fasting insulin } [\mu\text{U/mL}] / (\text{FPG } [\text{mmol/L}] - 3.5)$)

Actual values, change and percent change from baseline in the above PD endpoints at each time point will be summarized by treatment using descriptive statistics. Mean and individual plots of fasting insulin, C-peptide and glucagon levels (including analysis value, change from baseline and percent change from baseline) versus time point will be presented by treatment. All data for the above PD endpoints will be presented in a listing.

9.4 MMRM for PD Endpoints Calculated using NCA

The following PD endpoints following MMTT will be calculated using NCA with Phoenix[®] WinNonlin[®] Version 8.3 or higher (Certara USA, Inc., Princeton, NJ) where data permit:

- Partial area under the baseline-corrected glucose, C-peptide, insulin, and glucagon levels versus time curve from time 0 to 4 hours ($\Delta\text{AUC}_{0-4\text{h}}$) where baseline is defined as the average of the three premeal measurements during MMTT on each day. All baseline values will be set to zero for NCA. Negative values that resulted from baseline adjustment will be set to zero. Actual sampling times will be used to calculate $\Delta\text{AUC}_{0-4\text{h}}$ and all data will be included in the analysis (including data collected outside predefined collection windows).

A similar approach of MMRM as detailed in [Section 9.1](#) will be used to fit untransformed $\Delta\text{AUC}_{0-4\text{h}}$ change from baseline for glucose, C-peptide, insulin, and glucagon levels. Difference of the LSM with the corresponding 95% CIs between each dose level of DR10624 and placebo will be presented at each time point in the table. Actual values and change from baseline at each time point will be summarized by treatment using descriptive statistics. All $\Delta\text{AUC}_{0-4\text{h}}$ data for glucose, C-peptide, insulin, and glucagon will be presented in a listing. Glucose, C-peptide, insulin, and glucagon levels during MMTT will also be presented in a listing and plots.

9.5 Summary of CGM Outcome Measures

The following CGM endpoints will be derived in subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes at screening. A CGM-measured hypoglycemic event is defined in [protocol Section 6.3.1.2](#). All derived CGM endpoints on each study day will be listed by treatment and all CGM data will also be presented in a listing:

- TIR as defined in [Section 2.2](#)
- TAR in the following categories:
 - >10.0 mmol/L
 - >13.9 mmol/L

- >16.7 mmol/L
- TBR in the following categories:
 - <3.9 mmol/L
 - <3.3 mmol/L
 - <3.0 mmol/L
- Daily average glucose
- Daily glucose variability measured by CV

9.6 Summary of MRI-PDFF

Actual values, change and percent change from baseline in MRI-PDFF at each time point will be summarized using descriptive statistics by treatment. The same analysis will be repeated in subjects with MRI-PDFF $\geq 8\%$ at baseline. Mean and individual plots of MRI-PDFF (including analysis value, change from baseline and percent change from baseline) versus time point will be presented by treatment. All MRI-PDFF data will be presented in a listing.

9.7 Summary of Liver Stiffness Measured by FibroScan

Frequency counts and percentages at each time point will be summarized by treatment in subjects with MRI-PDFF $\geq 8\%$ at baseline for the following categorical variables:

- Fibrosis score
- Liver stiffness result
- Controlled attenuation parameter (CAP) score
- Steatosis

Shift from baseline in FibroScan interpretation at each time point will be summarized by treatment and overall. All liver stiffness data measured by FibroScan will be presented in a listing.

9.8 Summary of Liver Function Parameters and Endpoints

Actual values, change from baseline at each time point in the following liver function parameters will be summarized using descriptive statistics by treatment and presented in a listing:

- ALT
- AST

- ALP
- GGT
- FIB-4
- NFS

$$\text{FIB-4} = \text{age (years)} \times \text{AST (U/L)} / [\text{platelet (PLT) count } (\times 10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}]$$

$$\text{NFS} = -1.675 + 0.037 \times \text{age (year)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{Impaired fasting glucose or diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{PLT count } (\times 10^9/\text{L}) - 0.66 \times \text{albumin (g/dL)}.$$

The following baseline characteristics will be used to derive FIB-4 and NFS using the above formula:

- Age
- BMI
- Impaired fasting glucose or diabetes status is defined as a history of diabetes or fasting glucose at screening > upper limit of normal

Mean and individual plots of the above liver function parameters (including analysis value, change from baseline and percent change from baseline) versus time point will be presented by treatment.

10. Safety Analysis

All safety summaries and analyses will be based upon the safety analysis set.

10.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. All AEs will be assessed from the time of study drug dosing until end of study (EOS) visit and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after exposure. Partial start dates and times in AE will be used to determine if the AE occurred before or after the first dose of study drug. If missing start dates or times cannot be compared with the date and time of the first dose of study drug, then the corresponding AE will be assumed to be TEAE.

A SAE is defined as any AE that results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal activities of daily living, or a congenital anomaly or birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The AE's relationship to study treatment will be evaluated by the investigator. The following relationships will be collected on eCRF: related or not related.

The severity of AEs will be classified by the investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 5.0, November 2017) as Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5.

The following AEs will be defined as AESI based on [protocol Section 6.3.1.2](#):

- Confirmed hypoglycemia events
- Injection site reactions
- Grade 3 or higher anaphylaxis

An overall AE summary will be generated presenting the frequency and percentage of subjects and the number of AEs for the following by study part, treatment and overall:

- Any AE
- Any TEAE
- Any treatment-related TEAE
- Any grade 3 or higher TEAE
- Any treatment-related grade 3 or higher TEAE
- Any SAE
- Any treatment-related SAE
- Any AESI
 - Treatment Emergent Confirmed hypoglycemia events
 - Injection site reactions
 - Grade 3 or higher anaphylaxis
- Any TEAE leading to treatment discontinuation

- Any treatment-related AE leading to treatment discontinuation
- Any TEAE resulting in death

All AEs will be coded using MedDRA (version 25.0 or above). The TEAEs will be summarized by study part, SOC, PT, by severity and relationship to study treatment. Treatment-related AEs will be summarized by study part, SOC, PT and by severity. Treatment-related AEs leading to treatment discontinuation will also be summarized by study part, SOC, and PT.

The TEAE summary tables will be sorted by SOC and PT. System organ class will be displayed in descending order of overall frequency then alphabetically. Preferred term will be displayed in descending order of overall frequency and then alphabetically within SOC. A subject with 2 or more events within the same level of summarization will be counted only once in that level using the most severe incident or most related incident. Percentages will be based on the number of subjects in the safety analysis set.

All AEs will be presented in a data listing. Separate data listings will be generated for treatment-related AEs, SAEs, AESIs, injection site reactions, confirmed hypoglycemia events and TEAEs leading to treatment discontinuation.

10.2 Clinical Laboratory Evaluations

Detailed clinical laboratory tests are specified in [protocol Section 6.3.2](#) and will be performed at the time points indicated in the schedule of assessments: [Table 16.1](#) (Part 1), [Table 16.2](#) (Part 2) and [Table 16.4](#) (Part 3).

Actual values and change from baseline for hematology, serum chemistry, coagulation and quantitative urinalysis at each time point will be summarized by study part, treatment and overall using descriptive statistics. Shift from baseline in terms of low/normal/high for hematology, serum chemistry and coagulation, and in terms of normal/abnormal for all urinalysis tests at each time point will also be summarized by study part, treatment and overall. All clinical laboratory test results (including calcitonin) will be presented in the data listings. Laboratory values that are outside of the normal reference range will be flagged in the data listings.

10.3 Vital Sign Measurements

The following vital sign measurements will be measured at the time points indicated in the schedule of assessments: [Table 16.1](#) (Part 1), [Table 16.2](#) (Part 2) and [Table 16.4](#) (Part 3).

- Systolic and diastolic blood pressure
- Pulse rate
- Respiratory rate
- Body temperature

Actual values and change from baseline values for vital sign measurements at each time point will be summarized by study part, treatment and overall using descriptive statistics. All vital sign measurements will be presented in a listing.

10.4 12-Lead and Holter ECG

Single or triplicate 12-lead and Holter ECG will be performed at the time points indicated in the schedule of assessments: [Table 16.1](#) (Part 1), [Table 16.2](#) (Part 2) and [Table 16.4](#) (Part 3).

Baseline for 12-lead ECG measurements is defined as the last non-missing measurement (Part 1) or average of the last triplicate measurements (Part 2 and Part 3) before the first dose of study drug. Baseline for 12-lead ECG interpretation is defined as the worst case of the last non-missing triplicate assessments before the first dose of study drug.

Baseline for Holter ECG measurements is defined as the average of the replicated measurements extracted at the last time point before the first dose of study drug. Baseline

for Holter ECG interpretation is defined as the worst measurement before the first dose of study drug. The last measurement will be selected if two or more measurements are included as the worst measurement.

Actual values and change from baseline in the following ECG measurements at each time point will be summarized by study part, treatment and overall using descriptive statistics. The average of any triplicate 12-lead and replicated Holter ECG measurements at each time point will be derived and included in the summary of actual values and change from baseline:

- Heart rate
- PR interval
- QRS duration
- QT interval
- QT interval corrected for heart rate using Fridericia's formula (QTcF) interval
- RR interval

Shift from baseline in 12-lead and Holter ECG interpretation at each time point will also be summarized by study part, treatment and overall. The worst case of the first non-missing triplicates of 12-lead or replicated Holter ECG assessments at each post baseline time point will be included in the shift table.

The number and percentage of subjects with morphological or rhythm abnormalities in 12-lead and Holter ECG at each time point will be summarized by study part, treatment and overall. Each 12-lead and Holter ECG abnormality code based on the worst ECG assessment at each time point will be included in the summary table.

The number and percentage of subjects with the following categories in 12-lead and Holter ECG at each time point will be summarized by study part, treatment and overall:

- QTcF interval
 - ≤ 450 msec
 - > 450 to ≤ 480 msec
 - > 480 to ≤ 500 msec
 - > 500 msec
 - Change from baseline
 - ≤ 30 msec
 - > 30 to ≤ 60 msec

- > 60 msec

All 12-lead and Holter ECG results will be presented in listings.

10.5 Physical Examination

Physical examination will be performed at the time points indicated in the schedule of assessments: [Table 16.1](#) (Part 1), [Table 16.2](#) (Part 2) and [Table 16.4](#) (Part 3). Shift from baseline in physical examination interpretation at each time point will also be summarized by study part, treatment and overall. All physical examination results will be presented in listings.

11. Immunogenicity Analysis

Blood samples for immunogenicity will be collected at the time points indicated in the schedule of assessments: [Table 16.1](#) (Part 1), [Table 16.2](#) (Part 2) and [Table 16.4](#) (Part 3). All immunogenicity analysis will be performed using the immunogenicity analysis set.

The number and percentage of subjects with negative and positive ADA assessments including ADA with in vitro neutralizing effect (NADA) (if applicable) at each time point will be summarized by study part, treatment and overall. The titer results for positive ADA assessment at each time point will also be summarized by study part, treatment and overall using descriptive statistics. If titer is BLQ, the LLN/2 will be used for summary. The followings will also be summarized by study part, treatment and overall:

- Positive ADA assessment at baseline
- ADA incidence:
 - Negative ADA assessment at baseline with any positive ADA assessment post baseline
 - Positive ADA assessment at baseline with at least 4-fold increase in titer values post baseline
- All negative ADA assessments post baseline

All immunogenicity data will be presented in listings.

12. Exploratory Analysis

Satiety test using VAS will be performed at the time points indicated in the schedule of assessments: [Table 16.2](#) (Part 2). Baseline for satiety test is defined as the seven satiety assessment on study Day -1 to the corresponding timepoint. Actual values and change from time-matched baseline in satiety test will be summarized by treatment and overall using summary statistics. All satiety data will be presented in a listing.

The relationship between ADA status (ADA incidence: yes or no) and PK parameters including $t_{1/2}$, CL/F and V_z/F will be explored using graphs. The above PK parameters will be compared using median plots by study part, cohort and ADA status.

For Part 3, PK parameters including C_{max} , AUC_{0-t} and AUC_{0-inf} will be compared using median plots by cohort and BMI subgroup (BMI at screening $\geq 28 \text{ kg/m}^2$ and $< 28 \text{ kg/m}^2$). Scatter plots will also be used to visualize the relationship between the above PK parameters and BMI at baseline for each cohort.

13. Interim Analysis

No formal interim analyses are planned for this study.

14. Changes in the Planned Analysis

Mixed model repeated measures will be fitted for the natural logarithm transformed endpoints in fasting lipid profile, HbA1c, c peptide, fasting insulin, glucagon, homeostatic model assessment index of insulin resistance (HOMA IR) and homeostatic model assessment index of beta-cell function (HOMA-B) considering data characteristics.

Hypoglycemic events will be summarized as collected in AE tables.

Any changes from this SAP will be documented in the clinical study report (CSR) for this study.

15. References

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

16. Schedule of Assessments

16.1 Schedule of Assessments - Part 1

Phase	Screening	Check-in (Baseline)	In-clinic Period							Follow-up Period				
Procedure Error! Reference source not found. Day	-28 to -2	-1	1	2	3	4	5	6	7	8	11	15	22	29/EOS/ ET Error! Reference source not found.
Admission to clinic		X												
Discharge from clinic Error! Reference source not found.									X					
Outpatient visit										X	X	X	X	X
Informed consent	X													
Demographics	X													
Serology ^(c)	X													
Serum FSH ^(d)	X													
Inclusion/exclusion criteria	X	X												
Medical history	X	X												
Height, weight, and BMI ^(e)	X	X							X					X
Physical examination ^(f)	X	X							X					X
Vital sign measurements ^(g)	X	X	X	X	X	X	X	X	X			X		X
12-lead ECG ^(h)	X	X							X					X
12-lead Holter recording ⁽ⁱ⁾		X	X	X	X	X								
Clinical laboratory testing ^(j)	X	X			X		X		X			X		X
Fasting glucose and lipid profile ^(k)	X	X			X					X				X
Urine drug/alcohol screen ^(l)	X	X												
Pregnancy test ^(m)	X	X												X
Calcitonin	X													
Study drug administration ⁽ⁿ⁾			X											
PK blood sample collection ^(o)			X	X	X	X	X	X	X	X	X	X	X	X
ADA sample collection ^(p)			X							X		X		X
AEs ^(q)			← X →											

Prior/concomitant medications	X
Abbreviations: ADA, antidrug antibody; AEs, adverse events; BMI, body mass index; ECG, electrocardiogram; EOS, end-of-study; ET, early termination; FSH, follicle-stimulating hormone; PK, pharmacokinetic; QTcF, QT interval corrected for heart rate using Fridericia's formula; SRC, safety review committee. Notes: Administration of the next higher dose level in Part 1 will only proceed after the safety and available PK data obtained through Day 15 after dosing have been evaluated in a blinded fashion by the SRC for each dose cohort. (a) When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time window as possible. For blood draws, a window of ± 10 minutes is allowed for the 6-hour postdose sampling and a window of ± 60 minutes is allowed from 24 hours postdose (Day 2) up to 168 hours postdose (Day 8) sampling. On Days 11, 15, 22, and 29, a window of ± 1 day is allowed. (b) Discharge following scheduled safety assessments and the 144-hour (Day 7) PK sample collection. (c) Serology testing will include hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus types 1 and 2 antibodies. (d) Females only. A serum FSH test may be performed at screening to confirm postmenopausal status. (e) Height and weight will be measured, and BMI calculated at screening only. Only weight will be measured at check-in, Day 7, and Day 29/EOS/ET. (f) A full physical examination will be performed at screening. A brief physical examination will be performed at check-in, Day 7, and Day 29/EOS/ET. Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Further details are provided in protocol Section 6.3.6. (g) Vital signs will be measured at screening and check-in, within 30 minutes prior to study drug dosing on Day 1, 1 hour post drug dosing on Day 1, on Day 2, Day 3, Day 4, Day 5, Day 6, Day 7, Day 15, and Day 29/EOS/ET after the subject has been in the semi-supine position for at least 5 minutes. A window of ± 20 minutes from nominal time will be allowed for all vital sign measurements. Vital signs may be measured at additional time points at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Further details on vital sign measurements are provided in protocol Section 6.3.3. (h) Single 12-lead ECG recordings will be made at screening, check-in, Day 7, and Day 29/EOS/ET after the subject has been in the semi-supine or supine position for at least 5 minutes. A window of ± 120 minutes from nominal time will be allowed for all ECG recordings, if necessary. In the event a value is outside of the reference range, this will be confirmed by 2 further repeat measurements, which will then be calculated as a mean of the original value and the 2 repeat measurements. Further details on safety ECG recordings are provided in protocol Section 6.3.4. (i) The 12-lead Holter monitor will be started on Day -1 at least 12 hours before dosing on Day 1 and will continue until at least 72 hours after dosing on Day 1. Further details are included in protocol Section 6.3.5. (j) Clinical laboratory testing will occur at screening, check-in, Day 3, Day 5, Day 7, Day 15 and Day 29/EOS/ET. Blood samples will be collected and prepared per the clinic's standard procedures. Further details on clinical laboratory assessments, including a complete list of assessments, are provided in protocol Section 6.3.2.	

- (k) Fasting glucose and fasting lipid profile will be assessed at screening, check-in, Day 3, Day 8, and Day 29/EOS/ET. If time points coincide with serum chemistry collection, analytes for fasting glucose and fasting lipid profile will be collected as part of the serum chemistry sample.
- (l) Urine drug and alcohol screen will occur at screening and check-in per the clinic's standard procedures.
- (m) Women of childbearing potential only. A serum pregnancy test will be performed at screening and on Day 29/EOS/ET. A urine pregnancy test will be performed at check-in.
- (n) The time of study drug dosing will be called "0" hour and is denoted with grey shading. The study drug will be administered SubQ in the abdomen. Subjects will fast overnight for at least 10 hours before dosing and will remain fasted for 2 hours after. Water is permitted as desired. Further details are provided in [protocol Section 5.1](#).
- (o) Blood samples for PK analysis of DR10624 in serum will be collected at: predose and at 2, 4, 6 (Day 1), 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 hours (Day 7) following study drug dosing during the in-clinic period and at every scheduled outpatient visit until Day 29/EOS/ET (168 [Day 8], 240 [Day 11], 336 [Day 15], 504 [Day 22], and 672 hours [Day 29] following study drug dosing).
- (p) Blood samples for immunogenicity analysis of ADAs will be collected at: predose on Day 1 and following study drug dosing on Days 8, 15, and Day 29/EOS/ET.
- (q) Adverse events will be assessed from the time of study drug dosing until Day 29/EOS/ET and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. Further details on collection and reporting of AEs are provided in [protocol Section 6.3.1](#).
- (r) Follow-up/EOS visits will occur until Day 29/EOS/ET.

16.2 Schedule of Assessments - Part 2

Phase		Screening	Check-in (BL)	In-clinic Period		Outpatient Visits																In-clinic Period		Outpatient Visits																									
Procedure ²	Week	-6		1																2	3	4	5	6	7	8	9	10	11	12																13	14	15	16
	Day	-42 to -3	-2 to -1	1	2	3	4	5	6	7	8	15	22	28	29	36	43	50	57	64	71	77	78	79	80	81	82	83	84	85/ EOT	92	99	106/ EOS																
Admission to clinic ^{a)}			X																			X																											
Discharge from clinic ^{b)}					X																		X																										
Outpatient visit ^{c)}						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X	X	X															
Informed consent		X																																															
Demographics		X																																															
Serology ^(e)		X																																															
Serum FSH ^{e)}		X																																															
Inclusion/exclusion criteria		X	X																																														
Medical history		X	X																																														
Height, weight, waist circumference, and BMI ^{f)}		X	X									X			X				X											X			X																
Physical examination ^{g)}		X	X			X																	X							X			X																
Vital sign measurements ^{h)}		X	X	X		X					X	X	X	X	X	X	X	X	X	X	X	X			X				X			X																	
12-lead ECG ⁱ⁾		X	X	X		X					X	X	X	X			X		X		X				X				X				X																
Clinical laboratory testing ^{j)}		X	X			X			X		X		X		X	X		X			X								X				X																
Fasting glucose ^{k)}		X	X			X					X	X	X	X		X	X	X	X			X			X				X				X																
Glucometer ^{k)}					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X															
Fasting Insulin, C-peptide, Glucagon ^{l)}		X	X								X	X	X	X					X			X							X																				

Phase		Screening	Check-in (BL)	In-clinic Period	Outpatient Visits																In-clinic Period	Outpatient Visits																		
Procedure ²	Week	-6		1																11	12																13	14	15	16
	Day	-42 to -3	-2 to -1	1	2	3	4	5	6	7	8	15	22	28	29	36	43	50	57	64	71	77	78	79	80	81	82	83	84	85/ EOT	92	99	106/ EOS							
Urine drug/Alcohol screen ^{m)}		X	X																																					
Pregnancy test ⁿ⁾		X	X												X				X												X			X						
Study drug administration ^{o)}				X							X	X	X		X	X	X	X	X	X	X		X																	
PK blood sample collection ^{p)}				X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X						
Fasting lipid profile ^{q)}		X	X								X	X			X				X												X			X						
ADA sample collection ^{r)}				X							X				X								X											X						
Satiety test ^{s)}			X											X										X																
Adiponectin ^{t)}			X												X				X												X									
Calcitonin ^{u)}		X																	X															X						
Continuous glucose monitoring ^{v)}		← X →													← X →							← X →																		
MMTT ^{w)}			X												X									X																
HbA1c ^{x)}		X	X													X			X												X									
MRI-PDFF ^{y)}		X																	X													X								
FibroScan ^{z)}		X																													X									
AEs ^{aa)}					← X →																																			
Prior/concomitant medications		← X →																																						

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

Notes:

1. Dose escalation in Part 2 will occur only after the available real time PK, safety, and tolerability data (including reported AEs, physical examinations, vital signs, 12-lead ECGs, and clinical laboratory results) from at least 8 subjects, who have received at least 6 doses of DR10624 or placebo in the preceding dose cohort are assessed and the study drug is deemed safe and well tolerated by the SRC.
2. If a subject, who has received at least one dose of the study drug, withdraws from the study, the subject may be asked to have necessary assessments listed in the protocol within 4 weeks after the last dose this subject receives.
 - a) When procedures overlap or occur at the same time point, all blood draws should follow vital signs or ECGs, and PK sampling should be timed to occur last and as close to the scheduled time window as possible.
 - b) Subjects will reside within the clinic from the evening of Day –2 until discharge on Day 2 (24 hours after dosing) and will return to the clinic on the evening of Day 77 until discharge on Day 79 (24 hours after Day 78 dosing). A window of ± 1 day is allowed for the second in-clinic period (Days 77, 78, and 79).
 - c) Discharge following scheduled safety assessments and the 24-hour PK sample collection.
 - d) Subjects will return to the clinic on Days 3, 4, 5, 6, 7, 8, 15, 22, 28, 29, 36, 43, 50, 57, 64, 71, 80, 81, 82, 83, 84, 85, 92, 99 and 106 for outpatient visits. EOS visit will occur on Day 106/EOS. A window of ± 1 day is allowed for all visits starting from Days 15.
 - e) Serology testing will include hepatitis B surface antigen, hepatitis C virus antibody, human immunodeficiency virus types 1 and 2 antibodies, and SARS-CoV-2 (as per site practice).
 - f) Females only. A serum FSH test may be performed at screening to confirm postmenopausal status.
 - g) Height, waist circumference, and weight will be measured, and BMI will be calculated at screening. Additionally, weight and waist circumference will be measured, and BMI will be calculated on Days –1, 15, 29, 57, 85, and 106/EOS or at ET.
 - h) A full physical examination will be performed at screening. A brief physical examination will be performed at Day –1, Day 4, Day 79, and Day 106/EOS or at ET. A symptom-directed physical examination will be performed at Day 85. Interim physical examinations may be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Further details are provided in [protocol Section 6.3.6](#).
 - i) Vital signs will be measured at screening and Day –1; within 30 minutes prior to study drug dosing on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78; Day 4, Day 28, Day 81, Day 85, and Day 106/EOS or at ET after the subject has been in the semi-supine position for at least 5 minutes. A window of ± 20 minutes from nominal time will be allowed for all vital sign measurements. Vital signs may be measured at additional time points at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Further details on vital sign measurements are provided in [protocol Section 6.3.3](#).
 - j) Triplicate 12-lead ECG recordings will be made at screening, on Day –1, prior to study drug dosing on Days 1, 8, 15, 22, 43, 57, 71, and 78; on Day 4 (72 hours after the first dose), Day 28, Day 81 (72 hours after the last dose), Day 85, and Day 106/EOS or at ET after the subject has been in the semi-supine or supine position for at least 10 minutes. The triplicates will be performed at approximately 1-minute intervals. Each ECG

recording (trace) will last 10 seconds. ECG should be collected immediately prior to PK sample collection. Further details on safety ECG recordings are provided in [protocol Section 6.3.4](#).

- k) Clinical laboratory testing, including hematology, serum chemistry, urinalysis, and coagulation testing, will occur at screening, on Day –1, prior to study drug dosing on Days 15, 36, 43, and 57; and on Days 4, 7, 28, 77, 85, and 106/EOS or at ET. Blood samples will be collected and prepared per the clinic’s standard procedures. Further details on clinical laboratory assessments, including a complete list of assessments, are provided in [protocol Section 6.3.2](#). On Day -1, Day 57, and on Day 85, NFS and FIB-4 will be calculated using following formula: $FIB-4 = Age \times AST / (PLT \text{ count} \times \sqrt{ALT})$; $NFS = -1.675 + 0.037 \times age + 0.094 \times \text{body mass index (BMI, kg/m}^2) + 1.13 \times \text{Impaired fasting glucose or diabetes (Yes 1, No 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelets (10}^9/\text{L)} - 0.66 \times \text{albumin (g/dl)}$.
- l) Fasting glucose will be assessed at screening, on Days –1, 4, 8, 15, 22, 28, 36, 43, 50, 57, 78, 81, 85, and Day 106/EOS or at ET. If both fasting glucose and clinical laboratory will be tested in a visit, the glucose level in clinical laboratory may be adopted, additional fasting glucose test is not required. A glucometer will be provided to all subjects in Part 2. Subjects will routinely monitor fasting blood glucose at least twice weekly throughout the study period and will be counseled on identification and management of hypoglycemia and hyperglycemia.
- m) Fasting insulin, C-peptide, and glucagon will be assessed at screening and on Days –1, 8, 15, 22, 28, 57, 78, and Day 85 or at ET.
- n) Urine drug and alcohol screen will occur on screening and Day –2 per the clinic’s standard procedures.
- o) Women of childbearing potential only. A serum pregnancy test will be performed at screening and Day 106/EOS or at ET and urine pregnancy test will be performed on Day –2, Day 29, Day 57, and Day 85.
- p) Study drug dosing occurs on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78 denoted with grey shading. All doses of study drug will be administered SubQ in the abdomen. Subjects will fast overnight for at least 10 hours before dosing and will remain fasted for 2 hours after. Water is permitted as desired. On Day 8 to Day 71 subjects will be domiciled in the clinic for a minimum of 30 minutes postdose for safety monitoring and observation of injection site reactions. Further details are provided in [protocol Section 5.1](#).
- q) For PK blood draws, all predose blood draws on Days 1 to 78 should be completed within 60 mins before dosing. For first and twelfth dose, a window of ± 10 minutes is allowed for the 4-and 6-hour postdose sampling and a window of ± 60 minutes is allowed for 24 hours postdose through the 168 hours postdose sampling. For twelfth dose, a window of ± 1 day is allowed for 336 hours postdose through the 672 hours postdose sampling. Further details are provided in [Section 16.3](#). The time of drug dosing on Day 1 and Day 78 will be called “0” hour respectively.
- r) Blood samples for assessment of fasting lipid profile will be collected at screening and Days –1, 8, 15, 29, 57, 85, and Day 106 (EOS or at ET). Fasting triglyceride may be repeated up to two times 1 week later if the initial results do not fall within the desired range at screening. Baseline will be defined as the result of Day –1. Fasting triglyceride may be repeated once if the initial results do not fall within the desired range. If there are some repeat items in the lipid profile and clinical laboratory tests at a visit, a repeat test is not required.
- s) Blood samples for immunogenicity analysis of ADAs will be collected at: predose on Days 1, 8, 29, and 78 and on Day 106/EOS or at ET.

- t) A commercially available visual analogue scale will be used to assess satiety at 0 (premeal), 1 (± 5 min), 2 (± 5 min), 3 (± 10 min), 4 (± 10 min), 5 (± 10 min), and 6 hours (± 10 min) from the start time of the meal during every MMTT measurement.
- u) Blood samples for adiponectin will be collected from all subjects on Days -1, 29, 57, and Day 85 or at ET.
- v) Blood samples for calcitonin will be collected from all subjects at screening, on Day 57, and on Day 106/EOS or at ET.
- w) Subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes at screening will be fitted for baseline continuous glucose monitoring with a blinded sensor during the 14-day pre-randomization phase prior to check-in and up to predose on Day 1. If the day of dosing changes or any subjects have completed their CGM earlier than check-in and are within the screening window then the subjects will be considered for admission and dosing. Additional blinded sensors configured to record glucose concentrations will be fitted from Day 22 to Day 36, and Day 71 to Day 85. Further details are provided in [protocol Section 6.3.7](#).
- x) On Day -1, Day 28 and Day 79, a standard mixed meal (470 kcal, ~66% carbohydrate, 18% fat, and 16% protein) will be served. Baseline sampling for biomarkers will be collected premeal at -30 (± 5 min), -15 (± 5 min), and -5 (within 5 min) minutes. A serial sampling for biomarkers will be collected at 10 (± 2 min), 15 (± 2 min), and 30 minutes (± 2 min), and at 1, 1.5, 2, 3, and 4 (± 5 min) hours from the start time of the meal.
- y) Blood samples for assessment of HbA1c will be collected at screening, on Days -1, 29, 57, and Day 85 or at ET.
- z) MRI-PDFF measurements will be performed at screening and between Day 85 to 99. In subjects with abnormal blood glucose, elevated HbA1c, or a history of diabetes, the MRI-PDFF at screening will be performed prior to the 14-day predose CGM measurements. If applicable, MRI-PDFF will be conducted at ET only if the subject has received ≥ 6 weeks of treatment with study drug. For subjects that early terminate, MRI-PDFF measurement will be arranged as soon as possible.
- aa) FibroScan measurement will be performed at screening, and on Days 85 (a window of ± 2 days is allowed), or if applicable, at ET visit (only if subject has received ≥ 6 weeks of treatment with study drug) in subjects with baseline hepatic fat of at least 8% measured by MRI-PDFF.
- bb) Adverse events will be assessed from the time of study drug dosing until Day 106/EOS and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. Note: Symptoms of hypoglycemia will be solicited during the in-clinic period and at all outpatient visits until Day 106/EOS. Confirmed hypoglycemic events are defined in [protocol Section 6.3.1.2](#). Further details on collection and reporting of AEs are provided in [protocol Section 6.3.1](#).

16.3 Pharmacokinetic Sampling Schedule - Part 2

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

Note: Blood samples for PK analysis of DR10624 in serum will be collected on Day 1 at: predose and at 4, 6 (Day 1), 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), and 144 (Day 7) hours postdose and on Day 78 at: predose and 4, 6 (Day 78), 24 (Day 79), 48 (Day 80), 72 (Day 81), 96 (Day 82), 120 (Day 83), 144 (Day 84), 168 (Day 85), 336 (Day 92), 504 (Day 99), and 672 hours (Day 106) postdose. The time of drug dosing on Day 1 and Day 78 will be called “0” hour respectively. Additional predose blood samples (trough) will be collected on Days 8 (168 hours postdose Day 1), 15, 22, 29, 36, 43, 50, 57, 64, and 71.

16.4 Schedule of Events - Part 3

Phase	Screening	Check-in (Baseline)	In-clinic Period							Follow-up Period					
Procedure ^(a)	Day	−28 to −2	−1	1	2	3	4	5	6	7	8	11	15	22	29/EOS/ ET
Admission to clinic			X												
Discharge from clinic ^(b)										X					
Outpatient visit ^(c)											X	X	X	X	X
Informed consent	X														
Demographics	X														
Serology ^(d)	X														
Serum FSH ^(e)	X														
Inclusion/exclusion criteria	X	X													
Medical history	X	X													
Height, weight, and BMI ^(f)	X	X								X			X		X
Physical examination ^(g)	X	X								X					X
Vital sign measurements ^(h)	X	X	X	X	X	X	X	X	X	X			X		X
12-Lead ECG ⁽ⁱ⁾	X	X				X				X					X
Clinical laboratory testing ^(j)	X	X			X		X			X			X		X
Urine/Alcohol drug screen ^(k)	X	X													
Pregnancy test ^(l)	X	X													X
Calcitonin	X														
Study drug administration ^(m)				X											
PK blood sample collection ⁽ⁿ⁾				X	X	X	X	X	X	X	X	X	X	X	X
ADA sample collection ^(o)				X							X		X		X
AEs ^(p)				X											
Prior/concomitant medications				X											
Abbreviations: ADA, antidrug antibody; AEs, adverse events; BMI, body mass index; ECG, electrocardiogram; EOS, end-of-study; ET, early termination; FSH, follicle-stimulating hormone; PK, pharmacokinetic; QTcF, QT interval corrected for heart rate using Fridericia’s formula; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SRC, safety review committee.															
Notes: Administration of the next higher dose level in Part 3 will be determined by the SRC following an evaluation of available safety, tolerability, and PK data for subjects in Part 1 and the safety and available PK data obtained through Day 15 of the preceding dose cohort of Part 3.															

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

^(p) Adverse events will be assessed from the time of study drug dosing until Day 29/EOS and should be followed until they are resolved, stable, or judged by the investigator to be not clinically significant. Further details on collection and reporting of AEs are provided in [protocol Section Error! Reference source not found..](#)

Statistical Analysis Plan (SAP) Client Approval Form

Client:	Zhejiang Doer Biologics Co., Ltd.
Protocol Number:	DR10624-101
Document Description:	Final Statistical Analysis Plan
SAP Title:	A PHASE 1, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO EVALUATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF SINGLE- AND MULTIPLE-ASCENDING SUBCUTANEOUS DOSES OF DR10624
SAP Version Number:	Version 1.0
Effective Date:	31Oct2024

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For PPD: Xue Shan, Biostatistician

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Approved by:

签署人：  Yibin Lu, Biostatistician 签名原因：我已审查此文档 签名时间：31-Oct-2024 12:58:40 AM PDT Zhejiang Doer Biologics Co., Ltd. C44FC480EAF4009AACAA1C21620C529	Date (DD-MMM-YYYY)
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