Title: A Phase 2b, Randomized, Multicenter, Double-Blind, Dose-Ranging Study to Assess the Efficacy, Safety and Pharmacokinetics of Intravenous TAK-954 in Critically Ill Patients With Enteral Feeding Intolerance

NCT Number: NCT03477903

Protocol Approve Date: 28 February 2018

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.

TAKEDA PHARMACEUTICALS

PROTOCOL

A Phase 2b, Randomized, Multicenter, Double-Blind, Dose-Ranging Study to Assess the Efficacy, Safety and Pharmacokinetics of Intravenous TAK-954 in Critically Ill Patients With Enteral Feeding Intolerance

TAK-954 in Critically Ill Patients With Enteral Feeding Intolerance

Sponsor:	Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as "Millennium," "Sponsor," or "Takeda".		
Study Number:	2002		
IND Number:	114408	**EudraCT Number:**	2017-003206-41
Compound:	TAK-954		
Date:	28 February 2018	**Version/Amendment Number:**	01

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
16 Jan 2018	Initial version	Not applicable	Global*
28 February 2018	01	Nonsubstantial	Global*

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

A separate contact information list will be provided to each site.

Takeda Development Center Americas, Inc. (TDC) sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given in Section 3.1 and relevant guidelines provided to the site.

Contact Type/Role	Country Contact
Serious adverse event and pregnancy reporting Medical Monitor (medical advice on protocol and study drug) Responsible Medical Officer (carries overall responsibility for the conduct of the study)	PPD

1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

Electronic Signatures are provided on the last page of this document.

PPD

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix D of this protocol.

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

1.3 Protocol Amendment 01 Summary of Changes

Rationale for Amendment 01

This document describes the changes in reference to the protocol incorporating Amendment No. 01. The primary reason for this amendment is the clarification and correction of study procedures.

Minor grammatical, editorial, and formatting changes are included for clarification purposes only.

For specific descriptions of text changes and where the changes are located, see Appendix F.

Changes in Amendment 01

1. CCI [redacted]
2. CCI [redacted]
3. Deletion of the reinstitution of subjects' treatment in case of relapse.
4. Additional criteria for discontinuation or withdrawal of a subject was added.
5. Clarification of neurological examinations.
6. Removal of glycosylated hemoglobin (HbA1c) and thyroid stimulating hormone testing.
7. Correction of electrocardiograms (ECGs) time points.
8. Correction of clinical laboratory sample collections and amount of blood needed for the study.
9. Clarification of cardiovascular adverse events of special interest (AESI).
10. Deletion of the submission of the original copy of the serious adverse event (SAE) form to the sponsor.
11. Clarification of the collection of height measurement.
12. Correction of time from Randomization to drug administration.

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2.0 STUDY SUMMARY

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<tr><td colspan="2">Name of Sponsor(s):
Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
Please note: Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, may be referred to in this protocol as “Millennium,” “Sponsor,” or “Takeda”.</td><td colspan="2">Compound:
TAK-954</td></tr>
<tr><td>Title of Protocol: A Phase 2b, Randomized, Multicenter, Double-Blind, Dose-Ranging Study to Assess the Efficacy, Safety, and Pharmacokinetics of Intravenous TAK-954 in Critically Ill Patients With Enteral Feeding Intolerance</td><td>IND No.: 114408</td><td>EudraCT No.:
2017-003206-41</td></tr>
<tr><td>Study Number: 2002</td><td colspan="2">Phase: 2b</td></tr>
<tr><td colspan="3">Study Design:
This is a phase 2b, randomized, multicenter, double-blind, double-dummy, dose-ranging, active-controlled study to evaluate the efficacy, safety, and pharmacokinetics (PK) of intravenous (IV) TAK-954 in critically ill subjects with enteral feeding intolerance (EFI). The primary objective of this study is to assess the treatment effect of IV TAK-954 in improving the average daily protein adequacy received through enteral nutrition.
During the Screening Period, subjects receiving enteral feed and meeting eligibility criteria for enrollment will be identified and those that meet the protocol definition of EFI, defined as a single gastric residual volume (GRV) measurement of ≥250 mL with vomiting/retching within the last 24 hours or a single GRV measurement of ≥500 mL, with or without vomiting/retching within the last 24 hours, will be eligible for randomization. Patients should be enrolled within 24 hours of developing EFI.
Approximately 200 subjects will be enrolled in this study and randomized in a 1:1:1:1 ratio to 1 of 4 parallel treatment groups (0.1, 0.3, or 1 mg of TAK-954 diluted to 100 mL with normal saline administered by IV infusion over 60 minutes once daily (QD) and 2 mL of normal saline IV injection at other times to make a 3 times a day (TID) dosing regimen; OR 100 mL normal saline IV infusion over 60 minutes QD and 10 mg metoclopramide [5 mg/mL] IV injection TID). Subject randomization will be stratified based on their baseline NUTrition RIsk in Critically Ill (NUTRIC) score (either low [0-4] or high [5-9]) to ensure that approximately equal numbers of subjects will be randomized into each treatment group from a high or low NUTRIC score group. The study design incorporates adaptive features in order to provide an opportunity to modify 1 or more aspects of the study based on accumulating data and mitigate the risks associated with unanticipated variability.
An interim analysis will be performed after approximately 25 subjects within each cohort have completed the study. Potential modifications to the design of the study based on Bayesian methods following the interim analysis include: dropping of inefficacious dose(s), dropping of doses due to safety concerns, inclusion of new dose(s) (less than 1 mg), and sample size adjustment.
The 24:00 clock will start at the beginning of the treatment infusion on Day 1. Subjects will receive blinded TAK-954 or metoclopramide at approximately the same time (plus or minus 2 hours) on the dosing days. Subjects will receive randomized treatment for a minimum of 5 days and up to a maximum of 14 days. Treatment may be discontinued upon EFI resolution and subject’s feeding goal rate is achieved between 5 to 14 days of drug administration. Subjects whose EFI resolves and goal feeding rate is achieved earlier will remain on study medication to complete at least 5 days of treatment. At the discretion of the treating physician and investigator, the participant may remain on study drug for up to 14 days if they remain feed tolerant and they are advanced to their goal feeding rate. All subjects will follow the same feeding protocol. Treatment failures by protocol (Figure 6.a) will be discontinued from the study and standard of care will be implemented.
Subjects will also be discontinued if continuous tube feeding is no longer being provided in the intensive care unit ([ICU] eg, the patient is discharged to the ward, liquid nutrient is ceased by treating clinicians and the participant is</td></tr>
</table>

allowed oral intake, or new abdominal pathology that requires enterally feeding to be ceased) or the subject dies.

Subjects assessed by the treating physician as requiring different management to what is currently specified in the feeding protocol (eg, requiring rescue medication or post-pyloric tube placement) will be considered as treatment failures and be withdrawn from study treatment. Subjects with unresolved EFI following the 14-day Treatment Period should be managed by the treating physician according to local standard of care. Subjects will be followed up to 30 days for safety and up to 90 days for cardiovascular events and survival after receiving their last dose of study treatment. Choice of feeding formula will be at the discretion of the treating physician but will be within a defined nutritional breakdown (1.2 to 2 g/kg/day of proteins and up to 1.5 kcal/mL).

The nutritional requirements of an individual subject will be determined as per standard of care at the site. During the Treatment Period, nutritional parameters including nutritional prescription, daily feed volume, calories, and protein delivered will be recorded. Blood glucose will be monitored throughout the study and kept within an acceptable range according to individual site protocols. Protein homeostasis will be monitored through step wise measurement of protein absorption (nitrogen balance), and endogenous protein production (pre-albumin). Indirect measures including motilin, cholecystokinin, pancreatic polypeptide, C-reactive protein and interleukin-6 will also be assessed.

Primary Objective:

The primary objective of this study is to assess the treatment effect of IV TAK-954 in improving the average daily protein adequacy received through enteral nutrition.

Secondary Objectives:

The secondary objectives of this study are to:

- Assess the treatment effect of TAK-954 on GRV.
- Assess the safety and tolerability of multiple IV doses of TAK-954.
- Assess the treatment effect of TAK-954 on the ability to meet average target daily nutritional goals.
- Assess the treatment effect of TAK-954 on clinical outcomes.
- Evaluate the PK of TAK-954.

Subject Population: Critically ill subjects admitted to the ICU and identified to have EFI.

Number of Subjects:	**Number of Sites:**
Approximately 200 subjects will be randomized into 1 of 4 treatment groups	Estimated total: 40 sites in North America, Europe, and Australia.
Dose Levels: TAK-954 0.1, 0.3, and 1 mg QD Metoclopramide 10 mg TID	**Route of Administration:** TAK-954 (IV) Placebo (IV) Metoclopramide (IV)
Duration of Treatment: Minimum of 5 days not to exceed 14 days of treatment, or until resolution of EFI, whichever comes first.	**Period of Evaluation:** Up to approximately 104 days.

Main Criteria for Inclusion:

Subjects who:

- Are males or females (not pregnant) 18 years and older.
- Have at least a size 12-Fr nasogastric or orogastric tube with its distal tip at least 10 cm below the esophago-gastric junction confirmed radiographically (the tip of the tube must be in the body or the antrum of the stomach and not in the fundus).
- Are intubated and mechanically ventilated in the ICU.
- Are expected to remain alive, mechanically ventilated, and to receive continuous enteral feeding for ≥48 hours following randomization.

- Have developed EFI, defined as a single GRV measurement of ≥250 mL in the presence of vomiting/retching within 24 hours, or a single GRV measurement of ≥500 mL, with or without vomiting/retching within the last 24 hours.

Main Criteria for Exclusion:

Subjects who:

- Have a current or prior major esophageal or gastric surgery or direct luminal trauma on this admission (subjects with lower abdominal surgery are not excluded unless enteral feeding is contraindicated).
- Have a mechanical bowel obstruction, short bowel syndrome, or the presence of an active gastric pacemaker.
- Have pre-existing hepatic disease that meets Child-Pugh Class B (moderate; total score 7 to 9 points) or C (severe; total score 10 to 15 points); see Appendix A.
- Has alanine aminotransferase >8×upper limit of normal (ULN).
- Have an estimated glomerular filtration rate <30 mL/min.
- Were admitted primarily for the treatment of a drug overdose.
- Have a post-pyloric or gastrostomy tube in place at randomization that may be used for enteral nutrition.
- Are receiving parenteral nutrition at Screening.
- Are in diabetic ketoacidosis or nonketotic hyperosmolar coma.
- Have clinically significant electrocardiogram (ECG) abnormalities indicative of acute cardiac instability as determined by the investigator at Screening; more than first degree atrioventricular block; >5 beats of non-sustained ventricular tachycardia (VT) at a rate >120 bpm; ECG changes consistent with acute myocardial ischemia or infarction.
- Note: Controlled atrial fibrillation (AF) or supraventricular tachycardia (SVT) is allowed with heart rate under 100 bpm.
- Have a QT interval with Fridericia correction method (QTcF) interval ≥450 msec or with other factors that increase the risk of QT prolongation or arrhythmic events at Screening. Subjects with bundle branch block and a prolonged QTcF should be reviewed by a cardiologist for potential inclusion.
- Have a different nutrient requirement than allowed in the standardized feeding protocol (1.2 to 2 g/kg/day of proteins and up to 1.5 kcal/mL).
- Have received erythromycin or metoclopramide in the previous 24 hours before Screening; domperidone or azithromycin in the previous 72 hours, or need ongoing macrolide antibiotics. Subjects on chronic treatment with metoclopramide or that have received continuous treatment (≥7 days) with metoclopramide during this hospital stay should be excluded.
- In the opinion of the treating physician, treatment with metoclopramide is contraindicated or would not be in their best interest.
- Have received agents known to directly influence the serotonin type 4 (5-HT_4)/acetylcholine pharmacologic mechanism (eg, serotonin-specific reuptake inhibitors, anticholinergic agents, or acetylcholinesterase inhibitors) within 72 hours before Randomization.
- Are receiving drugs that may cause serotonin syndrome (eg, gamma-aminobutyric acid [GABA] receptor antagonists, monoamine oxidase inhibitors, 5-HT_4 agonists, N-methyl-D-aspartate receptor antagonists, norepinephrine and serotonin reuptake inhibitors, linezolid, tramadol).

Main Criteria for Evaluation and Analyses:

The primary efficacy endpoint will be the average daily protein adequacy received through enteral nutrition (defined by % of goal protein delivered per day [% protein goal delivered = actual protein achievement / total patient-specific target protein]) over the first 5 days of study treatment.

Secondary Endpoints for This Study are the:

- Average daily protein adequacy received through enteral nutrition (defined by % of goal protein delivered per day [% protein goal delivered = actual protein achievement / total patient-specific target protein]) over the study treatment period.
- Average daily change in 24-hour GRV over the first 5 days of study treatment.
- Average daily caloric adequacy received through enteral nutrition (defined by % of goal calories achieved per day [% calorie goal achieved = actual calorie achievement / total patient-specific target calories]) over the first 5 days of study treatment and over the study treatment period.
- Time to resolution of EFI defined as GRV <250 mL in the absence of symptoms.
- Proportion of subjects achieving at least 80% of daily goal calories through enteral nutrition and maintaining it for at least 2 consecutive days and/or the rest of the Treatment Period.
- Proportion of subjects achieving at least 80% of daily goal protein through enteral nutrition and maintain it for at least 2 consecutive days and/or the rest of the Treatment Period.
- PK parameters of TAK-954: Observed concentration at the end of a dosing interval (C_{trough}) on Day 5.

Exploratory Endpoints for This Study are the:

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Statistical Considerations:

The primary efficacy endpoint will be the average daily protein adequacy received through enteral nutrition (defined by % of goal protein delivered per day [% protein goal delivered = actual protein achievement / total patient-specific target protein]) over the first 5 days of study treatment. Bayesian methods will be used to assess treatment effect. For each comparison between metoclopramide and TAK-954, a non-informative prior will be assumed for the distribution of treatment effect. At the end of the study, the posterior distribution of treatment effect for each TAK-954 arm against metoclopramide will be derived and 95% credible intervals will be calculated. Additionally, simultaneous 95% confidence intervals for each dose of TAK-954 against metoclopramide will also be computed using Dunnett's method.

The safety objectives will be evaluated using safety data through the duration of ICU stay and for up to 90 days after the end of treatment and will be listed by subject and summarized by treatment using the frequency of events or descriptive statistical summaries, as appropriate. All subjects who received at least 1 dose of study medication will be included in the safety evaluation. Summary tables will be provided for AEs, hematology, and chemistry laboratory evaluations, vital signs, 12-lead ECG findings, and concomitant medications. Baseline characteristics such as type of reason for ICU referral or patient category for mixed ICUs (medical, surgical, burn, trauma), main diagnosis, NUTRIC score, Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE), medication of interests (opioids, propofol, proton pump inhibitors, laxatives) and muscle mass (mid-upper arm circumference) measurements will be summarized descriptively.

Concentration data for each time point for TAK-954 will be summarized by descriptive statistics.

Descriptive statistics, graphical methods, and statistical modeling as appropriate will be used to explore the relationship between baseline levels/response and the levels of various biomarkers.

Sample Size Justification:

This study will randomize approximately 200 subjects into 4 treatment groups with an initial equal (1:1:1:1) randomization scheme. This sample size is based on simulation of go/no-go decision making using a Bayesian approach. If a new dose is introduced after the interim analysis, then the randomization scheme may be adjusted to increase the proportion of new subjects being assigned to the new dose. Subject randomization will be stratified based on their baseline modified NUTRIC score (either low [0-4] or high [5-9]) to ensure that approximately equal numbers of subjects will be randomized into each treatment group from a high or low NUTRIC score.

Interim Analysis:

Interim analysis will be performed after approximately 100 subjects have completed the study; ie, 25 subjects within each cohort. Efficacy and safety data will be used to determine if stopping criteria for individual dose groups are met. Interim decision making for efficacy will be performed based on a futility stopping rule. Futility assessments in each dose group will be conducted based on the predictive probability of success (PPoS) of the primary efficacy endpoint.

The criteria for success for each dose group is that posterior probability (standardized treatment effect >0.2|Data) > 80% based on the updated distribution of the treatment effect at the end of the study. This will be assessed separately for each arm, assuming a positive treatment effect indicates improvement. If the PPoS at the interim in a dose group is below a pre-determined threshold (20%;), 2 actions may be taken:

- The futility stopping rule will be met and patient enrollment will be discontinued in this dosing group. Subjects currently in that dosing group will complete the study receiving that dose if safety is not a concern.
- Subjects not already randomized will be split equally among any of the remaining dose groups after the interim analysis or reassigned to a new dose level.

In addition to the above formal criteria, all available efficacy and safety data from the current study, as well as all available data from the other TAK-954 studies, will be used to guide the potential modification of design of the study, including dropping of inefficacious dose(s), dropping of doses due to safety concerns, and inclusion of new dose(s) (less than 1 mg).

3.0 STUDY REFERENCE INFORMATION

3.1 Study-Related Responsibilities

The sponsor will perform all study-related activities with the exception of those identified in the Study-Related Responsibilities template. The vendors identified in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

The sponsor will select a Signatory Coordinating Investigator from the investigators who participate in the study. Selection criteria for this investigator will include significant knowledge of the study protocol, the study drug, their expertise in the therapeutic area and the conduct of clinical research as well as study participation. The Signatory Coordinating Investigator will be required to review and sign the clinical study report and by doing so agrees that it accurately describes the results of the study.

3.3 List of Abbreviations

5-HT_4	serotonin type 4
5-HT	serotonin
ADL	activities of daily living
AE	adverse event(s)
AESI	adverse events of special interest
AF	atrial fibrillation
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APACHE	Acute Physiology and Chronic Health Evaluation
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
$AUC_{24,ss}$	area under the concentration-time curve from time 0 to time 24, at steady state
AUC_{∞}	area under the concentration-time curve from time 0 to infinity
AV	atrioventricular
BMI	body mass index
bpm	beats per minute
CEC	cardiovascular endpoint committee
C_{max}	maximum plasma observed concentration
$C_{max,ss}$	maximum observed concentration during a dosing interval, at steady state
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	observed concentration at the end of a dosing interval
CYP	cytochrome P450
eCRF	electronic case report form
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EFI	enteral feeding intolerance
EN	enteral nutrition
FAS	full analysis set
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GRV	gastric residual volume
hCG	human chorionic gonadotropin
HCV	hepatitis C virus

ICH	International Council on Harmonisation
ICU	intensive care unit
ID	identification
IDMC	independent data monitoring committee
IEC	independent ethics committee
IL-6	interleukin-6
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
LAR	legally authorized representative
LFT(s)	liver function tests
LOS	length of stay
MACE	major adverse cardiac events
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect-level
NUTRIC	Nutrition RIsk in Critically Ill
PD	pharmacodynamic(s)
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PN	parenteral nutrition
PPoS	predictive probability of success
PPS	per protocol set
QD	once daily
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event(s)
SAP	statistical analysis plan
SOFA	Sequential Organ Failure Assessment
SUSARs	suspected unexpected serious adverse reactions
SVT	supraventricular tachycardia
$t_{1/2z}$	terminal disposition phase half-life
TDC	Takeda Development Center
THRX-513466	metabolite of TAK-954
THRX-913682	metabolite of TAK-954
TID	3 times a day
TPN	total parenteral nutrition
ULN	upper limit of normal
VT	ventricular tachycardia

3.4 Corporate Identification

TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4.0 INTRODUCTION

4.1 Background

TAK-954 is a highly selective and potent serotonin type 4 (5-HT_4) receptor agonist that has shown prokinetic activity throughout the gastrointestinal (GI) tract in experimental models and is being developed for short-term (acute) use in the treatment of critically ill patients with enteral feeding intolerance (EFI).

Critically ill patients who require enteral feeding frequently have reduced GI motility including delayed gastric emptying, and develop EFI, which can lead to several complications including not meeting daily calorie and protein requirements [1]. Development of malnourishment in these patients is associated with 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].

Nonclinical studies completed to date include a safety pharmacology battery (neurobehavioral, cardiovascular, and respiratory systems), intravenous (IV) and oral single-dose studies in rats, oral single-dose studies in dogs, and oral 28-day and 13-week repeat-dose studies in rats and dogs. TAK-954 was also tested in in vitro and in vivo genotoxicity studies, embryo-fetal toxicity studies in rats and rabbits, and ex vivo and in vivo local tolerance studies. Toxicokinetic analysis of TAK-954 plasma levels was conducted in the Good Laboratory Practice repeat-dose studies.

CCI

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[redacted]

CCI

The purpose of this phase 2, randomized, multicenter, double-blind, double-dummy, dose-ranging, active-controlled study is to evaluate the safety, efficacy, and PK of IV TAK-954 in critically ill subjects with EFI.

Please refer to the TAK-954 Investigator's Brochure for complete information on the investigational product.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

4.2 Rationale for the Proposed Study

Critical illness is typically associated with a catabolic stress state and critically ill patients are at particular risk of malnutrition, which can occur in up to 50% of cases and is a significant clinical issue associated with increased morbidity and mortality [4-8].

Evidence favors the initiation of early enteral nutrition (EN) as opposed to parental nutrition (PN) (unless otherwise contraindicated) in critically ill patients, particularly those at high nutritional risk (ie, at high risk for under-nutrition and/or malnutrition). Of those that do receive enteral feeding, a large proportion of patients receive inadequate nutrition placing them at high risk for malnutrition or worsening of pre-existing malnutrition [4-9]. One of the key factors contributing to the development or worsening of existing malnutrition in critically ill patients is impaired GI motility, which is common in ICU patients and associated with serious complications [10-15].

Impaired GI motility is the primary cause for EFI; a condition characterized by high gastric residual volume (GRV), and vomiting with an associated increased risk for aspiration and aspiration pneumonia [10,16,17]. Results of a retrospective analysis of data from an international observational cohort study of nutrition practices among 167 ICUs demonstrated that in critically ill,

mechanically-ventilated patients receiving EN via the intragastric route, feeding intolerance occurred frequently (approximately one-third of patients) and was associated with a reduction in the amount of nutrients delivered to patients, increased days with ventilation, longer duration of ICU stay, and increased mortality [15].

The longer it takes for adequate nutrition to be provided, the greater the nutritional deficit, contributing to the undernourishment in this at-risk group. As a result, re-establishment of enteral feeding to deliver the required daily calorie and protein is 1 of the goals of management of EFI, in line with current standard of care [18].

Strategies to prevent motility disorders in critically ill patients include head elevation, minimizing drugs with inhibitory effect on motility, ensuring electrolyte and fluid balance, and alternative perioperative anesthesia where possible.

Pharmacologic agents most commonly used for treating EFI are prokinetics. These are used off-label and in the short-term (generally <7 days) to treat EFI once it has occurred or to support enteral feeding. Prokinetic agents such as metoclopramide and erythromycin have demonstrated some efficacy in critical illness-related GI dysmotility although data are inconsistent. These agents have significant limitations including: they primarily affect upper GI tract motility (stomach, proximal small bowel), are associated with rapid tachyphylaxis (after 3 to 4 days), and are associated with SAEs [11-13,19-23].

5-HT_4 agonists have proven therapeutic potential in patients with GI motility disorders [20,24]. However, earlier agents lacked 5-HT_4 selectivity and their off-target activity increased the risk for important adverse effects. For example, metoclopramide, which is a dopamine-2 receptor antagonist, serotonin type 3 (5-HT_3) receptor antagonist, and indirect enhancement of cholinergic neurotransmission can cause extrapyramidal and cardiovascular effects; cisapride, which is a 5-HT_4 receptor agonist can cause cardiac dysrhythmias; and tegaserod, which is a serotonin type 1 and 2 (5-HT_1 and 5-HT_2) receptor agonist/antagonist, can cause ischemic cardiovascular adverse effects [20,25].

The development of highly selective 5-HT_4 receptor agonists (eg, velusetrag, naronapride, prucalopride) has resulted in more favorable benefit-to-risk profiles for this drug class due to much lower affinity for targets known to be associated with serious adverse effects. TAK-954 belongs to this group of compounds of highly selective 5-HT_4 receptor agonists. It is a potent, highly selective, 5-HT_4 receptor agonist with evidence of activity throughout the GI tract and low risk for off-target effects. Impaired GI motility associated with critical illness may affect multiple GI segments. Therefore, a prokinetic agent with activity beyond the upper GI tract may be more effective in improving overall GI motility and the complication of EFI than agents that primarily affect the stomach and upper small bowel.

TAK-954 is being developed for short-term use for the treatment of patients with EFI. TAK-954 has prokinetic effects that can be targeted at impaired GI motility which is the most common barrier to delivering adequate nutrition via enteral feeding in critically ill patients. Within an ICU setting, an IV formulation is convenient and desired. TAK-954 will be delivered as an IV administration when patients are confirmed as having EFI.

4.3 Benefit/Risk Profile

Study participants with EFI are expected to see an improvement based on the prokinetic effect of TAK-954 and metoclopramide.

Potential risks of TAK-954 use include findings from prior studies; there were no SAEs or severe AEs observed in 2 oral dose studies in healthy volunteers, Studies 0060 and 0061. Following multiple IV doses in healthy subjects in Study 0095, TAK-954 was generally well tolerated at doses ranging from 0.1 to 0.5 mg QD for 5 consecutive days. No SAEs were reported. The most common AEs (ie, headache and postural dizziness) were not serious and resolved with treatment discontinuation.

The principal mitigation for these risks includes appropriate selection of the study populations, detailed safety plan for important potential and identified risks, which permits close monitoring, including regular neurological examination, and rapid institution of appropriate care as needed, and utilization of experienced ICU staff trained in study procedures.

Metoclopramide is currently the most widely used prokinetic agent in treating ICU patients who develop EFI and has a well-established safety profile that includes hyperprolactinemia and extrapyramidal disorders (acute dystonia) that are generally completely reversible after treatment discontinuation. Chronic metoclopramide use can be associated with tardive dyskinesia, which is characterized by involuntary movements of the face, tongue or extremities that may not reverse after discontinuation of the treatment, but this is a rare complication described only after usage of metoclopramide for at least 3 months. The pharmacological effects of metoclopramide in enhancing peristalsis and GI motility are driven by antagonism of the dopamine-2/dopamine-3 receptors and peripheral 5-HT_4 agonist effect. The treatment will last only until the resolution of EFI or for a maximum of 14 days.

Overall, the risk:benefit profile is therefore considered appropriate for this study.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

The primary objective of this study is to assess the treatment effect of IV TAK-954 in improving the average daily protein adequacy received through enteral nutrition.

5.1.2 Secondary Objectives

The secondary objectives of this study are to:

- Assess the treatment effect of TAK-954 on GRV.
- Assess the safety and tolerability of multiple IV doses of TAK-954.
- Assess the treatment effect of TAK-954 on the ability to meet average target daily nutritional goals.
- Assess the treatment effect of TAK-954 on clinical outcomes.
- Evaluate the PK of TAK-954.

5.1.3 Exploratory Objectives

The exploratory objectives are to study:

CCI

[redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

The primary efficacy endpoint will be the average daily protein adequacy received through enteral nutrition (defined by % of goal protein delivered per day [% protein goal delivered = actual protein achievement / total patient-specific target protein]) over the first 5 days of study treatment.

5.2.2 Secondary Endpoints

The secondary endpoints for this study are the:

- Average daily protein adequacy received through enteral nutrition received through enteral nutrition (defined by % of goal protein delivered per day [% protein goal delivered = actual protein achievement / total patient-specific target protein]) over the study treatment period.
- Average daily change in 24-hour GRV over the first 5 days of study treatment.
- Average daily caloric adequacy received through enteral nutrition (defined by % of goal calories achieved per day [% calorie goal achieved = actual calorie achievement / total patient-specific target calories]) over the first 5 days of study treatment and over the study treatment period.
- Time to resolution of EFI defined as GRV <250 mL in the absence of symptoms.
- Proportion of subjects achieving at least 80% of daily goal calories through enteral nutrition and maintaining it for at least 2 consecutive days and/or the rest of the Treatment Period.
- Proportion of subjects achieving at least 80% of daily goal protein through enteral nutrition and maintain it for at least 2 consecutive days and/or the rest of the Treatment Period.
- PK parameters of TAK-954: Observed concentration at the end of a dosing interval (C_{trough}) on Day 5.

5.2.3 Safety Endpoints

Safety and tolerability will be evaluated based on the occurrence of AEs, physical examination findings, vital signs and weight, electrocardiograms, and clinical laboratory parameters (chemistry, hematology, and urinalysis).

5.2.4 Exploratory Endpoints

The exploratory endpoints for this study include:

- CCI
- [redacted]

- CCI
- [redacted]

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 2b, randomized, multicenter, double-blind, double-dummy, dose-ranging, active-controlled study to evaluate the efficacy, safety, and PK of IV TAK-954 in critically ill subjects with EFI.

During the Screening Period, subjects receiving enteral feed and meeting eligibility criteria for enrollment will be identified and those that meet the protocol definition of EFI, defined as a single GRV measurement of ≥250 mL with vomiting/retching within the last 24 hours, or a single GRV measurement of ≥500 mL with or without vomiting/retching within the last 24 hours, will be eligible for randomization. Patients should be enrolled within 24 hours of developing EFI.

Approximately 200 subjects will be enrolled in this study and randomized in a 1:1:1:1 ratio to 1 of 4 parallel treatment groups (0.1, 0.3, or 1 mg of TAK-954 diluted to 100 mL with normal saline administered by IV infusion over 60 minutes QD and 2 mL of normal saline IV injection at other times to make a 3 times a day (TID) dosing regimen; or 100 mL normal saline IV infusion over 60 minutes QD and 10 mg metoclopramide [5 mg/mL] IV injection TID). Subject randomization will be stratified based on their baseline NUTRIC score (either low [0-4] or high [5-9]) to ensure that approximately equal numbers of subjects will be enrolled in each treatment group from a high or low NUTRIC score group. The study design incorporates adaptive features in order to provide an opportunity to modify 1 or more aspects of the study based on accumulating data and mitigate the risks associated with unanticipated variability.

An interim analysis will be performed after approximately 100 subjects (ie, 25 subjects within each cohort) have completed the study. Potential modifications to the design of the study based on Bayesian methods following the interim analysis include: dropping of inefficacious dose(s), dropping of doses due to safety concerns, and inclusion of new dose(s) (less than 1 mg).

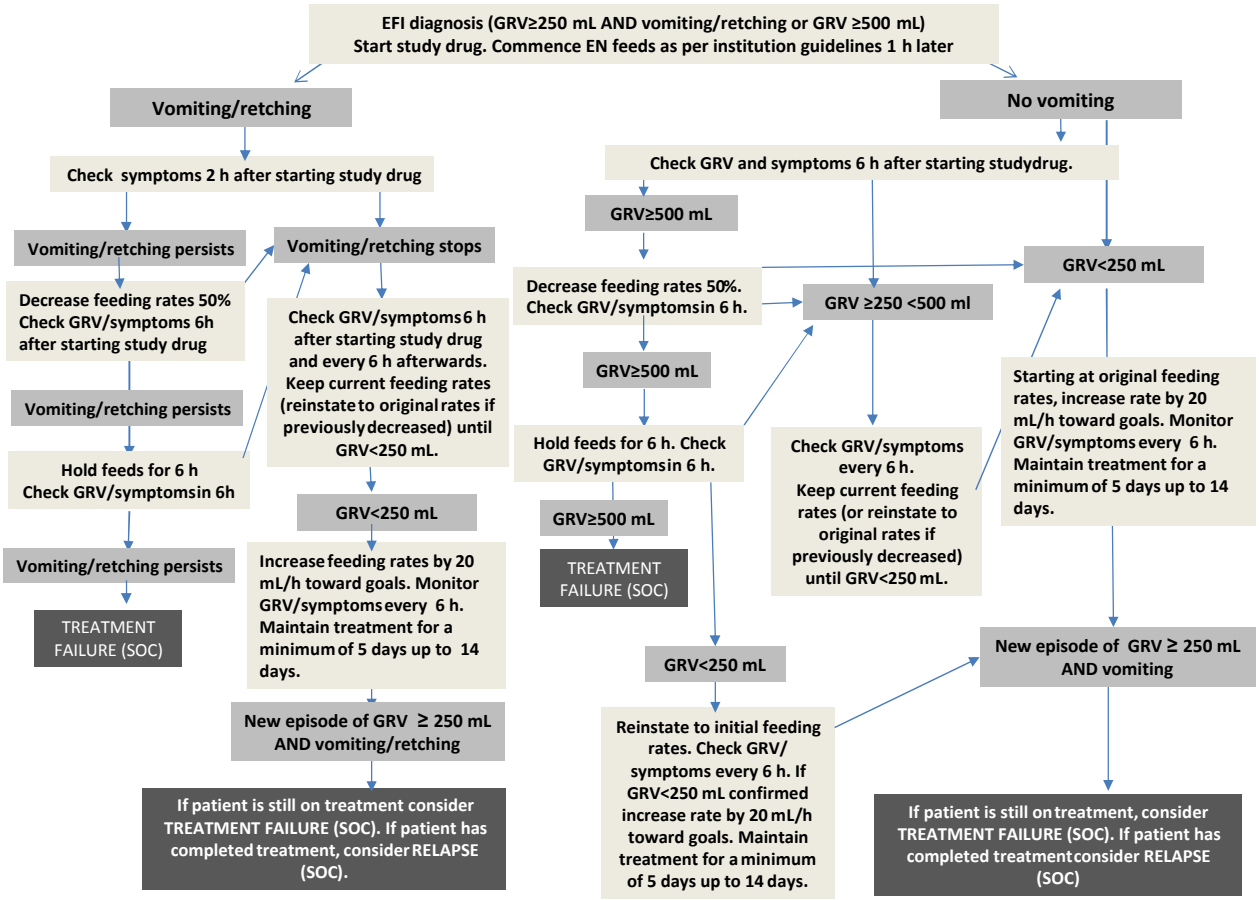
The 24:00 clock will start at the beginning of the treatment infusion on Day 1. Subjects will receive blinded TAK-954 or metoclopramide at approximately the same time each day (plus or minus 2 hours) on the dosing days. Subjects will receive randomized treatment for a minimum of 5 days and up to a maximum of 14 days. Treatment may be discontinued upon EFI resolution and subject's feeding goal rate is achieved between 5 to 14 days of drug administration. Subjects whose EFI resolves and goal feeding rate is achieved earlier will remain on study medication to complete at least 5 days of treatment. At the discretion of the treating physician and investigator, the participant may remain on study drug for up to 14 days if they remain feed tolerant and they are advanced to their goal feeding rate. All subjects will follow the same feeding protocol. Treatment failures by protocol (Figure 6.a) will be discontinued from the study and standard of care will be implemented.

Subjects will also be discontinued if continuous tube feeding is no longer being provided in the ICU (eg, the patient is discharged to the ward, liquid nutrient is ceased by treating clinicians and the participant is allowed oral intake, or new abdominal pathology that requires enterally feeding to be ceased) or the subject dies.

The nutritional requirements of an individual subject will be determined as per standard of care at the site. During the Treatment Period, nutritional parameters including nutritional prescription, daily feed volume, calories, and protein delivered will be recorded. Blood glucose will be monitored throughout the study and kept within an acceptable range according to individual site protocols. Protein homeostasis will be monitored through stepwise measurement of protein absorption (nitrogen balance) and endogenous protein production (pre-albumin). Indirect measures including C-reactive protein (CRP) and interleukin-6 (IL-6) will also be assessed.

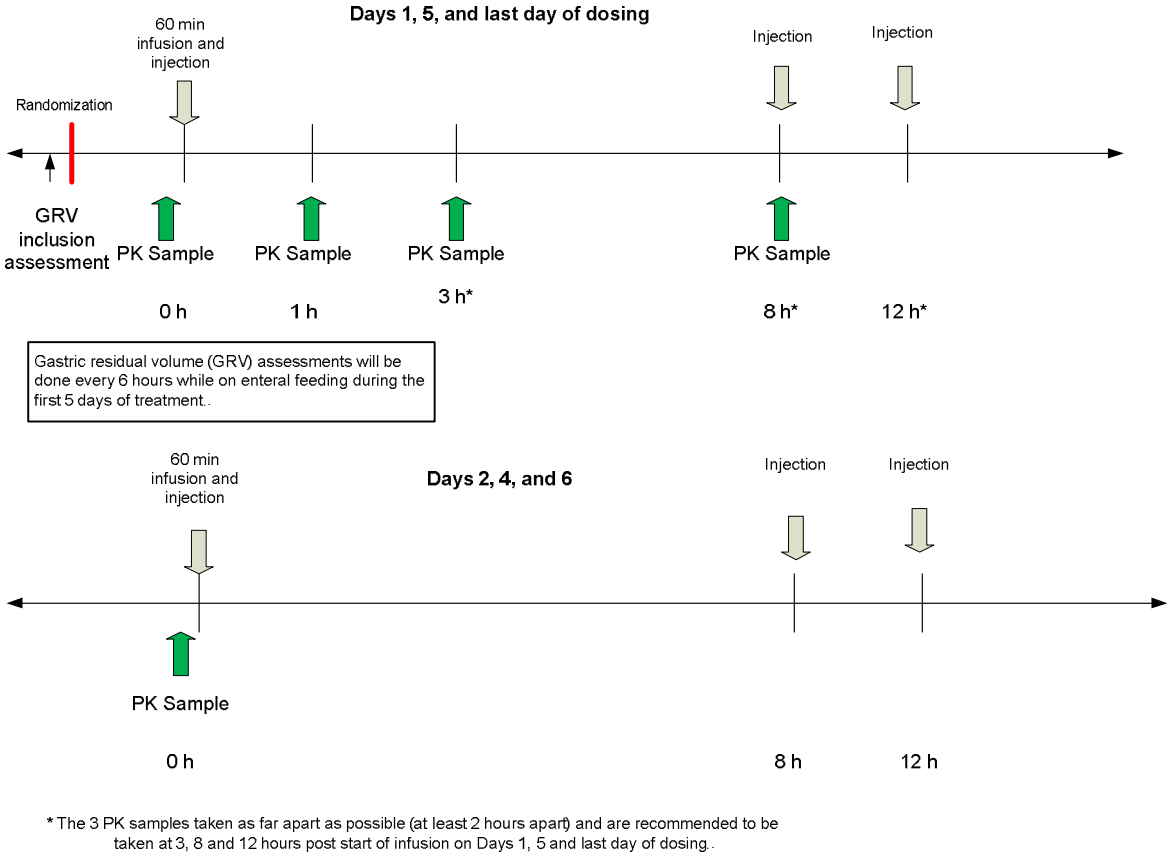
A schematic of the study design is included as Figure 6.b. A schedule of assessments is listed in Appendix A.

Figure 6.a EFI Feeding Protocol



Notes: (1) EN feeding should be continuous. (2) GRV residual should be given back to patient. (3) Treatment can be maintained beyond 5 days of treatment until a maximum of 14 days at physician's discretion.

Figure 6.b Schematic of Study Design



* The 3 PK samples taken as far apart as possible (at least 2 hours apart) and are recommended to be taken at 3, 8 and 12 hours post start of infusion on Days 1, 5 and last day of dosing.

6.2 Justification for Study Design, Dose, and Endpoints

Study Design:

The definition of EFI is inconsistent across the literature, but patients with EFI are often diagnosed at the bedside based on the presence of a "large" GRV. The definition of a "large" GRV is variable across studies, though a recent systematic review of the literature identified 250 mL as the most widely used threshold [26]. The presence of symptoms suggestive of impaired GI motility such as vomiting is often used alone or in combination with large GRVs to support the diagnosis of EFI. The inter-observer reliability of GI symptoms suggestive of EFI has not been previously assessed but can be problematic; and thus some matter experts suggest using a combination of both large GRVs and symptoms as a more appropriate approach that can improve inter-observer reliability [26].

The validity of this approach is supported by the results of an observational study including data from 1888 critically ill patients from 167 ICUs in 21 countries. In this study, critically ill patients with EFI defined by the presence of large GRVs (>200 mL) alone or in combination with

symptoms received significantly less feed volume, had fewer ventilator-free days and increased ICU stay compared with those without EFI [15]. The symptom most commonly associated with EFI was vomiting/retching. The relation between large GRVs (>300 mL) and poor clinical outcomes was also confirmed by Wang et al in a study including 455 ICU patients and 255 non-ICU patients [27].

Our study is proposing a definition of EFI based on the presence of GRV ≥250 mL and vomiting/retching within the last 24 hours, which appear to be in agreement with current daily practice [15,26,28] or GRV≥ 500 mL with or without vomiting/retching within the last 24 hours, the latter criteria having been endorsed by the recent European Society of Intensive Care Medicine clinical practice guidelines and American Society for Parenteral and Enteral Nutrition recommendations.

In critically ill patients with feeding intolerance, therapeutic options include the use of prokinetic agents, PN, or post-pyloric placement of a feeding tube. Prokinetic agents, however, are considered first-line treatment [29]. Of the available pharmaceutical options, metoclopramide is currently the most widely used prokinetic agent in treating ICU patients who develop EFI. Its GI motility effect is due to dopamine antagonist effect, enhancing peristalsis in the upper GI [30], and peripheral 5-HT_4 agonist effect [31]. As such, metoclopramide IV (10 mg TID) has been selected as the comparator in this study.

The use of placebo in this patient population, therefore, would not only pose challenges to recruitment due to misalignment with current clinical practice, but would also be considered unethical given the nature of the condition.

For this study, minimal treatment duration of 5 days has been established based on the average duration of EFI [15] with the possibility to extend the treatment duration for up to 14 days for outlier patients with persistent or relapsing intolerance.

Study Doses

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[redacted]

In studies in which metoclopramide has been used in the treatment of patients with EFI, doses have included 10 mg IV TID and 10 mg IV 4 times a day [32-36]. Due to concerns regarding neurological and other AEs associated with metoclopramide, the United States, Europe, and other countries have restricted its use with a dose and duration limitation. In this study, metoclopramide IV 10 mg TID will be used for up to 14 days.

Study Endpoints

Most feeding protocols in the ICU recommend stopping, withholding, or reducing enteral feeding in the presence of large GRVs [37]. Accordingly, patients with EFI are less likely to achieve nutritional targets and thus are at increased risk of malnutrition complications and worse outcomes. Therefore, the main goals of our study are to assess the ability of TAK-954, a selective 5-HT_4 agonist with prokinetic activity, to improve nutritional goals by decreasing GRVs and thus preventing feeding protocol interruptions or decreasing rate of delivery. Improvement of GI motility should also help to prevent malnutrition complications by facilitating the delivery of nutrients from the stomach to the intestine. In fact, a growing body of evidence suggests that increased delivery of nutrients, especially proteins, is associated with better clinical outcomes [38-40]. The primary efficacy endpoint of this study will, therefore, be the average daily protein adequacy received through enteral nutrition (defined by % of goal protein delivered per day [% protein goal delivered = actual protein achievement/total patient-specific target protein]) over the first 5 days of study treatment.

Biomarkers

CCI

[redacted]

CCI

[redacted]

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for TAK-954, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of GCP that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Sites

In the event that the sponsor, an institutional review board (IRB)/independent ethics committee (IEC) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed before randomization or first dose or other.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria before entry into the study:

1. In the opinion of the investigator, the subject, or the subject's legally acceptable representative (LAR), is capable of understanding and complying with protocol requirements.
2. The subject or, when applicable, the subject's LAR, signs and dates a written, informed consent form and any required privacy authorization before the initiation of any study procedures.
3. The subject is male or female (and not pregnant) and is at least 18 years old.
4. The subject has at least a size 12-Fr nasogastric or orogastric tube with its tip at least 10 cm below the esophagogastric junction confirmed radiologically (the tip of the tube must be in the body or the antrum of the stomach and not in the fundus).
5. The subject is intubated and mechanically ventilated in the ICU.
6. The subject is expected to remain alive, mechanically ventilated, and receive continuous enteral feeding for ≥48 hours following randomization.
7. Have EFI, defined as a single GRV measurement of ≥250 mL with vomiting/retching within the last 24 hours, or a single GRV measurement of ≥500 mL with or without vomiting/retching within the last 24 hours.
8. A female subject of childbearing potential* willing and agreeable to use highly effective contraception or sexual abstinence during the course of the study and up to 30 days posttreatment.

*Definitions of highly effective methods of contraception are defined in Section 9.1.10 and reporting responsibilities are defined in Section 9.1.11.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Has received any investigational compound within 30 days before Screening.
2. Has received TAK-954 in a previous clinical study or as a therapeutic agent.
3. Has an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. Is under consideration for withdrawal of life-sustaining treatments within the next 72 hours.

5. Has had major esophageal or gastric surgery or direct luminal trauma on this admission (subjects with lower abdominal surgery are not excluded unless enteral feeding is contraindicated).
6. Has mechanical bowel obstruction, short bowel syndrome, or the presence of an active gastric pacemaker.
7. Have pre-existing hepatic disease that meets Child-Pugh Class B (moderate; total score 7 to 9 points) or C (severe; total score 10 to 15 points); see Appendix A.
8. Has alanine aminotransferase (ALT) >8×upper limit of normal (ULN).
9. Has an estimated glomerular filtration rate (GFR) <30 mL/min.
10. Is required to take excluded medications listed in Section 7.3.
11. Has been admitted primarily for treatment of a drug overdose.
12. Has a presence of a post-pyloric tube in place at Randomization that may be used for EN.
13. Is receiving PN at Screening.
14. Is in diabetic ketoacidosis or non-ketotic hyperosmolar coma.
15. Has 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 ventricular tachycardia (VT) at a rate >120 beats per minute (bpm); ECG changes consistent with acute myocardial ischemia or infarction.

    Note: Controlled atrial fibrillation (AF) or supraventricular tachycardia (SVT) is allowed with heart rate under 100 bpm at Baseline.
16. Has QTcF interval ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events at Screening. Subjects with bundle branch block and a prolonged QTcF should be reviewed by a cardiologist for potential inclusion.
17. Has a different nutrient requirement than allowed in feeding protocol (outside a range of 1.2 to 2 g/kg/day of proteins and up to 1.5 kcal/mL)
18. Have received erythromycin or metoclopramide in the previous 24 hours before Screening; domperidone or azithromycin in the previous 72 hours, or need ongoing macrolide antibiotics. Patients on chronic treatment with metoclopramide or that have received continuous treatment (≥7 days) with metoclopramide during this hospital stay should be excluded.
19. Is in the opinion of the treating physician not eligible for treatment with metoclopramide.
20. Has received agents known to directly influence the 5-HT_4/acetylcholine prokinetic mechanism (eg, serotonin-specific reuptake inhibitors, anticholinergic agents, or acetylcholinesterase inhibitors) within the 72 hours before Randomization.
21. Has a history of hypersensitivity or allergies to TAK-954 or metoclopramide.

22. Is female and lactating or pregnant or intending to become pregnant within 30 days after last dose of the study drug; or intending to donate ova during such time period.

7.3 Excluded Medications

Use of excluded agents (prescription or nonprescription) is outlined in Table 7.a.

Table 7.a Excluded Medications

Medication	
Prokinetics: cisapride, metoclopramide, erythromycin, domperidone, azithromycin.	Gamma-aminobutyric acid (GABA) receptor antagonists: bicuculline, securinine, metrazol, flumazenil.
Selective serotonin reuptake inhibitors: escitalopram, citalopram, fluoxetine, sertraline, paroxetine, fluvoxamine.	5-HT_4 agonists: cisapride, mosapride, prucalopride, renzapride, tegaserod, metoclopramide.
N-methyl-D-aspartate receptor antagonists: phencyclidine, ketamine, tiletamine, methoxetamine, dextromethorphan, pethidine, levorphanol, methadone, dextropropoxyphene, tramadol, ketobemidone.	Monoamine oxidase inhibitors: isocarboxazid, tranylcypromine, selegiline, phenelzine.
Serotonin and norepinephrine reuptake inhibitors: venlafaxine, duloxetine, desvenlafaxine, milnacipran, levomilnacipran.	

Note: Opioids, propofol, proton pump inhibitors, and laxatives can be prescribed but their use (time, dose, duration of administration) should be clearly documented.

7.4 Diet, Fluid, Activity Control and Treatment Facilities

Subjects must be mechanically ventilated, critically ill ICU patients receiving EN and developing EFI by study definition. In the investigators judgement, subjects are expected to remain alive and require ICU treatment for ≥48 hours. All study subjects will follow the same feeding protocol following development of EFI and randomization. Choice of feeding formula will be at the discretion of the treating physician but must be within a defined nutritional breakdown (1.2 to 2 g/kg/day of proteins and up to 1.5 kcal/mL).

7.5 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.20.

1. Treatment failures:

   - Subjects assessed by the treating physician as requiring different management to what is currently specified in the feeding protocol (eg, requiring rescue medication or post-pyloric tube placement) will be considered as treatment failures and be withdrawn from study treatment.

- Treatment failures by protocol (Figure 6.a) will be discontinued from the study and standard of care will be implemented.

2. Subjects will also be discontinued if continuous tube feeding is no longer being provided in the ICU (eg, the patient is discharged to the ward, liquid nutrient is ceased by treating clinicians and the participant is allowed oral intake, or new abdominal pathology that requires enterally feeding to be ceased) or the subject dies.
3. Treatment discontinuation due to an AE: The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE. Specific events that require treatment discontinuation (see Section 10.1.6) include:
   - Prolonged QT: Second episode of G2 (QTcF >480 and ≤500 msec), Grade 3 (QTcF >500 msec) or Grade 4 (QTcF >500 msec or >60 msec change from Baseline with Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia).
   - Second or third degree heart block. Treatments with study drug may be continued in second degree heart block Mobitz I (Wenckebach) after medical monitor review.
   - Second occurrence of G4 (life threatening) SVT that is considered related by the investigator.
   - Suspected serotonin syndrome.
   - G2–G4 extrapyramidal disorder.
4. Liver function tests:
   - Subjects with ALT<3×ULN at Baseline who develop ALT >3×ULN with total bilirubin >2×ULN while on treatment with study drug.
   - Subjects with ALT 3 to 8×ULN at Baseline who develop a 2-fold increase in ALT over the Screening value.
5. Study drug interruption for 2 consecutive days.
6. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
7. Voluntary withdrawal. The subject (or subject's LAR) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category.
8. Study termination. The sponsor, IRB, IEC or regulatory agency terminates the study.
9. Pregnancy. The subject is found to be pregnant.

Note: If the subject is confirmed to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.

10. If any site personnel are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study.
11. Other.

    Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.6 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.5. In addition, a subject (or subject's LAR) may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to all or any of the drugs defined below.

8.1.1.1 TAK-954

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8.1.1.2 Metoclopramide

Metoclopramide Injection United States Pharmacopeia is a sterile solution. It is formulated in 5 mg/mL and provided in 2 mL fill vials or ampules. Metoclopramide will be labeled in accordance with regulatory requirements.

8.1.1.3 Ancillary Materials

All ancillary supplies will be provided by either the site or the sponsor, based upon availability. If provided by the sponsor, unused ancillary supplies will be accounted for and disposed of as directed by the sponsor or a designee.

8.1.2 Storage

Study drug and active comparator must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug and active comparator must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day. The required storage condition for TAK-954 study drug is refrigeration between 2°C and 8°C. Metoclopramide should be stored according to the labeled storage conditions.

8.1.3 Dose and Regimen

Subjects will be enrolled in this study and randomized in a 1:1:1:1 ratio to 1 of 4 parallel treatment groups (0.1, 0.3, or 1.0 mg of TAK-954 or 10 mg metoclopramide) within a design model that incorporates adaptive features in order to provide an opportunity to modify 1 or more aspects of

the study based on accumulating data, and mitigate the risks associated with unanticipated variability.

Additional information regarding the dosing instructions for TAK-954 can be found in the Pharmacy Manual.

Table 8.a describes the dose that will be provided to each group.

Table 8.a Dose and Regimen

Treatment Group	Dose	Treatment Description	
		IV Infusion	IV Injection
A	0.1 mg TAK-954 QD	TAK-954 0.1 mg (1 mL) diluted to 100 mL with normal saline administered over 60 min QD.	2 mL of normal saline TID.
B	0.3 mg TAK-954 QD	TAK-954 0.3 mg (3 mL) diluted to 100 mL with normal saline administered over 60 min QD.	2 mL of normal saline TID.
C	1.0 mg TAK-954 QD	TAK-954 1.0 mg (10 mL) diluted to 100 mL with normal saline administered over 60 min QD.	2 mL of normal saline TID.
D	Metoclopramide 10 mg TID	Normal saline 100 mL administered over 60 min QD.	Metoclopramide 10 mg (2 mL) TID

8.1.4 Overdose

An overdose is defined as an accidental administration of study drug, to a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented in an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.0.

SAEs associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

TAK-954 has been investigated in clinical studies up to 20 mg orally. AEs observed at 5 mg orally (exposure approximately 3-fold higher than that predicted for a 1 mg IV dose) or higher included mild orthostatic hypotension in 1 subject after they received a single oral 5 mg dose and mild AV dissociation in 2 subjects after they received a single oral 10 mg dose. In the event of an IV overdose, discontinue the treatment of study drug, treat the subject symptomatically and provide supportive care as needed. Dialysis is not anticipated to be of benefit.

8.2 Study Drug Assignment and Dispensing Procedures

The investigator or the investigator's designee will access the Interactive Response Technology (IRT) at Screening to obtain the subject study number. The investigator or the investigator's designee will also utilize the IRT to randomize the subject into the study. During this contact, the investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at Screening. Subjects will be assigned in a 1:1:1:1 ratio to receive the

treatments of 0.1, 0.3, 1.0 mg of TAK-954, or 10 mg metoclopramide according to the randomization schedule.

Subject randomization will be stratified based on their baseline NUTRIC score (either low [0-4] or high [5-9]) to ensure that approximately equal numbers of subjects will be enrolled in each treatment group from a high or low NUTRIC score group.

Specific procedures related to treatment assignment/dispensation, requests for resupply of study drug, or reporting of lost or damaged shipments of study drug are outlined in the Study Manual.

8.3 Randomization Code Creation and Storage

Randomization personnel of the sponsor/ the designee of the sponsor will generate the randomization schedule and will provide it to the IRT vendor before the start of this study. All randomization information will be stored in a secured area, accessible only by authorized personnel.

8.4 Study Drug Blind Maintenance

The study drug blind will be maintained using the IRT.

Since the maintenance of the blind may be compromised because of results from drug concentrations and/or PD assessments, such results should not be disclosed before formal unblinding of study. In the event that results must be reported to the investigator before breaking the blind, all efforts should be made to maintain the blind (eg, as changing a medication identification [ID] number in order to avoid identification of subjects by the laboratory site personnel).

8.5 Unblinding Procedure

For unblinding a subject, the study drug blind can be obtained by the investigator, by accessing the IRT.

The sponsor must be notified as soon as possible if the study drug blind is broken. The date, time, and reason the blind is broken must be recorded in the source documents and the same information (except the time) must be recorded on the eCRF.

If any site personnel are unblinded, study drug must be stopped immediately and the subject must be withdrawn from the study.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee or destroyed locally.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all

sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment as instructed per the documentation accompanying the shipment. If there are any discrepancies between the packing list versus the actual product received, the sponsor or its designee must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot/medication ID used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry date and amount dispensed including initials, and signature of the person dispensing the drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

Before site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction or destroyed locally. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction or destroyed locally.

In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, the sponsor or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 14.5.

Informed consent or assent must be obtained before the subject entering into the study, and before any protocol-directed procedures are performed.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained, and used throughout the subject's participation in the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained may include date of birth, sex, and ethnicity (as described by the subject or subject representative), height, weight, and smoking status of the subject at Screening if available.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. Ongoing conditions are considered concurrent medical conditions (see Section 9.1.8). Medication history information to be obtained includes any medication relevant to eligibility criteria stopped at or within 72 hours before signing of informed consent.

A number of additional characteristics will be recorded at Baseline including patient/ICU type (eg, medical, surgical, burn, trauma), disease severity (Acute Physiology and Chronic Health Evaluation [APACHE] and Sequential Organ Failure Assessment [SOFA]), nutritional risk (NUTRIC score: variables include age, APACHE II, SOFA, number of comorbidies, and days from hospitalization to ICU admission), protein metabolism (nitrogen balance) and muscle mass measurement variables, comorbidity and comedication use (including opioids, anesthetics and noradrenergic agents), and medications of interest (opioids, propofol, proton pump inhibitors, laxatives) to evaluate the prognostic value of these baseline characteristics on treatment outcomes.

9.1.3 Physical Examination Procedure

A baseline physical examination (defined as the assessment before first dose of study drug) will consist of the following body systems: (1) cardiovascular system; (2) respiratory system; (3) GI system; (4) nervous system looking mainly for hypertonicity, reflexes, and clonus; and (5) other. All subsequent physical examinations should assess clinically significant changes from the assessment before first dose examination. This should be recorded in the medical history page or as a pretreatment SAEs deemed related to study procedures, if applicable.

Neurological examinations looking for hypertonicity, reflexes, and clonus will also be performed at Baseline, on Days 2, 5, 8, and 12, and at 3 days following the last dose.

9.1.4 Weight, Height and BMI

A subject should have weight and height collected as per the standard of care. Body mass index (BMI) will be derived from the subject's height and weight.

9.1.5 Vital Sign Procedure

Vital signs will include semi-supine blood pressure (systolic and diastolic) and pulse (beats per minute). Clinically significant abnormal blood pressure and respiratory rate will be captured as an AE as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

9.1.6 Documentation of Nutritional Content of Feed

All subjects will have recorded the calorie, protein, and fat content of the feed being received per mL. Feed should be commercially available and have a calorie content between 1.0 and 1.5 kcal/mL. Protein content of feed used at a particular site should be consistent within 1.2-2 g/kg/day and therefore supplemental protein for individual patients is not allowed. It is recommended that the same feed is used for all subjects at each site.

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician. Concomitant medication is not provided by the sponsor. On each study day, subjects, their representatives or their treating physician will provide information on use of any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication must be recorded in the eCRF.

9.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the Screening examination, according to the judgment of the investigator. The condition (ie, diagnosis) should be described and the reason for admittance to ICU should be recorded.

9.1.9 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Details of these procedures and required safety monitoring will be given in the laboratory manual.

Table 9.a lists the tests that will be obtained for each laboratory specimen.

Table 9.a Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis (24 hour collection)
RBC	ALT	Urea (for nitrogen balance)
WBC	Albumin	
Hemoglobin	Alkaline phosphatase	
Hematocrit	aspartate aminotransferase (AST)	
Platelets	Total bilirubin	
Prothrombin time	Total protein	
INR	Creatinine	
	Blood urea nitrogen	
	Creatine kinase	
	γ-glutamyl transferase (GGT)	
	Potassium	
	Sodium	
	Glucose	
Other:		
Serum/Plasma		
Hepatitis panel, including HBsAg and anti-HCV		
Female subjects only:		
Beta human chorionic gonadotropin ([hCG] for pregnancy)		

GGT=γ-glutamyl transferase, HbsAg=hepatitis B virus surface antigen, hCG=human chorionic gonadotropin, HCV=hepatitis C virus, INR=international normalized ratio, RBC=red blood cell, TSH=thyroid stimulating hormone, WBC=white blood cell.

Any clinically significant laboratory result will be captured as an AE as per the Common Terminology Criteria for Adverse Events (CTCAE).

Treatment with study drug should be discontinued in subjects who develop liver function test (LFT) elevation as described in Section 10.1.6.5.

A baseline 24-hour urine sample will be taken to assess nitrogen balance as soon as the subject is enrolled and at Day 5 or end of treatment.

9.1.10 Contraception and Pregnancy Avoidance Procedure

Animal studies for TAK-954 have demonstrated embryotoxicity and there is a lack of adequate reproductive toxicity data in humans.

Given that TAK-954 did not exhibit genotoxic potential in the standard battery of genotoxicity assays and the $t_{1/2z}$ of TAK-954, the duration of contraception for 30 days is considered acceptable. This is in line with the Clinical Trials Facilitation Group "Recommendations related to contraception and pregnancy testing in clinical trials".

Females of reproductive potential, as well as fertile men and their partners who are female of reproductive potential, must agree to abstain from sexual intercourse or to use 2 highly effective forms of contraception from the time of giving informed consent, during the study, and for 30 days

(females and males) following the last dose of study drug. An effective form of contraception is defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, double-barrier method (eg, synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel) or male partner sterilization.

The following definitions apply for contraception and pregnancy avoidance procedures:

A woman is considered a woman of childbearing potential (fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Sterilized males should be at least 1 year postbilateral vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate or have had bilateral orchidectomy.

9.1.11 Pregnancy

If any subject is confirmed to be pregnant during the study, she should be withdrawn and TAK-954 should be immediately discontinued. In addition, any pregnancies in the partner of a male subject during the study or for 30 days after the last dose should also be recorded following authorization from the subject's partner. A pregnancy notification form should be submitted within 24 hours of learning of the pregnancy to the contact listed in Section 1.0.

If the female subject and/or female partner of a male subject agree to the primary care physician being informed, the investigator should notify the primary care physician that the female subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received.

All pregnancies, including female partners of male subjects, in subjects on active study drug will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the sponsor. An evaluation after the birth of the child will also be conducted.

9.1.12 ECG

A standard single 12-lead ECG will be performed as follows:

- Before the 60-minute IV infusion on Day 1 (Baseline).
- Days 1 and 2:
  - Approximately 1, 2, and 8 hours after the start of the 60-minute infusion.
- At the end of the infusion (approximately 1 hour after the start of the 60 minute IV infusion) on every other day of treatment.
- At the end of the infusion (approximately 1 hour after the start of the 60 minute IV infusion) on the last day of study drug.

In addition, a 12-lead ECG will be performed when needed, if a subject develops symptoms suggestive of cardiovascular origin (eg, dizziness, chest pain).

The investigator (or a qualified observer at the study site) will interpret the ECG using 1 of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant. Clinically significant findings from ECGs or cardiac telemetry will be captured as AEs as per CTCAE v4.03. The time that a 12 lead ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, and QT interval. The sponsor will derive QTcF.

Holter monitoring for approximately 10 subjects per study arm is ONLY required for the first 24 to 48 hours following the start of study infusion. This assessment would be performed only in a subset of sites.

9.1.13 Pharmacogenomic Sample Collection

9.1.13.1 Optional Pharmacogenomic(PGx) Sample Collection

Consent must be obtained from the subject or LAR prior to collection of the whole blood.

DNA forms the basis for the genes that make the body produce proteins such as enzymes, drug transporters or drug targets, and may be evaluated for the genetic contribution how the drug is broken down, or how the drug affects the body. This is called a "Pharmacogenomics research study." Specific purposes of this study include:

- Identifying genetic reasons why certain people respond differently to TAK-954.
- Finding out more information about how TAK-954 works.
- Generating information needed for research, development, and regulatory approval of tests to predict response to TAK-954.
- Identifying variations in genes related to the biological target of TAK-954.
- Identifying the presence of allelic variants in drug metabolizing enzymes, drug transporters, or putative drug targets.

This information may be used, for example, to develop a better understanding of the safety and efficacy of TAK-954 and other study drugs, to increase understanding of the disease/condition being studied, and for improving the efficiency, design and study methods of future research studies.

Detailed instructions for collection, storing, handling, and shipping samples will be provided in the laboratory manual.

9.1.14 Glucose Monitoring

Blood glucose will be monitored throughout the study and kept within an acceptable range as per local guidelines.

9.1.15 Biomarker Sample Collection

CCI

[redacted]

9.1.16 PK Sample Collection and Analysis

9.1.16.1 Collection of Plasma for PK Sampling

Subjects will have PK samples collected prior to and at the end of the infusion, and an additional 3 samples after the end of the infusion on Days 1, 5, and the last day of dosing. The 3 PK samples should be taken as far apart as possible (at least 2 hours apart) and are recommended to be taken at 3, 8 and 12 hours postinfusion on Days 1, 5, and the last day of dosing. A trough (predose) sample will be obtained on Days 2, 4, and 6. Times indicated are relative to the start of the infusion. It is important that date and time of each sample collection be accurately recorded. The date and time of start and end of infusion should also be accurately recorded. If indicated, these collected samples may also be assayed in an exploratory manner for metabolites and/or additional PD markers if deemed necessary for interpretation of the data.

9.1.17 Primary Specimen Collection and Blood Volume

Primary specimen collection and approximate blood volumes are provided in Table 9.b.

Table 9.b Primary Specimen Collection

Specimen Name	Primary Specimen	Description of Intended Use	Sample Collection
Plasma sample for TAK-954 PK	Plasma	PK measurements	Mandatory
CCI [redacted]			

Table 9.c Approximate Blood Volume

Sample Type	Sample Volume (mL)	Estimated Blood Collection		Total Volume (mL)
		Number of Samples	Treatment Days	
Clinical laboratory tests	22	11	Screening; Baseline (predose Day 1) if more than 24 hours from the Screening labs; Days 2 3,5, and every other day up to Day 13; last day of study drug; and 3 days after the last dose.	**242**
CCI [redacted]				
CCI [redacted]				
CCI [redacted]				
CCI [redacted]				
Total Approximate Blood Sampling Volume				**368**

The maximum volume of blood at any single day is approximately 60 mL, and the approximate maximum total volume of blood for the study is 370 mL. Clinical laboratory samples will be collected as per standard of care and will not be duplicated.

9.1.18 Muscle Mass Measurement

Muscle mass measurements will be taken by recording mid-upper arm circumference at Baseline and the end of treatment.

9.1.19 Nitrogen Balance Procedure

A 24-hour urine sample will be taken to assess nitrogen balance as soon as the subject is enrolled and at Day 5 or end of treatment. The calculation [48] is as follows:

Nitrogen Balance (g/d) = Nitrogen Intake (g/d)−Urinary Urea Nitrogen (g/d)/0.85 – 2 (g/d).

9.1.20 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is withdrawn at the Screening visit, the investigator should complete the eCRF. The IRT should be contacted as a notification of screen failure.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- AEs/SAEs caused by a protocol-mandated intervention.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).

- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other study-specific reason.
- Other (specify reason).

Subject identification numbers assigned to subjects who fail Screening should not be reused.

9.1.21 Documentation of Randomization

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the subject is found to be not eligible for randomization, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Schedule of Observations and Procedures

The schedule for all study-related procedures and for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time points.

9.2.1 Post Study Care

Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment SAEs

After informed consent, but before initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (eg, SAEs related to invasive procedures).

10.1.2 AEs

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.
- Untoward finding caused by a study procedure (eg, a bruise after blood draw) should be recorded as an AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

- If abnormal laboratory values are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. If the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as an AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as an AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences changes in the severity of an AE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled before signing of informed consent are not considered AEs/SAEs. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs/SAEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any study medication without manifested side effects are NOT considered AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
    - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT assessed by the investigator or the sponsor that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.
    - Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10.a).

Table 10.a Takeda Medically Significant AE List

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes / ventricular fibrillation / VT	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
Spontaneous abortion / stillbirth and fetal death	Neuroleptic malignant syndrome / malignant hyperthermia

Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

10.1.5 Severity of AEs

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to CTCAE version 4.03 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). AEs not listed by the NCI CTCAE will be graded displayed in Table 10.b.

Table 10.b NCI CTCAE

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) (a).
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatening consequences; urgent intervention indicated.
5	Fatal AE; an event that results in the death of the subject.

(a) Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

10.1.6 Management of Specific AEs

10.1.6.1 Cardiovascular Disorders

Cardiovascular Events:

Tegaserod, a nonselective 5-HT_4 agonist, was withdrawn from the market in 2007 based on pooled clinical trial results that suggested increased risk of cardiovascular ischemic events.

Suspected cardiovascular events that include ischemic heart disease, cerebrovascular accident (eg, transient ischemic attack and stroke), venous or arterial thromboembolic events, and heart failure, should be reported as an adverse events of special interest (AESI) to the sponsor within 24 hours irrespective of the seriousness. These events will be adjudicated by a cardiovascular endpoint committee (CEC) and reviewed by the independent data monitoring committee (IDMC). The details will be described in the of the CEC and IDMC charter.

QT Prolongation

Cisapride, a nonselective 5-HT_4 agonist and a potent human ether-à-go-go–related gene blocker, was withdrawn from the market due to the risk of prolonged QT interval and sudden death.

In TAK-954 clinical studies, only 1 subject in Study 0082 had QTcF over 450 msec. This subject received TAK-954 0.5 mg IV was in the ICU following an emergency evacuation of a spontaneous posterior fossa intraparenchymal hemorrhage. She had medical history of AF on warfarin, mitral valve replacement, and biventricular pacemaker, and on Screening, her QTcF was 461 msec. She had a maximum QTcF of 496 msec on Day 1 and she was not treated for this finding.

Any QT prolongation event assessed as Grade 2 or worse (QTcF interval longer than 480 msec), irrespective of the seriousness, should be reported as an AESI to the sponsor within 24 hours and managed according to the following guidelines (Table 10.c). Heart-rate corrected QT interval will be calculated using Fridericia's formula ($QTcF=QT/RR^{1/3}$).

Table 10.c Management of QT Prolongation by NCI CTCAE Grade

NCI CTCAE Grade	Management
Grade 2 (QTcF >480 and ≤500 msec)	• Levels of electrolytes (potassium, calcium, and magnesium) should be checked and supplementation given to correct any values outside the normal range. • Concomitant therapies should be reviewed and adjusted as appropriate for medications with known QT prolonging effects. • If no other cause is identified and the investigator believes it is appropriate, particularly if QTcF remains elevated (after the above measures have been implemented, or as determined by the investigator), study treatment may be interrupted for 1 to 2 days, and an ECG should be rechecked regularly. • If QTcF has recovered or improved <450 msec and the investigator believes it is safe to do so, rechallenge with study treatment should be considered after discussion with the medical monitor. • ECGs should be conducted at least weekly (eg, at every scheduled visit) for 2 weeks following QTcF reduction ≤480 msec. • Discontinue treatment with study drug if patient the subject develops a second episode of Grade 2 QT prolongation.
Grade 3 (QTcF >500 msec) or Grade 4 (QTcF > 500 msec or >60 msec change from Baseline with Torsades de pointes or polymorphic VT or signs/symptoms of serious arrhythmia)	• Subjects should have continuous cardiac monitoring and be discharged only after review by a cardiologist. • Treatment with study treatment should be permanently discontinued.

AV Dissociation/Heart Block

CCI [redacted]

Treatment with study drug should be discontinued with the occurrence of any second or third degree heart block and these events should be reported to the sponsor as AESI within 24 hours.

Treatments with study drug may be continued in second degree heart block Mobitz I (Wenckebach) after Medical monitor review.

SVT

CCI [redacted]

Any SVT assessed as Grade 2 or worse with heart rate over 130 bpm irrespective of the seriousness should be reported as an AESI to the sponsor within 24 hours and managed according to the following guidelines.

Table 10.d Management of SVT by NCI CTCAE Grade

NCI CTCAE Grade	Management
Grade 2: Symptomatic; non-urgent medical intervention indicated Or G3: Urgent medical intervention indicated	• Rule out other etiology such as pain, hypovolemia or pyrexia. • If no other cause is found and SVT is persistent **with heart rate >130** bpm: study drug should be interrupted for 1 to 2 days • Treatment can be restarted if the patient is hemodynamically stable with careful monitoring.
G4: Life-threatening consequences; urgent intervention indicated	Study drug should be discontinued and the patient managed as per local guidelines.

Hypotension

CCI

If subjects develop a significant hypotension, which is defined as mean arterial pressure <60 mmHg, and no other etiology is identified, treatment with study drug should be interrupted for 1 to 2 days to manage the hypotension event. If subjects develop a second occurrence of significant hypotension and the events is considered related to study drug (ie, no other cause is identified), dosing with study treatment should be permanently discontinued.

10.1.6.2 Neurological Disorders

Serotonin Syndrome

Serotonin syndrome, a potentially life threatening adverse drug reaction, may result from drugs that increase the serotonergic activity in the central nervous system. The most commonly implicated classes of drugs are selective serotonin reuptake inhibitors. The clinical features may include agitation, confusion, diarrhea, hyperthermia, tachycardia, hypertension, mydriasis, hypertonicity, and hyperreflexia.

If a subject develops any of the following clinical features (Hunter's criteria):

- Spontaneous clonus.
- Inducible clonus PLUS agitation or diaphoresis.
- Ocular clonus PLUS agitation or diaphoresis.
- Tremor PLUS hyperreflexia.

- Hypertonia PLUS temperature above 38ºC PLUS ocular clonus or inducible clonus.

Discontinue treatment with study drug. In addition, review the subject medications and discontinue any medication(s) that may be associated with serotonin syndrome. Suspected serotonin syndrome should be reported to the sponsor as an SAE with 24 hours.

10.1.6.3 Extrapyramidal Disorder

Acute dystonic reactions occur in approximately 1 in 500 patients treated with the dosages of 30 to 40 mg/day of metoclopramide. These symptoms may include involuntary movements of limbs and facial grimacing, torticollis, oculogyric crisis, rhythmic protrusion of tongue, bulbar type of speech, trismus, or dystonic reactions resembling tetanus. Rarely, dystonic reactions may present as stridor and dyspnea, possibly due to laryngospasm (https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021793s008lbl.pdf).

If a subject develops extrapyramidal signs, manage as per table below. Any extrapyramidal clinical findings equal to or more than G2 should be reported to the sponsor as an AESI within 24 hours.

Table 10.e Management of Other Extrapyramidal Disorder by NCI CTCAE Grade

NCI CTCAE Grade	Management
G1: Mild involuntary movements	• Discuss with medical monitor and confirm if the patient developed extrapyramidal disorders. • If extrapyramidal disorder is confirmed, discontinue treatment with study drug.
G2: Moderate involuntary movements; limiting instrumental ADL G3: Severe involuntary movements or torticollis; limiting self-care ADL G4 Life-threatening consequences; urgent intervention indicated	• Discontinue treatment with study drug. • Inject 25 to 50 mg diphenhydramine hydrochloride IV or benztropine mesylate, 1 to 2 mg intramuscularly, may also be used. • Continuous monitoring of the cardiovascular and respiratory functions should be carried out according to clinical status.

10.1.6.4 Diarrhea

AEs of diarrhea (new onset or change from Baseline) should be investigated for underlying etiology and reported as per CTCAE grading system as follows:

- G1: Increase of <4 stools per day over Baseline; mild increase in ostomy output compared to Baseline.
- G2: Increase of 4 to 6 stools per day over Baseline; moderate increase in ostomy output compared to Baseline.
- G3: Increase of ≥7 stools per day over Baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to Baseline; limiting self-care of activities of daily living.
- G4: Life-threatening consequences; urgent intervention indicated.

- G5: Death.

Diarrhea Grade 3 and above should be reported as AESI to the sponsor within 24 hours.

10.1.6.5 Abnormal LFTs

Treatment with study drug should be discontinued in subjects who develop LFT elevations in the following situations: (1) Subjects with ALT <3×ULN at Baseline who develop ALT >3×ULN with total bilirubin >2×ULN while on treatment with study drug. 2) Subjects with ALT 3 to 8×ULN at Baseline who develop a 2-fold increase in ALT over the baseline value while on treatment with study drug. Either of these findings should be recorded as a serious AESI and reported as per Section 10.2.2. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis A or B or other acute liver disease or medical history/concurrent medical conditions. In addition, the investigator should contact the medical monitor for any increase in LFTs without clear etiology.

Follow-up laboratory tests as described in Section 9.1.9 must also be performed. In addition, an LFT Increases eCRF must be completed and transmitted with the Takeda SAE form (as per Section 10.2.2).

In addition, an LFT Increases eCRF must be completed providing additional information on relevant recent history, risk factors, clinical signs and symptoms and results of any additional diagnostic tests performed.

10.1.6.6 AESI

An AESI (serious or non-serious) is 1 of scientific and medical concern specific to the compound or program, for which ongoing monitoring and these events must be reported within 24 hours of awareness to the sponsor.

The following events will be reported as AESI:

- Cardiovascular events (ischemic heart disease, cerebrovascular accident [eg, transient ischemic attack and stroke], venous or arterial thromboembolic events, and heart failure).
- QT prolongation G2 or above.
- 2nd or 3rd degree heart block.
- SVT G2 or above with heart rate over 130 msec.
- Suspected serotonin syndrome.
- Extrapyramidal disorders G2 and above.
- Diarrhea Grade 3 or higher.
- LFTs elevation as defined in Section 10.1.6.5.

10.1.7 Causality of AEs

The relationship of each AE to study drugs will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study-specific procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

The start date of the AE/SAE is the date that the first signs/symptoms were noted by the subject and/or investigator.

10.1.10 Stop Date

The stop date of the AE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.11 Frequency

Episodic AEs (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Drug

- Dose interrupted – the dose was interrupted due to the particular AE. Subjects will discontinue treatment with study drug if the interruption is more than 2 days.
- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.

10.1.13 Outcome

- Recovered/resolved – Subject returned to first assessment status with respect to the AE.
- Recovering/resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to Baseline; the subject died from a cause other than the particular AE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis.
- Fatal – the AEs which are considered as the cause of death.
- Unknown – the course of the AE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

Collection of SAEs caused by a protocol-mandated intervention will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug (Day 1) or until screen failure.

Collection of AEs will commence from the time that the subject is first administered study drug (Day 1). Routine collection of AEs will continue until the Follow-up Visit.

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a SAE caused by a protocol-mandated intervention must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or there is a satisfactory explanation for the change.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to Baseline or until there is a satisfactory explanation for the changes

observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date.
3. Frequency.
4. Severity as per CTCAE.
5. Investigator's opinion of the causal relationship between the event and administration of study drugs (related or not related).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug.
8. Outcome of event.
9. Seriousness.

10.2.1.3 AESI

AESI have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

As soon as an SAE or AESI is entered into the electronic data capture system, an alert is sent to the attention of the contact listed in Section 1.1 and to the safety database.

The information should be completed as fully as possible but contain, at a minimum:

A short description of the event and the reason why the event is categorized as serious.

- Subject identification number.
- Investigator's name.
- Name of the study drug(s).
- Causality assessment.

The SAE eCRF should be transmitted within 24 hours of first onset or notification of the event. However, as a back-up, if required, the SAE form should be completed and reported to the attention of the contact listed in Section 1.1.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs or IECs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators, and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor supplied drug or that would be sufficient to consider changes in the study drug/sponsor supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB or IEC.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 IDMC

An IDMC will be utilized in TAK-954-2002 for safeguarding the interest of study participants, assessing the safety and efficacy of the interventions during the study, and for monitoring the overall conduct of the clinical study while maintaining the integrity of the study. The IDMC will conduct ongoing review of SAEs, conduct periodic scheduled reviews of safety, and conduct an interim review of efficacy and safety data as well as available data from other studies. The IDMC, based on these assessments, will provide recommendations as to the adaptive changes specified in the protocol: stopping, continuing, or adding a new dose in the study, or sample size modification. The IDMC will only advise termination of a dosing group based on safety concerns, overwhelming efficacy, or prespecified futility criteria. In order to enhance the integrity of the study, the IDMC may also formulate recommendations relating to the selection/recruitment/retention of participants, management of the study participants, improving adherence to protocol-specific regimens, and the procedures for data management and quality control.

Details of the IDMC, including meeting frequency, will be captured in a charter prior to the start of the study.

11.2 Independent CEC

An independent CEC consisting of 2 cardiovascular experts and 1 neurologist will be established to prospectively review and adjudicate all suspected cardiovascular events in a blinded fashion to determine if the reported event meets the criteria for MACE. The procedures and rules of adjudication of these events by the CEC will be described in a separate charter.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization Drug Dictionary.

12.1 eCRFs

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by the sponsor's personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, temporary media such as thermal sensitive paper, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to

enable evaluations or audits from regulatory authorities, the sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the subject's chart to ensure long term legibility. Furthermore, International Council on Harmonisation (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the study site agreement between the investigator and sponsor.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.

Refer to the study site agreement for the sponsor's requirements on record retention. The investigator and the head of the institution should contact and receive written approval from the sponsor before disposing of any such documents.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to unblinding of subject's treatment assignment. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

A blinded data review will be conducted prior to unblinding of subject's treatment assignment. This review will assess the accuracy and completeness of the study database, subject evaluability, and appropriateness of the planned statistical methods.

13.1.1 Analysis Sets

The full analysis set (FAS) will include all subjects who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid post-baseline value for assessment of primary efficacy. In FAS efficacy summaries, subjects will be analyzed by the treatment to which they were randomized.

The per-protocol set (PPS) will include all FAS subjects who had no major protocol violations. If more than 5% of the total subjects in the FAS have major protocol violations, analyses based on the PPS will be performed for the primary efficacy variable only.

The safety set will include all subjects who have received at least 1 dose of study drug. Subjects in this set will be analyzed according to the treatment they actually received. This analysis set will be used for safety analyses only.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by each treatment group and overall. Summary statistics (N, mean, SD, median, minimum, and maximum) will be generated for continuous variables (eg, age and weight) and the number and percentage of subjects within each category will be presented for categorical variables (eg, sex, ethnicity, and race). Individual subject demographic and baseline characteristics data will be listed.

13.1.3 Efficacy Analysis

Primary Endpoints:

The primary efficacy endpoint will be the average daily protein adequacy received through enteral nutrition (defined by % of goal protein delivered per day [% protein goal delivered = actual protein achievement / total patient-specific target protein]) over the first 5 days of study treatment.

As subjects remain in the ICU for the study and given the short duration of the assessment period the percentage of missing values is not expected to be large. Where subjects have less than five days then the average of the available days will be used.

The main analysis of the primary endpoint will use Bayesian methods. A non-informative prior distribution for the difference between metoclopramide and each TAK-954 dose will be assumed,

this distribution will be updated using Bayesian methods at two stages. An interim analysis will be conducted after approximately 100 subjects (ie, 25 subjects per treatment arm) have completed the study. At the interim analysis, the posterior distribution of the difference will be estimated from the prior distribution and the study data. The distribution will again be updated at study end when all available data will be used to estimate the final posterior distribution for each difference, from which 95% credible intervals will be calculated for each TAK-954 dose.

Additionally, an analysis of covariance (ANCOVA) model will be used, with baseline as a covariate and treatment and site as a factor. Unadjusted 95% confidence intervals will be estimated; additionally, simultaneous 95% confidence intervals of each dose of TAK-954 against metoclopramide will also be computed using Dunnett's method.

The FAS will be the primary population for the analysis of the primary endpoint, with the per-protocol population considered as a sensitivity analysis.

Secondary Endpoints:

The secondary endpoints, average daily protein adequacy over the study treatment period, average daily change in 24 hours GRV over the first 5 days of treatment, and average daily caloric adequacy will also be analyzed using ANCOVA.

Time to resolution of EFI will be analyzed using survival analysis methods. Log-rank tests of each TAK-954 dose against metoclopramide will be estimated and Kaplan-Meier plots will be presented. Additionally, a proportional hazards model may be used to examine the effect of covariates, such as site.

The proportion of subjects achieving at least 80% of daily goal calories and maintaining it for at least 2 consecutive days and/or the rest of Treatment Period and the proportion of subjects achieving at least 80% of daily goal protein and maintain it for at least 2 consecutive days and/or the rest of the Treatment Period will each be analyzed using a logistic regression model with treatment group and site as factors in the model. Incidence of all-cause mortality up to 30 days after the end of treatment will be summarized descriptively.

13.1.4 PK Analysis

No formal PK analyses will be performed on concentration-time data. Summary statistics of predose concentrations will be summarized by dose. Individual concentration-time data will be included in listings only.

A more detailed description of these analyses will be given in a separate analysis plan. The results from these analyses will not be included in the clinical study report and will be a standalone report.

13.1.5 Safety Analysis

AEs will be summarized using the safety analysis set.

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class. The definition of treatment-emergent AEs will be provided in the SAP. AEs

will be coded using MedDRA and will be summarized by system organ class and preferred term in the core treatment period and entire study.

AEs that were reported more than once by a subject during the same period will be counted only once for that subject and period at the maximum severity.

Clinical Evaluations:

Absolute values and changes from Screening/Baseline in clinical safety laboratory tests, vital signs, ECG parameters, and weight will be summarized for each treatment group using descriptive techniques. Values outside normal ranges and potentially clinically significant values will be flagged and tabulated.

13.2 Interim Analysis and Criteria for Early Termination

Interim analysis will be performed after approximately 100 subjects have completed the study (ie, 25 subjects within each cohort). Efficacy and safety data will be used to determine if stopping criteria for individual dose groups are met. Interim decision making for efficacy will be performed based on a futility stopping rule. Futility assessments in each dose group will be conducted based on the predictive probability of success (PPoS) of the primary efficacy endpoint.

The criteria for success for each dose group is that posterior probability (standardized treatment effect >0.2|Data) > 80% based on the updated distribution of the treatment effect at the end of the study. This will be assessed separately for each arm, assuming a positive treatment effect indicates improvement. If the PPoS at the interim in a dose group is below a pre-determined threshold (20%), 2 actions may be taken:

- The futility stopping rule will be met and patient enrollment will be discontinued in this dosing group. Subjects currently in that dosing group will complete the study receiving that dose if safety is not a concern.
- Subjects not already randomized will be split equally among any of the remaining dose groups after the interim analysis or reassigned to a new dose level.

In addition to the above formal criteria, all available efficacy and safety data from the current study and as well as data from the other TAK-954 studies will be used to guide the potential modification of design of the study, including dropping of inefficacious dose(s), dropping of doses due to safety concerns and inclusion of new dose(s) (less than 1 mg).

13.3 Determination of Sample Size

This study will randomize approximately 200 subjects into 4 treatment groups with an initial equal (1:1:1:1) randomization scheme. This sample size is based on simulation of go/no-go decision making using a Bayesian approach. If a new dose is introduced after the interim analysis, then the randomization scheme may be adjusted to increase the proportion of new subjects being assigned to the new dose. Subject randomization will be stratified based on their baseline NUTRIC score (either low [0-4] or high [5-9]) to ensure that approximately equal numbers of subjects will be randomized into each treatment group from a high or low NUTRIC score group.

14.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator guarantees access to source documents by the sponsor or its designee (contract research organization) and by the IRB or IEC.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee (as long as blinding is not jeopardized), including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study subjects. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the subject's source documents. In the event of a significant deviation, the site should notify the sponsor or its designee (and IRB or EC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the subject, or confound interpretation of primary study assessment.

The sponsor will assess any protocol deviation; if it is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated, it will be reported to regulatory authorities as a serious breach of GCP and the protocol.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an

auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare products Regulatory Agency). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator guarantees access for quality assurance auditors to all study documents as described in Section 14.1.

14.4 IRB and/or IEC Approval

IRBs and IECs must be constituted according to the applicable state and federal/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained. Those Americas sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study. The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will ship drug and/or notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives notification no protocol activities, including Screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

14.5 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and the subject authorization form. The informed consent form, subject authorization form, and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject or their LAR. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's LAR may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's LAR, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's LAR, determines he or she will participate in the study, then the informed consent form and subject authorization form must be signed and dated by the subject, or the subject's LAR, at the time of consent and prior to the subject entering into the study. The subject or the subject's LAR should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization at the time of consent and prior to subject entering into the study; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent form, subject authorization form and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form and subject information sheet (if applicable) shall be given to the subject or their LAR.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's LAR in the same manner as the original informed consent. The date the revised

consent was obtained should be recorded in the subject's medical record, and the subject or their LAR should receive a copy of the revised informed consent form.

14.6 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 14.5).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

14.7 Publication, Disclosure, and Clinical Trial Registration Policy

14.7.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

14.7.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, the sponsor will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for American investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

14.7.3 Clinical Trial Results Disclosure

The sponsor will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

14.8 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

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Appendix A Schedule of Study Procedures

Study Day/Week:	Screening	Treatment Period				3 Day Posttreatment Follow-up	Study Completion /Early Termination (follow-up contact)	Follow-up phone call
Days		Day 1 Baseline (predose)	Day 1 Postdose	Day 2 up to Day 13	End of treatment/ last day of study drug		30 days +/-3 days after last dose	90 days (+/-7 days) after last dose
Informed consent	X							
Inclusion/exclusion criteria	X	X						
Randomization (a)		X						
Demographics and medical history	X							
NUTRIC score (b)	X							
Medication history	X	X						
Physical examination (including neurology examination) (c)	X	X		X	X	X		
Vital signs (d)	X	X	X	X	X	X		
Weight, height, and BMI (e)	X				X			
Concomitant medications (including opioid consumption) (f)	X	X	X	X	X	X		

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

Study Day/Week:	Screening	Treatment Period				3 Day Posttreatment Follow-up	Study Completion /Early Termination (follow-up contact)	Follow-up phone call
Days		Day 1 Baseline (predose)	Day 1 Postdose	Day 2 up to Day 13	End of treatment/ last day of study drug		30 days +/-3 days after last dose	90 days (+/-7 days) after last dose
Concurrent medical conditions	X	X		X	X			
12-lead ECG (g)	X	X	X	X	X	X		
Holter monitoring (h)			X	X				
Clinical laboratory tests (i)	X	X		X	X	X		
Glucose monitoring	X	X		X	X			
Plasma sample for TAK-954 PK (j)		X	X	X	X			
Enteral feeding	X	X	X	X	X			
Hepatitis panel	X							
Study drug dosing (k)			X	X	X			
GRV (l)	X	X	X	X	X			
Muscle mass (mid-upper arm circumference measurement)		X			X			

Footnotes are on last table page.

Appendix A Schedule of Study Procedures (continued)

Study Day/Week:	Screening	Treatment Period				3 Day Posttreatment Follow-up	Study Completion /Early Termination (follow-up contact)	Follow-up phone call
Days		Day 1 Baseline (predose)	Day 1 Postdose	Day 2 up to Day 13	End of treatment/ last day of study drug		30 days +/-3 days after last dose	90 days (+/-7 days) after last dose
CCI [redacted]								
CCI [redacted]								
CCI [redacted]								
Urine sample to assess nitrogen balance (o)	X				X			
Serum pregnancy test (beta hCG) (p)	X							
Pretreatment SAEs	X							
SAE/AE assessment (q)		X	X	X	X	X	X	Mortality and cardiovascular events for 90 days postdose

Footnotes are on the following page.

(a) The dose is to be given within 6 hours of randomization.
(b) NUTRIC score variables include age, APACHE II, SOFA, number of comorbidies, and days from hospitalization to ICU admission.
(c) A neurological examination will be conducted at Baseline, on Days 2, 5, 8, and 12 while subjects are receiving study drug, and at 3 days following last dose.
(d) Vital signs will be collected 30 minutes prior to the start of the infusion, 30 minutes after the infusion starts and at the end of the infusion. Temperature will only be collected at the start of the infusion. Blood pressure and heart rate will be captured every 4 hours for the first 48 hours after the first dose of study drug.
(e) Height will only be collected at Baseline. BMI will be derived.
(f) Concomitant medications will be collected from the signing of the informed consent through 3 days after the last dose of study medication (inclusive).
(g) 12-lead ECG will be performed before the 60 minute IV infusion on Day 1 (Baseline); approximately 1, 2, and 8 hours after the start of the 60 minute IV infusion on Days 1 and 2; at the end of the infusion (approximately 1 hour after the start of the infusion) on every other day of treatment, and at the end of the infusion (approximately 1 hour after the start of the 60 minute IV infusion) on the last day of study drug. In addition, a 12-lead ECG will be performed when needed, if a subject develops symptoms suggestive of cardiovascular origin (eg, dizziness, chest pain).
(h) Holter Monitoring is ONLY required for the first 24 to 48 hours following the start of study infusion for approximately 10 subjects per arm in a subset of sites.
(i) Sodium, potassium, bicarbonate, glucose, blood urea nitrogen, creatinine, hematology, total bilirubin, alkaline phosphatase, ALT, AST, and GGT will be done at Screening, Baseline, Days 2, 3, 5, and every other day until the last day of study drug, and 3 days after the last day of study drug. For both hematology and chemistry values, if labs are done on that calendar day for routine clinical care, they will not be drawn additionally for the study on that day. No laboratory tests are needed at Baseline if the interval between Screening and Baseline is less than 24 hours.
(j) A PK sample will be obtained at 0 (predose) and 1 (just after the end of the infusion) hour on Days 1, 5, and last day of dosing. An additional 3 PK samples after the end of the infusion on Days 1, 5, and last day of dosing will be collected. The 3 PK samples should be taken as far apart as possible (at least 2 hours apart) and are recommended to be taken at 3, 8 and 12 hours post start of infusion on Days 1, 5 and last day of dosing. A trough (predose) sample will also be obtained on Days 2, 4 and 6. Times indicated are relative to the start of the infusion. The exact date and time of PK sample collection must be recorded as well as the start and end of infusion.
(k) Subjects will receive study medication as a 1-hour infusion at approximately (±2 hours) the same time on the dosing days.
(l) GRV assessments will be performed every 6 hours while on enteral feeding and in accordance with the feeding protocol.
(m) CCI [redacted]
(n) CCI [redacted]
repeated.
(q) After informed consent, but before initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (eg, SAEs related to invasive procedures). Subjects will be followed up to 30 days for safety and up to 90 days for cardiovascular events and survival after receiving their last dose of study treatment.

Appendix B Responsibilities of the Investigator

Clinical research studies sponsored by the sponsor are subject to ICH GCP and all the applicable local laws and regulations. The responsibilities imposed on investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which must be completed and signed before the investigator may participate in this study.

The investigator agrees to assume the following responsibilities by signing a Form FDA 1572:

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) Screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Ensure that valid informed consent has been obtained for each subject who participates in the study, and document the date of consent in the subject's medical chart. Valid informed consent is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the study. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject or the subject's legally acceptable representative.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.
12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix C Elements of the Subject Informed Consent

In seeking informed consent, the following information shall be provided to each subject or their LAR:

1. A statement that the study involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the study.
7. A description of the subject's responsibilities.
8. A description of the conduct of the study.
9. A statement describing the treatment(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects of the treatment that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.
15. For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of or where further information may be obtained.
16. The anticipated prorated payment(s), if any, to the subject for participating in the study.
17. The anticipated expenses, if any, to the subject for participating in the study.
18. An explanation of whom to contact for answers to pertinent questions about the research (investigator), subject's rights, and IRB/IEC and whom to contact in the event of a research-related injury to the subject.

19. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject otherwise is entitled, and that the subject or the subject's legally acceptable representative may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
20. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
21. A statement that the subject or the subject's LAR will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.
22. A statement that results of PGx analysis will not be disclosed to an individual, unless prevailing laws require the sponsor to do so.
23. The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated.
24. A written subject authorization (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the study. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) That personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) It is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) That personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the study drug(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical studies;
    d) That subjects agree not to restrict the use and disclosure of their personal information (including personal health information) upon withdrawal from the study to the extent that the restricted use or disclosure of such information may impact the scientific integrity of the research; and
    e) That the subject's identity will remain confidential in the event that study results are published.

25. Female subjects of childbearing potential (eg, nonsterilized, premenopausal female subjects) who are sexually active must use highly effective contraception (as defined in the informed consent) from Screening throughout the duration of the study, and for 30 days after last dose. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for 30 days after last dose. If the partner or wife of the subject is found to be pregnant during the study, the investigator will offer the subject the choice to receive unblinded treatment information.
27. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Appendix D Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, United States, and Japan), including the following:

- Takeda, its affiliates, and licensing partners.
- Business partners assisting Takeda, its affiliates, and licensing partners.
- Regulatory agencies and other health authorities.
- IRBs and IECs.

Investigator's personal information may be retained, processed, and transferred by Takeda and these other parties for research purposes including the following:

- Assessment of the suitability of investigator for the study and/or other clinical studies.
- Management, monitoring, inspection, and audit of the study.
- Analysis, review, and verification of the study results.
- Safety reporting and pharmacovigilance relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to the study.
- Preparation and submission of regulatory filings, correspondence, and communications to regulatory agencies relating to other medications used in other clinical studies that may contain the same chemical compound present in the study drug.
- Inspections and investigations by regulatory authorities relating to the study.
- Self-inspection and internal audit within Takeda, its affiliates, and licensing partners.
- Archiving and audit of study records.
- Posting investigator site contact information, study details and results on publicly accessible clinical trial registries, databases, and websites.

Investigator's personal information may be transferred to other countries that do not have data protection laws that offer the same level of protection as data protection laws in investigator's own country.

Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix E Hepatic Function Categories Based on Child-Pugh Score

Classification of clinical severity:
Mild (Class A): total score 5-6 points.
Moderate (Class B): total score 7-9 points.
Severe (Class C): total score 10-15 points.

Assessment Parameters	**Points Scored for Observed Findings**		
	1 point	**2 points**	**3 points**
Encephalopathy grade (a)	none	1 or 2	3 or 4
Ascites	absence	slight	moderate
Serum bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
INR	<1.7	1.7-2.3	>2.3

Source:
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf.
(a) Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second (cps) waves.
Grade 2: Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves.
Grade 3: Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: Unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity.

Appendix F Detailed Description of Amendments to Text

The primary section(s) of the protocol affected by the changes in Amendment No. 01 are indicated. The corresponding text has been revised throughout the protocol.

Change 1: Added exploratory endpoint CCI [redacted]

The primary change occurs in Section 5.2.4 Exploratory Endpoints.

Added text: CCI [redacted]

Rationale for Change:

CCI [redacted]

Section 2.0 STUDY SUMMARY also contains this change.

Change 2: Removed exploratory endpoint EQ-5D.

The primary change occurs in Section 5.2.4 Exploratory Endpoints.

Deleted text: CCI [redacted]

Rationale for Change:

It was determined the amount of data that would be generated would not be clinically meaningful at this stage.

Section 2.0 STUDY SUMMARY also contains this change.

Change 3: Deletion of the reinstitution of subjects' treatment in case of relapse.

The primary change occurs in Section 6.1 Study Design.

Deleted text: ~~If EFI relapses after drug discontinuation, subjects' treatment can be reinstituted if 14 days of drug treatment has not occurred.~~

Rationale for Change:

Significant logistic issues do not justify the amount of data that will be generated.

Section 2.0 STUDY SUMMARY and Figure 6.a EFI Feeding Protocol also contains this change.

Change 4: Additional criteria for discontinuation or withdrawal of a subject was added.

The primary change occurs in Section 7.5 Criteria for Discontinuation or Withdrawal of a Subject:

Added text: 1. **Treatment failures:**

• Subjects assessed by the treating physician as requiring different management to what is currently specified in the feeding protocol (eg, requiring rescue medication or post-pyloric tube placement) will be considered as treatment failures and be withdrawn from study treatment.

• **Treatment failures by protocol (Figure 6.a) will be discontinued from the study and standard of care will be implemented.**

2. **Subjects will also be discontinued if continuous tube feeding is no longer being provided in the ICU (eg, the patient is discharged to the ward, liquid nutrient is ceased by treating clinicians and the participant is allowed oral intake, or new abdominal pathology that requires enterally feeding to be ceased) or the subject dies.**

Rationale for Change:

Clarification of reasons for treatment failure.

28. **Change 5.** Additional criteria for discontinuation or withdrawal of a subject was added.

Clarification of neurological examinations.**:**

The change occurs in Section 9.1.3 Physical Examination Procedure.

Initial wording:	Neurological examinations will also be performed at Screening and on Days 2, 5, 8 and 12 and at 3 days following last dose.
Amended or new wording:	Neurological examinations **looking for hypertonicity, reflexes, and clonus** will also be performed **at Baseline,** ~~at Screening and~~ on Days 2, 5, 8 and 12, and at 3 days following last dose.

Rationale for Change:

Assessing neurological signs at Baseline and after treatment with study drug.

Appendix A Schedule of Study Procedures also contains this change.

Change 6: Removal of glycosylated hemoglobin (HbA1c) and thyroid stimulating hormone testing.

The primary change occurs in Section 9.1.9 Procedures for Clinical Laboratory Samples.

Description of change: HbA1c (at Screening) and thyroid stimulating hormone (TSH) at Screening only were deleted from the table.

Rationale for Change:

Inadvertently included to original protocol and not needed for safety.

29. **Change 7:** CCI [redacted] Added exploratory endpoint CCI [redacted]

30. CCI [redacted]

31.

32.

33.

34.

CCI [redacted]

The primary change occurs in Section 9.1.12 ECG:

Amended or new wording:

A standard single 12-lead ECG will be performed as follows:

- Before ~~each~~ **the 60 minute** IV infusion **on Day 1 (Baseline)**.
- Days 1 and 2:
  - ~~Within 30 minutes of the end of the infusion.~~
  - **Approximately** 1 (~~immediately after the end of the infusion~~), 2, and 8 hours after the start of the **60-minute** infusion.
- **Approximately** 1 hour (~~immediately~~ after the **start** ~~end~~ of the **60-minute** infusion) on every other day of treatment.
- **Approximately 1 hour (immediately after the end of the 60 minute IV infusion) on the last day of study drug.**

Rationale for Change:

Clarification of the timing for collection of ECGs at C_{max}.

Appendix A Schedule of Study Procedures also contains this change.

Change 8: Correction of clinical laboratory sample collections and amount of blood needed for the study.

The primary change occurs in 9.1.17 Primary Specimen Collection and Blood Volume:

Description of change:	Clinical laboratory test collection time points were corrected in Table 9.c Approximate Blood Volume.
Amended or new wording:	The maximum volume of blood at any single day is approximately **60** ~~70~~ mL, and the approximate **maximum** total volume of blood for the study is ~~270~~ **370** mL. Clinical laboratory samples ~~(110 mL)~~ will be collected as per standard of care **and will not be duplicated**.

Rationale for Change:

To correct the time points for the collection of clinical laboratory samples, and to correct the total maximum amounts of blood taken during the study.

Appendix A Schedule of Study Procedures also contains this change.

Change 9: Clarification of cardiovascular adverse events of special interest (AESI).

The change occurs in 10.1.6.6 AESI:

Initial wording:	• Cardiovascular events as described in Section 10.1.6.1.
Amended or new wording:	• Cardiovascular events **(ischemic heart disease, cerebrovascular accident [eg, transient ischemic attack and stroke], venous or arterial thromboembolic events, and heart failure)** ~~as described in Section 10.1.6.1~~.

Rationale for Change:

Clarification of the cardiovascular events related to the collection of AESI.

Change 10: Deletion of the submission of the original copy of the serious adverse event (SAE) form to the sponsor.

The change occurs in Section 10.2.2 Collection and Reporting of SAEs:

Deleted text: ~~The investigator should submit the original copy of the SAE form to the sponsor.~~

Rationale for Change:

Template text that was inadvertently left in the protocol was deleted as the investigator is required to report primarily via electronic data capture and not electronic data capture and paper.

Change 11: Clarification of the collection of height measurement.

The change occurs in Appendix A Schedule of Study Procedures:

Description of change: Footnote (e) was added: Height will only be collected at Baseline. BMI will be derived. Sequential footnotes were relettered.

Rationale for Change:

Clarification of height measurement.

Change 12: Correction of time from Randomization to drug administration.

The change occurs in Appendix A Schedule of Study Procedures:

Description of change: The time from Randomization to initiation of study drug was changed from 2 hours to 6 hours.

Rationale for Change:

This criteria for dosing with 2 hours of randomization was too restrictive.

Amendment 01 to A Phase 2, Randomized, Multi-Center, Double-Blind, Dose-Ranging Study to Assess the Efficacy, Safety, and Pharmacokinetics of Intravenous TAK-954 in Critically Ill Patients With Enteral Feeding Intolerance

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
PPD	Statistical Approval	01-Mar-2018 15:32 UTC
	Clinical Pharmacology Approval	01-Mar-2018 16:24 UTC
	Clinical Approval	01-Mar-2018 18:07 UTC
	Pharmacovigilance Approval	01-Mar-2018 18:59 UTC