Clinical Study Protocol

NCT Number: NCT04557189

Title: A Randomized Double-Blind, Sponsor-Open, Double-Dummy, Proof of Concept Phase 2 Study to Evaluate the Efficacy and Safety of TAK-951 Versus Ondansetron in the Prophylaxis of Postoperative Nausea and Vomiting in High-Risk Subjects

Study Number: TAK-951_2001

Document Version and Date: Amendment 4 / 13 September 2021

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

TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized Double-Blind, Sponsor-Open, Double-Dummy, Proof of Concept Phase 2 Study to Evaluate the Efficacy and Safety of TAK-951 Versus Ondansetron in the Prophylaxis of Postoperative Nausea and Vomiting in High-Risk Subjects

TAK-951 Versus Ondansetron Prophylaxis for Postoperative Nausea and Vomiting in High-Risk Subjects

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421		
Study Number:	TAK-951-2001		
IND Number:	141732	**EudraCT Number:**	Not applicable
Compound:	TAK-951		
Date:	13 September 2021	**Version/Amendment Number:**	4

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
13 September 2021	Amendment 4	Substantial	Global
28 July 2021	Amendment 3	Substantial	Global
11 January 2021	Amendment 2	Substantial	Global
22 September 2020	Amendment 1	Substantial	Global
23 June 2020	Initial protocol	Not applicable	Global

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

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	United States 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)	[redacted]

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 Conference 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

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

[redacted]

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 Conference 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.

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in 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 4 Summary of Changes

Protocol Amendment 4 Summary and Rationale:

This section describes changes in reference to the protocol incorporating Amendment 4. The primary reason for this amendment is to add additional samples for pharmacokinetic (PK) analysis to better assess TAK-951 PK profiling in subjects undergoing anesthesia.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 4			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 9.1.13 PK, DNA measurements, and Immunogenicity Sample Collection and Analysis Section 9.3.3 Hospital Discharge/Early Termination Appendix A Schedule of Study Procedures	Table 9.c: Added 2 pharmacokinetic (PK) samples from 10-18 hours and 22-26 hours and an associated footnote. Appendix A: Added an additional 22- to 26-hour PK sample that may coincide with discharge.	To better assess TAK-951 PK profiling in subjects undergoing anesthesia.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** TAK-951	
Title of Protocol: A Randomized Double-Blind, Sponsor-Open, Double-Dummy, Proof of Concept Phase 2 Study to Evaluate the Efficacy and Safety of TAK-951 Versus Ondansetron in the Prophylaxis of Postoperative Nausea and Vomiting in High-Risk Subjects	**IND No.:** 141732	**EudraCT No.:** Not Applicable
Study Number: TAK-951-2001	**Phase: 2**	

Study Design:

This is a phase 2 randomized, double-blind, sponsor-open, double-dummy, active-controlled study designed to assess the efficacy of TAK-951 to prevent the development of postoperative nausea and vomiting (PONV) in high-risk subjects undergoing elective surgery under general anesthesia. The study will also assess the safety, immunogenicity, and tolerability of TAK-951 in subjects undergoing elective surgery under general anesthesia. This is a double-blind study; the investigator and subjects are blinded to treatment assignment. The study will be conducted sponsor-open. Sponsor discussions with investigators and within the study team will be conducted in a blinded manner (ie, no unblinded information will be communicated to blinded investigators, site staff or blinded study monitoring personnel).

Subjects will be screened for enrollment up to 28 days before surgery. To be enrolled into the study and randomized to study drug, subjects will be required to meet all inclusion criteria and none of the criteria for exclusion. On the day of surgery, eligible subjects with 3 or more PONV risk factors will be randomized to either Treatment Group A to receive ondansetron placebo intravenously ([IV] administered in not less than 30 seconds, preferably over 2 to 5 minutes) immediately before induction of anesthesia and prophylaxis with 4 mg TAK-951 subcutaneously (SC) approximately 30 to 45 minutes before the end of surgery (defined as wound closure) or Treatment Group B to receive 4 mg ondansetron IV (administered in not less than 30 seconds, preferably over 2 to 5 minutes) immediately before induction of anesthesia and TAK-951 placebo SC approximately 30 to 45 minutes before the end of surgery.

Study drugs will be dosed sequentially: ondansetron or matching ondansetron placebo prior to induction of anesthesia [ie, before surgery], and TAK-951 or matching TAK-951 placebo prior to wound closure [ie, during surgery]. After randomization to Treatment Group A or B, subjects must demonstrate eligibility based on heart rate (HR), blood pressure, and cardiovascular stability before administration of each dose of study drug; these postrandomization criteria for study drug treatment are in addition to exclusion criterion #14 (Section 7.2) which applies to subject eligibility for enrollment and randomization. For subjects who have been randomized but not yet received ondansetron or matching ondansetron placebo at induction, the vital sign requirements in exclusion criterion #14 are applicable before administration of ondansetron or matching ondansetron placebo (see Section 6.1 for details). Similarly, HR and blood pressure requirements must be met and cardiovascular stability demonstrated immediately before administration of TAK-951 or matching TAK-951 placebo. Specific criteria to determine eligibility for TAK-951 or matching TAK-951 placebo are detailed in Section 6.1. Subjects who do not receive the first dose of study drug (ie, ondansetron or matching ondansetron placebo) due to the vital sign requirements will be discontinued from the study. Subjects who do not receive the second dose of study drug (ie, TAK--951 or matching TAK-951 placebo) due to the vital sign requirements in Section 6.1 will be unblinded to the investigator; those who received placebo at induction of anesthesia as their first dose of study drug will be discontinued from the study, and those who received ondansetron will continue to be monitored and assessed to study completion per-protocol. The decision to hold either dose of study drug/matching placebo will be recorded in the electronic case report form.

Only subjects undergoing elective surgery under general anesthesia that is expected to last at least 1 hour from induction of anesthesia to wound closure are eligible to participate in the study. The anesthesia protocol will allow the use of premedication with midazolam or fentanyl. Induction will be accomplished with propofol. Nitrous oxide will not be permitted. Anesthesia will be maintained with either sevoflurane or desflurane but total intravenous anesthesia

or propofol infusions for maintenance of anesthesia will not be permitted. Neuromuscular blocking agents may be used at the discretion of the anesthesiologist. Reversal, if utilized, will be accomplished with neostigmine and glycopyrrolate. Intraoperative analgesia may be accomplished with fentanyl or sufentanil as indicated. Postoperatively, the analgesic regimen will be left to the discretion of the physician. Patient-controlled analgesia and analgesic adjuncts, such as nonsteroidal anti-inflammatory drugs and pregabalin, are allowed. Intraoperative steroids will not be permitted.

Antiemetics, other than the study drugs, are prohibited within 24 hours before and up to 24 hours after surgery except for postoperative rescue therapy. Subjects having 1 or more episodes of vomiting, retching, or significant nausea, defined as nausea score ≥4 measured on a 0 to 10 verbal response scale (VRS) after surgery, (0 = no nausea at all and 10 = the worst nausea imaginable) or upon subject's request, will receive the recommended rescue therapy and will be considered a treatment failure. Treatment failures will be analyzed and reported at the 6 hour time point (meeting criteria above from time 0 to 6 hours) and at the 24-hour time point (meeting above criteria from time 0 to 24 hours).

Subjects will be monitored for the occurrence of emesis and the occurrence and severity of any nausea within the first 24 hours after surgery. Emesis will be defined as vomiting, the forceful discharge of even the smallest amount of stomach contents; or retching defined as the same muscular actions as vomiting but without expulsion of stomach contents. Nausea will be defined as the urge to vomit without the presence of expulsive muscular movements. The severity of nausea will be recorded by the site staff using a subject-reported 0 to 10 VRS, where 0 represents no nausea and 10 represents the worst nausea imaginable at 30 minutes and 1, 2, 6, and 24 hours after completion of surgery (wound closure). Any spontaneous complaints of nausea by subjects will also be noted and assessed for severity.

Subjects may be discharged 24 hours after completion of surgery and all scheduled procedures before discharge. Subjects will attend the clinic for a follow-up visit on Day 14±2 for assessment of concomitant medications, adverse events (AEs), and blood sample for immunogenicity assessment.

An interim analysis may be conducted when approximately 50 subjects have received both doses of double-blind study drug/matching placebo before surgery and during surgery and then have either completed all study procedures or withdrawn from the study with the objective of conducting a futility analysis. Additional descriptive analysis for primary and selected secondary and/or exploratory efficacy endpoints may be performed for both treatment arms to aid the internal decision-making. Other additional interim analysis of safety and/or efficacy may be conducted and would be defined in the statistical analysis plan (SAP).

Primary Objective:

The primary objective of this study is to assess the efficacy of a single-dose of TAK-951 compared with ondansetron to prevent PONV in the immediate postoperative period (within 6 hours post surgery) in high-risk subjects undergoing elective surgery under general anesthesia.

Secondary Objectives:

The secondary objectives of this study are:

- To assess the efficacy of TAK-951 to prevent PONV up to 24 hours post surgery compared with ondansetron.
- To assess the pharmacokinetics (PK) of TAK-951 in subjects undergoing elective surgery under general anesthesia.
- To assess the safety, immunogenicity, and tolerability of TAK-951 in subjects undergoing elective surgery under general anesthesia.

Exploratory Objective:

The exploratory objective of this study is:

[redacted]

surgery and subjects requiring rescue therapy for breakthrough PONV within 3 and 6 hours post surgery.

Subject Population: Subjects aged ≥18 years with 3 or more risk factors for PONV undergoing elective surgery under general anesthesia.

Number of Subjects: Allow a sample size of up to approximately 100 subjects who have received both doses of double-blind study drug/matching placebo dosed per protocol as: • Ondansetron 4 mg: ~50 - 70 subjects • 4 mg TAK-951: ~50 subjects A maximum of 160 subjects will be randomized in this study.	**Number of Sites:** Estimated total: 10 sites in the United States
Dose Levels: <u>Group A:</u> • Prophylaxis with ondansetron placebo IV immediately before induction and 4 mg TAK-951 SC approximately 30 to 45 minutes before the end of surgery (wound closure). <u>Group B:</u> • Prophylaxis with 4 mg ondansetron IV immediately before induction and TAK-951 placebo SC approximately 30 to 45 minutes before the end of surgery (wound closure).	**Route of Administration:** • 4 mg TAK-951: SC • Ondansetron placebo: IV • 4 mg ondansetron: IV • TAK-951 placebo: SC
Duration of Treatment: Up to 24 hours	**Period of Evaluation:** 14±2 days after TAK-951 dose
Main Criteria for Inclusion: Subject eligibility is determined according to the following criteria before entry into the study: 1. Male or female subjects aged ≥18 years at screening. 2. Subjects undergoing elective surgery under general anesthesia, expected to last for at least 1 hour from induction of anesthesia to wound closure. 3. Subject is expected to require, or has agreed to stay, at least 1 overnight in the hospital. 4. The subject's American Society of Anesthesiologist physical status is ASA I-III. 5. Subjects with 3 or more Apfel risk factors: a) Female sex. b) Nonsmoking (never smoked or stopped smoking ≥12 months ago). c) History of PONV or motion sickness. d) Planned use of postoperative opioid analgesics. 6. Subjects of nonchildbearing potential or subjects of childbearing potential willing and agreeable to use highly effective contraception or sexual abstinence during the study and up to 30 days post treatment.	
Main Criteria for Exclusion: 1. Subjects who are expected to remain intubated post anesthesia. 2. Subjects who experience vomiting 24 hours before surgery or are diagnosed with gastroparesis, cyclic vomiting syndrome, or other condition associated with chronic nausea and vomiting. 3. Subjects with a history of allergic reaction to, intolerances of, or contraindications for any of the study medications or required anesthetic agents, including any component of the formulation of ondansetron or TAK-951. 4. Subjects who have received, or are expected to receive, any excluded drug preoperatively within 24 hours before induction, during surgery, or within 24 hours after surgery. 5. Subjects scheduled to receive neuraxial anesthesia (eg, epidural, spinal, or caudal anesthesia), regional blocks, or	

total IV anesthesia, and/or has planned to receive different drugs for premedication, induction, maintenance, or reversal of anesthesia than those specified in the protocol.

6. Subjects who have an allergy or contraindication to the recommended and available rescue therapy for treatment of PONV.
7. Subjects expected to require the use of a nasogastric or oral gastric tube after surgery.
8. Female subjects who are pregnant or lactating.
9. Subjects with documented history of alcohol and/or drug abuse within 1 year of study medication.
10. Subjects who have any other significant, uncontrolled organic or systemic medical condition or social circumstance that, in the investigator's opinion, make participation in this clinical study inappropriate.
11. Subjects found at screening to have a QTcF (QT interval with Fridericia correction method) interval ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events. Assessments showing bundle branch block and a prolonged QTcF should be discussed with the study monitor and the sponsor for potential inclusion.
12. Subjects who have direct family history of premature sudden death or channelopathy, personal history of Brugada syndrome (right bundle branch block pattern with ST elevation in leads V1-V3), long QT, short QT, arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy or catecholaminergic polymorphic ventricular tachycardia (VT).
13. Subjects who have had 3 incidents of vasovagal syncope within the last 5 years.
14. Subjects with an average HR <55 or >100 bpm or a systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg during screening or prior to randomization on the day of surgery.

    Note: Vital sign criteria must be met postrandomization, before administration of ondansetron or matching ondansetron placebo and as gating criteria before administration of TAK-951 or matching TAK-951 placebo (see Section 6.1 for details). Subjects who exhibit signs suggestive of cardiovascular instability (as evaluated by the anesthesiologist) before administration of either dose of study drug/matching placebo should not be dosed, and the corresponding decision should be recorded.
15. Subjects with a clinically significant electrocardiogram (ECG) abnormality indicative of acute cardiac instability as determined by the investigator at screening, including more than first degree atrioventricular block, nonsustained or sustained VT, or ECG changes consistent with acute myocardial ischemia or infarction.
16. Subjects with a history of acute myocardial ischemia within the last 12 months.
17. Subjects receiving beta blockers chronically or between screening and surgery that cannot be safely withheld on the day of surgery in the investigator's judgment. Subjects receiving certain other cardiovascular medications, such as vasodilators for hypertension, chronically or between screening and surgery that in the investigator's judgment cannot be adequately managed in the perioperative setting considering the potential vasodilator effects of TAK-951 and anesthesia standard of care. The investigators must consult with the medical monitor regarding eligibility of subjects who are receiving beta blockers, vasodilators, and other classes of medications that act on HR or blood pressure.
18. Subjects with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN) or total bilirubin >1.5 times the ULN.
19. Subjects with known liver disease or positive for hepatitis B or C. For hepatitis B/C, the subject has 1 of the following at screening:
    - Chronic hepatitis B virus infection: positive for hepatitis B surface antigen (HBsAg).
    - Chronic hepatitis C virus (HCV) infection: positive for HCV antibody that is confirmed with a positive HCV RNA viral load test (those treated and cured for HCV infection are allowed).
20. Subjects who have participated in an interventional clinical study or been exposed to any experimental drug within 30 days before enrollment of this study.
21. Subjects who are an immediate family member, study site employee, or 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.

Main Criteria for Evaluation and Analyses:

Primary Endpoint:

The primary efficacy endpoint is complete response in the immediate postoperative period (6 hours post surgery), defined as no emesis (vomiting or retching) and no need for rescue therapy (indicated if vomiting/retching and/or nausea score ≥4 or upon subject's request) (Yes/No).

Secondary Endpoints:

- Complete response within 24 hours post surgery (Yes/No).
- Emesis in the first 6 hours post surgery (Yes/No).
- Emesis within 24 hours post surgery (Yes/No).
- Absence of nausea in the first 6 hours post surgery (Yes/No).
- Absence of nausea within 24 hours post surgery (Yes/No).
- Requiring rescue therapy for breakthrough PONV within 24 hours post surgery (Yes/No).
- Time from end of surgery to first emetic event (vomiting or retching).
- Peak nausea VRS score (0 = no nausea at all, and 10 = the worst nausea imaginable) at 30 minutes and 1, 2, 6, and 24 hours after completion of surgery in subjects who have not required rescue therapy.
- Total response within 24 hours post surgery, defined as no emesis, no nausea (VRS <1), and no need for rescue therapy (Yes/No).
- TAK-951 individual plasma concentrations.
- Safety:
  - AEs.
  - Vital signs.
  - ECG.
  - Laboratory values (hematology and chemistry).
  - Immunogenicity assessment (positive/negative anti-drug antibody and titer).

Exploratory Endpoints

- [redacted]
- efined as no emesis (vomiting or retching) and no need for rescue therapy (indicated if vomiting/retching and/or nausea score ≥4 or upon subject's request) (Yes/No).
- Emesis within the first 3 hours post surgery (Yes/No).
- Absence of nausea within the first 3 hours post surgery (Yes/No).
- Requiring rescue therapy for breakthrough PONV within 3 hours post surgery (Yes/No).
- Requiring rescue therapy for breakthrough PONV within 6 hours post surgery (Yes/No).

Statistical Considerations

Analysis Sets:

The Full Analysis Set (FAS) will include all subjects who were randomized to treatment and received both doses of double-blind study drug (ie, ondansetron or matching ondansetron placebo, and TAK-951 or matching TAK-951 placebo) before surgery and during surgery. Subjects will be analyzed according to their randomized treatment, regardless of whether they receive an investigational product that is different from that to which they were randomized.

The Per-Protocol Analysis Set (PPAS) will include all subjects who are in the FAS and do not violate the terms of the protocol in a way that would impact the study output significantly. All decisions to exclude subjects for the per-protocol population will be made before the unblinding of the study. Analyses using the PPAS will be provided as a sensitivity analysis.

The Safety Analysis Set will include all subjects who were randomized to treatment and received both doses of double-blind study drug (ie, ondansetron or matching ondansetron placebo, and TAK-951 or matching TAK-951 placebo) before surgery and during surgery. In safety summaries, subjects will be analyzed according to the treatment they actually received.

The PK Analysis Set will consist of all subjects who receive study drug and have at least 1 evaluable PK sample.

Efficacy Analysis:

The primary and secondary efficacy analyses and summaries will be based on the FAS. Sensitivity analyses will be conducted for the primary and secondary efficacy endpoints using the PPAS. To evaluate the impact of the identified dosing error at some participating sites, additional sensitivity analysis may be performed in the Safety Analysis Set by the actual treatment received.

Primary Efficacy Analysis: The primary efficacy analysis will be comprised of estimation of the treatment difference with respect to the primary efficacy endpoint. The proportions of complete responders 6 hours post surgery in the TAK-951 and ondansetron groups, along with the treatment difference in proportions, will be estimated along with the associated 2-sided 80% and 95% confidence intervals (CIs). The point estimate of the treatment difference between TAK-951 and ondansetron and the associated CIs will be based on the Cochran-Mantel-Haenszel method adjusting for the number of Apfel risk factors. In the event that the number of responders or non-responders in either treatment group is too small (ie, ≤5), the exact method (eg, Clopper-Pearson CI for proportions in each treatment group and exact unconditional confidence limits for treatment difference) will be performed instead. Subjects who are missing data needed to determine endpoint status will be considered as treatment failures (non-responder imputation).

Subgroup analyses by the number of simplified Apfel risk factors (3 or 4) and postoperative opioid analgesics opioid usage (yes or no) for the primary endpoint will be performed using the statistical methods used for the primary efficacy analysis. Point estimates and the associated 80% CI and 95% CI for the true treatment difference between TAK-951 and ondansetron will be presented for the subgroups.

Secondary Efficacy Analysis: The binary secondary endpoints include: emesis in the first 6 hours and within 24 hours post surgery, absence of nausea in the first 6 hours and within 24 hours post surgery, requiring rescue therapy for breakthrough PONV within 24 hours post surgery, and total response within 24 hours post surgery, will be analyzed similarly to the primary efficacy endpoint. The peak nausea VRS score at 30 minutes and 1, 2, 6, and 24 hours after completion of surgery in subjects will be analyzed using a mixed-effect model repeated measures (MMRM). This MMRM model will include treatment, the number of Apfel risk factors, timepoint, and treatment-by-timepoint interaction as fixed effects, and subject as a random effect. Point estimates and the associated 80% and 95% CIs for treatment difference between TAK-951 and ondansetron by timepoint will be presented. The time from the end of surgery to the first emetic event endpoints will be analyzed using the Cox proportional hazards model. Point estimate and the associated 80% and 95% CIs for the hazard ratio for TAK-951 versus ondansetron will be provided.

Safety Analysis: Safety data being collected in a double-blinded fashion will be summarized using the Safety Analysis Set and will include AEs, clinical safety laboratory tests, vital signs, ECG parameters, and weight. Subjects who are ineligible to receive the second dose of study drug (ie, TAK-951 or matching TAK-951 placebo) due to failure to meet the vital sign requirements outlined in Section 6.1 will be unblinded to the investigator; their safety data collected will be summarized separately.

Interim Analysis:

An interim analysis for futility based on the primary efficacy endpoint may be conducted based on Bayesian predictive probability after approximately 50 subjects have received both doses of double-blind study drug/matching placebo before surgery and during surgery and then have either completed all study procedures or withdrawn from the study. The study may be stopped if the Bayesian predictive probability calculated based on the interim TAK-951 primary endpoint data meets the prespecified stopping rule criteria for futility; otherwise, the study will continue as planned in the absence of safety concerns. Futility is nonbinding. Additional descriptive analysis for primary and selected secondary and/or exploratory efficacy endpoints may be performed for both treatment arms to aid the internal decision-making. Other additional interim analysis of safety and/or efficacy may be conducted and would be defined in the SAP.

Sample Size Justification:

The sample size was calculated based on primary efficacy analysis (ie, estimation of treatment difference with respect to the primary efficacy endpoint). Assuming true complete response rates at 6 hours of 60% and 80% in the ondansetron and TAK-951 groups respectively, given approximately 50 subjects per treatment group, the half width of a 2-sided 80% CI and a 2-sided 95% CI for treatment difference between TAK-951 and ondansetron in primary efficacy endpoint complete response rate at 6 hours will be approximately 11.5% and 17.5%, respectively, based on CIs using the normal approximation for the binomial distribution. This level of precision with the chosen sample size was considered acceptable for the statistical objective of this trial.

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

Takeda 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 drug used in the study, 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

ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CBL	change from baseline
COVID-19	coronavirus disease 2019
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
ECG	electrocardiogram
(e)CRF	(electronic) case report form
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
[redacted]	
GLP	Good Laboratory Practice
HBsAg	hepatitis B virus surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HR	heart rate
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measures
MRD	multiple rising dose

NSVT	nonsustained ventricular tachycardia
PACU	postanesthesia care unit
PD	pharmacodynamic
PK	pharmacokinetic
PONV	postoperative nausea and vomiting
PPAS	Per-Protocol Analysis Set
PTE	pretreatment event
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
t_{max}	time to maximum plasma concentration
ULN	upper limit of normal
USPI	United States Prescribing Information
VRS	verbal rating scale
$V_{,ss}$	volume of distribution at steady state after intravenous administration
VT	ventricular tachycardia
WOCBP	women of childbearing potential

3.4 Corporate Identification

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

4.0 INTRODUCTION

4.1 Background

The term postoperative nausea and vomiting (PONV) is used to define any nausea, vomiting, or retching occurring in the immediate postoperative period. The mechanism leading to PONV is complex and seems to involve multiple emetic pathways. The incidence of PONV varies from 30% of all surgical patients to up to 80% of high-risk patients [1]. Some of the most relevant risk factors for PONV are not always modifiable as they are inherent patient characteristics (female sex, nonsmoking status, prior history of PONV, and history of motion sickness). Other proven risk factors are related to the use of volatile agents or nitric oxide as anesthetics, intraoperative and postoperative use of opioid, and duration of anesthesia/surgery. Certain types of procedures such as gynecologic; ophthalmic; ear, nose, and throat (ENT); or thyroid surgeries have also been described to be associated with an increased risk of PONV, though this risk has not been confirmed in large prospective trials [2]. The Simplified Apfel Risk Score includes the 4 most relevant risk factors for PONV (female sex, history of PONV and/or of motion sickness, nonsmoking status, and postoperative use of opioids) that is currently used in clinical practice and research as a simple tool to identify subjects at higher risk of PONV. Results from an international study including 2722 subjects undergoing surgery confirmed that each of the risk factors included in the Apfel Risk Score increases the risk of PONV by 20% [1].

[redacted]

4.1.1 Nonclinical Background

[redacted]

[redacted]

Administration of the beta-blocker propranolol to dogs before TAK-951 administration resulted in a smaller HR increase than was seen with TAK-951 alone, while the combination of both propranolol and TAK-951 resulted in a greater decrease in blood pressure (BP) compared with that seen following administration of either treatment alone.

TAK-951 administration to sevoflurane-anesthetized dogs resulted in decreases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) immediately following dosing, which were maximal within 10 minutes postdose and partially recovered but remained decreased relative to predose levels up to 1 hour postdose, with a similar magnitude of change at all doses. There was a minimal increase in heart rate (HR) noted within 15 minutes postdose that remained through the anesthesia monitoring. Following recovery from the anesthesia and return to their home cage, there was a decrease in SBP and DBP with marked increases in HR noted for the remainder of the monitoring. The magnitude of the SBP, DBP, and HR changes in the conscious animals were generally dose related. Additional details are presented in the IB (edition 05).

In safety pharmacology studies, no adverse effects of TAK-951 were identified in the central nervous and respiratory systems in Good Laboratory Practice (GLP)-compliant studies in rats. TAK-951 was not a significant inhibitor of the human ether à-go-go–related gene (hERG) channel, the human sodium channel hNav1.5, human L-type calcium channel hCav1.2, or human hyperpolarization-activated, cyclic nucleotide-gated channel 4 (hHCN4) in vitro. Cardiovascular (CV) assessments were conducted through a series of non-GLP- and GLP-compliant safety pharmacology studies in dogs using implanted telemetry. Administration of TAK-951 resulted in an increase in HR and a decrease in both SBP and DBP, among other changes in CV parameters. These effects were observed at all doses evaluated, and therefore the lowest dose was the lowest-observed-effect-level for CV changes. The use of individualized QT correction demonstrated TAK 951 had either no effect, or a minor (5 ms) effect on the corrected QT interval (QTc) interval. Fasting status did not affect TAK-951-related changes in HR, SBP, or DBP.

[redacted]

The plasma PK of TAK-951 was characterized in rats, dogs, minipigs, and monkeys with high clearance and moderate volume of distribution at steady state after intravenous administration (V_{ss}) in rats, low clearance and low to moderate V_{ss} in dogs and minipigs, and low clearance and V_{ss} in monkeys and moderate to high bioavailability; good absorption; and a time to maximum plasma concentration (t_{max}) in the range of 0.33 to 1.67 hours (indicating rapid absorption) in rats, dogs, minipigs, and monkeys.

Repeat-dose subcutaneous (SC) administration of TAK-951 to rats and dogs for up to 14 days in duration was well tolerated. The only notable toxicity was injection site reactions, which generally recovered within 1 week. This observation of injection site reaction suggests that TAK-951 may have irritant properties when administered by SC injection to the same site for 7 consecutive days. Additionally, in rats there was a minimal TAK-951–related finding in eosinophil count that had no corresponding microscopic changes.

4.1.2 Clinical Background

A recently completed single-rising dose (SRD) and multiple rising dose (MRD) phase 1 first-in-human (FIH) study (TAK-951-1001) provided characterization of the single-dose and multiple-dose PK at multiple dose levels as well as the safety and tolerability profile of [redacted] TAK-951. This current phase 2 study will [redacted] test the antiemetic/antinausea mechanism [redacted] in humans.

Following single SC dose administration, TAK-951 was readily absorbed with median t_{max} across the dose groups ranging from 1.03 to 2.08 hours and mean apparent terminal half-life across the dose groups ranging from 2.54 to 6.40 hours. Following multiple SC twice-daily dose administration 8 hours apart, TAK-951 was readily absorbed with median t_{max} across the dose groups ranging from 1.00 to 2.03 hours after the first dose on Days 1 and 5 and mean apparent terminal-half-life across the dose groups ranging from 3.89 to 4.86 hours on Day 5.

Of a total 96 subjects randomized in the SRD portion of the TAK-951-1001 study, 72 (75%) subjects received active study drug (TAK-951) and 24 (25%) subjects received placebo. Overall, 33 (34.4%) subjects reported a total of 50 treatment-emergent adverse events (TEAEs): 29 subjects (40.3%) in the TAK-951 group and 4 (17%) in the placebo group. Of the 29 subjects in the TAK-951 group, 23 (79%) subjects reported a TEAE related to TAK-951; 27 (93%) subjects reported Grade 1, and 2 (7%) subjects reported Grade 3 events. There were 4 subjects reporting grade 1 events in the placebo group. The most commonly reported (≥3 subjects) TEAEs were palpitations (6), dizziness postural (5), dizziness (4), postural orthostatic tachycardia syndrome, back pain, and orthostatic hypotension (3 each).

Safety results from the FIH study demonstrated a transient increase in HR within the first hour of TAK-951 dosing as well as decreases in SBP and DBP that were more prominent with postural changes (orthostatic) in some individuals within the first 2 hours post dosing. In semirecumbent position, the largest mean change from baseline (CBL) in SBP and DBP was -25 and -15 mm Hg in the TAK-951 [redacted] cohorts, compared with -2.3 and 1.0 mm Hg in the placebo group at the same timepoint. In orthostatic position, the largest mean CBL in SBP and DBP was -10.3 and 4 mm Hg in the TAK-951 [redacted] cohort compared with 4.0 and -5 mm Hg in the placebo group. In semirecumbent position, the largest mean CBL in HR was 31 bpm in the TAK-951[redacted] cohort compared with -6.0 bpm in the placebo group. In orthostatic position, the largest mean CBL in HR was 34 bpm in the TAK-951[redacted] cohort compared with 15 bpm in the placebo group.

Of a total 32 subjects randomized in the MRD portion of the TAK-951-1001 study, 24 subjects received active study drug (TAK-951) and 8 subjects received placebo. A higher percentage of

subjects in the overall TAK-951 group (62.5%) compared with the pooled placebo group (37.5%) had TEAEs. In the pooled placebo group, 3 of 8 (37.5%) subjects had TEAEs; all 3 events were considered mild, and 1 was considered related to the study drug. In the overall TAK-951 group, 15 of 24 (62.5%) subjects had TEAEs. Eleven subjects reported Grade 1 TEAEs, three reported Grade 2 TEAEs, and one reported a Grade 3 event. One SAE of ventricular tachycardia was reported in a subject in the [redacted] TAK-951 cohort. Eleven (45.8%) subjects reported TEAEs that were considered related to the study drug. No subjects had an AE leading to study drug discontinuation, and no subjects died. Refer to the most recent version of the TAK-951 IB for detailed safety results including summarization of vital sign changes.

There was 1 SAE, nonsustained ventricular tachycardia (NSVT), in the MRD portion of the TAK-951-1001 study. The subject [redacted] experienced the event approximately 5 hours and 23 minutes after receiving the first dose of TAK-951/placebo (t_{max} on Day 1 typically ranged from 0.5 to 2 hours). The subject was asymptomatic at the time of the event and continued to receive a total of 10 doses as planned. The additional doses were well tolerated, with no additional AEs or additional episodes of ventricular arrhythmias reported. Based on a literature review of the prevalence of background NSVT rates in the general population as well as the time course of the event [6,7], the sponsor was unable to confirm causality or rule out a direct effect of the study drug as the cause of this event.

4.2 Rationale for the Proposed Study

PONV is one of the main causes of patients' dissatisfaction after anesthesia/surgery [8]; it may delay discharge from the hospital and can lead to serious complications, such as wound dehiscence, dehydration, electrolyte imbalance, esophageal tears, and aspiration of gastric content [9]. The physiopathology of PONV is complex and involves different pathways and receptors. Therefore, current guidelines recommend use of a combination of antiemetics with different mechanisms of action for subjects at high risk for PONV [9]. Data from an interventional study conducted in more than 5000 subjects given none, 1, 2, or 3 antiemetics suggested a simple additive rather than synergistic relationship between 5-HT3 antagonists, dopamine antagonists, and corticosteroid antiemetics, with each of these agents decreasing the relative risk of PONV by about 25%. This finding has been later corroborated in numerous combination prophylaxis studies [10,11].

[redacted]

This study is being conducted to assess the efficacy of TAK-951 in preventing PONV in high-risk subjects undergoing elective surgery under general anesthesia.

[redacted]

[redacted]

4.3 Benefit/Risk Profile

Based on nonclinical findings from studies conducted with TAK-951, and given the compound's proposed mechanism of action, the anticipated potential benefits of TAK-951 include effective treatment of nausea and vomitin [redacted] If the nonclinical data are confirmed in humans, patients at high-risk of PONV may demonstrate a decreased incidence of PONV when treated prophylactically with TAK-951. Note, that patients will be continuously monitored and will receive appropriate rescue therapy (standard of care), which will be available upon request, in case of lack of therapeutic response.

[redacted] and decreased BP [redacted] and a proposed mechanism of vasodilation (refer to IB Section 6.4.1), it is hypothesized that TAK-951 causes vasodilation, which leads to decreased blood pressure and tachycardia.

TAK-951 administration to sevoflurane-anesthetized dogs resulted in decreases in systemic BP (including SBP and DBP) immediately following dosing, which were maximal within 10 minutes postdose and partially recovered, but remained decreased relative to predose levels up to 1 hour postdose, with a similar magnitude of change at all doses. There was a minimal increase in HR noted within 15 minutes postdose that remained through the anesthesia monitoring. Following recovery from the anesthesia and return to their home cage, there was a decrease in systemic BP (including SBP and DBP) with marked increases in HR noted for the remainder of the monitoring. The magnitude of the BP and HR changes in the conscious animals were generally dose related. The observed transient drops in SBP and DBP may be consistent with a possible vasodilatory mechanism of TAK-951, which should be taken into account when TAK-951 is coadministered in an acute care setting with other agents that have potential cardiovascular effects.

Based on the completed TAK-951 FIH study, 2 ongoing TAK-951 studies, nonclinical studies conducted with TAK-951, [redacted] potential risks of TAK-951 include HR increase, decreased BP, and synergistic effect when combined with beta blockers, injection site reactions, and immunogenicity. Based on the data from the FIH study, effects on [redacted] are no longer considered as a potential risk.

Safety results from the FIH study demonstrated a transient increase in HR within the first hour of TAK-951 dosing as well as decreases in SBP and DBP that were more prominent with postural changes (orthostatic) in some individuals within the first 2 hours post dosing. The preliminary exposure-response analysis suggests a trend in increase in HR and decrease in DBP with increase in exposure at lower range but plateaus at higher exposure. Postural hypotension (<20 mm Hg in SBP or <10 mm Hg DBP within 3 minutes of standing) is considered an identified risk. In SRD, after receiving TAK-951, 3 subjects (4.2%) experienced orthostatic hypotension, including

1 subject with a Grade 3 event, and 5 subjects (6.9%) experienced postural dizziness, all Grade 1 in severity. In MRD, after receiving TAK-951, 2 subjects (8.3%) experienced orthostatic hypotension, both Grade 2 in severity, and 2 subjects (8.3%) experienced postural dizziness; Grade 1 in severity. Following the third dose on Day 2, there was no observed trend in HR after TAK-951 administration, suggesting an attenuation of effects on HR (IB edition 05).

The risks listed in the prescribing information associated with ondansetron include hypersensitivity reactions including anaphylaxis and bronchospasm, QT prolongation, torsades de pointe, and serotonin syndrome.

The risks listed in the prescribing information with midazolam, which will be used as anesthesia in the current study, include serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs are the most frequently seen findings following parenteral administration of midazolam in adults; these fluctuations include decreased tidal volume and/or respiratory rate, apnea, and variations in BP and pulse rate. Administration of intramuscular midazolam hydrochloride to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression.

The risks listed in the prescribing information associated with fentanyl, which will be used as anesthesia, include life-threatening respiratory depression, severe cardiovascular depression, serotonin syndrome, seizures, gastrointestinal adverse reactions, and drug interactions.

The risks listed in the prescribing information associated with propofol, which will be used as an inducing agent, include cardiorespiratory effects and risk of metabolic derangements and organ system failures, referred to as propofol infusion syndrome.

The most frequently reported risks during maintenance of anesthesia with sevoflurane are hypotension, followed by tachypnea, muscle tenseness, excitation, apnea, muscle fasciculations and emesis. The most frequently risks during maintenance of anesthesia with desflurane include headache, bradycardia, hypertension, nodal arrhythmia, tachycardia, nausea, vomiting, increased salivation, apnea, cough, laryngospasm, pharyngitis, and conjunctivitis.

To manage the risks to the subjects in this study, the following mitigations will be implemented:

1. Subjects with a history of serious hypersensitivity to any medication or any component of TAK-951 formulation or ondansetron, as well as those with a history of significant multiple and/or severe allergies, are excluded from this study.
2. Subjects will be excluded for HR <55 or >100 bpm and hypotension (defined as SBP <90 mm Hg or DBP <60 mm Hg) during screening and prior to randomization on the day of surgery.
3. TAK-951 or matching TAK-951 placebo will not be administered if there are signs suggestive of cardiovascular instability during surgery (as evaluated by the anesthesiologist). Specific HR and BP criteria must be met immediately prior to TAK-951 or matching TAK-951 placebo dosing as detailed in Section 6.1 to avoid administration of TAK-951 in subjects whose predose vital signs meet the criteria for low (or borderline low) BP, bradycardia, or tachycardia.

4. Subjects whose QT interval with Fridericia correction method (QTcF) is ≥450 msec or those with other factors that increase the risk of QT prolongation or arrhythmic events will be excluded.
5. Vital signs (HR and BP) will be collected in duplicate and averaged at all time points. Vital signs will be collected at screening, before dosing with ondansetron or matching ondansetron placebo (ie, before surgery), immediately before dosing with TAK-951 or matching TAK-951 placebo (ie, during surgery), and at the end of surgery (defined as wound closure) and recorded in the electronic case report form ([e]CRF). During surgery, vital signs will be monitored continuously for safety purposes. During the immediate postsurgical period, vital signs will be monitored upon admittance to the postanesthesia care unit (PACU) and collected every 15 minutes until 1 hour post surgery, then every 30 minutes until 4 hours post surgery, then every hour until 8 hours post surgery, then every 6 hours until 24 hours post surgery, and again at discharge.
6. ECGs will be monitored continuously by telemetry during surgery and for the first 24 hours post surgery. A standard 12-lead ECG will be performed at screening, on Day 1 before surgery, on admittance to the PACU (approximately 1 hour post dose), and before hospital discharge. In case of symptoms (palpitations or dizziness) or if abnormalities are identified on telemetry, a 12-lead ECG will be performed.
7. Detailed guidance is provided to the investigator (Section 10.2.4 Management of Specific AEs) for management of potential risk of increased HR and decreased BP related to TAK-951.
8. Administration of study drug must occur in a controlled environment to ensure close monitoring of subjects by the anesthesiologist and access to appropriate rescue medications.
9. Well-defined study stopping rules are provided that take into consideration the possible risk of increased HR and decreased BP.
10. An external Data Monitoring Committee (DMC) will be utilized for safeguarding the interest of study participants and assessing safety while maintaining the integrity of the study. The DMC will meet on a periodic basis during the conduct of the study as well as ad hoc for any safety concerns or in case any one of the stopping criteria are met.

Subjects will be evaluated for the development of antidrug antibodies (ADA) as part of the study.

Overall, the current mitigation strategies have been deemed adequate to monitor the safety of the subjects participating in the 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 efficacy of a single-dose of TAK-951 compared with ondansetron to prevent PONV in the immediate postoperative period (within 6 hours post surgery) in high-risk subjects undergoing elective surgery under general anesthesia.

5.1.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the efficacy of TAK-951 to prevent PONV up to 24 hours post surgery compared with ondansetron.
- To assess the PK of TAK-951 in subjects undergoing elective surgery under general anesthesia.
- To assess the safety, immunogenicity, and tolerability of TAK-951 in subjects undergoing elective surgery under general anesthesia.

5.1.3 Exploratory Objective

The exploratory objective of this study is:

[redacted]

- To assess the binary responses of complete response, emesis, and absence of nausea within the first 3 hours post surgery and subjects requiring rescue therapy for breakthrough PONV within 3 and 6 hours post surgery.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary efficacy endpoint is complete response in the immediate postoperative period (6 hours post surgery), defined as no emesis (vomiting or retching) and no need for rescue therapy (indicated if vomiting/retching and/or nausea score ≥4 or upon subject's request) (Yes/No).

5.2.2 Secondary Endpoints

- Complete response within 24 hours post surgery (Yes/No).
- Emesis in the first 6 hours post surgery (Yes/No).
- Emesis within 24 hours post surgery (Yes/No).
- Absence of nausea in the first 6 hours post surgery (Yes/No).
- Absence of nausea within 24 hours post surgery (Yes/No).
- Requiring rescue therapy for breakthrough PONV within 24 hours post surgery (Yes/No).
- Time from end of surgery to first emetic event (vomiting or retching).
- Peak nausea verbal rating scale (VRS) score (0 = no nausea at all, and 10 = the worst nausea possible) at 30 minutes and 1, 2, 6, and 24 hours after completion of surgery in subjects who have not required rescue therapy.

- Total response within 24 hours post surgery, defined as no emesis, no nausea (VRS <1), and no need for rescue therapy (Yes/No).
- TAK-951 individual plasma concentrations.
- Safety:
  - Adverse events (AEs).
  - Vital signs.
  - ECG.
  - Laboratory values (hematology and chemistry).
  - Immunogenicity assessment (positive/negative ADA and titer).

5.2.3 Exploratory Endpoints

[redacted]

- Complete response within the first 3 hours post surgery, defined as no emesis (vomiting or retching) and no need for rescue therapy (indicated if vomiting/retching and/or nausea score ≥4 or upon subject's request) (Yes/No).
- Emesis within the first 3 hours post surgery (Yes/No).
- Absence of nausea within the first 3 hours post surgery (Yes/No).
- Requiring rescue therapy for breakthrough PONV within 3 hours post surgery (Yes/No).
- Requiring rescue therapy for breakthrough PONV within 6 hours post surgery (Yes/No).

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a phase 2 randomized, double-blind, sponsor-open, double-dummy, proof-of-concept study designed to assess the efficacy of TAK-951 compared with ondansetron in the prophylaxis of PONV in high-risk subjects undergoing elective surgery under general anesthesia. The study will also assess the safety, immunogenicity, and tolerability of TAK-951 in subjects undergoing elective surgery under general anesthesia. This is a double-blind study; the investigator and subjects are blinded to treatment assignment. The study will be conducted sponsor-open. Sponsor discussions with investigators and within the study team will be conducted in a blinded manner (ie, no unblinded information will be communicated to blinded investigators, site staff or blinded study monitoring personnel).

Subjects aged ≥18 years with 3 or more risk factors for PONV who are undergoing elective surgery under general anesthesia will be screened for enrollment up to 28 days before surgery. To be enrolled into the study and randomized to study drug, subjects will be required to meet all inclusion criteria and none of the criteria for exclusion. Antiemetics, other than the study drugs, are

prohibited within 24 hours before and up to 24 hours after surgery except for postoperative rescue therapy. Only subjects undergoing elective surgery under general anesthesia that is expected to last at least 1 hour from induction of anesthesia to wound closure are eligible to participate in the study. The anesthesia protocol will allow the use of premedication with midazolam or fentanyl. Induction will be accomplished with propofol. Nitrous oxide will not be permitted. Anesthesia will be maintained with either sevoflurane or desflurane, but total IV anesthesia or propofol infusions for maintenance of anesthesia will not be permitted. Neuromuscular blocking agents may be used at the discretion of the anesthesiologist. Reversal, if utilized, will be accomplished with neostigmine and glycopyrrolate. Intraoperative analgesia may be accomplished with fentanyl or sufentanil as indicated. Postoperatively, the analgesic regimen will be left to the discretion of the physician. Patient-controlled analgesia and analgesic adjuncts, such as nonsteroidal anti-inflammatory drugs and pregabalin, are allowed. Intraoperative steroids will not be permitted.

On the day of surgery, eligible subjects with 3 or more PONV risk factors will be randomly assigned to either Treatment Group A to receive ondansetron placebo IV (administered in not less than 30 seconds, preferably over 2 to 5 minutes) immediately before induction of anesthesia [Zofran USPI] and prophylaxis with 4 mg TAK-951 SC approximately 30 to 45 minutes before the end of surgery (defined as wound closure) or Treatment Group B to receive 4 mg ondansetron IV (administered in not less than 30 seconds, preferably over 2 to 5 minutes) immediately before induction of anesthesia and TAK-951 saline placebo SC administered approximately 30 to 45 minutes before the end of surgery.

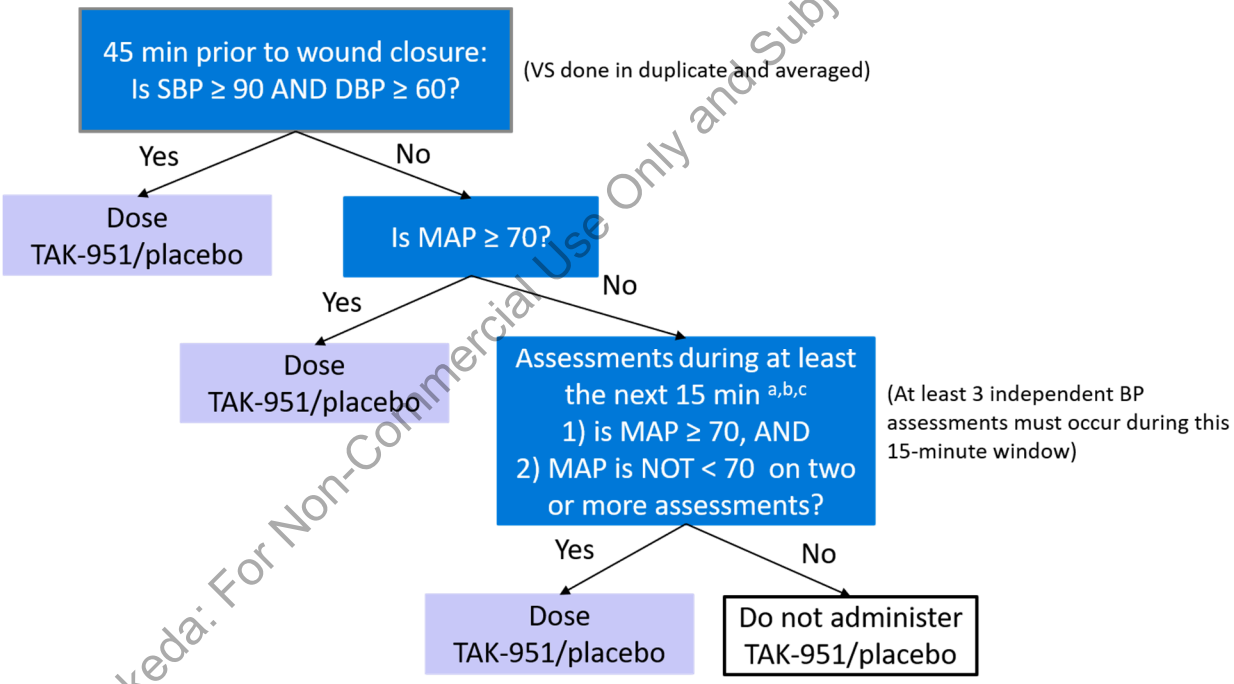
Study drugs will be dosed sequentially: ondansetron or matching ondansetron placebo prior to induction of anesthesia [ie, before surgery], and TAK-951 or matching TAK-951 placebo prior to wound closure [ie, during surgery]. After randomization to Treatment Group A or B, subjects must demonstrate eligibility based on HR, BP, and cardiovascular stability before administration of each dose of study drug; these postrandomization criteria for study drug treatment are in addition to exclusion criterion #14 (Section 7.2) which applies to subject eligibility for enrollment and randomization.

For subjects who have been randomized but have not yet received ondansetron or matching ondansetron placebo, all subjects must demonstrate average of duplicate measurements of (1) HR ≥55 and ≤100 bpm, (2) SBP ≥90 mm Hg, and (3) DBP ≥60 mm Hg prior to administration of ondansetron or matching ondansetron placebo at induction. Subjects who fail to meet these criteria should not receive ondansetron or matching ondansetron placebo and will be discontinued from the study. The corresponding decision to hold the dose and withdraw the subject should be recorded in the (e)CRF (see Section 7.7).

Immediately prior to administration of TAK-951 or matching TAK-951 placebo, all subjects must demonstrate average of duplicate measurements of (1) HR ≥55 and ≤100 bpm, (2) SBP ≥90 mm Hg, and (3) DBP ≥60 mm Hg. If these gating criteria are not met, further assessment of BP and HR must be performed as follows to determine eligibility for TAK-951 or matching TAK-951 placebo dosing (both HR and BP criteria must be met before proceeding with the second dose of study drug):

1. If the average SBP is <90 mm Hg or the average DBP is <60 mm Hg, then the average mean arterial pressure (MAP) should be measured and evaluated. If the average of duplicate measurements of MAP is ≥70 mm Hg, then dosing with TAK-951 or matching TAK-951 placebo may proceed. If the duplicate average MAP is <70 mm Hg, the anesthesiologist may reassess eligibility for dosing. During the next 15 minutes (reassessment period of up to 15 ±2 minutes), the MAP will be recorded from at least 3 independent BP cuff cycle readouts; if the MAP is <70 mm Hg on 2 or more repeat assessments, TAK-951 or matching TAK-951 placebo should not be administered and the corresponding decision to discontinue dosing should be recorded in the (e)CRF. If the MAP is ≥70 mm Hg during the 15-minute reassessment period and the MAP is not <70 mm Hg on 2 or more repeat assessments, TAK-951 or matching TAK-951 placebo dosing may proceed. A categorical decision tree for determining TAK-951 or matching TAK-951 placebo dosing eligibility based on BP is provided in Figure 6.a.

Figure 6.a BP Criteria for TAK-951 or Matching TAK-951 Placebo Dosing



BP: blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SBP: systolic blood pressure; VS: vital sign.

[a] Reassessment period up to 15 ±2 minutes for 3 independent BP readings.

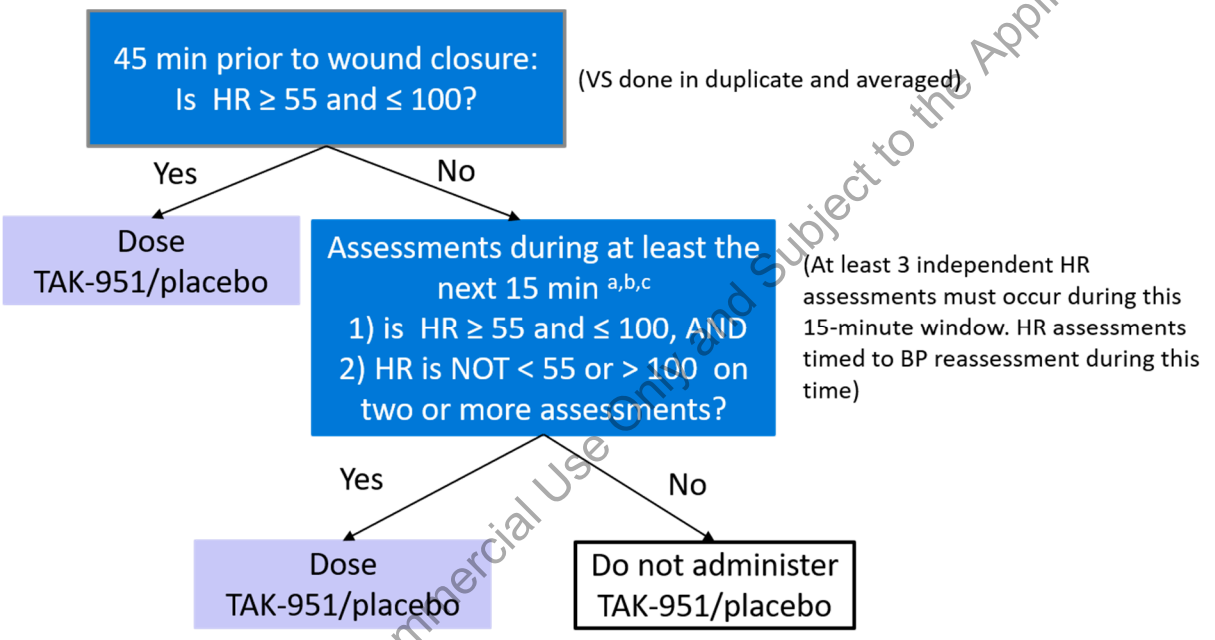
[b] Assessments will be single measurements (NOT duplicate averages) during the 15-minute window.

[c] If the answer to either question (1 or 2) is "No" then TAK-951/placebo should not be administered.

2. If the average HR is <55 or >100 bpm, the anesthesiologist may reassess within the next 15 minutes (reassessment period of up to 15 ±2 minutes). Although HR is continuously monitored, recorded HR(s) will align with the BP cuff readout (if BP is recorded, the same

timepoint[s] will be used). If the HR is <55 or >100 bpm on 2 or more independent assessments during the 15-minute reassessment period, TAK-951 or matching TAK-951 placebo should not be administered and the corresponding decision to discontinue dosing should be recorded in the (e)CRF. If the HR is ≥55 or ≤100 bpm during the 15-minute reassessment period and is not <55 or >100 bpm on 2 or more repeat assessments, TAK-951 or matching TAK-951 placebo dosing may proceed. A categorical decision tree for determining TAK-951 or matching TAK-951 placebo eligibility based on HR is provided in Figure 6.b.

Figure 6.b HR Criteria for TAK-951 or Matching TAK-951 Placebo Dosing



BP: blood pressure; HR: heart rate; VS: vital sign.
[a] Reassessment period up to 15 ±2 minutes for 3 independent HR assessments.
[b] Assessments will be single measurements (NOT duplicate averages) during the 15-minute window.
[c] If the answer to either question (1 or 2) is "No" then TAK-951/placebo should not be administered.

If there are signs suggestive of cardiovascular instability during surgery or the subject fails to meet the defined vital sign criteria above (as evaluated by the anesthesiologist), TAK-951 or matching TAK-951 placebo should not be administered and the corresponding decision to hold the dose and withdraw the subject should be recorded in the (e)CRF (see Section 7.7). Subjects who do not receive TAK-951 or matching TAK-951 placebo will be unblinded to the investigator; those who received placebo at induction of anesthesia as their first dose of study drug will be discontinued from the study, and those who received ondansetron will continue to be monitored and assessed to study completion per-protocol.

Subjects having 1 or more episodes of vomiting/retching or significant nausea, defined as nausea score ≥4 measured on a 0 to 10 verbal response scale (VRS) after surgery, (0 = no nausea at all and

10 = the worst nausea imaginable) or upon subject's request, will receive recommended rescue therapy as outlined in Section 7.5 and be considered a treatment failure (see Appendix B).

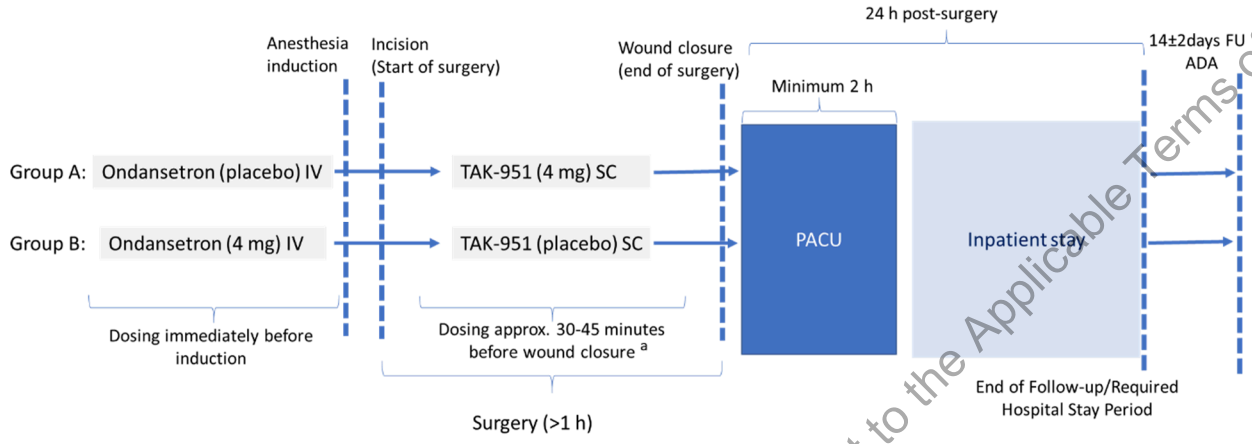
Subjects will be monitored for the occurrence of emesis and the occurrence and severity of any nausea within the first 24 hours after surgery. Emesis will include vomiting, defined as the forceful, discharge of even the smallest amount of stomach contents; or retching, defined as the same muscular actions as vomiting but without expulsion of stomach contents. Nausea will be defined as the urge to vomit without the presence of expulsive muscular movements. The subject will be questioned by the site staff about the severity of nausea using a subject-reported 0 to 10 VRS, where 0 represents no nausea and 10 represents the worst nausea imaginable at 1, 2, 6, and 24 hours after completion of surgery (wound closure). Any spontaneous complaints of nausea by subjects will also be noted and assessed for severity.

Subjects may be discharged 24 hours post surgery after completion of all scheduled procedures. There will be a follow-up visit on Day 14±2 for assessment of concomitant medications, AEs and blood sample for immunogenicity assessment.

An interim analysis for futility may be conducted after approximately 50 subjects have received both doses of double-blind study drug/matching placebo before surgery and during surgery and then have either completed all study procedures or withdrawn from the study. The study may be stopped if the Bayesian predictive probability calculated based on the interim data meets the prespecified stopping rule criteria for futility; otherwise in the absence of safety concerns, the study will continue without modification. Futility is nonbinding. Additional descriptive analysis for primary and selected secondary and/or exploratory efficacy endpoints may be performed for both treatment arms to aid the internal decision-making. Other additional interim analysis of safety and/or efficacy may be conducted and would be defined in the SAP.

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

Figure 6.c Schematic of Study Design



ADA: antidrug antibody; FU: follow-up; IV: intravenous; PACU: postanesthesia care unit; SC: subcutaneous.
[a] Vital sign criteria must be met according to Figure 6.a and Figure 6.b for eligibility to receive second dose of study drug (ie, TAK-951 or matching TAK-951 placebo) during surgery, approximately 30 to 40 minutes before wound closure.

6.2 Justification for Study Design, Dose, and Endpoints

A randomized, double-blind, double-dummy, active-controlled study design is considered adequate to assess the safety, efficacy, and tolerability of TAK-951 for the prophylaxis of PONV in high-risk subjects aged ≥18 years who are undergoing elective surgery under general anesthesia.

The proposed double-dummy design will ensure study blinding while the active-controlled study design will ensure that all enrolled subjects receive active medication.

Ondansetron is approved and widely used to prevent nausea and vomiting that may be caused by surgery, cancer chemotherapy, or radiation treatment and as such, is considered an appropriate active comparator for use in this study. The dose and route of administration of ondansetron is aligned with the label for the prophylaxis of PONV.

As TAK-951 is currently in the early stages of development, there is no information on efficacy. Information on the safety and PK profile of TAK-951 is based on the recently completed TAK-951-1001 FIH study in healthy volunteers (see Section 4.1.2 for details). Based on the tolerability and exposure/concentration data and population PK modeling, a dose of 4 mg was chosen for this study.

The PK and safety endpoints are standard for this type of study, are used widely, and are recognized as reliable, accurate, and relevant.

Recording of reports of emesis and presence and severity of nausea spontaneously and at predetermined intervals after surgery is a standard and appropriate means of assessing the efficacy of investigational medicinal products for the prophylaxis of PONV.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

If during the study any of the following study stopping criteria listed below are met, the study will be stopped and the safety data will be reviewed by an external DMC. A recommendation will be made to continue, modify, temporarily suspend, and/or terminate the study.

- New information or other evaluation regarding the safety or efficacy of the study drug indicates a change in the known benefit/risk profile for TAK-951 such that the benefit/risk ratio is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) compromises the ability to achieve the primary study objectives or compromises subject safety.
- Two or more subjects experience a National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher AE considered related to study drug by the investigator and/or by the sponsor. Monitoring will occur from TAK-951 administration to 24 hours after surgery.
- Two or more subjects who, during the operative period, experience a >30% decrease in SBP or DBP after TAK-951 administration compared with gated vital sign values immediately before TAK-951 dosing (see Section 6.1 for details) or have an absolute HR >120 bpm following TAK-951 dosing that are considered related to TAK-951 study drug by the investigator and/or by the sponsor.
- One subject experiences an SAE considered to be drug-related by the investigator and/or by the sponsor.
- One subject experiences an event listed as a Takeda Medically Significant Event (Table 10.a) that is considered drug-related by the investigator.
- One subject who, during the postoperative period, experiences a >50% change in SBP or DBP compared with preoperative vital signs that is considered related to TAK-951 study drug by the investigator and/or sponsor. This event will be reported as an SAE to the sponsor within 24 hours of observation by the investigator.
- One subject who, during the postoperative period, has an absolute HR >120 bpm with symptoms (eg, palpitations, light-headedness) that is considered related to TAK-951 study drug by the investigator and/or sponsor. This event will be reported as an SAE to the sponsor within 24 hours of observation by the investigator.
- Vital signs following TAK-951 or matching TAK-951 placebo administration during the operative period should be compared with vital signs obtained in the operating room just before TAK-951 or matching TAK-951 placebo dosing. Vital signs after TAK-951 or matching TAK-951 placebo administration following the operative period (when patient is in PACU and on the floor) should be compared with the preoperative vital signs (before induction and before administration of any premedication) obtained the day of surgery.

- One subject experiences a clinically significant arrhythmia that is considered drug-related by the investigator and/or by the sponsor.

One interim analysis, with the objective of potentially stopping the trial for futility, may be conducted when approximately 50 subjects have received both doses of double-blind study drug/matching placebo before surgery and during surgery and then have either completed all study procedures or withdrawn from the study.

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), 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

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

7.1 Inclusion Criteria

1. Male or female subjects aged ≥18 years at screening.
2. Subjects undergoing elective surgery under general anesthesia, expected to last for at least 1 hour from induction of anesthesia to wound closure.
3. Subject is expected to require, or has agreed to stay, at least 1 overnight in the hospital.
4. The subject's American Society of Anesthesiologist physical status is ASA I-III.
5. Subjects with 3 or more Apfel risk factors:
   a) Female sex.
   b) Nonsmoking status (never smoked or stopped smoking ≥12 months ago).
   c) History of PONV or motion sickness.
   d) Planned use of postoperative opioid analgesics.
6. Subjects of nonchildbearing potential or subjects of childbearing potential willing and agreeable to use highly effective contraception or sexual abstinence during the study and up to 30 days post treatment. See Sections 9.1.10 and 9.1.11 for definitions.

7.2 Exclusion Criteria

1. Subjects who are expected to remain intubated post anesthesia.
2. Subjects who experience nausea or vomiting within 24 hours before surgery or are diagnosed with gastroparesis, cyclic vomiting syndrome, or other condition associated with acute or chronic nausea and vomiting.
3. Subjects with a history of allergic reaction to, intolerances of, or contraindications for any of the study medications or required anesthetic agents, including any component of the formulation of ondansetron or TAK-951.
4. Subjects who have received, or are expected to receive, any excluded drug preoperatively within 24 hours before induction, during surgery, or within 24 hours after surgery. See Section 7.4 for details.
5. Subjects scheduled to receive neuraxial anesthesia (eg, epidural, spinal, or caudal anesthesia), regional blocks, or total IV anesthesia, and/or planned to receive different drugs for premedication, induction, maintenance, or reversal of anesthesia than those specified in the protocol.
6. Subjects who have an allergy or contraindication to the recommended and available rescue therapy for treatment of PONV (see Section 7.5 for list of recommended medications).
7. Subjects expected to require the use of a nasogastric or oral gastric tube after surgery.
8. Female subjects who are pregnant or lactating.
9. Subjects with documented history of alcohol and/or drug abuse within 1 year of study medication.
10. Subjects who have any other significant, uncontrolled organic or systemic medical condition or social circumstance that, in the investigator's opinion, make participation in this clinical study inappropriate.
11. Subjects found at screening to have a QTcF ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events. Assessments showing bundle branch block and a prolonged QTcF should be discussed with the study monitor and the sponsor for potential inclusion.
12. Subjects who have direct family history of premature sudden death or channelopathy, personal history of Brugada syndrome (right bundle branch block pattern with ST elevation in leads V1-V3), long QT, short QT, arrhythmogenic right ventricular dysplasia, hypertrophic cardiomyopathy or catecholaminergic polymorphic ventricular tachycardia (VT).
13. Subjects who have had 3 incidents of vasovagal syncope within the last 5 years.
14. Subjects with an average HR <55 or >100 bpm or an SBP <90 mm Hg or DBP <60 mm Hg during screening or prior to randomization on the day of surgery.

    Note: Vital sign criteria must be met postrandomization, before administration of ondansetron or matching ondansetron placebo and as gating criteria before administration of TAK-951 or

matching TAK-951 placebo (see Section 6.1 for details). Subjects who exhibit signs suggestive of cardiovascular instability (as evaluated by the anesthesiologist) before administration of either dose of study drug/matching placebo should not be dosed, and the corresponding decision should be recorded.

15. Subjects with a clinically significant ECG abnormality indicative of acute cardiac instability as determined by the investigator at screening, including more than first-degree atrioventricular block, nonsustained or sustained VT, or ECG changes consistent with acute myocardial ischemia or infarction.
16. Subjects with a history of acute myocardial ischemia within the last 12 months.
17. Subjects receiving beta blockers chronically or between screening and surgery that cannot be safely withheld on the day of surgery in the investigator's judgment. Subjects receiving certain other cardiovascular medications, such as vasodilators for hypertension, chronically or between screening and surgery that in the investigator's judgment cannot be adequately managed in the perioperative setting considering the potential vasodilator effects of TAK-951 and anesthesia standard of care. The investigators must consult with the medical monitor regarding eligibility of subjects who are receiving beta blockers, vasodilators, and other classes of medications that act on HR or BP.
18. Subjects with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 times the upper limit of normal ULN or total bilirubin >1.5 times the ULN.
19. Subjects with known liver disease or positive for hepatitis B or C. For hepatitis B/C, 1 of the following is present at screening:
    - Chronic hepatitis B virus infection: positive for hepatitis B surface antigen (HBsAg).
    - Chronic hepatitis C virus (HCV) infection: positive for HCV antibody that is confirmed with a positive HCV RNA viral load test (those treated and cured for HCV infection are allowed).
20. Subjects who have participated in an interventional clinical study or been exposed to any experimental drug within 30 days before enrollment of this study.
21. Subjects who are an immediate family member, study site employee, or 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.

7.3 Potential Drug Interactions

7.3.1 Synergistic Effect When Combined With Propranolol and Sevoflurane

TAK-951 administration to sevoflurane-anesthetized dogs resulted in decreases in systemic BP (including SBP and DBP) immediately following dosing, which were maximal within 10 minutes postdose and partially recovered, but remained decreased relative to predose levels up to 1 hour postdose, with a similar magnitude of change at all doses. There was a minimal increase in HR noted within 15 minutes post dose that remained through the anesthesia monitoring. Following

recovery from the anesthesia and return to their home cage, there was a decrease in systemic BP (including SBP and DBP) with marked increases in HR noted for the remainder of the monitoring. The magnitude of the BP and HR changes, measured in intervals of 4 hours, in the conscious animals were generally dose-related.

The effects of TAK-951 in combination with the beta blocker propranolol on the CV system were investigated in telemeterized conscious dogs in a non–GLP-compliant exploratory study. Propranolol partially suppressed the TAK-951–mediated HR effects, limiting the magnitude and duration of the HR increase. Administration of either TAK-951 or propranolol decreased BP. Combination treatment resulted in a greater BP decrease relative to either treatment alone.

7.4 Excluded Medications

Excluded medications include:

- Antiemetics, other than the study drugs, are prohibited within 24 hours before and up to 24 hours after surgery except for postoperative rescue therapy. Any drug given in the 24-hour postoperative period that would be expected, by virtue of its pharmacology, to exert a clinically meaningful antiemetic effect, even if not administered for that purpose (eg, metoclopramide administered for postoperative ileus), are not permitted.
- Nitrous oxide will not be permitted during surgery.
- Total IV anesthesia or propofol infusions for maintenance of anesthesia will not be permitted during surgery.
- Intraoperative steroids will not be permitted.

7.5 Rescue Therapy

Subjects will be assigned 1:1 on a double-blind basis to ondansetron, an approved medication for PONV prophylaxis, or TAK-951, an investigational treatment. Recommended rescue therapy should be given in accordance with product package inserts, the assessments in this protocol, standard of care for rescue treatment for PONV, and the "Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting" [14]. Rescue treatment should be based on timing of rescue relative to investigational product dosing, local standard of care, and drug availability. Specific recommendations for rescue therapy in this study are as follows:

1. If rescue therapy is required within 6 hours of administration of study drug (TAK-951 or time-matched placebo), promethazine 6.25 mg IV or amisulpride 10 mg IV are recommended.
2. If rescue therapy is required 6 or more hours after administration of study drug (TAK-951 or time-matched placebo), ondansetron 4 mg IV is recommended. If further rescue therapy is required, promethazine 6.25 mg IV or amisulpride 10 mg IV are recommended.

Other rescue treatment alternatives are not recommended. In choosing rescue treatment recommendations for PONV at any time after study drug, the potential for PK and pharmacodynamic (PD) interactions (including those with a risk for potential QTc prolongation) should be considered, with reference to the ondansetron package insert, promethazine package

insert, BARHEMSYS (amisulpride) package insert, and TAK-951 IB, particularly if timing of rescue is within 6 hours of administration of study drug (TAK-951 or matching placebo).

7.6 Diet, Fluid, Activity Control

Subjects should remain in a semirecumbent position, lateral semirecumbent position (if actively vomiting to avoid the risk of aspiration), or seated (if tolerated) and monitored closely for at least 3 hours after administration of study drug due to the risk of postural hypotension. Subjects should avoid standing or walking unaccompanied during this interval of time.

There are no specific restrictions on diet and fluids associated with this study. Sites should follow their standard guidelines or Enhanced Recovery After Surgery protocol.

7.7 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 (e)CRF using the following categories. For screen failure subjects, refer to Section 9.1.14.

1. Pretreatment event (PTE) or AE.
    - The subject has experienced a PTE or 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 PTE or AE.
    - Subjects with liver test abnormalities should be evaluated to determine whether study drug should be continued, interrupted, or discontinued (Appendix G).
2. Significant protocol deviation. The discovery after randomization that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Ineligibility for first dose of study drug. The subject was ineligible to receive the first dose of study drug (ie, ondansetron or matching ondansetron placebo) based upon vital sign criteria outlined in Section 6.1.
4. Ineligibility for second dose of study drug, after receiving placebo as first dose. The subject received placebo as the first study drug (ie, randomized to ondansetron placebo) but was not eligible to receive the second dose of study drug (ie, TAK-951) based upon vital sign criteria outlined in Section 6.1.
5. 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.
6. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the (e)CRF.

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 and/or lack of efficacy should not be recorded in the "voluntary withdrawal" category).

7. Study termination by the sponsor.
8. Study termination by the IRB or regulatory agency.
9. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately as described in Section 9.1.11.

10. Lack of efficacy. The investigator has determined that the subject is not benefiting from study treatment; and, continued participation would pose an unacceptable risk to the subject.

7.8 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 7.7. In addition, a subject 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.

The following subjects will be replaced:

- Discontinued subjects who were ineligible to receive the first dose of study drug (ie, ondansetron or matching ondansetron placebo) based upon vital sign criteria outlined in Section 6.1.
- Discontinued subjects who were ineligible to receive the second dose of study drug (ie, TAK-951 or matching TAK-951 placebo) based upon vital sign criteria outlined in Section 6.1.
- Subjects may be replaced as appropriate based on significant protocol deviations.

Discontinued or withdrawn subjects for any other reason will not be replaced.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug and Materials

8.1.1 Study Drugs

In this protocol, the term study drug refers to all or any of the drugs defined below. TAK-951 SC injection and ondansetron will be provided to the investigator by the sponsor in an open-label manner. These medications will be prepared and blinded by the unblinded site pharmacist before administration.

Details regarding the dosage form description and strengths or composition for the extemporaneous preparation of the active drug and placebo can be found in the pharmacy manual or in the referenced compounding manual when applicable. Study drug will be packaged to support enrollment and replacement of subjects as required.

8.1.1.1 TAK-951

TAK-951 will be supplied [redacted] in an appropriately labeled carton with a single panel label that will contain, but not be limited to, the sponsor's name and address, protocol number, packaging job/lot number, name and strength of the product, caution statement, and storage conditions.

Additional reference information and administration instructions can be found in the pharmacy manual.

8.1.1.2 Ondansetron

Ondansetron will be supplied as 4 mg/2 mL (2 mg/mL), from a commercial source, and provided in labeled glass vials packaged in an appropriately labeled carton. Additional reference information and administration instructions can be found in the pharmacy manual.

8.1.1.3 Placebo

Placebo will be 0.9% normal saline supplied by the study sites.

8.1.2 Clinical Study Drug Labeling

A clinical label will be affixed to study drug containers in accordance with local regulatory requirements.

8.1.3 Clinical Study Drug Inventory and Storage

Study drug must be stored in a secure, limited-access location under the storage conditions specified on the label and must remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained.

TAK-951 must be stored at -25°C to -15°C with protection from light.

Ondansetron must be stored at 20° to 25°C (68°F to 77°F) per United States Pharmacopeia at a controlled room temperature with protection from light.

The temperature excursion information can be found in the pharmacy manual or in the referenced compounding manual when applicable. Receipt and dispensing of study drug must be recorded by authorized personnel at the study site.

8.1.4 Dose and Regimen

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

Table 8.a Dose and Regimen

Treatment Group	Dose	Treatment Description
		Prophylaxis
A	Ondansetron placebo IV	Immediately before induction administered in not less than 30 seconds, preferably over 2 to 5 minutes
	4 mg TAK-951 SC	~30 to 45 minutes before the end of surgery [a]
B	4 mg ondansetron IV	Immediately before induction administered in not less than 30 seconds, preferably over 2 to 5 minutes
	TAK-951 placebo SC	~30 to 45 minutes before the end of surgery [a]

IV: intravenous; SC: subcutaneous.
[a] The end of surgery is defined as wound closure.

8.1.5 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by 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 the (e)CRF 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 CRF(s) according to Section 10.0.

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

In the event of drug overdose, the subject should be treated symptomatically.

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 ratio to receive prophylaxis with 4 mg TAK-951 or 4 mg ondansetron according to the randomization schedule.

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 or the sponsor's designee will generate the randomization schedule and will provide it to the IRT vendor before the start of the 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 the 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, changing a medication ID number in order to avoid identification of subjects by the laboratory site personnel).

This is a double-blind study; the investigator and subjects are blinded to treatment assignment. The study will be conducted sponsor-open. Sponsor discussions with investigators and within the study team will be conducted in a blinded manner (ie, no unblinded information will be communicated to blinded investigators, site staff, or blinded study monitoring personnel).

8.5 Unblinding Procedure

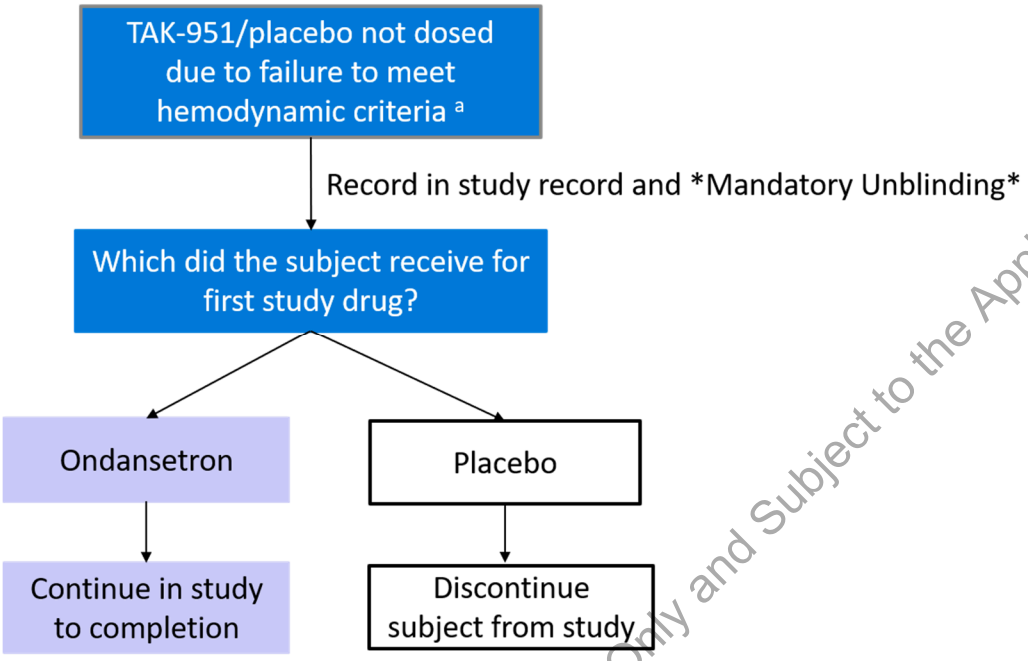
For subjects who receive both doses of study drug (ie, ondansetron or matching ondansetron placebo, and TAK-951 or matching TAK-951 placebo):

- The study drug blind shall not be broken by the investigator unless information concerning the study drug is necessary for the medical treatment of the subject. All study assessments and causality assessment should be performed, if possible, before unblinding. In the event of a medical emergency, if possible, the medical monitor should be contacted before the study drug blind is broken to discuss the need for unblinding.
- If any site personnel are unblinded, the subject must be withdrawn from the study.

For subjects who receive the first dose of study drug (ie, ondansetron or matching ondansetron placebo), but are ineligible to receive the second dose of study drug (ie, TAK-951 or matching TAK-951 placebo) due to failure to meet the vital sign criteria described in Section 6.1:

- The blind shall be broken by the investigator. If the subject received ondansetron placebo as the first dose of study drug, they should be discontinued from the study. If the subject received ondansetron as the first dose of study drug, they should remain in the study for ongoing monitoring and assessments to study completion per-protocol. A schematic of the unblinding procedure for subjects who do not receive TAK-951 or matching TAK-951 placebo is presented in Figure 8.a.

Figure 8.a Unblinding Procedure for Subjects Ineligible to Receive TAK-951 or Matching TAK-951 Placebo



[a] Vital sign criteria for eligibility to receive TAK-951 or matching TAK-951 placebo detailed in Section 6.1.

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, including subjects who are unblinded due to study drug ineligibility (ie, failure to meet the vital sign criteria outlined in Section 6.1). 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 in the (e)CRF.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

The investigator or designee must ensure that the study drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of study drug (TAK-951 or ondansetron), the investigator or designee must maintain records of all study drug deliveries to the site, site inventory, dispensation and use by each subject, destruction of drug supply at the site, and/or study drug returned to the sponsor or designee.

Upon receipt of sponsor-supplied drug, the investigator or designee must promptly verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct and that the study drug is in good condition. If there are any discrepancies between the packing list versus the actual product received, the sponsor (or representative) must be contacted to resolve the issue as outlined in the pharmacy manual. The packing list should be filed in the investigator's essential document file.

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

- Frequent verification that actual inventory matches documented inventory.
- Verification that the log is completed for the drug lot (or medication ID number) used to prepare each dose.
- Verification that all containers used are documented accurately on the log.
- Verification that required fields are completed accurately and legibly.

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

The investigator or designee must record the current inventory of all study drugs (TAK-951 and ondansetron) 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; date and amount dispensed including initials, seal, or signature of the person dispensing the drug; and the date and amount returned to the site by the subject, including the initials, seal, or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

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 15.2.

Informed consent must be obtained and signed before the subject enters 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; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information, medical history, and medication history will be obtained at the screening visit and before surgery. 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 before 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 before signing of informed consent.

The Simplified Apfel Risk Score includes the 4 most relevant risk factors for PONV (female sex, history of PONV and/or of motion sickness, nonsmoking status, and postoperative use of opioids) that is currently used in clinical practice and research as a simple tool to identify subjects at higher risk of PONV.

9.1.3 Physical Examination Procedure

A baseline physical examination conducted at the screening visit will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; and (10) lymph nodes. Any subsequent physical examinations should assess clinically significant changes from the assessment before the screening examination.

9.1.4 Height, Weight, and BMI

Height and weight will be measured wearing indoor clothing and with shoes off and will be measured at the screening visit only. Body mass index (BMI) is calculated using metric units with the formula provided below. Height is recorded in centimeters without decimal places. Weight is collected in kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: $\text{BMI} = \text{weight (kg)}/\text{height (m)}^2$

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height = 176 cm (1.76 meters) and weight = 79.2 kg, then $\text{BMI}=79.2/1.76^2=25.56818\ \text{kg/m}^2$

The values should be reported to 1 decimal place by rounding. Thus, in the above example, BMI would be reported as 25.6 kg/m^2.

9.1.5 Vital Sign Procedure

Vital signs (HR, BP, respiratory rate [RR]) will be collected in duplicate and averaged at all time points. Vital signs will be collected at screening, before dosing with ondansetron or matching ondansetron placebo (ie, before surgery), immediately before dosing with TAK-951 or matching TAK-951 placebo (ie, during surgery), and at the end of surgery (defined as wound closure, see Figure 6.c) and recorded in the (e)CRF. During surgery, vital signs will be monitored continuously for safety purposes. HR and BP will be collected in duplicate for all vital sign measurements within a 2-minute interval and the results averaged for higher accuracy. Vital signs can be repeated within 10 minutes, if at screening or before surgery, the physician believes that these are artificially high due to subject's anxiety. Body temperature will also be taken before surgery and approximately 8 and 24 hours post surgery or TAK-951 dosing.

Immediately prior to TAK-951 or matching TAK-951 placebo dosing, criteria for BP and HR must be met and cardiovascular stability demonstrated (see Section 6.1, Figure 6.a, and Figure 6.b). If there are signs suggestive of cardiovascular instability during surgery (as evaluated by the anesthesiologist), TAK-951 or matching TAK-951 placebo should not be administered and the corresponding decision should be recorded in the (e)CRF.

During the immediate postsurgical period, vital signs will be monitored upon admittance to the PACU and collected every 15 minutes until 1 hour post surgery, then every 30 minutes until 4 hours postsurgery, then every hour until 8 hours postsurgery, then every 6 hours until 24 hours postsurgery, and again at discharge.

When vital signs are scheduled at the same time as blood draws, the vital signs will be taken just before blood draws.

9.1.6 Efficacy/Patient Reported Outcomes Measurement

9.1.6.1 Postsurgery Assessment of Nausea

Postoperative nausea (described as the desire to vomit without the presence of expulsive muscular movements) will be scored using a self-reported, 11-point numerical VRS where 0 represents "no nausea" and 10 represents the "worst nausea possible." Significant nausea is defined as a VRS ≥4.

The presence and severity of subject-reported nausea anytime during the 24-hour follow-up period will be recorded by the site staff in a paper form (see Appendix B) and the (e)CRF. Nausea will also be assessed by direct questioning by the site staff at 30 minutes and 1, 2, 6, and 24 hours post surgery (wound closure) and results will be recorded similarly.

9.1.6.2 Emetic Events

Emesis is defined as vomiting (the forceful discharge of even the smallest amount of stomach contents) or retching (the same muscular movements as vomiting but without expulsion of stomach contents). The occurrence and timing of emetic events will be monitored and documented by the subject or site staff in a paper form (see Appendix C) and the (e)CRF.

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 or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the (e)CRF.

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.

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 study procedures manual.

Clinical laboratory evaluations (hematology and serum chemistry) do not need to be repeated on the day of surgery if the screening assessments were performed within 2 weeks, did not show any clinically relevant abnormalities, and were discussed with the medical monitor. If repeated, baseline clinical labs performed on the day of surgery do not need to be reviewed before dosing.

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

Table 9.a Clinical Laboratory Tests

Hematology	**Serum Chemistry**
Red blood cells	AST
White blood cells	ALT
Hemoglobin	Albumin
Hematocrit	Alkaline phosphatase
Platelets	Total bilirubin
	Total protein
	Creatinine
	Blood urea nitrogen
	GGT
	Glucose
	Potassium
	Sodium
Other:	
Serum	**Urine**
Hepatitis panel, including HBsAg and anti-HCV Immunogenicity Female subjects only: Beta hCG (for pregnancy) in female subjects of childbearing potential FSH in female subjects for whom menopause is suspected	Female subjects only: hCG (for pregnancy)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; FSH: follicle-stimulating hormone; GGT: γ-glutamyl transferase; HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; HCV: hepatitis C virus.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis for hCG. The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results. A central laboratory will perform the ADA assessments.

For subjects with treatment-emergent ALT elevations ≥3 times the ULN, see Appendix G for additional monitoring, evaluation, and follow-up recommendations.

The investigator (or designee) is responsible for transcribing or attaching laboratory results to the (e)CRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

9.1.10 Contraception and Pregnancy Avoidance Procedure

9.1.10.1 Male Subjects and Their Female Partners

From signing of informed consent, throughout the duration of the study, and for 5 half-lives or 30 days after the last dose of study drug, nonsterilized** male subjects who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with or without spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. Women of childbearing potential who are partners of male subjects are also advised to use additional contraception as shown in the list containing highly effective/effective contraception below.

9.1.10.2 Female Subjects and Their Male Partners

From signing of informed consent, throughout the duration of the study, and for 5 half-lives or 30 days after the last dose of study drug, female subjects of childbearing potential* who are sexually active with a nonsterilized male partner** must use at least 1 highly effective method of contraception (Section 9.1.10.3). In addition, they must be advised not to donate ova during this period.

9.1.10.3 Definitions and Procedures for Contraception and Pregnancy Avoidance

The following definitions apply for contraception and pregnancy avoidance procedures.

* A woman is considered a woman of childbearing potential (WOCBP), ie, 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. A high follicle-stimulating hormone (FSH) level in the postmenopausal range (FSH >40 IU/mL) may be used to confirm a postmenopausal state in younger women (eg, those aged <45 years) or women who are not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

** Sterilized men 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.

The following procedures apply for contraception and pregnancy avoidance.

1. Highly effective methods of contraception are defined as "those, alone or in combination, that result in a low failure rate (ie, less than 1% failure rate per year when used consistently and correctly)". In this study, where medications and devices containing hormones are included, the only acceptable methods of contraception are as follows:

    - Nonhormonal methods:
        - Intrauterine device.
        - Bilateral tubal ligation.

  - Vasectomized partner (provided that partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success).
  - True sexual abstinence, but only if this is in line with the preferred and usual lifestyle of the subject. True abstinence is defined as refraining from heterosexual intercourse during the entire period of the study, from 1 month before the first dose until 5 half-lives or 30 days after last dose.

- Hormonal methods: Hormonal contraception may be susceptible to interaction with the investigative compound, comparator, or concomitant medications, which may reduce the efficacy of the contraception method.
  - Combined (estrogen and progestogen) hormonal contraception associated with inhibition of ovulation initiated at least 3 months before the first dose of study drug OR combined with a barrier method (male condom, female condom, or diaphragm) if for shorter duration until she has been on contraceptive for 3 months;
    - Oral.
    - Intravaginal (eg, ring).
    - Transdermal.
  - Progestogen-only hormonal contraception associated with inhibition of ovulation initiated at least 3 months prior to the first dose of study drug OR combined with a barrier method (male condom, female condom, or diaphragm) if shorter until she has been on contraceptive for 3 months;
    - Oral.
    - Injectable.
    - Implantable.

2. Effective methods of contraception (there may be a higher than 1% failure rate) are:
   - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or creams, PLUS male condom).
   - Progestogen-only hormonal contraception in which inhibition of ovulation is not the primary mode of action PLUS condom with or without spermicide.
3. Unacceptable methods of contraception are:
   - Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods).
   - Spermicides only.
   - Withdrawal.
   - No method at all.

- Use of female and male condoms together.
- Cap/diaphragm/sponge without spermicide and without condom.
- Sexual abstinence is NOT an acceptable method of contraception.

4. Subjects will be provided with information on effective/highly effective methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova or sperm donation during the course of the study.
5. During the course of the study, all subjects (male and female) will receive continued guidance with respect to the avoidance of pregnancy or sperm donation as part of the study procedures. Such guidance should include a reminder of the following:
   - Contraceptive requirements of the study.
   - Reasons for use of barrier methods (ie, condom) in males with pregnant partners.
6. In addition to a negative serum human chorionic gonadotropin (hCG) pregnancy test at screening, female subjects of childbearing potential must also have confirmed menses in the month before first dosing (no delayed menses) and a negative urine hCG pregnancy test on the day of surgery before receiving any dose of study medication.

9.1.10.4 General Guidance With Respect to the Avoidance of Pregnancy

Such guidance should include a reminder of the following:

- Contraceptive requirements of the study
- Reasons for use of barrier methods (ie, condom) in men with pregnant partners.
- Important in all studies with IMPs/comparators/background medications that are known for teratogenicity/fetotoxicity or in the absence of reproductive toxicity results.

From signing of informed consent and throughout the duration of the study and for 5 half-lives or 30 days after the last dose, WOCBP (ie, nonsterilized, premenopausal female subjects) who are sexually active must use acceptable methods of contraception. Also, from signing of informed consent, throughout the duration of the study, and for 5 half-lives or 30 days after the last dose, nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use contraception. Such subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy during the course of the study. Serum and urine hCG pregnancy tests will be performed at screening and before surgery, respectively, and subjects will receive continued guidance with respect to avoiding pregnancy as part of the study procedures (Appendix A).

In addition to a negative serum hCG pregnancy test at screening, subjects also must have a negative urine hCG pregnancy test on the day of the dose of study drug (predose) before receiving any dose of study drug.

In addition, male subjects must be advised not to donate sperm from signing of informed consent to 5 half-lives after the last dose of study drug.

9.1.11 Pregnancy

If pregnancy occurs following study drug administration, defined as within 30 days of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the contact listed in Section 1.0.

Should the pregnancy occur during or after administration of blinded drug, the investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator.

If the female subject and/or female partner of a male subject agrees 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 (blinded or unblinded, as applicable).

All pregnancies, including female partners of male subjects, in subjects on active study drug (including comparator) will be followed up to final outcome, using the pregnancy form. Pregnancies will remain blinded to the study team. 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 and Telemetry Procedure

ECGs will be monitored continuously by telemetry during surgery and for the first 24 hours postsurgery. A standard 12-lead ECG will be performed at screening, on Day 1 before surgery, on admittance to the PACU (approximately 1 hour post dose), and before hospital discharge. In case of symptoms (eg, palpitations or dizziness) or if abnormalities are identified on telemetry, a 12-lead ECG will be performed. 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. ECG parameters will be entered into the database for all subjects. All tracings will be available as a source document for review and verification by the sponsor. ECGs for all SAEs will be submitted to the sponsor for review.

The time that the ECG was performed will be recorded. The following parameters will be recorded on the (e)CRF from the subject's ECG trace: HR, RR interval, PR interval, QT interval, and QRS interval, and QTcF.

9.1.13 PK, DNA measurements, and Immunogenicity Sample Collection and Analysis

9.1.13.1 Collection of Blood/Plasma/Serum

Blood sample for plasma for determination of TAK-951 concentration will be collected from all subjects at time windows specified in Table 9.c. Plasma samples may be analyzed for ondansetron concentration, and the results may be reported separately. The samples will be analyzed for plasma

concentration of TAK-951 and ondansetron (if performed) by validated methods. Table 9.b summarizes sampling for PK, DNA measurements, and immunogenicity assessments. Further details of the collection and procedures will be given in the study procedures manual.

Table 9.b Sample Collection for PK, DNA Measurements, and Immunogenicity Assessments

Specimen Name	Primary Specimen	Primary Specimen Derivative	Description of Intended Use	Sample Collection
Plasma sample for TAK-951 PK	Plasma	N/A	PK measurements	Mandatory
Buccal epithelial cells sample for DNA	Buccal swabs	DNA	DNA measurements	Optional
Serum sample for immunogenicity	Serum	N/A	Immunogenicity assessments	Mandatory

N/A: not applicable; PK: pharmacokinetic.

It is important that the date and time of administration of the study drug dose before collection of the PK sample be recorded accurately in the source documents and the (e)CRF. Similarly, it is important that the date and time that each blood sample is drawn is accurately recorded in the (e)CRF.

The sparse sampling time windows for blood draws for the analysis of plasma concentrations of TAK-951 are shown in Table 9.c.

Table 9.c PK Sampling Time Windows

PK Sampling Time Windows After SC Dose for Treatment Groups A and B					
	Window 1	Window 2	Window 3	Window 4 [a]	Window 5
PK sampling	1-3 h	4-6 h	7-9 h	10-18 h	22-26 h

PK: pharmacokinetic; SC: subcutaneous.
[a] PK sample at 10-18 h should be as close to 14 h as feasible.

Blood samples collected outside the exact nominal time windows will not be captured as protocol deviations as long as the date and exact time of the sample collection is noted on the source document and (e)CRF. Plasma samples may be used for future metabolite identification and/or further evaluation of the bioanalytical methods. These data will be used for internal exploratory purposes and will not be included in the clinical study report.

9.1.13.2 Immunogenicity

Protein products have the potential to induce anti-drug immune response which may affect the safety and efficacy of TAK-951. Detection and analysis of ADA formation is a helpful tool in understanding drug immunogenicity, efficacy, and safety. To understand drug immunogenicity, serum samples will be collected before surgery (the baseline sample), at discharge/early termination, and at the follow-up visit.

[redacted], an ADA assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, the incidences of ADA formation cannot be directly compared with the other products. ADA samples will be taken in all parts of the study across all cohorts.

9.1.13.3 DNA Measurements

DNA sampling is optional in this study and will only be performed for subjects who provide consent to participate in this assessment.

[redacted] This information may be used to develop a better understanding of the safety and efficacy of TAK-951 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.

DNA research is an evolving science and further assessments may be performed based on newly available data.

Subjects who consent and provide a buccal swab for DNA analysis can withdraw their consent at any time and request disposal of a stored sample. Any remaining sample that can be identified as coming from the subject will be destroyed. The investigator and sponsor may continue to use and distribute any information and test results gathered before the request to withdraw.

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

9.1.13.4 Bioanalytical Methods

The validated bioanalytical method for TAK-951 will be used for the analysis.

9.1.14 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 (e)CRF. The IRT should be contacted as a notification of screen failure.

The primary reason for screen failure is recorded in the (e)CRF using the following categories:

- PTE/AE.
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal <specify reason>.
- Study termination.

- Other <specify reason>.

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

9.1.15 Documentation of Randomization

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

If the subject is found to be not eligible for randomization to treatment, the investigator should record the primary reason for failure on the applicable (e)CRF.

9.2 Monitoring Subject Treatment Compliance

Study site personnel will administer study drug and record in the (e)CRF.

9.3 Schedule of Observations and Procedures

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

9.3.1 Screening

Subjects will be screened within 28 days before surgery. Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0. See Section 9.1.14 for procedures for documenting screening failures.

Procedures to be completed at screening include:

- Informed consent.
- Inclusion/exclusion criteria.
- Demographics, medical history, and medication history.
- Concomitant medications/therapies.
- Simplified Apfel Risk Score.
- Physical examination.
- Height, weight, BMI, and vital signs (BP, HR, and RR).
- Serum pregnancy test (hCG).
- FSH, if applicable.
- HBsAg and HCV.
- Screening clinical laboratory tests.
- 12-lead ECG.
- PTE/AE assessment.

9.3.2 Day 1

9.3.2.1 Before Surgery

Procedures to be completed before surgery include:

- Inclusion/exclusion criteria.
- Demographics, medical history, and medication history.
- Concomitant medications/therapies.
- Vital signs (BP, HR, and RR).
- Body temperature.
- Urine pregnancy test (hCG).
- Clinical laboratory evaluations.
- 12-lead ECG.
- Randomization to treatment.
- AE assessment.
- Sampling for immunogenicity.
- Sampling for DNA.
- Administration of IV study drug or placebo immediately before induction of anesthesia (see Section 6.1 for eligibility based on vital sign criteria).

9.3.2.2 During Surgery

Procedures to be completed during surgery include:

- Vital signs (BP, HR, and RR).
- Concomitant medications/therapies.
- Telemetry.
- Administration of SC study drug or placebo (see Section 6.1 for eligibility based on vital sign criteria).
- Assessment of anesthesia and surgical procedure time.
- AE assessment.
- Plasma sample for TAK-951 PK. The PK sample for the first window (1 to 3 hours after SC administration of study drug; see Table 9.c), may be during surgery or in the postsurgery observational period (Section 9.3.2.3).

9.3.2.3 Postsurgery Observational Period

Procedures to be completed during the postsurgery observational period on Day 1 include:

- Vital signs (BP, HR, and RR)
- Body temperature (at approximately 8 hours post surgery).
- Concomitant medications/therapies.
- 12-lead ECG.
- Telemetry.
- Assessment of nausea.
- Assessment of emetic events.
- AE assessment.
- Plasma samples for TAK-951 PK (see Table 9.c).

9.3.3 Hospital Discharge/Early Termination

Procedures to be completed at hospital discharge/early termination include:

- Vital signs (BP, HR, and RR).
- Body temperature (at approximately 24 hours post surgery).
- Concomitant medications/therapies.
- Clinical laboratory evaluations.
- 12-lead ECG.
- Assessment of nausea.
- Assessment of emetic events (up to 24 hours ± 30 minutes post surgery).
- AE assessment.
- Plasma samples for TAK-951 PK (see Table 9.c and Appendix A).
- Serum sample for immunogenicity.

9.3.4 Follow-up Visit

There will be 1 follow-up visit after hospital discharge, during which the following procedures will be performed and documented:

- Concomitant medications/therapies.
- AE assessment.
- Serum sample for immunogenicity.

For all subjects who received study drug, the investigator must complete the End of Study (e)CRF page.

9.3.5 Poststudy 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.

9.4 Biological Sample Retention and Destruction

In this study, specimens for genome/gene analysis will be collected as described in Section 9.1.13. Details are provided in the study lab manual.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 PTEs

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but before administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

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 PTEs and 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 PTEs or 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.

- PTEs/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses versus signs and symptoms:

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

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or 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 or ECG re-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 or ECG findings 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 a PTE or 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 PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or 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 a PTE/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 a PTE/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 PTEs or AEs:

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

- 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 intensity of AEs/serious PTEs:

- If the subject experiences changes in intensity of an AE/serious PTE, 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 PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as a PTE or an AE. 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 PTEs or AEs 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 medication without manifested side effects are NOT considered PTEs or AEs but instead will be documented on the appropriate form (Dosing Injection or Dosing Intravenous). Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the (e)CRF.

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 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
Torsades de pointes/ventricular fibrillation/ventricular tachycardia	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
COVID-19–related disease	Neuroleptic malignant syndrome/malignant hyperthermia
COVID-19 pneumonia	Spontaneous abortion/stillbirth and fetal death

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.

PTEs that fulfill 1 or more of the aforementioned serious criteria are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.5 AEs of Special Interest

AEs of special interest for TAK-951 include injection site reactions, hypotension, and tachycardia.

These AEs will be monitored by the investigator and sponsor.

10.1.6 Intensity of PTEs and AEs

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to NCI CTCAE v5.0. AEs not listed by the NCI CTCAE will be graded as 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 ADL.
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.

ADL: activities of daily living; AE: adverse event.

10.1.7 Causality of AEs

The relationship of each AE to study drug(s) 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 PTEs and 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 procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

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

10.1.11 Frequency

Episodic AEs/PTE (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

- 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).
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.13 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- 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/PTE 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/PTE state remaining "Not Recovered/Not Resolved."
- Resolved With Sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs are considered as the cause of death.
- Unknown – the course of the AE/PTE 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 PTE and AE Collection Period

Collection of PTEs 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 or until

screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time that the subject is first administered study drug on the day of surgery. Routine collection of AEs will continue until the follow-up visit.

10.2.1.2 PTE and 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 serious PTE 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. Nonserious PTEs, related or unrelated to the study procedure, need not to be followed up for the purposes of the protocol.

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 PTEs and AEs will be documented in the PTE/AE page of the (e)CRF, 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, stop date, and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).
8. Outcome of event.
9. Seriousness.

After discharge and before the 14-day follow-up visit all the patients will be instructed to contact the site immediately in case of an AEs. The site will collect all the follow-up information for proper medical evaluation by the investigator.

10.2.1.3 AEs of Special Interest

AEs of special interest for TAK-951 include injection site reactions, hypotension, and tachycardia.

If an AE of special interest that occurs during the treatment period or the follow-up period is considered to be clinically significant based on the criteria below, it should be recorded on the SAE form. The form should be completed and reported to the pharmacovigilance department within 24 hours.

The investigator should submit the original copy of the SAE form to the sponsor.

AEs of special interest criteria include:

- Laboratory value threshold, if applicable.
- Premature termination for the AE of special interest, if applicable.
- Any other specific criteria.

AEs of special interest should be recorded as AEs in the (e)CRF. 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:

A Takeda SAE form must be completed, in English, and signed by the investigator immediately or within 24 hours of first onset or notification of the event. 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 form should be transmitted within 24 hours 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.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.2.3 Reporting of Abnormal Liver Function Tests

For any subject with ALT ≥3 times the ULN ***AND*** total bilirubin >2 times the ULN ***OR*** international normalized ratio (INR) >1.5 times the ULN for which an alternative etiology has not been found, report the event as an SAE, contact the Medical Monitor and Takeda Trial Clinician within 24 hours, and follow the additional monitoring, evaluation, and follow-up recommendations in Appendix G.

10.2.4 Management of Specific AEs

10.2.4.1 Hypotension

If a subject develops symptoms suggestive of hypotension or postural hypotension, BP should be assessed for evidence of hypotension, which should be managed as per local guidelines, and the medical monitor should be contacted.

10.2.4.2 Injection Site Reactions

If a subject develops a CTCAE Grade 3 (ulceration or necrosis; severe tissue damage, operative intervention need) or 4 (life-threatening consequences; urgent intervention indicated) event, administration of TAK-951 should be discontinued, immediate treatment provided, and the medical monitor contacted.

10.2.4.3 Hypersensitivity

If anaphylaxis or other serious allergic reactions occur, study drug administration should be discontinued immediately and appropriate management initiated (eg, epinephrine, antihistamines, and further immediate care as necessary).

10.2.4.4 Sinus Tachycardia

CTCAE Grade 2 sinus tachycardia (ie, symptomatic; nonurgent medical intervention indicated) with HR ≥120 bpm. Evaluate ECG for abnormalities, manage as per local guidelines, and call the medical monitor immediately.

10.2.4.5 Potential Drug Interaction

Based on the available nonclinical dog CV pharmacology study of concomitant dosing of TAK-951 and propranolol in dogs, a potential risk of synergistic effect on BP when TAK-951 was combined with propranolol has been identified. Caution should be taken if TAK-951 is given with any antihypertensive medication, specifically beta blockers or vasodilating agents. If beta blockers are deemed necessary in an acute care setting as part of standard of care, use of a short-acting, selective beta blocker should be considered. Standard anesthesia protocol should be followed for management of HR and BP changes, and treatment should be based upon underlying etiology.

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, 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. 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 in accordance with local regulations.

11.0 STUDY-SPECIFIC COMMITTEES

11.1 External DMC

An external independent DMC will conduct ongoing reviews of safety data and the results from interim analysis for futility if performed. The DMC will make recommendations to the study team as described in the DMC charter.

Details of the DMC, including meeting frequency, approach to maintaining the study blind through appropriate firewalls, will be captured in the DMC charter before the start of the study.

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 (e)CRFs

Completed (e)CRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply study sites with access to (e)CRFs. Additionally, the contract research organization (CRO) will make available (e)CRF Completion Guidelines that will provide clear details on how to complete the forms. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities.

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 Takeda personnel (or designees) and will be answered by the site.

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

(e)CRFs 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 (e)CRFs. The completed (e)CRFs 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 (e)CRFs, 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 Conference 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 before unblinding of subjects' 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 before unblinding of subjects' 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 to treatment and received both doses of double-blind study drug (ie, ondansetron or matching ondansetron placebo, and TAK-951 or matching TAK-951 placebo) before surgery and during surgery. Subjects will be analyzed according to their randomized treatment, regardless of whether they receive an investigational product that is different from that to which they were randomized.

The Per-protocol Analysis Set (PPAS) will include all subjects who are in the FAS and do not violate the terms of the protocol in a way that would impact the study output significantly. All decisions to exclude subjects for the per-protocol population will be made before the unblinding of the study. Analyses using the PPAS will be provided as a sensitivity analysis.

The Safety Analysis Set will include all subjects who were randomized to treatment and received both doses of double-blind study drug (ie, ondansetron or matching ondansetron placebo, and TAK-951 or matching TAK-951 placebo) before surgery and during surgery. In safety summaries, subjects will be analyzed according to the treatment they actually received.

The PK set will consist of all subjects who receive study drug and have at least 1 evaluable PK sample.

The immunogenicity set will consist of all subjects who receive at least 1 dose of study drug, have an ADA status assessment at baseline, and at least 1 postbaseline sample.

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, Apfel Risk Score, sex, ethnicity, and race). Individual subject demographic and baseline characteristics data will be listed.

13.1.3 Efficacy Analysis

The primary and secondary efficacy analyses and summaries will be based on the FAS. Sensitivity analyses based on the PPAS will also be performed for primary and secondary efficacy endpoints. Unless otherwise stated, all efficacy analyses will be based on estimation approach using a 2-sided CI with an α of 20% and 5% respectively. Formal hypothesis testing will not be performed.

To evaluate the impact of the identified dosing errors at some participating sites, additional sensitivity analyses may be performed in the Safety Analysis Set by the actual treatment received.

Primary Efficacy Analysis: For the primary efficacy endpoint, complete responders 6 hours post surgery in the TAK-951 and ondansetron groups, along with the treatment difference in proportions, will be estimated and the associated 2-sided 80% and 95% CIs calculated. The point estimate of the treatment difference between TAK-951 and ondansetron and the associated CIs will be based on the Cochran-Mantel-Haenszel method, adjusting for the number of Apfel risk factors. In the event that the number of responders or nonresponders in either treatment group is

too small (ie, ≤5), the exact method (eg, Clopper-Pearson CI for proportions in each treatment group and exact unconditional confidence limits for treatment difference) will be performed instead. Subjects who are missing data needed to determine endpoint status will be considered as treatment failures.

Subgroup analyses by the number of simplified Apfel risk factors (3 or 4) and postoperative opioid analgesics usage (yes or no) for the primary endpoint will be performed using the statistical methods used for the primary efficacy analysis. Point estimates and the associated 80% CI and 95% CI for the true treatment difference between TAK-951 and ondansetron will be presented for the subgroups.

Secondary Efficacy Analysis: The binary secondary endpoints include: emesis in the first 6 hours and within 24 hours post surgery, absence of nausea in the first 6 hours and within 24 hours post surgery, requiring rescue therapy for breakthrough PONV within 24 hours postsurgery, and total response within 24 hours post surgery, will be analyzed similarly to the primary efficacy endpoint. The peak nausea VRS score at 30 minutes and 1, 2, 6, and 24 hours after completion of surgery in subjects will be analyzed using a mixed-effect model repeated measures (MMRM). This MMRM model will include treatment, the number of Apfel risk factors, timepoint, and treatment-by-timepoint interaction as fixed effects, and subject as a random effect. Point estimates and the associated 80% CI and 95% CIs for treatment difference between TAK-951 and ondansetron by timepoint will be presented. The time from the end of surgery to the first emetic event endpoints will be analyzed using the Cox proportional hazards model. Point estimate and associated 80% and 95% CIs for the hazard ratio for TAK-951 versus ondansetron will be provided.

Exploratory Efficacy Analysis: The binary exploratory endpoints will be analyzed similarly to the primary efficacy endpoint.

13.1.4 PK Analysis

No formal noncompartmental PK analyses will be performed on concentration-time data. Summary statistics of plasma concentrations will be summarized using the PK set. Individual concentration-time data will be included in listings only.

A population PK and exposure-response analysis for efficacy and safety endpoints may be conducted as deemed necessary by sponsor, and 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 DNA Analysis

The DNA measurements data will be analyzed separately, and a separate report will be prepared.

13.1.6 Immunogenicity Analysis

Immunogenicity will be summarized using the immunogenicity set. Descriptive statistics will be used to summarize subjects in the following categories: ADA negative, ADA positive, low or high ADA titer.

The relationships among immunogenicity status (ADA and ADA titer), PK, and safety may be explored. Further details will be provided in the SAP.

13.1.7 Safety Analysis

Safety data being collected in a double-blinded fashion will be summarized using the Safety Analysis Set and will include AEs, clinical safety laboratory tests, vital signs, ECG parameters, and weight. Subjects who are ineligible to receive the second dose of study drug (ie, TAK-951 or matching TAK-951 placebo) due to failure to meet the vital sign requirements outlined in Section 6.1 be unblinded to the investigator; their safety data collected will be summarized separately.

13.1.7.1 AEs

The definition of treatment-emergent AEs will be provided in the SAP. AEs will be coded using MedDRA and will be summarized by SOC 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.

13.1.7.2 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

The interim safety reviews will be conducted by the external DMC.

An interim analysis for futility based on the primary efficacy endpoint may be conducted based on Bayesian predictive probability after approximately 50 subjects have received both doses of double-blind study drug/matching placebo before surgery and during surgery and then have either completed all study procedures or withdrawn from the study. The purpose of this interim analysis is to assess the mechanism of action of TAK-951 in human subjects. Statistical simulations will be conducted based on the observed interim data to determine the Bayesian predictive probability of achieving certain desired complete response rate at 6 hours after administration of TAK-951 using the FAS. To evaluate the impact of the identified dose errors in investigational product volume at some sites, additional descriptive analyses for primary and selected secondary and/or exploratory efficacy endpoints may be performed for both treatment arms to aid the internal decision-making. There is no plan to evaluate stopping for overwhelming efficacy in this study.

The interim analysis will be performed by a firewalled unblinded reporting team in a manner that maintains the study blind to the investigators, site staff, and study subjects. Given that this is a sponsor-open study, the interim safety and efficacy review results will be presented to the DMC and reviewed by the sponsor but remain blinded to the investigators, site staff, blinding monitoring personnel, and study subjects. The DMC will indicate to the sponsor whether futility criteria have been met.

- Stop the study for futility if the Bayesian predictive probability of achieving a complete response rate at 6 hours of at least 30% meets the prespecified stopping rule for futility (futility is nonbinding).

Exploratory data-driven analysis may be requested by the sponsor to identify safety concerns and/or efficacy of TAK-951 in subjects. The interim analysis may be used by the sponsor to assess the numbers of subjects that will be replaced.

Complete details related to the unblinding and analysis of the interim futility evaluation and interim safety and efficacy reviews will be described in the SAP, data access management plan, and in the DMC charter.

Other additional interim analysis of safety and/or efficacy may be conducted for sponsor internal decision-making and would be defined in the SAP.

13.3 Determination of Sample Size

The sample size was calculated based on primary efficacy analysis (ie, estimation of treatment difference with respect to the primary efficacy endpoint). Assuming true complete response rates at 6 hours of 60% and 80% in the ondansetron and TAK-951 groups, respectively, and given approximately 50 subjects per treatment group, the half width of a 2-sided 80% CI and a 2-sided 95% CI for treatment difference between TAK-951 and ondansetron in primary efficacy endpoint complete response rate at 6 hours will be approximately 11.5% and 17.5%, respectively, based on CIs using the normal approximation for the binomial distribution. This level of precision with the chosen sample size was considered acceptable for the statistical objective of this trial.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 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 (e)CRFs. Source documents are defined as original documents, data, and records. The investigator and the study site guarantee access to source documents by the sponsor or its designee (CRO) and by the IRB. In the event a monitor cannot visit the site in a timely manner, alternative monitoring approaches, such as remote source verification or telephone contact may be used to ensure data quality and integrity and maintain patient safety.

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, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of (e)CRFs and associated source documents. It is important that the investigator and other study personnel are available during 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, 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, 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.

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. If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 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 D. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRBs

The IRBs must be constituted according to the applicable state, federal, and 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. If any member of the IRB 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 for the protocol's review and approval. This protocol, the IB, 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 for approval. The IRB'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 (ie, before shipment of the sponsor-supplied drug or study specific activity). The IRB 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/notify site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the study. Until the site receives drug/notification, no protocol activities, including screening, may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB 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, and submission of the investigator's final status report to IRB. All IRB 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 and sponsor.

15.2 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 (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and 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 if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor before use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject.

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.

The subject, or the subject's legally acceptable representative, 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 determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject at the time of consent and prior to the subject entering into the study. The subject 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 (if applicable) at the time of consent and before the subject enters 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 (if applicable), 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 (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative 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 should receive a copy of the revised informed consent form.

Subjects who consented and provided a DNA sample for analysis can withdraw their consent and request disposal of a stored sample at any time before analysis. The sponsor must be notified of consent withdrawal.

15.3 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 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, Food and Drug Administration [FDA], Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs 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 15.2).

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 [e]CRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 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.

15.4.2 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, Takeda 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 Americas 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.

15.4.3 Clinical Trial Results Disclosure

Takeda 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.

15.5 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.

16.0 REFERENCES

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17.0 APPENDICES

Appendix A Schedule of Study Procedures

	Day -28 to 1		Day 1			Day 14±2
	Screening	**Before Surgery**	**During Surgery**	**Postsurgery Observational Period**	**Hospital Discharge /ET**	**Follow-up Visit**
Informed consent	X					
Inclusion/exclusion criteria	X	X				
Demographics and medical history	X	X				
Medication history	X	X				
Concomitant medications/therapies	X	X	X	X	X	X
Simplified Apfel Risk Score	X					
Physical examination	X					
Height, weight, BMI	X					
Vital signs (HR, BP, and RR) [a]	X	X	X	X	X	
Body temperature [a]		X		X	X	
Serum or urine pregnancy test (hCG) [b]	X	X				
FSH [b]	X					
HBsAg and anti-HCV	X					
Clinical laboratory evaluations (hematology and serum chemistry) [c]	X	X			X	
12-lead ECG [d]	X	X		X	X	
Telemetry [d]			X	X		
Randomization to treatment		X				
Administration of study drug for prophylaxis [a, e]		X	X			
Assessment of anesthesia and surgical procedure time [f]			X			
Assessment of nausea [g]				X	X	
Assessment of emetic events [h]				X	X	
AE assessment	X	X	X	X	X	X

	Day -28 to 1		Day 1			Day 14±2
	Screening	**Before Surgery**	**During Surgery**	**Postsurgery Observational Period**	**Hospital Discharge /ET**	**Follow-up Visit**
Plasma sample for TAK-951 PK [i]			X	X	X [i]	
Buccal epithelial cells sample for DNA		X				
Serum sample for immunogenicity [j]		X			X	X

BMI: body mass index; BP: blood pressure; ECG: electrocardiogram; (e)CRF: electronic case report form; ET: early termination; FSH: follicle-stimulating hormone; [redacted] HBsAg: hepatitis B surface antigen; hCG: human chorionic gonadotropin; HCV: hepatitis C virus; HR: heart rate; HRQOL: health-related quality of life; IV: intravenous; PACU: postanesthesia care unit; PK: pharmacokinetic; RR: respiratory rate; SC: subcutaneous.

[a] Vital signs (HR, BP) will be collected in duplicate and averaged at all time points. Vital signs will be collected at screening, before dosing with ondansetron or matching ondansetron placebo (ie, before surgery), immediately before dosing with TAK-951 or matching TAK-591 placebo (ie, during surgery), and at the end of surgery (ie, wound closure) and recorded in the (e)CRF. See Section 6.1 for eligibility to receive study drug/matching placebo based on predefined vital sign criteria for cardiovascular stability. During surgery, vital signs will be monitored continuously for safety purposes. RR will also be collected at these same timepoints. Vital signs will also be collected in the immediate postsurgical period, see Section 9.1.5 for additional postsurgical details. Body temperature will also be taken before surgery and approximately 8 and 24 hours postsurgery.

[b] Women of child-bearing potential must be confirmed negative for pregnancy by serum hCG at screening and by urine hCG the day of surgery, before dosing. See Section 9.1.10.3 for details.

[c] Clinical laboratory evaluations (hematology and serum chemistry) do not need to be repeated on the day of surgery if the screening assessments were performed within 2 weeks, did not show any clinically relevant abnormalities, and were discussed with the medical monitor.

[d] ECGs will be monitored continuously by telemetry during surgery and for the first 24 hours post surgery. A standard 12-lead ECG will be performed at screening, on Day 1 before surgery, on admittance to the PACU (approximately 1 hour post dose), and before hospital discharge or as needed if symptoms or abnormalities in the telemetry. See Section 9.1.12 for details.

[e] TAK-951 or TAK-951 placebo will be administered approximately 30 to 45 minutes before end of surgery (wound closure) in eligible subjects (see Section 6.1). Ondansetron 4 mg IV or ondansetron IV placebo will be administered immediately before induction of anesthesia.

[f] Anesthesia time will be assessed from anesthesia induction until extubation. Surgery time will be defined as the time from incision to the end of wound closure.

[g] The presence and severity of subject-reported nausea anytime during the 24-hour follow-up period will be recorded by the site staff. Nausea will also be assessed by direct questioning by the site staff at 30 minutes and 1, 2, 6, and 24 hours post surgery, and results will be recorded (see Appendix B).

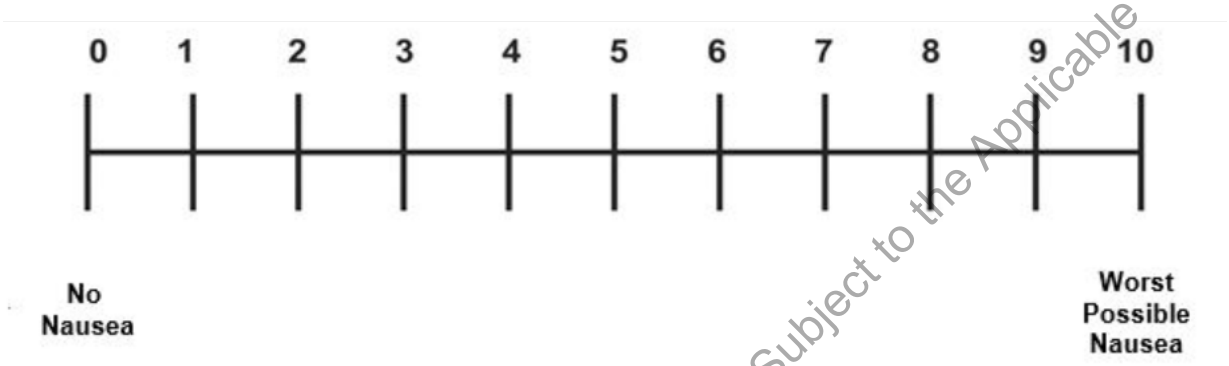
[h] Time and number of emetic events (vomiting and/or retching) will be noted (see Appendix C). Assessment of emetic events should occur during postsurgical observational period up to 24 hours ±30 minutes postsurgery.

[i] PK samples should be collected according to sampling time windows after dosing presented in Table 9.c. The fifth PK sample during the 22- to 26-hour window may coincide with hospital discharge.

[j] Sample for immunogenicity is collected before surgery (baseline), at discharge/early termination, and at the follow-up visit.

Appendix B Verbal Rating Scale (VRS) for Nausea

Please rate the severity of your nausea (desire to vomit without the presence of expulsive muscular movements) using the scale below, where 0 represents "no nausea" and 10 represents the "worst nausea possible."



Date and Time of assessment:

Appendix C Emetic Events

Please contact the site staff immediately for assistance in case of emesis.

Emesis is defined as vomiting (the forceful discharge of even the smallest amount of stomach contents) or retching/dry-heaves (the same muscular movements as vomiting but without expulsion of stomach contents).

To be filled out by the subject or site staff.

Date and time of emetic event(s): (mark each check box as applicable)

□ Vomiting

□ Retching

Appendix D 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 before 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 Code of Federal Regulations (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. Obtain valid informed consent from 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 (e)CRFs, 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 E Elements of the Subject Informed Consent

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

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 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 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 pharmacogenomic 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. Regular pregnancy tests will be performed throughout the study for all female subjects of childbearing potential. 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 F 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 G Guidance on Liver Test Abnormality Monitoring, Evaluation, and Follow-up

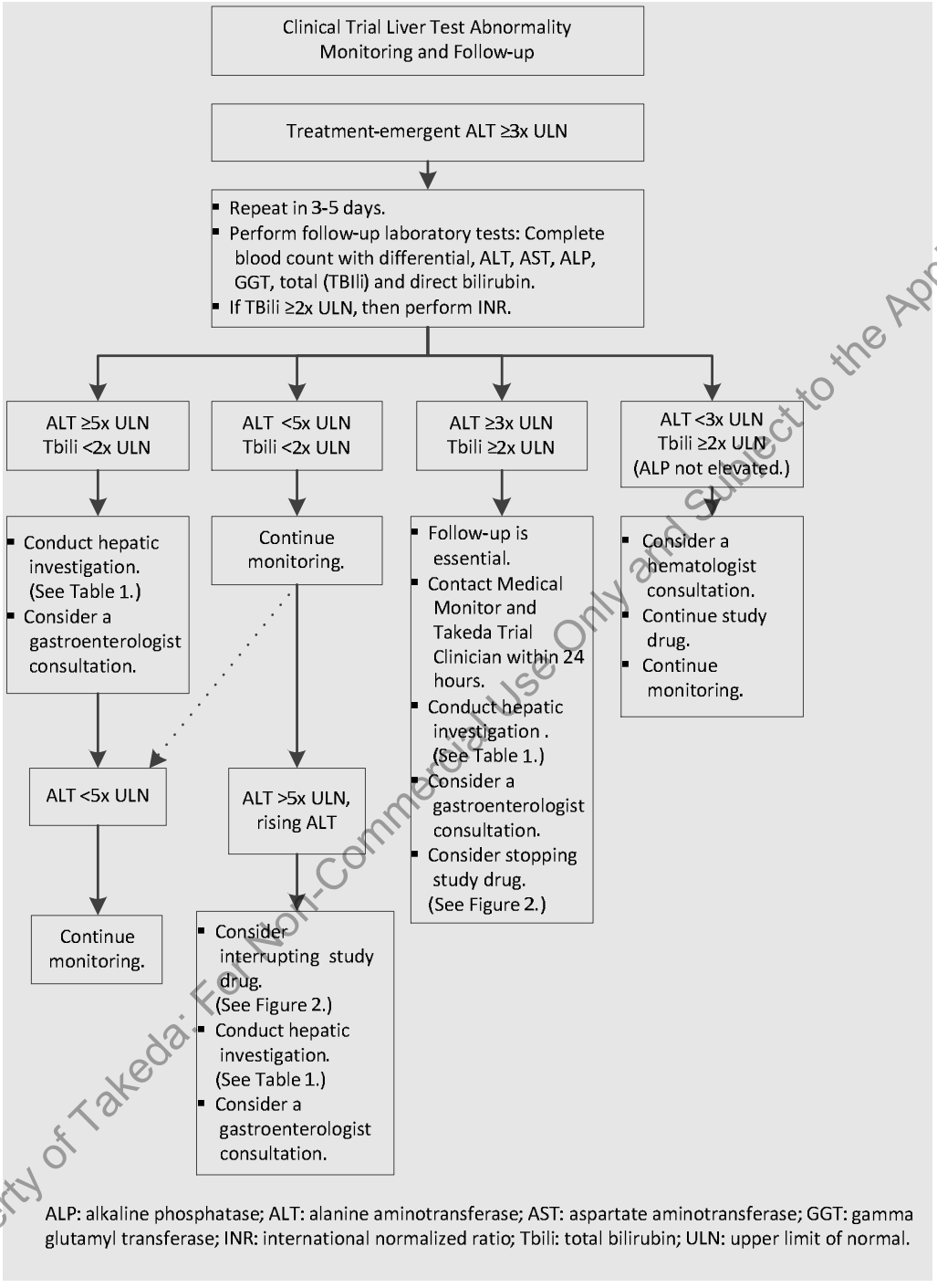
Investigators must be vigilant for abnormal liver test results in subjects during the clinical trial. Transient fluctuations in serum aminotransferases occur commonly in clinical trial subjects, but it is crucial that the investigator identifies and evaluates subjects with possible hepatic injury. This guidance is intended to aid investigations of abnormal liver test results in clinical trial subjects who had no known liver disease and had either normal or near normal baseline liver test results (ie, ALT <2 times the ULN, total bilirubin <1.5 times the ULN, and alkaline phosphatase <1.5 times the ULN) at the time of enrollment.

In evaluating trial subjects with abnormal liver test results, the investigator should perform follow-up laboratory tests to confirm the abnormal test results and monitor the subject. If the abnormal liver test results are confirmed, then the subject should be monitored and, if necessary, additional diagnostic tests should be performed as shown in Figure 17.a. Suggested hepatic investigations are listed in Table 17.a. Criteria for considering discontinuation of study drug are shown in Figure 17.b.

Subjects with Combined Elevations in Aminotransferase and Bilirubin

If a subject has elevated ALT ≥3 times the ULN with concurrent elevated total bilirubin >2 times the ULN *or* elevated INR >1.5, the investigator must contact the medical monitor and Takeda trial clinician within 24 hours. Hepatic investigations as suggested in Table 17.a should be initiated. Any event of elevated ALT ≥3 times the ULN with concurrent elevated total bilirubin >2 times the ULN *or* elevated INR >1.5 for which an alternative etiology has not been identified must be reported as an SAE.

Figure 17.a Liver Test Abnormality Monitoring and Follow-up



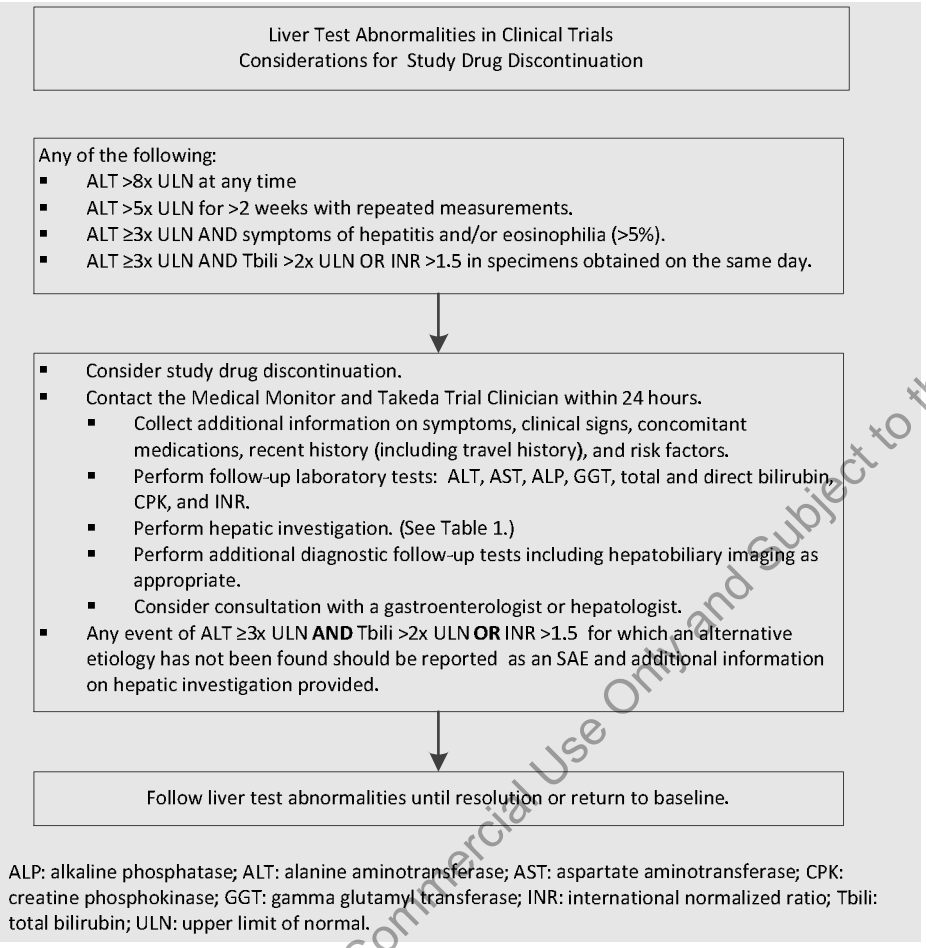
ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma glutamyl transferase; INR: international normalized ratio; Tbili: total bilirubin; ULN: upper limit of normal.

Table 17.a Hepatic Investigation

Medical history	• Concomitant medications (including over-the-counter medications, such as acetaminophen and herbal supplements). • Medical conditions (eg, ischemia, hypotension, severe hypoxemia, congestive heart failure, sepsis). • Alcohol intake. • Hepatobiliary disorder. • Previous liver disease or metabolic syndrome (eg, obesity, insulin resistance, diabetes, or dyslipidemia). • Travel history.
Physical examination (symptoms, signs, and laboratory results)	• General malaise, fatigue, nausea, or vomiting. • Right upper quadrant pain or tenderness, fever, jaundice, rash. • Eosinophilia >5%.
Hepatic/hepatobiliary imaging	• Perform as appropriate (eg, abdominal ultrasound, computed tomography, magnetic resonance imaging, or other hepatobiliary imaging).
Viral hepatitis serology	• Hepatitis A antibody (total and IgM). • Hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody (IgM), hepatitis C antibodies. • Hepatitis E (IgG and IgM). • Consider PCR for hepatitis B, C, and E. • Consider Epstein-Barr virus serology (viral capsid antigen, nuclear antigen, early antigen). • Consider cytomegalovirus serology (IgG and IgM).
Autoimmune hepatitis serology	• Antinuclear antibody. • Anti-smooth muscle antibody. • Anti-liver-kidney microsomal antibody.

IgG: immunoglobulin G; IgM: immunoglobulin M; PCR: polymerase chain reaction.

Figure 17.b Liver Test Abnormalities: Considerations for Study Drug Discontinuation



ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CPK: creatine phosphokinase; GGT: gamma glutamyltransferase; INR: international normalized ratio; Tbili: total bilirubin; ULN: upper limit of normal.

Appendix H Protocol History

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
13 September 2021	Amendment 4	Substantial	Global
28 July 2021	Amendment 3	Substantial	Global
11 January 2021	Amendment 2	Substantial	Global
22 September 2020	Amendment 1	Substantial	Global
23 June 2020	Initial protocol	Not applicable	Global

Protocol Amendment 3 Summary of Changes

This document describes changes from the study protocol incorporating Amendment No. 3. The primary reason for this amendment is to clarify the scope of interim analysis due to dosing errors in investigational product volume identified at some study sites. Given dosing errors, the study is modified to sponsor-open to inform decision-making on the interim efficacy analysis and for oversight of the study. The study will remain blinded to investigators, study site staff, and subjects.

Associated updates to the efficacy analysis, interim analysis, criteria for discontinuation, and study drug blind maintenance have also been made.

Changes in Amendment 3:

1. The protocol title was updated because the study is modified to sponsor-open.
2. Added language to clarify that a maximum of 160 subjects will be randomized in this study and that the sample size may be adjusted to potentially increase the sample size to allow approximately 100 subjects who have received both doses of double-blind study drug/matching placebo dosed per protocol.
3. Updated clinical background to include final data from first-in-human (FIH) study TAK-951-1001.
4. Provided additional exploratory objective/endpoints.
5. Added language to modify the study to sponsor-open.
6. The description of the interim analysis was modified as described above.
7. Inclusion criterion 5 was updated for clarification and consistency between Section 2.0 Study Summary and Section 7.0 Selection and Discontinuation.
8. Inclusion criterion 6 was updated to clarify inclusion of subjects of nonchildbearing potential.
9. Language added to include additional sensitivity analysis.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Changes in Amendment 3:

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Title page Section 2.0 Study Summary	Wording "sponsor-open" was added to the protocol title.	The protocol title was updated because the study has been modified to sponsor-open.
Section 2.0 Study Summary	Added language to clarify the sample size.	To clarify that a maximum of 160 subjects will be randomized in this study and that the sample size will allow approximately 100 subjects who have received both doses of double-blind study drug/matching placebo dosed per protocol. Provided flexibility in number of subjects dosed with ondansetron 4 mg to allow subjects not dosed per protocol to be replaced with 1:1 randomization.
Section 4.1.2 Clinical Background	Updated to include final data from FIH study TAK-951-1001.	To align with Investigator's Brochure (IB) Edition 05 update.
Section 4.3 Benefit/Risk Profile	Updated to include final data from study TAK-951-1001 and modified the language for dose dependence of vital sign changes.	To align with IB Edition 05 update.
Section 2.0 Study Summary Section 5.1.3 Exploratory Objective Section 5.2.3 Exploratory Endpoints	Added exploratory objective/ endpoints.	To clarify that exploratory analysis will be conducted and to list those exploratory objective/endpoints.
Section 2.0 Study Summary Section 6.1 Study Design	Changed the sentence "All subjects in the study will be required to receive general anesthesia, expected to last at least 1 hour from induction of anesthesia to wound closure" to "Only subjects undergoing elective surgery under general anesthesia that is expected to last at least 1 hour from induction of anesthesia to wound closure are eligible to participate in the study."	To clarify that this description in Sections 2.0 and 6.1 is consistent with inclusion criterion #2 as described in Section 7.2.
Section 2.0 Study Summary Section 6.1 Study Design Section 8.4 Study Drug Blind Maintenance	Added language to modify the study to sponsor-open.	To clarify that given dosing errors, the study is modified to sponsor-open to inform decision-making on the interim efficacy analysis and for oversight of the study. The study will remain blinded to investigators, study site staff, and subjects.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 2.0 Study Summary Section 6.1 Study Design	Addition of wording "if utilized."	To clarify that anesthesia reversal, if utilized, will be accomplished with neostigmine and glycopyrrolate only.
Section 2.0 Study Summary Section 6.1 Study Design Section 13.2 Interim Analysis and Criteria for Early Termination	Language was updated for interim analysis.	To clarify that given the identified dose errors in investigational product volume at some sites, additional descriptive analysis for primary and selected secondary and/or exploratory efficacy endpoints may be performed for both treatment arms to aid the internal decision-making. Other additional interim analysis of safety and/or efficacy may be conducted and would be defined in the statistical analysis plan (SAP).
Section 6.2 Justification for Study Design, Dose, and Endpoints	The following text was removed: "A total of 128 subjects (96 in the SRD part and 32 in MRD part) had been enrolled in the TAK-951-1001 FIH study at the time this protocol amendment was written. The SRD data from the study have been unblinded to prepare a regulatory response and are summarized in Section 4.1.2. The MRD part of the study has completed in the clinic, but data remain blinded and the database has not been locked; a brief overview of blinded data is provided in Section 4.1.2."	Removed TAK-951-1001 FIH study data from this section on study design as it is no longer relevant to this section, and prior protocol had preliminary data from the study, which was not complete. Overview of updated complete final data from this study is provided elsewhere in the protocol (Section 4.1.2).
Section 7.1 Inclusion Criteria	Term "planned" was added to inclusion criterion 5.	Update was made for clarification and consistency between Section 2.0 Study Summary and Section 7.0 Selection and Discontinuation.
Section 2.0 Study Summary Section 7.1 Inclusion Criteria	Inclusion criterion 6 was updated to include subjects of nonchildbearing potential.	To clarify intent that subjects of nonchildbearing potential are also eligible for the study.
Section 7.8 Procedures for Discontinuation or Withdrawal of a Subject	Language added to criteria for replacing subjects.	To clarify that subjects may be replaced as appropriate based on significant protocol deviations.

Protocol Amendment 3		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 9.1.13.1 Collection of Blood/Plasma/Serum	Clarification added that plasma samples for pharmacokinetic (PK) analyses will be collected as per Table 9c. The following sentence was removed: "However, only plasma samples from subjects receiving TAK-951 will be analyzed." The remaining text was revised to explain that plasma samples may be analyzed for ondansetron concentration, and the results may be reported separately.	To clarify the intent for PK analysis.
Section 2.0 Study Summary Section 13.1.3 Efficacy Analysis	Language added to include additional sensitivity analysis.	To clarify that additional sensitivity analysis to evaluate the dosing error may be performed for final analysis.
Section 13.1.3 Efficacy Analysis	Exploratory efficacy analysis added.	To clarify that exploratory efficacy analysis (binary exploratory endpoints) will be performed.
Section 13.1.4 PK Analysis	Text updated to state that exposure-response analysis for efficacy and safety endpoints may be conducted as deemed necessary by sponsor.	To increase the flexibility of population-level analyses.
Secion 14.1 Monitoring Visits	Text "due to COVID-19 pandemic" was removed.	To expand to allow remote source data verification in other settings as appropriate.

Protocol Amendment 2 Summary of Changes

This document describes the changes from the protocol incorporating Amendment No. 2. The primary reason for this amendment is to clarify eligibility prior to each study drug administration based on vital sign monitoring after randomization (ie, predefined heart rate [HR] and blood pressure [BP] criteria must be met prior to induction of anesthesia before surgery) to receive ondansetron or matching ondansetron placebo, and prior to wound closure (ie, during surgery) to receive TAK-951 or matching TAK-951 placebo.

Associated updates to the exclusion criteria, criteria for discontinuation, defined statistical analysis sets, and interim analysis have also been made.

Changes in Amendment 2:

1. Updated the Responsible Medical Officer and approvers in Section 1.0.

2. Clarified and updated the vital sign criteria for study drug eligibility and the monitoring procedures to implement these criteria.
3. Provided criteria for discontinuation from the study based on vital sign requirements for eligibility to receive study drug.
4. Added language to replace subjects who are discontinued due to vital sign criteria for study drug eligibility. Added unblinding procedures for subjects who are ineligible to receive study drug.
5. Clarified the timing of the interim analysis.
6. Revised and clarified an exclusion criterion that applies vital sign requirements to both enrollment (screening) and randomization.
7. Updated the definitions of the Full Analysis Set (FAS) and the Safety Analysis Set.
8. Removed the modified intent-to-treat (mITT) Analysis Set.
9. Updated the clinical background and justification for study design to include new data from the first in-human (FIH) clinical study TAK-951-1001.
10. Added clarification for efficacy and safety analyses regarding subjects who do not receive the second dose of study drug.
11. Updated the list of study mitigations for risk management to align with the clarifications to the vital sign criteria for study drug eligibility.
12. Clarified the vital sign measurement interval from a nonclinical study of TAK-951 and sevoflurane administration.
13. Added risk for potential QTc prolongation with rescue therapy for postoperative nausea and vomiting (PONV).

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
1.	Section 1.1 Contacts Section 1.2 Approval	Updated the Responsible Medical Officer and signatories.	A new clinical lead has been assigned to the study.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
2.	Section 2.0 Study Summary Section 6.1 Study Design Section 9.1.5 Vital Sign Procedure Section 9.3.2 Day 1	Text added clarifying Day 1 study procedures and eligibility to receive both doses of study drug (ie, ondansetron or matching ondansetron placebo, and TAK-951 or matching TAK-951 placebo) based on BP and HR requirements. Figures illustrating the procedure for determining eligibility to receive TAK-951 or matching TAK-951 placebo based on BP and HR criteria have also been added to Section 6.1.	As TAK-951 and ondansetron should not be given to subjects with signs of cardiovascular instability, clarification on vital sign monitoring and administration of study drug has been added. The decision trees for BP and HR (Figure 6.a and Figure 6.b, respectively) provide further clarity to site personnel.
3.	Section 2.0 Study Summary Section 8.5 Unblinding Procedure	Language added for unblinding by the investigator when a subject is ineligible to receive the second dose of study drug (ie, TAK-951 or matching TAK-951 placebo) due to failure to meet vital sign requirements. A decision tree (Figure 8.a) for unblinding and whether or not the subject will be discontinued from the study was also added.	Subjects who do not receive the second dose of study drug due to failure to meet the vital sign requirements will be excluded from efficacy analyses (definition of FAS). To determine whether or not the subject will be discontinued from the study, the blind must be broken by the investigator.
4.	Section 2.0 Study Summary Section 6.1 Study Design Section 7.7 Criteria for Discontinuation or Withdrawal of a Subject Section 7.8 Procedures for Discontinuation or Withdrawal of a Subject	Language added to criteria for discontinuation: All subjects who do not receive the first dose of study drug due to failure to meet the vital sign criteria, and all subjects who receive placebo as the first dose but do not receive the second dose of study drug (ie, TAK-951) due to failure to meet the vital sign criteria will be discontinued from the study. Subjects who receive ondansetron as the first dose but do not receive the second dose of study drug due to failure to meet the vital sign criteria will remain in the study per-protocol until completion or withdrawal from the study, but will be excluded from the FAS.	Subjects who do not receive the first or second dose of study drug due to failure to meet the vital sign requirements will be excluded from efficacy analyses (definition of FAS). These subjects will be replaced so efficacy analyses may be conducted on approximately 100 subjects who have received both doses of double-blind study drug/matching placebo. To determine whether or not the subject will be discontinued from the study, the blind must be broken by the investigator (see above).

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
5.	Section 2.0 Study Summary Section 6.1 Study Design Section 6.3.1 Criteria for Premature Termination or Suspension of the Study Section 13.2 Interim Analysis and Criteria for Early Termination	Clarification that the interim analysis will be performed when approximately 50 subjects have received both doses of study drug (ie, ondansetron or matching ondansetron placebo, and TAK-951 or matching TAK-951 placebo) and have either completed or withdrawn from the study. Added that futility will be nonbinding.	Subjects who are ineligible to receive the second dose of study drug (ie, TAK-951 or matching TAK-951 placebo) due to failure to meet vital sign requirements will be unblinded to the investigator and therefore excluded from efficacy analyses (definition of FAS), including the interim analysis.
6.	Section 2.0 Study Summary Section 7.2 Exclusion Criteria	Revised and clarified exclusion criterion 14.	BP and HR exclusion criteria for eligibility to receive study drug has been updated for clarity (safety reasons mentioned above). This criterion now applies to eligibility for enrollment (screening) in addition to eligibility for randomization.
7.	Section 2.0 Study Summary Section 13.1.1 Analysis Sets	Analysis sets updated to clarify that the FAS and Safety Analysis Set will include only subjects who receive both doses of study drug (ie, ondansetron or matching ondansetron placebo, and TAK-951 or matching TAK-951 placebo), before surgery and during surgery. The mITT Analysis Set has been removed.	The FAS and Safety Analysis Set were updated to accommodate the changes made above, which eliminated the need for the mITT Analysis Set.
8.	Section 2.0 Study Summary Section 13.1.7 Safety Analysis	Language was added for the safety analyses of subjects who are ineligible to receive the second dose of study drug (ie, TAK-951 or matching TAK-951 placebo) due to failure to meet vital sign requirements. These subjects will be unblinded to the investigator. Subjects who received ondansetron as their first dose of study drug will remain in the study per-protocol until completion or withdrawal from the study; however, their safety data will be summarized separately.	To determine whether or not a subject who does not receive the second dose of study drug will be discontinued or remain in the study, the blind must be broken by the investigator. Once the blind is broken, subjects will not be included in the Safety Analysis Set.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
9.	Section 4.1.2 Clinical Background 6.2 Justification for Study Design, Dose, and Endpoints	Blinded safety overview from Part 3 (multiple rising dose [MRD]) of Study TAK-951-1001 added.	Part 3 of Study TAK-951-1001 has recently completed, and blinded safety results have been included in this protocol amendment.
10.	Section 4.3 Benefit/Risk Profile	Updated list of study mitigations for risk management.	Clarification on vital sign monitoring and study drug eligibility have been added for the reasons mentioned above.
11.	Section 6.3.1 Criteria for Premature Termination or Suspension of the Study	Updated list of criteria for premature termination or suspension of the study to include substantial vital sign changes (including SAEs) considered by the investigator and/or sponsor to be related to TAK-951 study drug. Clarification on these postoperative BP and HR measurements were also added regarding when and how these SAEs should be reported.	For the reasons mentioned above, vital sign changes deemed related to TAK-951 that are potentially harmful to study subjects could result in termination of the study.
12.	Section 7.3.1 Synergistic Effect When Combined With Propranolol and Sevoflurane	Clarification added regarding the BP and HR effects of TAK-951 in combination with propranolol or sevoflurane in dogs.	Based on the global vital sign clarifications (see safety reasons above), details regarding the vital sign interval in studies with dogs have been added. Unlike the 6-hour interval between vital sign measurements from 8 to 24 hours postsurgery in this study, vital signs were collected every 4 hours in the referenced study in dogs.
13.	Section 7.5 Rescue Therapy	Risk for potential QTc prolongation added.	When selecting rescue treatment for PONV, the potential for QTc prolongation should be considered.
14.	Section 9.3.2 Day 1	Clarification added that plasma samples for PK analyses can be collected during surgery or in the postsurgery observational period for the first window (1 to 3 hours after subcutaneous administration of study drug). Reference was also made to Table 9.c for clarity on PK sampling.	Update was made for clarification, to avoid site confusion.

Protocol Amendment 2			
Summary of Changes Since the Last Version of the Approved Protocol			
Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
	Location	***Description***	***Rationale***
15.	Appendix A Schedule of Study Procedures	Clarification on vital sign measurements prior to administration of both doses of study drug/matching placebo.	Updated to match changes made elsewhere to the protocol.
16.	Appendix H Protocol History	Protocol history appendix, detailing updates in Protocol TAK-951-2001 Amendment 1.	Standard operating procedures of the sponsor require a protocol history appendix for all amendments beyond Amendment 1.

Protocol Amendment 1 Summary of Changes

This section describes the changes from the protocol incorporating Amendment No. 1. Results from completed nonclinical studies were added to the background.

Information and an exclusion criterion with beta blockers were added, given the hypothesized synergistic effects of these drugs with TAK-951.

Changes in Amendment 1:

1. Updated the approvers in Section 1.2.
2. Updated nonclinical background with new nonclinical data.
3. Updated clinical background to include new data from first-in-human (FIH) study.
4. Revised benefit/risk profile to include new nonclinical and clinical safety data.
5. Added secondary endpoints and analyses for absence of nausea.
6. Removed physical examination from secondary endpoints.
7. Clarified criteria for premature termination of the study.
8. Added an exclusion criteria for subjects who may be allergic to rescue therapy.
9. Added an exclusion criteria for subjects on antihypertensive medications.
10. Modified exclusion criteria to exclude subjects with active hepatitis B.
11. Added new section 7.3 Potential Drug Interactions, Section 7.3.1 Synergistic Effect When Combined With Propranolol and Sevoflurane.
12. Added Section 7.5 for Rescue Therapy.
13. Revised parameters in vital sign monitoring procedures.

14. Clarified that subjects who are hepatitis B surface antigen (HBsAg)-positive are excluded from the study.
15. Clarified that urinalysis sample is for pregnancy testing only.
16. Modified clinical term for nonhormonal method of contraception.
17. Clarified that electrocardiogram (ECG) tracings are collected in the clinical database for all subjects, but only submitted to the sponsor in the event of serious adverse events (SAEs).
18. Added section for more information on potential drug interactions.
19. Clarified when Data Monitoring Committee (DMC) review will be conducted.
20. Updated definition of Full Analysis Set (FAS).
21. Added language in case sites are affected by the coronavirus disease 2019 (COVID-19) pandemic.

In this amendment, minor grammatical, editorial, formatting, and administrative changes not affecting the conduct of the study are included for clarification and administrative purposes only.

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 1.2 Approval	Updated the signatories.	A new clinical lead and clinical pharmacology lead has been assigned to the study.
Section 4.1.1 Nonclinical Background	Revised Section 4.1.1 with new nonclinical data provided in the Investigator's Brochure (IB) update.	To align with IB Edition 04 update.
Section 4.1.2 Clinical Background	Revised Section 4.1.2 with new data from FIH study.	To align with IB Edition 04 update.
Section 4.3 Benefit/Risk Profile	Added data on concomitant dosing.	Given the hypothesized mechanism of vasodilation leading to decreased blood pressure (BP) and increased heart rate (HR), there is potential to worsen hypotension with administration of these medications.

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 5.2.2 Secondary Endpoints Section 2.0 Study Summary	Added endpoints for absence of nausea in the first 6 hours and within 24 hours postsurgery. Removed physical examinations as a secondary endpoint.	Added absence of nausea endpoints to include these assessments based on agency feedback. Physical examination should not be listed as an individual secondary endpoint. Worsening of physical findings will be encompassed by reported adverse events, which are a secondary endpoint and detailed analysis will be performed.
Section 6.3.1 Criteria for Premature Termination of Suspension of the Study	Modified the HR criteria for premature termination of the study.	Clarified that >30% change in BP and HR was intended to be used as stopping criteria during the operative period (while patients were under sedation) as recommended previously by expert consultants. Also clarified that reference time point of comparison for those changes should be the vital signs obtained during the operative period immediately before study drug (TAK 951/matching placebo) is given. Clarified the reference time points of vital sign comparisons for the >50% stopping rule.
Section 7.2 Exclusion Criteria Section 2.0 Study Summary	Added exclusion criteria for subjects who may be allergic to rescue therapy.	To exclude subjects who may have an allergy or contraindication to the recommended and available rescue therapy.
Section 7.2 Exclusion Criteria Section 2.0 Study Summary	Added exclusion criteria for subjects who are unable to discontinue antihypertensives perioperatively before surgery, including beta blockers. Updated exclusion criteria language for hepatitis B infection.	Given hypothesized mechanism of vasodilation leading to decreased BP and increased HR, there is potential to worsen hypotension with administration of these medications. To exclude subjects with active hepatitis B (HBsAg positive).
Section 7.3 Potential Drug Interactions, 7.3.1 Synergistic Effect When Combined With Propranolol and Sevoflurane (new section)	Added new section to describe the potential for a synergistic effect of TAK-951 with beta blockers.	Given hypothesized mechanism of vasodilation leading to decreased BP and increased HR, there is potential to worsen hypotension with administration of these medications.

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 7.5 Rescue Therapy	Added section to clarify recommendations for rescue therapy.	Added section to clarify recommendations for rescue therapy (ie, treatment of nausea and vomiting in the postoperative period) per Agency feedback.
Section 9.1.5 Vital Sign Procedure Section 9.3.1 Screening Section 9.3.2 Day 1 Section 9.3.3 Hospital Discharge/Early Termination Appendix A Schedule of Study Procedures	Added respiratory rate (RR) and body temperature to the list of vital signs measured.	Given the potential perioperative effects of anesthesia and surgery on RR and body temperature, these parameters will be added as safety assessments.
Section 9.1.9, Table 9.a Clinical Laboratory Tests Section 9.3.1 Screening Appendix A Schedule of Study Procedures	Removed hepatitis B core antibody to align with updated exclusion criteria.	To align with exclusion criteria that subjects with active hepatitis B will be excluded from the study.
Section 9.1.9 Procedures for Clinical Laboratory Samples	Added language to clarify that urinalysis sample is for human chorionic gonadotropin (hCG) testing only.	To clarify that urinalysis is for pregnancy testing only.
Section 9.1.10.3 Definitions and Procedures for Contraception and Pregnancy Avoidance	Changed the term “bilateral tubal occlusion” to “bilateral tubal ligation.”	To clarify the correct clinical terminology for highly effective method of contraception should be listed as bilateral tubal ligation and not occlusion.
Section 9.1.12 ECG and Telemetry Procedure	Modified sentence regarding submitting the ECG tracings to the sponsor.	To clarify that ECG tracings are collected in the clinical database for all subjects but only submitted to the sponsor in the event of SAEs. All tracings will be available as a source document for review and verification by the sponsor.
Section 10.2.4.5 Potential Drug Interaction (new section)	Added new section to describe potential drug interactions with vasodilating agents.	Given hypothesized mechanism of vasodilation leading to decreased BP and increased HR, there is potential to worsen hypotension with administration of these medications.
Section 11.1 External DMC	Modified language to clarify when DMC review will be conducted.	To clarify the timing of safety review and interim analysis.

Protocol Amendment 1		
Summary of Changes Since the Last Version of the Approved Protocol		
Sections Affected by Change	**Description of Each Change and Rationale**	
Location	***Description***	***Rationale***
Section 13.1.1 Analysis Sets	Updated definition of FAS.	Updated definition of FAS to "all subjects who were randomized to treatment," following the intent-to-treat principle.
Section 14.1 Monitoring Visits	Added language to justify alternative monitoring methods in case of monitoring interruptions due to the pandemic.	To add language in the case sites are affected by COVID-19 pandemic.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	15-Sep-2021 16:42 UTC
	Clinical Pharmacology Approval	15-Sep-2021 16:45 UTC
	Clinical Science Approval	15-Sep-2021 20:08 UTC
	Pharmacovigilance Approval	16-Sep-2021 04:37 UTC