ClinicalTrials.gov Posted Document Cover Page

Clinical Study Statistical Analysis Plan (SAP)

PROTOCOL TITLE: A Single-blind, Randomized, Placebo-controlled, Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of JTT-662 Administered for 28 Days in Subjects with Type 2 Diabetes Mellitus on Metformin Monotherapy

PROTOCOL NUMBER: AT662-U-20-003

SAP DATE: 10 March 2021

NCT NUMBER: NCT04465877

Akros Pharma Inc.

Protocol AT662-U-20-003

A Single-blind, Randomized, Placebo-controlled, Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of JTT-662 Administered for 28 Days in Subjects with Type 2 Diabetes Mellitus on Metformin Monotherapy

Statistical Analysis Plan

Version 1.0
10 MARCH 2021

SIGNATURE PAGE

Protocol Number:	AT662-U-20-003
Protocol Title:	A Single-blind, Randomized, Placebo-controlled, Multiple Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of JTT-662 Administered for 28 Days in Subjects with Type 2 Diabetes Mellitus on Metformin Monotherapy

The signatures below indicate approval of the Statistical Analysis Plan

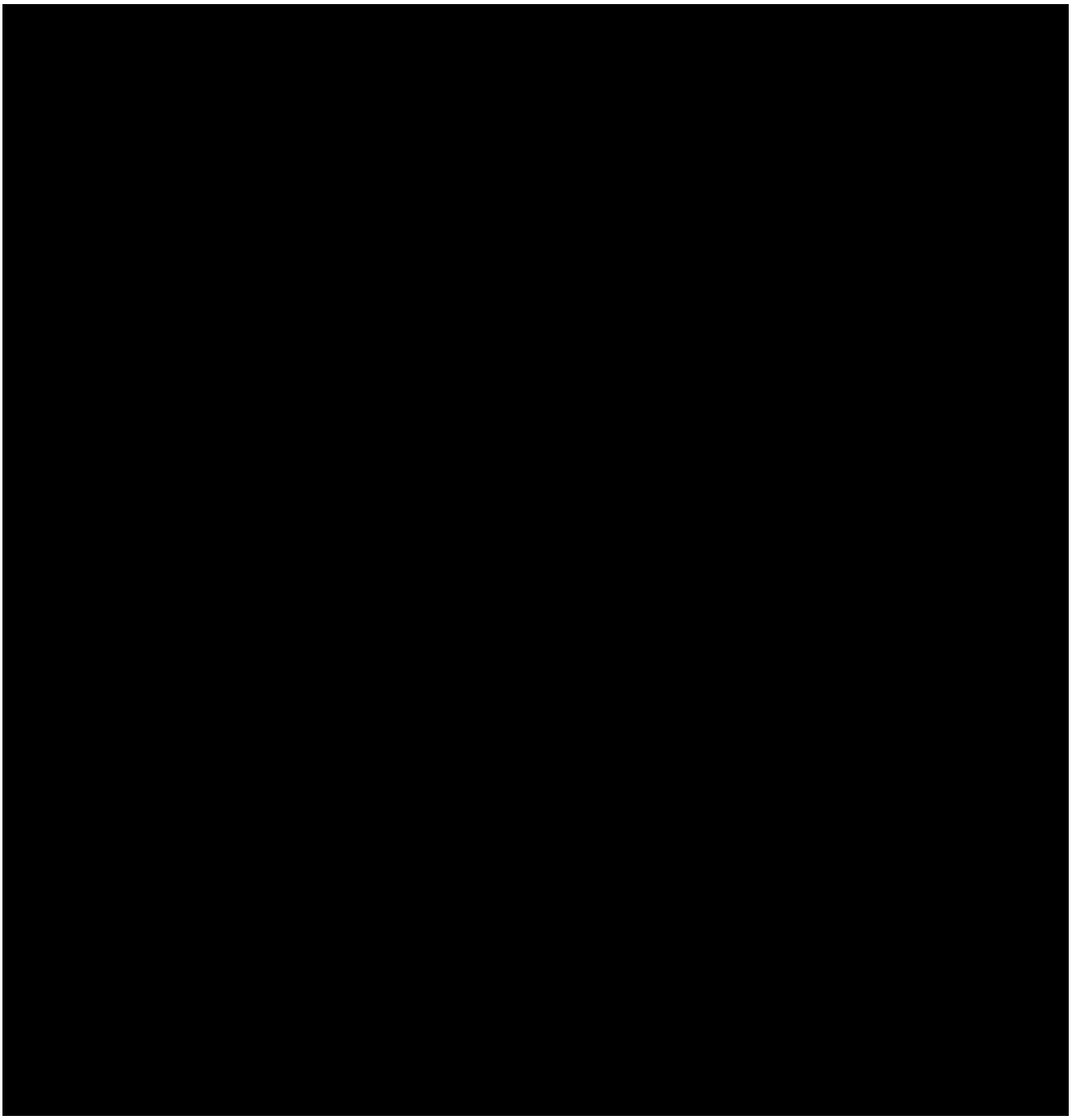


TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
AR_{AUCtau}	Accumulation ratio of area under the concentration-time curve during a dosing interval
AR_{Cmax}	Accumulation ratio of maximum concentration
$AR_{Ctrough}$	Accumulation ratio based on trough concentration
ATC	Anatomical Therapeutic Chemical
AUC	Area under the concentration-time curve
AUC_{tau}	Area under the concentration-time curve during a dosing interval
$AUEC_{0-4}$	Area under the observed effect-time curve from the time of starting breakfast until the 4-hour time point
$AUEC_{0-24}$	Area under the observed effect-time curve from the time of starting breakfast until the 24-hour time point
β-hCG	β human chorionic gonadotropin
BLQ	Below the lower limit of quantification
BMI	Body mass index
[redacted]	
CI	Confidence interval
CL_F	Apparent oral clearance of drug following extravascular administration (total body clearance)
C_{max}	Maximum concentration
COVID-19	Coronavirus Disease
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration during multiple dosing prior to next dose
[redacted]	
CV	Coefficient of variation
ECG	Electrocardiogram
eCRF	electronic case report form
eGFR	Estimated glomerular filtration rate
FPG	Fasting plasma glucose
HbA1c	Hemoglobin A1c/ Glycosylated Hemoglobin
HBsAg	Hepatitis B surface antigen

HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
[redacted]	
ICF	Informed consent form
IR	Insulin resistance
λ_z	Apparent elimination rate constant in the terminal phase by non-compartmental analysis
LLN	Lower limit of normal
[redacted]	
MDRD	Modification of Diet in Renal Disease Study
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not applicable
PCS	Potentially clinically significant
PD	Pharmacodynamic(s)
[redacted]	
PK	Pharmacokinetic(s)
PPG	Postprandial glucose
PT	Preferred Term
[redacted]	
QD	Once daily
RBC	Erythrocytes (red blood cells)
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Standard deviation
SOC	System organ class
$t_{1/2}$	Elimination half-life associated with the terminal slope (λ_z) of a semi-logarithmic concentration-time curve
$t_{1/2(eff)}$	Effective half-life
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
TEPCS	Treatment-emergent potentially clinically significant
[redacted]	
t_{max}	Time to reach peak or maximum concentration following drug administration
[redacted]	

UCE_{0-24}	Urinary calcium excretion from the time of dosing until the 24-hour time point
UGE_{0-24}	Urinary glucose excretion from the time of dosing until the 24-hour time point
ULN	Upper limit of normal
$UNaE_{0-24}$	Urinary sodium excretion from the time of dosing until the 24-hour time point
V_z_F	Volume of distribution during terminal phase (λz) following extravascular administration
WBC	Leukocytes (white blood cells)

1 INTRODUCTION

This statistical analysis plan describes the statistical methods and data presentations to be used in the listings, summary tables and figures of the Phase 1 study AT662-U-20-003.

This document is consistent with the statistical methods section of the final study protocol (Amendment 1, Version 2.0, dated 29 January 2021) and includes additional detail of the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability summaries to be included in the clinical study report (CSR).

2 STUDY OBJECTIVES

- To assess the safety and tolerability of multiple oral doses of JTT-662 in subjects with Type 2 Diabetes Mellitus (T2DM) on metformin monotherapy
- To evaluate the PK of multiple oral doses of JTT-662 in subjects with T2DM on metformin monotherapy
- To evaluate the PD of multiple oral doses of JTT-662 in subjects with T2DM on metformin monotherapy

3 STUDY DESIGN

This is a single-blind, randomized, placebo-controlled, multiple dose study to assess the safety, tolerability, PK and PD of JTT-662 administered for 28 Days in subjects with T2DM on metformin monotherapy.

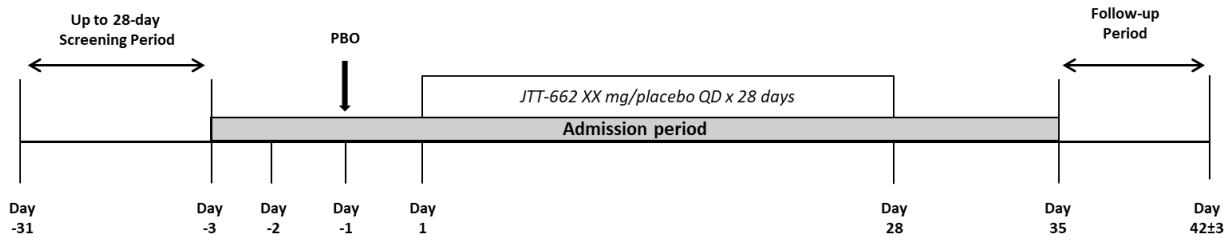
Approximately 36 subjects are planned to be randomized into three cohorts (JTT-662 5 mg [Cohort 1], 10 mg [Cohort 2] and 20 mg [Cohort 3]). Within each cohort, 9 subjects will be randomized to receive JTT-662 and 3 subjects will be randomized to receive placebo. Cohorts 1 and 2 may proceed simultaneously. Cohort 3 will be initiated only after review of the safety, tolerability, PK (up to Day 29 for Cohort 2) and available PD data from Cohorts 1 and 2 by the Sponsor, the Medical Monitor and the Investigator. The planned dose in Cohort 3 may be changed (not to exceed 40 mg) based on the data review.

For all cohorts, eligible subjects will be admitted to the site on Day -3 and will be administered a single dose of placebo on Day -1 following an overnight fast (for at least 10 hours) and 30 minutes before the start of a standard breakfast. JTT-662 or placebo will be administered once-daily (QD) for 28 consecutive days (Day 1 through Day 28) following an overnight fast (for at least 10 hours) and 30 minutes before the start of a standard breakfast.

Subjects will be discharged from the site on Day 35 and will return to the site on Day 42±3 for the Follow up Visit.

3.1 Study Procedures

Figure 1. Study Schema



XX = 5 mg (Cohort 1), 10 mg (Cohort 2) or 20 mg (Cohort 3)
PBO = placebo single dose
QD = once daily

Table 1. Schedule of Study Procedures (Screening through Day -1)

	Screening Period	Admission Period																	
(Day)	-31 to -4[a]	-3[a]			-2[a]			-1[a]											
Time from JTT-662/Placebo Administration (hr)		-72±3	-68	-62	-48±3	-44	-38	-24.5	-24	-23.5	-23	-22.5	-22	-21.5	-20	-19.5	-16	-13.5	-12
COVID-19 Test	X	X																	
Informed Consent	X																		
Inclusion/Exclusion Criteria	X	X																	
Demographic Information	X																		
Medical History	X	X						X											
Previous/Concomitant Medications	X	X																	
Review Study Restrictions	X	X																	
Weight (kg)	X	X						X											
Height (cm) and BMI	X																		
Drugs of Abuse and Alcohol Screen	X	X																	
Viral Serology	X																		
Serum Pregnancy test (all females)	X	X																	
eGFR	X																		
Physical Examination	X	X																	
Vital Signs	X	X						X											
12-Lead ECG	X	X						X											
Serum Biochemistry	X	X																	
Hematology	X	X																	
Coagulation	X	X																	
Urinalysis	X	X																	
HbA1c	X																		
Plasma Glucose[b]	X	X							X	X	X	X	X	X		X			
Bristol Stool Chart Fecal Assessment[c]	X	X	←																→
Meals		X	X	X	X	X	X			X						X		X	
Placebo Administration									X										
Calcium, Sodium and Glucose Urine Collection[d]									←						↔		↔		→
Adverse Events	X	X			X				X						X				X

a. Multiple assessments scheduled for the same time point should be performed within 60 minutes of the scheduled time. Administration of study drug, plasma glucose and [redacted] sample collection [redacted]) should have priority with respect to the scheduled (nominal) time; however, if scheduled at the same time point, study drug administration should occur last. Vital signs and 12-lead ECGs should occur prior to blood sample collection.
b. When blood samples for plasma glucose, [redacted] are scheduled at the same time point as a meal, the blood samples will be collected prior to the meal.
c. Subjects' general stool patterns will be assessed by the site staff using the BSC assessment at the Screening Visit. Subjects will be trained by a member of the site staff to perform the BSC assessment unassisted during the 3-day period prior to Day -3; the subjects will record the assessments in the BSC source document. The date and time of each subject bowel movement should be recorded anytime a subject has a bowel movement during the admission period (from Day -3, Hour -68 to Day 35, Hour 168) and each stool should be characterized using the BSC. All BSC assessments should be recorded in the CRF.
d. Shaded urine collection intervals represent continuous calcium, sodium and glucose urine collection. The intervals depicted by the bidirectional arrows represent the duration of each individual collection interval. An aliquot for urine calcium, sodium and glucose analysis should be obtained from the pooled sample at the end of each collection interval.
[redacted]

Table 2. Schedule of Study Procedures (Day 1 and Day 2)

(Day)	1[a]															2[a]				
Time from JTT-662/Placebo Administration (hr)	-0.5	0	0.5	1	1.5	2	2.5	3	4	4.5	6	8	10	10.5	12	0	0.5	4.5	10.5	12
Physical Examination	X															X				
Weight (kg)	X															X				
Vital Signs	X				X				X						X	X		X		
12-Lead ECG	X				X				X						X	X		X		
Serum Biochemistry	X															X				
Hematology	X															X				
Coagulation	X																			
Urinalysis	X															X				
[redacted]																				
Plasma Glucose[b]		X	X	X	X	X	X			X						X				
[redacted]																				
Ketone Bodies (β-hydroxybutyrate and acetoacetate)	X															X				
Bristol Stool Chart Fecal Assessment[c]	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Meals			X							X				X			X	X	X	
Randomization		X																		
JTT-662/Placebo Administration		X														X				
JTT-662 PK Blood Samples[d]		X	X	X	X	X		X	X		X	X	X		X	X				
Calcium, Sodium and Glucose Urine Collection[e]	←	—	↔	—	—	—	—	—	↔	—	—	—	↔	—	→	→				
[redacted]																				
Adverse Events		X							X						X	X		X		X

a. Multiple assessments scheduled for the same time point should be performed within 60 minutes of the scheduled time. Administration of study drug, PK, plasma glucose and [redacted] sample collection should have priority with respect to the scheduled (nominal) time; however, if scheduled at the same time point, study drug administration should occur last. However, if scheduled at the same time point, study drug administration should occur last. Vital signs and 12-lead ECGs should occur prior to blood sample collection.
b. When blood samples [redacted] are scheduled at the same time point as a meal, the blood samples will be collected prior to the meal.
c. Anytime a subject has a bowel movement, the date and time should be recorded and the stool should be characterized using the Bristol Stool Chart.
d. When a PK sample is scheduled at the same time point as study drug administration, the PK sample should be collected first.
e. Shaded urine collection intervals represent continuous calcium, sodium and glucose urine collection. The intervals depicted by the bidirectional arrows represent the duration of each individual collection interval. Aliquots for urine calcium, sodium, and glucose analysis should be obtained from the pooled sample at the end of each collection interval.

Table 3. Schedule of Study Procedures (Day 3 through Day 15)

	Admission Period																						
(Day)	3 to 13[a]					14[a]													15[a]				
Time from JTT-662/Placebo Administration (hr)	0	0.5	4.5	10.5	12	-0.5	0	0.5	1	1.5	2	2.5	4	4.5	6	8	10.5	12	0	0.5	4.5	10.5	12
Physical Examination	X[e]					X																	
Vital Signs	X[e]		X[e]			X				X			X					X					
12-Lead ECG	X[e]		X[e]			X				X			X					X					
Weight (kg)	X[e]					X																	
Serum Biochemistry	X[e]					X																	
Hematology	X[e]					X																	
Coagulation	X[e]					X																	
Urinalysis	[e]					X																	
[redacted]																							
Plasma Glucose[b]	[e]						X	X	X	X	X	X		X									
[redacted]																							
Ketone Bodies (β-hydroxybutyrate and acetoacetate)						X																	
Bristol Stool Chart Fecal Assessment[c]	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	←	→	→	→	→
Meals		X	X	X				X						X			X			X	X	X	
JTT-662/Placebo Administration	X						X												X				
JTT-662 PK Blood Samples	X[e]						X				X				X			X	X				
Calcium, Sodium and Glucose Urine Collection[d]							←	←	←	←	←	←	←	←	←	←	←	←	→				
[redacted]																							
Adverse Events	X		X		X		X						X					X	X		X		X

a. Multiple assessments scheduled for the same time point should be performed within 60 minutes of the scheduled time. Administration of study drug, PK, plasma glucose and [redacted] sample collection should have priority with respect to the scheduled (nominal) time; however, if scheduled at the same time point, study drug administration should occur last. Vital signs and 12-lead ECGs should occur prior to blood sample collection.
b. When blood samples [redacted] are scheduled at the same time point as a meal, the blood samples will be collected prior to the meal.
c. Anytime a subject has a bowel movement, the date and time should be recorded and the stool should be characterized using the Bristol Stool Chart.

d. Shaded urine collection intervals represent continuous calcium, sodium and glucose urine collection. The intervals depicted by the bidirectional arrows represent the duration of each individual collection interval. An aliquot for urine calcium, sodium and glucose analysis should be obtained from the pooled sample at the end of each collection interval. Performed on Days 7 and 10 only.

Table 4. Schedule of Study Procedures (Day 16 and Day 29)

	Admission Period																						
(Day)	16 to 27[a]					28[a]														29[a]			
Time from JTT-662/Placebo Administration (hr)	0	0.5	4.5	10.5	12	-0.5	0	0.5	1	1.5	2	2.5	3	4	4.5	6	8	10	10.5	12	24	24.5	28.5	34.5
Physical Examination	X[e]					X																		
Weight (kg)	X[e]					X																		
Vital Signs	X[e]		X[e]			X				X				X						X				
12-Lead ECG	X[e]		X[e]			X				X				X						X				
Serum Biochemistry	X[e]					X																		
Hematology	X[e]					X																		
Coagulation	X[e]					X																		
Urinalysis	X[e]					X																		
[redacted]																								
Plasma Glucose[b]	X[e]						X	X	X	X	X	X			X									
[redacted]																								
Ketone Bodies (β-hydroxybutyrate and acetoacetate)						X																		
Bristol Stool Chart Fecal Assessment[c]	←																							→
Meals		X	X	X				X							X				X			X	X	X
JTT-662/Placebo Administration	X						X																	
JTT-662 PK Blood Samples	X[f]						X	X	X	X	X		X	X		X	X	X		X	X			
Calcium, Sodium and Glucose Urine Collection[d]							←							→		←	→			←	→			
[redacted]																								
Adverse Events	X		X		X		X							X						X	X			X

a. Multiple assessments scheduled for the same time point should be performed within 60 minutes of the scheduled time. Administration of study drug, PK, plasma glucose and [redacted] sample collection should have priority with respect to the scheduled (nominal) time; however, if scheduled at the same time point, study drug administration should occur last. Vital signs and 12-lead ECGs should occur prior to blood sample collection.
b. When blood samples [redacted] are scheduled at the same time point as a meal, the blood samples will be collected prior to the meal.
c. Anytime a subject has a bowel movement, the date and time should be recorded and the stool should be characterized using the Bristol Stool Chart.
d. Shaded urine collection intervals represent continuous calcium, sodium and glucose urine collection. The intervals depicted by the bidirectional arrows represent the duration of each individual collection interval. An aliquot for urine calcium, sodium and glucose analysis should be obtained from the pooled sample at the end of each collection interval.
e. Performed on Days 19 and 24 only.
f. Performed on Day 21 only.

Table 5. Schedule of Study Procedures (Day 30 through Follow-Up Visit)

	Admission Period																Follow-Up Period
(Day)	30[a]			31[a]			32[a]			33[a]			34[a]			35[a]	42 ±3[a]
Time from JTT-662/Placebo Administration (hr)	48.5	52.5	58.5	72.5	76.5	82.5	96.5	100.5	106.5	120.5	124.5	131	144.5	148.5	154.5	168	
Previous/Concomitant Medications																	X
Review Study Restrictions																	X
Weight (kg)				X												X	X
Serum Pregnancy test (all females)																	X
Physical Examination				X												X	X
Vital Signs				X												X	X
12-Lead ECG				X												X	X
Serum Biochemistry				X												X	X
Hematology				X												X	X
Coagulation				X												X	X
Urinalysis				X												X	X
[redacted]																	
Ketone Bodies (β-hydroxybutyrate and acetoacetate)[b]																X	X
JTT-662 PK Blood Samples				X						X						X	X
Bristol Stool Chart Fecal Assessment[c]																→	X
[redacted]																	
Meals	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X		X	X		X	X		X	X		X	X		X	X	X

a. Multiple assessments scheduled for the same time point should be performed within 60 minutes of the scheduled time. PK blood sample collection should have priority with respect to the scheduled (nominal) time. Vital signs and 12-lead ECGs should occur prior to blood sample collection.
b. When ketone bodies (β-hydroxybutyrate and acetoacetate) samples are scheduled at the same time point as a meal, the blood samples will be collected prior to the meal.
c. The date and time of each subject bowel movement should be recorded up to Day 35, Hour 168. During the Follow-up Period, the subject will perform the assessment unassisted. Each stool should be characterized using the Bristol Stool Chart.

3.2 Number of Subjects to be Enrolled

Approximately 36 subjects with T2DM are planned to be enrolled in this study, as follows:

Cohort 1: JTT-662 5 mg or placebo
(9 active: 3 placebo)
Cohort 2: JTT-662 10 mg or placebo
(9 active: 3 placebo)
Cohort 3: JTT-662 20 mg or placebo
(9 active: 3 placebo)

To ensure an adequate number of completers, replacement subjects may be enrolled in the study at the discretion of the Sponsor, as appropriate. Each replacement subject will be assigned the same treatment as the subject that is being replaced.

3.3 Randomization and Treatment Assignments

In each cohort, 12 subjects will be randomized to receive JTT-662 or placebo (9 active: 3 placebo) on Day 1. The randomization code will be prepared by an unblinded statistician or designee using an in house program written in SAS®, a computer software package.

Eligible subjects will be assigned to a treatment according to the list of subject randomization assignments.

3.4 Blinding of Treatment Assignment

On the morning of Day -1, all subjects will receive a single oral dose of placebo in an unblinded manner, following an overnight fast (for at least 10 hours) and 30 minutes before the start of a standard breakfast. From the morning of Day 1 to the morning of Day 28, all randomized subjects will receive either JTT-662 or placebo QD in a single-blind manner, following an overnight fast (for at least 10 hours) and 30 minutes before the start of a standard breakfast. JTT-662 and placebo tablets will be supplied as unbranded tablets which are identical in appearance.

The pharmacist at the site will be responsible for packaging and dispensing the study drug in order to maintain the blind. The treatment assigned to each subject will not be disclosed to the subject; however, the Investigator and site staff will be unblinded. The treatment codes will be controlled by the site's pharmacy or designee.

The laboratory performing the JTT-662, metabolite and metformin (if analyzed) plasma concentration assessments [redacted] will be unblinded to facilitate analysis of all samples from the JTT-662-treated subjects and appropriate samples from the placebo-treated subjects.

3.5 Breaking the Blind

Not applicable.

4 ANALYSIS PARAMETERS

4.1 Baseline Parameters

4.1.1 Demographic Parameters and baseline characteristics

Demographic variables include age, gender, ethnicity, race, weight, height and body mass index (BMI) measured at the Screening Visit. Hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) will be measured at the Screening Visit as part of the inclusion criteria assessments.

4.1.2 Medical History

A complete medical history will be obtained at the Screening Visit. The medical history will include past and present conditions prior to the informed consent form (ICF) signature date. Between the ICF signature date and Day 1, prior to dosing, the Investigator should exercise medical and scientific judgement in deciding whether a medical condition, clinically significant laboratory or assessment finding (e.g., clinically significant abnormalities in 12-lead electrocardiogram [ECG], physical examination, vital signs and laboratory test results that are evidently chronic in nature) could be considered medical history or an adverse event (AE).

4.1.3 Prior and Concomitant Medications

Prior/concomitant medications will be assessed throughout the study for all subjects by the investigator.

The information related to the medication (name of drug, dose, route of administration, duration of administration, reason for initiation of each medication) and/or the procedures (e.g., name[s] of therapy, duration of therapy, reason for initiation) will be recorded.

4.2 Pharmacokinetic Parameters

Blood samples will be obtained according to the schedules summarized in Table 1 through Table 5 for the quantification of JTT-662 in plasma.

If needed, PK plasma samples obtained for JTT-662 analysis from this study may be used for metformin concentration determination. The laboratory performing the metformin concentration determination will be unblinded to facilitate analysis of the plasma samples from the JTT-662-treated subjects.

The actual dosing time and sample collection time will be collected for PK data analysis. In addition, the dose and time(s) of dosing of metformin during the PK collection period will also be recorded.

The PK parameters of JTT-662 will be determined from the plasma concentration-time profiles for all subjects in the PK population. Actual sampling times will be used in all computations involving sampling times. Additional PK parameters may also be estimated from the plasma PK data. The PK parameters will be derived by non-compartmental analysis using Phoenix® WinNonlin® (Version 6.4 or higher) and/or SAS® (Version 9.4 or higher).

For the purpose of PK analysis, concentrations that are below the lower limit of quantification (BLQ) will be treated as zero with the exception that a BLQ value between two positive concentrations will be set as missing. Missing concentrations will be treated as missing from the PK parameter calculations. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing. A minimum of 4 consecutive measurable concentration-time data points will be required to perform the PK analysis on an individual subject profile.

The following PK parameters will be calculated from PK profiles.

JTT-662 in plasma:

Parameter	Definition
AUC_{tau}	Area under the concentration-time curve during the dosing interval
CL_F	Apparent oral clearance of drug following extravascular administration (total body clearance)
C_{max}	Maximum concentration
$t_{1/2(eff)}$	Effective half-life
$t_{1/2}$	Elimination half-life associated with the terminal slope (λz) of a semi-logarithmic concentration time curve
t_{max}	Time to reach peak or maximum concentration following drug administration
C_{trough}	Trough concentration during multiple dosing prior to next dose
λ_z	Apparent elimination rate constant in the terminal phase by non-compartmental analysis
V_z_F	Volume of distribution during terminal phase (λz) following extravascular administration
AR_{Cmax}	Accumulation ratio of maximum concentration
AR_{AUCtau}	Accumulation ratio of area under the concentration-time curve during a dosing interval
$AR_{Ctrough}$	Accumulation ratio based on trough concentration

In the linear up/log down method of AUC calculation, the linear trapezoidal rule is used any time when the concentration data are not decreasing, and the logarithmic trapezoidal rule is used any time when the concentration data are decreasing. The AUCs, terminal phase half-life ($t_{1/2}$) and effective half-life ($t_{1/2(eff)}$) will be calculated [redacted]

4.3 Pharmacodynamic Assessments

Postprandial glucose (PPG): Blood samples to assess plasma glucose will be collected according to the schedules summarized in Table 1 through Table 4 and area under the observed effect-time curve from the start of breakfast until the 4-hour time point ($AUEC_{0-4}$) will be calculated. The PD parameters will be estimated using [redacted]. Below Limit of

Quantification values will be treated as zero for PD parameter estimation. Area under the observed effect-time curve will be calculated using the linear trapezoidal rule.

4.5 Safety Parameters

4.5.1 Adverse Events

Adverse events occurring (initial occurrence or a worsening of a pre-existing condition) after the ICF has been signed and up to the day when the decision to screen fail the subject is made (for screen failure subjects), up to 7 days (for subjects discontinuing the study after dosing on Day -1, but before dosing on Day 1) or 14 days (for subjects discontinuing the study after dosing on Day 1) after the last dose of study drug will be reported and entered in the case report forms (CRFs).

The Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 will be used to map verbatim AEs to preferred term (PT) and their respective primary system organ class (SOC). However, a different (non-primary) system organ class may be selected where appropriate after a medical review of the mapping.

4.5.2 Clinical Laboratory Assessments

Hematology, coagulation, serum biochemistry, and urinalysis are collected as scheduled in Table 1 through Table 5. The following information will be derived for each of the hematology, coagulation, serum biochemistry, urinalysis, and other parameters:

- Change from baseline at all post-baseline time points
- Classification relative to the normal range ('Low', 'Normal', or 'High')
- Potentially clinically significant (PCS) abnormalities, if applicable

In addition, the following tests will be performed:

- **Serum Pregnancy Test:** Blood samples to assess pregnancy status by beta-human chronic gonadotropin (β-hCG) will be collected from all female subjects according to the schedules summarized in Table 1 and Table 5.
- **Estimated glomerular filtration rate:** Estimated glomerular filtration rate (eGFR) will be calculated at the Screening Visit using the 4-variable Modification of Diet in Renal Disease Study (MDRD) equation:

  eGFR (mL/min/1.73 m^2) = 175 × Serum Creatinine $^{-1.154}$ × age $^{-0.203}$ × 1.212 (if participant is black) × 0.742 (if female).
- **Viral Serology**: Blood samples to assess Hepatitis B surface antigen (HBsAg), Hepatitis C virus (HCV) antibodies and human immunodeficiency virus (HIV) antibodies will be obtained at the Screening Visit.
- **Drugs of Abuse and Alcohol Screen:** Urine samples to assess amphetamine, barbiturates, benzodiazepine, cannabinoids, cocaine, ethanol, opiate, oxycodone, methadone and methylenedioxymethamphetamines will be obtained according to the schedule summarized in Table 1.
- **Ketone Bodies:** Blood samples to assess ketone bodies (β-hydroxybutyrate and acetoacetate) will be collected according to the schedules summarized in Table 2 through Table 5.

[redacted]

- **Urine Calcium, Sodium and Glucose:** Urine samples to assess calcium, sodium and glucose will be collected according to the schedules summarized in Table 1 through Table 4.

4.5.3 Vital Signs

Vital sign assessments including systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature (°C) will be performed according to schedules summarized in Table 1 through Table 5. The following information will be derived for all vital signs and body weight:

- Change from baseline at all post-baseline time points
- PCS abnormalities

4.5.4 12-Lead Electrocardiogram

12-lead ECG recordings and conduction intervals including interval from beginning of the QRS complex in the frontal plane to the next QRS complex (RR), interval from beginning of the P wave to the beginning of the QRS complex in the frontal plane (PR), duration of QRS complex in the frontal plane (QRS), interval from beginning of the QRS complex to end of the T wave in the frontal plane (QT) and Fridericia-corrected QT interval (QTcF) will be obtained according to the schedules summaried in Table 1 through Table 5. The following information will be derived for each of the 12-lead ECG measurements:

- Change from baseline at all post-baseline time points
- PCS abnormalities

The overall clinical interpretation of an ECG will be assessed as follows: normal, abnormal not clinically-significant or abnormal clinically-significant.

4.5.5 Physical Examinations

Physical examinations will be performed by a physician or qualified designee according to the schedules summarized in Table 1 through Table 5, and will include examination of the following body systems: general appearance, skin (including hair and nails), HEENT (head, ears, eyes, nose, throat), neck/thyroid, chest/lungs, cardiovascular, gastrointestinal, neurological, psychiatric/emotional, lymphatic and musculoskeletal.

Clinically-significant abnormal physical examination findings will be recorded as medical history or AE where appropriate.

4.5.6 Other Safety Assessments

Height and weight measurements will be performed according to the schedules summarized in Table 1 through Table 5. The BMI will be calculated at the Screening Visit using the following equation: (weight (kg)/[height (m)]^2), where the weight in kilograms will be documented to one decimal place and the height in centimeters will be rounded to the nearest whole number.

In addition, the following assessments will be performed according to the schedules summarized in Table 1 through Table 5:

- **Bristol Stool Chart:** Subjects will report their stool pattern to the site staff at three visits (Screening Visit, Day -3 and the Follow-up Visit). During the Admission Period (Day -3 through Day 35), every time a subject has a bowel movement, a member of the site staff will assist the subject in characterizing the stool using the Bristol stool chart (BSC) including documentation of the date and time.

- **Coronavirus Disease Test:** Respiratory specimens (e.g., nasopharyngeal, oropharyngeal, nasal) will be collected at the Screening Visit and on Day -3 to assess for the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ribonucleic acid that causes COVID-19 using reverse transcription polymerase chain reaction.

5 ANALYSIS POPULATIONS

Randomized Population: All subjects randomized to receive JTT-662 or placebo on Day 1.

Safety Population: All subjects who receive at least one dose of JTT-662 or placebo, including those who do not complete the study. Subjects who were dosed on Day -1 only (placebo run-in) will also be included in the safety population.

Pharmacokinetic Population: All randomized subjects who received at least one dose of JTT-662 starting on Day 1, and have evaluable JTT-662 plasma concentration data. Subjects will be excluded or partially excluded from the statistical analysis of PK parameters if they significantly violated the inclusion or exclusion criteria or deviated significantly from the protocol.

Pharmacodynamic Population: All randomized subjects who received at least one dose of JTT-662 or placebo starting on Day 1, and have evaluable PD data to facilitate the calculation of PD parameters. Subjects will be excluded or partially excluded from the statistical analysis if they significantly violated the inclusion or exclusion criteria or deviated significantly from the protocol.

6 STATISTICAL METHODS

The statistical analysis will be conducted following the principles specified in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96).

No formal inferential test will be performed in this Phase 1 study.

All statistical tabulations and analyses will be performed using [redacted]. Any changes to the analyses described in this plan will be detailed in the CSR.

All results collected in the database will be presented in listings. All continuous data will be listed with the same precision as will be presented in the database. Data listings will be sorted by treatment group, subject ID, and time point.

Unless otherwise noted, continuous variables will be summarized using number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum. For PK parameters, summary statistics will also include the coefficient of variation (CV%) and geometric mean (geometric mean will not be presented for t_{max}). For plasma concentrations and PD parameters, summary statistics will also include the CV%. Categorical variables will be summarized using the frequency count and the percentage of subjects in each category.

All subjects randomized to placebo on Day 1 will be included in the placebo treatment group unless otherwise specified.

In the data listings, study day relative to first dose of study drug on Day 1 may be presented. Study day relative to first dose of study drug on Day 1 will be calculated as: event date – first dose date on Day 1 (+ 1 if event date ≥ first dose date on Day 1).

Baseline will be the latest non-missing measurement prior to the first dose of study drug on Day 1, unless otherwise specified [redacted]

For safety summaries, the unscheduled and repeat assessments will not be summarized; however, all results will be included in the data listings.

Disposition, demographics, and baseline characteristics and all categorical safety parameters will be summarized by each treatment group and overall.

6.1 Sample Size

Approximately 36 subjects (3 cohorts, 12 subjects per cohort [9 active: 3 placebo]) will be randomized into this study. The sample size is not statistically determined.

6.2 Subject Disposition

Summaries of analysis populations and subject disposition will be presented by treatment group and overall for the safety population and will contain the following information:

- Number and percent of subjects in each population (safety, randomized, PK, PD)
- Number and percent of subjects who were dosed (safety population)
- Number and percent of subjects who completed the dosing period
- Number and percent of subjects who completed the study including follow-up visit
- Number and percent of subjects who discontinued early and reason for early discontinuation

Subject disposition and analysis populations will be tabulated and presented in listings. Percentage will be calculated based on number of subjects in the safety population. Screen failure reasons will also be summarized and listed.

6.3 Protocol Deviation Reporting

Protocol deviations will be listed.

6.4 Subject Demographics and Baseline Characteristics

Subject demographic data and baseline characteristics will be summarized using descriptive statistics and include the following parameters collected at screening: sex, age, race, ethnicity, height, body weight, BMI, HbA1c and FPG. Demographic data and baseline characteristics will be presented by treatment group and overall for the safety population and also be listed.

6.5 Medical and Surgical History

Medical and surgical history will be coded using the MedDRA (Version 23.0). Medical history data along with the corresponding SOC and PT coded from the MedDRA dictionary will be presented in the data listing.

6.6 Extent of Exposure

Exposure data will be presented in the data listing.

6.7 Pharmacokinetic Analysis

Pharmacokinetic analysis will be performed for JTT-662 for the PK population.

6.7.1 Method of Pharmacokinetic data representation

The PK data including individual data and descriptive statistics for plasma concentrations, PK parameters and the result of PK data analysis will be represented with three significant values except for CV% which will be represented to one decimal place.

All concentration values reported as no results (not collected or not determined) values will be treated as missing. Plasma concentration values that are BLQ will be set to zero for calculation of summary statistics and plotting mean concentration profiles.

6.7.2 Descriptive Statistics of Plasma Concentrations

The plasma concentration data will be summarized by JTT-662 dose levels and nominal time point. Mean and individual plasma concentration-time profiles will be plotted by dose levels on linear and semi-logarithmic scales. Scheduled (nominal) sampling times will be used for all summary tables and plots of plasma concentration data.

6.7.3 Descriptive Statistics of Pharmacokinetic Parameters

The PK parameters will be summarized by JTT-662 dose levels and day for the PK population.

6.7.4 Statistical Analysis of Pharmacokinetic Parameters

Dose proportionality of C_{max} and appropriate AUC values on Day 1 and Day 28 will be assessed for JTT-662. The relationship between each parameter and dose is written as a power function:

$$\text{Parameter} = A*\text{dose}^{b} \quad \text{(Equation 1)}$$

Where "A" is a constant, "b" is the proportionality constant and "parameter" is the PK parameter of interest (e.g., C_{max} and AUC_{tau}). Each PK parameter will be plotted against dose. The exponent, b, will be estimated by performing linear regression of the (natural) log-transformed parameter on the log-dose, since taking logarithm on both sides of (Equation 1) gives the linear relationship, log parameter = a + b*log dose, where a = log(A). Therefore the exponent, b, is estimated by the slope of the resulting regression line. A value of b close to 1 indicates dose proportionality. Dose proportionality will be assessed descriptively by presenting the estimate of b, its standard error and the 90% confidence interval (CI).

The estimated geometric means at each dose level, the estimate of the slope (b), its 90% and 95% CIs, and model residual error will be obtained from the model. Furthermore, the geometric means based on the raw data and the dose normalized ratio for each pair of doses will be presented. C_{max} and AUC_{tau} will be plotted against dose on the log-scale.

The sample SAS code (with appropriate changes) for calculating the slope of dose proportionality will be:

```
PROC MIXED DATA= DATASET;
        MODEL LNPKPARM=LNDOSE /SOLUTION CL ALPHA=0.1*;
        ODS OUTPUT SOLUTIONF=SOLUTION1(RENAME= (ESTIMATE=EST STDERR=SE));
RUN;
*alpha = 0.05 and 0.1
```

In addition, a model fit test will be performed by testing the quadratic term in a quadratic regression, and the p-value for the quadratic term will be presented.

The sample SAS code (with appropriate changes) will be used for quadratic regression:

```
PROC GLM DATA= DATASET;
        MODEL LNPKPARM=LNDOSE LNDOSE*LNDOSE/SOLUTION CL ALPHA=0.1;
RUN;
```

6.8 Pharmacodynamic Analysis

Observed values and change from baseline of PPG concentrations will be summarized by treatment group and time point in terms of the number of subjects, arithmetic mean, SD, CV%, median, minimum and maximum. Baseline for PPG concentrations will be the pre-dose (Hour 0) value of the PPG profile on each PPG collection day. Concentrations will be listed, mean and individual plots will also be presented.

The plasma glucose excursion defined as the maximum glucose value observed after breakfast (0-4 hours after breakfast) minus the pre-dose (Hour 0) value will also be summarized for observed values and change from baseline on Days -1, 1, 14 and 28. Day -1 will be baseline.

Area under the observed effect-time curve from the time of starting breakfast until the 4-hour time point ($AUEC_{0-4}$) will be calculated for PPG on Days -1, 1, 14 and 28 for the PD population. Observed values and change from baseline of $AUEC_{0-4}$ will be summarized descriptively. Baseline will be the corresponding parameter value on Day -1.

A linear mixed effect model including day as the fixed effect and subject as the random effect will be fitted on the the PD parameter for each treatment group separately. The difference of the least square means of $AUEC_{0-4}$ between the compared days (Day 1 vs. Day -1, Day 14 vs. Day -1, Day 28 vs. Day -1 and Day 28 vs. Day 14) and the 90% and 95% CIs of the least square mean difference will be calculated.

The following sample SAS code may be used, with appropriate changes, for the analysis:

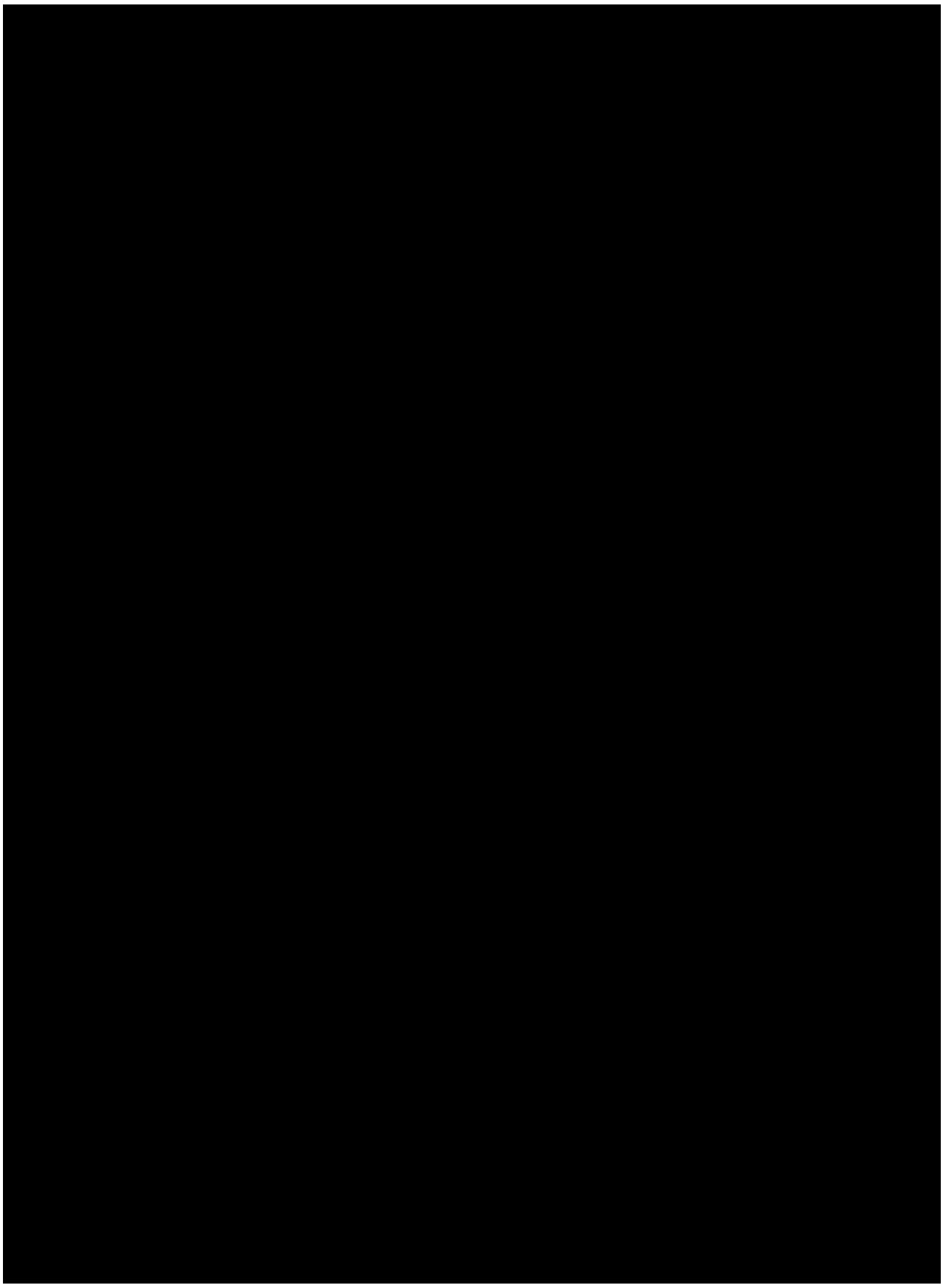
```
PROC MIXED DATA=DATASET;
BY TREATMENT;
   CLASS SUBJID DAY;
   MODEL PDPARVAL = DAY / DDFM=KR;
   RANDOM SUBJID;
   LSMEANS DAY / CL;
   ESTIMATE ‘Day 1 Vs. Day -1' Day 1 0 0 -1/ALPHA = 0.05 CL;
   ESTIMATE ‘Day 14 Vs. Day -1' Day 0 1 0 -1/ALPHA = 0.05 CL;
   ESTIMATE ‘Day 28 Vs. Day -1 ' Day 0 0 1 -1/ALPHA = 0.05 CL;
   ESTIMATE ‘Day 28 Vs. Day 14 ' Day 0 -1 1 0/ALPHA = 0.05 CL;
   ESTIMATE ‘Day 1 Vs. Day -1' Day 1 0 0 -1/ALPHA = 0.1 CL;
   ESTIMATE ‘Day 14 Vs. Day -1' Day 0 1 0 -1/ALPHA = 0.1 CL;
   ESTIMATE ‘Day 28 Vs. Day -1 ' Day 0 0 1 -1/ALPHA = 0.1 CL;
   ESTIMATE ‘Day 28 Vs. Day 14 ' Day 0 -1 1 0/ALPHA = 0.1 CL;
  RUN;
```

Additionally, the change from baseline (Day -1) of $AUEC_{0-4}$ will be analyzed using the mixed effect model with repeated measures (MMRM). The model will include fixed effects for treatment, day, and treatment by day interaction, subject as repeated measures and baseline value as a covariate. The difference of the least squares means between each JTT-662 dose group relative to placebo at the same day will be estimated, along with two-sided 90% and 95% CIs and p-values. Least squares means will also be presented.

The following sample SAS code may be used, with appropriate changes, for the analysis:

```
PROC MIXED DATA=DATASET;
   CLASS DAY TREATMENT;
   MODEL CHG = DAY TREATMENT DAY*TREATMENT BASELINE / DDFM=KR;
   REPEATED /SUBJECT=SUBJECT(TREATMENT) TYPE=UN*;
   LSMEANS DAY*TREATMENT /PDIFF CL ALPHA=0.1**;
  RUN;
```

* Other covariance structure will be used if UN leads to non-convergence of the model.
** alpha = 0.05 and 0.1.



6.10 Analysis of Safety Data

Safety analyses will be conducted on the Safety Population and will be performed for all safety variables specified below.

The safety evaluation will include AEs, clinical safety laboratory tests (e.g., hematology, serum biochemistry, coagulation, urinalysis), vital signs, 12-lead ECGs, BSC findings, ketone bodies, [redacted] urinary calcium excretion from the time of dosing until the 24-hour time point (UCE_{0-24}) and urinary sodium excretion from the time of dosing until the 24-hour time point ($UNaE_{0-24}$) and UGE_{0-24}.

Observed and change from baseline of vital signs, ECG parameters and clinical laboratory data will be presented in tabular form with arithmetic mean, SD, median, minimum and maximum, or in frequency tabulation form as appropriate. For the laboratory safety data, out of range values and PCS abnormalities will be flagged in the data listings.

Potentially clinically significant abnormalities will be defined according to the Akros Safety Reporting Standards [redacted] Potentially clinically significant values for vital signs, ECG, and laboratory data will be flagged in data listings.

Treatment-emergent PCS values will be summarized, presenting the number and percentage of subjects who had at least one PCS value after study drug administration on Day 1. The denominator is always the number of subjects in the safety population, regardless of whether the subject had any post-baseline measurements. The numerator is any PCS value in the treatment-emergent period if the baseline is normal or missing; and is any worsening PCS value in the treatment-emergent period if the baseline is also a PCS value.

A worsening PCS is defined as a > (<) 0 change from baseline if a high (low) value indicating undesirable outcome; or the PCS value is in the opposite direction of the baseline PCS value.

6.10.1 Adverse Events

Adverse events will be coded using the MedDRA (Version 23.0) and will be summarized by SOC and PT.

A treatment-emergent adverse event (TEAE) is defined as any AE with an onset date/time at or after the placebo dosing on Day -1. A pre-treatment AE is defined as any AE with an onset date before the placebo dosing on Day -1.

The summary of TEAEs will be presented for the following groups:

- Placebo run-in: including AEs with onset between the placebo dosing on Day -1 and before dosing on Day 1 for all subjects in the safety population.
- Placebo treatment group: including AEs with onset at or after the placebo dosing on Day 1 for the subjects who are randomized to placebo on Day 1.
- JTT-662 5 mg: including AEs with onset at or after the JTT-662 5 mg dosing on Day 1 for the subjects who are randomized to JTT-662 5 mg on Day 1.

- JTT-662 10 mg: including AEs with onset at or after the JTT-662 10 mg dosing on Day 1 for the subjects who are randomized to JTT-662 10 mg on Day 1.
- JTT-662 XX mg (XX represents JTT-662 dose level for Cohort 3): including AEs with onset at or after the JTT-662 XX mg dosing on Day 1 for the subjects who are randomized to JTT-662 XX mg on Day 1.

The overall incidence of TEAEs (number and percentage of subjects) as well as the number of events will be summarized for each treatment group.

Summaries of TEAEs will include the following: Incidence of TEAEs (overview including number and percentage of participants with any TEAEs, serious TEAEs, discontinuations due to TEAEs, drug-related TEAEs, severe TEAEs, all deaths (AEs leading to death regardless of treatment emergence) and TEAEs leading to death; event counts will also be included).

The TEAEs will be summarized by SOC, PT, and treatment group using frequency counts and percentages (number and percentage of subjects with an event). Each subject may only contribute once to each of the incidence rates, regardless of the number of occurrences. In addition, the following summaries will be performed for the summary groups as described above:

- TEAEs by SOC, PT
- TEAEs by SOC, PT and maximum reported severity
- TEAEs by SOC, PT and causality
- TEAEs by PT (in order of descending frequency in the total JTT-662 group).
- Serious Adverse Events (SAE) by SOC, and PT

Listings of AEs, SAEs, AEs leading to study discontinuation will also be presented. The AEs with onset in the placebo run-in period will be flagged in the listings.

6.10.2 Safety Laboratory Assessments

Observed and change from baseline for each parameter of continuous safety laboratory values (hematology, serum chemistry, coagulation, and urinalysis) will be summarized by treatment group at each time point using descriptive statistics.

Any post-baseline abnormal laboratory finding will be assessed to calculate overall treatment-emergent potentially clinically significant (TEPCS) status as described in tables PCS Criteria for Laboratory Parameters. Values assessed as TEPCS will be summarized categorically per treatment group and overall.

A listing of all safety laboratory data for each subject at each time point will be presented. Out of range values and PCS values will be flagged in the data listing. Safety laboratory values that are outside the normal ranges will be presented in a separate listing together with normal ranges values. For the listing presenting all abnormal values, if a subject has any abnormal value for a test, all values of that test of the subject will be presented.

Qualitative urine parameters are generally reported by a descriptive score, which may differ between laboratories. For pooling the data, a four-point scale is used. A clinical review will be performed on the mapping of the descriptive scores to the four-point scale; and the descriptive scores will be remapped where appropriate. The four-point scale will be used in the summary of the PCS abnormality analysis.

Five-point scale	Four-point scale
Negative	Negative
Trace	Rare/Mild
1+	Rare/Mild
2+	Moderate
3+	Severe

The mean profile by treatment group will be presented for selected laboratory parameters.

If the non-numeric result is reported for quantitative laboratory parameter then for summary and analysis it will be changed as follows into numerical value:

a) If less than '<' sign is used then the value will be reduced by 1 point from the last precision digit
b) If greater than '>' sign is used then 1 point will be added to the last precision digit.

Eg: if the laboratory parameter is reported to 2 decimal precision, <40.01 then for summary and analysis it will be treated as 40.00, if laboratory parameter is reported as whole number >40 then it will be considered as 41 and if the parameter is reported with 1 decimal precision <40.1 then it will be considered as 40.0.

Potentially Clinically Significant Criteria for Laboratory Parameters

Hematology

Parameter			[redacted]
CDISC Code	**SDTM**	**Definition**	
C51948	Leukocytes	White blood cell count	
C51946	Erythrocytes	Red blood cell count	
C64848	Hemoglobin	Hemoglobin	
C64796	Hematocrit	Hematocrit	
C64799	Ery. Mean Corpuscular Volume	Mean corpuscular volume	
C64798	Ery. Mean Corpuscular HGB Concentration	Mean corpuscular hemoglobin concentration	
C51951	Platelets	Platelets	
Differential WBC			
C64827	Neutrophils/ Leukocytes	Neutrophils (%)	
C63321	Neutrophils	Neutrophils	
C64820	Lymphocyte/ Leukocytes	Lymphocytes (%)	
C51949	Lymphocytes	Lymphocytes	
C64824	Monocytes/ Leukocytes	Monocytes (%)	
C64823	Monocytes	Monocytes	
C64604	Eosinophils/ Leukocytes	Eosinophils (%)	
C64550	Eosinophils	Eosinophils	
C64471	Basophils/ Leukocytes	Basophils (%)	
C64470	Basophils	Basophils	

[redacted]

Biochemistry

Parameter		
CDISC Code	**SDTM**	**Definition**
C64858	Protein	Total protein
C64431	Albumin	Albumin
C64467	Aspartate Aminotransferase	Aspartate aminotransferase
C64433	Alanine Aminotransferase	Alanine aminotransferase
C38037	Bilirubin	Total bilirubin
C64481	Direct Bilirubin	Direct bilirubin
C64432	Alkaline Phosphatase	Alkaline phosphatase
C64855	Lactate Dehydrogenase	Lactate dehydrogenase
C64847	Gamma Glutamyl Transferase	Gamma glutamyl transferase
C64489	Creatine Kinase	Creatine kinase, Creatinine phosphokinase
C125949	Urea Nitrogen	Blood urea nitrogen
C64547	Creatinine	Creatinine
C64814	Urate	Uric acid
C64809	Sodium	Sodium
C64495	Chloride	Chloride
C64853	Potassium	Potassium
C64488	Calcium	Calcium
C64857	Phosphate	Inorganic phosphorus, Inorganic phosphate
C105586	Cholesterol	Total cholesterol
C105587	HDL Cholesterol	High density lipoprotein cholesterol
C105588	LDL Cholesterol	Low density lipoprotein cholesterol
C64812	Triglycerides	Triglycerides
C105585	Glucose	Glucose

Parameter		
CDISC Code	**SDTM**	**Definition**
C64548	C Reactive Protein	C-reactive protein

Coagulation

Parameter		
CDISC Code	**SDTM**	**Definition**
C64805	Prothrombin Intl. Normalized Ratio	Prothrombin
C38462	Activated Partial Thromboplastin Time	Activated partial thromboplastin time

Urinalysis

Parameter		
CDISC Code	**SDTM**	**Definition**
C64832	Specific Gravity	Urine specific gravity
C45997	pH	Urinary pH
C105585	Glucose	Qualitative urine glucose
C64858	Protein	Qualitative urine protein
C74686	Occult Blood	Urine occult blood
C64854	Ketones	Qualitative urine ketone bodies
C38037	Bilirubin	Qualitative urine bilirubin
C64816	Urobilinogen	Qualitative urine urobilinogen

6.10.3 Vital Signs and Body Weight

Observed values and change from baseline for continuous vital signs parameters (blood pressure, heart rate, respiratory rate, and temperature) and weight will be summarized by treatment group at each time point using descriptive statistics. Percent change from baseline in weight will also be summarized descriptively by treatment group.

Any post-baseline abnormal vital sign finding assessed as TEPCS values will also be summarized. Vital sign data will be listed by subject and time point collected. In addition, values meeting PCS criteria will be flagged in the listing.

Potentially Clinically Significant Criteria for Vital Sign Values

Parameter			[redacted]
CDISC Code	**SDTM**	**Definition**	
C49676	Pulse Rate	Pulse rate	
C25298	Systolic Blood Pressure	Systolic blood pressure	
C25299	Diastolic Blood Pressure	Diastolic blood pressure	
C49678	Respiratory Rate	Respiratory rate	
C25206	Temperature	Body temperature	
C25208	Weight	Body weight	

[redacted]

6.10.4 Electrocardiogram

Observed values and change from baseline for each parameter of continuous ECG parameters (RR interval, PR interval, QRS duration, QT interval, and QTcF interval) will be summarized by treatment group at each time point using descriptive statistics.

The overall ECG interpretation will be summarized by treatment group at each time point using descriptive statistics.

Any post-baseline abnormal ECG findings assessed as TEPCS values will also be summarized.

ECG data will be listed by subject at each visit and time point collected with indicated clinically significant results. In addition, values meeting PCS criteria will be flagged in listing.

Potentially Clinically Significant Criteria for ECG Parameters

Parameter		
CDISC Code	**SDTM**	**Definition**
C117773	PR Interval, Aggregate	PR
C117791	RR Interval, Aggregate	RR
C117779	QRS Duration, Aggregate	QRS
C117783	QT Interval, Aggregate	QT interval
C117784	QTcB Interval, Aggregate	Bazett-corrected QT interval
C117786	QTcF Interval, Aggregate	Fridericia-corrected QT interval

6.10.5 Prior and Concomitant Medications and Procedures

Prior medications are defined as those medications that started and stopped prior to the placebo dosing on Day -1. Concomitant medications are defined as those medications with a start date on or after placebo dosing on Day -1 or started prior to the placebo dosing on Day -1 and continued after the placebo dosing on Day -1.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (Version March 2020) and classified according to Anatomical Therapeutic Chemical (ATC) code levels 2 (therapeutic sub-level) and 3 (pharmacological sub-level). Prior medications and concomitant medications will be presented in the data listings. Concomitant medications will be summarized by treatment, ATC Level 3 term and PT. The concomitant procedures will also be listed.

6.10.6 Other Safety Data

Observed values and change from baseline of ketone bodies will be summarized by treatment group and time point.

Listing with subjects impacted by COVID-19 will be presented. Also, eGFR values will be listed.

Urine Calcium, Glucose and Sodium

The $UCE_{0\text{-}24}$, $UGE_{0\text{-}24}$ and $UNaE_{0\text{-}24}$ will be computed for Days -1, 1, 14 and 28. Observed values and change from baseline (Day -1) of total excreted amount within 24 hours will be summarized by treatment group and day. Descriptive statistics for 24-hour urine volume and fluid intake on Days -1, 1, 14 and 28 will be also presented for observed values and change from baseline.

Statistical analysis for change from baseline in $UGE_{0\text{-}24}$ in the original scale will be performed using MMRM similar to that for PPG $AUEC_{0\text{-}24}$.

Bristol Stool Chart

Total number of stools and percent of stools at each stool type will be summarized by treatment group. Post-treatment highest stool type score will be also derived for each subject, and number and percent of subjects by the highest stool type will be summarized by treatment group and overall. A plot will be created for individual assessments over time.

Other safety parameters may be summarized as appropriate.

6.11 Interim Analysis

An interim analysis is not planned for this study.

6.12 Handling of Dropouts or Missing Data

Missing data will not be imputed. Any PK concentrations reported missing data will be handled according to the specifications in Section 4.2.

6.13 Multicenter Studies

This is a single-center study.

6.14 Examination of Subgroups

None

7 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

There are no changes in the study conduct relative to the study protocol. The protocol specifies that the natural logarithm of the PD parameter values will be analyzed. This SAP has changed to analyze the PD parameters in the original scale, as it is considered more appropriate to assume normal distribution for the PD parameters and analyze change from baseline, which could be negative values, in the original scale.

8 QUALITY CONTROL AND QUALITY ASSURANCE METHODS FOR DATA ANALYSIS

The following steps will be taken to ensure the accuracy, consistency, completeness and reliability of the statistical reports:

- Production of statistical analysis plan and statistical analysis reports in accordance with [redacted] Standard Operating Procedures (SOP) and guidelines.

After database lock, the data will be retrieved from the database using SAS® version 9.4 or higher.