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Clinical Study Protocol

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

PROTOCOL DATE: 29 January 2021

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Akros Pharma Inc.
Clinical Study Protocol

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PROTOCOL NUMBER:	AT662-U-20-003
DATE:	29 January 2021
IND NUMBER:	[redacted]
SPONSOR:	Akros Pharma Inc. 302 Carnegie Center, Suite 300 Princeton, NJ 08540
SPONSOR CONTACT:	[redacted] Akros Pharma Inc [redacted]
MEDICAL MONITOR:	[redacted]

Signature Page

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The signatures below indicate approval of the protocol.

Investigator's Statement of Agreement:

I acknowledge possession of the JTT-662 Investigator's Brochure (IB) and this protocol. Having fully reviewed all the information provided, I consider it ethically justifiable to give the study drug to subjects according to the agreed protocol. I will conduct the study in full accordance with this protocol and all applicable laws and regulations, including but not limited to current Good Clinical Practices.

Investigator _____ _____
(Signature) Date

_____
(Printed Name)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
^{14}C-JTT-662	^{14}C-labeled JTT-662
ADR	Adverse drug reaction
AE	Adverse event
Ae_{total}	Cumulative amount excreted into urine over entire collection interval
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
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
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC_{inf}	Area under the concentration-time curve from the time of dosing to infinity
AUC_{last}	Area under the concentration-time curve from the time of dosing to the last quantifiable time point
AUC_{tau}	Area under the concentration-time curve during a dosing interval
AUC_{0-24}	Area under the concentration-time curve from the time of dosing until the 24-hour time point
AUEC	Area under the observed effect-time curve
$AUEC_{0-4}$	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
BCRP	Breast cancer resistance protein
βhCG	Human chorionic gonadotropin
BMI	Body mass index
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CGGM	Congenital glucose-galactose malabsorption
[redacted]	
CI	Confidence interval
CL_F	Apparent oral clearance of drug following extravascular administration (total body clearance)
CL_r	Renal clearance
COVID-19	Coronavirus Disease
C_{max}	Maximum concentration
C_{trough}	Trough concentration during multiple dosing prior to next dose
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	

Abbreviation	Definition
CV	Coefficient of variation
CYP	Cytochrome P450
ΔAUCs	Area under the concentration-time curve of changes
DPP-4	Dipeptidyl peptidase-4
ECG	Electrocardiogram
eGRF	Estimated glomerular filtration rate
fe_{total}	Fraction of systemically available drug excreted into the urine over entire collection interval
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GLUT	Glucose transporter
GMR	Geometric mean ratio
GSIS	Glucose-stimulated insulin secretion
HbA1c	Glycosylated hemoglobin
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
[redacted]	
HR	Heart rate
hr	Hour(s)
IB	Investigator's Brochure
IC_{50}	Half maximal (50%) inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDF	International Diabetes Federation
IMP	Investigation medicinal product
IP	Inorganic phosphorous
IR	Insulin resistance
IRB	Institutional Review Board
λ_z	Apparent elimination rate constant in the terminal phase by non-compartmental analysis
MAD	Multiple ascending dose
[redacted]	
NOAEL	No observed adverse effect level
OGTT	Oral glucose tolerance test
PCS	Potentially clinically significant
PD	Pharmacodynamic(s)
[redacted]	
PK	Pharmacokinetic(s)
PPG	Postprandial glucose

Abbreviation	Definition
PR	Interval from beginning of the P wave to the beginning of the QRS complex in the frontal plane
[redacted]	
QD	Once daily
QRS	Duration of QRS complex in the frontal plane
QT	Interval from beginning of the QRS complex to end of the T wave in the frontal plane
QTcF	Fridericia-corrected QT interval
RBC	Erythrocytes (red blood cells)
RR	Interval from beginning of the QRS complex in the frontal plane to the next QRS complex
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SGLT	Sodium glucose co-transporter
SGLT1	Sodium glucose co-transporter 1
SGLT2	Sodium glucose co-transporter 2
SOC	System organ class
SD	Standard deviation
$t_{1/2}$	Elimination half-life associated with the terminal slope (λ_z) of a semilogarithmic concentration-time curve
$t_{1/2(eff)}$	Effective half-life
T2DM	Type 2 diabetes mellitus
TEAE	Treatment-emergent adverse event
t_{max}	Time to reach peak or maximum concentration following drug administration
[redacted]	
UGE_{0-24}	Urinary glucose excretion from the time of dosing until the 24-hour time point
UCE_{0-24}	Urinary calcium excretion from the time of dosing until the 24-hour time point
$UNaE_{0-24}$	Urinary sodium excretion from the time of dosing until the 24-hour time point
V_z_F	Volume of distribution during terminal phase (λ_z) following extravascular administration
WBC	Leukocytes (white blood cells)

Protocol Synopsis

STUDY 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
CLINICAL PHASE	Phase 1
STUDY DURATION	Study duration will be approximately 11 weeks per subject: • Up to a 28-day Screening Period • A 38-day Admission Period • An approximately 7-day Follow-up Period
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 pharmacokinetics (PK) of multiple oral doses of JTT-662 in subjects with T2DM on metformin monotherapy • To evaluate the pharmacodynamics (PD) of multiple oral doses of JTT-662 in subjects with T2DM on metformin monotherapy

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.
NUMBER OF SUBJECTS TO BE RANDOMIZED	Approximately 36 subjects with T2DM are planned to be randomized 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.

KEY ELIGIBILITY CRITERIA	1. Male or female, 18 to 65 years (inclusive) of age at the Screening Visit; 2. Subjects with a documented diagnosis of T2DM of at least 12 weeks prior to the Screening Visit; 3. Subjects on a stable oral dose (i.e., the dose and schedule of administration has not changed) of metformin monotherapy for at least 12 weeks prior to the Screening Visit and until Day -3; 4. Subjects with a glycosylated hemoglobin (HbA1c) value of ≥6.5% and ≤10.0% at the Screening Visit; 5. Subjects with a fasting plasma glucose (FPG) value of ≤280 mg/dL at the Screening Visit and on Day -3; 6. Subjects with a body mass index (BMI) of 25 to 40 kg/m^2 (inclusive) at the Screening Visit.
INVESTIGATIONAL PRODUCT **FORMULATION,** **PLANNED DOSAGES,** **ROUTE AND TIME OF ADMINISTRATION**	JTT-662 1 mg and 10 mg tablets (identical in appearance) 5 mg, 10 mg and 20 mg Oral QD administration for 28 days from Day 1 through Day 28 following an overnight fast (for at least 10 hours) and 30 minutes before the start of a standard breakfast
REFERENCE PRODUCT, **FORMULATION,** **PLANNED DOSAGES,** **ROUTE AND TIME OF ADMINISTRATION**	Placebo Tablets (identical in appearance to JTT-662 Tablets) Not applicable Single oral administration on Day -1 following an overnight fast (for at least 10 hours) and 30 minutes before the start of a standard breakfast. Oral QD administration for 28 days from Day 1 through Day 28 following an overnight fast (for at least 10 hours) and 30 minutes before the start of a standard breakfast.
EVALUATION CRITERIA	Safety Assessments: • Adverse events (AEs), clinical laboratory safety tests (e.g., hematology, serum biochemistry, coagulation), vital signs, 12-lead electrocardiogram (ECG), Bristol Stool Chart findings, ketone bodies, [redacted] FPG and urinary calcium, sodium and glucose excretion

EVALUATION CRITERIA (CONT'D)	Pharmacokinetic Assessments: • JTT-662 in plasma: maximum concentration (C_{max}), trough concentration during multiple dosing prior to next dose (C_{trough}), time to reach peak or maximum concentration following drug administration (t_{max}), area under the concentration-time curve during the dosing interval (AUC_{tau}), volume of distribution during terminal phase (V_z_F), apparent oral clearance of drug following extravascular administration (total body clearance) (CL_F), elimination half-life associated with the terminal slope (λ_z) of a semilogarithmic concentration-time curve ($t_{1/2}$), effective half-life ($t_{1/2(eff)}$), accumulation ratio of maximum concentration (AR_{Cmax}) and accumulation ratio of area under the concentration-time curve during a dosing interval (AR_{AUCtau}), and accumulation ratio based on trough concentration ($AR_{Ctrough}$) Pharmacodynamic Assessments: • Postprandial glucose (PPG): area under the observed effect-time curve from the start of breakfast until the 4-hour time point ($AUEC_{0-4}$) [redacted]
SAFETY ANALYSIS	The safety evaluation will summarize recorded AEs, Bristol Stool Chart findings, clinical safety laboratory test results, vital signs, 12-lead ECG parameters and any other parameters deemed necessary for safety assessment.

PHARMACOKINETIC ANALYSIS	Appropriate PK parameters for JTT-662 (e.g., C_{max}, t_{max}, apparent elimination rate constant in the terminal phase by non-compartmental analysis [λ_z], $t_{1/2}$) will be derived by non-compartmental analysis using Phoenix® WinNonlin® (Version 6.4 or higher). Additional PK parameters may be calculated, as appropriate. Appropriate analyses to assess dose proportionality of JTT-662 exposure will be performed using a power model.
PHARMACODYNAMIC ANALYSIS	Pharmacodynamic effects of JTT-662 on PPG will be assessed.
STATISTICAL METHODS	Appropriate statistical analysis will be performed using the computer program SAS for Windows® (SAS Institute Inc., Cary, NC 27512-8000, USA).

1 INTRODUCTION

1.1 Background

1.1.1 Type 2 Diabetes Mellitus

As published by the International Diabetes Federation (IDF) in 2019, it is estimated that 463 million people around the world have diabetes, and unless effective measures are taken, the number of patients with diabetes is expected to increase continuously in the future and to reach 700 million by 2045.[1] Since around 90% of diabetic patients are classified to have non-insulin-dependent (type 2) diabetes mellitus (T2DM), measures to treat T2DM are urgently needed around the world, and there is a continuing strong demand for the development of new treatment drugs.

Type 2 diabetes mellitus (T2DM) develops due to insufficient insulin action resulting from impaired insulin secretion and insulin resistance (IR) induced by interactions of various genetic factors and additional environmental factors such as overeating, lack of exercise, obesity and stress. Postprandial hyperglycemia is one of the earliest abnormalities of glucose homeostasis associated with T2DM and is exaggerated in diabetic patients with fasting hyperglycemia.[2-5] The chronic hyperglycemic state promotes the occurrence and development of diabetic complications including microvascular complications (retinopathy, nephropathy and neuropathy) and macrovascular complications (ischemic heart disease, cerebrovascular disorder and arteriosclerosis obliterans).[6]

1.1.2 Treatment of Type 2 Diabetes Mellitus

There are several epidemiologic studies indicating that postprandial hyperglycemia can be a critical risk factor of macroangiopathy in patients with diabetes and abnormal glucose tolerance.[7-12] An intervention study of acarbose, an α-glucosidase inhibitor (α-GI), and a meta-analysis including multiple clinical studies have shown that amelioration of postprandial hyperglycemia can suppress development of diabetes mellitus and further decrease the risk of macroangiopathy.[13,14] These results have revealed the importance of ameliorating postprandial hyperglycemia. There is a growing recognition that postprandial hyperglycemia should be controlled from an early stage of diabetes in parallel with glycosylated hemoglobin (HbA1c).

For glycemic control in patients with T2DM, various drugs such as metformin, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists and basal insulin are currently used, and appropriate combination drug therapies using drugs with different mechanisms of action are then implemented.[15] Currently available oral hypoglycemic drugs that ameliorate postprandial hyperglycemia are α-GIs (delay carbohydrate absorption), meglitinides (enhance acute insulin secretion), DPP-4 inhibitors (enhance glucose-stimulating insulin secretion by increasing the GLP-1 levels) and SGLT2 inhibitors (block glucose reabsorption in the proximal renal tubule). The α-GIs have a weaker effect on lowering HbA1c compared with other oral hypoglycemic drugs, and cause gastrointestinal (GI) symptoms such as diarrhea, abdominal distention and flatus. Meglitinides have a risk of causing hypoglycemia, because they enhance

insulin secretion. In addition, after the pathological condition progresses to an insulin-dependent state, they become less effective. Furthermore, these drugs have to be taken three times daily before each meal, leading to low drug compliance rates. The DPP-4 inhibitors and SGLT2 inhibitors do not have a very strong ameliorating effect on postprandial hyperglycemia. Based on these, there is a strong demand for new oral hypoglycemic drugs that ameliorate postprandial hyperglycemia, decrease HbA1c levels more effectively, have a superior safety profile, allow once daily (QD) dosing regimens and are widely effective regardless of the stage of T2DM.

1.1.3 Sodium Glucose Co-Transporter 1 Inhibitor

Glucose is transported intracellularly or extracellularly by cell membrane proteins called sodium glucose co-transporters (SGLTs) and glucose transporters (GLUTs). Sodium glucose co-transporters are involved in the active transport of glucose against the concentration gradient coupling with sodium transport, and GLUTs facilitate diffusion transport along the concentration gradient. It has been reported that these transporter families have multiple isoforms that differ in their tissue expressions and affinities for monosaccharides.[16] Sodium glucose co-transporter 1 (SGLT1), which was cloned in 1987, is a 73-kDa membrane protein consisting of 664 amino acid residues and is mainly expressed in the brush border membrane of the small intestine. It plays a critical role in transporting glucose and galactose from the luminal surface to the epithelial cells in the small intestine. It is also expressed in the renal tubule and is partially involved in reabsorption of glucose filtered in the glomeruli.[16] Meanwhile, glucose filtered in the glomerulus is reabsorbed in the renal tubule mainly by SGLT2.[16] It has been reported that the expression of messenger ribonucleic acid and protein of SGLT1 in the small intestine is increased in patients with T2DM, Otsuka Long-Evans Tokushima Fatty rats (a type 2 diabetic model) and streptozotocin-induced diabetic rats with chronic hyperglycemia. This suggests that glucose absorption from the GI tract is enhanced in diabetes mellitus.[17-19] Congenital glucose-galactose malabsorption (CGGM) is caused by a defect in glucose and galactose transport in the brush border membrane of the small intestine due to an SGLT1 dysfunctional mutation. Congenital glucose-galactose malabsorption is characterized by watery diarrhea similar to the diarrhea that can develop in infants following ingestion of breast milk or regular infant formulas, both of which contain glucose and galactose. It is known that such severe diarrhea can be controlled with fructose-based formulas that do not contain glucose or galactose.[20] Elevation of plasma glucose levels after glucose loading was completely prevented in patients with CGGM, indicating that SGLT1 plays a critical role in absorption of dietary glucose in the intestine.[21,22] It is assumed that SGLT1 inhibition in the small intestine will reduce the absorption of dietary glucose effectively. Therefore, SGLT1 inhibitors are expected to prevent postprandial glucose (PPG) elevations independent of endogenous insulin effect by modulating the glucose absorption in the small intestine. This characteristic suggests that SGLT1 inhibitors have a low potential of causing hypoglycemia, body weight gain and burden on β-cell function, and thus provides an opportunity of combination therapies with currently available drugs for the treatment of T2DM.

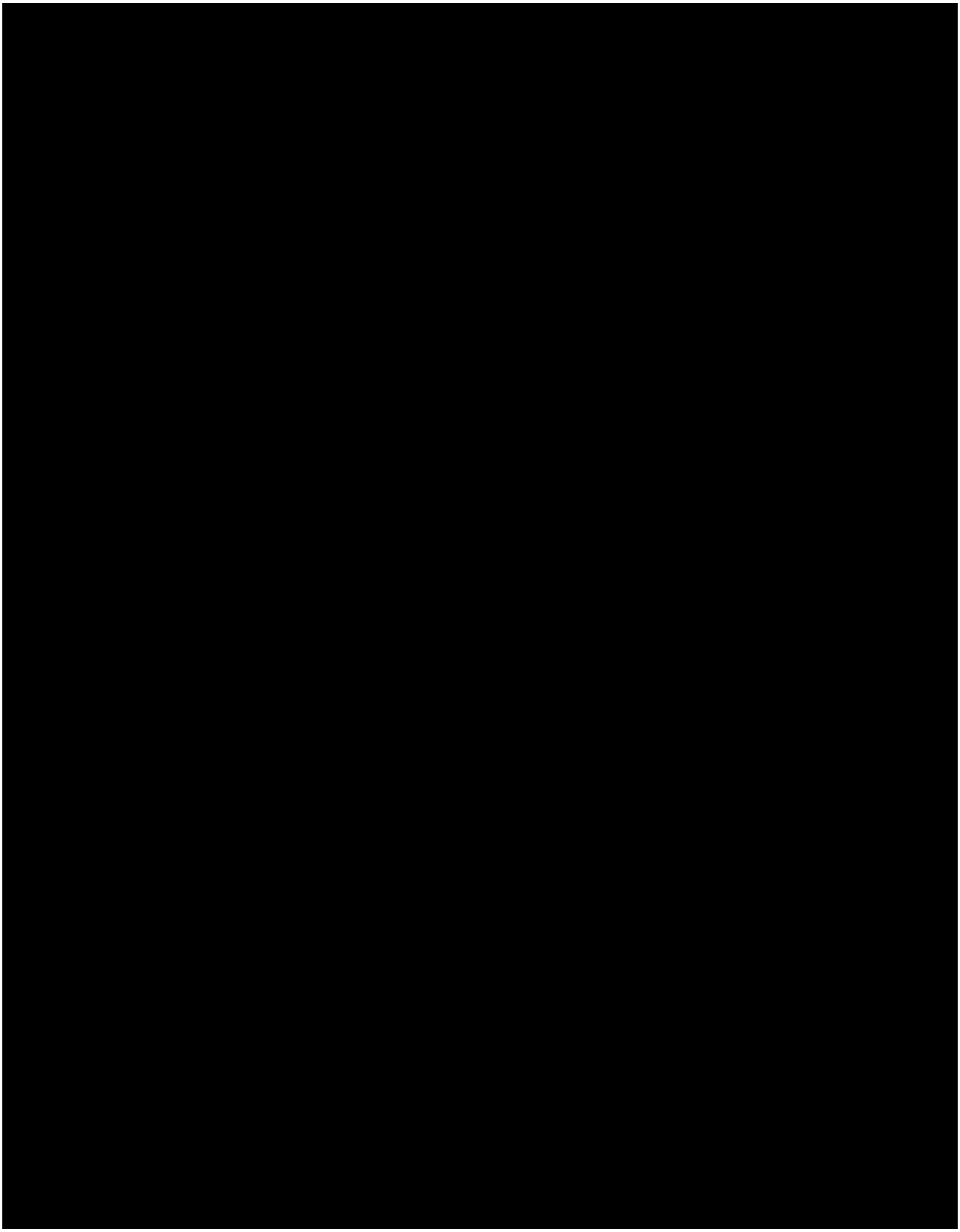
1.2 JTT-662

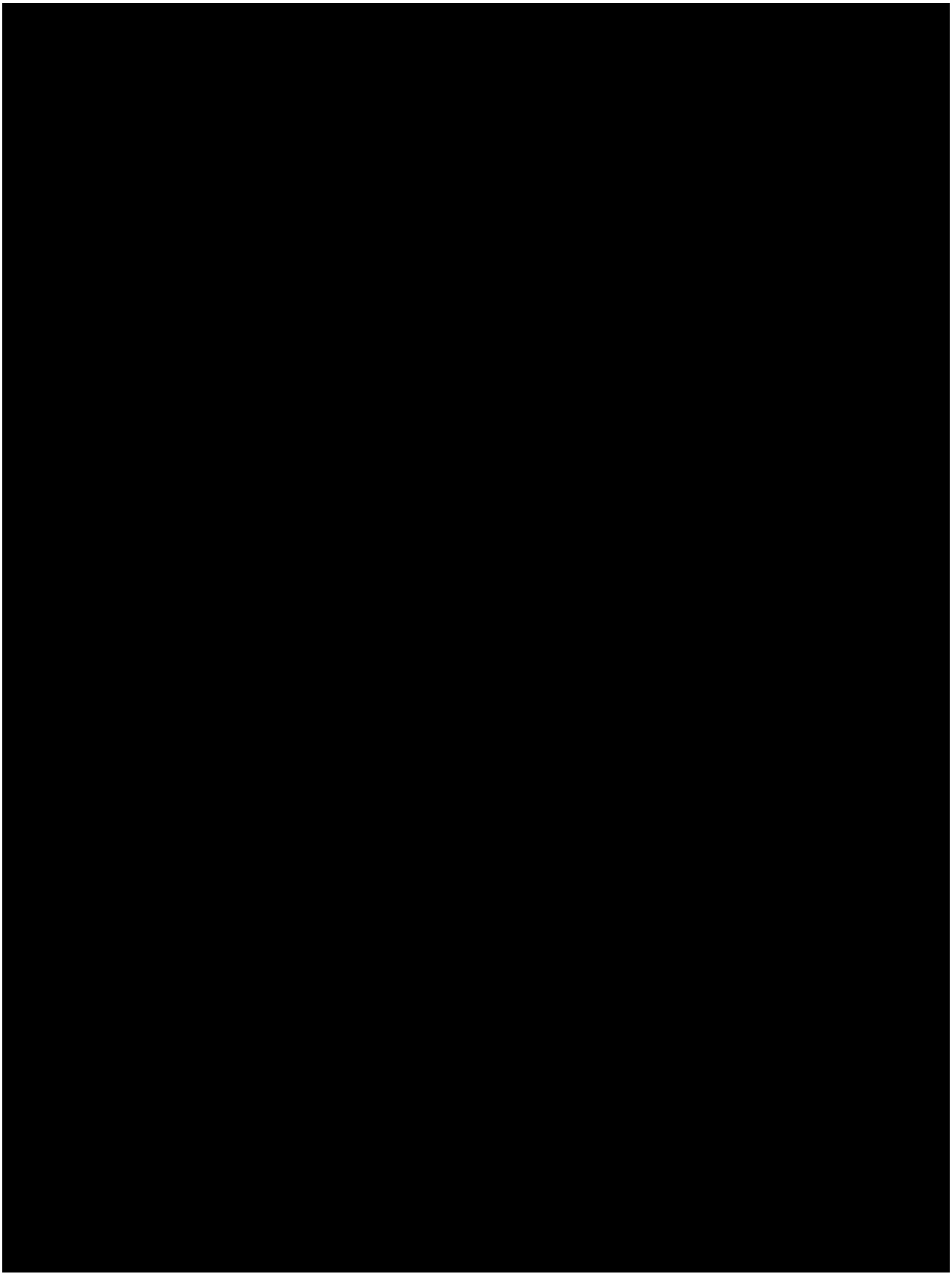
[redacted]

A brief summary of the nonclinical findings to date is included below. Additional details are described in the JTT-662 Investigator's Brochure (IB).

1.2.1 Nonclinical Information

[redacted]





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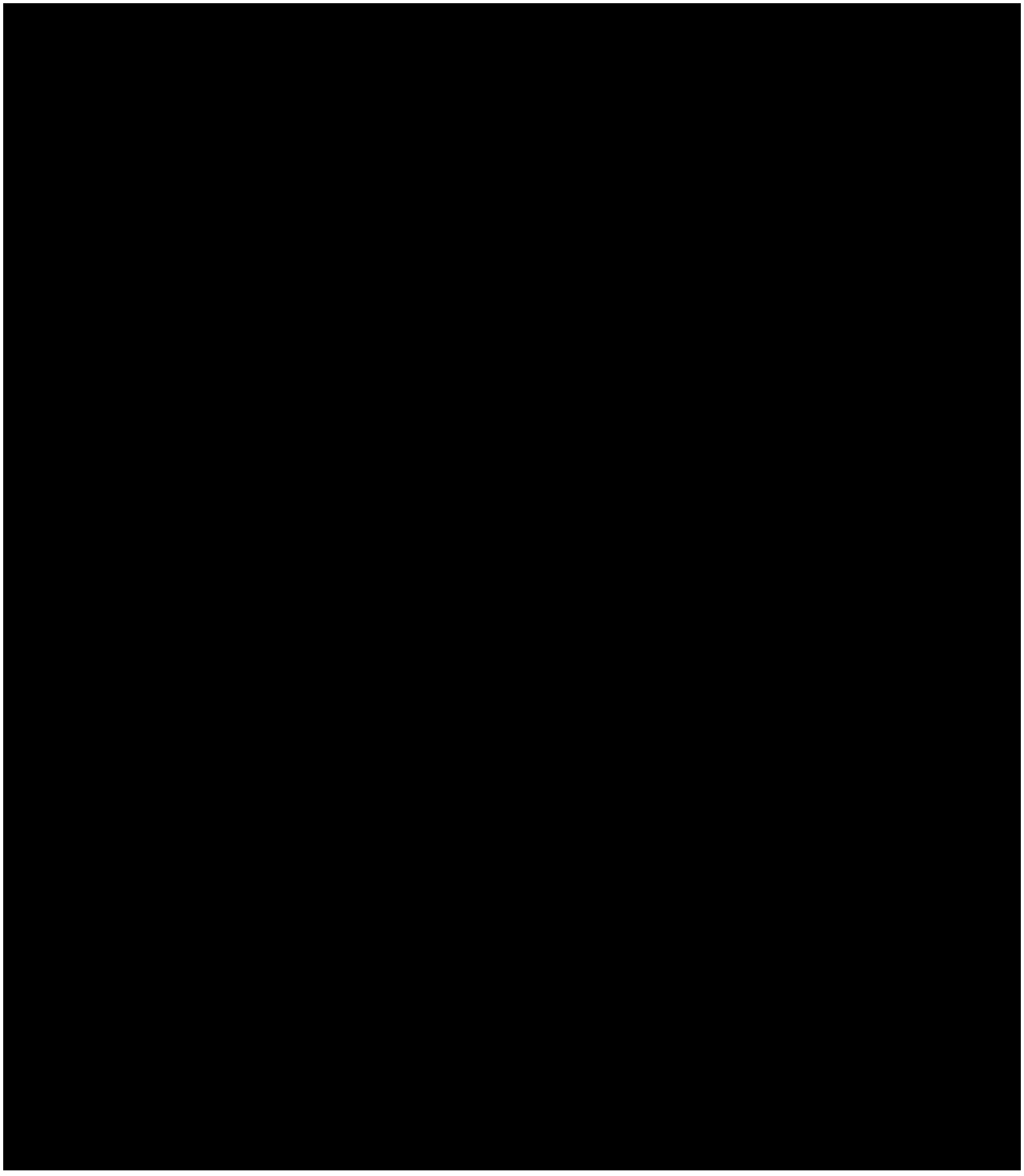
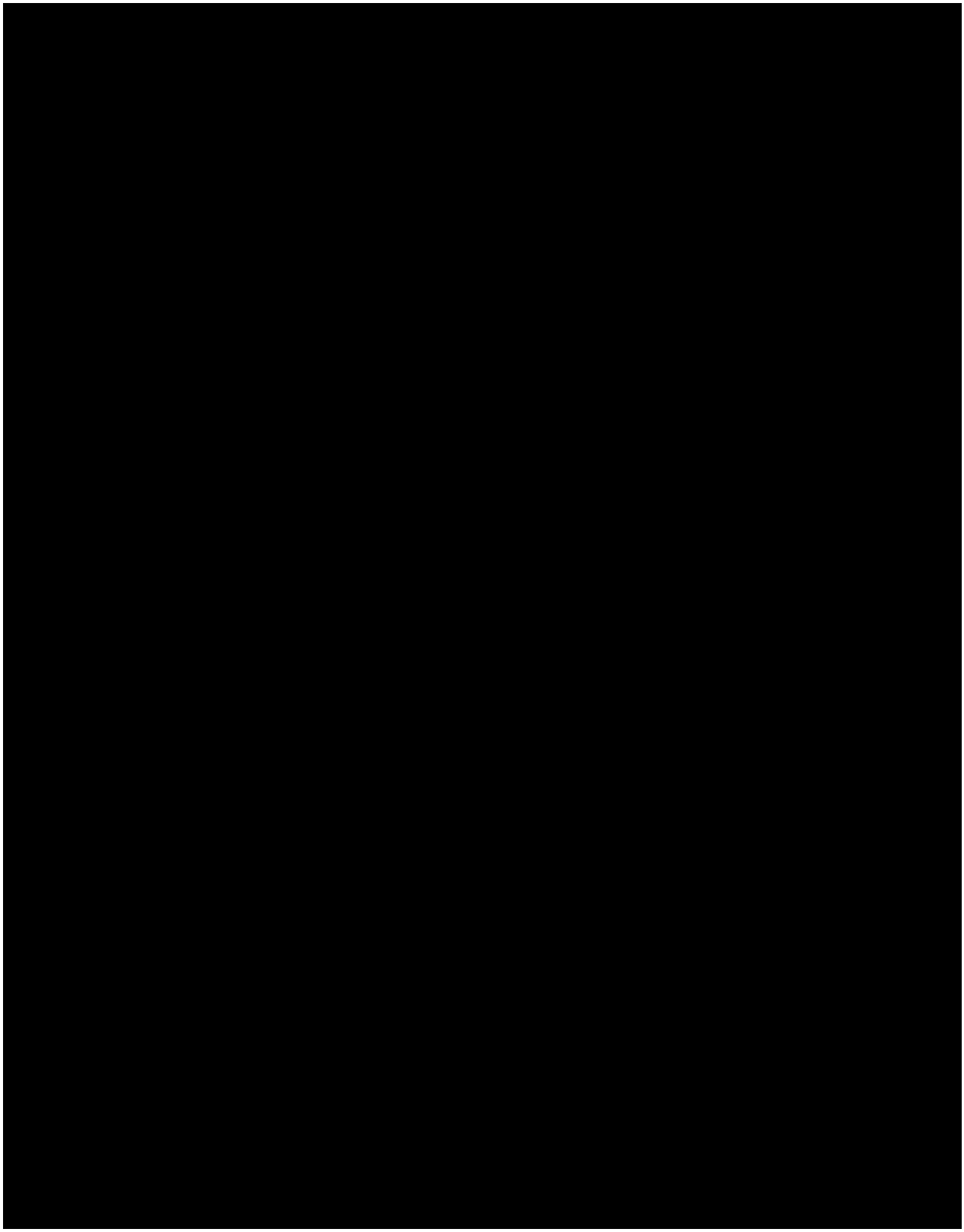
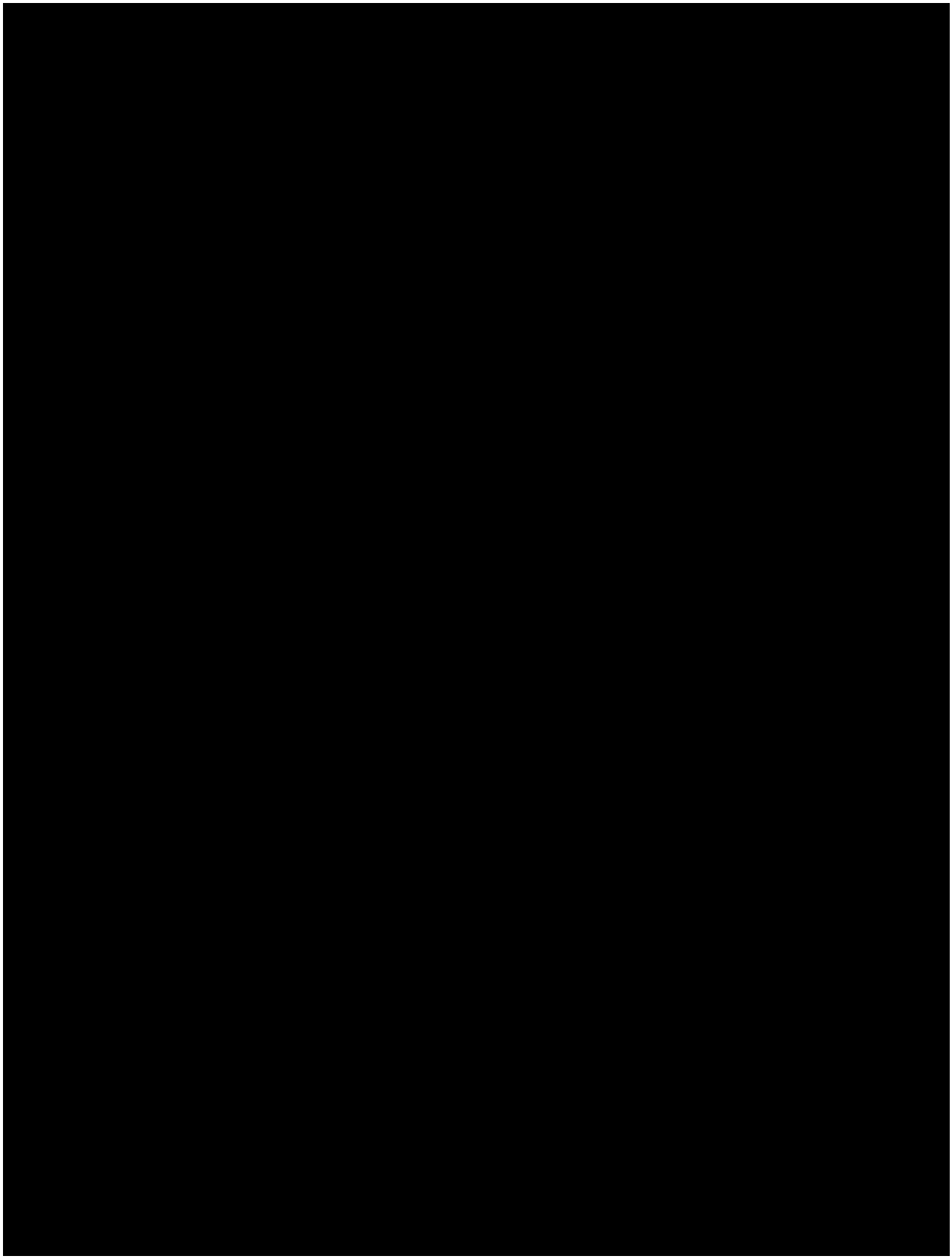
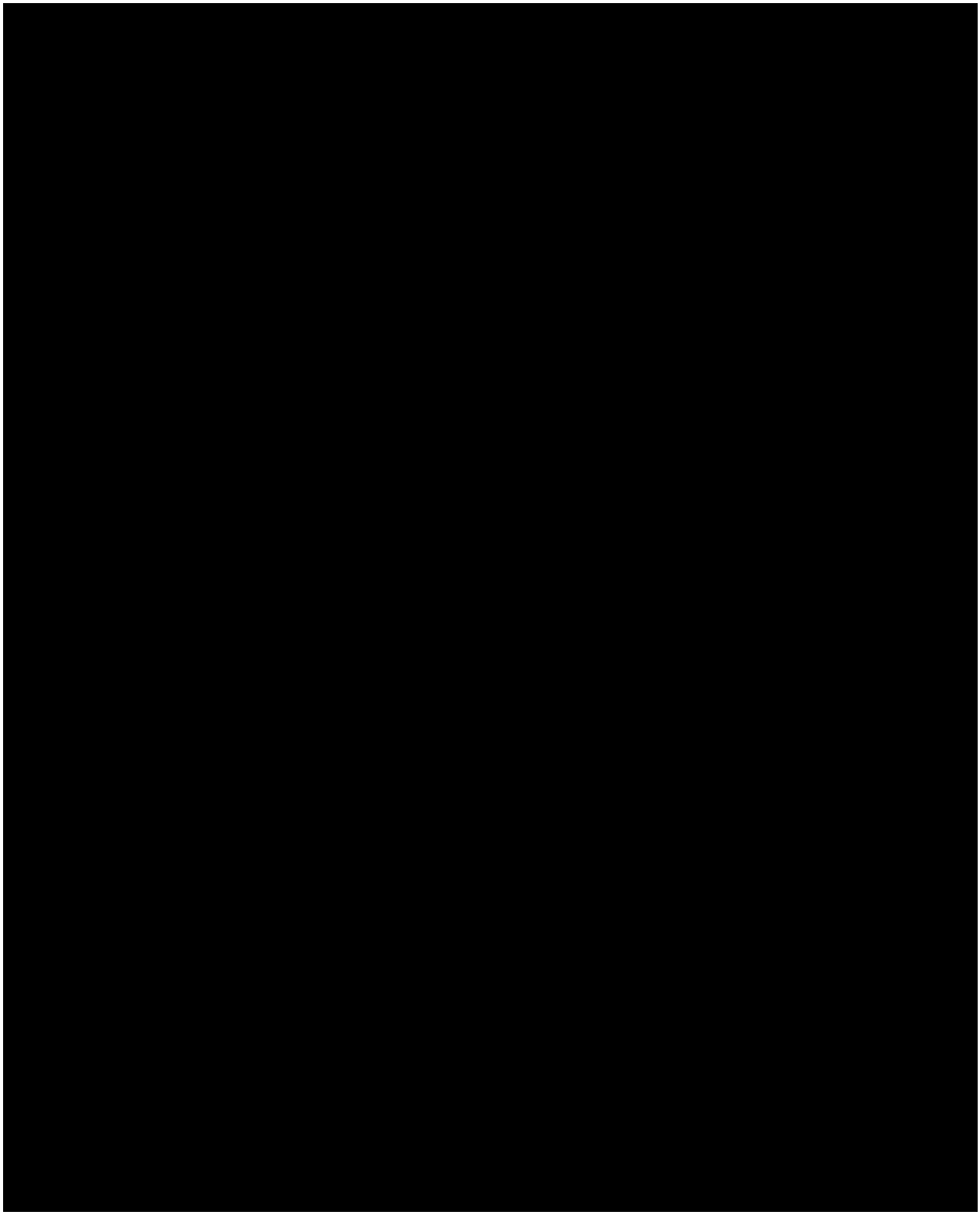
1.2.2 Clinical Information

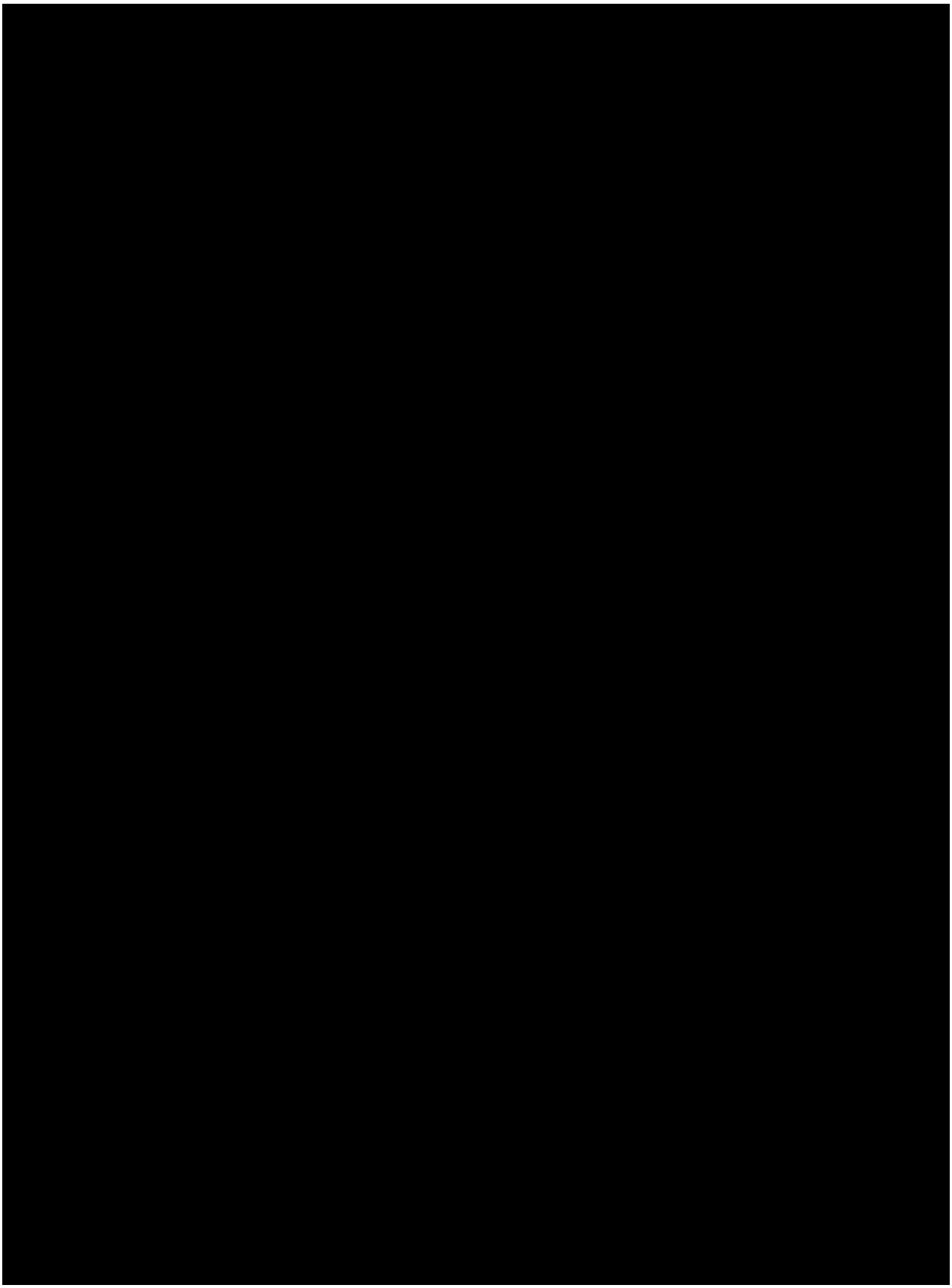
[redacted]











[redacted]

1.3 Justification of Dose Selection

The objective of this single-blind, randomized, placebo-controlled, multiple dose study is to evaluate the safety, tolerability, PK and pharmacodynamics (PD) of JTT-662 following QD administration for 28 days in subjects with T2DM on metformin monotherapy.

The planned JTT-662 doses for this study are 5 mg QD, 10 mg QD and 20 mg QD, [redacted]

[redacted]

The secondary objective of this study is to evaluate the effect of multiple doses of JTT-662 on PPG. [redacted]

In this study, to assure safety, the subjects will remain in-house at the site for the duration of dosing and for approximately 7 days after the last dose, under the direct oversight by the Investigator and the continuous supervision of the site research staff. During this period, extensive safety assessments, including AE collection and evaluation, laboratory, 12-lead ECG and vital sign assessments will be carried out to identify and address any emerging safety signals. After completion of the two lower dose cohorts, dose escalation to the highest planned dose level will be implemented following careful review of the appropriate safety parameters (i.e., AEs, laboratory safety tests, 12-lead ECG and vital sign parameters), PK data (up to Day 29 for Cohort 2) and PD data including exposure comparison with nonclinical data, dose proportionality and PD assessments from the previous cohorts.

2 STUDY OBJECTIVES

- To assess the safety and tolerability of multiple oral doses of JTT-662 in subjects with 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 INVESTIGATIONAL PLAN

3.1 Number of Sites and Subjects

Approximately 36 male and female subjects with T2DM are planned to be randomized in the study at a single site. To ensure an adequate number of completers, replacement subjects may be enrolled in the study at the discretion of the Sponsor, as appropriate.

3.2 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 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.

3.3 Selection of Study Population

In response to the ongoing coronavirus disease (COVID-19) pandemic, the site will make every effort to proactively avoid enrolling subjects suspected of or positive for COVID-19. Special policies to protect the study participants and staff at the site against COVID-19 will be developed and agreed upon with the Sponsor prior to the start of the study. The specific procedures regarding this will be described in appropriate separate documents.

Written informed consent must be obtained prior to performing any study-related procedures. A copy of the informed consent will be provided to each subject.

3.3.1 Inclusion Criteria

To qualify for the study, the subject must satisfy the following criteria:

1. Male or female, 18 to 65 years (inclusive) of age at the Screening Visit;
2. Subjects with a documented diagnosis of T2DM of at least 12 weeks prior to the Screening Visit;
3. Subjects on a stable oral dose (i.e., the dose and schedule of administration has not changed) of metformin monotherapy for at least 12 weeks prior to the Screening Visit and until Day -3;
4. Subjects with a HbA1c value of ≥6.5% and ≤10.0% at the Screening Visit;
5. Subjects with a FPG value of ≤280 mg/dL at the Screening Visit and on Day -3;
6. Subjects with a body mass index (BMI) of 25 to 40 kg/m^2 (inclusive) at the Screening Visit;
7. Subjects who have clinical laboratory test results (excluding glucose-related parameters) clinically acceptable to the Investigator at the Screening Visit and on Day -3;
8. Females may participate if they meet one of the following criteria:
   - surgically sterile (e.g., hysterectomy, bilateral salpingectomy, bilateral oophorectomy), or
   - post-menopausal, as defined by permanent cessation of menstruation for ≥12 months without an alternative medical cause at the Screening Visit.

   All other females will be considered of childbearing potential and must agree to be compliant with either:
   a) practice sexual abstinence*, or
   b) have same-sex partner and not planning a pregnancy, or
   c) use one highly effective contraceptive method of birth control, which includes intrauterine devices, male partner sterilization (at least six months prior to screening with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate and the vasectomized male partner should be the sole partner for that subject), tubal ligation, intrauterine hormone-releasing systems, or
   d) use a double-barrier method of birth control, which includes a combination of male condom with either diaphragm, cervical cap or vaginal sponge, all with spermicide;

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and concomitant use of a female and male condom are not acceptable methods of contraception.

The above-described contraception methods must be maintained during treatment and until 30 days after the last dose of study drug.

9. Males may participate if they agree to one of the following criteria:
   - practice sexual abstinence, have same-sex partner, use a barrier contraceptive method with spermicide (for the duration of the treatment period and until 30 days after the last dose of study drug), or
   - be sterilized at least six months prior to screening (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

   Notes: Males who are sterile or who have sterile or post-menopausal female partners are not required to use contraception with that partner. Males must not donate sperm for the duration of the study and for 30 days after the last dose of study drug.

   If the female partner is of childbearing potential, she must agree to use at least one of the acceptable forms of birth control listed above (in addition to the method utilized by the male subject) for the duration of the study and for at least 30 days after the subject takes the last dose of study drug.

[redacted]

11. Able and willing to give written informed consent.

3.3.2 Exclusion Criteria

The following criteria will exclude a subject from participating in the study:

1. Subjects who have a known history or presence of type 1 diabetes mellitus, Maturity Onset Diabetes of the Young (MODY) or secondary forms of diabetes (i.e., diabetes that results as a consequence of another medical condition);
2. Subjects who have had a dose change or change in schedule of administration of metformin monotherapy from the Screening Visit through Day -3;
3. Subjects who test positive for COVID-19 at the Screening Visit or on Day -3;
4. Subjects who have a known history or presence of diabetic complications including: retinopathy, nephropathy, neuropathy, gastroparesis, ketoacidosis, lactic acidosis, hyperosmolar coma or clinically significant foot ulcers or blisters;
5. Subjects with acute coronary syndrome (e.g., myocardial infarction or unstable angina), clinically significant cardiac arrhythmia, New York Heart Association class II through IV heart failure, history of percutaneous coronary intervention (or similar procedures), history of coronary artery bypass graft surgery, cerebrovascular accident or transient ischemic attack within 24 weeks prior to Screening Visit or a history of severe peripheral vascular disease (e.g., manifested by claudication);
6. Subjects with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.0 × upper limit of normal (ULN) or total bilirubin >1.5 × ULN at the Screening Visit;

7. Subjects who have taken anti-diabetic medications (other than metformin) or medications that act mainly in the GI tract (e.g., orlistat, acarbose) within 12 weeks prior to the Screening Visit or from the Screening Visit to Day -3;
8. Subjects who have taken non-diabetic medications (e.g., diuretics and sympathomimetics), which may affect glucose homeostasis, within 12 weeks prior to the Screening Visit or from the Screening Visit to Day -3, *except* if the subject has been on a stable dose from 12 weeks prior to the Screening Visit and from the Screening Visit to Day -3;
9. Subjects who have participated in a clinical study involving an investigational drug or device within 30 days, five half-lives, or twice the duration of the biological effect of the investigational product, if known (whichever is longer) prior to the Screening Visit;
10. Subjects with uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥95 mmHg) at the Screening Visit;

    Notes: Up to three repeat measurements are allowed at the discretion of the Investigator. Subjects who are taking anti-hypertensive medication(s), must be on a stable dose for at least 12 weeks prior to the Screening Visit and from the Screening Visit through Day -3.
11. Subjects who have taken systemic steroids within 2 weeks prior to Day -3;

    Note: Inhaled, intranasal and topical corticosteroids are permitted as needed.
12. Subjects who have used medications, which could affect gastric motility or result in diarrhea, within 2 weeks prior to Day -3;
13. Smokers or subjects who have used tobacco or nicotine-containing products within 12 weeks prior to the Screening Visit or from the Screening Visit to Day -3;
14. Subjects who report a general pattern of two or more episodes of Type 6 or 7 bowel movements per day, based on Bristol Stool Chart definitions provided at the Screening Visit;
15. Subjects who report a general pattern of two or more episodes of Type 6 or 7 bowel movements per day within 3 days prior to Day -3, based on Bristol Stool Chart definitions provided at the Screening Visit;
16. Subjects who cannot comply with the planned study menu due to clinically significant food allergies or intolerances;
17. Subjects who have diets incompatible with the planned study menu;
18. Subjects who have recent significant changes in weight (i.e., ≥7%) within 12 weeks prior to Day -3;
19. Subjects with a known pre-existing condition or GI surgery interfering with normal GI anatomy or motility, and/or hepatic function (with the exception of Gilbert's syndrome), biliary function (e.g., cholecystectomy) that could interfere with the absorption, metabolism, and/or excretion of the study drug;
20. Subjects with a history or presence of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell carcinoma of the skin or cervical carcinoma *in situ* within 6 months prior to Screening Visit;

21. Subjects with a history or presence of any lymphoproliferative disorders (e.g., Epstein Barr Virus related lymphoproliferative disorder, lymphoma, leukemia, multiple myeloma) or signs and symptoms suggestive of current lymphatic disease, such as Hodgkin's or Non-Hodgkin's lymphoma;
22. Subjects with impaired renal function defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 using the 4-variable Modification of Diet in Renal Disease equation) at the Screening Visit:

    eGFR (mL/min/1.73 m^2) = 175 × Serum Creatinine $^{-1.154}$ × age $^{-0.203}$ × 1.212 (if subject is black) × 0.742 (if female).
23. Subjects who test positive for hepatitis B virus surface antigen (HBsAg), hepatitis C virus (HCV) antibodies or human immunodeficiency virus (HIV) antibodies at the Screening Visit;
24. Subjects with a history of drug or alcohol abuse within 24 weeks prior to the Screening Visit;

    Notes: Alcohol abuse is defined as an average weekly intake of >21 drinks for males or >14 drinks for females. One drink is equivalent to 12 ounces (360 mL) of beer, 5 ounces (150 mL) of wine or 1.5 ounces (45 mL) of hard liquor.
25. Subjects who have a positive test result for drugs of abuse or alcohol at the Screening Visit or on Day -3, unless results are due to a medically relevant reason;
26. Females who are pregnant as determined by a positive serum beta human chorionic gonadotropin (βhCG) test result at the Screening Visit or on Day -3;
27. Females who are lactating at the Screening Visit or on Day -3;
28. Subjects who have donated more than 500 mL of blood or received any blood or blood products within 8 weeks prior to Day -3;
29. Subjec who have previously participated in a JTT-662 study [redacted];
30. Subjects with any other condition that, in the opinion of the Investigator, would compromise the safety of the subjects or confound the study objectives;
31. Subjects who are unwilling or unable to comply with the requirements of the study.

3.4 Discontinuation of Subjects from the Study/Study Drug

A subject may prematurely discontinue from the study/study drug administration under the following conditions:

- Withdrawal by Subject: subjects have the right to withdraw from the study at any time. However, if a subject withdrew because of an AE, the reason for discontinuation should be documented as an AE.
- Investigator Decision: the Investigator decides a subject should be discontinued. The reason for the decision should be documented.
- Adverse Event: a medical condition(s), requiring study drug discontinuation, whether or not related to the study drug (e.g., COVID-19).
- Non-compliance with Study Drug

- Protocol Deviation: the subject is non-compliant with protocol requirements, as determined by Akros or the Investigator. These are limited to important protocol deviations (e.g., Good Clinical Practice [GCP] deviations, important deviations related to the inclusion or exclusion criteria).
- Lost to Follow-up
- Death
- Study Terminated by Sponsor: the sponsor may suspend or terminate the study or part of the study at any time for any reason (see Section 3.5).
- Pregnancy
- Other: (e.g., subjects who have taken placebo on Day -1 but are not randomized on Day 1 into Cohort 3 will be discontinued from the study).

Subjects who test positive for COVID-19 after study drug administration on Day 1 will be discontinued from study drug and appropriate follow-up actions will be taken as per the site's standard operating procedures and COVID-19 management guidelines.

Subjects who discontinue the study/study drug after placebo adminstration on Day -1 but before randomization on Day 1 will be discharged from the site at the discretion of the Investigator. These subjects will be requested to complete a follow-up telephone call from the site within 7 days after being discontinued from the study. The follow-up call will be conducted to assess the general health of the subject. In addition, the subject will be asked to report if any AEs occurred, if any medication was taken and if there were any changes to medications during the 7 day period after the subject was discontinued from the study.

Subjects who discontinue the study/study drug after study drug administration on Day 1 will be requested to undergo all procedures described for Day 35 as soon as possible after the last dose of study drug. Additionally, these subjects will be requested to return to the site and complete all procedures described for the Follow-up Visit approximately 14 days after the last dose of study drug.

For all early discontinued subjects (after study drug administration on Day 1), every effort will be made to collect at least three blood samples for JTT-662 PK assessments at approximately 3-hour intervals, starting as close as possible to the time when the study drug was discontinued.

Any subject withdrawn from study drug due to an AE, SAE or clinically significant abnormal laboratory test result will be evaluated by the Investigator. The subject will be treated and/or followed-up until the symptoms or laboratory values have either resolved or are assessed as stable by the Investigator.

3.5 Study Suspension and Termination

The sponsor may suspend or terminate the study at any time for any reason, including decisions made by the Investigator, Medical Monitor and Sponsor based on the review of the safety and/or PK data.

Dosing will be suspended, or escalation to Cohort 3 will be postponed depending on the review of the information by the Investigator, Medical Monitor and the Sponsor, if any of the following criteria are met:

1. A serious adverse drug reaction (i.e., SAE considered related to JTT-662) develops in one subject;
2. Severe non-serious AEs considered related to JTT-662 develop in two subjects in the same cohort, either within or not within the same system-organ-class.

3.6 Study Procedures

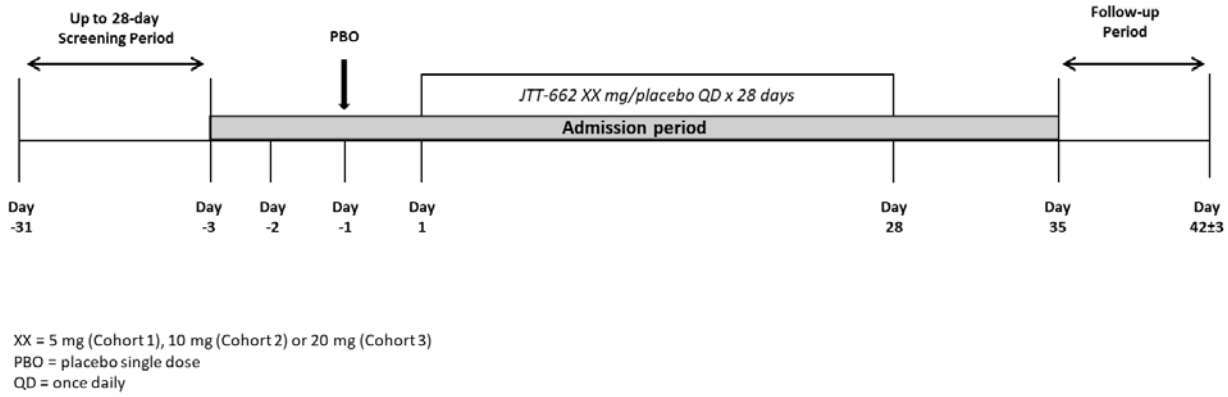


Figure 1. Planned Study Schema

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			
[redacted]																			
Bristol Stool Chart Fecal Assessment	X	X	←																→
Meals		X	X	X	X	X	X			X						X		X	
Placebo Administration									X										
Calcium, Sodium and Glucose Urine Collection[d]									←						→		←		
[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, plasma glucose [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 [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 for [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]							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 [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 for [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 7 and 10 only.

Table 4. Schedule of Study Procedures (Day 16 through 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 [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 for [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)																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.

3.6.1 Informed Consent

Written informed consent must be obtained prior to performing any study-related procedures. A copy of the informed consent will be provided to the subject.

3.6.2 Screening Period

Day -31 to Day -4

At the Screening Visit, subjects should arrive to the site under the fasted condition (overnight fast, at least 10 hours prior to blood and urine sample collection). If a subject arrives for the visit not having fasted (for at least 10 hours prior to blood and urine sample collection), all study procedures except the blood/urine collection assessments may be performed; the blood/urine collection will be rescheduled on a subsequent day within the Screening Period and the subject will be reminded to fast for at least 10 hours. In light of the current COVID-19 pandemic, the site will test all subjects for COVID-19 during the Screening Visit. If the subject tests positive, the subject will not be allowed to participate in the study.

Subjects who do not fulfill the eligibility criteria for this study are considered screen failures and these subjects must not be randomized. The reason for screen failure will be recorded in the CRF. Subjects who were previously randomized and received study drug on Day 1 cannot be re-screened in this study. Subjects who previously screen failed or discontinued the study prior to study drug administration on Day 1, could be re-screened in this study at the Investigator's discretion.

Please refer to Table 1 for the list of screening procedures to be performed in the study. Repeat testing of vital signs (refer to exclusion #10) and safety laboratory tests are permitted, at the discretion of the Investigator. If the repeat test results are not clinically acceptable to the Investigator, the subject should be excluded from the study.

Subjects' general stool patterns will be self-reported, based on Bristol Stool Chart definitions, 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 date, time and stool type of each stool on a site-provided document.

3.6.3 Admission Period

Day -3 to Day 35

Prior to Day -3 visit, the site should remind the subject to bring the BSC assessment document to the site and to fast at least 10 hours before arriving at the site.

On the morning of Day -3, the site will test all subjects for COVID-19. If a subject tests positive, the subject will not be allowed to participate in the study.

[redacted]

During the Admission Period, subjects are required to fast overnight for at least 10 hours prior to blood and urine sample collection (except for non-fasting PK, PD and urine calcium, sodium and glucose measurements). Study restrictions must be followed (Section 3.6.5). Please refer to Table 1 through Table 5 for the list of procedures to be performed during the Admission Period.

Subjects will be discharged from the site on Day 35. A subject may be required to remain at the site for a longer period (e.g., subject has ongoing AEs or has abnormal lab test results), at the discretion of the Investigator. Prior to discharge on Day 35, subjects must be re-trained by a member of the site staff to perform the BSC assessment unassisted. The subjects will record the date, time and stool type of each stool during the Follow-up period on a site-provided source document.

If a subject discontinues the study/study drug prematurely, refer to Section 3.4 for follow-up actions.

3.6.4 Follow-up Period

Day 42±3

The Follow-up Visit will occur approximately 14 days after the last dose of study drug. Subjects should arrive under the fasted condition (i.e., overnight fast, at least 10 hours prior to blood and urine sample collection). Please refer to Table 5 for the list of follow-up procedures to be performed.

Subjects who discontinue the study/study drug after study drug adminstration on Day -1 but before randomization on Day 1 will be discharged from the site at the discretion of the Investigator. These subjects will be requested to complete a Follow-up telephone call from the site within 7 days after being discontinued from the study.

Subjects who discontinue the study/study drug after study drug administration on Day 1 will be requested to undergo all procedures described for Day 35 as soon as possible after the last dose of study drug. Additionally, these subjects will be requested to return to the site and complete all procedures described for the Follow-up Visit approximately 14 days after the last dose of study drug.

For all early discontinued subjects (after study drug administration on Day 1), every effort will be made to collect at least three blood samples for JTT-662 PK assessments at approximately 3-hour intervals, starting as close as possible to the time when the study drug was discontinued.

Any subject withdrawn from treatment due to an AE, SAE or clinically significant abnormal laboratory test result will be evaluated by the Investigator. The subject will be treated and/or followed-up until the symptoms or laboratory results have either resolved or are assessed as stable by the Investigator.

3.6.5 Study Diet and Restrictions

3.6.5.1 Study Diet

The standard meals used for this study will be in accordance with the recommendations of the American Diabetes Association (50-60% of calorie intake from carbohydrates, 15-20% from protein and 25-35% from fat[31]). Total daily caloric intake will be approximately 2300 kcal.

On Days -1, 1, 14 and 28, identical meals for breakfast, identical meals for lunch and identical meals for dinner will be served for all subjects. Subjects should consume each meal completely and within 30 minutes. The percent consumed for each meal on Days -1, 1, 14 and 28 as well as all fluid intake (i.e., volume), including that taken during meal times, will be recorded in the case report form (CRF).

The menu of the standard meals will be prepared by a certified/registered dietician at the study site according to the meal components as defined above and finalized after agreements from the Investigator and the Sponsor. This diet should not include citrus drinks (especially grapefruit juice), grapefruit, sour oranges, caffeinated products or alcohol.

[redacted]

3.6.5.2 Study Restrictions

Alcohol, Diet and Exercise Restrictions:

- Subjects must fast for at least 10 hours prior to study drug administration (Day -1 until Day 28) and prior to blood sample collections on Days 31 and 35.
- Alcohol is not permitted from 48 hours prior to the Admission Period through the Follow-up Visit.
- Caffeinated products are not permitted for at least 72 hours prior to the Admission Period through the Follow-up Visit.
- Citrus containing foods, specifically grapefruit juice, grapefruit and sour oranges, are not permitted for at least 7 days prior to the Admission Period through the Follow-up Visit.
- Strenuous exercise should be avoided for at least 7 days prior to the Admission Period through the Follow-up Visit.

3.6.6 Previous and Concomitant Medication

3.6.6.1 Permitted Medications

- Tylenol at doses < 2 g/day is permitted at any time during the study
- Inhaled, intranasal and topical corticosteroids are permitted at any time during the study
- Stable* oral metformin dose
- Stable* anti-hypertension medications
- Stable* dyslipidemia medications [redacted]

[redacted]

*Medication regimens are considered stable if the dose and schedule of administration has not changed within 12 weeks prior to the Screening Visit and up to the Follow-up Visit.

Notes: Subjects will remain on their pre-study stable permitted concomitant medication doses (e.g., oral doses of metformin, anti-hypertension medications) during the Admission Period and through the Follow-up Period of the study. All concomitant medications should be administered and stored according to product labelling and will not be provided by the Sponsor.

Other concomitant medications may be considered on a case by case basis after review by the Medical Monitor, the Investigator and the Sponsor.

3.6.6.2 Prohibited Medications

Use of the following prescription and non-prescription medications could confound the efficacy or pose a safety risk to subjects and are not permitted for the periods indicated below:

- 12 weeks prior to the Screening Visit until the Follow-up Visit: diabetic medications (other than metformin), medications that act mainly in the GI tract (e.g., orlistat, acarbose), P-gp substrates (digoxin, apixaban, edoxaban, rivaroxaban and dabigatran) and tobacco or nicotine-containing products.
- 12 weeks prior to the Screening Visit until the Follow-up Visit: non-diabetic medications that may affect glucose homeostasis (e.g., diuretics and sympathomimetics). *Exception*: if the subject has been on a stable dose for at least 12 weeks prior to the Screening Visit and from the Screening Visit to Day -3. These medications need to be agreed upon by the Investigator and the Sponsor.

- 30 days or 5 half-lives, which is longer, prior to the Screening Visit until the Follow-up Visit: investigational drug or device

[redacted]

Other medications (including vitamins, herbal and dietary supplements) may be considered on a case by case basis and will be allowed (if agreed between the Investigator and the Sponsor) if the medication is not expected to interfere with study procedures or compromise subject safety.

[redacted]

The site should contact the Medical Monitor if a subject requires concomitant therapy. All medications taken by the subject (whether permitted or excluded by the protocol) must be documented in the CRF.

3.6.7 Procedure Definitions

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 [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. Additional safety assessments (e.g., vital signs, 12-lead ECG, serum biochemistry, hematology, coagulation, urinalysis) may be performed if deemed necessary by the Investigator. Refer to the laboratory manual for specific instructions for the collection and processing of COVID-19 tests, blood and urine samples.

3.6.7.1 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.

3.6.7.2 Previous and Concomitant Medications/Procedures

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) should be investigated. If the medications and/or procedures are measures taken to treat an AE, the AE should be recorded as the reason for initiation of the medication/procedure in the CRF.

3.6.7.3 Physical Examination

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), head, ears, eyes, nose, throat, neck/thyroid, chest/lungs, cardiovascular, GI, neurological, psychiatric/emotional, lymphatic and musculoskeletal.

3.6.7.4 Height and Weight Measurements, and Body Mass Index Calculation

Height and weight measurements will be performed according to the schedules summarized in Table 1 through Table 5. Subjects will remove their shoes and wear light clothing in order to be consistent between measurements of height and/or weight. 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.

3.6.7.5 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 ICF signature date. Between the ICF signature date and Day -1, prior to placebo 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 ECG, physical examination, vital signs and laboratory test results that are evidently chronic in nature) could be considered medical history or an AE.

3.6.7.6 Vital Signs

Vital sign assessments including systolic and diastolic blood pressure, HR, respiratory rate and body temperature (°C) will be performed according to the schedules summarized in Table 1 through Table 5. Subjects must lay in the supine position for at least 5 minutes in preparation for blood pressure and HR assessments. Repeat testing of vital signs is permitted (refer to exclusion #10), if considered appropriate by the Investigator.

3.6.7.7 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 summarized in Table 1 through Table 5. Subjects must lay supine for at least five minutes prior to 12-lead ECG assessments.

3.6.7.8 Adverse Events

Adverse events information will be collected at the specified time points in Table 1 through Table 5, as well as at any time when a site staff becomes aware of an AE after signing the ICF.

3.6.7.9 Serum Pregnancy Test

Blood samples to assess pregnancy status by βhCG will be collected from all female subjects according to the schedules summarized in Table 1 and Table 5.

3.6.7.10 Estimated glomerular filtration rate

Estimated glomerular filtration rate (eGFR) will be calculated at the Screening Visit using the 4-variable 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).

3.6.7.11 Serum Biochemistry

Blood samples to assess ALT, albumin, alkaline phosphatase, AST, bilirubin (direct and total), BUN, calcium, carbon dioxide, chloride, creatine kinase, creatinine, gamma-glutamyl transferase, globulin, glucose, high-density lipoprotein cholesterol, high sensitivity C-reactive protein, lactate dehydrogenase, low-density lipoprotein cholesterol (calculated), phosphate, potassium, total protein, sodium, total cholesterol, triglycerides and urate will be obtained under the fasted condition according to the schedules summarized in Table 1 through Table 5.

3.6.7.12 Hematology

Blood samples to assess complete blood count including erythrocytes (RBC), hematocrit, hemoglobin, platelet count, leukocytes (WBC) and differential (percent and absolute [neutrophils, eosinophils, basophils, lymphocytes, monocytes]) will be obtained under the fasted condition according to the schedules summarized in Table 1 through Table 5.

3.6.7.13 Coagulation

Blood samples to assess prothrombin time and activated partial thromboplastin time (aPTT) will be obtained as measures of blood coagulation according to the schedules summarized in Table 1 through Table 5. International normalized ratio will also be calculated.

3.6.7.14 Viral Serology

Blood samples to assess HBsAg, HCV antibodies and HIV antibodies will be obtained at the Screening Visit.

3.6.7.15 Drugs of Abuse and Alcohol Screen

Urine samples to assess amphetamine, barbiturates, benzodiazepines, cannabinoids, cocaine, ethanol, opiates, oxycodone, methadone and methylenedioxymethamphetamines will be obtained according to the schedule summarized in Table 1.

3.6.7.16 Urinalysis

Urine samples to assess bilirubin, occult blood, color, glucose, ketones, leukocyte esterase, nitrite, logarithmic measure of hydrogen ion concentration, protein, specific gravity, turbidity and urobilinogen, as well as for a microscopic exam including bacteria, casts, crystals, epithelial cells, mucous threads, RBC, trichomonas, WBC and yeast budding, will be obtained under the fasted condition according to the schedules summarized in Table 1 through Table 5. Samples for urinalysis may be obtained from the first void of the morning when in-house, if applicable.

3.6.7.17 Glycosylated Hemoglobin

Blood samples to assess HbA1c will be collected [redacted]

[redacted]

3.6.7.19 Plasma Glucose

Blood samples to assess plasma glucose will be collected according to the schedules summarized in Table 1 through Table 4.

3.6.7.20 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]

3.6.7.28 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).

At the Screening Visit, the subjects' stool pattern will be recorded based on the subjects' recollection and review of the BSC definitions. Subjects will be trained by a member of the site staff on how to perform the assessment and document the stool type, date and time on the BSC source document, which will be provided to each subject for completion during the 3 days prior to Day -3. On Day -3, the completed BSC source document will be returned to the site.

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 BSC including documentation of the date and time (see Appendix 1).

A BSC source document will be provided to the subject for completion during the Follow-up Period. At the Follow-up Visit, completed site-provided BSC source documents will be returned to the site by the subjects.

3.6.7.29 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.

3.6.7.30 Pharmacokinetic Procedures

3.6.7.30.1 Blood Samples for Pharmacokinetic Assessments

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 may be used for JTT-662 metabolite profiling. The laboratory performing JTT-662 metabolite profiling will be unblinded to facilitate analysis of the plasma samples from the JTT-662-treated subjects and the placebo-treated subjects. The residual PK plasma samples from this study may also be used for additional exploratory biomarkers and/or metabolomic evaluations, if needed.

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-622-treated subjects.

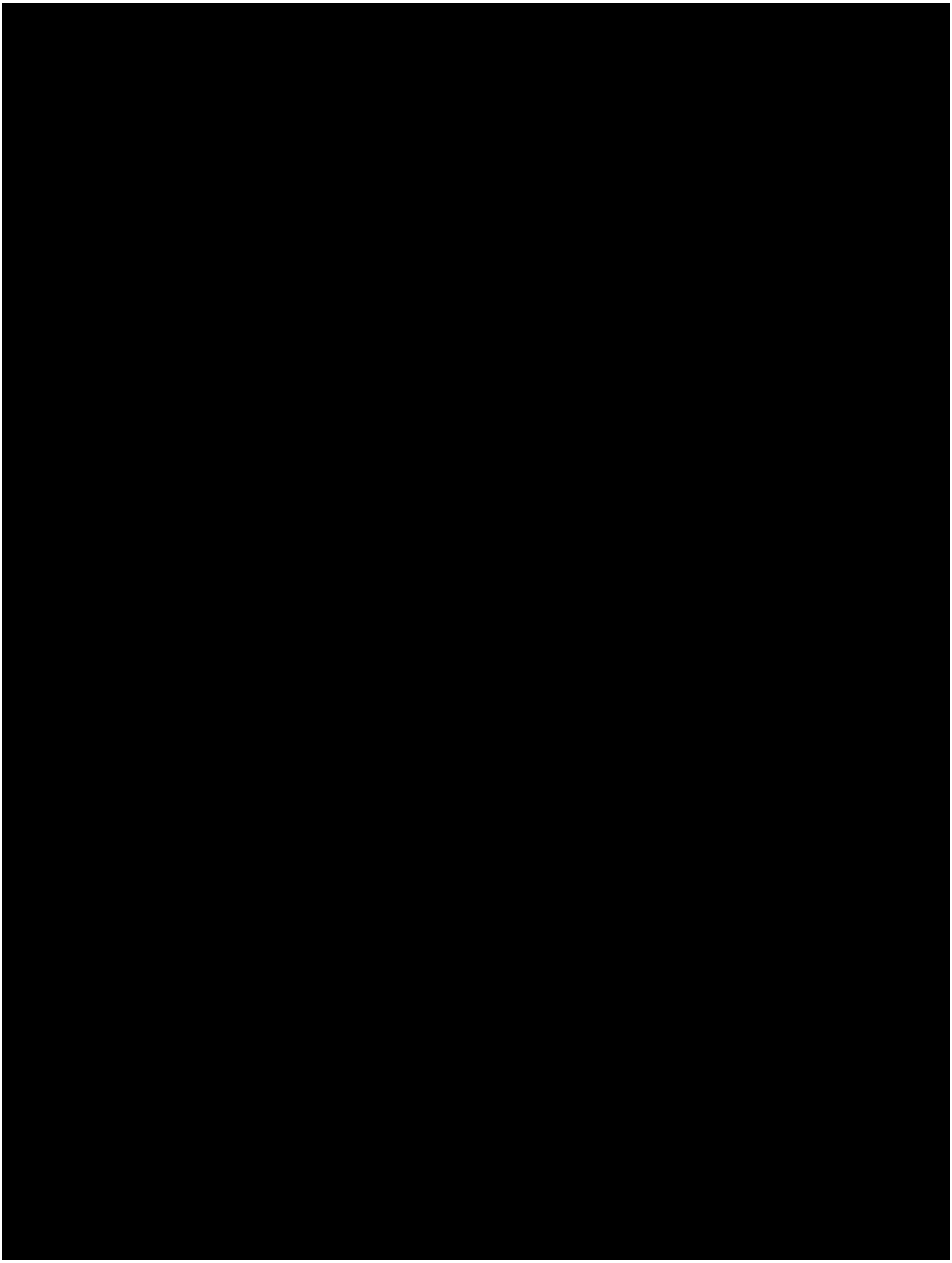
The actual dosing time and sample collection time will be collected for PK data analysis. In addition, the site must accurately record the dose and time(s) of dosing of metformin during the PK collection period.

Refer to the laboratory manual for specific instructions for the collection and processing of blood samples for PK assessments.

3.6.7.30.2 Analysis of JTT-662/Placebo in Plasma

JTT-662 will be analyzed in plasma using a validated high-performance liquid chromatography/tandem mass spectrometry method. All samples from JTT-662-treated subjects will be analyzed. Plasma samples obtained on Day 28 at hours 2 and 4 from placebo-treated subjects will be analyzed. For placebo-treated subjects that discontinue the study prior to Day 28, the samples obtained on Day 1 at hours 2 and 4 will be analyzed. Additional plasma samples from placebo-treated subjects may be analyzed as needed.

3.6.8 Clinical Institutions and Laboratories



3.7 Adverse Events

3.7.1 Safety Definitions

Akros complies with the following International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) AE definitions:

Adverse Event: An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

For the purpose of this study, AEs are defined as any medical conditions occurring or worsening after the ICF signature.

Any pre-existing conditions or signs and/or symptoms present in a subject prior to signing the ICF should be recorded as medical history. Any medical occurrences which are new or worsened from the time of informed consent and up to and including the Follow-up Visit must be reported as AEs or SAEs. All AEs and SAEs must be recorded irrespective of whether they are considered study drug related. For additional details regarding medical history and AEs, please refer to Section 3.6.7.

Subjects will be monitored throughout the study for adverse reactions to the study drug and/or procedures. Questions will be posed in a non-leading manner so as not to bias the response. In addition to questioning at specific time points, subjects will be encouraged to spontaneously report any AEs. Any subject with an AE, SAE or clinically significant abnormal laboratory test result will be evaluated by the Investigator and will be treated and/or followed-up until the symptoms or laboratory values have resolved or are assessed as stable by the Investigator. A physician or appropriate personnel, either at the Investigative site or at a nearby hospital emergency room, will administer treatment of any SAEs. When appropriate, medical tests and examinations may be performed to ensure that an AE has fully resolved.

Serious Adverse Event: An SAE is defined as any AE that meets any of the following criteria:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is an important medical event

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

Adverse Drug Reaction: All noxious and unintended responses to an investigational medicinal product (IMP), related to any dose administered.

Note: The phrase "responses to a medicinal product" means that a causal relationship between the medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Unexpected Adverse Drug Reaction: An adverse drug reaction (ADR) of which nature (specificity) or severity is not consistent with the applicable product information (e.g., IB).

Death: Death represents an outcome and an SAE criterion, not an event term. The medical condition with the fatal outcome should be reported unless the cause of death is unknown, in which case the term “Death” is acceptable.

Inpatient Hospitalization/Prolongation of Hospitalization: Any admission (even if less than 24 hours) to a healthcare facility. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., medical floor to the coronary care unit). Initial and prolonged hospitalizations that **do not** meet this SAE criterion include those due to social and/or convenience reasons (e.g., lack of personal care at home, unable to transfer to non-acute facility), admission to rehabilitation/hospice/skilled nursing facilities, emergency room visits, same-day/outpatient/ambulatory procedures, and those for pre-planned, elective procedures for a pre-existing condition that did not worsen after the ICF has been signed (no AE recorded). However, if the hospitalization was prolonged due to a complication of a pre-existing condition, the complication (same diagnosis) would qualify as an SAE.

Disability: A substantial disruption of a person’s ability to conduct normal life functions.

Life-threatening: Any AE that places the patient or subject, in the view of the Investigator, at immediate risk of death, i.e., it does not include an event that had it occurred in a more severe form, might have caused death.

Physical Examination, Vital Signs, Laboratory Test and ECG Abnormalities: Any abnormalities fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE in the CRF. Any abnormal vital sign, physical finding or laboratory/ECG result which is clinically significant (i.e., meets one or more of the following conditions) should be recorded as a single entry on the AE page of the CRF:

- Accompanied by clinical signs/symptoms,
- Leads to permanent discontinuation of study drug,
- Requires a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

This does not apply to abnormal vital signs, physical finding or laboratory/ECG results that do not meet the clinical-significance criteria, are part of an AE which has already been reported, are associated with the disease being studied (unless judged by the Investigator as more severe than expected for the subject's condition), or conditions present or detected at the start of the study and do not worsen.

The Investigator will exercise medical and scientific judgement in deciding whether an abnormal clinical laboratory finding or other abnormal assessment is clinically significant.

3.7.2 Assessing Adverse Events

When completing appropriate forms for reporting an AE, the Investigator should assess the AEs as follows:

Reported Term for Adverse Event:
Individual signs or symptoms, will be recorded AEs, in the absence of a diagnosis. If a diagnosis is available based on the signs or symptoms, the diagnosis, should be recorded as the AE term.

Seriousness of Adverse Event:

- Serious: The AE meets a criterion of the SAE definition.
- Not Serious: The AE does not meet a criterion of the SAE definition.

Severity of Adverse Event:
The severity of an AE should be graded as one of the following three grades: mild, moderate or severe. To determine the severity of AEs, refer to "Common Terminology Criteria for Adverse Events (CTCAE)" and categorize Grade 1, Grade 2 and Grade 3 or higher grades of CTCAE[32] into mild, moderate and severe, respectively. The investigator should determine the severity, taking into account the general status of the subject, baseline values, outcomes, as well as the severity grade. An AE of Grade 4 or Grade 5 should be assessed whether or not it meets the criteria listed under the SAE definition (see Section 3.7.1).

- Mild: The AE is usually transient and may require only minimal treatment or therapeutic intervention. The AE does not generally interfere with usual activities of daily living.
- Moderate: The AE is usually alleviated with additional specific therapeutic intervention. The AE interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

- Severe: The AE interrupts usual activities of daily living, or significantly affects clinical status of the subject, or may require intensive therapeutic intervention.

Relationship to the Study Drug (Causality) of Adverse Event:

The Investigator's causality assessment is the determination whether there is a reasonable possibility that the IMP caused or contributed to the AE. Generally, the facts (evidence) or arguments to suggest causal relationship should be documented. Factors to be taken into consideration when assessing causality include: subject's underlying and pre-existing conditions, prior/concomitant medications, timing of onset relative to study drug (i.e., JTT-662 or placebo) administration, the known PK characteristics of study drug, the currently-known safety profile of study drug, known class effects of similar mechanism of action drugs, the de-challenge/re-challenge response (if available) and any other information that is considered relevant by the Investigator. Causality will be judged in two categories: "not related" or "related".

- Not Related: Sufficient information exists to indicate that the etiology is clearly related to a cause other than the study drug.
- Related: The AE follows a reasonable temporal sequence from the administration of the study drug; follows a known or expected response pattern to the study drug; is confirmed by improvement on stopping the dosage of the study drug (de-challenge); and cannot be reasonably explained by the participant's clinical state.

Action Taken with Regard to Study Drug:

- Dose Not Changed: The subject was on treatment with the study drug when the AE occurred, and the study drug dosing was maintained at the same dose level.
- Drug Interrupted: The subject was on treatment with the study drug when the AE occurred, and the study drug dosing was temporarily discontinued and then re-started.
- Drug Withdrawn: The subject was on treatment with the study drug when the AE occurred, and the study drug dosing was permanently discontinued.
- Not Applicable: The subject was not receiving treatment with the study drug when the AE occurred (i.e., AE occurred before placebo dosing on Day -1 or after the last study drug administration), or if the subject died.

Outcome of Adverse Event:

One outcome should be recorded for each AE and the outcome of each AE should be classified as follows:

- Not Recovered/Not Resolved: The subject has not yet recovered from the AE; the event has not improved (follow-up of all SAEs and all related AEs will be continued until the overall clinical outcome is ascertained).
- Recovering/Resolving: The subject has not yet recovered from the AE, however, the event is improving (follow-up of all SAEs and all related AEs will be continued until the overall clinical outcome is ascertained).
- Recovered/Resolved: The subject recovered from the AE with no sequelae.
- Recovered/Resolved with Sequelae: The subject recovered from the AE with sequelae.
- Fatal: The subject's death was a result of the AE.

Start Date and Time, and End Date and Time of Adverse Event:

The start date and time of each AE with an onset time during the period for AE assessment should be recorded. The end date and time of each AE should be recorded in the following manner:

- If the outcome of AE is "Recovered/Resolved" or "Recovered/Resolved with Sequelae", record the date and time of the AE outcome.
- If the outcome of AE is "Fatal," record the date of the death.
- If the outcome of AE is "Recovering/Resolving" or "Not recovered/Not resolved", the end date and time of the AE outcome should NOT be recorded.

For AEs related to abnormalities in parameters such as vital signs, ECGs, record the date/time when the test was performed as the start date/time and end date/time. For AEs related to abnormalities in laboratory values, record the date/time when the sample was collected for the test as the start date/time and end date/time.

If an identical AE occurs repeatedly in a subject, the Investigator (or designee) should judge whether it is a single event or a composite of more than one event considering the features, frequency and severity of the AE from a medical perspective.

3.7.3 Reporting Adverse Events

Adverse Events Reporting:

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 CRFs. Conditions detected prior to the ICF signature should be documented as medical history. Other conditions identified between the ICF signature and Day 1 (prior to dosing) could be included in the medical history, based on the Investigator's medical and scientific judgement. For guidance, refer to Section 3.6.7.5 of the protocol.

Adverse events will be reported on the AE CRF page.

When a subject withdraws from the study due to a non-serious AE, whether or not related to study drug, the Investigator must notify Akros within 24 hours of the study center being informed of the withdrawal.

Serious Adverse Event Reporting:

Reporting by Investigator

Detailed instructions regarding SAE reporting will be provided in the appropriate documents outside of this protocol. A brief, non-all-inclusive summary is provided below.

Any SAE experienced by a study subject after signing the informed consent up to the day when the decision to screen fail the subject is made (for screen failure subjects), 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 to the Sponsor or designee. Additionally, SAEs that occur after this period will also be reported to The Sponsor or designee, if the Investigator considers the SAE related to the study drug.

Serious AEs (both initial reports and follow-up information) must be reported to the Sponsor or designee within 24 hours of the Investigator's (site's) awareness or notification of the event.

The Investigators should make every effort to provide complete information when reporting the SAE (both for initial reports, as well as for follow-ups).

Notes: The Investigator should make every effort to assess the causality of the SAE prior to transmission of the initial SAE report, even if the Investigator has minimal information. The SAE report should be amended, if the Investigator changes his/her opinion of causality based on the follow-up information.

Personal information that could potentially identify the subject MUST NOT be included in any document that is sent to Sponsor or designee as per ICH GCP Principles 2.11 and other applicable laws and legislations.

The Investigator must continue to follow the subject until the SAE has subsided, the condition becomes chronic in nature, the condition stabilizes (in case of persistent impairment), or the subject dies. Within 24 hours of receipt of follow-up information, the Investigator must submit it to the Sponsor or designee.

The Investigator is also required to submit SAE reports to the IRB, in accordance with local requirements. The Investigator will receive all Suspected Unexpected Serious Adverse Reaction (SUSAR) reports for onward submission to their local IRB, as required.

Reporting by the Sponsor

Competent authorities will be informed by the Sponsor or designee of SUSARs.

Exposure *in Utero* Reporting:

If a female subject or a female partner of a male subject participating in the study becomes pregnant after the subject receives study drug on Day 1 and up to 30 days after the last dose of study drug, the Investigator should report the pregnancy to the Sponsor or designee within 24 hours of being notified. To report the pregnancy, the site must complete the Exposure *in Utero* Form which is provided separately to the Investigator.

The female subject or the female partner of a male subject should be followed by the Investigator until completion of the pregnancy if the subject received active (i.e., JTT-662) treatment. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor or designee. At the completion of the pregnancy, the Investigator should document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death or congenital anomaly), the Investigator should follow the procedures for reporting an SAE as described above.

Overdose Reporting:

An overdose is a significant variation from the recommended/scheduled dosage for a product. For the purposes of this study, overdose is defined as any confirmed use of study drug more than indicated by the protocol. Information on overdose in subjects is collected by the Sponsor or designee, *via* a separate form provided to the Investigator. If a subject experiences an overdose during the course of the study, the Investigator or qualified designee must report it to the Sponsor or the designee as soon as possible after he/she first becomes aware of it. If any overdose leads to an AE or SAE, the AE should be documented and the SAE should be reported to the Sponsor or designee, as described under the SAE reporting section.

3.8 Identification of Treatments

3.8.1 Method of Assigning Subjects to Treatment Groups

After signing the ICF, potential study subjects will be assigned a screening number (XXX) consecutively. The screening number will be used throughout the study. Following confirmation of eligibility on Day 1, the pharmacist at the site will assign a four digit randomization number XXYY, where XX represents the cohort number (beginning with 01) and YY represents a consecutively assigned number beginning with 01 ending with 12 in each cohort. Subjects that took placebo on Day -1 but are not randomized into Cohort 1 on Day 1, Hour 0 can be randomized into Cohort 2 on the same day, if still eligible, and will be assigned a randomization number XXYY where XX represents the cohort number (beginning with 02) and YY represents a consecutively assigned number.

To ensure an adequate number of evaluable subjects, 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. The first digit in the randomization number of the replacement subject will be five (i.e., the replacement subject for the first subject [0101], becomes 5101).

3.8.2 Identity of Investigational Products

[redacted]

3.8.3 Storage and Handling Procedures

JTT-662 Tablets, 1 mg or 10 mg and Placebo Tablets should be stored between 20 – 25°C in a secure location with restricted access.

3.8.4 Clinical Supplies Packaging

A sufficient quantity of JTT-662 Tablets, 1 mg or 10 mg and Placebo Tablets will be supplied by Akros or designee, to the site.

Bulk JTT-662 and Placebo Tablets are packaged in glass bottles with a low-density polyethylene cushioning material, two alumina/silica desiccant packs (1 g) and capped with a polypropylene screw cap fitted with a polypropylene/polyethylene liner. Each bottle contains 30 tablets of either JTT-662 (1 mg or 10 mg) or Placebo Tablets, and will be labeled appropriately. Each label will bear appropriate text as specified by regulatory requirements.

Glass bottles and closures will be provided by Akros or designee, to the pharmacy for subject-specific packaging of JTT-662 or Placebo Tablets. Each label will bear the appropriate text as specified by regulatory requirements.

Study drug should be packaged for subject administration on the day of dosing, however, if this is not feasible, the weekday dose may be packaged up to 24 hours prior to dosing. Weekend dosing may be packaged up to 72 hours in advance of dosing.

3.8.5 Administration of Study Drug and Metformin

On the morning of Day -1, all subjects will receive a single oral administration of placebo following an overnight fast (for at least 10 hours) and 30 minutes before the start of a standard breakfast. On the morning of Day 1, randomized subjects will receive oral QD administration of JTT-662 or placebo, for 28 days from Day 1 through Day 28 following an overnight fast (for at least 10 hours) and 30 minutes before the start of a standard breakfast. Standardized lunch and dinner will be provided at 4.5 and 10.5 hours, respectively, post-dose. Metformin should be administered with food as per the label.

Water will be restricted for 1 hour before and after study drug administration for all cohorts. The planned dose levels and the number of tablets to be administered are provided below:

Cohort	Study Treatment	Number of Tablets (Per Dose)
1	Day -1: Placebo single dose Day 1 through Day 28: JTT-662 5 mg (or placebo) QD	Five tablets of placebo Five tablets of JTT-662 1 mg or five tablets of placebo
2	Day -1: Placebo single dose Day 1 through Day 28: JTT-662 10 mg (or placebo) QD	One tablet of placebo One tablet of JTT-662 10 mg or one tablet of placebo
3*	Day -1: Placebo single dose Day 1 through Day 28: JTT-662 20 mg (or placebo) QD	Two tablets of placebo Two tablets of JTT-662 10 mg or two tablets of placebo

* Cohort 3 will be initiated only after a 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. [redacted]

Tablets will be administered with 240 mL of potable water, followed by a hand check, if applicable, and a mouth check. Subjects having difficulty swallowing the required number of tablets with 240 mL of water may receive additional, documented amount of water sufficient to complete drug administration. Only authorized members of the site will administer the study drug. Dosing times will be staggered between subjects for practical reasons. The time of dosing will be recorded for each subject.

All subjects should remain semi-recumbent for 2 hours after study drug administration except for non-supine assessments, breakfast and restroom visits.

3.8.6 Management of Clinical Supplies

The Investigator will have responsibility for the control and proper administration of all study-related drugs (which includes any investigational product or interacting product) in accordance with this protocol. The Investigator at the site is responsible for ensuring that all study-related drugs will be stored at recommended storage temperatures, in a secured area, free of environmental extremes, with restricted access. The Investigator at the site also agrees that all study-related drugs will be dispensed only to study subjects who have provided written informed consent and have met all inclusion criteria and none of the exclusion criteria.

3.8.7 Randomization

Approximately 36 healthy subjects will be randomized in this study in 3 planned cohorts. 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. Akros or designee will provide the randomization code to the pharmacy at the site, as well as to select laboratories, as appropriate (see Section 3.8.8).

3.8.8 Blinding

On the morning of Day -1, all subjects will receive a single oral dose of placebo in an unblinded manner. From the morning of Day 1 to the morning of Day 28, all randomized subjects will receive JTT-662 or placebo QD in a single-blind manner. 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 (see Section 3.6.7.30).

3.8.9 Breaking the Blind

Not applicable.

3.9 Statistical Methods

This section provides an abbreviated statistical analysis plan (SAP) for safety, PK, PD [redacted] parameters. A formal SAP will be developed at a later time. Statistical issues not addressed in the present section may be developed in the formal SAP. Any deviations to the SAP will be discussed in the study report.

3.9.1 Subject Populations for Analysis

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

Safety Population: All subjects who received at least one dose of JTT-662 or placebo, including those who do not complete the study.

Pharmacokinetic Population: All randomized subjects who received at least one dose of JTT-662 or placebo, 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, 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 violate the inclusion or exclusion criteria or deviated significantly from the protocol.

3.9.2 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.

3.9.3 Interim Analysis

Interim analysis is not planned for this study.

3.9.4 Safety Analysis

All subjects in the safety population will be included in the safety data analysis.

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

Adverse events will be coded using the Medical Dictionary for Regulatory Activities and will be summarized by SOC and preferred term.

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

Observed values and change from baseline of ketone bodies, [redacted] FPG will be summarized by treatment and time point.

Urine Calcium, Sodium and Glucose

Urinary calcium excretion from the time of dosing until the 24-hour time point (UCE_{0-24}), UGE_{0-24} and $UNaE_{0-24}$ will be computed for Days -1, 1, 14 and 28. Observed and change from baseline of total excreted amount within 24 hours will be summarized by treatment and day.

Statistical analysis for change from baseline in UGE_{0-24} will be performed using a mixed effect model with repeated measures (MMRM). The model will include fixed effects for treatment, day, treatment by day interaction and baseline value. The treatment difference of 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.

Bristol Stool Chart

Total number of stools and percent of stools at each stool type will be summarized by treatment. 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.

Other safety parameters may be summarized as appropriate.

3.9.5 Pharmacokinetic Analysis

Pharmacokinetic analysis will be performed on the PK population unless otherwise stated.

3.9.5.1 Pharmacokinetic Parameters

The following 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) as appropriate. Additional PK parameters may be calculated, as appropriate.

- JTT-662 in plasma: C_{max}, trough concentration during multiple dosing prior to next dose (C_{trough}), t_{max}, AUC_{tau}, V_z_F, CL_F, $t_{1/2}$, $t_{1/2(eff)}$, accumulation ratio of maximum concentration (AR_{Cmax}) and accumulation ratio of area under the concentration-time curve during a dosing interval (AR_{AUCtau}), and accumulation ratio based on trough concentration ($AR_{Ctrough}$).

3.9.5.2 Pharmacokinetic Data Analysis

Descriptive statistics will be performed for all subjects in the PK population. The plasma concentration data and the PK parameters will be summarized in terms of the number of subjects (n), arithmetic mean, SD, CV%, median, minimum and maximum by treatment and day. In addition, geometric mean will be reported for all PK parameters except t_{max}.

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% CI.

3.9.6 Pharmacodynamic Analysis

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.

Postprandial glucose (PPG) concentrations will be summarized by treatment group and time point in terms of the number of subjects, arithmetic and geometric means, standard deviation, CV%, median, minimum and maximum.

A linear mixed effect model including day as the fixed effect and subject as the random effect will be fitted on the natural logarithm of the PD parameter for each treatment group separately. The ratio of the geometric means (Day 1/Day -1, Day 14/Day -1 and Day 28/Day -1) of $AUEC_{0-4}$ and the 90% and 95% CIs of the GMR will be calculated.

Additionally, the change from baseline of $AUEC_{0-4}$ will be analyzed using the MMRM model. The model will include fixed effects for treatment, day, treatment by day interaction, subject as repeated measures and baseline value. The treatment differences between each JTT-662 dose group relative to placebo at the same day will be estimated, along with two-sided 90% and 95% confidence intervals (CIs) and p-values.

3.10 Quality Control and Quality Assurance

This study will be conducted in compliance with the protocol, GCP as defined by the United States 21 Code of Federal Regulations (CFR) Parts 50, 56 and 312, Sponsor policies and procedures and all applicable state regulations.

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

a) Routine site monitoring;
b) CRF review against source documents;
c) Data management quality control checks;
d) Statistical quality control checks;
e) Continuous data acquisition and cleaning; and
f) Quality control of final report.

A representative from Akros and/or authorized representatives may conduct periodic audits of the site and study processes, including, but not limited to, the clinical database and the final report. The study may also be subject to inspection by regulatory authorities. The Investigator hereby agrees to allow access to required subject records and other documentation and facilities related to the review and conduct of the study.

4 INVESTIGATOR OBLIGATIONS

4.1 Institutional Review

The Investigator shall assure that an IRB that complies with the requirements set forth in the US 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The Investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

All advertisements used in conjunction with this study must be reviewed and approved by Akros prior to use and the IRB, if applicable. The IRB's approval will be documented in writing and sent to the Investigator. The Investigator will forward a copy of the IRB approval document to Akros.

The Investigator will not begin the study until Akros has authorized release of investigational drug product.

Any amendments to the protocol must be approved in writing by the IRB prior to implementation by the Investigator. However, any change to the protocol to eliminate an apparent immediate hazard to the subjects may be implemented immediately, provided that the IRB is subsequently notified in accordance with US 21 CFR Part 56.104(c).

The Investigator will also provide the IRB with a current copy of the IB at the start of the study, as well as an updated version of the IB if revised during the study or supplement(s) to the IB if prepared during the study.

A progress report will be submitted by the Investigator to the IRB at intervals established by the IRB and not less than annually. The Investigator will retain a copy of this report in the Investigator's Documentation File. After completion or termination of the study, the Investigator will submit a final report to the IRB. Copies of all reports will be provided to Akros.

4.2 Subject Consent

In obtaining and documenting informed consent, the Investigator should comply with the applicable regulatory requirement(s), i.e., US 21 CFR Part 50 and should adhere to GCP. Prior to the beginning of the study, the Investigator should have the IRB written approval of the written informed consent form and any other written information to be provided to subjects.

The written informed consent form and any other written information to be provided to subjects must be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form and written information must receive the IRB approval in advance of use. The subject must be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

The Investigator or a person designated by the Investigator, should fully inform the subject of all pertinent aspects of the study including the written information and the approval by the IRB. A copy shall be given to the person signing the form.

4.3 Data Collection

It is the Investigator's responsibility to ensure that data are collected and reported according to the study protocol. The Investigator will ensure the accuracy, completeness and timeliness of the data reported on the CRF and in all required reports. Efforts should be made to complete the CRFs as soon as possible after the scheduled visit and to have all CRFs completed within 3 days after Day 42.

Additionally, laboratory data [redacted] may be received by Clinical Data Management from the appropriate clinical laboratory(ies) [redacted] in electronic format. These data files may be merged with the clinical database.

4.3.1 Case Report Forms

Electronic CRFs will be produced according to protocol requirements and access/training will be provided to the site in order for the Research Staff to record the data obtained on each subject during the study.

Case Report Forms must be completed for each subject who signed the ICF to participate in the study.

Case Report Forms will be reviewed by the Clinical Monitor. At a minimum, important safety, eligibility and endpoint data as defined in the data management plan will be verified against source documents. The CRFs must be kept up-to-date so that they always reflect the latest observations on the subjects randomized in the study. All records should be kept in conformance to applicable national laws and regulations.

4.3.2 Source Documents

It is the responsibility of the Investigator to collect and record all study data on source documents. The Investigator must provide access to source data/documents for study-related monitoring, audits, IRB review and regulatory inspection.

4.4 Adherence to Protocol

By signing the Investigator Signature Page of this protocol, the Investigator confirms in writing that he/she has read, understands and will strictly adhere to the study protocol. This study will be conducted in accordance with GCP regulations. Additional information regarding management of protocol amendments can be found in Section 5.2.

4.5 Reporting Adverse Events

For details regarding AE and SAE reporting, see Section 3.7.3.

4.6 Investigator's Final Report

Upon completion of the study, the Investigator will provide Akros with a copy of the summary of the study's outcome provided to the IRB.

4.7 Records Retention

The Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity and use by subjects. If the investigation is terminated, suspended, discontinued or completed, the Investigator shall return the unused supplies of the drug to the sponsor or otherwise provide for disposition of the unused supplies of the drug under the US 21 CFR Part 312.59.

The Investigator shall retain records required to be maintained under this part for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the Food and Drug Administration is notified.

Akros should inform the Investigator(s)/institution(s) in writing of the need for record retention and should notify the Investigator(s)/institution(s) in writing when the study related records are no longer needed.

Custody of the records may be transferred to another responsible party, acceptable to Akros, who agrees to abide by the retention policies. Written notice of transfer must be submitted to Akros. The Investigator must contact Akros and obtain prior written permission prior to disposing of or transferring any study records.

4.8 Confidentiality

The Investigator, Akros and its representatives, agree to protect the privacy and confidentiality of the protected health information in accordance with applicable laws and regulations.

Subject's medical information obtained by the study is confidential and disclosure to third parties is prohibited unless required by law. The Investigator shall retain all such information and any other information designated by Akros as confidential or is otherwise of reasonably confidential nature, in confidence and shall not use such information for any purpose other than the performance of obligations pursuant to the agreement with Akros and designated affiliates or contractors, as the case may be, without prior written authorization from Akros.

At the subject's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection on request by representatives of regulatory authorities, Akros and the IRB(s) if appropriate.

4.9 Publications

The Investigator agrees that all data, calculations, interpretations, opinions and recommendations regarding the study shall be the sole and exclusive property of Akros and that Akros may make any use thereof at its discretion without obligation to Investigator. The Investigator agrees to consider the results as information subject to confidential and use restrictions.

In the event that the study results are published in the scientific literature by Akros, acknowledgment will be made to the Investigator(s) in the accepted style, as appropriate. The names of the Investigators or their representatives shall not be used by Akros in publications, for advertising, for other commercial purposes or otherwise, without appropriate written permission, unless required by law or government regulation.

Individual study center manuscript(s) for publication, text for talks, abstracts of papers, poster presentations and similar material will be submitted to Akros for review and comment prior to publication or disclosure. In order to ensure that Akros will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to Akros for review at least sixty (60) days prior to submission for publication, public dissemination or review by a third party committee. Akros will have sixty (60) days from receipt of such information to review and comment on and discuss the contents thereof with the Investigator.

If Akros requests, the Investigator will remove any and all confidential information (other than study results) prior to submitting or presenting the materials. Upon Akros request, the Investigator will delay submitting or presenting the materials for a further sixty (60) days to permit Akros to take necessary actions to protect its confidential information, including filing of patent applications thereon.

5 STUDY MANAGEMENT

5.1 Monitoring

Monitoring visits will be conducted by Akros or designee according to applicable regulations and guidelines for GCP. The Investigator will permit Akros and/or designee to make regular site visits during the study. The frequency of monitoring visits will be agreed upon by Akros and/or designee. At each visit, the Investigator and staff will be expected to cooperate with Akros or designee for the review and verification of protocol compliance, AE reporting, CRFs, source documents, clinical supplies and inventory records and any additional records as may have been previously arranged between the Investigator and Akros or designee.

The Investigator and/or other designated study personnel are expected to contact the Akros monitor or designee as needed regarding study concerns and/or questions.

5.2 Management of Protocol Amendments and Deviations

With the exception of emergency situations, implementation of any change in the protocol that affects safety of the subjects, scope of the investigation or scientific quality of the study will not be permitted until Akros and the Investigator have approved the protocol amendment and the IRB responsible for review and approval of the study has reviewed and approved the protocol change.

Implementation of changes that do not affect the safety of subjects, scope of the investigation or scientific quality of the study cannot be made until the protocol changes are reviewed and approved by Akros and the Investigator. The IRB must be notified of these protocol changes. The Investigator will not deviate from the protocol without prior written approval from Akros.

5.3 Study Termination

The study may be terminated at any time at the request of Akros with proper and timely notification of all parties concerned. The IRB will be informed promptly and reasons for the termination or suspension will be provided by Akros, as specified in the applicable regulatory requirements. The study can be considered complete and/or terminated after Akros has received the following data and materials:

- Laboratory findings, clinical data and all special test results from screening through the end of the Follow-up Period
- CRFs properly completed by appropriate study personnel (including correctly answered and closed system or manually-generated edit checks) and signed by the Investigator
- Completed Drug Accountability Records
- Statement of outcome for each SAE reported

- Approval/notification of protocols and protocol amendments from IRB as well as relevant health authorities (if applicable)

5.4 Sponsor's Final Report

A final report will be prepared by Akros or a designee at the conclusion of this clinical study.

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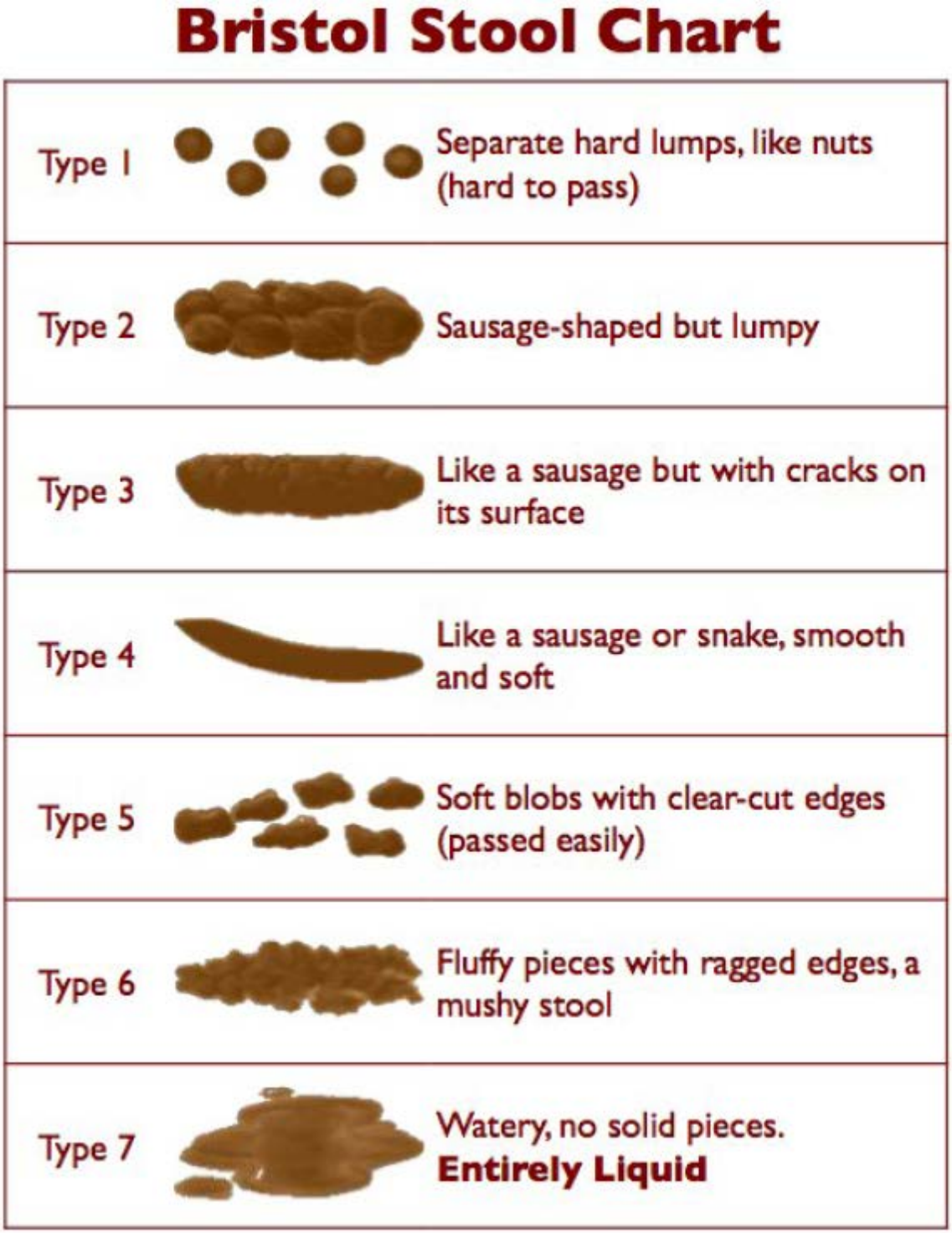
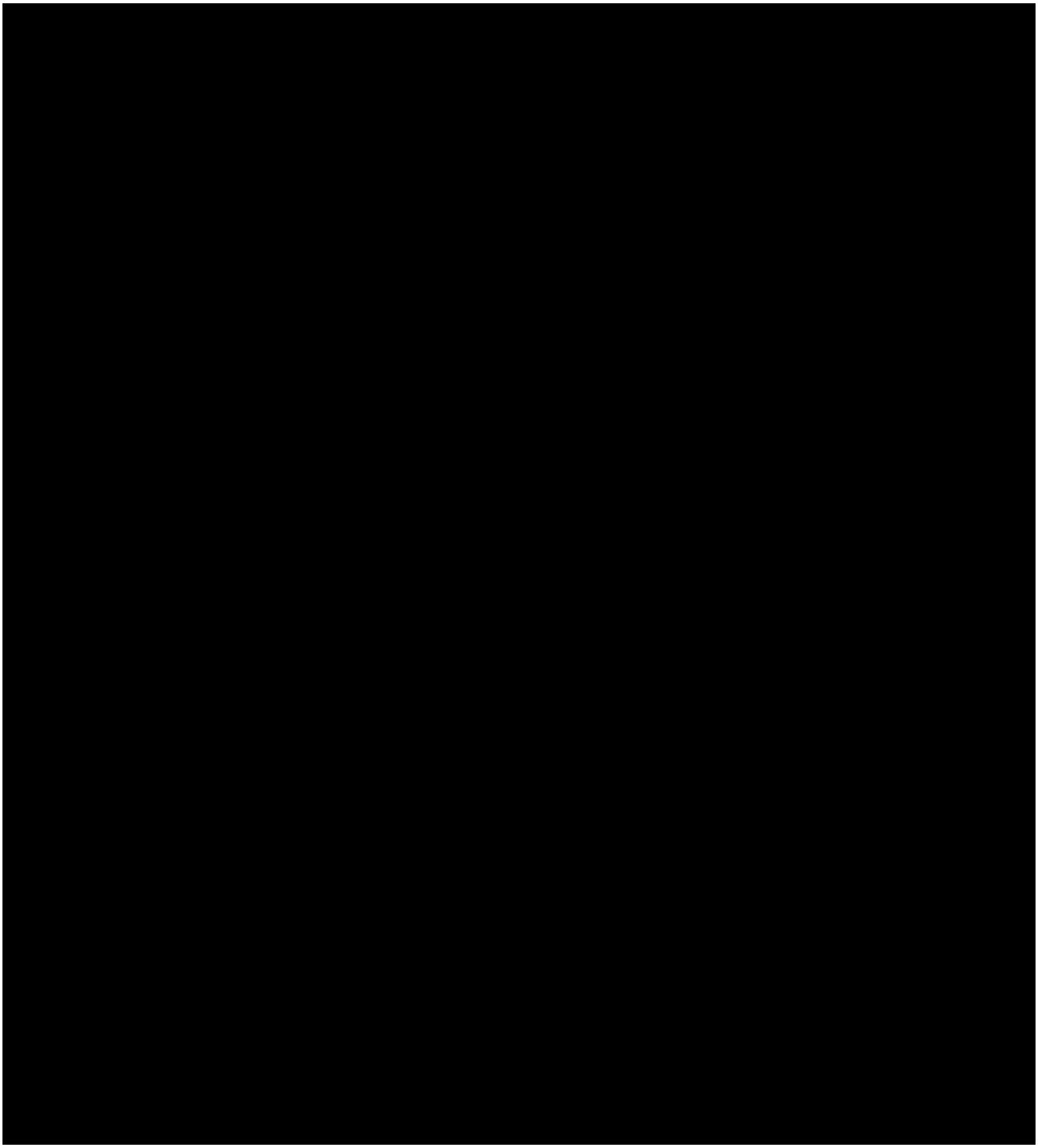
7 APPENDICES

Appendix 1. Bristol Stool Chart





Appendix 3. Strategies for Treatment of Hypoglycemia in Subjects with T2DM

JTT-662 is expected to have a glucose-lowering effect by reducing intestinal glucose absorption *via* selective inhibition of SGLT1. JTT-662 did not cause hypoglycemia in animals or in healthy subjects receiving JTT-662 [redacted] Therefore, the risk of hypoglycemia in T2DM subjects may be low (even in combination with metformin). However, appropriate precautionary measures should be taken to ensure early recognition and appropriate management of hypoglycemic events throughout the study duration.

[redacted]

In reporting an AE of hypoglycemia, the following definitions should be used:

- Asymptomatic hypoglycemia: plasma glucose measurements <70 mg/dL (<3.9 mmol/L) without associated symptoms.
- Symptomatic hypoglycemia: plasma glucose measurements <70 mg/dL (<3.9 mmol/L) and associated with characteristic symptoms of hypoglycemia (e.g., chills, sweats, shakes, tachycardia, altered mental status, dizziness/lightheadedness, withdrawn attitude).
- Severe hypoglycemia: plasma glucose measurements <50 mg/dL (<2.7 mmol/L) regardless of symptoms.

Symptoms associated with plasma blood glucose levels of 70 mg/dL (3.9 mM) or greater should be reported as such, and not reported as hypoglycemia.

Managing Hypoglycemic AEs:

- The Investigator (or designee) will educate the subjects to recognize signs and symptoms associated with hypoglycemia and to notify the site staff immediately if they occur.

[redacted]

- If the subjects experience severe hypoglycemia, parenteral glucose may be considered.
- In case of emergency (e.g., stupor, coma, abnormal breathing, general or focal seizures) the local emergency services should be immediately contacted by the site staff.
- If repeated hypoglycemic episodes are encountered by a subject without an underlying explanatory condition, the Investigator may decide to discontinue JTT-662 administration in that subject.

The above are suggested measures, and the Investigator should exercise medical and scientific judgement in treating subjects, as other standard of care strategies could apply.