Statistical Analysis Plan

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

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: TAK-951-2001

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

PHASE 2

Version**:** 5

Date**:** 25 February 2022

Prepared by:

[redacted]

Based on:

Protocol Version: Version/Amendment 4

Protocol Date: 13 September 2021

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

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3.0 LIST OF ABBREVIATIONS

Acronym	Definition
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
CI	confidence interval
COVID	coronavirus disease
CRF	case report form
CRO	contract research organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
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
MedDRA	Medical Dictionary for Regulatory Activities

Acronym	Definition
mITT	modified intent-to-treat
MMRM	mixed-effect model repeated measures
MRD	multiple rising dose
PACU	postanesthesia care unit
PD	pharmacodynamic
PK	pharmacokinetic
PONV	postoperative nausea and vomiting
PPAS	per-protocol analysis set
PT	preferred term
PTE	pretreatment event
SAE	serious adverse event
SAF	Safety analysis set
SBP	systolic blood pressure
SC	subcutaneous
SOC	system organ class
SRD	single-rising dose
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
USPI	United States Prescribing Information
VRS	verbal rating scale
$V_{z,ss}$	volume of distribution during the terminal phase of steady state
VT	ventricular tachycardia
WOCBP	women of childbearing potential

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objective is:

- To assess the efficacy of a single-dose of TAK-951 compared with ondansetron to prevent postoperative nausea and vomiting (PONV) in the immediate postoperative period (within 6 hours post-surgery) in high-risk subjects undergoing elective surgery under general anesthesia.

4.2 Secondary Objectives

The secondary objectives 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.

4.3 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.

4.4 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 intravenous (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. Subject 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 subcutaneous (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 post-randomization criteria for study drug treatment are in addition to exclusion criterion #14 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.

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 4.a.
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 4.b.

   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 rating scale (VRS) after surgery, (0 = no nausea at all and 10 = the worst nausea imaginable) or upon subject's request, will receive rescue therapy as per local standard of care guidelines and be considered a treatment failure (see Appendix B of the protocol).

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.

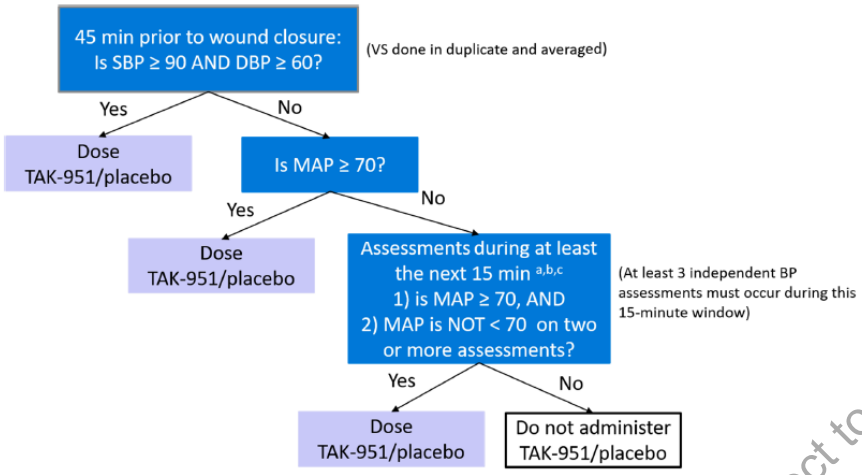
Subjects may be discharged 24 hours post-surgery after completion of all scheduled procedures. There will be a follow-up visit on Day 14±2 for assessment of concomitant medications, adverse events (AEs) and blood sample for immunogenicity assessment.

An interim analysis (IA) 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 IA(s) of safety and/or efficacy may be conducted based on different data cut(s). Should sponsor decided to perform additional IA(s), the analysis details would be defined in a subsequent version of this SAP.

A maximum of 160 subjects may be randomized to allow approximately 100 subjects to receive both doses of double-blind study drug/matching placebo per protocol.

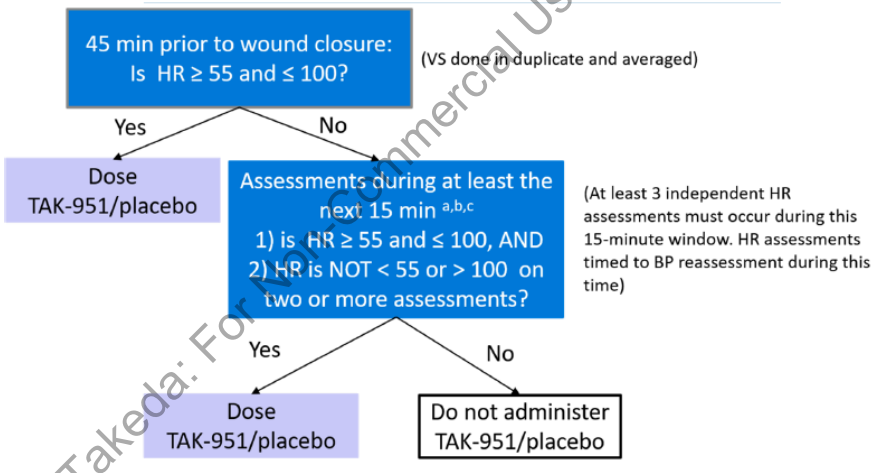
A schematic of the study design is included as Figure 4.c. A schedule of assessments is listed in Appendix A of the protocol.

Figure 4.a BP Criteria for TAK-951 or Matching TAK-951 Placebo Dosing



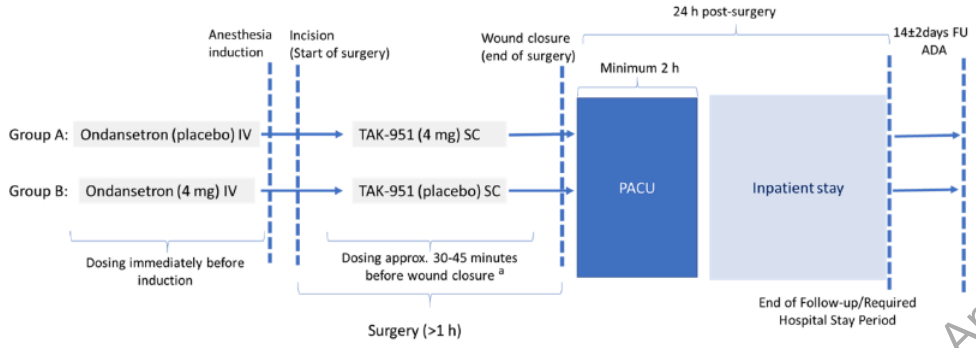
BP: blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SBP: systolic blood pressure; VS: vital sign.
[a] Reassessment period up to 15 ±2 minutes for 3 independent BP readings.
[b] Assessments will be single measurements (NOT duplicate averages) during the 15-minute window.
[c]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

Figure 4.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.

Figure 4.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 4.a and Figure 4.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.

5.0 ANALYSIS ENDPOINTS

5.1 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 Secondary Endpoints

The secondary endpoints are:

- 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 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).

5.3 Exploratory Endpoints

The exploratory endpoints are:

- [redacted]

The following exploratory endpoints were added per protocol amendment 3 dated 28Jul2021.

- 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 6 hours post-surgery (Yes/No).
- Requiring rescue therapy for breakthrough PONV within 3 hours post-surgery (Yes/No).

6.0 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.

7.0 METHODS OF ANALYSIS AND PRESENTATION

The final analysis will be performed after the final database lock at the end of the study (EOS).

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.

7.1 General Principles

All statistical analyses will be conducted using SAS® Version 9.4, or higher.

No formal statistical testing will be performed. The statistical analysis will be based on the estimation approach. The CIs reported will be 2-sided 80% and 95%, unless stated otherwise.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Where appropriate, variables will be summarized descriptively by analysis visit. For the categorical variables, counts and percentages of each possible value will be tabulated. The denominator for the percentage will be based on the number of subjects in each treatment group (column total) unless otherwise specified. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be presented.

All data will be descriptively summarized by treatment groups and overall respectively.

7.1.1 Efficacy Endpoint Definitions

Endpoint	Definition
Complete response in the immediate postoperative period (6 hours post-surgery) (Yes/No)	Complete response is 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) within 6 hours post-surgery.
Complete response within 24 hours post-surgery (Yes/No)	Complete response is 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) within 24 hours post-surgery.
Complete response within the immediate postoperative period (3 hours post-surgery) (Yes/No)	Complete response is 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) within 3 hours post-surgery.
Emesis in the first 6 hours post-surgery (Yes/No)	Emesis (vomiting or retching) within 6 hours post-surgery.
Emesis within 24 hours post-surgery (Yes/No)	Emesis (vomiting or retching) within 24 hours post-surgery.
Emesis within the first 3 hours post-surgery (Yes/No)	Emesis (vomiting or retching) within 3 hours post-surgery.
Absence of nausea in the first 6 hours post-surgery (Yes/No)	Absence of nausea is defined as VRS score <1 without any rescue medication taken within 6 hours post-surgery.
Absence of nausea within 24 hours post-surgery (Yes/No)	Absence of nausea is defined as VRS score <1 without any rescue medication taken within 24 hours post-surgery.
Absence of nausea within the first 3 hours post-surgery (Yes/No)	Absence of nausea is defined as VRS score <1 without any rescue medication taken within 3 hours post-surgery.
Requiring rescue therapy for breakthrough PONV within 24 hours post-surgery (Yes/No)	Taking (or received) rescue therapy (indicated if vomiting/retching and/or nausea score ≥4 or upon subject's request) within 24 hours post-surgery.
Requiring rescue therapy for breakthrough PONV within 6 hours post-surgery (Yes/No)	Taking (or received) rescue therapy (indicated if vomiting/retching and/or nausea score ≥4 or upon subject's request) within 6 hours post-surgery.
Requiring rescue therapy for breakthrough PONV within 3 hours post-surgery (Yes/No)	Taking (or received) rescue therapy (indicated if vomiting/retching and/or nausea score ≥4 or upon subject's request) within 3 hours post-surgery.
Time from end of surgery to first emetic event (vomiting or retching)	Time from the date/time of end of surgery to the date/time of first emetic event (vomiting or retching). If a subject did not have an emetic event within 24 hours post-surgery, they will be censored at 24 hours post-surgery or early termination whichever comes first. Units will be in hours.
Peak nausea VRS score (0 = no nausea at all, and 10 = the worst nausea imaginable)	Max VRS score at each timepoint (30 minutes and 1,2,6 and 24 hours after end of surgery) in subjects who have not required rescue therapy (indicated if vomiting/retching and/or nausea score ≥4 or upon subject's request).
Total response within 24 hours post-surgery (Yes/No)	Total response is defined as no emesis, no nausea (VRS <1), and no need for rescue therapy within 24 hours post-surgery.

7.1.2 Definition of Study Days

Study Day 1 is defined as the day of randomization. Other study days are defined relative to the Study Day 1 with Day 2 being the day after, and Day -1 being the day prior to Study Day 1.

7.1.3 Definition of Study Visit Windows

Baseline is defined as the last non-missing measurement prior to the first dose of study drug.

All data will be analyzed using the protocol defined nominal visits, unless otherwise stated.

Analysis Window Convention for Post-surgery VS Measurements

The post-surgery VS data will be collected from the subject entering PACU until 24-hour post-surgery by scheduled timepoints during Day 1 Post-surgery Observational Period. Given that such scheduled post-surgery timepoints are not collected on the eCRF, the timepoints will be derived based on the actual time for the VS assessment taken relative to the time for the subject entering the PACU during Day 1 Post-surgery Observational Period, including unscheduled VS assessment collected during this time period.

The analysis timepoint windows for the post-surgery timepoints are defined by the middle point of the two consecutives scheduled timepoints. Unless otherwise states, if a subject has more than one timepoint with a VS assessment included within a window, the assessment closest to the target time will be used. In case of ties between observations located on different sides of the target time, the later assessment will be used. In case of ties located on the same side of the target day (i.e., more than one value for the same timepoint), the mean of the values will be used.

Table 7.a Analysis Window Convention for Day 1 Post-surgery VS Measurements (excluding temperature).

Visit	Scheduled Timepoints	Target Time	Time Range: (if VS assessment time relative to the time subject entering PACU lies within the range)
Day 1 before surgery [a]	NA	NA	NA
Day 1 during surgery [a]	NA	NA	NA
Day 1 post surgery [b]			
End of Surgery [c]	Prior to Extubation	Extubation	≤ 0
End of Surgery (After Extubation) [d]	After Extubation and on or before PACU admin time	Extubation	>0 and on or before PACU admin time.
Every 15mins for 1hr post-surgery	15 mins Post-Surgery	15 mins	>0 and ≤ 22.5 mins
	30 mins Post-Surgery	30 mins	>22.5 mins and ≤ 37.5 mins
	45 mins Post-Surgery	45 mins	>37.5 mins and ≤ 52.5 mins
	1 hour Post-Surgery	60 mins	>52.5 mins and ≤ 75 mins

Table 7.a Analysis Window Convention for Day 1 Post-surgery VS Measurements (excluding temperature).

Visit	Scheduled Timepoints	Target Time	Time Range: (if VS assessment time relative to the time subject entering PACU lies within the range)
	1.5 hours Post-Surgery	90 mins	>75 mins and ≤105 mins
Every 30mins 2-4hrs post-surgery	2 hours Post-Surgery	120 mins	>105 mins and ≤135 mins
	2.5 hours Post-Surgery	150 mins	>135 mins and ≤165 mins
	3 hours Post-Surgery	180 mins	>165 mins and ≤195 mins
	3.5 hours Post-Surgery	210 mins	>195 mins and ≤225 mins
	4 hours Post-Surgery	240 mins	>225 mins and ≤270 mins
Every hour until 8hrs post-surgery	5 hours Post-Surgery	300 mins	>270 mins and ≤330 mins
	6 hours Post-Surgery	360 mins	>330 mins and ≤390 mins
	7 hours Post-Surgery	420 mins	>390 mins and ≤450 mins
	8 hours Post-Surgery	480 mins	>450 mins and ≤660 mins
Every 6hrs until 24hrs post-surgery	14 hours Post-Surgery	840 min	>660 mins and ≤1020 mins
	20 hours Post-Surgery	1200 min	>1020 mins and ≤1440 mins
Hospital discharge/Early termination [a]	NA	NA	NA

[a] Data will be taken from the corresponding CRF pages and analyzed based on protocol-defined nominal visits.
[b] Data will be taken from CRF page "Day 1 Postsurgery Observational Period" and unscheduled visits falling into the window. The analysis timepoints will be derived following the timepoint windowing convention.
[c] If there are multiple VS assessments within this window, the VS assessment immediately prior to extubation time will be selected. Otherwise, it will be set to missing.
[d] If there are multiple VS assessments within this window, the VS assessment closest to the extubation time will be selected. Otherwise, it will be set to missing. If subject already has 'End of Surgery' timepoint, then 'End of Surgery (After Extubation)' will not be mapped.

Table 7.b Analysis Window Convention for Day 1 Post-surgery VS Measurements – Temperature.

Visit	Scheduled Timepoints	Target Time	Time Range: (if VS assessment time relative to the time subject entering PACU lies within the range)
Day 1 before surgery [a]	NA	NA	NA
Day 1 post surgery [b]			
	8 hours Post-Surgery	480 mins	>0 and ≤960 mins
	24 hours Post-Surgery	1440 min	>960 mins and ≤1560 mins
Hospital discharge/Early termination [a]	NA	NA	NA

[a] Data will be taken from the corresponding CRF pages and analyzed based on protocol-defined nominal visits.
[b] Data will be taken from CRF page "Day 1 Postsurgery Observational Period" and unscheduled visits falling into the window. The analysis timepoints will be derived following the timepoint windowing convention.

7.1.4 Conventions for Missing Adverse Event Dates

Every effort will be made to determine the actual onset date for the event or to obtain a reliable estimate for the onset date from the investigator.

For AEs or serious adverse events (SAEs), a missing or incomplete onset date will be imputed according to the following conventions:

1. If an onset date is missing, the derived onset date will be calculated as the first non-missing valid date from the following list (in order of precedence):
   - First study drug date.
   - Consent date (for SAEs only).
2. If an onset date is incomplete, the derived onset date will be calculated following:
   - Missing day, but month and year present: the day will be imputed as the 1st of the month. If the first study drug dose occurs in the same month and year but after the imputed date, the derived onset date will be set equal to the first study drug date.
   - Missing day and month, but year present: the day and month will be imputed as the 30th June of the year. If the first study drug dose occurs in the same year but after the imputed date, the derived onset date will be set equal to the first study drug date. If the EOS date occurs in the same year but before the imputed date, the derived onset date will be set equal to the first study drug date.

For AEs or SAEs, a missing or incomplete end date will be imputed according to the following conventions:

1. If an end date is missing, the derived end date will be imputed the last assessment date.
2. If an end date is incomplete, the derived end date will be calculated following:
   - Missing day, but month and year present: the day will be imputed as the last date (for example February 2009 will be imputed as 28 February 2009) of the month. Missing day and month, but year present: the day and month will be imputed as the 31st December of the year.

7.1.5 Conventions for Missing Concomitant Medication Dates

Start and stop dates for all concomitant medications are collected on the case report form (CRF). However, in case of missing or partial information in these dates, the following rules will be used:

If the start date is unknown or partial:

- If the day is missing, the start day will be the first day of the month.
- If the month is missing,
  - If the year is the same as the date of first dose of study drug, the start month will be the month of the dose first study drug.
  - If the year is not the same as the date of first dose of study drug, the start month will be January.
- If the year is missing, the start year will be the minimum of the year of the first clinic visit or the year of the informed consent date.
- If the entire start date is unknown, the start date will be the date of first study drug administration.

If the stop date is missing, partial or "ongoing:"

- If the day is missing, the stop day will be the last day of the month reported.
- If the month is missing,
  - If the year is the same as the date of last assessment, the stop month will be the month during which the last assessment occurred.
  - If the year is not the same as the year of the last assessment, then the end month will be December.
- If the year is missing, the stop year will be the year in which the last assessment occurred.
- If the entire stop date is unknown or if the medication is "ongoing", the stop date will be the date of last assessment.

7.1.6 Methods for Handling of Missing Efficacy Data

The missing dichotomous efficacy data (eg, complete response in the immediate postoperative period) will be handled using the non-responder imputation method, ie, any subject with missing information for determination of endpoint status will be considered as having an undesirable outcome in the analysis.

Missing data for longitudinal continuous endpoints will not be imputed but handled using a mixed-effect model repeated measures (MMRM) assuming missing at random (MAR) mechanism.

Missing data for time to event endpoints will not be imputed.

Other missing data handling method may be explored.

7.2 Analysis Sets

The analysis sets used for analysis will include the following:

Full Analysis Set (FAS): The FAS will include all subjects who are 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.

Per-protocol Analysis Set (PPAS): The PPAS is a subset of the FAS. The 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 PPAS will be made prior to the unblinding of the study. Analyses using the PPAS will be provided as a sensitivity analysis.

Safety Analysis Set (SAF): The SAF will include all subjects who were randomized to treatment and received both doses of double-blind study drug (i.e, 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.

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

Immunogenicity Set: The Immunogenicity Set will consist of all subjects who receive at least 1 dose of study drug TAK-951, have an ADA status assessment at baseline, and at least 1 postbaseline sample.

All Randomized Set: The All Randomized Set will consist of all subjects who were randomized to treatment.

7.3 Disposition of Subjects

7.3.1 Study Information

General study information will be provided, including the date the first subject signed informed consent, the date of the last subject's last visit/contact, the date of the last subject's last visit for collection of data for primary endpoint, MedDRA version, WHO Drug version and SAS version used for creating the datasets.

7.3.2 Disposition of Subjects

Summary of the subject disposition will be summarized for each treatment group and overall, and will include the following:

- Summary of screen failures using all subjects who were not randomized.
- Summary of eligibility for randomization using all subjects who signed the informed consent form.
- Summary of study subjects randomized by site, geographic region using the All Randomized Set.
- Summary of subjects for each pre-defined population using the All Randomized Set: all randomized set, full analysis set, per-protocol set, safety analysis set, PK set and Immunogenicity set.
- Summary of subjects for each pre-defined population using the Safety Analysis Set: safety analysis set, PK set and Immunogenicity set.
- Summary of subjects randomized but not treated, randomized but only received the first dose of study drug and ineligible to receive the second dose of study drug, completing study drug and completing study, and disposition of subjects based on the reasons for discontinuation of treatment and for failing to complete the study using the All Randomized Set and Safety Analysis Set. Significant protocol deviations will be summarized descriptively using the All Randomized Set.

When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

Supporting data listings for randomization scheme, screen failures, subject disposition, and significant protocol deviations will be provided.

7.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristics variables will be summarized by each treatment group and overall using the FAS.

For continuous variables (age, weight, height, body mass index [BMI]), summary statistics (N, mean, SD, median, minimum, and maximum) will be generated. 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: $BMI = weight\ (kg)/height\ (m)^2$

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 $BMI=79.2/1.76^2=25.56818\ kg/m^2$

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.

For categorical or ordinal variables (gender, ethnicity, race, Apfel risk score, Apfel risk factors, female reproductive system status, substance use), the number and percentage of subjects in each category will be presented. 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.

Individual subject demographic and baseline characteristics data will be listed.

7.5 Medical History and Concurrent Medical Conditions

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA, version 18 or higher) coding system.

During the screening period and prior to surgery, a complete medical history will be compiled for each subject. The history will be summarized by system organ class (SOC), preferred term (PT) and by each treatment group and overall based on the Safety Analysis Set.

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the screening examination according to the judgment of the investigator. The condition (ie, diagnosis) should be described and will be summarized by system organ class and preferred term based on the Safety Analysis Set.

Individual subject medical history and concurrent medical condition data will be listed.

7.6 Medication History and Concomitant Medications

During the screening period and prior to surgery, a complete medication history will be compiled for each subject. The medication history will be coded using WHO Drug and summarized by standardized medication name based on the Safety Analysis Set.

Concomitant medication is any drug given in addition to the study drug. Concomitant medications will be coded using WHO Drug. The number and percentage of subjects taking

concomitant medications will be tabulated by standardized medication name WHO drug generic term in the Safety analysis set, and categorized as follows:

- Concomitant medications that started and stopped prior to baseline.
- Concomitant medications that started prior to and were ongoing at baseline and those that started after baseline.

Data listing(s) for medication history and concomitant medication will be provided.

7.7 Study Drug Exposure and Compliance

The date and time of each dose for each subject will be reported in the data listing for all subjects in the Safety Analysis Set. No other summary statistics for the extent of exposure to study investigational products or compliance calculations will be performed for this study.

7.8 Efficacy Analysis

The primary 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. Other sensitivity analyses based on the SAF will also be performed for primary, secondary and exploratory endpoints Missing data will be handled according to Section 7.1.6.

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.

Data listings for primary and secondary efficacy endpoints will be provided.

7.8.1 Primary Efficacy Endpoint(s)

For the primary efficacy endpoint, the proportion of complete responders in first 6 hours post-surgery in the TAK-951 and ondansetron groups will be calculated with the corresponding 2-sided 95% confidence interval using normal approximation. The treatment difference in proportions of complete responders in 6 hours post-surgery between TAK-951 and ondansetron will be estimated and the associated 2-sided 80% and 95% CIs calculated. Point estimate of the treatment difference between TAK-951 and ondansetron and the associated CIs will be based on the Cochran-Mantel-Haenszel (CMH) method, adjusting for the number of Apfel risk factors (3 or 4). In addition, a 2-sided 40% CI of treatment difference in proportion of complete responders in 6 hours post-surgery between TAK-951 and ondansetron will be constructed as well for internal decision making.

In the event that the number of complete responders or non-responders in either treatment group is too small (i.e., ≤5), the exact method [e.g., Clopper-Pearson CI for proportions in each treatment group and exact unconditional confidence limits for treatment difference (Chan and Zhang, 1999)] will be performed instead. Subjects with missing data to determine endpoint status will be considered as undesired treatment outcome (ie, non-responders).

7.8.2 Secondary Efficacy Endpoint(s)

The binary secondary efficacy endpoints are

- 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), and
- Total response within 24 hours post-surgery (Yes/No)

The secondary efficacy endpoints 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 will be analyzed using a mixed-effect model repeated measure (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 with unstructured covariance structure for the observed data up to 24 hours after completion of surgery. 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 will be analyzed using the Cox proportional hazard model with treatment group and the number of Apfel risk factors as independent variables. Point estimate and associated 80% and 95% CIs for hazard ratio for TAK-951 versus ondansetron will be provided. Kaplan-Meier (KM) estimates by treatment groups as well as KM plot will be presented. Subjects without documented emetic event within 24 hours post-surgery will be censored at 24 hours post-surgery.

In addition, line charts for the following endpoints will be generated by treatment group:

- Proportion of subjects with complete response in first 6 and within 24 hours post-surgery,
- Proportion of subjects with no emesis in the first 6 and within 24 hours post-surgery,
- Proportion of subjects with absence of nausea in the first 6 and within 24 hours post-surgery, and
- Peak nausea VRS score by timepoint up to 24 hours post-surgery.

7.8.3 Exploratory Efficacy Endpoint(s)

[redacted]

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

separately. The results from DNA measurements data will not be included in the clinical study report (CSR) but a separate report.

The following additional exploratory efficacy endpoints were added in the protocol amendment 3 and will be included in the final analysis. These endpoints will be analyzed using the Full Analysis Set (FAS) in a similar way as the primary efficacy endpoint.

- Complete response within the first 3 hours post-surgery, defined as 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 6 hours post-surgery (Yes/No).
- Requiring rescue therapy for breakthrough PONV within 3 hours post-surgery (Yes/No).

7.8.4 Sensitivity Analysis

To assess the robustness of the analysis for primary efficacy endpoint and secondary efficacy endpoints, the following sensitivity analysis will be performed:

- The primary and secondary efficacy endpoint analysis will be repeated using the PPAS.
- In the event of unintentional unblinding after implementing the protocol amendment 2 specified unblinding procedure due to ineligibility to receive the TAK-951 or matching TAK-951 placebo during surgery, additional sensitivity analysis may be performed to evaluate the impact of unintentional unblinding on the primary efficacy endpoint by removing the subjects whose treatment assignment was unintentionally unblinded from the FAS.
- To evaluate the identified dosing error at some sites, additional sensitivity analysis for the primary and selected secondary and exploratory efficacy endpoints may be conducted in a similar way as primary efficacy endpoint using the SAF, in which subjects will be analyzed by the actual treatment they received (e.g., ondansetron, TAK-951 4 mg, [redacted]).

Additional sensitivity analysis may be performed as appropriate.

7.8.5 Subgroup Analysis

The subpopulations of interest are outlined in Table 7.c.

Table 7.c List of subgroups of interest

Subgroup of Interest	Subgroup Categories
Apfel risk factor	3,4
Opioid analgesics usage	Yes, No

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 in a similar way as the primary analysis of the primary efficacy endpoint using the FAS. The treatment effect in proportions by treatment groups and associated 95% confidence interval method will be provided for each subgroup.

- For Subgroup analyses by the number of simplified Apfel risk factors (3 or 4), point estimate of the treatment difference between TAK-951 and ondansetron and associated 80% and 95% confidence intervals using the normal approximation will be presented for each subgroup.
- For Subgroup analyses by postoperative opioid analgesics usage (yes or no), point estimate of the treatment difference between TAK-951 and ondansetron and associated 80% and 95% confidence intervals using the CMH method adjusting for the number of simplified Apfel risk factors (3 or 4) will be presented for each subgroup.

In the event that the number of complete responders is too small (ie, ≤5), the exact method [ie, Clopper-Pearson CI for proportions in each treatment group and exact unconditional confidence limits for treatment difference (Chan and Zhang, 1999)] will be performed instead.

The results will be tabulated and the corresponding forest plots for the subgroup analyses will be presented as well.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

7.9.1 Pharmacokinetic 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 presented in a data listing.

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 CSR and will be a standalone report.

7.9.2 Pharmacodynamic Analysis

Not applicable

7.10 Other Outcomes

7.10.1 Immunogenicity

Immunogenicity will be summarized using the Immunogenicity Set.

Immunogenicity results will be summarized using the number and percentage of subjects in the immunogenicity categories (Table 7.d) by treatment group and nominal timepoint where appropriate. In addition, the analysis of ADA prevalence (i.e., the number and proportion of subjects who are ADA positive, including being pre-existing ADA positive, at any timepoint

during the study) and ADA incidence (i.e., the number and proportion of subjects who are treatment emergent ADA positive or/and treatment-boosted ADA positive, excluding being pre-existing ADA positive, during the study) will be presented by treatment arm. Missing ADA data will not be imputed.

Table 7.d List of Immunogenicity Category and Definitions

Immunogenicity Category	Definition
ADA Negative	Subject who does not have positive ADA response at baseline and in all postbaseline assessments
ADA Positive	Subjects who have confirmed positive ADA status in baseline or at least 1 postbaseline assessments
Pre-existing ADA Positive	• Subject who has positive ADA response in the baseline sample and none of the postbaseline samples, **or** • Subject who has positive ADA response in both baseline and postbaseline samples but the maximum titer of the postbaseline ADA is <4 times the baseline titer value.
Treatment-boosted ADA Positive	• Subject who has positive ADA response in both baseline and postbaseline samples, **and** • The titer of the maximum postbaseline ADA is ≥4 times that of the baseline titer value.
Treatment Emergent ADA positive	• Subject who has negative ADA in baseline sample, and • Subject who has positive ADA response in any postbaseline assessment.
High ADA titer (for ADA positive only)	Subject who has at least 1 postbaseline ADA titer >16
Low ADA titer (for ADA positive only)	Subject whose postbaseline ADA titers are all ≤16

Relationship between subject level ADA Status (ADA Positive and ADA Negative) and other endpoints (PK concentration, Primary endpoint and Hypersensitivity Related Adverse Events) may be summarized, if deemed necessary.

All immunogenicity data will be provided in by-subject listings based on immunogenicity analysis set.

7.11 Safety Analysis

Safety data being collected in a double-blinded fashion will be summarized using the Safety Analysis Set with the actual treatment received (i.e., Ondansetron vs TAK-951). The analysis of safety endpoints will include AEs, clinical laboratory values, vital signs, ECG, and weight. No statistical inference will be made for safety analyses.

Subjects who are ineligible to receive the second dose of study drug (i.e., TAK-951 or matching TAK-951 placebo) due to failure to meet the vital sign requirements outlined in Section 4.0 will be unblinded to the investigator; their safety data collected will be summarized separately.

7.11.1 Adverse Events

A pretreatment event (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.

A Treatment Emergent AE (TEAE) is defined as any AEs newly occurring or worsening from the first dose and 14 days after last dose of study drug. A Serious TEAE is defined as SAE newly occurring or worsening from the first dose to up to 14 days after last dose of study drug, regardless of relationship to study drug. SAEs will also be collected from last dose of study drug to EOS.

Adverse events (AEs) will be coded by MedDRA (version 24.1 or higher). The number and percentage of subjects with TEAEs, serious TEAEs, and SAEs will be summarized by System Organ Class, High Level Term, and Preferred Term. AEs will also be summarized by intensity, and by relationship (causality) to study investigational product respectively. All AEs and SAEs collected in the database (including those starting prior to first dose of study drug) will be listed. Any other information collected (eg, relationship to study drug, action taken etc.) will be listed as appropriate.

The intensity of all AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0). AEs not listed by the NCI CTCAE will be graded as displayed in Table 7.e.

Table 7.e 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.

In summary, AEs will be summarized by each treatment group and overall using the Safety Analysis Set as follows:

- Overview of TEAEs - number and percentage of subjects, number of events;

- Pretreatment AEs by system organ class (SOC), high level term (HLT), and preferred term (PT) - number and percentage of subjects;
- TEAEs by system organ class (SOC), high level term (HLT), and preferred term (PT) - number and percentage of subjects;
- Most frequent TEAEs by PT (sorted by frequency, occurring in ≥ 5% of subjects in any treatment arm) - number and percentage of subjects;
- TEAEs by relationship to study drug and by SOC, HLT and PT - number and percentage of subjects;
- TEAEs by intensity (toxicity grade) and by SOC, HLT and PT - number and percentage of subjects;
- TEAEs for toxicity grade 3 or higher by relationship and by SOC, HLT and PT - number and percentage of subjects;
- TEAEs leading to treatment discontinuation by SOC, HLT, and PT - number and percentage of subjects;
- Serious TEAEs by SOC, HLT and PT - number and percentage of subjects;
- Serious TEAEs by relationship to study drug and by SOC, HLT and PT - number and percentage of subjects;
- Serious TEAEs by intensity (toxicity grade) and by SOC, HLT and PT - number and percentage of subjects;
- TEAEs resulting in death by PT - number and percentage of subjects;
- AEs of special interest (AESI) by SOC, HLT, and PT (see Appendix A) - number and percentage of subjects.

Key guidelines for determining the incidence of AEs are as follows:

- AEs with missing or unknown intensity will be considered as severe (or Grade 3).
- AEs with missing or unknown relationship to study drug will be counted as related.
- A subject with 2 or more AEs within the same level of the MedDRA term will be counted only once in that level.
- SOCs will be sorted in alphabetical order. Within an SOC, adverse events will be sorted in descending order of total number of subjects with the preferred term among all the treatment groups.
- For the summary of TEAEs by SOC, HLT and PT and intensity (toxicity grade), if a subject experiences more than 1 episode of a particular coded adverse event, the subject will be counted only once by the maximum toxicity grade of the episode (preferred term). Similarly, if a subject has more than 1 adverse event within an SOC, the subject will be counted only once by the maximum toxicity grade in that SOC.

- In selected summaries, adverse events will be summarized by the number of events reported in addition to the number and percentage of subjects with events.

Data listings for TEAEs, TEAEs leading to study discontinuation, SAEs, deaths, and AESI will be presented. The AEs will be listed by treatment, study center, subject number and onset date of the adverse event. The listing will contain: subject identifier, age, sex, body weight, race, adverse event (preferred term and reported term), treatment group and time of TAK-951 or Placebo, relationship to study procedure, TEAE,SOC, onset date, end date or whether the event was ongoing, duration, intensity, action taken concerning study drug, causality to study drug, the outcome, whether the adverse event was an SAE and whether the event was an AESI.

7.11.2 Clinical Laboratory Evaluations

Blood samples for analysis of the Hematology, Serum Chemistry, Serum and Urine parameters are shown in following table:

Table 7.f 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 (BUN)
	GGT
	Glucose
	Potassium
	Sodium
Other:	

Serum	**Urine**
Hepatitis panel, including HBsAg and anti-HCV	Female subjects only:
Immunogenicity	hCG (for pregnancy)
Female subjects only:	
Beta hCG (for pregnancy) in female subjects of childbearing potential	
FSH in female subjects for whom menopause is suspected	

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 analysis of the laboratory data will include parameters tabulation for each assessment visit by treatment group using the Safety Analysis Set, using the following:

- Number of subjects with non-missing values (n),
- Arithmetic mean,
- Median,
- Standard deviation (SD),
- Minimum and maximum observed values (Min, Max).

For the post-baseline assessments, the summary will also include the change from baseline values. Subjects with markedly abnormal values for laboratory tests will be tabulated (see Appendix D for details).

Individual subject clinical laboratory data will be listed by timepoint.

7.11.3 Vital Signs

Vital signs, including heart rate, respiratory rate, systolic and diastolic blood pressure, weight and temperature will be summarized descriptively by visit and timepoint for absolute values and change from baseline using the Safety Analysis Set. The visit will include Before Surgery, During Surgery, Day 1 Post-Surgery, and Hospital Discharge. There are multiple timepoints during Day 1 Post-Surgery Observational Period and such timepoints will be derived by applying the timepoint windowing convention as described in Section 7.1.3. Subjects with markedly abnormal values for vital signs values will be tabulated (see Appendix D for details).

Box plots for absolute value and change from baseline of vital signs by timepoint will also be generated. Individual subject vital signs data will be listed by timepoint.

7.11.4 12-Lead ECGs

ECG parameters including HR, RR interval, PR interval, QT interval, and QRS interval, and QTcF will be summarized descriptively by visit for absolute values and change from baseline using the Safety Analysis Set. Overall interpretation by visit will also be tabulated.

Box plots for absolute value and change from baseline of ECG parameters by timepoint will also be generated. Values outside normal ranges and potentially clinically significant values will be flagged.

7.11.5 Safety Analysis for Subjects Ineligible to Receive TAK-951/Placebo

The following additional safety analysis will be performed for 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 4.0 and unblinded to the investigator.

- Overview of TEAEs - number and percentage of subjects, number of events;

- Summary of subjects with markedly abnormal values for laboratory tests;
- Summary of subjects with markedly abnormal values for vital signs values;
- Data listing of subjects with ECG values outside normal ranges and potentially clinically significant values.

7.12 Interim Analysis

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

1st IA:

The 1st IA 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. In order to evaluate the impact of 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. There is no plan to evaluate stopping for overwhelming efficacy in this study.

If applicable, the interim futility analysis may 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, and study subjects.

The Sponsor will be informed by the DMC if the futility criteria have been met and decide whether to 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 (see Section 7.12.3 for details). 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 will be described in the data access management plan (DAMP) and DMC charter.

2nd IA:

The 2nd interim analysis (IA) of safety, efficacy, and PK data will be conducted to support sponsor internal decision making. This 2nd IA will be based on the selected data from the study TAK-951-2001 once approximately 80 fully dosed subjects have received both doses of double-

blind study treatment (i.e., TAK-951/placebo and Ondansetron/placebo) and completed their 14-day safety follow-up. The statistical analyses of the selected clinical data of the TAK-951-2001 will be used in this additional IA and will follow the statistical methodologies described in this SAP.
Complete details related to the unblinding will be described in the data access management plan (DAMP) and DMC charter

7.12.1 Efficacy Endpoints

1st IA:

The efficacy endpoint of interest for interim futility analysis is the primary efficacy endpoint, complete response in first 6 hours post-surgery. Complete response is 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) in the immediate postoperative period (6 hours post-surgery).

The primary efficacy endpoint, complete response rate in the first 6 hours post-surgery, will be used to derive Bayesian predictive probability for interim decisions.

Descriptive analysis for the primary efficacy endpoint and selected secondary and exploratory efficacy endpoints will be performed in the FAS by randomized treatment (ondansetron vs TAK-951 4 mg) and in the SAF by actual treatment received (e.g., ondansetron, TAK-951 4 mg, [redacted] separately:

- Complete response within the first 6 hours post-surgery (Yes/No)
- Emesis within the first 6 hours post-surgery (Yes/No).
- Time from end of surgery to first emetic event (vomiting or retching).
- Complete response within the first 3 hours post-surgery (Yes/No)
- Emesis within the first 3 hours post-surgery (Yes/No).

The interim efficacy data will be analyzed in a similar way as primary efficacy endpoint, including count, percentage, and 2-sided 40%, 80% and 95% CIs.

2nd IA:

The 2nd IA will include the same primary, secondary, and exploratory efficacy endpoints as mentioned above for the 1st IA, however, additional secondary efficacy endpoints will also be included.

The following additional secondary endpoints will be included:

- Complete response within 24 hours post-surgery (Yes/No),
- Emesis within 24 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), and
- Total response within 24 hours post-surgery (Yes/No)

The additional secondary efficacy endpoints of the 2nd IA will be analyzed in a similar way as the secondary efficacy endpoint of the 1st IA.

The futility analysis will not be performed for the 2nd IA.

7.12.2 Bayesian Predictive Probability for the 1st IA

Only subjects in the FAS who were randomized to receive TAK-951 will be included in the interim futility analysis.

Statistical simulation will be conducted based on the observed interim data and simulated post-IA data to derive the Bayesian predictive probability of achieving a complete response rate at 6 hours of at least 30% (ie, ≥30%) in TAK-951 arm, using non-informative prior distribution Beta (1,1) assuming the number of complete responders at 6 hours post-surgery for TAK-951 follows binomial distribution. See Figure 7.a for details of IA data flow.

- Prior distribution of complete response rate at 6 hours post-surgery for TAK-951: $\theta \sim Beta(a, b)$, where a = 1 and b = 1.

$$f(\theta \mid a,b) = \frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)} \theta^{a-1}(1-\theta)^{b-1}$$

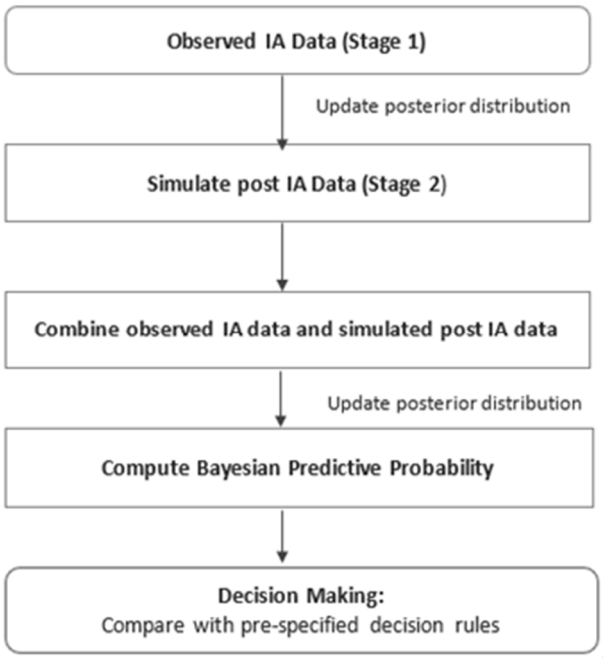
- Posterior distribution of complete response rate at 6 hours post-surgery based on the observed interim data from TAK-951: $\theta | X \sim Beta(a + r, b + x - r)$.

$$\binom{x}{r} \theta^{x}(1-\theta)^{x-r} \frac{\Gamma(a+b)}{\Gamma(a)\Gamma(b)} \theta^{a-1}(1-\theta)^{b-1} \sim \theta^{r+a-1}(1-\theta)^{x+b-r-1}.$$

where

- a = 1, b = 1;
- r = number of complete responders observed at interim;
- x = number of subjects randomized to TAK-951 in the FAS at interim;
- N = planned total number of subjects randomized to TAK-951 in the FAS = 50;
- Number of subjects post-IA randomized to TAK-951 in the FAS = N – x = 50 – x.

Figure 7.a IA Data Flow



7.12.3 Interim Decision Rules

1st IA:

The DMC will consider the following guidelines based on the Bayesian predictive probability for making recommendations at IA.

The threshold for a futility decision rule will be a Bayesian predictive probability of treatment success less than 0.3 at the time of the futility analysis, where treatment success is defined as a complete response rate at 6 hours in TAK-951 arm of at least 30% at the end of study:

- If the Bayesian predictive probability (complete response rate at 6 hours in TAK-951 ≥30%) <0.3, then terminate the study for futility.
- If the Bayesian predictive probability (complete response rate at 6 hours in TAK-951 ≥30%) ≥0.3, then continue the study as planned.

In addition to the above formal criteria, relevant safety data may be used to guide the potential modification of design of the study. The DMC may also recommend that the study be stopped because of concerns about the safety for the study participants. Potential modifications that the DMC can recommend at IA include:

- Continue trial without modifications.
- The trial has met prespecified criteria for futility.

Any recommendation other than "continue trial without modifications" must be accompanied by justifications for the recommendations and other follow up requirements as deemed necessary. The sponsor may or may not follow the recommendation of futility stopping.

2nd IA:

The 2nd interim analysis (IA) will primarily support DMC for safety monitoring and no formal decision rules for efficacy analyses will be applied.

7.12.4 Multiplicity Adjustment

1st IA:

The 1st IA is for futility analysis and aimed to aid the internal decision making. It does not intend to stop the study for overwhelming efficacy. Hence, no multiplicity adjustment is necessary for the final analysis.

2nd IA:

The 2nd IA is aimed to aid the internal decision making. It does not intend to stop the study for overwhelming efficacy. Hence, no multiplicity adjustment is necessary for the final analysis.

7.12.5 Data to be Presented

1st IA:

A list of TLFs generated for the 1st IA are specified in the Appendix B.

2nd IA:

The 2nd IA will be based on the selected data from the study TAK-951-2001 once approximately 80 fully dosed subjects have received both doses of double-blind study treatment (i.e., TAK-951/placebo and Ondansetron/placebo) and completed their 14-day safety follow-up. The list of TLFs to be generated for this planned 2nd IA are specified in Appendix C. Additional data-summaries or listings requested by the DMC may be generated.

The analysis of immunogenicity data will not be conducted for the 2nd IA. However, it will be performed for the final analysis.

7.13 Additional Analysis Related to COVID

Depending on the prevalence of coronavirus disease (COVID) infections and illness in regions where the study is conducted, additional analysis may be performed to evaluate the impact of COVID on the efficacy and safety of all participating subjects, including but not limited to the following:

- COVID related discontinuation, including discontinuation due to adverse events in light of COVID infection and discontinuation due to COVID-related reasons other than COVID-infection (e.g., travel limitation, reduced site staff, etc.).

- COVID related AEs, including preferred term that contains "COVID-19", "SARS-CoV-2", "SARS-CoV-2" and "Coronavirus".
- All SAEs in COVID infected subjects.
- All protocol deviations related to COVID.
- Data listing of all subjects affected by COVID-19 related study disruption, including subject ID, site ID, and description of how individual's participation was altered.
- Data listing of all subjects taking COVID-19 vaccine during the course of study, if data permits.
- If any site is closed due to COVID, sensitivity analysis may be performed for primary efficacy endpoint by excluding all affected subjects from the closed site.

7.14 Changes in the Statistical Analysis Plan

SAP Version	Date	Revision History
1.0	6Oct2020	NA
2.0	16Feb2021	The following changes have been made in this version of SAP per Protocol Amendment 2 dated 11Jan2021: – updated study procedure, dosing eligibility, and IA timing in Section 4.4; – updated the definitions for FAS and SAF, removed mITT population, and added All Randomized Set in Section 7.2; – updated the summary of subject disposition in Section 7.3.2; – removed the sensitivity analysis using the mITT in Section 7.8; – added potential additional sensitivity analysis in the event of unintentional unblinding in Section 7.8.4; – updated the safety analysis in Section 7.11; and – clarified the timing and analysis population for IA in Section 7.12. The following additional changes were also made in this version of SAP: – added analysis window convention for post-surgery VS assessments collected during Day 1 Post-surgery Observational Period in Section 7.1.3; – updated the immunogenicity analysis per ADA data availability in Section 7.10.1; – clarified the VS analysis in Section 7.11.3; – added box plots to ECG analysis in Section 7.11.4; – added additional data listing for subjects taking COVID-19 vaccine during the course of study in Section 7.13; and – removed VS markedly abnormality criteria for HR by revised clinical guideline in Appendix D.
3.0	10May2021	The following changes were made to this version of SAP: - added 5 additional exploratory efficacy endpoints in Sections 5.3 and 7.1.1, and the associated analysis in Section 7.8.3;

SAP Version	Date	Revision History
		- clarified the endpoint definition for "requiring rescue therapy" and "absence of nausea" in Section 7.1.1; - clarified the analysis for summary of screening failure in Section 7.3.2; - clarified the potential DMC recommendation for interim futility analysis in Section 7.12; - clarified the analysis for COVID-19 related AEs in Section 7.13; and - updated TLFs for the 1st IA in Appendix B.
4.0	2Aug2021	The following changes were made to this version of SAP per Protocol Amendment 3 dated 28Jul2021: - updated the study to double-blind (sponsor-open) in cover page and Sections 4.4; - updated the analysis windowing rule in Table 7.a; - added additional sensitivity analysis to evaluate the impact of dosing error for final analysis in Section 7.8.4; - added the reference for exact unconditional confidence limits for treatment difference in Section 7.8 and Section 8. - clarified the PK analysis in Section 7.9.1; - updated the interim analysis by adding additional descriptive efficacy analysis to aid the internal decision making in Section 12; - added additional IA efficacy tables in Appendix B.
5.0	22Feb 2022	The following changes were made to this version of SAP: - updated the definition of Immunogenicity Set in the Section 7.2 - updated the definition of Screen Failures in Section 7.3.2 and align analysis sets used in the table shells - updated Section 7.8 as sensitivity analyses are also performed based on SAF - Replaced TAK-951 >4 mg by [redacted] in the Sections 7.8.4 and 7.12.1 - updated Section 7.10.1 - updated the Section 7.12 - added Appendix C for the tables to be generated for the 2nd IA

8.0 Reference

Chan I. and Zhang Z. Test-based exact confidence intervals for the difference of two binomial proportions. *Biometrics.* 1999; 55(4) 1202-1209.

Appendix A AEs of Special Interest

Based on the mechanism of action of TAK-951, certain AESIs have been predefined. The categories of AESIs, are described below. AESI will be summarized by investigator-indicated AESI in the eCRF and derived-AESI per the MedDRA terms or definition below.

AESIs	MedDRA Terms or definitions
Injection site reaction	Injection Site Reaction (HLT)
Hypotension	Hypotension (PT)
Tachycardia	Tachycardia (PT)

Appendix B Table, Figures, and Listings for the 1st IA

A separate document labeled as "DMC TLF shells" was summarized the interim futility analysis report presentation details. The unblinded IA results were presented to the DMC.

Number	Table Title	Blinded	Unblinded
1	Demographics – FAS	Y	Y
2	Baseline Characteristics – FAS	Y	Y
3	Subject Disposition – All Randomized Set	Y	Y
4	Summary of Primary Efficacy Endpoint and Bayesian Predictive Probability Assessment in Subjects Randomized to TAK-951 – FAS	Y	Y
5	Overview of TEAEs – Safety Analysis Set	Y	Y
6	TEAEs by System Organ Class, High Level Term, and Preferred Term – Safety Analysis Set	Y	Y
7	TEAEs by Maximum Toxicity Grade by System Organ Class, High Level Term, and Preferred Term – Safety Analysis Set	Y	Y
8	TEAEs Considered Related to Study Drug by System Organ Class, High Level Term, and Preferred Term - – Safety Analysis Set	Y	Y
9	Serious TEAEs by System Organ Class, High Level Term, and Preferred Term – Safety Analysis Set	Y	Y
10	Serious TEAEs Considered Related to Study Drug by System Organ Class, High Level Term, and Preferred Term – Safety Analysis Set	Y	Y
11	TEAEs Leading to Discontinuation by System Organ Class, High Level Term, and Preferred Term – Safety Analysis Set	Y	Y
12	Treatment-Emergent Injection Site Reaction Adverse Events by System Organ Class, High Level Term, Preferred Term and Treatment Group – Safety Analysis Set	Y	Y
13	Treatment-Emergent Hypotension Adverse Events by System Organ Class, High Level Term, Preferred Term and Treatment Group – Safety Analysis Set	Y	Y
14	Treatment-Emergent Tachycardia Adverse Events by System Organ Class, High Level Term, Preferred Term and Treatment Group – Safety Analysis Set	Y	Y
15	Listing of Treatment-Emergent Adverse Events Leading to Death – Safety Analysis Set	Y	Y
16	TEAEs of Toxicity Grade 3 or Higher by System Organ Class, High Level Term, and Preferred Term – Safety Analysis Set	Y	Y
17	Summary of Markedly Abnormal Lab Test: Hematology – Safety Analysis Set	Y	Y
18	Summary of Markedly Abnormal Lab Test: Serum Chemistry – Safety Analysis Set		
19	Summary of Markedly Abnormal Vital Signs – Safety Analysis Set	Y	Y
20	Summary of 12-Lead ECG Parameters and Change from Baseline by Visit – Safety Analysis Set	Y	Y

Additional efficacy tables for primary and selected secondary/exploratory efficacy endpoints were provided.

Number	Table Title	Blinded	Unblinded
21	Summary of Complete Responders in First 6 Hours Post-Surgery by Randomized Treatment Group – FAS	N	Y
22	Summary of Complete Responders in First 6 Hours Post-Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
23	Summary of Emesis in First 6 Hours Post-Surgery by Randomized Treatment Group – FAS	N	Y
24	Summary of Emesis in First 6 Hours Post-Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
25	Summary of Complete Responders in First 3 Hours Post-Surgery by Randomized Treatment Group – FAS	N	Y
26	Summary of Complete Responders in First 3 Hours Post-Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
27	Summary of Emesis in First 3 Hours Post-Surgery by Randomized Treatment Group – FAS	N	Y
28	Summary of Emesis in First 3 Hours Post-Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
29	Summary of Time from End of Surgery to First Emetic Event by Randomized Treatment Group – FAS	N	Y
30	Summary of Time from End of Surgery to First Emetic Event by Actual Treatment Received – Safety Analysis Set	N	Y

Appendix C Table, Figures, and Listings for the 2nd IA

The unblinded IA results will be provided to the DMC.

Number	Table Title	Blinded	Unblinded
1	Demographics – FAS	Y	Y
2	Baseline Characteristics – FAS	Y	Y
3	Subject Disposition – All Randomized Set	Y	Y
4	Subject Disposition – Safety Analysis Set	Y	Y
5	Overview of TEAEs – Safety Analysis Set	Y	Y
6	TEAEs by System Organ Class, High Level Term, and Preferred Term – Safety Analysis Set	Y	Y
7	TEAEs by Maximum Toxicity Grade by System Organ Class, High Level Term, and Preferred Term – Safety Analysis Set	Y	Y
8	TEAEs Considered Related to Study Drug by System Organ Class, High Level Term, and Preferred Term - – Safety Analysis Set	Y	Y
9	Serious TEAEs by System Organ Class, High Level Term, and Preferred Term – Safety Analysis Set	Y	Y
10	Serious TEAEs Considered Related to Study Drug by System Organ Class, High Level Term, and Preferred Term – Safety Analysis Set	Y	Y
11	TEAEs Leading to Discontinuation by System Organ Class, High Level Term, and Preferred Term – Safety Analysis Set	Y	Y
12	Treatment-Emergent Injection Site Reaction Adverse Events by System Organ Class, High Level Term, Preferred Term and Treatment Group – Safety Analysis Set	Y	Y
13	Treatment-Emergent Hypotension Adverse Events by System Organ Class, High Level Term, Preferred Term and Treatment Group – Safety Analysis Set	Y	Y
14	Treatment-Emergent Tachycardia Adverse Events by System Organ Class, High Level Term, Preferred Term and Treatment Group – Safety Analysis Set	Y	Y
15	Listing of Treatment-Emergent Adverse Events Leading to Death – Safety Analysis Set	Y	Y
16	TEAEs of Toxicity Grade 3 or Higher by System Organ Class, High Level Term, and Preferred Term – Safety Analysis Set	Y	Y
17	Summary of Markedly Abnormal Lab Test: Hematology – Safety Analysis Set	Y	Y
18	Summary of Markedly Abnormal Lab Test: Serum Chemistry – Safety Analysis Set	Y	Y
19	Summary of Markedly Abnormal Vital Signs – Safety Analysis Set	Y	Y
20	Summary of 12-Lead ECG Parameters and Change from Baseline by Visit – Safety Analysis Set	Y	Y

Additional efficacy tables for primary and selected secondary/exploratory efficacy endpoints will be provided.

Number	Table Title	Blinded	Unblinded
21	Summary of Complete Responders in First 6 Hours Post-Surgery by Randomized Treatment Group – FAS	N	Y
22	Summary of Complete Responders in First 6 Hours Post-Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
23	Summary and Analysis of Complete Response Within 24 Hours Post Surgery by Randomized Treatment Group – FAS	N	Y
24	Summary and Analysis of Complete Response Within 24 Hours Post Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
25	Summary of Emesis in First 6 Hours Post-Surgery by Randomized Treatment Group – FAS	N	Y
26	Summary of Emesis in First 6 Hours Post-Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
27	Summary and Analysis of Emesis Within 24 Hours Post Surgery by Randomized Treatment Group – FAS	N	Y
28	Summary and Analysis of Emesis Within 24 Hours Post Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
29	Summary and Analysis of Absence of Nausea Within 24 Hours Post Surgery by Randomized Treatment Group – FAS	N	Y
30	Summary and Analysis of Absence of Nausea Within 24 Hours Post Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
31	Summary and Analysis of Rescue Therapy for Breakthrough PONV Within 24 Hours Post Surgery by Randomized Treatment Group – FAS	N	Y
32	Summary and Analysis of Rescue Therapy for Breakthrough PONV Within 24 Hours Post Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
33	Summary and Analysis of Total Response Within 24 Hours Post Surgery by Randomized Treatment Group – FAS	N	Y
34	Summary and Analysis of Total Response Within 24 Hours Post Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
35	Summary of Complete Responders in First 3 Hours Post-Surgery by Randomized Treatment Group – FAS	N	Y
36	Summary of Complete Responders in First 3 Hours Post-Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
37	Summary of Emesis in First 3 Hours Post-Surgery by Randomized Treatment Group – FAS	N	Y
38	Summary of Emesis in First 3 Hours Post-Surgery by Actual Treatment Received – Safety Analysis Set	N	Y
39	Summary of Time from End of Surgery to First Emetic Event by Randomized Treatment Group – FAS	N	Y
40	Summary of Time from End of Surgery to First Emetic Event by Actual Treatment Received – Safety Analysis Set	N	Y

Appendix D Criteria for Identification of Markedly Abnormal Laboratory Values and Vital Sign Values.

Hematology—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
Hemoglobin	SI	<0.8 × LLN	>1.2 × ULN
Hematocrit	SI	<0.8 × LLN	>1.2 × ULN
RBC count	SI	<0.8 × LLN	>1.2 × ULN
WBC count	SI	<0.5 x LLN	>1.5 x ULN
Platelet Count	SI	$<75 \times 10^9$/L	$>600 \times 10^9$/L

LLN=lower limit of normal, RBC=red blood cell, ULN=upper limit of normal, WBC=white blood cell.

Serum Chemistry—Criteria for Markedly Abnormal Values

Parameter	Unit	Low Abnormal	High Abnormal
ALT	SI	--	>3x ULN
AST	SI	--	>3x ULN
GGT	SI	--	>3*ULN, if baseline is normal; >2*baseline, if baseline is high abnormal
Alkaline phosphatase	SI	--	>3*ULN, if baseline is normal; >2*baseline, if baseline is high abnormal
Total Bilibrubin	SI	--	>1.5*ULN, if baseline is normal; >1.5*baseline, if baseline is high abnormal
Albumin	SI	<25 g/L	--
Total protein	SI	<0.8x LLN	>1.2x ULN
Creatinine	SI		>177 μmol/L
Blood urea nitrogen	SI		>10.7 mmol/L
Sodium	SI	<130 mmol/L	>150 mmol/L
Potassium	SI	<3.0 mmol/L	>5.5 mmol/L
Glucose	SI	<3 mmol/L	>10 mmol/L*
Chloride	SI	<75 mmol/L	>126 mmol/L
Calcium	SI	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	
Bicarbonate	SI	<8.0 mmol/L	

ALT=alanine aminotransferase, AST=aspartate aminotransferase, GGT=γ-glutamyl transferase, LLN=lower limit of normal, ULN=upper limit of normal.

Appendix E Criteria for Markedly Abnormal Values for Vital Signs

Parameter	Unit	Lower Criteria	Upper Criteria
Systolic blood pressure	mm Hg	<85	>140
Diastolic blood pressure	mm Hg	<50	>90
Body temperature	°C	<35.6	>37.7
	°F	<96.1	>99.9
Heart rate (traditional clinical consensus)	bpm	<60	>100
Respiratory Rate	breath per minute	<12	>16
BMI		<18.5	>25.0 • Class 1: BMI of 30 to <35 • Class 2: BMI of 35 to <40 • Class 3: BMI of 40 or higher.

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	28-Feb-2022 17:02 UTC