Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

ClinicalTrials.gov Identifier: NCT01953081
Theravance Study Identifier: TD-8954-0082
Takeda Study Identifier: TAK-954-0082

CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Double-Blind Study to Evaluate the Safety, Tolerability, and Pharmacodynamics of a Single Dose of Intravenous TD-8954 Compared With Metoclopramide in Critically Ill Patients With Enteral Feeding Intolerance
Sponsor Study No.:	0082
Date:	09 April 2014, Amendment 3
Test Product:	TD-8954
US IND:	114408
Sponsor:	Theravance, Inc. 901 Gateway Boulevard South San Francisco, California 94080 USA Telephone: (650) 808-6000 Facsimile: (650) 808-6464
Clinical Study Director:	PPD

This study will be conducted according to the principles of Good Clinical Practice.

CONFIDENTIAL

PROTOCOL SYNOPSIS

Study Number and Title: Study 0082: A Randomized, Double-Blind Study to Evaluate the Safety, Tolerability and Pharmacodynamics of a Single Dose of Intravenous TD-8954 Compared with Metoclopramide in Critically Ill Patients With Enteral Feeding Intolerance

Study Short Title: TD-8954 Single Dose, Intravenous, Safety and Pharmacodynamic Study in Enteral Feeding Intolerance

Estimated Number of Study Centers and Countries or Regions: Up to ten Clinical Research Centers in Australia and the United States

Background and Rationale:

Critical illness is well recognized as being associated with hypercatabolism, resulting in loss of muscle mass, impaired organ function, and reduced reparative and immune function {1}. In critically ill patients, the addition of nutritional deprivation or malnutrition is associated with further impairment of immunological function, increased risk of infection, prolongation of mechanical ventilation, increased length of intensive care unit (ICU) and hospital stay and ultimately higher mortality {2, 3}. To minimize the complications associated with malnutrition during critical illness, the practice of nutritional support (by either enteral or parenteral routes) has become a standard treatment in these patients.

Enteral nutritional support is preferred in critical illness as it is inexpensive, has fewer infective complications, and is associated with preservation of gut mucosal barrier function, compared with parenteral feeding. Disturbances in gastrointestinal motility, however, are common, and subsequent intolerance of nasogastric (NG) feeding occurs in up to 60% of critically ill patients {4}. This compromises the nutritional status of patients and increases their risk of gastroesophageal reflux and aspiration, which adversely affects both morbidity and mortality {5, 6}.

Serotonin (5-hydroxytryptamine) type 4 (5-HT_4) receptor agonists are established as efficacious gastrointestinal (GI) prokinetic agents for the treatment of indications involving GI tract dysfunction characterized by reduced motility. TD-8954 is a potent and highly selective 5-HT_4 receptor agonist being evaluated for the treatment of clinically significant GI motility disorders, including ileus and enteral feeding intolerance (EFI) in critically ill patients. Critical illness often adversely affects GI motility, and severe GI dysmotility has been described in mechanically ventilated patients, for whom the most obvious consequence is EFI.

TD-8954 has been evaluated in single and multiple ascending dose studies in healthy male and female subjects aged 18 to 64 years old at doses ranging from 0.1 mg to 20 mg given orally (PO). The most common adverse events were mild to moderate headache, nausea, and vomiting in the single-dose regimen and mild to moderate headache and diarrhea in the multiple-dose regimen. There were no serious adverse events (SAE) reported in either study. Moderate transient orthostatic hypotension was reported in one of six subjects (17%) in the 10-mg single-dose group and two of six subjects (33%) in the 20-mg single-dose group; mild fever was observed in one of six subjects (17%) in the 5-mg multiple-dose group. Atrioventricular dissociation was reported as an AE with mild severity in two of three subjects (67%) after the Day 1 dosing in the 10-mg multiple-dose group, which resolved spontaneously without treatment, and upon review of available electrocardiograms (ECGs)

PROTOCOL SYNOPSIS (CONTINUED)

by 3 independent cardiologists, was not viewed to be dose limiting. Dose escalation was stopped at 20 mg because of the occurrence of moderate orthostatic hypotension in two subjects in the 20 mg single-dose cohort. No clinically significant ECG abnormalities were observed in the 20 mg single-dose cohort. No clinically significant changes in hematology, clinical chemistry, or urinalysis were observed.

TD-8954 has also been evaluated in a repeated intravenous (IV) dose study (0095) in healthy adults aged 18 to 45 years old at IV doses ranging from 0.1 mg to 0.5 mg once daily (QD) for up to 5 consecutive days. No SAEs were reported for this trial. The most common AEs (i.e., headache, postural dizziness) were not clinically significant, resolved spontaneously, and did not recur with subsequent dosing. Two subjects (one TD-8954 and one placebo) experienced modest and transient increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which were not clinically significant and resolved spontaneously. Additionally, three subjects (two receiving TD-8954 0.5 mg, one receiving TD-8954 0.1 mg) experienced modest and transient cardiovascular AEs (i.e., postural tachycardia, postural dizziness) after the first dose; these events were not clinically significant and resolved spontaneously, and were not observed upon re-challenge (subsequent dosing) of subjects.

The pharmacokinetics of TD-8954 following multiple IV doses of 0.1 and 0.5 mg revealed a half-life of approximately 18 hours. Steady state was achieved in 3 days and there was <2-fold accumulation in PK after 5 days of daily dosing with 0.5 mg.

Overall, the observed safety and pharmacokinetic (PK) profiles support continued evaluation of TD-8954.

The current study is being conducted to evaluate the safety, tolerability and early efficacy of IV TD-8954 in critically ill subjects, aged 18 to 85 years, who are admitted to the intensive care or trauma unit, require mechanical ventilation, and are intolerant to enteral feeding.

Dose Rationale:

CCI

[redacted]

CCI

[redacted]

t

PROTOCOL SYNOPSIS (CONTINUED)

CCI [redacted]

Objectives:

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of a single IV dose of TD-8954 in subjects with enteral feeding intolerance (EFI)
- To evaluate the pharmacodynamics (PD) of IV TD-8954 in subjects with EFI based on gastric emptying as measured by scintigraphy

Secondary objectives of this study are as follows:

- To evaluate the pharmacokinetics (PK) of IV TD-8954
- To evaluate the PD of IV TD-8954 based on gastric emptying assessment by ^{13}C breath test

Additional objectives of this study are as follows:

- CCI [redacted]

Study Design: This is a Phase 2a, randomized, double-blind study to evaluate the safety, tolerability, and PD of single-dose IV TD-8954 compared with metoclopramide in critically ill patients with EFI.

Up to a total of 60 subjects will be enrolled in this study. Subjects will be randomized in a 1:1 ratio to one of two parallel treatments to receive either a single dose of 0.5 mg IV TD-8954 (Treatment Group A) or 10 mg IV metoclopramide every 6 hours for 24 hours (Treatment Group B).

PROTOCOL SYNOPSIS (CONTINUED)

Study medication will be prepared double-blinded in double-dummy fashion such that subjects randomized to Treatment Group A will receive a 1-hour IV infusion of TD-8954 0.5 mg and IV injections of 0.9% sodium chloride every 6 hours (sham metoclopramide; total of 4 injections), and subjects randomized to Treatment Group B will receive a 1-hour IV infusion of 0.9% sodium chloride (sham TD-8954) and IV injections of 10 mg metoclopramide every 6 hours (total of 4 injections). The first dose of metoclopramide or sham metoclopramide will be administered up to 15 minutes prior to the end of the TD-8954 or sham TD-8954 infusion.

Immediately after dosing with study medication has finished (i.e., at the end of the one-hour infusion and after receiving the first injection of metoclopramide/sham metoclopramide), subjects will receive a standard test 'meal' consisting of 100 mL of Ensure® containing 106 kcal with 21% of fat, mixed with 100 µL ^{13}C octanoate, and will undergo breath test assessment through 240 minutes after dosing with study medication (Table 1). At selected sites 20 MBq ^{99m}Technitium calcium phytate or ^{99m}Technitium sulphur colloid will be added to the test 'meal' and those subjects will undergo scintigraphic assessment through 240 minutes after dosing with study medication. In addition, subjects who have not received CCI [redacted] In addition, at the end of the scintigraphy and breath test, the stomach will be emptied, the aspirate volume will be recorded, the aspirate will be discarded, feeding will be recommenced at the goal rate (as determined according to the usual ICU feeding protocol), and CCI [redacted].

Blood samples for safety and TD-8954 PK assessments will be collected beginning on Day 1 through the 72 hours after dosing. In addition, after safety assessments through Day 5 have been completed the subject's active participation in the study will conclude; however, information regarding the subject's enteral feeding outcome and their ICU and hospital discharge status will be collected up to Day 30.

Study Procedures:

Screening

- A screening period of up to 24 hours will precede randomization into the study; however, subjects may be enrolled as soon as eligibility criteria are met.
- During the screening period, all consented subjects will have a medical history, physical examination, ECG, and safety laboratory tests performed.

Pre-dose and Treatment Period

- Upon confirmation of eligibility, next of kin or legal authorized representative will be approached for consent and if consent is obtained subjects will be randomized into the study. Feed administration will cease and the stomach will be aspirated and the

PROTOCOL SYNOPSIS (CONTINUED)

volume will be documented. The subject will then be fasted for 2 hours, after which pre-dose procedures will be performed, and will receive study medication and undergo Day 1 study procedures according to Table 1.

- Immediately following study medication administration, subjects will receive a test meal and undergo scintigraphy (at selected sites) and breath test assessments (at all sites) over the subsequent 240 minutes.
- Following the completion of the 4 hour scintigraphic and breath test measurements, the stomach will be aspirated and the volume documented, then feeding will be recommenced at goal rate and CCI [redacted]
- In subjects who are eligible to participate CCI [redacted]
- Additional blood samples will be collected for motilin plasma levels at pre-dose (prior to start of infusion) and 15, 30, 60, 120, 180, and 360 minutes (0.25, 0.5, 1, 2, 3, and 6 hours) after the end of infusion.
- Vital signs, ECGs, adverse events and concomitant medications will be recorded on a daily basis during the treatment period according to Table 1.

Follow up

- Twenty-four hours after dosing with study medication, subjects will resume standard therapy as necessary based on investigator judgment.
- Subjects will be followed for 72 hours after dosing with study medication on Day 1 for TD-8954 PK and through Day 5 for safety, at which time the subject's active participation in the study concludes.
- In addition, the outcome of enteral feeding and ICU and hospital discharge will be collected for each subject when available up to Day 30.

Duration of Study Participation:

Following a screening period of up to 24 hours, eligible subjects who qualify will participate in the study for 5 days, consisting of treatment and follow-up, for a total duration of up to 6 days of active participation.

Number of Subjects per Group:

Up to 60 subjects will be randomized to one of two treatment groups, either TD-8954 or metoclopramide, in a 1:1 ratio.

Study Population:

Adult men and women, 18 through 85 years of age (inclusive), who are intubated, on mechanical ventilation, receiving enteral feeding, and meet the inclusion and exclusion criteria below:

Inclusion Criteria:

1. Adult male or female 18 to 85 years of age (inclusive)
2. Anticipated to live and be able to undergo active treatment, complete all study procedures and follow up for more than 4 days from enrollment into the study
3. If on vasopressors at the time of randomization, stable or reduced vasopressor

PROTOCOL SYNOPSIS (CONTINUED)

requirements (as assessed by the investigator) compared to the previous calendar day

4. Intubated, on mechanical ventilation, and anticipated to remain on mechanical ventilation for 2 days after enrollment into the study
5. Receiving enteral feeding and assessed to have developed EFI, as defined by a GRV measurement ≥200 mL within the 24 hours before randomization
6. For a female subject of childbearing potential, a documented negative pregnancy test at screening
7. Provided written informed consent in accordance with guidelines set by the hospital and approved by the Institutional Review Board or Ethics Committee

Exclusion Criteria:

1. Receipt of any investigational agent or use of an investigational medical device within 30 days of screening or previous receipt of TD-8954 in a clinical trial
2. Known hypersensitivity to TD-8954 or formulation excipients
3. Known hypersensitivity or contraindication to metoclopramide
4. History of diabetic or idiopathic gastroparesis
5. Screening blood glucose >15 mmol/L (270 mg/dL) while receiving insulin
6. Impaired renal function, as defined by estimated creatinine clearance rate eCCR<30 mL/min, as determined by the Cockcraft-Gault formula, unless receiving intermittent or continuous dialysis at the time of randomization

   eCCR = ((140 – Age) * Mass * 1 if Male or 0.85 if Female) / (72 * Serum Creatinine))
7. Bilirubin concentration in blood >2 times the upper limit of normal
8. ALT or AST >3 times upper limit of normal
9. Alkaline phosphatase >2 times upper limit of normal
10. Contraindication to enteral feeding
11. Significant direct GI tract trauma, as determined by the Principal Investigator (PI) to be contraindicated for this study
12. Opioid or other drug overdose as the primary reason for admission to Intensive Care Unit (ICU)
13. Receipt of a drug that can be used as a gastric prokinetic agent in the previous 24 hours (e.g., erythromycin, metoclopramide), 48 hours for domperidone, or receipt of azithromycin within the previous 2 weeks or any other drug given in the timeframe that in the opinion of the principal investigator could potentially confound the efficacy results of the study, unless the prokinetic drug has been stopped and 2 consecutive GRVs done at a minimum of 4 hours apart prior to randomization remain >200 mL
14. Receipt of agents known to directly influence the 5-HT_4/acetylcholine prokinetic mechanism (e.g., serotonin-specific reuptake inhibitors, anticholinergic agents or acetylcholinesterase inhibitors) within the 72 hours before randomization
15. A sustained (≥1 minute) pulse rate ≥150 bpm that is determined to be clinically significant and required treatment within 24 hours before randomization
16. Mean QTc interval greater than 450 msec in males or greater than 470 msec in females (after triplicate measures performed 1 minute apart)

PROTOCOL SYNOPSIS (CONTINUED)

17. History of congenital long QT syndrome
18. Clinically significant electrocardiogram (ECG) abnormalities indicative of acute cardiac instability, as determined by the investigator, at screening; more than first degree AV block; >5 beats of non-sustained VT at a rate >120 BPM; ECG changes consistent with acute myocardial ischemia or infarction.
19. A history of or current major esophageal or gastric surgery on this admission (major lower abdominal surgery will not result in exclusion unless this carries a contraindication to enteral feeding)
20. Gastric pacemaker

CCI

[redacted]

Test Product, Dose, and Route of Administration; Regimen; Duration of Treatment:

Test product in this study will be a single dose of TD-8954 (0.5 mg) administered as a 1-hour IV infusion using an IV pump (Treatment Group A). Study medication will be prepared as double-blind in double-dummy fashion, such that subjects randomized to Treatment Group A will also receive sham metoclopramide IV injections every 6 hours for 24 hours (four injections in total). The first sham metoclopramide IV injection will be administered up to 15 minutes prior to the end of the TD-8954 IV infusion. The 2nd, 3rd, and 4th sham metoclopramide injections will be administered at 6, 12, and 18 hours after the first sham metoclopramide injection.

Reference Therapy, Dose, and Route of Administration; Regimen; Duration of Treatment:

Reference therapy in this study will be metoclopramide 10 mg administered every 6 hours for 24 hours by IV injection (Treatment Group B).

Study medication will be prepared double-blinded in double dummy fashion such that subjects randomized to Treatment Group B will receive 1-hour IV infusion of 0.9% sodium chloride using an IV pump (sham TD-8954) and up to 15 minutes prior to the end of the infusion will receive an IV injection of 10 mg metoclopramide. Subjects randomized to Treatment Group B will also receive 10 mg metoclopramide injections at 6, 12, and 18 hours after the first metoclopramide injection.

PROTOCOL SYNOPSIS (CONTINUED)

Study Evaluations

Safety Assessments:

Adverse events will be reviewed and collected from the time of consent through the final follow-up assessment on Day 5. Serious Adverse Events will be collected through Day 30.

- Vital signs (heart rate, blood pressure, and ventilation status), ECGs and safety laboratory assessments will be collected and monitored pre-dose and post-dose through the final follow-up assessment on Day 5 according to the schedule in Table 1.

Pharmacokinetic Assessments:

All TD-8954 PK sampling times are to be calculated on the basis of the start time of IV infusion administration (TD-8954 or sham TD-8954), with the exception of the time point taken immediately before infusion completion. The schedule for collection times is presented in the schedule of study procedures (Table 1).

Pharmacodynamics/Efficacy Assessments:

- Scintigraphy and breath test assessments on Day 1 (Table 1)
- GRV assessments (screening, pre-dose and at 6-hour intervals throughout the study, except during scintigraphy and breath test assessments) (Table 1)
- CCI [redacted]
- Blood collections for motilin plasma levels (Table 1)
- Outcome of enteral feeding (i.e., type of nutritional support they are receiving such as enteral feeding, TPN or PPN,) and disposition of subject on Day 30 (i.e., ICU and hospital discharge, if available)

Statistical Methods:

Sample Size:

CCI [redacted] A sample size of 30 critically ill subjects in each group (60 in total) should provide initial characterization of safety assessments within this setting.

Study Endpoints:

The primary endpoints of the study are:

- Safety and tolerability of TD-8954 in critically ill patients (adverse events, ECGs, laboratory assessments and vital signs)
- Scintigraphic percentage retention at 180 minutes

The secondary endpoints of the study are:

- Scintigraphic parameters (percentage retention at 60,120, and 240 minutes, gastric emptying $t_{1/2}$, area under the retention curve in available subjects)
- Breath test parameters ($t_{1/2}$,t_{lag} and GEC)
- Pharmacokinetic parameters of IV TD-8954

Additional exploratory PD endpoints are:

- CCI [redacted]

PROTOCOL SYNOPSIS (CONTINUED)

- CCI
- [redacted]

Analysis:

The co-primary safety objective will be evaluated using safety data through Day 5 and will be listed by subject and summarized by treatment using the frequency of event or descriptive statistical summaries, as appropriate. All safety data will be presented in listings. Summary tables will be provided for adverse events, hematology and chemistry laboratory evaluations, vital signs, 12-lead ECG findings, and concomitant medications.

The co-primary endpoint of mean percentage retention at 180 minutes will be summarized and compared descriptively using one-sided 95% confidence intervals (two-sided 90% confidence intervals).

Scintigraphy and breath test parameters will be summarized.

CCI
[redacted]

General Statistical Reporting:

All continuous variables will be presented using an 8-point descriptive summary (n, mean, standard deviation, median, Interquartile range (Q1, Q3), minimum and maximum) by treatment group and 24-hour period (Day), as available. Categorical variables will be summarized by frequency and by percentage of subjects in corresponding categories. For vital signs and ECG parameters, absolute values and change from baseline will be summarized descriptively by treatment group and day at each time point.

Additional analyses may be conducted as appropriate.

SCHEDULE OF STUDY PROCEDURES

Table 1: Schedule of Study Procedures

Procedure	Screening (up to 24 hours before randomization)	Day 1		Day 2	Day 3	Day 4	Day 5 / Study Completion/Early Withdrawal[m]	Follow up[l]
		Baseline (immediately before dosing)	Post-Dose					
Informed Consent	X							
Review Inclusion/Exclusion Criteria	X	X						
Medication and Medical History	X	X						
Vital Signs[a]	X	X	X	X[o]	X[o]	X[o]	X[o]	
Physical Examination	X						X	
12-Lead ECG[a]	X	X	X	X	X	X	X	
Urine Pregnancy Test[b]	X							
Hematology and Chemistry	X			X	X	X	X	
Randomization		X						
Study Drug Dosing[c]			X	X				
CCI								
Test Meal[e]			X					
Scintigraphy[f]			X					
^{13}C Breath Test[g]			X					
PK Samples for TD-8954[h]		X	X	X	X	X		
CCI								
Plasma Motilin Samples[j]		X	X					
Restart enteral feeding at goal rate[k]			X					
Concomitant Medications	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	
APACHE II Parameters[n]	X	X					X	
Outcome Measures[l]							X	X

SCHEDULE OF STUDY PROCEDURES (CONTINUED)

Abbreviations: ECG, electrocardiogram; CCI; PK, pharmacokinetic; CCI

a 12-Lead ECGs will be collected (in triplicate at intervals of approximately 1 minute), at the following time points: screening, pre-dose (immediately prior to randomization), and 1(+/- 15 min), 6 (+/- 15 min), 12(+/- 15 min), 24(+/- 15 min) , and 48 (+/- 15 min) hours after the start of the infusion; vital signs will be performed at screening, and pre-dose (within 30 min prior to infusion), 0.5, 1, 2, 6, and 12 hours post-dose. 12-Lead ECGs done on Study Day 3 and Day 4 will be a single collection and not triplicate.

b Urine pregnancy test will be performed for all females subjects of child-bearing potential. If previously done during this hospitalization it does not need to be repeated.

c Subjects will receive study medication as a one-time 1-hour infusion and four single IV boluses (every 6 hours x 4) beginning on Day 1 through Day 2.

d CCI .

e Immediately after dosing with study medication has finished (i.e., at the end of the one-hour infusion and after injection of study medication), subjects will receive a standard test 'meal' consisting of 100 mL of Ensure® containing 106 kcal with 21% of fat, mixed with 20 MBq 99mTechnitium-Calcium phytate or 99mTechnitium sulphur colloid (at selected sites) and 100 µL ^{13}C octanoate, and if eligible to participate, 1000 mg paracetamol/acetaminophen.

f At selected sites immediately after the 1-hour IV infusion completes (TD-8954 or sham TD-8954),subjects will begin scintigraphy testing including measures at 0 min, 60min, 2 hrs, 3 hrs, and 4 hrs following administration of the test meal. Timepoints at 60 min and 2 hrs will be optional, all other timepoints are required.

g Immediately after the 1-hour IV infusion completes and the test meal has been given (TD-8954 or sham TD-8954),subjects will begin ^{13}C breath testing measurements every 15 minutes up to and including 4 hrs following administration of the test meal. Prior to the test meal samples will be taken at two time points at least 5 minutes apart and can be taken up to 30 minutes prior to test meal,

h PK samples for TD-8954 will be collected beginning on Day 1 through 4 according to the following schedule:

- Day 1: Pre-dose within 30 minutes of dosing, 30 min after the start of the infusion, 60 minutes after the start of the infusion (immediately prior to infusion completion), 75 min (+/- 15 min), 90 min (+/- 15 min), 2(+/- 15 min), 3(+/- 15 min), 4(+/- 15 min), 6(+/- 15 min), 8(+/- 15 min), 10(+/- 15 min), and 12 hours(+/- 15 min) after the start of the TD-8954/sham TD-8954 infusion.
- Days 2-4: 24(+/- 15 min), 48(+/- 15 min) and 72 hours (+/- 15 min) after dosing on Day 1.

i CCI

j Plasma samples for motilin levels will be collected at pre-dose (prior to infusion), and 15min (+/- 5 min),. 30min (+/- 5 min),., 60min (+/- 10 min), 2 hrs. (+/- 15 min), 3 hrs. (+/- 15 min), and 6 hrs. (+/- 15 min), (0.25, 0.5, 1, 2, 3 and 6 hours) after the end of infusion.

k CCI

l

m Subjects who withdraw early should have these procedures performed.

n. APACHE II parameters will be collected at screening, on treatment day prior to dosing (most recent variables, i.e., most temporal to treatment start) and on study day 5 (worst available values for Day 5).

o. On Day 2-4 vital signs will be documented twice, one will be the highest value and one will be the lowest value noted for each variable in that calendar day.

TABLE OF CONTENTS

PAGE

TABLE OF CONTENTS (CONTINUED)

PAGE

TABLE OF CONTENTS (CONTINUED)

PAGE

TABLE OF CONTENTS (CONTINUED)

PAGE

TABLES

FIGURES

APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
5-HT_4	serotonin type 4 receptor
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BLQ	below the level of quantification
BP	blood pressure
bpm	beats per minute
BMI	body mass index
BUN	blood urea nitrogen
CFR	(United States) Code of Federal Regulations
CI	confidence interval
CL_r	renal clearance
C_{max}	peak plasma concentration (observed)
CRF	case report form
CV	coefficient of variation
eCCR	estimated creatinine clearance rate
ECG	electrocardiogram
EDC	electronic data capture
EFI	enteral feeding intolerance
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
CCI	[redacted]
GI	gastrointestinal
CCI	[redacted]
hERG	human *ether-à-go-go*-related gene
HLGT	high level group term
HLT	high-level term
HR	heart rate
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	intensive care unit
IEC	Independent Ethics Committee
IQR	interquartile range
IRB	Institutional Review Board
ITT	intent to treat
IV	intravenous
IWRS	Interactive Web Response System

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
K_i	binding affinity
LLT	lower level term
MedDRA	Medical Dictionary for Regulatory Activities (MedDRA®)
NG	nasogastric
PAT	paracetamol/acetaminophen absorption test
PD	pharmacodynamic(s)
PI	principal investigator
PK	pharmacokinetic(s)
PP	per protocol
PPN	partial parental nutrition
QD	once a day
QTc	corrected QT interval
QTcF	QT interval corrected using Fridericia's formula
REB	Research Ethics Board
SAE	serious adverse event
SDRC	Safety Data Review Committee
SG	Subgroup
SOC	system organ class
SOP	standard operating procedure
$t_{½}$	terminal elimination half-life
T_{max}	time to reach peak plasma concentration (observed)
TEAE	treatment emergent adverse event
TMF	Trial master file
TPN	total parenteral nutrition
V_z/F	oral volume of distribution during terminal phase

1 INTRODUCTION

Critical illness is well recognized as being associated with hypercatabolism, resulting in loss of muscle mass, impaired organ function, and reduced reparative and immune function {1}. In critically ill patients, the addition of nutritional deprivation or malnutrition is associated with further impairment of immunological function, increased risk of infection, prolongation of mechanical ventilation, increased length of intensive care unit (ICU) and hospital stay and ultimately higher mortality {2, 3}. To minimize the complications associated with malnutrition during critical illness, the practice of nutritional support (by either enteral or parenteral routes) has become a standard treatment in these patients.

Enteral nutritional support is preferred in critical illness as it is inexpensive, has fewer infective complications and is associated with preservation of gut mucosal barrier function, compared with parenteral feeding. Disturbances in gastrointestinal (GI) motility, however, are common, and subsequent intolerance of nasogastric (NG) feeding occurs in up to 60% of critically ill patients {4}. This compromises the nutritional status of patients and increases their risk of gastroesophageal reflux and aspiration, which adversely affects both morbidity and mortality {5, 6}.

TD-8954 has been evaluated in single and multiple ascending dose studies in healthy male and female subjects aged 18 to 64 years old at doses ranging from 0.1 mg to 20 mg given orally (PO). The most common adverse events (AE) were mild to moderate headache, nausea, and vomiting in the single dose regimen, and mild to moderate headache and diarrhea in the multiple dose regimen. There were no serious adverse events (SAE) reported in either study. Moderate transient orthostatic hypotension was reported in one of six subjects (17%) in the 10mg single-dose group and two of six subjects (33%) in the 20 mg single-dose group; mild fever was observed in one of six subjects (17%) in the 5 mg multiple-dose group. Atrioventricular dissociation reported as an AE with mild severity in two of three subjects (67%) after the Day 1 dosing in the 10 mg multiple-dose group, which resolved spontaneously without treatment, and upon review of available electrocardiograms (ECG) by 3 independent cardiologists, was not viewed to be dose limiting. No clinically significant changes in hematology, clinical chemistry, or urinalysis were observed. Evidence of GI prokinetic activity (increased bowel movement frequency, and reduced consistency and time to the first bowel movement) was observed at all dose levels.

TD-8954 has also been evaluated in a repeated IV dose study (0095) in healthy adults aged 18 to 45 years old at IV doses ranging from 0.1 mg to 0.5 mg once daily (QD) for up to 5 consecutive days. No SAEs were reported for this trial. The most common AEs (i.e., headache, postural dizziness) were not clinically significant, resolved spontaneously, and did not recur with subsequent dosing. Among these AEs, two subjects (one TD-8954 and one placebo) experienced modest and transient increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which were not clinically significant and resolved spontaneously. Additionally, three subjects (two receiving TD-8954 0.5 mg, one receiving TD-8954 0.1 mg) experienced modest and transient cardiovascular AEs (i.e., postural tachycardia, postural dizziness) after the first dose; these events were not clinically significant and resolved spontaneously, and were not observed upon re-challenge (subsequent dosing) of subjects.

The half-life of TD 8954 in plasma ranged from 16.0 to 19.1 hours after repeat oral administration and steady state exposure was achieved by Day 4. Plasma exposure following repeat TD 8954 administration increased by approximately two-fold from Day 1 to Day 10. The PK of TD-8954 following multiple IV doses of 0.1 and 0.5 mg revealed a half-life of approximately 18 hours. Steady state was achieved in 3 days and there was <2 fold accumulation in pharmacokinetic (PK) after 5 days of daily dosing with 0.5 mg.

Overall, the observed safety and PK profiles support continued evaluation of TD-8954.

The current study is being conducted to evaluate the safety, tolerability and early efficacy of IV TD-8954 in critically ill subjects aged 18 to 85 years, who are admitted to the intensive care or trauma unit, require mechanical ventilation, and are intolerant to enteral feeding.

1.1 Rationale

Serotonin (5-hydroxytryptamine) type 4 (5-HT_4) receptor agonists are established as efficacious gastrointestinal (GI) prokinetic agents for the treatment of indications involving GI tract dysfunction characterized by reduced motility. TD-8954 is a potent and highly selective 5-HT_4 receptor agonist being evaluated for the treatment of clinically significant GI motility disorders, including ileus and enteral feeding intolerance (EFI) in critically ill patients. Critical illness often adversely affects GI motility, and severe GI dysmotility has been described in mechanically ventilated patients, for whom the most obvious consequence is EFI.

1.2 Nonclinical Profile

A review of the nonclinical profile of TD-8954 can be found in the current version of the TD-8954 Investigator's Brochure (IB). The following is a brief summary of the pertinent findings.

1.2.1 Pharmacology

In vitro, TD-8954 displays preferential binding to 5-HT_4 receptors over all other 5-HT receptor subtypes. TD-8954 is a high-affinity, potent agonist with high or moderate intrinsic activity at human recombinant 5-HT_4 receptors and 5-HT_4 receptors in guinea pig isolated colon, respectively. TD-8954 is highly selective for the 5-HT_4 receptor, demonstrating little activity at the human *ether-à-go-go*-related gene (hERG) potassium channel or 5-HT_{3A} or 5-HT_{2B} receptors. TD-8954 has at least 2,500-fold selectivity for recombinant 5-HT_4 receptors over 75 different receptors, ion channels, neurotransmitter transporters, and enzymes {7}.

TD-8954 has demonstrated prokinetic activity in several in vitro and in vivo assays. In human isolated colonic circular muscle, TD-8954 is associated with inhibition of spontaneous, electrically evoked, and carbachol-induced contractions, actions consistent with its 5-HT_4 agonist properties and with the role of the 5-HT_4 receptor in supporting the defecation reflex. In vivo potency and efficacy have been demonstrated in guinea pig models of colonic transit and stool production and in a rat model of esophageal relaxation following subcutaneous or intraduodenal administration. TD-8954 produces robust increases in GI contractility in dogs following oral dosing.

1.2.2 Toxicology

The summary of toxicology data can be found in the current version of the TD-8954 IB.

1.2.3 Pharmacokinetics

The PK, excretion, metabolism, and tissue distribution of TD-8954 were evaluated in rats and dogs following a single IV dose or oral administration. TD-8954 demonstrates excellent systemic exposure after oral dosing in rats and dogs. In both species, food has no significant effect on the extent of absorption of TD-8954 following oral dosing. Multiple-dose PK studies were performed in rats and dogs following oral administration as part of the exploratory multiple-dose toxicity studies in 7-day studies. Following 7 days of dosing, there

was no accumulation of TD-8954 in the plasma at 10, 30, and 100 mg/kg in rats, with near dose proportionality on Day 7. Following daily oral administration for 7 days in dogs, a two- to three-fold increase in TD-8954 C_{max} and AUC_{0-24} was observed, except in females at the high-dose group where a minimal increase in C_{max} was observed.

1.3 Clinical Experience

A description of the clinical profile of TD-8954 can be found in the TD-8954 Investigator's Brochure. To date, TD-8954 as a powder in capsule formulation for oral administration (TD-8945 PO) has been evaluated in a single ascending dose study and a multiple ascending dose study in healthy male and female subjects aged 18 to 64 years old at doses ranging from 0.1 mg to 20 mg. In addition, TD-8954 has also been evaluated in a repeated IV dose study in healthy adults aged 18 to 45 years old at IV doses ranging from 0.1 mg to 0.5 mg QD for up to 5 consecutive days.

In the single ascending dose study (0060), healthy male and female volunteers aged 18 to 50 years old were administered 0.1, 0.5, 1, 2, 5, 10, and 20 mg TD-8954 PO or placebo. The most common adverse events were mild to moderate headache, nausea, and vomiting; dose escalation was stopped at 20 mg due to the occurrence of moderate orthostatic hypotension in two subjects at that dose level. No clinically significant ECG abnormalities were observed in the 20 mg single-dose cohort. No clinically significant changes in hematology, clinical chemistry, or urinalysis were observed. Evidence of GI prokinetic activity (increased bowel movement frequency, softer stool consistency, and reduced time to the first bowel movement postdose) was observed at all dose levels with maximum effects at the doses of 0.2 mg and 0.5 mg. The half-life of TD-8954 was approximately 13.1 to 19.5 hours indicating that once-daily dosing is appropriate and that steady state exposure was expected to be achieved after three to four days of dosing. In plasma, the ratio of metabolite to parent for AUC_{0-24} was <0.4% for THRX-513466 and <0.2% for THRX-913682 at doses above 2 mg TD-8954 and 5 mg TD-8954, respectively. The observed safety, PD, and PK profiles support continued evaluation of TD-8954.

In the multiple ascending dose study (0061), healthy male and female volunteers aged 25 to 64 years old were administered 0.2, 1, 5, or 10 mg TD-8954 PO or placebo for 10 days. Safety results from these subjects demonstrated that oral administration of TD-8954 once-daily for 10 days was safe and well tolerated at doses ≤5 mg. The most common adverse events were mild headache and diarrhea. Two subjects in the 10 mg dose group

prematurely discontinued dosing due to the occurrence of intermittent atrioventricular dissociation. The events were considered mild in severity and resolved without intervention, and upon review of available ECGs by 3 independent cardiologists, was not viewed to be dose limiting. There were no safety signals in the clinical laboratory (chemistry, hematology, coagulation, or urinalysis) or respiratory rate data. Evidence of TD-8954-induced prokinetic effects were seen at all TD-8954 PO dose levels. The half-life of TD-8954 in plasma ranged from 16.0 to 19.1 hours after repeat oral administration and steady state exposure was achieved by Day 4. Plasma exposure following repeat TD-8954 administration increased by approximately two-fold from Day 1 to Day 10.

TD-8954 has also been evaluated in a repeated IV dose study (0095) in healthy adults aged 18 to 45 years old at IV doses ranging from 0.1 mg to 0.5 mg QD for up to 5 consecutive days. No SAEs were reported for this trial. The most common AEs (i.e., headache, postural dizziness) were not clinically significant, resolved spontaneously, and did not recur with subsequent dosing. Two subjects (one receiving TD-8954 and one receiving placebo) experienced modest and transient increases in ALT and AST which were not clinically significant and resolved spontaneously. Additionally, three subjects (two receiving TD-8954 0.5 mg, one receiving 0.1 mg) experienced modest and transient cardiovascular AEs (i.e., postural tachycardia, postural dizziness) after the first dose; these events were not clinically significant and resolved spontaneously, and were not observed upon re-challenge (subsequent dosing) of subjects. Evidence of TD 8954-induced prokinetic effects (time to first bowel movement) was seen in both IV cohorts but increased number of bowel movements on the first day of dosing was only seen with the 0.5 mg IV dose. The PK of TD-8954 following multiple IV doses of 0.1 and 0.5 mg revealed a half-life of approximately 18 hours. Steady state was achieved in 3 days and there was <2 fold accumulation in PK after 5 days of daily dosing at the 0.5 mg dose.

The observed safety, PD, and PK profiles support continued evaluation of TD-8954.

1.4 Risks and Benefits

TD-8954 is potentially useful in treating GI disorders such as constipation, gastroparesis, and EFI, the disorder of interest in this study. Data from two clinical trials with TD-8954 PO, and one trial with TD-8954 IV, the route proposed in this study, showed bowel movement frequency was increased.

The most common AEs associated with TD-8954 PO are GI-related, e.g., nausea, vomiting, abdominal pain/discomfort, and diarrhea consistent with its mechanism of action and headache. Healthy volunteers who received a single dose of TD-8954 PO up to 20 mg or multiple doses of TD-8954 PO up to 10 mg experienced the onset of GI-related events or headache very early in treatment (Days 1-2), and these events generally resolved within a few days. In the IV study, the most commonly reported AEs associated with TD-8954 IV were central nervous system-related including headaches and postural dizziness. For both AEs, the onset occurred shortly after dosing on day 1 and resolved the same day, and did not recur on subsequent days upon re-dosing.

Three subjects who received a single dose of TD-8954 PO had AEs of orthostatic hypotension on standing (one subject dosed at 10 mg had mild severity; two subjects dosed at 20 mg had moderate severity). The events resolved without treatment. One subject who received multiple 5-mg doses of TD-8954 PO had a mild AE of pyrexia. In the IV study, three subjects experienced postural dizziness upon standing (two moderate events after 0.5 mg, and one mild event after 0.1 mg), and in all three cases, the events occurred shortly after dosing and resolved the same day and did not recur upon further dosing.

Transient HR increases have been observed with TD-8954 PO and IV following the first dose of the compound and with repeated dosing, most commonly upon standing. The clinical relevance of these observations is not known but they were not considered to be clinically significant. ECGs will be performed routinely and frequently to ensure cardiac status is not significantly affected.

In this study, which will be the first study with intravenous (IV) TD-8954 in a patient population, subjects will be admitted to the intensive care or trauma unit, and will be mechanically ventilated and sedated. It is anticipated that as a result of their underlying illness vital signs and ECGs will be monitored closely. Section 6.5 discusses the algorithm for halting the infusion, adjusting the dose or stopping the study in the event significant safety concerns emerge.

The IB also contains descriptions of rare adverse effects (e.g., ischemic colitis and vascular ischemia), which have not occurred in TD-8954 studies but have been associated with other 5-HT_4-related compounds.

2 OBJECTIVES

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of a single IV dose of TD-8954 in subjects with EFI
- To evaluate the pharmacodynamics (PD) of IV TD-8954 in subjects with EFI based on gastric emptying as measured by scintigraphy

Secondary objectives of this study are as follows:

- To evaluate the pharmacokinetics (PK) of IV TD-8954 in subjects with EFI
- To evaluate the PD of IV TD-8954 in subjects with EFI based on gastric emptying assessment by ^{13}C breath test

Additional objectives of this study are as follows:

- CCI
- [redacted]
- [redacted]
- [redacted]

3 STUDY DESIGN

3.1 Overview

This is a phase 2a, randomized, double-blind study to evaluate the safety, tolerability and PD of single-dose IV TD-8954 compared with metoclopramide in critically ill patients with EFI. The schedule of study assessments is summarized in Table 1 and the study design is illustrated in Figure 1.

A total of 60 subjects will be enrolled in this study. Subjects will be randomized in a 1:1 ratio to one of two parallel treatments to receive either a single dose of 0.5 mg IV TD-8954 (Treatment Group A) or 10 mg IV metoclopramide every 6 hours for 24 hours (Treatment Group B).

Study medication will be prepared double-blinded in double-dummy fashion such that subjects randomized to Treatment Group A will receive a 1-hour IV infusion of TD-8954 0.5 mg and IV injections of 0.9% sodium chloride every 6 hours (sham metoclopramide; total of 4 injections), and subjects randomized to Treatment Group B will receive a 1-hour IV infusion of 0.9% sodium chloride (sham TD-8954) and IV injections of 10 mg metoclopramide every 6 hours (total of 4 injections). The first dose of metoclopramide or sham metoclopramide will be administered immediately after the end of the TD-8954 or sham TD-8954 infusion.

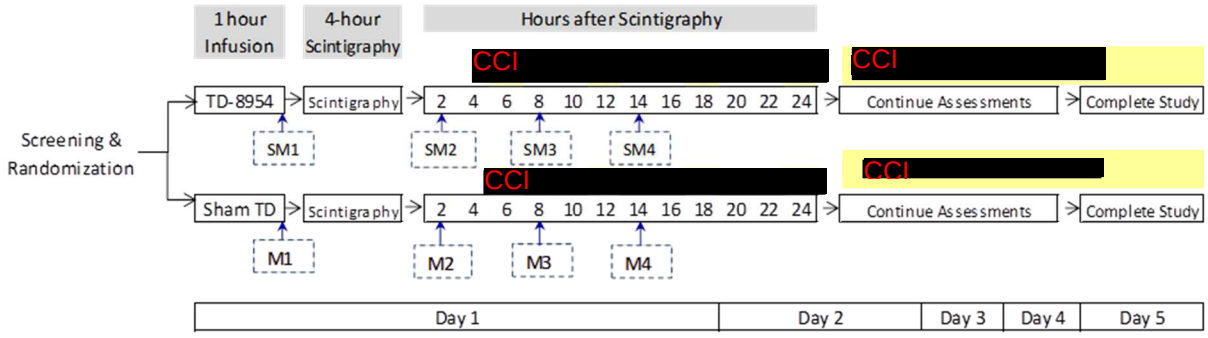
Immediately after dosing with study medication has finished (i.e., at the end of the one-hour infusion and after injections of study medication), subjects will receive a standard scintigraphy (at selected sites) and breath test 'meal' consisting of 100 mL of Ensure® containing 106 kcal with 21% of fat, mixed with 20 MBq ^{99m}Technitium-Calcium phytate or ^{99m}Technitium sulphur colloid (for those undergoing scintigraphy) and 100 µL ^{13}C octanoate, and will undergo scintigraphic and breath test assessments through 240 minutes after dosing with study medication (Table 1). In addition, subjects who have not received [redacted]

CCI [redacted]

In addition, at the end of the scintigraphic study and breath test assessments, the stomach will be emptied, the aspirate volume will be recorded, the aspirate will be discarded, feeding will be recommenced at the goal rate (as determined according to the usual ICU feeding protocol), and CCI [redacted].

Blood samples for safety and TD-8954 PK assessments will be collected beginning on Day 1 through Day 4 after dosing. In addition, after safety assessments through Day 5 have been completed the subject's participation in the study will conclude; however information regarding the subject's CCI [redacted]

Figure 1: Study Design



M = metoclopramide injection
SM = Sham metoclopramide injection
GRV = gastric residual volume measurement

3.2 Rationale for Study Design

The study design is intended to balance first time exposure of patients with EFI to TD-8954 with the need to obtain adequate safety, PK and PD data in this population. TD-8954 has shown tolerability in healthy volunteers and evidence of GI prokinetic activity (e.g., increased bowel movement frequency). To help determine if TD-8954 may be useful in treating EFI, the study will evaluate tolerability, PD activity and PK in a population of patients with EFI using an active comparator. Because EFI patients typically are critically ill and in need of nutritional support, this study will test a single dose of TD-8954 that has demonstrated both tolerability and PD activity in healthy volunteers.

CCI [redacted]

The study design takes into account the underlying critical illness in the study population. Instead of placebo, the comparator is metoclopramide, a product that is an accepted standard treatment for EFI. The use of scintigraphy will allow for comprehensive evaluation of upper GI tract activity between metoclopramide and TD-8954. Other measures of PD activity, such as breath test, CCI [redacted] will be assessed to help inform alternative measures of TD-8954 activity for future studies.

Eligible patients will be intubated, on mechanical ventilation and expected to remain on mechanical ventilation for 2 days after enrollment. As such, all patients will receive intensive care monitoring for the duration of the study, which will allow timely assessment of study drug effects on vital signs and ECG, and prompt identification of any adverse events. Once the 24-hour post-scintigraphy assessments are completed, standard of care treatment for EFI will be available to all patients.

3.3 Selection of Doses and Duration of Treatment

Two clinical trials have been conducted using an oral formulation of TD-8954 administered as single doses of 0.1, 0.5, 1, 2, 5, 10, and 20 mg and as multiple doses of 0.2, 1, 5, and 10 mg QD for up to 10 days. The highest tested acceptable dose was 5 mg QD (in the multiple dose ascending study) and resulted in an $AUC_{0\text{-}24}$ of 387 ng•hr/mL and C_{max} of 27.7 ng/mL.

TD-8954 has also been evaluated in a multiple dose IV study in healthy adult subjects (18 to 45 years old) at doses ranging from 0.1 mg to 0.5 mg QD for 5 consecutive days. TD-8954 was shown to be generally well tolerated upon repeated IV doses, and no SAEs were reported. Postural tachycardia and postural dizziness reported with both the 0.1 mg and 0.5 mg IV TD-8954 doses are not anticipated to be of concern for the intended study population of patients with EFI who are receiving mechanical ventilation and not expected to be ambulatory during the treatment period.

On the basis of the multiple ascending dose IV exposures in healthy subjects, and the binding affinity (K_i) value of TD-8954 at the human recombinant 5-$HT_{4(c)}$ receptor subtype,

an IV dose of 0.5 mg QD is estimated to result in 94% receptor occupancy at C_{max} and 60% at C_{trough}. A TD-8954 dose of 0.5-mg IV QD was associated with marked reductions in the time to first bowel movement, a PD endpoint assumed be relevant to efficacy in patients with EFI. Also, the TD-8954 0.5 mg IV dose was associated with an increased in the number of bowel movements on the first day of dosing compared with placebo and the 0.1 mg IV dose. In this study, which will evaluate a single dose of TD-8954, the IV dose of 0.5 mg has been selected on the basis on prior human data and is anticipated to be well tolerated in the intended study population and to demonstrate an effect of increased GI motility.

The planned dose was calculated by the established 1:1 ratio of IV:oral exposure from clinical data. The IV dose selected (0.5 mg once daily) is not projected to exceed the exposure observed from the 5-mg PO QD dose of 387 ng•hr/mL (AUC_{0-24}) and 27.7 ng/mL (C_{max}). On the basis of the outcome of this study as currently designed, this protocol may be formally amended to evaluate lower (0.05 mg or 0.1 mg) IV doses of TD-8954 in subjects with EFI.

Considering the single-dose design of this study and the acceptable pharmacokinetic profile of TD-8954, elderly subjects (up to 85 years) are included in this study. At 0.5 mg IV QD, there is a safety margin of 4-fold for C_{max} and 9-fold for AUC_{0-24} compared with 5-mg PO QD dosing.

3.4 Study Endpoints

The primary endpoints of the study are:

- Safety and tolerability of TD-8954 in patients with EFI (adverse events, ECGs, laboratory assessments and vital signs)
- Scintigraphic percentage retention at 180 minutes

The secondary endpoints of the study are:

- Scintigraphic parameters (percentage retention at 60,120, and 240 minutes, gastric emptying $t_{1/2}$, area under the retention curve in available subjects)
- Breath test parameters ($t_{1/2,}$ t_{lag} and GEC),
- Pharmacokinetic parameters of IV TD-8954

Additional exploratory PD endpoints are:

- CCI
- [redacted]

3.5 Minimization of Bias

This study will utilize a double-dummy study drug preparation schema involving TD-8954 and sham TD-8954 and metoclopramide and sham metoclopramide, therefore study subjects, site staff, and Theravance staff involved in safety review will be blinded to the study treatment. The assignment of subjects to TD-8954 or metoclopramide will be made by an Interactive Web Response System (IWRS) maintained by BioClinica. The IWRS will use the total APACHE score from screening to stratify the subjects into either a group with a total score ≤ 20 or > 20. Only the unblinded pharmacy staff will have access to the unblinded randomization/allocation notification. This staff will not be involved in any observation, monitoring, or reporting required by the study protocol, other than drug accountability and dispensing records.

3.5.1 Blinding

TD-8954 solution for IV infusion will be supplied to the site pharmacy in 5-mL vials with the contents labeled (i.e., open label). Commercially available 0.9% sodium chloride for injection in sterile infusion bags will be used as both the diluents for TD-8954 infusion, sham TD-8954 infusion, and sham metoclopramide preparation. The unblinded pharmacy staff will prepare the assigned dose for each subject within 8 hours of dosing based upon the subject's randomized treatment assignment in a blinded fashion such that treatment identity cannot be determined by the subject, nurse or physician.

In the absence of any clinically significant AEs, all site study staff (except the unblinded pharmacy staff), Theravance clinical study personnel, and the site monitors will remain blinded to the treatment allocation of each study subject (starting on Day 1) until all safety data have been obtained from all subjects.

In the event of a medical emergency, the identity of the study drug may be unblinded at the clinical site. The unblinded pharmacist or other authorized pharmacy staff member will have access in the IWRS to unblind. If a medical emergency arises during which the identity of the study drug assignment is needed to determine appropriate treatment for the study subject, the code for an individual subject will be provided to the investigator by the unblinded pharmacist or other authorized pharmacy staff member. If possible, the site is strongly encouraged to speak with the Theravance Clinical Study Director before breaking the blind. Reasons for breaking the blind will be documented in the subject's source documents and in the Case Report Form (CRF). Written documentation that the code was broken will be provided to Theravance.

In the event of unblinding triggered by the stopping rules in Section 6.5.4, the unblinded designee from Theravance Biometrics Department will record the scenario of events including discussion with the unblinded site staff in a note to file. The note will be filed in the Theravance Trial Master File at the conclusion of the study.

3.5.2 Treatment Assignment

The 60 subjects will be randomized in a 1:1 ratio to receive TD-8954 or metoclopramide (and TD-8954 sham or metoclopramide sham) according to the randomization schedule provided by BioClinica. Subject eligibility will be confirmed within the 24 hours before a subject is enrolled into the study. Once eligibility is confirmed, the subject will be assigned treatment by the IWRS according to the randomization schedule and the subject will receive study medication without delay.

4 STUDY POPULATION

Adult men and women, 18 through 85 years of age (inclusive), who are intubated, on mechanical ventilation, receiving enteral feeding and meet the inclusion and exclusion criteria listed below. Eligibility in this study may be determined based on results from physical, laboratory and/or electrocardiographic examinations that have been performed as part of the subjects existing hospital care.

4.1 Inclusion Criteria

Subjects who meet the following criteria will be eligible for study enrollment:

1. Adult male or female 18 to 85 years of age (inclusive)
2. Anticipated to live and be able to undergo active treatment, complete all study procedures and follow up for more than 4 days from enrollment into the study
3. If on vasopressors at the time of randomization, stable or reduced vasopressor requirements (as assessed by the investigator) compared to the previous calendar day
4. Intubated, on mechanical ventilation and anticipated to remain on mechanical ventilation for 2 days after enrollment into the study
5. Receiving enteral feeding and assessed to have developed EFI as defined by a GRV measurement ≥200 mL within the 24 hours before randomization
6. For a female subject of childbearing potential, a documented negative pregnancy test at screening
7. Provided written informed consent in accordance with guidelines set by the hospital and approved by the Institutional Review Board or Ethics Committee

4.2 Exclusion Criteria

Subjects who satisfy any of the following criteria are not eligible for study enrollment:

1. Receipt of any investigational agent or use of an investigational medical device within 30 days of screening or previous receipt of TD-8954 in a clinical trial
2. Known hypersensitivity to TD-8954 or formulation excipients
3. Known hypersensitivity or contraindication to metoclopramide
4. History of diabetic or idiopathic gastroparesis
5. Screening blood glucose >15 mmol/L (270 mg/dL) while receiving insulin
6. Impaired renal function, as defined by estimated creatinine clearance rate (eCCR) <30 mL/min, as determined by Cockcraft-Gault formula , unless receiving intermittent or continuous dialysis at the time of randomization

   eCCR = ((140 – Age) * Mass * 1 if Male or 0.85 if Female) / (72 * Serum Creatinine))

7. Bilirubin concentration in blood >2 times the upper limit of normal

8. ALT or AST >3 times upper limit of normal
9. Alkaline phosphatase >2 times upper limit of normal
10. Contraindication to enteral feeding
11. Significant direct GI tract trauma, as determined by the PI to be contraindicated for this study
12. Opioid or other drug overdose as the primary reason for admission to ICU
13. Receipt of a drug that can be used as a gastric prokinetic agent in the previous 24 hours (e.g., erythromycin, metoclopramide), 48 hours for domperidone, or receipt of azithromycin within the previous 2 weeks or any other drug given in the timeframe that in the opinion of the principal investigator could potentially confound the efficacy results of the study, unless the prokinetic drug has been stopped and 2 consecutive GRVs done at a minimum of 4 hours apart prior to randomization remain >200 mL
14. Receipt of agents known to directly influence the 5-HT_4/acetylcholine prokinetic mechanism (e.g., serotonin-specific reuptake inhibitors, anticholinergic agents or acetylcholinesterase inhibitors) within the 72 hours before randomization
15. A sustained (≥1 minute) pulse rate ≥150 bpm that is determined to be clinically significant and required treatment within 24 hours before randomization
16. Mean QTc interval greater than 450 msec in males or greater than 470 msec in females (after triplicate measures performed 1 minute apart)
17. History of congenital long QT syndrome
18. Clinically significant electrocardiogram (ECG) abnormalities indicative of acute cardiac instability, as determined by the investigator at screening; more than first degree AV block; >5 beats of non-sustained VT at a rate >120 BPM; ECG changes consistent with acute myocardial ischemia or infarction.
19. A history of or current major esophageal or gastric surgery on this admission (major lower abdominal surgery will not result in exclusion unless this carries a contraindication to enteral feeding)
20. Gastric pacemaker

4.3 CCI

CCI

5 STUDY DRUGS

All study drug supplied by Theravance must be stored in a secure location accessible only to designated study personnel.

5.1 Description of Study Drugs

Study drugs in this study will be TD-8954 (or sham TD-8954) and metoclopramide (or sham metoclopramide). TD-8954 is the test product and metoclopramide will be the reference therapy. For control purposes, study drug will be prepared in blinded, dummy-double fashion by an unblinded pharmacist. Normal saline (0.9% sodium chloride for IV injection) will be used as the sham component and will be provided by the investigative site using commercially available supplies. Further details regarding each are provided below.

5.1.1 TD-8954 and Sham TD-8954

TD-8954 solution for intravenous infusion (TD-8954 IV) is formulated as a 0.1 mg/mL solution of TD-8954 in water for injection with pH adjusted to 5.0 ± 0.5 using hydrochloric acid, and is packaged in 5-mL single-use glass vial containers. TD-8954 solution for IV infusion will be diluted in 0.9% sodium chloride for infusion via infusion pump and should not be less than concentration of 0.02 mg/mL. If necessary to maintain this concentration, infusion via syringe pump may be substituted. The required storage condition for TD-8954 vials is controlled refrigeration at 2°C to 8°C. Sham TD-8954 will be prepared using 0.9% sodium chloride for infusion in identical packaging (infusion bag) and following the same procedure as TD-8954.

Further details regarding preparation of TD-8954 IV drug product for infusion are described in the Pharmacy Manual.

5.1.2 Metoclopramide and Sham Metoclopramide

The dose and regimen of metoclopramide will be 10 mg administered by IV injection every 6 hours for 24 hours (i.e., 4 doses). Metoclopramide will be provided by the investigative site using commercially available supplies. Sham metoclopramide will be prepared using 0.9% sodium chloride for injection in identical packaging (syringes) and following the same procedure as metoclopramide.

Preparation of metoclopramide for injection is described in the Pharmacy Manual and according to manufacturer's instructions.

5.2 Dosage and Administration

As stated in Section 5.1, the study drugs in this study will be TD-8954 and metoclopramide, and for control purposes, study drug will be prepared in blinded, dummy-double fashion involving sham TD-8954 and sham metoclopramide by an unblinded pharmacist. Further details of the pharmacy aspects of this study including drug receiving, storage, labeling, and administration are provided in a Pharmacy Manual that is separate from this protocol. A summary of the dosage and administration information are provided below.

The planned doses and regimens to be evaluated in this study include 0.5 mg TD-8954 administered as a single infusion over 60 minutes; and 10 mg metoclopramide administered as an IV bolus every 6 hours for 24 hours (for a total of 4 doses).

The unblinded pharmacy staff will prepare the assigned treatment (either TD-8954 or metoclopramide and the corresponding sham control) for each subject within 8 hours of scheduled dosing. TD-8954 and sham TD-8954 will administered by IV infusion using an IV pump or syringe pump, over a period of 60 minutes. Metoclopramide or sham metoclopramide will be administered by IV bolus up to 15 minutes prior to the end of the TD-8954/sham TD-8954 infusion. For all treatments, the timing (including start and stop of infusion), dose, and volume infused/injected will be recorded in subject records and the case report form (CRF). In addition, actual treatment received will be recorded in the pharmacy records, but will only be available to the unblinded pharmacy staff, until after the study has completed.

5.3 Treatment Compliance

Study drug will be given in the ICU under the supervision of a qualified physician. Following dose administration, a visual inspection of the study drug containers (i.e., IV bag and syringe) will be performed and noted in the subject records after each dose to confirm the complete dose was administered. In addition to other requirements for documentation of drug accountability, the start time and stop time of the infusion pump, infusion rate(s), if dose was withheld or incomplete TD-8954 or metoclopramide), and any stop/start interval(s) will be captured in subject records.

5.4 Drug Accountability and Reconciliation

The investigator or designee is responsible for maintaining accountability records for all study drug(s) received from Theravance, in accordance with applicable government

regulations and study procedures. The accountability record will include entries for receipt, distribution or dispensing, and destruction of the material(s). Unused and expired study drugs will be disposed of in accordance with written instructions from Theravance.

If it is required by Theravance, interim reconciliation of each study drug and associated source documents will be conducted by an independent Theravance unblinded site monitor. The unblinded site monitor will not have any site management responsibilities other than reconciling the study drug accountability records. The unblinded pharmacy staff will prepare the assigned dose for each subject on the basis of the subject's randomized treatment assignment. The study drug accountability records and randomization schedule will be maintained in a secure area so that only the unblinded pharmacy staff will have access; these individuals will not be involved in any aspects of the study involving direct management of the subject, other than preparing study drug and maintaining study drug records. Final reconciliation of each study drug will be completed by the site monitor after the database has been locked and prior to study drug disposal.

Site personnel will not dispose of study drug vials either used or unused until the Theravance site monitor has reviewed and reconciled all drug accountability data. The Theravance site monitor will advise the site when it is appropriate to dispose of study drug. Copies of the study drug accountability records will be provided to Theravance at completion of the study.

6 STUDY PROCEDURES

6.1 Schedule of Study Procedures

The schedule of study procedures and procedure collection times is summarized in Table 1.

6.2 Total Blood Volume

The total volume of blood to be drawn from each subject for PK, CCI, motilin levels and safety laboratory assessments is approximately 110 mL for a completed subject.

6.3 Procedures by Visit

6.3.1 Screening

The screening visit will be performed within 24 hours before the planned dosing. Screening activities will comprise the following:

- Written informed consent will be obtained in accordance with guidelines set by the hospital and approved by the Institutional Review Board or Ethics Committee
- Review of inclusion and exclusion criteria
- Medication and medical history
- Vital signs
  - Heart rate (HR) and blood pressure (BP)
  - Temperature
  - Ventilation status
- Physical examination
- Height and weight (historical information acceptable if unable to measure directly)
- 12-lead ECG (in triplicate at intervals of approximately 1 minute),
  - Blood collection
  - Hematology
  - Serum chemistry
  - Coagulation
  - Urine pregnancy test (for females of child bearing potential if not already done during this hospitalization)
- Concomitant medications
- Gastric Residual Volume
- Apache II parameters at ICU entry

6.3.2 Day 1

6.3.2.1 Day 1 Baseline

The following procedures will be performed on the day of randomization prior to study drug administration:

- Review of medication and medical history
- Confirm the subject remains eligible for the study
- 12-lead ECG (in triplicate at intervals of approximately 1 minute), to be performed immediately prior to randomization
- Randomization
- Vital signs: HR and BP, temperature, and ventilation status, to be performed within 30 minutes prior to the start of the infusion
- Blood samples, within 30 minutes before dosing:
    - Baseline TD-8954 PK sample
    - Baseline plasma motilin sample
    - Baseline PK sample for paracetamol/acetaminophen/acetaminophen, for those subjects eligible to participate in CCI
- Approximately 2 hours prior to study drug infusion, aspirate stomach and document volume (i.e., GRV), begin 2 hour fast
- Adverse event assessment
- Review of concomitant medication
- Apache II parameters closest to dosing

6.3.2.2 Day 1 Study Drug Administration

The following procedures will be performed on day 1 following randomization:

- TD-8954, 0.5 mg, or sham TD-8954, IV infusion for 60 minutes
- Metoclopramide, 10 mg, or sham metoclopramide, IV bolus, to be given up to 15 minutes prior to the end of the TD-8954/sham TD-8954 infusion
- Vital signs: HR and BP, temperature, and ventilation status, to be performed at 30 min after the start of infusion
- Blood samples:
    - TD-8954 PK samples to be collected at 30 min(+/- 5 min), and 60 min(+/- 5 min), (just prior to infusion end) after start of infusion

6.3.2.3 Day 1 Post Study Drug Administration

The following procedures will be performed on Day 1 following the end of study drug administration:

- Administration of test meal (immediately following the end of the TD-8954/sham TD-8954 infusion)
- At selected sites scintigraphy will begin immediately following the administration of the test meal (0 minutes), and at 60 min, 2, 3, and 4 hrs after the administration of the test meal. (Timepoints at 60 min and 2 hrs will be optional. All other timepoints are required.)
- Breath testing will occur immediately following the administration of the test meal (every 15 minutes up to and including the 4 hour timepoint after the complete administration of the test meal. Prior to the test meal samples will be taken at two time points at least 5 minutes apart and can be taken up to 30 minutes prior to the test meal.
- Vital signs: HR and BP, temperature, and respiratory rate, to be performed at 60 min, 2, 3, 4, 6, 8, 10 and 12 hours after the start of the infusion.
- ECG (in triplicate at intervals of approximately 1 minute), at 60 min (+/- 15 min), and 6 hours (+/- 15 min) and 12 hours (+/- 15 min), after the start of the infusion
- Blood samples:
    - TD-8954 PK samples to be collected (+/- 15 min), at 75 min, 90 min and, 2, 3, 4, 6, 8, 10 and 12 hours after the start of the infusion
    - Plasma motilin samples to be collected at 15min. (+/- 5 min), 30min. (+/- 5 min), 60min. (+/- 10 min), 2 hours (+/- 15 min), 3 hours (+/- 15 min) and 6 hours (+/- 15 min) after the end of the infusion of study drug
    - Paracetamol/acetaminophen/acetaminophen PK samples, for those subjects eligible to participate in CCI to be collected at 15 min, 30 min., 60 min, 90 min., 2, 3, and 4 hours after the administration of the test meal containing paracetamol/acetaminophen. These samples should be drawn at the same time as the PK samples for the TD-8954
- CCI [redacted]
- Metoclopramide, 10 mg, or sham Metoclopramide to be given every 6 hours after the first dose of Metoclopramide for a total of 4 doses
- Adverse event assessment
- Review of concomitant medication

6.3.3 Day 2

The following procedures will be performed on Day 2 (beginning 24 hours after the start of the infusion on Day 1):

- Vital signs: HR and BP, temperature, and ventilation status, will be collect twice, the first will be the highest value and the second will be the lowest value noted during the calendar day.
- ECG (in triplicate at intervals of approximately 1 minute), at approximately 24 hours (+/- 15 min), from the start of the infusion on Day 1

- CCI [redacted], or more frequently if necessary to provide adequate care of the subject at the discretion of the investigator
- Blood samples:
  - Hematology
  - Serum chemistry
  - TD-8954 PK samples to be collected at 24 hours after the start of the infusion
- Adverse event assessment
- Review of concomitant medication

6.3.4 Day 3

The following procedures will be performed on Day 3 (beginning 48 hours after the start of the infusion on Day 1):

- Vital signs: HR and BP, temperature, and ventilation status, will be collect twice, the first will be the highest value and the second will be the lowest value noted during the calendar day.
- ECG, at approximately 48 hours (+/- 15 min), from the start of the infusion on Day 1 (this will be a single ECG)
- CCI [redacted]
- Blood samples:
  - Hematology
  - Serum chemistry
  - TD-8954 PK samples to be collected at 48 hours after the start of the infusion
- Adverse event assessment
- Review of concomitant medication

6.3.5 Day 4

The following procedures will be performed on Day 4 (beginning 72 hours after the start of the infusion on Day 1):

- Vital signs: HR and BP, temperature, and ventilation status, will be collect twice, the first will be the highest value and the second will be the lowest value noted during the calendar day.
- ECG, at approximately 72 hours (+/- 15 min), from the start of the infusion on Day 1 (this will be a single ECG)
- CCI [redacted]
- Blood samples:
  - Hematology
  - Serum chemistry

- TD-8954 PK samples to be collected at 72 hours after the start of the infusion
- Adverse event assessment
- Review of concomitant medication

6.3.6 Day 5 End of Study or Early Termination

The following procedures will be performed on Day 5 for completed subjects or for subjects who terminate early:

- Physical examination
- Vital signs: HR and BP, temperature, and ventilation status, will be collect twice, the first will be the highest value and the second will be the lowest value noted during the calendar day
- ECG, at approximately 96 hours (+/- 15 min), from the start of the infusion on Day 1
- Apache II parameters, the worst noted on Day 5
- CCI
- Blood samples:
  - Hematology
  - Serum chemistry
- Adverse event assessment
- Review of concomitant medication
- Outcome measures: enteral feeding and nutrition information

If a subject discontinues the study early, every effort should be made to conduct this visit as an Early Termination Visit for collection of final safety assessments. Study termination will be considered the date that the subject withdraws from or completes the study, even if that date does not correspond to a protocol-specific visit.

6.3.7 Follow-up

As part of subject follow up enteral feeding and nutrition outcome information will be collected. In addition the status and date of ICU and hospital discharge will be collected up to Day 30.

6.4 Description of Study Assessments

6.4.1 Safety Assessments

6.4.1.1 Medical History

Medical history evaluation will be performed at screening to aid in the eligibility determination of the subject. Follow-up history on Day 1 pre-dose will focus on any medical events that may have occurred since screening.

For the schedule of medical history conduct refer to Table 1.

6.4.1.2 Physical Examination

Physical examination at screening will be performed by a physician and will include examination of the body systems appropriate for a patient in the critical care setting. Where appropriate, relevant documentation previously gathered in the subject's chart during the present hospitalization should be used.

Follow-up examinations will be abbreviated and symptomatic, largely focused on evaluation of adverse events, if any.

For the schedule of physical examination conduct refer to Table 1.

6.4.1.3 Vital Signs

Systolic and diastolic BP, HR, ventilation status, and body temperature will be recorded at the schedule provided in Table 1.

6.4.1.4 Apache II

Apache II parameters will be collected from the time that the subject entered the ICU, immediately prior to receiving study drug and on Day 5. For the parameters on Day 5 the worst values for the whole 24 hour period of Day 5 should be noted on the CRF.

6.4.1.5 Laboratory Tests

The following laboratory assessments will be performed at the schedule as specified in Table 1.

Hematology:

- Hematocrit and hemoglobin; red blood cell count; white blood cell count, including differential count by microscopy with total neutrophils, eosinophils, basophils, monocytes, lymphocytes; mean corpuscular volume; mean corpuscular hemoglobin; and mean corpuscular hemoglobin concentration; and platelet count

Serum chemistry:

- Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, lactate dehydrogenase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase,

Urine:

- Urine pregnancy test at screening (females of child bearing potential only). Documentation of negative pregnancy test results must be available before enrollment into the study. If completed during this hospitalization it does not need to be repeated.

6.4.1.6 Electrocardiograms

ECGs will be collected at each time point specified in the schedule of procedures (Table 1).

The investigator's assessment of whether an ECG observation is clinically significant or not clinically significant must be recorded on the printed ECG recording.

6.4.1.7 Adverse Events

AEs will be recorded following signing of the informed consent through the end of study visit or at the time of early termination. AEs may be observed by the site study or ICU personnel or spontaneously reported by the subject or reported in response to a standard question from study personnel.

6.4.2 Pharmacokinetic Assessments

Blood samples are collected according to the schedule of procedures in Table 1 and every effort should be taken to ensure the samples are collected on schedule. Any samples collected beyond 10% of the nominal time for that timepoint will be reported as deviations.

Between 4 to 6 mL of whole blood will be collected at various time points for PK sampling. Please refer to the Study 0082 Pharmacokinetic Sample Collection Manual for further methodology for collection, handling, storage, and shipping of plasma PK samples.

6.4.3 Pharmacodynamic Assessments

6.4.3.1 Scintigraphy and ^{13}C Breath Test

Immediately after dosing with study medication has finished (i.e., at the end of the one-hour infusion and after injections of study medication), subjects will receive a standard test 'meal' consisting of 100 mL of Ensure® containing 106 kcal with 21% of fat, mixed with 100 µL ^{13}C octanoate, and will undergo breath test assessments through 240 minutes after dosing with study medication (Table 1). At selected sites 20 MBq ^{99m}Technitium calcium phytate or ^{99m}Technitium-Sulphur colloid will be added to the test 'meal' and those subjects will undergo scintigraphic assessment through 240 minutes after dosing with study medication.

6.4.3.2 CCI

CCI

6.4.4 CCI

CCI

6.5 Safety Data Review and Stopping Rules

6.5.1 Safety Data Review Committee

A Safety Data Review Committee (SDRC) will be composed of the Clinical Study Director, Medical Monitor, PK scientist, study statistician, and an independent external clinician experienced in the safety data review of ICU patients.

In addition, a Clinical Operations representative will attend the SDRC meetings. Additional members may be added as needed at the discretion of the Clinical Study Director.

A SDRC meeting will be held to review data and monitor safety in the following situations:

- After each group of 12 patients up to 48 patients has finished the 5 day follow-up (i.e., 12, 24, 36, and 48 patients)
- Occurrence of any of the situations described in Table 2.

Ad hoc SDRC meetings may be scheduled by the Clinical Study Director and/or Medical Monitor as needed.

Available safety data, including demographic data, ECG results, vital signs, adverse events, and laboratory results, will be reviewed. In addition, available blinded PK data may be reviewed. Data for SDRC review will be provided and reviewed in a blinded fashion by treatment group (i.e., "group A or group B; actual treatment assignment will not be revealed). At the request of the study director, unblinding will be performed by an unblinded member of the Theravance Biometrics Department.

If dose reductions occur in >4 of the first 12 subjects or >30 % of enrolled subjects upon enrollment of ≥24 subjects, the medical monitor or clinical trial director may request unblinding of the SDRC to treatment allocation of such subjects. If subsequent review shows that the absolute majority of such patients were randomized to the TD-8954 treatment arm, the SDRC can mandate a dose reduction of TD-8954 to 0.25 mg in all patients subsequently enrolled into the study and randomized to receive TD-8954.

In the event that a stopping rule is met (Table 2), the SDRC may recommend the study be discontinued, the protocol be amended to reduce future TD-8954 doses, or the study be continued per the current protocol. Dosing decisions/recommendations made by the SDRC will be communicated to the Principal Investigators by the Clinical Study Director and Clinical Operations. The discussion with the Principal Investigator will be documented in writing and filed in the site regulatory binder and the Theravance Trial Master File (TMF).

6.5.2 Infusion Adjustment Rules for Individual Subjects

The investigator may use his/her clinical judgment to determine whether to prematurely stop a subject's ongoing study drug/placebo infusion.

In addition, the study drug infusion rate should be reduced by 50% if the following situation occurs during the infusion:

- Sustained (≥1 minute) increase of HR from pre-dose of ≥15 bpm

In addition, the study drug infusion should be interrupted if any of the following situations occur during the infusion:

- Sustained (≥1 minute) heart rate ≥150 bpm or sustained (≥1 minute) increase from pre-dose of ≥30 bpm
- Sustained (≥1 minute) mean arterial pressure <60 mmHg or a sustained (≥1 minute) decrease from pre-dose >10 mmHg
- Adverse event of at least moderate severity that the Investigator suspects may be related to the infusion

After observing the subject for ≥5 minutes, if there is improvement in the condition that led to the temporary stop, the infusion may be resumed at the Investigator's discretion with the rate equal to half the prior infusion rate. If the infusion is tolerated, the infusion rate may be further increased at the Investigator's discretion. The resumed infusion should be stopped 60 minutes after the original infusion start time (i.e., the original planned infusion stop time).

After 30 minutes, if there is no improvement in the condition that led to the interruption, the infusion should not be resumed. The infusion should not be resumed or continued ≥60 minutes after the start time of the infusion (i.e., after the original planned infusion stop time).

If the infusion is stopped momentarily for any reasons other than safety (e.g., pump failure), the infusion may be resumed at the prior infusion rate. The infusion should not be resumed or continued ≥60 minutes after the start time of the infusion (i.e., after the original planned infusion stop time).

The remaining infusion should be weighed to determine the volume that was administered to the patient.

Subsequent study activities should remain on the original schedule. For example, the IV injection of metoclopramide/sham metoclopramide should occur 60 minutes after the original start time of the infusion even if the infusion was stopped prematurely.

The reason for any premature discontinuation, temporary interruption, or changes in administration rate of the infusion must be documented in the source documents and the

CRF. Theravance should be notified of the situation, including the subject's condition after the change to the infusion.

6.5.3 Post-Infusion Adverse Events

Theravance must be notified before initiating dosing in additional subjects if an AE from the same organ class (e.g., cardiovascular) that is suspected of being related to TD-8954 is observed in either:

- ≥3 of the first 10 subjects dosed; or
- ≥30% of dosed subjects once >10 subjects have been dosed

If one of the stopping rules described in Table 2 are met, no further subjects should initiate dosing and the action described in Table 2 should be followed.

6.5.4 Stopping Rules

Table 2 describes the scenarios and number of subjects involved to be used for halting initiation of dosing for additional subjects in the study while safety is being evaluated.

Table 2: Stopping Rules

Scenario	Number of Subjects	Action
Suspected TD-8954-related severe or serious adverse drug reaction	≥1 subject	• Do not initiate dosing in additional subjects. Notify Theravance. • SDRC reviews AE and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. Consider unblinding to determine relatedness to investigational product.* • If a severe or serious adverse event is determined by the SDRC to be related to study drug and clinically or medically significant, no further administration at this dose should proceed. • The study protocol may be amended to continue the study at a lower TD-8954 dose upon unanimous decision of the SDRC. • Clinical Study Director and Clinical Operations will discuss the SDRC decision with the Investigator and document the discussion in writing
Suspected TD-8954-related moderate adverse drug reaction of the same system class (e.g., cardiovascular)	3 of the first 10 dosed subjects or 30% of subjects when >10 have been dosed	• Do not initiate dosing in additional subjects. Notify Theravance. • SDRC reviews AE and all relevant safety data for evidence of relationship to treatment and clinical or medical significance. Consider unblinding to evaluate relatedness to investigational product.* • Upon unanimous decision by the SDRC, one of the following decisions may be made: – Discontinue the study – Amend the protocol to study a lower TD-8954 dose – Continue the study as planned • Clinical Study Director and Clinical Operations will discuss the SDRC decision with the Investigators and document the discussion in writing
Sustained (≥1 min) heart rate ≥150 bpm or sustained (≥1 min) increase from pre-dose of ≥30 bpm	3 of the first 10 dosed subjects or 30% of subjects when >10 have been dosed	
Sustained (≥1 min) mean arterial pressure <60 mmHg or a sustained (≥1 min) decrease from pre-dose >10 mmHg	3 of the first 10 dosed subjects or 30% of subjects when >10 have been dosed	

* A subject's treatment assignment should be unblinded only when knowledge of the treatment is essential for the further management of the subject, as well as the safety of subjects currently enrolled, or future subjects in the study.

6.6 Concomitant Medications

All concomitant medications, including name of medication, date started and stopped, route of administration, indication, and dose will be recorded in the source documentation and on the CRF.

The medications listed in the inclusion and exclusion criteria (Section 4) should be avoided during the 24 hour period beginning with study drug infusion, and should only be administered during this period if deemed necessary by the investigator to provide adequate supportive care. CCI [redacted]

6.7 Restrictions

Standard of care treatment for EFI may be started 24 hours after the end of scintigraphy and or breath test at the Investigator's discretion. If standard of care treatment for EFI is initiated before this time, the reason should be documented in the subject's source documents and on the CRF.

CCI [redacted]

6.8 Discontinuation

6.8.1 Subject Discontinuation/Early Termination

Any subject (or his or her legally authorized representative) may withdraw their consent to participate in the study at any time without prejudice. The investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may be discontinued at any time at the discretion of the investigator and in accordance with his or her clinical judgment. When possible, the tests and evaluations listed for the Early Termination visit should be carried out. If a subject withdraws before completing the study, the reason for withdrawal is to be documented on the CRF.

Theravance will be notified of all subject withdrawals.

Reasons for which the investigator or Theravance may withdraw a subject from the study or a subject may choose to terminate participation before completion of the study include, but are not limited to, the following:

- Adverse event
- Subject choice
- Major violation of the protocol
- Termination of the study by Theravance
- Other

Subjects who discontinue study drug early because of an adverse reaction should be encouraged to continue their participation in the end of study safety assessments.

6.8.2 Subject Replacement

Subjects who prematurely discontinue will not be replaced.

6.8.3 Study Discontinuation

Theravance reserves the right to discontinue this study at any time for any reason.

6.9 Pregnancy

If a female subject becomes pregnant during the study, the Theravance clinical study director (or designee) must be notified immediately. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7 ADVERSE EVENTS

7.1 Regulatory Definition of an Adverse Event

In the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice, Section 1.2 defines an AE as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily 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.

7.2 Adverse Event Definition for the Purposes of this Study

For the purposes of this Theravance clinical study, adverse events will be collected from the time the informed consent is signed through Day 5 while Serious Adverse Events will be collected through Day 30 as noted in Section 7.4. Adverse Events will be defined as follows:

An AE is any untoward medical occurrence in a subject who has signed an informed consent form and is participating in a clinical investigation. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, whether or not considered related to the study drug (investigational product).

Preexisting events that increase in frequency or severity or change in nature during or as a consequence of participation in clinical studies will also be considered as adverse events. An AE may also include pre- or post-treatment complications that occur as a result of a protocol-mandated procedure (such as a biopsy).

Any medical condition or clinically significant laboratory abnormality with an onset date prior to the time the subject signed the informed consent form is considered to be preexisting and should be documented in the medical history CRF, if applicable for the study.

Whenever possible, the diagnosis (rather than a series of terms related to a diagnosis) should be recorded as the AE term.

An AE does not include the following:

- Medical or surgical procedures (such as surgery, endoscopy, tooth extraction, or transfusion); the condition that leads to the procedure is an adverse event

- Preexisting diseases or conditions present or detected before signing an informed consent form that do not worsen
- Situations where an untoward medical occurrence has not occurred (such as hospitalization for elective surgery or social and/or convenience admissions)
- Overdose of either study drug or concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation

7.3 Assessment of Adverse Events

All AEs will be assessed by the investigator and recorded in the case report form, including the dates of onset and resolution, severity, relationship to study drug, outcome, and action taken with study drug.

Clinical severity of AEs should be recorded and graded using the mild, moderate or severe grading system described below.

Mild	= Awareness of signs or symptoms, but easily tolerated
Moderate	= Discomfort sufficient to cause interference with usual activities
Severe	= Incapacitation with inability to work or perform usual activities

If the subject is unable to communicate, the investigator should use his/her clinical judgment to determine the severity of any AEs the subject may experience.

The relationship to study drug therapy should be assessed using the following definitions:

- **Not Related:** Evidence exists that the adverse event has an etiology other than the study drug (such as a preexisting condition, underlying disease, intercurrent illness, or concomitant medication).
- **Possibly/Probably Related:** A temporal relationship exists between the event onset and administration of the study drug. It cannot be readily explained by the subject's clinical state or concomitant therapies and appears with some degree of certainty to be related based on the known therapeutic and pharmacologic actions of the drug. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. It should be emphasized that ineffective treatment should not be considered as causally related in the context of adverse event reporting.

These criteria in addition to good clinical judgment should be used as a guide for determining the causal assessment. If it is felt that the event is not related to study drug therapy, then an alternative explanation should be provided.

7.4 Serious Adverse Events

A serious adverse event (SAE) is defined as any adverse drug experience occurring from the time the informed consent is signed through Study Day 30 at any dose that results in any of the following outcomes:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events)
- Congenital anomaly/birth defect in the offspring of a subject who received study drug
- Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are as follows:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm
  - Blood dyscrasias or convulsions that do not result in hospitalization
  - Development of drug dependency or drug abuse

Additional Considerations for Serious Adverse Events

- Death is an outcome of an adverse event and not an adverse event in itself. In reports of death due to disease progression, where no other information is provided, the death will be assumed to have resulted from progression of the disease being treated with the study drug(s).
- All deaths, regardless of cause, must be reported for subjects if the death occurs while the subject is participating in the study.
- “Occurring at any dose” does not imply that the subject is receiving study drug at the time of the event; dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.
- “Life-threatening” means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.
- “Inpatient hospitalization” means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.
- The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

7.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Abnormal laboratory findings (such as clinical chemistry, hematology, or urinalysis) or other abnormal assessments (such as electrocardiograms [ECGs], X-rays, or vital signs) that are associated with signs and/or symptoms or are considered clinically significant in the judgment of the investigator must be recorded as AEs or SAEs if they meet the definition of an adverse event (or serious adverse event), as described in Sections 7.1 (Adverse Events) and 7.4 (Serious Adverse Events).

7.6 Serious Adverse Event Reporting

Any SAE that occurs after a subject signs an informed consent form through the follow-up visit (or at the time a subject is determined to be ineligible for the study and who does not enroll in the study), regardless of causal relationship, must be reported to Theravance within 24 hours of the investigator's knowledge of the event.

To report an SAE in the US, complete and fax the Serious Adverse Event Report Form to the following:

Theravance Clinical Drug Safety

Fax: PPD

To report an SAE in Australia, complete and e-mail the Serious Adverse Event Report Form to:

PPD

For medical questions regarding an SAE, contact the Theravance medical monitor by telephone as follows:

Theravance Medical Monitor Contact Information:

PPD

Or alternate

PPD

For fatal or life-threatening events, also fax copies of hospital case reports, autopsy reports, and other documents when requested. Additional information may be requested from the investigator to ensure the timely completion of accurate safety reports.

An SAE may qualify for reporting to regulatory authorities if the SAE is possibly attributable to the study drug and is unexpected/unlisted based on the current TD-8954 Investigator's Brochure. In this case, all investigators will receive notification of the event. The investigator is responsible for notifying the Institutional Review Board or Ethics Committee and documenting the notification, as required by local regulatory authorities and in accordance with the local institutional policy.

7.7 Adverse Event Follow-up

A subject experiencing an AE or SAE will be followed by the investigator or his/her trained delegate(s) through the follow-up visit or until the investigator and/or Theravance has determined that the AE or SAE has resolved or a stable clinical endpoint is reached, whichever is longer. Theravance may request follow-up of certain adverse events until resolution and documentation of assessments made during this period.

The investigator must take all therapeutic measures necessary for resolution of an SAE. Any medications necessary for treatment of the SAE must be recorded in the concomitant medication section of the case report form.

8 STATISTICAL CONSIDERATIONS

8.1 General Considerations

All individual data will be listed as measured. All statistical summaries and analyses will be performed using SAS software (SAS Institute, Cary, North Carolina, USA).

Continuous data will be summarized using an CCI [redacted].

Categorical data will be summarized using the CCI [redacted].

Any changes to the protocol-specified analyses will be pre-specified in the Statistical Analysis Plan prior to data lock.

8.1.1 Multiple Comparison Handling

The primary purpose of this study is to assess the safety and tolerability of IV TD-8954 in critically ill patients with enteral feeding intolerance and explore potential endpoints to measure pharmacodynamic activity. The co-primary endpoints, both the safety and pharmacodynamic endpoint, CCI [redacted]

CCI [redacted]

8.1.2 Missing Data

CCI [redacted]

CCI

[redacted]

8.1.3 Derived and Transformed Data

CCI

[redacted]

8.2 Sample Size and Power

The sample size of this study was selected on the basis of clinical considerations for early development studies. A sample size of 30 critically ill subjects in each group (60 in total) should provide initial characterization of safety assessments within this setting.

8.3 Interim Analyses

Interim analyses will be conducted every 12 subjects after completion of the blinded safety review (Section 6.5.1).

In addition to blinded individual subject data review,blinded treatment group level summaries of available scintigraphic, breath test, CCI [redacted] will be reviewed in aggregate format (e.g., subject-specific data may be represented with a dummy subject identifier to maintain the study blind at the subject level for the Study team.)

No adjustment to the type I error control is planned for the interim analyses.

8.4 Analysis Sets

8.4.1 Safety Analysis Set

The primary analysis set for safety analyses will include all randomized subjects who received at least one dose of study drug. All data collected during the course of the study will be included in the safety summaries. Subjects who receive study drug other than that to which they were assigned will be analyzed according to the study drug received.

8.4.2 Pharmacokinetic Analysis Set

The pharmacokinetic (PK) analysis set will consist of all randomized subjects who received at least one dose of study drug and have an evaluable PK profile.

8.4.3 Intent-to-Treat Analysis Set

The Intent-to-Treat (ITT) analysis set will include all randomized subjects who received at least one dose of study drug.

8.5 Per-protocol Analysis Set

The per-protocol (PP) analysis set will include all subjects in the ITT analysis set who completed study procedures of both scintigraphy and breath tests on Day 1.

8.6 Analysis Groups

Subjects will be grouped by actual treatment.

8.6.1 Examination of Subgroups

Due to the underlying heterogeneity of the study population, multiple potential subgroups are of interest. In cases where there are 4 or more subjects meeting a subgroup criterion in both treatment groups, a sensitivity/subgroup analysis will be summarized by treatment

group. Potential subgroups are defined in Section 8.11 using Baseline characteristics to subgroup the population.

8.7 Analysis Objectives

The primary endpoints of this study are:

- To evaluate the safety and tolerability of a single IV dose of TD-8954 in subjects with enteral feeding intolerance (EFI)
- To evaluate the pharmacodynamics (PD) of IV TD-8954 in subjects with EFI based on gastric emptying as measured by scintigraphy

Secondary endpoints of this study are:

- To evaluate the pharmacokinetics (PK) of IV TD-8954 in subjects with EFI
- To evaluate the PD of IV TD-8954 in subjects with EFI based on gastric emptying assessment by ^{13}C breath test

8.7.1 Pharmacokinetic parameters of IV TD-8954Exploratory Objectives

Additional objectives of this study are:

- CCI
- [redacted]
- [redacted]
- [redacted]

8.8 Primary Endpoints

The co-primary safety endpoint is to evaluate the safety and tolerability of a single dose of IV TD-8954 in critically ill subjects with enteral feeding intolerance. The endpoints to be evaluated will include AEs, laboratory abnormalities, ECGs and vital signs measurements.

The co-primary PD endpoint of this study is mean percentage retention at 180 minutes as measured by scintigraphy following a standard liquid meal (liquid scintigraphy).

8.9 Secondary Endpoints

8.9.1 CCI

CCI [redacted]

8.9.2 ^{13}C Breath test Endpoints

^{13}C breath test endpoints include:

- Gastric emptying t_{50} ($t_{1/2}$): time at which 50% of the AUC of the extrapolated gastric emptying curve is met
- Gastric emptying t_{lag}: time to maximal emptying (peak) of the gastric emptying curve
- Gastric emptying coefficient (GEC)

8.9.3 Pharmacokinetic Endpoints

The PK endpoints of this study are to characterize the plasma PK parameters of IV TD-8954 following administration of a single dose using standard noncompartmental methods. Plasma PK parameters will include C_{max}, T_{max}, $t_{1/2}$, AUC_{0-24}, AUC_{0-inf}, AUC_{0-t}, Vz, and CL.

8.10 Exploratory Endpoints

8.10.1 CCI

CCI [redacted]

8.10.2 CCI

CCI [redacted]

8.10.3 CCI

CCI

8.10.4 CCI

CCI

8.10.5 CCI

CCI

8.11 Demographics and Other Baseline Characteristics

Demographic and baseline measurements will be summarized using the standard 8-point descriptive summary overall and by treatment group. Subject's demographic characteristics will be summarized. Demographic characteristics include:

- Age
- Sex
- Race
- Height, weight, and BMI (Admission or Study Day 1, if available)

Subject's Baseline characteristics will be summarized. Select Baseline characteristics will form the basis for potential subgroup (SG) analyses; denoted by [SG] and will be defined in the Statistical analysis Plan prior to data lock. Baseline characteristics include:

- CCI
-
-

- Days in ICU prior to Study Day 1 [SG]
- Admission diagnosis (%) (i.e., Sepsis, Respiratory failure/Pneumonia, Trauma, Renal failure, Head injury, Burns, Diabetes mellitus, Other) [SG]
- Blood glucose level
- Serum creatinine and eCCR
- APACHE II Score (Admission) [SG] Select concomitant medications (%) (i.e., opioids/benzodiazepine, propofol, inotropes/vasopressors, insulin) [SG]

In addition, the APS variables of the APACHE II will be summarized for time points post Admission.

For analyses of demographics and other baseline characteristics, the Safety analysis set will be used.

8.12 Analysis of Pharmacokinetics

Serial blood sampling will be performed on Day 1. Plasma concentrations of TD-8954 IV will be determined and PK parameters estimated. Additional analyses may be conducted as appropriate.

Concentrations of TD-8954 will be determined in plasma using a validated bioanalytical assay(s). Individual subject TD-8954 concentration time data will be displayed using scheduled sampling times. A 7-point descriptive summary will be calculated for each sampling time. Plasma concentrations of the study drug over time will be plotted in semi logarithmic and linear formats as mean ± SD. Plasma concentration time data for each subject will be analyzed using standard non-compartmental methods.

Plasma PK parameters will include C_{max}, T_{max}, $t_{1/2}$, AUC_{0-24}, AUC_{0-inf}, AUC_{0-t}, Vz, and CL. For all PK data analyses, the PK analysis set will be used.

8.13 Analysis of Pharmacodynamics

For all PD analyses, the PD analysis set will be used. In addition, if data is available, PD analyses will be repeated using the subgroups as specified in Section 8.6.1.

8.13.1 Scintigraphy

The mean percentage retention at 60, 120, 180, and 240 minutes post dose, for those timepoints that are available, will be summarized by treatment group and compared descriptively using one-sided 95% confidence intervals between treatment groups. CCI

CCI [redacted]

The proportion of delayed emptying, using scintigraphy (liquid meal), will be summarized using the categorical data summary and 95% CIs.

Figures will descriptively summarize the full retention curve on a subject level and on a treatment group level.

8.13.2 ^{13}C Breath test

^{13}C breath test endpoints will be calculated using the Ghoos method individually for each subject. ^{13}C breath test endpoints will be summarized using an 8-point descriptive summary by treatment group. CCI [redacted]

Figures will descriptively summarize the full gastric emptying curve on a subject level and on a treatment group level.

8.13.3 CCI [redacted]

CCI [redacted]

8.13.4 CCI

CCI

8.13.5 CCI

CCI

8.13.6 CCI

CCI

8.14 Analysis of Safety

Safety will be evaluated by assessment of clinical laboratory tests, periodic physical examination, including vital signs and by the documentation of AEs. Concomitant medication intake will also be recorded. Safety data will be analyzed by incidence (frequencies) of treatment-emergent adverse events (TEAE) and laboratory abnormalities using the 8-point descriptive summary.

All safety data collected on or after the date of the first dose of study drug through to completion of the follow-up evaluation will be summarized by treatment group. Data for the pre-treatment period will be included in data listings. Safety variables to be summarized include vital signs, AEs, clinical laboratory results (hematology and chemistry), and Frederica's method corrected QT interval (QTcF) from ECGs.

For all safety analyses, the Safety analysis population will be used.

8.14.1 Extent of Exposure

A subject's data for the extent of exposure to study drug will be generated from the study drug administration page of the CRF. Dosing information for individual subjects will be listed. Using drug administration data, estimates of exposure to TD-8954 will be summarized. Dose discontinuations and reasons for study drug discontinuation will be listed and summarized.

8.14.2 Adverse Events

Clinical and laboratory AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). System Organ Class (SOC), High-Level Group Term (HLGT), High-Level Term (HLT), Preferred Term, and Lower-Level Term (LLT) will be attached to the clinical database. Summaries (number and percentage of subjects) of TEAE (by SOC, HLT, and Preferred Term) will be provided by treatment group.

Events will be summarized based on the date of onset for the event. A TEAE will be defined as any AE that begins on or after the date of first dose of study drug up to the date of last dose of study drug plus the number of days in the follow-up period. AEs observed during the period from obtaining informed consent to the start of administration of study drug will be regarded separately from AEs observed after study drug administration (i.e., TEAEs).

All AEs and all TEAEs will be listed by subject. The frequency of subjects who experience TEAEs will be summarized overall and by treatment group. AEs will also be summarized by relationship to treatment (study drug) and severity.

A listing of AEs will be provided for all subjects who experience an SAE. Data listings will also be provided for subjects who discontinued the study due to any AE, as well as for a SAE.

8.14.3 Laboratory Evaluations

Clinical laboratory test results, including hematology, serum chemistry, serum pregnancy tests will be listed by subject.

Reference ranges provided by the laboratory for each parameter will be used to evaluate the clinical significance of laboratory test results, i.e., hematology and serum chemistry panels. Values falling outside of the relevant reference range will be flagged, as appropriate, in the

data listings. Abnormalities in clinical laboratory test results will be summarized for each dose group by enumeration of the number of subjects with values falling outside of the reference range by study day. Selected laboratory data will be summarized using the 8-point descriptive summary over time (by study day), by the change from baseline across time, values relative to normal ranges, and changes from baseline relative to normal ranges.

Laboratory abnormalities that occur before the first dose of study drug or after the subject have been discontinued from treatment for the length of the follow-up period will be included in a data listing.

8.14.4 Select Laboratory parameters

Motilin plasma levels will be summarized separately from other laboratory parameters using

CCI

[redacted]

8.14.5 ECG Analyses

Individual data for ECG, vital signs measurements, and physical examination findings will be listed by subject and summarized by incidence (frequencies) of events/abnormalities or descriptive statistical summaries, as appropriate.

PR interval, QT interval, QTcF interval, QRS duration, and HR will be summarized for each treatment group at observed time points and for the each time-matched change from pre-dose (Day -1). ECG data collected during the study will be presented in a listing.

Clinically relevant QTcF findings will be summarized by treatment using the predetermined, clinically relevant thresholds as presented in Table 3.

Table 3: Threshold Criteria for QTcF

Type of Value	Criteria
Observed QTcF (msec)	≤450 >450 and ≤480 >480 and ≤500 >500
Change in QTcF (msec)	≤30 >30 and ≤60 >60

Individual ECG data collected during the study will be presented in a listing. A separate listing of subjects with values of QTcF >500 msec or an increase >60 msec will be provided, as necessary.

The investigator's assessment of ECG observations as clinically significant or not clinically significant will be summarized for baseline and for each visit.

9 STUDY ADMINISTRATION

This study will be conducted in compliance with all applicable regulations.

9.1 Principal Investigator Responsibilities

Before beginning the study, the principal investigator (PI) at each site must provide to Theravance or its designee a fully executed and signed Form FDA 1572 and, if applicable, a financial disclosure form. For applicable studies, financial disclosure forms must also be completed for all subinvestigators who will be directly involved in the treatment or evaluation of research subjects in this study. (A subinvestigator is defined in ICH E6 as any individual member of the clinical study team designated and supervised by the investigator at a study site to perform critical study-related procedures and/or to make important study-related decisions [e.g., associates, residents, research fellows].)

The PI will ensure the following:

- He or she will conduct the study in accordance with the relevant, current protocol and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.
- He or she will personally conduct or supervise the study.
- He or she will inform any potential subjects, or any persons used as controls, that the drugs are being used for investigational purposes and he or she will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.
- He or she will report to the sponsor adverse experiences that occur in the course of the investigation in accordance with 21 CFR 312.64.
- He or she has read and understands the information in the TD-8954 Investigator's Brochure, including potential risks and side effects of the drug.
- His or her staff and all persons who assist in the conduct of the study are informed about their obligations in meeting the above commitments
- He or she will ensure that adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.
- He or she will ensure that the IRB/IEC complies with the requirements of 21 CFR Part 56, and other applicable regulations, and conducts initial and ongoing reviews and approvals of the study. He or she will also ensure that any change in research activity and all problems involving risks to human subjects or others are reported to the IRB/IEC. Additionally, he or she will not make any changes in the research without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human subjects.
- He or she agrees to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

9.2 Institutional Review Board/Independent Ethics Committee

Before beginning study-specific research, the investigator will obtain written confirmation that the IRB, IEC, or Research Ethics Board (REB) is properly constituted and compliant with ICH and GCP requirements, applicable laws, and local regulations. A copy of the confirmation from the IRB/IEC/REB will be provided to Theravance or its designee. The protocol, informed consent form (ICF), IB, and any other appropriate written information provided to the subjects that the IRB/IEC/REB may require to fulfill its responsibilities will be submitted to the IRB/IEC/REB in advance of the study. Theravance or its designee must approve the ICF and all subject recruitment materials before they are submitted to the IRB/IEC/REB. The study will not proceed until appropriate documents from the IRB/IEC/REB confirming unconditional approval of the protocol and the ICF are obtained by the investigator and copies are received by Theravance or its designee. If possible, the approval document should refer to the study by study protocol title and Theravance study number, identify the documents reviewed, and include the date of the review and approval. The written approval of the IRB/IEC/REB will be retained as part of the study file. The study may proceed before approval of consent forms and other study documents translated to a language other than the native language of the clinical site, provided that written IRB/IEC/REB approval of the translated documents is obtained before they are used. Any amendments to the protocol should be reviewed promptly.

The investigator must provide the appropriate periodic reports on the progress of the study to the IRB/IEC/REB and Theravance in accordance with local IRB/IEC/REB requirements and applicable governmental regulations, whichever is strictest.

9.3 Informed Consent

A properly executed ICF, in compliance with ICH E6 (GCP Guideline, Section 4.8), 21 CFR §50, and other applicable local regulations, will be obtained for each subject before randomization of the subject into the study. The investigator will prepare the ICF or revise the template ICF and provide the documents to Theravance (or designee) for approval before submission to the IRB/IEC/REB. Theravance and the IRB/IEC/REB must approve the documents before they are implemented.

The investigator will provide copies of the signed ICF to each subject (or the subject's legally authorized representative or next of kin) and will maintain the original in the subject's record file.

9.4 Data Recording and Quality Assurance

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used.

Electronic data capture (EDC) technology will be used for this study. All clinical information requested in this protocol will be recorded on the electronic case report forms approved by Theravance, or via other data collection methods, e.g., electronic laboratory data transfer. Study site personnel will enter (in English) study data into the CRFs for each randomized subject. Training on the EDC application will be completed and documented before access to the EDC system is given.

In the event of a CRF data change (e.g., correction of an error or addition of new information), corrections will be made to the CRF. Corrections to the CRFs, including the reason for change, will be automatically documented through the EDC system's audit trail.

The investigator is responsible for reviewing all CRFs, verifying them for accuracy, and approving them via an electronic signature. The investigator is designated as the signatory coordinating investigator.

An electronic copy of the CRF casebooks will be sent to the site for retention with other study documents after full completion of the study, i.e., after database lock.

The investigator is responsible for maintaining accurate, authentic, complete, and up-to-date records for each subject. The investigator is also responsible for ensuring the availability of any original source documentation related to the study (including any films, tracings, computer discs, tapes, and worksheets). In most cases the source is the subject's medical record. Data collected on the CRFs must match the source documents.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator's site and clearly identify those data that will be recorded in the CRF and for which the CRF will stand as the source document.

9.5 Document Retention

Until otherwise notified by the Theravance, an investigative site must retain in a controlled manner all study documents required by Theravance and by the applicable regulations. The investigative site must take measures to prevent accidental or premature destruction of essential documents, that is, documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced, including paper copies of study records (e.g., subject charts) and any original source documents that are electronic, as required by applicable regulations.

The investigator must consult a Theravance representative before disposal of any study records and must notify Theravance of any change in the location or disposition of the study files. If an investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study documents, custody must be transferred to a person who will accept the responsibility. Theravance must be notified in writing of the name and address of the new custodian and must approve this transfer of responsibility.

9.6 Confidentiality

The investigator or designee must explain to each subject, before enrollment into the study, that, for evaluation of study results, the subject's confidential medical information obtained during the study may be shared with the study sponsor, regulatory agencies, and the institutional review board (IRB) or independent ethics committee (IEC). The investigator (or designee) is responsible for obtaining written permission to use confidential medical information in accordance with country-specific regulations (such as the Health Insurance Portability and Accountability Act in the United States) from each subject or, if appropriate, the subject's legally authorized representative. If permission to use confidential medical information is withdrawn, the investigator is responsible for documenting that no further data from the subject will be collected.

Subject medical information obtained during this study is confidential, and disclosure to unauthorized third parties is prohibited. The pertinent sections of data protection laws will be complied with in full. Study records containing subject information will only be identified by the subject identification number, subject initials, date of birth, and study number, and not by the subject's full name, except the subject consent form, which is archived at the study center only. The subject's name will not be used in any public report of the study.

During the course of the study, a confidential subject identification list will be maintained by the investigator and archived at the investigative site.

Before and during the conduct of the study, no study-related details may be disclosed, i.e., placed on the internet, published, or otherwise publicized, or provided to a third party without prior written permission from Theravance. The policy for publication of data after completion of the study is described in Section 9.9 (Publication).

9.7 Access to Data and Documents

Upon receipt of the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Study data recorded on the CRFs must be verifiable to the source data. All original recordings, laboratory reports, and subject records generated by this study must be available to Theravance, representatives of Theravance, the IRB/IEC/REB, and applicable regulatory authorities, and they may be used for submission to regulatory authorities. In addition, all source data should be attributable (signed and dated), consistent with local medical practice. The investigator must therefore agree to allow direct access to all source data. Subjects (or their legally authorized representatives) must also allow access to their medical records, and subjects will be informed of this and will confirm their agreement when giving informed consent.

9.8 Quality Control: Study Monitoring and Auditing

Qualified individuals designated by Theravance will monitor all aspects of the study according to GCP and standard operating procedures (SOPs) for compliance with applicable government regulations. The investigator agrees to allow these monitors direct access to the clinical data and supplies, dispensing, and storage areas and, if requested, agrees to assist the monitors. The investigator and staff are responsible for being present or available for consultation during routinely scheduled site visits conducted by Theravance or its designees.

Members of Theravance's GCP Quality Assurance Department or designees may conduct an audit of a clinical site at any time during or after completion of the study. The investigator will be informed if an audit is to take place and advised as to the scope of the audit. Inspections and audits are typically carried out during the clinical and reporting phases of

this study to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, written SOPs and applicable laws, rules, and regulations.

Representatives of the FDA or other Regulatory Agencies, including IRB/IEC representatives may also conduct an audit of the study. If informed of such an inspection, the investigator should notify Theravance immediately. The investigator will ensure that the auditors have access to the clinical supplies, study site facilities, laboratory and all data (including original source documentation) and all study files are available, if requested.

Noncompliance with the protocol, ICH, GCP, or local regulatory requirements by an investigator, institution, institution staff, or representatives of Theravance will lead to prompt action by Theravance to secure compliance. Continued noncompliance may result in termination of the investigator's involvement in the study. The IRB/IEC/REB and relevant regulatory authority will be informed.

9.9 Publication

Theravance recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and presentation at seminars or conferences. Theravance will retain the ownership of the data collected in this study. The investigator will provide any proposed manuscript or abstract to Theravance before submission for publication or presentation of any results or data obtained in this study.

Additional details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study will be described in the Clinical Study Agreement between Theravance and the investigator.

10 REFERENCES

1. Barton R, Nutrition Support in Critical Illness. Nutrition in Clinical Practice August 1994;9:127-139,.
2. Harrington L, Nutrition in critically ill adults: key processes and outcomes. Crit Care Nurs N Am 16 (2004);459–65.
3. Slone DS, Nutritional support of the critically ill and injured patient. Crit Care Clin 20 (2004) 135-157.
4. De Beaux I, Chapman M, Fraser R, Finnis M, De Keulenaer B, Liberalli D, Satanek M. Enteral Nutrition in the Critically ill: A Prospective Survey in an Australian Intensive Care Unit. Anaesthesia and Intensive Care, Vol. 29, No 6, December 2001;619-622.
5. Heyland D, Cook DJ, Winder B, Brylowski L, Van demark H, Guyatt G. Enternal nutrition in the critically ill patient: A prospective study. Crit Care Med 1995;23:1055-60.
6. Dempsey D, Mullen J, Buzby G.The link between nutritional status and clinical outcome: can nutritional intervention modify it? Am J Clin Nutr 1988;47:352-6.
7. Beattie DT, Armstrong SR, Vickery RG, Tsuruda P, Campbell CB, Richardson C, McCullough JL, Daniels O, Kersey K, Li Y-P, Kim KH. The pharmacology of TD-8954, a potent and selective 5-HT_4 receptor agonist with gastrointestinal prokinetic properties. Front Pharmacol. 2011;2:1-13.
8. Frost SA, Alexandrou E, Bogdanovski T, Salamonson Y, Davidson PM, Parr MJ, Hillman KM. Severity of illness and risk of readmission to intensive care: a meta-analysis. Resuscitation. 2009 May;80(5):505-10.
9. Rosenberg AL, Hofer TP, Hayward RA, Strachan C, Watts CM. Who bounces back? Physiologic and other predictors of intensive care unit readmission. Crit Care Med. 2001 Mar;29(3):511-8.

11 APPENDICES

Appendix 1: Protocol Signature Form

A Randomized, Double-Blind Study to Evaluate the Safety, Tolerability and Pharmacodynamics of a Single Dose of Intravenous TD-8954 Compared With Metoclopramide in Critically Ill Patients With Enteral Feeding Intolerance

I have read the forgoing protocol and agree to conduct this study in accordance with the current protocol. I also agree to conduct the study in compliance with all applicable regulations.

Investigator's Name (print)

Investigator's Signature Date

Appendix 2: Examples of Gastric Prokinetic Agents

Gastric Prokinetic Agents

Generic	Trade Names examples
Metoclopramide	Maxeran, Maxolon, **Reglan**
Erythromycin	E.E.S., EMU-V, E-Mycin, Eryc, Eryhexal, Erymax, Ery-Tab, Erythrocin, Ilocap, Ilosone, Ilotycin
Domperidone	Motillium, **Motilium,** Motinorm Costi, Nomit
Prucalopride	**Resotrans**
Azithromycin	Azin, Azithrocin, Zedd, **Zithromax,** Zmax

Serotonin Specific Reuptake Inhibitors (SSRI)

Generic	Trade Names examples
Citalopram	Celapram, **Celexa,** Ciazil, Cipram, Cipramil, Cital, Citopam, Citrol, Citox, Dalsan, Emocal, Recital, Sepram, Seropram, Talam, Talohexal
Dapoxetine	Priligy
Escitalopram	Cipralex, Esertia, Esitalo, **Lexapro,** Seroplex,
Fluoxetine	Auscap, Fontex, Fluohexal, Lovan, **Prozac,** Sarafem, Zactin
Fluvoxamine	Dumyrox, Faverin, Favoxil, Fevarin, Floxyfral, **Luvox,** Movox
Paroxetine	Aropax, Deparoc, Deroxat, Divarius, Loxamine, Paroxat, **Paxil,** Rexetin, Seroxat, Sereupin, Xetanor
Sertraline	Asentra, Lustral, Serlain, Tresleen, **Zoloft**

Acetylcholinesterase Inhibitors

Generic	Trade Names examples
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Lycoremine, Nivalin, Razadyne, Razadyne ER, **Reminyl**
Neostigmine	
Pyridostigmine	Mestinon
Tacrine	Cognex

Anticholinergics

Generic	Trade Names examples
Atropine	
Scopolamine	Scopace
Benzatropine	Cogentin
Oxybutynin	**Ditropan,** Driptane, Lenditro, Lyrinel XL
Tolterodine	**Detrol,** Detrusitol
Dicycloverine	Bentyl
Dicyclomine	Bentyl
Hyoscyamine	HyoMax, Hyosyne, Levbid, Levsin, Symax Duotab
Methscopolamine	Pamine, Pamine Forte
Glycopyrrolate	Robinul
Propantheline	Pro-Banthine
Clidinium	Quarzan
Mepenzolate	Cantil

Appendix 3: Apache II Parameters

Physiological Variables	High Abnormal Range					Low Abnormal Range			
	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (°C)	≥ 41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤ 29.9°
Mean Arterial Pressure (mmHg)	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤ 39
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5
Oxygenation: A-aDO_2 or PaO^2 (mmHg) a. Fio_2≥0.5 record A-aDO2 b. Fio_2<0.5 record Pao_2	≥500	350 to 499	200 to 349		<200 $P0_2$ >70	 $P0_2$ 61 to 70		 $P0_2$ 55 to 60	 $P0_2$ <55
Arterial Ph (preferred) Serum HCO3 (venous mEq/l) (not preferred but may use if no ABG)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6		
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1
Glasgow Coma Score (GCS) Score =15 minus actual GCS									

A. Total Acute Physiology Score (Sum of 12 above point)
B. Age points (years) ≤44 =0; 45 to 54 =2; 55 to 64 =3; 65 to 74 =5; ≥75 =6
C. Chronic Health Points (see below)

Total Apache II Score (add together the points from A+B+C)

Chronic Health Points: If the patient has a history of severe organ system insufficiency or is immunocompromised as defined below, assign points as follows:

- 5 points for nonoperative or emergency postoperative patients
- 2 points for elective postoperative patients

Definitions: organ insufficiency or immunocompromised state must have been evident prior to this hospital admission and conform to the following criteria:

Liver – biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.

Cardiovascular – New York Heart Association Class IV.

Respiratory – Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or respirator dependency.

Renal – receiving chronic dialysis.

Immunocompromised – the patient has received therapy that suppresses resistance to infection (e.g., immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS).