CLINICAL STUDY PROTOCOL

NCT Number: NCT03827655

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Ranging Study to Evaluate the Efficacy and Safety of 2 Dose Regimens of Intravenous TAK-954 for the Prophylaxis and Treatment of Postoperative Gastrointestinal Dysfunction in Patients Undergoing Large- and Small-Bowel Resection

Study Number: TAK-954-2004

Protocol Version and Date:

Version 5.0: 25-March-2021

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TAKEDA PHARMACEUTICALS

PROTOCOL

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Ranging Study to Evaluate the Efficacy and Safety of 2 Dose Regimens of Intravenous TAK-954 for the Prophylaxis and Treatment of Postoperative Gastrointestinal Dysfunction in Patients Undergoing Large- and Small-Bowel Resection

Sponsor:	Takeda Development Center Americas, Inc. 95 Hayden Avenue Lexington, MA 02421		
Study Number:	TAK-954-2004		
IND Number:	140120	**EudraCT Number:**	2018-003318-42
Compound:	TAK-954		
Date:	23 March 2021	**Version/Amendment Number:**	5

Amendment History:

Date	Amendment Number	Amendment Type	Region
23 March 2021	Amendment 5	Substantial	Global
09 July 2019	Amendment 4	Substantial	Global
13 May 2019	Amendment 3	Substantial	Local (Germany)
23 April 2019	Amendment 2	Nonsubstantial	Local (Belgium)
19 December 2018	Amendment 1	Not applicable	Global
15 October 2018	Initial protocol	Not applicable	Global

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1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

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

Takeda Development Center Americas, Inc. (TDCA) 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	European Contact
Serious adverse event and pregnancy reporting	PRA PVS Clinical Operations: Email: MHGSafety@prahs.com Fax: +44 1792 525720	PRA PVS Clinical Operations: Email: MHGSafety@prahs.com Fax: +44 1792 525720
Medical Monitor (medical advice on protocol and study drug)	Medical Director, Clinical Science	Medical Director, Clinical Science
Responsible Medical Officer (carries overall responsibility for the conduct of the study)	Medical Director, Clinical Science	Medical Director, Clinical Science

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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

The signature of the responsible Takeda medical officer (and other signatories, as applicable) can be found on the signature page.

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

[redacted] MD Date
[redacted]
Gastrointestinal Motility Clinical Sciences

[redacted] PhD Date
[redacted]
Statistical & Quantitative Sciences

[redacted] PhD Date
[redacted]
Quantitative Clinical Pharmacology

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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 (Appendix B).

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

_____

Signature of Investigator Date

_____

Investigator Name (print or type)

_____

Investigator's Title

_____

Location of Facility (City, State/Province)

_____

Location of Facility (Country)

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1.3 Protocol Amendment Summary of Changes

Protocol Amendment 5 Summary and Rationale:

This section describes the changes in reference to the protocol incorporating Amendment 5.

The primary reason for this amendment is to maintain subject safety and study integrity and provide flexibility to study participants in the context of the global coronavirus disease 2019 (COVID-19) pandemic as permitted by local regulations. Study modifications to mitigate the impact of COVID-19 include the addition of Exclusion Criterion 15 for subjects with known COVID-19 infection, the addition of flexibility in procedures and the expansion of the duration of the screening period (including potential screening of subjects on the day of surgery), the allowance for a follow-up visit 14 days after the last dose to be performed via a phone call, the inclusion of COVID-19 as a reason for subject discontinuation from the study, and the allowance of electronic signature on the informed consent form if approved by the site institutional review boards/ethics committees.

Protocol Amendment 5 includes the addition of inclusion and exclusion criteria related to the American Society of Anesthesiologists (ASA) physical status classification and severe comorbidities to not enroll subjects with high risk of surgery.

This amendment also provides additional information from the updated Investigator's Brochure Edition 5 (13 April 2020) that clarified mean TAK-954 exposure, added completed TAK-954 studies, and provided additional information concerning the benefit-risk profile (Section 4.3 Benefit-Risk Profile).

In addition, this amendment clarifies the inclusion/exclusion criteria, changes to study assessments, and clarifies or modifies study procedures: removal of glucose-dependent insulinotropic peptide (GIP) and DNA blood sampling; adjustment of the number of and collection time windows of pharmacokinetic (PK) samples; adjustment of timing and number of electrocardiogram (ECG) procedures; and defined time assessment windows for the Day 14 visit, ECG procedures, and biomarker sampling.

Notably, just before this amendment, the planned interim analysis (IA) was conducted in accordance with the protocol to allow the internal monitoring committee (IMC) to review the safety and efficacy data. The IMC recommended the discontinuation of 2 active treatment arms, and Amendment 5 does update some of the language around dosing arms to reflect that change.

Additionally, a revised sample size is provided for the remaining 3 treatment arms based on blinded assessments that were conducted using efficacy assumptions of the original protocol before the IA to mitigate the statistical, clinical, and operational risks to this study due to COVID-19 pandemic (ie, not resulting from the IA and data monitoring committee review of IA).

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. Administrative changes incorporated in this amendment include changing the sponsor from

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Millenium Pharmaceuticals to Takeda due to legal entity changes, updated signatories, corrections and clarifications of discrepancies in Amendment 4.

Protocol Amendment 5			
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.	Title page Section 1.1 Contacts Section 2.0 STUDY SUMMARY	Changed sponsor from Millennium Pharmaceuticals to Takeda.	Legal entity change.
2.	Section 2.0 STUDY SUMMARY Figure 6.b Schematic of Study Design By Protocol Amendment 5 (added) Section 13.3 Determination of Sample Size	Revised to reflect the total sample size of 180 for the study. Added new figure to indicate study design after Protocol Amendment 5.	To clarify based on the actual subjects recruited before Protocol Amendment 5 and subjects needed in remaining dosing arms to reach an overall number of 50 subjects/arm for final analysis.
3.	Section 2.0 STUDY SUMMARY Section 5.1.2 Secondary Objectives	Clarified the secondary objective related to relative efficacy and safety was for accelerating the recovery of gastrointestinal (GI) function postsurgery. Specified time window of up to 10 days for study drug dosing for the secondary objective of determining efficacy and safety of preoperative dosing of intravenous TAK-954 relative to preoperative and postoperative regimens.	Clarification. To align time window of secondary objectives because "up to 10 days" of dosing was inadvertently omitted previously in this secondary objective.
4.	Section 2.0 STUDY SUMMARY Section 5.2.1 Primary Endpoint Section 5.2.2 Secondary Endpoints Section 6.1 Study Design Section 9.1.6 Primary Efficacy Measurement Section 13.1.3 Efficacy Analysis	Refined the definition of the primary efficacy endpoint time to resolution of upper and lower GI function by specifying "from the end of surgery", defined tolerance to solid food as "first occurrence" of absence of vomiting or clinically significant nausea for 1 calendar day after a solid meal, and clarified that the follow-up time for the primary endpoint is up to Day 10 postsurgery.	To clarify the definition of the primary endpoint.

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Protocol Amendment 5			
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 5.2.2 Secondary Endpoints	Clarified the timing for subjects requiring nasogastric (NG) tubes postsurgery and clarified plasma TAK-954 concentrations will be measured.	To clarify the presented information.
6.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 8.2 Study Drug Assignment and Dispensing Procedures	Removed minimum percentage of subjects required for each surgery type (laparoscopic or open procedures).	Updated to adjust for changes in standard of care (SOC) practices for targeted surgery types.
7.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Figure 6.b Schematic of Study Design By Protocol Amendment 5 (added) Section 8.2 Study Drug Assignment and Dispensing Procedures Section 13.2 IA and Criteria for Early Termination	Revised sample size of remaining arms based on blinded assessments that were conducted using efficacy assumptions of the original protocol before the interim analysis (IA). Removed the second IA. Revised the language to reflect these changes. Added new figure to indicate study design after Protocol Amendment 5.	To mitigate the statistical, clinical, and operational risks to this study due to coronavirus disease 2019 (COVID-19), the second IA was removed and the sample size of the remaining arms were revised based on blinded assessments that were conducted using efficacy assumptions of the original protocol before the IA.
8.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design	Randomizations into 2 treatment groups (TAK-954 0.1 mg/100 mL preoperative and daily and TAK-954 0.1 mg/100 mL preoperative only) have been discontinued based on the IA results.	Internal monitoring committee (IMC) recommendation based on review of safety and efficacy data from the IA in accordance with the approved protocol.
9.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 7.2 Exclusion Criteria Section 7.4 Criteria for	Modified protocol for impact of COVID-19 as follows: • Added Exclusion Criterion 15 for subjects with COVID-19. • Allowed changes to the procedure for collecting health-related	To include contingencies for impact of COVID-19.

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Protocol Amendment 5			
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***
	Discontinuation or Withdrawal of a Subject Section 9.1.1 Informed Consent Procedure Section 9.1.3 Physical Examination Procedure (Including Neurology Examination) Section 9.1.5 Vital Sign Procedure Section 9.1.12 Procedures for Clinical Laboratory Samples Section 9.1.15 ECG Procedure Section 9.1.21 Quality of Life Assessment (formerly Section 9.1.20) Section 12.1 CRFs (Electronic and Paper) Section 14.1 Study-Site Monitoring Visits Appendix A Schedule of Study Procedures	quality of life assessments. • Increased screening period start from Day -14 to Day -21. • Changed screening period end from Day -1 to Day 1 to allow for screening to occur on the day of but before randomization. • Allowed procedures such as the screening physical examinations, vital signs, laboratory tests, and electrocardiogram (ECG) performed on the day of but before surgery to be used as baseline. • Allowed vital signs, ECG, physical examination, and clinical laboratory parameters collected as SOC assessments within 21 days of randomization to be used for study screening purposes. • Allowed glycosylated hemoglobin (HbA1c) collected as SOC within 30 days of informed consent to be used for study screening purposes. • Allowed follow-up visit at 14 days post last dose to be performed via a phone call if necessary while an in-person visit is preferred. • Allowed electronic signature on the informed consent form if approved by site institutional review board/ethics committees. • Allowed remote source document verification as a method of study monitoring.	

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	Location	***Description***	***Rationale***
10.	Section 2.0 STUDY SUMMARY Section 6.1 Study Design Section 9.1.3 Physical Examination Procedure (Including Neurology Examination) Section 9.1.10 Documentation of Concomitant Medications Section 9.1.21 Quality of Life Assessment Appendix A Schedule of Study Procedures	Defined time assessment windows for the follow-up visit at 14 days post last dose.	To provide guidance for assessment window.
11.	Section 2.0 STUDY SUMMARY Section 7.1 Inclusion Criteria	Added inclusion criterion related to the American Society of Anesthesiologists (ASA) physical status classification limiting to ASA 1 to 3.	To exclude subjects at high risk for surgery (ie, ASA 4 or greater).
12.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria Section 10.1.6.4 Abnormal Liver Tests	Revised exclusion criteria for scheduled surgery and liver tests, added cardiac conduction abnormality, and added exclusion to support investigator's opinion as to whether study participation is appropriate for the subject.	To clarify exclusion criteria for eligibility assessment and to allow for any other circumstances in which the investigator does not advise study participation.
13.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Clarified the exclusion criterion on prior medication to reference the exclusion of alvimopan, erythromycin, prucalopride, metoclopramide, domperidone, or azithromycin in the 24 hours before starting **study drug** (not before surgery). Added cisapride, mosapride, and renzapride to this list of excluded medications.	Clarification on the timing of excluded medications. To be consistent between exclusion criteria and excluded medications.
14.	Section 2.0 STUDY SUMMARY Section 7.2 Exclusion Criteria	Added 2 exclusion criteria to exclude subjects with high risk cardiac and pulmonary comorbidities.	To exclude subjects at high risk for surgery due to comorbidities.

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Protocol Amendment 5			
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.	Section 2.0 STUDY SUMMARY Section 7.2Exclusion Criteria	Added exclusion criterion regarding emergency surgery.	To clarify as emergency surgery is not within the intended patient population of the study.
16.	Section 7.4 Criteria for Discontinuation or Withdrawal of a Subject	Revised study withdrawal criteria to discontinue dosing in the event that surgery results in significant resection of rectal tissue, a >50% resection of colon tissue, or an ostomy.	To remove subjects from the study for whom study drug treatment is no longer indicated.
17.	Section 7.4 Criteria for Discontinuation or Withdrawal of a Subject Section 9.1.12 Procedures for Clinical Laboratory Samples Section 10.1.6.4 Abnormal Liver Tests Section 10.1.6.5 AESI Appendix A Schedule of Study Procedures footnote (i)	Revised liver function tests to liver tests.	Clarified because "liver function" is not an accurate term.
18.	Section 7.4 Criteria for Discontinuation or Withdrawal of a Subject	Regarding voluntary withdrawal, added the possibility that the subject may withdraw from the study or study drug.	Clarification of withdrawal situations.
19.	Section 7.4 Criteria for Discontinuation or Withdrawal of a Subject	Added "Additional efforts should be made and documented to encourage subject to participate in the follow-up portion of the study."	Clarification of follow-up procedures.
20.	Section 7.4 Criteria for Discontinuation or Withdrawal of a Subject Table 10.b Management of QT Prolongation by NCI CTCAE Grade	Corrected definition of Grade 3 and Grade 4 prolonged QT interval.	To correct error in the definition of Grade 3 and Grade 4 prolonged QT interval.
21.	Section 8.1.4 Overdose	Clarified mean exposure.	To revise the protocol based on updates to the Investigator's Brochure Edition 5 (13 April 2020).

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22.	Section 9.1.14 Pregnancy	Removed wording to clarify that if a subject is confirmed to be pregnant during the study, the subject should not be withdrawn from the study, rather withdrawn from study drug, and that study follow-up visits should be completed.	To clarify that safety follow-up visits for pregnant subjects are expected to assess subject safety.
23.	Section 2.0 STUDY SUMMARY Section 13.1.1 Analysis Sets	Added definition for per-protocol set (PPS) and simplified safety analysis set (SAF) by removing wording related to subjects who receive more than 1 treatment and the 2 most common treatments used with equal frequency used as actual treatment.	Added the PPS and simplified the SAF.
24.	Section 2.0 STUDY SUMMARY Section 13.1.3 Efficacy Analysis Section 13.3 Determination of Sample Size	Cochran-Mantel-Haenszel test is replaced by Miettinen and Nurminen's method for comparing percentages in the final analysis. Clarified primary and secondary efficacy analyses.	Changed the method for comparison of percentages for robustness in case the expected cell counts are low. Study sample size is revised for the remaining 3 treatment arms based on blinded assessments conducted using efficacy assumptions of the original protocol before the IA to mitigate statistical, clinical, and operational risks to this study due to the COVID-19 pandemic.
25.	Section 4.2 Rationale for the Proposed Study Section 4.3 Benefit-Risk Profile	Added updates per the current Investigator's Brochure Edition 5 (13 April 2020).	To provide additional information based on updates to the Investigator's Brochure Edition 5 (13 April 2020).

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Change Number	**Sections Affected by Change**	**Description of Each Change and Rationale**	
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26.	Section 4.2 Rationale for the Proposed Study Section 9.1.16 DNA Blood Sample Collection (deleted) Table 9.b Primary Specimen Collection Appendix A Schedule of Study Procedures	Removed glucose-dependent insulinotropic peptide (GIP) and DNA sampling. Removed mention of fibrinogen from protocol.	Recent evidence indicates low likelihood of GIP and DNA analyses being a predictor of disease or response. Therefore, the collection of samples for DNA and GIP will be discontinued; however, exploratory endpoint for GIP will be retained. Collected samples for GIP measurements will be analyzed and reported in the clinical study report. Fibrinogen was included in error in the original protocol.
27.	Section 5.2.4 Exploratory Endpoints	Clarified that the exploratory endpoint would be from the end of surgery to the **first** insertion of NG tube.	Clarification.
28.	Section 6.2 Justification for Study Design, Dose, and Endpoints	Revised text to indicate a scintigraphy study (TAK-954-2003) was completed.	Updated clinical information for completed TAK-954-2003 study as this was completed since the last amendment.
29.	Section 7.3 Excluded Medications	Added alvimopan to excluded medications list.	Alvimopan was inadvertently omitted from this section but was in the exclusion criteria of excluded medications.

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30.	Section 7.5 Procedures for Discontinuation or Withdrawal of a Subject	Added clarification and specification that sites should make every effort to conduct follow-up assessments at 14, 30, and 90 days post last dose on subjects who have discontinued study drug early but who have not withdrawn consent and that subjects who did not receive study drug do not need follow-up visits.	To ensure that any subject who discontinues study drug will receive safety follow-up assessments per protocol.
31.	Section 7.5 Procedures for Discontinuation or Withdrawal of a Subject	Added study "drug" termination.	Clarification of study drug termination.
32.	Section 7.5 Procedures for Discontinuation or Withdrawal of a Subject	Removed "Discontinued or withdrawn subjects may be replaced."	Subjects will not be replaced.
33.	Section 8.1.3 Dose and Regimen Table 8.b Dose and Regimen as a Result of Protocol Amendment 5 (added)	Revised section to describe the 3 remaining treatment groups in addition to the original 5 groups.	IMC recommendation based on review of safety and efficacy data from the IA.
34.	Section 9.1.2 Demographics, Medical History, and Medication History Procedure	Revised to clarify that all medications are to be collected and not just excluded medications.	Clarification of medication history to be obtained.
35.	Section 9.1.3 Physical Examination Procedure (Including Neurology Examination) Section 9.1.5 Vital Sign Procedure Section 9.1.15 ECG Procedure Section 9.1.16 Biomarker Sample Collection (previously Section 9.1.17) Section 9.1.17.1 Collection of Plasma for PK Sampling (formerly Section 9.1.18) Appendix A Schedule of Study Procedures	Clarified timing of neurological examinations, vital sign assessments, and ECGs; prioritized timing of assessments in instances where several occur simultaneously; adjusted number and collection time windows of PK samples; and added additional assessment of liver tests.	To ensure consistency within the protocol, define priority of specific assessments, improve operational feasibility, and add additional liver testing assessments.

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36.	Section 9.1.6 Primary Efficacy Measurement Appendix A Schedule of Study Procedures	Defined timing of study procedure assessments relative to achievement of primary efficacy endpoint to include circumstances in which a minor protocol deviation might occur.	To clarify when a minor protocol deviation might occur relative to timing of primary efficacy measurement.
37.	Section 9.1.15 ECG Procedure	Clarified that ECG changes relative to baseline values are considered adverse events (AEs) if they meet the definition of clinical significance per CTCAE v5.0 or are the result of diagnosed pathology.	To clarify when ECG changes should be reported as AEs.
38.	Section 9.1.15 ECG Procedure	Added heart rate corrected QT interval will be calculated using Fridericia formula and specified the specific formula; added QRS as another ECG parameter for assessment and the same formula should be used to assess eligibility.	To specify method of calculating heart rate corrected QT interval, and include the QRS parameter for ECG assessment.
39.	Section 9.1.17 PK Sample Collection	Clarified that collected TAK-954 samples analyzed for metabolites, if indicated, would be reported in PK listings only.	Clarified that any results will not be provided in the clinical study report.
40.	Section 9.1.19 Documentation of Screen Failure (formerly Section 9.1.20)	Language was added to indicate that the screening electronic case report forms (eCRFs) should be completed and that follow-up visits are not necessary if a subject withdraws after signing the informed consent form. Also, the primary reason should be added to the subject source documents as well as the eCRF. Instructions were added that subjects may be rescreened 1 time.	Clarification of the procedure for screen failures.
41.	Section 9.1.8 Clinical Assessments	Clarified the investigator's assessment of the need for reinsertion of a prophylactic NG tube in the postoperative period.	Clarification.
42.	Section 10.1.4 SAEs	Deleted Table 10.a Takeda Medically Significant AE List.	This table has been retired per Takeda's standard practice.

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	Location	***Description***	***Rationale***
43.	Section 10.1.4 SAEs	Regarding serious adverse events (SAEs), removed "at any dose" because that excludes SAEs after informed consent and before dosing.	Correction of text.
44.	Section 10.2.1.2 AE Reporting	Deleted "Subjects experiencing a SAE caused by a protocol-mandated intervention must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation of the change."	Duplicated text contained in the next paragraph.
45.	Section 13.1.4 PK Analysis	Clarified plasma concentrations will be summarized by dose/regimen at study scheduled day/time point.	To specify summary statistics will be performed.
46.	Section 15.1 IRB and/or IEC Approval	Corrected subject incentives to subject reimbursements.	Subject reimbursement is the correct term.
47.	Appendix A Schedule of Study Procedures	Added footnote (e) for inclusion/exclusion criteria to explain that on baseline/Day 1, excluded medications in the 24 hours before surgery need to be reassessed.	Clarification of exclusion criteria regarding excluded medications.
48.	Appendix A Schedule of Study Procedures	Added "X"s to the screening column for concomitant medical procedures and concomitant medications. Added "X" at early termination for clinical laboratory evaluations to include pregnancy test. Added "X" to screening column for AE assessment.	Corrections.
49.	Appendix A Schedule of Study Procedures	Added "The start time of surgery is the start of general anesthesia" to footnote (m) regarding start and stop times of surgery.	Clarification.

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LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda Development Center Americas, Inc.	**Compound:** TAK-954	
Title of Protocol: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Dose Ranging Study to Evaluate the Efficacy and Safety of 2 Dose Regimens of Intravenous TAK-954 for the Prophylaxis and Treatment of Postoperative Gastrointestinal Dysfunction in Patients Undergoing Large- and Small-Bowel Resection	**IND No.:** 140120	**EudraCT No.:** 2018-003318-42
Study Number: 2004	**Phase:** 2b	

Study Design:

This phase 2, randomized, placebo-controlled, parallel 5-group, double-blind study is designed to determine: (1) if TAK-954 decreases the duration of gastrointestinal (GI) dysfunction in patients undergoing major abdominal open or laparoscopic-assisted surgeries that involve significant bowel manipulation, (2) whether preoperative dosing alone or a preoperative and postoperative dosing regimen is the most effective dosing regimen to decrease the duration of postoperative GI dysfunction (POGD) and improve clinical outcomes, and (3) the most appropriate dose and dosing regimen to advance into phase 3.

Subjects will be randomized in a 1:1:1:1:1 ratio into 1 of 5 parallel treatment groups:

- Regimen 1: Placebo (normal saline 100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function (ie, resolution of POGD) or for up to 10 days.
- Regimen 2: TAK-954 (0.1 mg/100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function or for up to 10 days.
- Regimen 3: TAK-954 (0.5 mg/100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function or for up to 10 days.
- Regimen 4: TAK-954 (0.1 mg/100 mL infusion over 60 minutes) preoperation and daily placebo infusions postoperation until return of upper and lower GI function or for up to 10 days.
- Regimen 5: TAK-954 (0.5 mg/100 mL infusion over 60 minutes) preoperation and daily placebo infusions postoperation until return of upper and lower GI function or for up to 10 days.

Subject randomization will be stratified by laparoscopic and open surgery procedures.

Following an interim analysis (IA) specified in Protocol Amendment 4, 2 of the above TAK-954 regimens are discontinued based on internal monitoring committee (IMC) recommendations. As a result, eligible subjects will be equally randomized to into 1 of 3 the remaining parallel treatment groups:

- Regimen 1: Placebo (normal saline 100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function (ie, resolution of POGD) or for up to 10 days.
- Regimen 3: TAK-954 (0.5 mg/100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function or for up to 10 days.
- Regimen 5: TAK-954 (0.5 mg/100 mL infusion over 60 minutes) preoperation and daily placebo infusions postoperation until return of upper and lower GI function or for up to 10 days.

It is standard of practice for the postoperative care of patients after colorectal surgery to implement an enhanced recovery pathway (ERP) to reduce the time to recovery of GI function (motility). To provide a consistent ERP as baseline therapy for all subjects, they will receive the same core features of an ERP for postoperative care as outlined below:

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Core ERPs:

- Minimize opioid use while maintaining adequate pain control through use of multimodal analgesia. Suggested analgesics include opioid alternatives such as nonsteroidal anti-inflammatory drugs (eg, ketorolac tromethamine IV), acetaminophen (paracetamol), or oral pregabalin when possible. It is recommended that at least 2 different analgesics with different mechanism of action are tried and failed before prescribing opioids.
- Maintenance of euvolemia and normal salt and electrolyte state in perioperative period.
- No routine use of prophylactic nasogastric (NG) tubes postsurgery. NG tubes should only be used if there is a documented medical reason to justify them.
- Use of a standardized risk-based strategy for postoperative nausea and vomiting (PONV) prophylaxis: use of preoperative antiemetic prophylaxis in patients with 1 or more risk factors of the simplified Apfel Score (female gender, planned postoperative use of opioids, nonsmokers, history of PONV/motion sickness).
- Early oral feeding postsurgery when possible. Clear liquids after the surgery on Day 1, advancing to soft diet on Day 2 if tolerant to liquids (no nausea or vomiting).
- Early mobilization starting after the surgery on Day 1 when possible.

Criteria for resolution of upper and lower GI function is time to first tolerance of solid food (defined as no vomiting or no clinically significant nausea for 1 calendar day after a solid meal) and time to first spontaneous bowel movement, whichever occurs later, up to Day 10 postsurgery.

Following hospital discharge, subjects will be instructed to contact their physician if they have recurring symptoms suggestive of POGD to evaluate the need for hospital readmission in case of relapse. All subjects will return to clinic for a follow-up visit 14 days (±4 days) post last dose; however, during the coronavirus disease 2019 (COVID-19) public health emergency, the follow-up visit 14 days post last dose may be conducted via phone call (eg, collection of AEs, concomitant medications, and monitoring) to extend flexibility to study subjects. In the case of a phone call follow-up, physical examination (including neurology examination), vital signs, or pregnancy test would not be collected; however, AEs will be assessed, including safety check on any emerging clinical signs or symptoms. Subjects may be requested to return to the site for further safety assessment due to reported AEs at the investigator's discretion. The type of visit (whether clinic visit or phone call) must be recorded in the study records. Quality of life assessments will be completed by the subject in their home on the same day as the safety follow-up call and completed questionnaires will be mailed to the clinic. Subjects will be contacted by phone 30 (±3 days) and 90 days (±7 days) posttreatment for a safety follow-up.

Two preplanned IAs will be conducted when *a priori* enrollment goals have been achieved. Bayesian approach will be applied after these IAs for decision making for potential study modification including futility, dose and dosing regimen decision, and sample size adjustment. In case dose modification is needed after the IA, the maximal dose for potential modification of doses/regimens will be 1.0 mg. The duration of drug administration (up to 10 days postsurgery) will not be changed. By this protocol amendment, the second IA is removed from the protocol.

Primary Objectives:

To assess the efficacy and safety of intravenous (IV) TAK-954 for accelerating the recovery of GI function postsurgery in patients undergoing open or laparoscopic-assisted partial small- or large-bowel resection.

Secondary Objectives:

- To determine efficacy and safety of preoperative dosing of IV TAK-954 relative to preoperative and postoperative regimens of up to 10 days of IV TAK-954 for accelerating the recovery of GI function postsurgery.
- To determine the relative efficacy and safety of 0.1 mg and 0.5 mg IV TAK-954 given either preoperatively alone or preoperatively and postoperatively compared with placebo of up to 10 days or resolution of GI dysfunction postsurgery for accelerating the recovery of GI function postsurgery.
- To determine the pharmacokinetics (PK) of TAK-954 in patients undergoing major abdominal surgery.

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<table>
<tr><td colspan="2">Subject Population: Patients undergoing elective open or laparoscopic-assisted partial small— or large—bowel resection.</td></tr>
<tr><td>Number of Subjects:
The planned total sample size prior to Protocol Amendment 5 is approximately 200 to 375 subjects:
TAK-954 0.1 mg/100 mL preoperative and daily: minimum of 25 and up to a maximum of 100 subjects.
TAK-954 0.1 mg/100 mL preoperative only: minimum of 25 and up to a maximum of 100 subjects.
TAK-954 0.5 mg/100 mL preoperative and daily: minimum of 25 and up to a maximum of 100 subjects.
TAK-954 0.5 mg/100 mL preoperative only: minimum of 25 and up to a maximum of 100 subjects.
Placebo: 100 subjects preoperatively and daily.
With this Protocol Amendment 5, the planned total sample size is approximately 180 subjects:
Enroll additional subjects to reach overall total of 50 subjects/remaining treatment groups (actually accumulated sample size at IA plus the number of additional subjects to be enrolled after the IA) for the study:
TAK-954 0.5 mg/100 mL preoperative and daily: minimum overall total of approximately 50 subjects.
TAK-954 0.5 mg/100 mL preoperative only: minimum overall total of approximately 50 subjects.
Placebo: overall total of approximately 50 subjects preoperatively and daily.</td><td>Number of Sites:
Estimated total: approximately 30 in North America and Europe.</td></tr>
<tr><td>Dose Levels:
Prior to Protocol Amendment 5: TAK-954 0.1 and 0.5 mg
Placebo
By Protocol Amendment 5: TAK-954 0.5 mg
Placebo</td><td>Route of Administration:
TAK-954 IV
Placebo IV</td></tr>
<tr><td>Duration of Treatment:
Resolution of postoperative GI function or 10 days.</td><td>Period of Evaluation:
Up to 10-day treatment period; 14-day observation period post last dose for recurrence of symptoms (inpatient or outpatient); safety follow-up 14 (±4 days), 30 (±3 days), and 90 days (±7 days) post last dose.</td></tr>
</table>

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Main Criteria for Inclusion:

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

- The subject is male or female (and not pregnant) and is at least 18 years old.
- The subject is scheduled to undergo a laparoscopic-assisted, or open partial small- or large-bowel, resection.
- The subject's American Society of Anesthesiologists (ASA) physical status classification is ASA 1 to 3.
- A female subject of childbearing potential willing and agreeable to use highly effective contraception or sexual abstinence during the course of the study and up to 30-days posttreatment.

Main Criteria for Exclusion:

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

- Has significant mechanical bowel obstruction that is not expected to resolve after the surgery, short bowel syndrome, pre-existing clinically significant GI motility disorder (eg, gastroparesis, scleroderma, chronic intestinal pseudo-obstruction), uncontrolled diabetes (glycosylated hemoglobin [HbA1c] >10%), has an active gastric pacemaker, or requires parenteral nutrition.
- Previous major abdominal surgery (eg, gastrectomy, gastric bypass, gastric sleeve, lap banding, Whipple, pancreatic resection, total/subtotal colectomy, hemicolectomy, extensive bowel resection).
- History of radiation therapy to the abdomen or pelvis.
- Scheduled to undergo any of the following surgeries: low anterior resection, total or subtotal colectomy, colostomy, ileostomy, or reversal of stoma, or has a diagnosis that requires rectal resection (eg, tumors in the anorectum) and will likely require lower anterior resection surgery. Subjects with planned surgery for which there is no anticipated significant rectal resection and is, therefore, likely to preserve anorectal function and continence postsurgery, will likely be eligible for inclusion in the study if they meet all the study inclusion/exclusion criteria (eg, subjects with lesions not involving the rectum [sigmoid colon and above]).
- Has pre-existing hepatic disease that meets Child-Pugh Class B (moderate; total score 7 to 9 points) or C (severe; total score 10 to 15 points).
- Has alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN), or total bilirubin >2 × ULN.
- Has an estimated glomerular filtration rate <30 mL/min.
- Has received alvimopan, erythromycin, prucalopride, metoclopramide, domperidone, cisapride, mosapride, renzapride, or azithromycin in the 24 hours prior to starting study drug.
- Has a resting heart rate of <50 beats per minute (bpm).
- Has clinically significant electrocardiogram (ECG) abnormalities indicative of cardiac conduction abnormality or acute cardiac instability as determined by the investigator at screening; more than first degree atrioventricular (AV) block; >5 beats of nonsustained ventricular tachycardia (VT) at a rate >120 bpm; or ECG changes consistent with acute myocardial ischemia or infarction.
- Has a QT interval with Fridericia correction method (QTcF) interval ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events at screening. The records of subjects with bundle branch block and a prolonged QTcF should be reviewed by a medically qualified person in consultation with the medical monitor and the sponsor for potential inclusion.
- Had acute myocardial infarction or ischemia within the past 12 months. Subjects with increased cardiac risks for surgery including coronary artery disease or prior myocardial infarction and evidence of reduced left ventricular function or history of angina should be assessed by the investigator for stability and control of their cardiac condition and risk of surgery, and excluded if in the investigator's opinion, participation in the study is not considered appropriate. The sponsor should be consulted if subjects with these conditions are considered by the investigator to be acceptable.

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- Had pulmonary embolism, deep venous thrombosis, or mechanical ventilation for any medical condition within the past 12 months. Subjects with a history of multiple venous thrombosis or pulmonary embolic events, history of a hypercoagulable condition, history of severe exacerbation for chronic obstructive pulmonary disease or evidence of pulmonary hypertension should be assessed by the investigator for stability and control of their conditions and risk of surgery, and excluded if in the investigator's opinion, participation in the study is not considered appropriate. The sponsor should be consulted if subjects with these conditions are considered by the investigator to be acceptable.
- Scheduled for abdominal surgery that is classified as emergency.

Main Criteria for Evaluation and Analyses:

The primary efficacy endpoint for this study is time from the end of surgery to resolution of upper and lower GI function (ie, time to tolerance of solid food [defined as first occurrence of no vomiting or no clinically significant nausea for 1 calendar day after a solid meal] and time to first spontaneous bowel movement, whichever occurs later) up to Day 10 postsurgery.

Secondary endpoints for this study are:

- Time from the end of the surgery (time the incision is closed) until ready for discharge (defined as the time until the subject presents effective intestinal transit [spontaneous bowel movement], tolerates solids without vomiting or clinically significant nausea for 1 calendar day after a solid meal, has satisfactory pain control with oral analgesics, and is medically stable/free of complications).
- Time from the end of surgery until the discharge order is written.
- Time from the end of the surgery to discharge from hospital.
- Time from end of surgery to tolerance of solid food (defined as first occurrence of intake of solids without vomiting or clinically significant nausea for 1 calendar day after a solid meal) up to Day 10 postsurgery.
- Time from end of surgery to first spontaneous bowel movement (defined as a stool not induced by the use of enemas or laxatives) up to Day 10 postsurgery.
- Percent of subjects with POGD ≥5 days, defined as subjects unable to tolerate solid foods, take anything by mouth, or requiring insertion or reinsertion of NG at or after 5 days postsurgery.
- Percentage of subjects requiring insertion of NG tube postsurgery, for drainage and symptom relief in case of persistent nausea and vomiting postsurgery up to Day 24 postsurgery (up to 10-day treatment period plus 14-day observation period post last dose for recurrence of symptoms).
- Time from end of surgery to first flatus up to Day 10 postsurgery.
- Observed plasma concentration of TAK-954 at the end of infusion on Day 1.

Statistical Considerations:

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

The per-protocol set (PPS) will include all FAS subjects who had no major protocol deviation that could confound the interpretation of the primary analyses based on the FAS. The major protocol deviations that lead to a subject's exclusion from the FAS to form the PPS will be specified in the statistical analysis plan. The PPS will be used to perform sensitivity analysis for the efficacy endpoints.

The safety analysis set (SAF) will include all subjects who were randomized and received at least 1 dose of double-blind study drug. In SAF, subjects will be analyzed according to the treatment they received.

In the final analyses of efficacy endpoints, for the 2 discontinued treatment arms, only the summary statistics (n, mean, SD, median, minimum, and maximum for continuous endpoints; number and percentage of subjects for categorical data; the number and percentages of events and censoring, median, minimum, and maximum for time to event endpoint) will be provided; for the remaining treatment groups after IA, the inferential statistics (point estimates of

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interest and 90% CIs and 1-sided p-values) for each treatment group and the TAK-954 doses/regimens in comparison with placebo will be provide along with summary statistics.

Primary Efficacy Analysis: The primary endpoint will be analyzed using the Cox proportional hazard model with treatment group as a single covariate, with Efron's method of tie handling, stratified by randomization stratification factor. Hazard ratios between TAK-954 doses/regimens and placebo and their 90% CIs based on the Cox model will be presented. P-values for the comparisons of TAK-954 doses/regimens and placebo will be calculated using Wald chi-square test based on the Cox model and presented. Median time to resolution of upper and lower GI function will be estimated by Kaplan-Meier survival analysis. The hazard ratios and median time differences between TAK-954 doses/regimens and placebo will be used to express the magnitude of treatment effects. The statistical tests will be 1-sided comparing TAK-954 doses/regimens to placebo. As a sensitivity analysis, the primary endpoint will be analyzed using the same method above based on PPS.

Secondary Efficacy Analysis: The secondary endpoints time to tolerance of solid food from the end of surgery, time to first spontaneous bowel movement from the end of surgery, time from the end of surgery until ready for discharge, time from the end of surgery until the discharge order is written, time from the end of surgery to discharge from hospital, and time from the end of surgery to first flatus will be analyzed using similar statistical methods described for the primary efficacy analysis.

The comparisons of TAK-954 dose levels and placebo in percent of subjects with POGD ≥5 days and the percent of subjects requiring insertion of NG tube postsurgery will be based on the Miettinen and Nurminen's method stratified by randomization stratification factor for risk difference.

Sample Size Justification:

Assuming 80% of subjects will have resolution of POGD at the end of study in the placebo group and 92.5% of subjects will have resolution of POGD at the end of study in the active TAK-954 doses, a total of approximately 300 subjects (100 per treatment group) will provide 80% power with a 0.05 2-sided significance level under Protocol Amendment 4.

In order to mitigate the statistical, clinical, and operational risks to this study in light of the COVID-19 pandemic, the probability of success of the study is re-estimated by blinded assessments using efficacy assumptions of Protocol Amendment 4. Specifically, by the removal of the second IA per this amendment and changing the statistical significance level from 2-sided 5% to 1-sided 5%, the resulting sample size is an overall total of 50 subjects for each remaining arm. Under these revised assumptions and the dropping of 2 arms, an overall total of approximately 180 subjects for the study will provide approximately 80% probability, for at least 1 remaining TAK-954 treatment arm, that TAK-954 is superior to placebo in time to resolution of upper and lower GI function at a 1-sided 5% significance level for the final analysis.

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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 clinical supplier list in the study manual. The vendors identified in the template for specific study-related activities will perform these activities in full or in partnership with the sponsor.

3.2 Principal Investigator/Coordinating Investigator

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

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3.3 List of Abbreviations

5-HT_4	5-hydroxytryptamine receptor 4
AE	adverse event
ASA	American Society of Anesthesiologists
AESI	adverse events of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC_{24}	area under the concentration-time curve from time 0 to 24 hours
$AUC_{24, ss}$	area under the concentration-time curve from time 0 to 24 hours at steady state
AV	atrioventricular
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
BMI	body mass index
bpm	beats per minute
CEC	cardiovascular endpoint committee
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CV	cardiovascular
ECG	electrocardiogram
eCRF	case report form (electronic or paper)
EQ-5D	EuroQol 5-Dimensions Questionnaire
ERP	enhanced recovery pathway(s)
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic peptide
HbA1c	glycosylated hemoglobin
hCG	human chorionic gonadotropin
IA	interim analysis
ICH	International Conference on Harmonisation
ID	identification
IEC	independent ethics committee
IL	interleukin
IMC	internal monitoring committee
IND	Investigational Drug Application
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
LOS	length of stay
MCP	monocyte chemoattractant protein

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MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NG	nasogastric
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic
PK	pharmacokinetic
POI	postoperative ileus
POGD	postoperative GI dysfunction
PONV	postoperative nausea and vomiting
PPS	per-protocol set
QD	once daily
QTcF	QT interval with Fridericia correction method
SAE	serious adverse event
SAF	safety analysis set
SAP	statistical analysis plan
SF-12	12-Item Short Form Health Survey
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
SVT	supraventricular tachycardia
VT	ventricular tachycardia
Takeda	Takeda Development Center Americas, Inc
ULN	upper limit of normal

3.4 Corporate Identification

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

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4.0 INTRODUCTION

4.1 Background

TAK-954 is a highly selective and potent serotonin type 4 (5-HT_4) receptor agonist that has shown prokinetic activity throughout the gastrointestinal (GI) tract in experimental models and is being developed for the acceleration of GI function recovery postsurgery.

Patients undergoing major abdominal surgery experience a temporary, nonobstructive impairment of upper and lower GI motility (function); a condition commonly known as postoperative ileus (POI) or postoperative GI dysfunction (POGD) [1]. It is estimated that clinically significant POI occurs in 17% of patients undergoing major abdominal surgery [2]. The analysis of a prospective database of 1,461 patients undergoing surgery in a high volume colorectal surgical department identified POI as 1 of the variables more likely associated with prolonged length of stay (LOS) in the hospital. As an average, patients developing symptomatic GI dysfunction in this study had an increase LOS of 3.45 days over the expected LOS rates of 8.17 days (interquartile range 4.7-11.9) for this cohort [3].

Signs and symptoms associated with postoperative inhibition of GI motility include abdominal distension/bloating, nausea and vomiting, lack of bowel sounds, gas and fluid accumulation in the bowel, delayed passage of flatus or stool, and intolerance to solid food and need for nasogastric (NG) tube insertion when these symptoms occur later in the postoperative period. This constellation of signs and symptoms is a leading cause of postsurgical complications and readmissions. Multiple factors are thought to contribute to the cause and duration of POGD: physical bowel manipulation, secretion of inflammatory mediators, electrolyte/fluid imbalance, and excessive use of opioid analgesics. Recent data suggest that upregulation of inflammatory pathways during surgery are a major factor in the development of POI and its duration [4].

Stimulation of 5-HT_4 receptors may activate anti-inflammatory and prokinetic mechanisms that promote earlier GI recovery, prevent, or decrease the duration of GI dysfunction, and facilitate earlier hospital discharge. Activation of enteric 5-HT_4 receptors is well known to enhance motility through-out the GI tract. Postoperative administrations of TAK-954 in a guinea pig model of POI led to a dose-dependent attenuation of the surgically-induced delay in GI transit. The potential prokinetic properties of TAK-954 have been evaluated in a small study in healthy volunteers where the administration of single doses of TAK-954 resulted in significantly shorter time to first stool and increases in the number of stools. In addition, the results of a pilot study in critically ill patients with increased gastric residual volumes suggested that a single IV dose of 0.5 mg consistently shortened gastric emptying of a radiolabeled meal as measured by scintigraphy. Additionally, 5-HT_4 agonists clinically reverse opioid-induced slowing of intestinal motility [5]. Results from a clinical study conducted in China suggest that postsurgical administration of a highly selective 5-HT_4 agonist in patients undergoing elective GI surgery was able to significantly decrease postsurgical recovery time and shorten LOS [6].

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4.2 Rationale for the Proposed Study

To date, 11 clinical studies have been completed:

Phase 1:

- Study 0060: a single ascending oral dose study in healthy subjects.
- Study 0061: a multiple ascending oral dose study in healthy subjects.
- Study 0095: a multiple repeat IV dose study in healthy subjects.
- TAK-954-1004: a 2-period crossover drug-drug interaction study of IV TAK-954 with the oral cytochrome P450 3A4 inhibitor, itraconazole in healthy subjects.
- TAK-954-1005: absorption, distribution, metabolism, and excretion study in healthy male subjects.
- TAK-954-1006: a single dose study in healthy subjects and subjects with varying degrees of hepatic impairment.
- TAK-954-1007: a single dose study in healthy subjects and subjects with varying degrees of renal impairment.
- TAK-954-1009: phase 1, randomized, double-blind, placebo-controlled, single ascending dose (SAD), 3-period, incomplete block design study in healthy subjects.

Phase 2:

- Study 0082: A phase 2a study in subjects who were critically ill and were being enterally fed.
- TAK-954-2002: a double-blind, double-dummy active control study in critically ill subjects with EFI. This study was terminated due to challenges with subject recruitment.
- TAK-954-2003: a dose-ranging, randomized, parallel, placebo-controlled study to assess the effect of TAK-954 on GI and colonic transit in patients with diabetic or idiopathic gastroparesis.

These studies have demonstrated acceptable PK characteristics and no major safety issues. This study will be the first phase 2 study to test the efficacy and safety of IV TAK-954 for accelerating the recovery of GI function postsurgery in patients undergoing open or laparoscopic-assisted partial small- or large-bowel resection.

Drug therapy for the prevention and/or management of POI (POGD) is limited. Alvimopan, an orally administered, peripherally acting mu-opioid antagonist, has been approved by the Food and Drug Administration (FDA) for accelerating the time to upper and lower GI recovery following partial large- or small-bowel resection with primary anastomosis. As alvimopan efficacy is related to opioid administration, its usefulness may become limited with the increasing practice of limiting opioid use during and postsurgery. Alvimopan prescribing is restricted to institutions and physicians with specific training (Risk Evaluation and Mitigation Strategy) and for short-term use

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(up to 7 days for a maximum of 15 doses) due to association of higher incidence of cardiac events upon long-term use. Initiatives aimed at reducing LOS, including the expanded use of laparoscopic colorectal surgery and enhanced recovery pathways (ERP), have been adopted by many hospitals and surgical services. ERP standardize perioperative care to facilitate "fast track" recovery. ERPs (including but not limited to early withdrawal of NG suction, early ambulation and provision of liquid (Day 1) and solid foods (Day 2), as well decreased opioid use) have had modest success in decreasing the duration of POI (1-2 days' decrease in LOS after colorectal surgery) [7]. Despite compliance with ERP and refined discharge criteria, some patients fail early discharge leading to a disproportionate use of healthcare resources. Data from a retrospective review of a prospectively maintained departmental database of patients at University Hospitals-Case Medical center suggested that approximately half of the patients undergoing major laparoscopic colonic surgery have a delayed discharge time (>4 days) despite the implementation of standardized early recovery plans. Patients with delayed discharge were significantly more likely to present with postoperative complications, 30-day reoperation rates and direct hospital cost. Risk factors associated with delayed discharge in this study include lower body mass index (BMI), comorbidity, acetylsalicylic acid use, prolonged surgical times, increased blood loss during surgery [8]. The significant risk of delayed postoperative recovery despite enhanced recovery after surgery implementation was also highlighted in another recent study that evaluated the incidence of prolonged POI (defined as the need for NG tube reinsertion) in patients undergoing colorectal surgery in a single site center in Switzerland. In this study, up to 24.7% of patients needed postoperative reinsertion of NG tube at the 3.9 ± 2.9 postoperative day [9]. All these data reinforce the need of additional pharmacological measures aimed at preventing POGD as this is the postoperative complication most likely related to prolonged length of hospital stay.

Manipulation of the intestines induces an inflammatory response [4]. In a guinea pig model of POI, preoperative administration of a 5-HT_4 agonist was reported to significantly accelerate and restore delayed upper and lower GI transit [10]. Stimulation of 5-HT_4 receptors increases vagal efferent activity resulting in activation of nicotinic alpha 7 acetylcholine receptors and inhibition of resident macrophage and splenic lymphocyte release of inflammatory mediators (eg, tumor necrosis factor-alpha) [11].

Rationale for Biomarker Evaluation

Increased levels of circulating inflammatory markers like interleukin (IL)-6, IL-10, monocyte chemoattractant protein (MCP)-1, high-sensitivity C-reactive protein (CRP), and alarmins like S100A8 and S100A12 following surgery have been associated with slower recovery and a longer stay in the intensive care unit [12]. In this study, inflammatory mediators, markers of tissue damage and motility-associated markers will be measured presurgery and postsurgery to evaluate TAK-954 treatment effects, as needed. Importantly, changes in cortisol level associated with postoperative nausea [13] will be evaluated as well as levels of glucose-dependent insulinotropic peptide (GIP) will also be measured to explore its relationship with vomiting and/or nausea.

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Rationale for Blood Sampling for DNA

Blood sampling for DNA analysis may be conducted to evaluate the contribution of genetic variance on drug response, for example, its efficacy and safety. Participation of study subjects in blood sampling for DNA sample collection is optional.

As genomics is an evolving science, currently many genes and their function are not yet fully understood. Future data may suggest a role of some of these genes in drug response or diseases, which may lead to additional hypothesis-generating exploratory research on stored samples.

4.3 Benefit-Risk Profile

Study participants undergoing open or laparoscopic-assisted partial small- or large-bowel resection and receiving TAK-954 may experience an acceleration of the recovery of GI function (motility) postsurgery. This may result in decreased time to tolerance to food ingestion, decreased symptoms of slow GI motility (nausea, vomiting, bloating, constipation), earlier hospital discharge, and decreased readmissions for symptoms of decreased GI motility.

Overall, TAK-954 is generally well tolerated at oral dosing up to 5 mg (for 10 days) and at IV dosing up to 2 mg, based upon overall clinical safety assessment. Aggregate AE review across clinical studies conducted to date shows that there were no deaths related to TAK-954 and a very low rate of severe AEs or AEs leading to study drug discontinuation. In an aggregate review of SAEs, all but 2 SAEs were considered not related to study drug by the investigator: 1 subject reported 2 SAEs (anastomotic leak and GI stoma complication) which were assessed as related to the blinded study treatment drug (TAK-954 or placebo) by the investigator in this study (TAK-954-2004). However, considering the events are common complications of extensive bowel resection secondary to underlying malignancy, the 2 serious adverse reactions (SARs) were assessed as not related to the blinded study drug by the sponsor. Most AEs were mild or moderate in severity, transient, and resolved spontaneously. The most common AEs in subjects receiving TAK-954 regardless of doses included headache, nausea, and diarrhea, which were not serious and resolved without treatment discontinuation, and without indicating any clear exposure response. Across the studies, a few subjects reported AEs of orthostatic hypotension and tachycardia. However, these events were nonserious, generally mild or moderate in severity, usually of short duration, and resolved spontaneously without significant clinical concern.

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

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

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5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective(s)

The primary objective of this study is to assess the efficacy and safety of IV TAK-954 for accelerating the recovery of GI function postsurgery in patients undergoing open or laparoscopic-assisted partial small- or large-bowel resection.

5.1.2 Secondary Objectives

The secondary objectives of this study are:

- To determine efficacy and safety of preoperative dosing of IV TAK-954 relative to preoperative and postoperative regimens of up to 10 days of IV TAK-954 for accelerating the recovery of GI function postsurgery.
- To determine the relative efficacy and safety of 0.1 and 0.5 mg IV TAK-954 given either preoperatively alone or preoperatively and postoperatively compared with placebo of up to 10 days or resolution of GI dysfunction postsurgery for accelerating the recovery of GI function postsurgery.
- To determine the PK of TAK-954 in patients undergoing major abdominal surgery.

5.1.3 Exploratory Objectives

The exploratory objectives are:

- To assess the effect of IV TAK-954 on circulating markers of inflammation, including but not limited to IL-6, IL-10, MCP-1, and CRP postsurgery.
- To assess the effect of IV TAK-954 on circulating markers associated with GI motility and/or nausea.
- To gain preliminary estimates of the incidence rate of postoperative complications and prolonged POGD (≥5 days) based on the type of surgery (laparoscopic vs open surgery), use of opioids, duration of surgical procedure, and ASA scores.
- To gain preliminary estimate of the effect of TAK-954 in preventing recurrence of GI dysfunction postsurgery.
- To gain preliminary estimate of the effect of TAK-954 in preventing POGD complications.

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5.2 Endpoints

5.2.1 Primary Endpoint

The primary efficacy endpoint is time from the end of the surgery to resolution of upper and lower GI function (ie, time to tolerance of solid food [defined as first occurrence of no vomiting or no clinically significant nausea for 1 calendar day after a solid meal] and time to first spontaneous bowel movement, whichever occurs later) up to Day 10 postsurgery.

5.2.2 Secondary Endpoints

The secondary endpoints for this study are:

- Time from the end of the surgery (time the incision is closed) until ready for discharge (defined as the time until the subject presents effective intestinal transit [spontaneous bowel movement], tolerates solids without vomiting or clinically significant nausea for 1 calendar day after a solid meal, has satisfactory pain control with oral analgesics, and is medically stable/free of complications).
- Time from the end of surgery until the discharge order is written.
- Time from the end of the surgery to discharge from hospital.
- Time from end of surgery to tolerance of solid food (defined as first occurrence of intake of solids without vomiting or clinically significant nausea for 1 calendar day after a solid meal) up to Day 10 postsurgery.
- Time from end of surgery to first spontaneous bowel movement (defined as a stool not induced by the use of enemas or laxatives) up to Day 10 postsurgery.
- Percent of subjects with POGD ≥5 days defined as subjects unable to tolerate solid foods, take anything by mouth, or requiring insertion or reinsertion of NG at or after 5 days postsurgery.
- Percentage of subjects requiring insertion of NG tube postsurgery, for drainage and symptom relief in case of persistent nausea and vomiting postsurgery up to Day 24 postsurgery (up to 10-day treatment period plus 14-day observation period post last dose for recurrence of symptoms).
- Time from end of surgery to first flatus up to Day 10 postsurgery.
- Observed plasma concentration of TAK-954 at the end of infusion on Day 1.

5.2.3 Safety Endpoints

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

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5.2.4 Exploratory Endpoints

The exploratory endpoints for this study will be:

- Change in circulating inflammatory markers including but not limited to IL-6, IL-10, MCP-1, and CRP, preoperatively compared with postoperatively across different treatment groups.
- Change in GIP and cortisol preoperatively compared with postoperatively across different treatment groups.
- Incidence rate of POGD recurrence for 14 days post last dose.
- Percentage of subjects with unplanned hospital readmissions due to recurrence of POGD.
- Percentage of subjects with postoperative complications, such as pneumonia, acute kidney failure, or documented anastomotic leak.
- Percentage of subjects requiring reoperation due to postoperative complications.
- Health-related quality of life as measured by 12-Item Short Form Health Survey (SF-12) and EuroQol 5-Dimensions Questionnaire (EQ-5D).
- Percentage of subjects with postoperative nausea and vomiting (PONV) within 24 hours after surgery, from Day 2 until discharge and at follow-up; defined as patients presenting with emetic events (nausea, vomiting, or retching) or requiring use of antiemetics.
- Peak nausea severity score from Day 1 until discharge using a numerical rating scale.
- Time from the end of the surgery to the first insertion of NG tube (for those requiring insertion of NG tube postsurgery).
- Percentage of subjects presenting complications or prolonged POGD (≥5 days) based on opioid use, type of surgery, duration of the surgical procedure, and ASA scores.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This phase 2, randomized, placebo-controlled, parallel 5-group, double-blind study is designed to determine: (1) if TAK-954 decreases the duration of GI dysfunction in patients undergoing major abdominal open or laparoscopic-assisted surgeries that involve significant bowel manipulation, (2) whether preoperative dosing alone or a preoperative and postoperative dosing regimen is the most effective dosing regimen to decrease the duration of POGD and improve clinical outcomes, and (3) the most appropriate dose and dosing regimen to advance into phase 3.

Subjects will be randomized in a 1:1:1:1:1 ratio into 1 of 5 parallel treatment groups:

- Regimen 1: Placebo (normal saline 100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function (ie, resolution of POGD) or for up to 10 days.

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- Regimen 2: TAK-954 (0.1 mg/100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function or for up to 10 days.
- Regimen 3: TAK-954 (0.5 mg/100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function or for up to 10 days.
- Regimen 4: TAK-954 (0.1 mg/100 mL infusion over 60 minutes) preoperation and daily placebo infusions postoperation until return of upper and lower GI function or for up to 10 days.
- Regimen 5: TAK-954 (0.5 mg/100 mL infusion over 60 minutes) preoperation and daily placebo infusions postoperation until return of upper and lower GI function or for up to 10 days.

Subject randomization will be stratified by laparoscopic and open surgery procedures.

With this Protocol Amendment 5, the planned total sample size is approximately 180 subjects. Two of the above TAK-954 regimens are discontinued based on IMC recommendations. As a result, eligible subjects will be equally randomized to into 1 of 3 of the remaining parallel treatment groups:

- Regimen 1: Placebo (normal saline 100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function (ie, resolution of POGD) or for up to 10 days
- Regimen 3: TAK-954 (0.5 mg/100 mL infusion over 60 minutes) preoperation and daily postoperation until return of upper and lower GI function or for up to 10 days.
- Regimen 5: TAK-954 (0.5 mg/100 mL infusion over 60 minutes) preoperation and daily placebo infusions postoperation until return of upper and lower GI function or for up to 10 days.

It is standard of practice for the postoperative care of patients after colorectal surgery to implement an ERP to reduce the time to recovery of GI function (motility). To provide a consistent ERP as baseline therapy for all subjects, they will receive the same core features of an ERP for postoperative care as outlined below:

Core ERP:

- Minimize opioid use while maintaining adequate pain control through use of multimodal analgesia. Suggested analgesics include opioid alternatives, such as nonsteroidal anti-inflammatory drugs (eg, ketorolac tromethamine IV), acetaminophen (paracetamol), or oral pregabalin, when possible. It is recommended that at least 2 different analgesics with different mechanism of action are tried and failed before prescribing opioids.
- Maintenance of euvolemia and normal salt and electrolyte state in perioperative period.
- No routine use of prophylactic NG tubes postsurgery. NG tubes should only be used if there is a documented medical reason to justify them.

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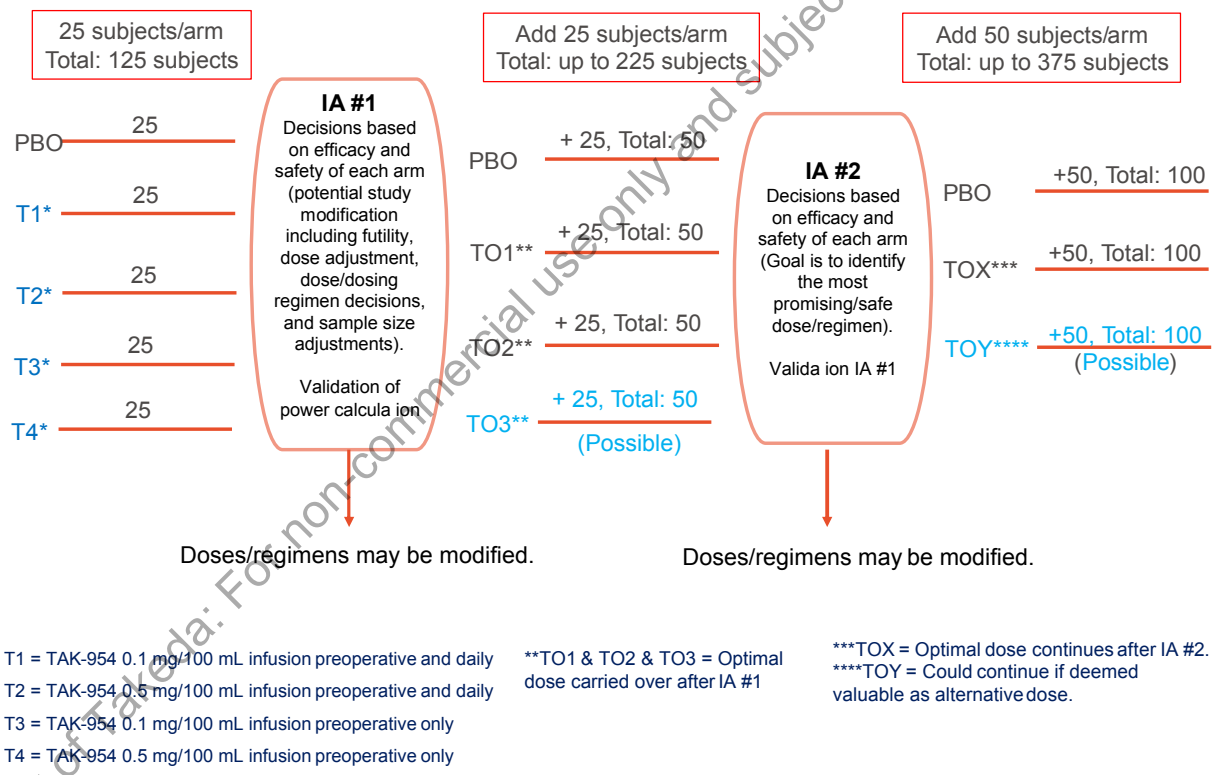
- Use of a standardized risk-based strategy for PONV prophylaxis: use of preoperative antiemetic prophylaxis in patients with 1 or more risk factors of the simplified Apfel Score (female gender, planned postoperative use of opioids, nonsmokers, history of PONV/motion sickness).
- Early oral feeding postsurgery when possible. Clear liquids after the surgery on Day 1, advancing to soft diet on Day 2 if tolerant to liquids (no nausea or vomiting).
- Early mobilization starting after the surgery on Day 1 when possible.

Schematics of the study design prior to Protocol Amendment 5 can be found in Figure 6.a and with the discontinuation of 2 treatment regimens and removal of the second IA in Figure 6.b. A schedule of assessments is listed in Appendix A.

Figure 6.a Schematic of Study Design Prior to Protocol Amendment 5



Abbreviations: IA, interim analysis; PBO, placebo.

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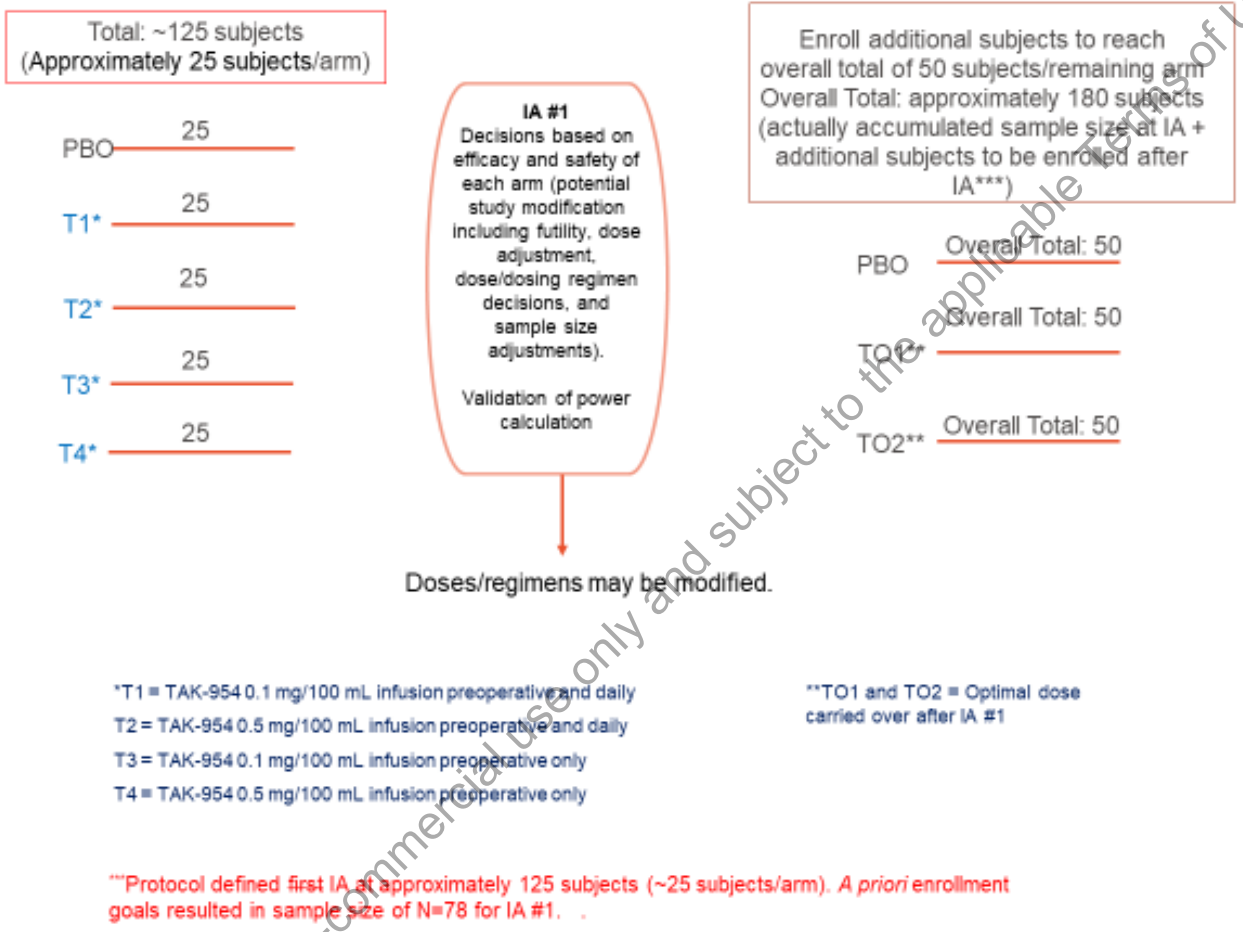
Figure 6.b Schematic of Study Design By Protocol Amendment 5



Abbreviations: IA, interim analysis; PBO, placebo.

Criteria for resolution of upper and lower GI function is time to first tolerance of solid food (defined as no vomiting or no clinically significant nausea for 1 calendar day after a solid meal) and time to first spontaneous bowel movement, whichever occurs later, up to Day 10 postsurgery.

Following hospital discharge, subjects will be instructed to contact their physician if they have recurring symptoms suggestive of POGD to evaluate the need for hospital readmission in case of relapse. All subjects will return to the clinic 14 days (±4 days) post last dose; however, during the COVID-19 public health emergency, the follow-up visit 14 days post last dose may be conducted via phone call (eg, collection of AEs, concomitant medications, and monitoring) to extend flexibility to study subjects. In the case of a phone call follow-up, physical examination (including neurology examination), vital signs, or pregnancy test would not be collected; however, AEs will be assessed, including a safety check on any emerging clinical signs or symptoms. Subjects may be requested to return to the site for further safety assessment, due to reported AEs, at the

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investigator's discretion. The type of visit (whether clinic visit or phone call) must be recorded in the study records. Quality of life assessments will be completed by the subject in their home on the same day as the safety follow-up call and completed questionnaires will be mailed to the clinic. Subjects will be contacted by phone 30 (±3 days) and 90 (±7 days) days posttreatment for a safety follow-up.

Two preplanned IAs will be conducted when *a priori* enrollment goals have been achieved. Bayesian approach will be applied after these IAs for decision making for potential study modification including futility, dose and dosing regimen decision, and sample size adjustment. In case dose modification is needed after the IA, the maximal dose for potential modification of doses/regimens will be 1.0 mg. The duration of drug administration (up to 10 days postsurgery) will not be changed. By this protocol amendment, the second IA is removed from the protocol.

6.2 Justification for Study Design, Dose, and Endpoints

Rationale for Study Design

The proposed adaptive design with bayesian approach has several benefits over traditional design and frequentist method. Adaptive designs have become popular in clinical trials because of its advantages of flexibility and efficiency gains, some of which also have the significant advantage of enrolling fewer patients to treatment arms with inferior outcomes.

Rationale for Dose

TAK-954 IV doses of 0.1 and 0.5 mg QD preoperatively and postoperatively for up to 10 days and 0.1 and 0.5 mg single doses preoperative administration were selected to be studied in this dose and dosing regimen study. These doses are expected to allow the characterization of the exposure/response (efficacy and safety) relationship for TAK-954. The exposure/response data generated from these dosing regimens will provide information for selecting optimal doses for future studies and dosing regimen and to maximize benefit/risk ratio. Several factors have been taken into account when selecting the doses and dosing regimen mentioned above, including safety, tolerability, PK, and pharmacodynamic (PD) data from healthy volunteers and critically-ill patients with delayed gastric emptying. TAK-954 was generally well tolerated in healthy volunteers following 0.5 mg IV administered for 5 days. TAK-954 0.1 and 0.5 mg doses appeared to reduce the time to first bowel movement and increase the number of bowel movements on the first day of dosing in healthy subjects. When compared with metoclopramide 10 mg IV every 6 hours, a single dose of 0.5 mg IV TAK-954 also demonstrated a consistent pattern to enhance gastric emptying in critically ill patients with delayed gastric emptying.

All available efficacy, safety, and tolerability data will be considered to determine potential changes to dose or regimen after each IA. The potential duration of drug administration (up to 10 days postsurgery) will not be changed. Additionally, the basic regimen (preoperation administration and postoperation administration) will not be altered.

Preliminary data suggest that a prokinetic and anti-inflammatory effect is achieved with 0.5 mg. Additionally, results from a completed scintigraphy study assessing the effect TAK-954 on gastric emptying, small bowel and colonic transit, as well as the safety and tolerability of doses of 0.1, 0.3,

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and 1.0 mg QD IV in patients with gastroparesis (TAK-954-2003), will be considered during the IA. This information, along with the IA results, will be used to decide if adjustments to the current doses tested in the TAK-954-2004 study are warranted.

The maximum dose that could potentially be used in the TAK-954-2004 study is 1.0 mg QD by IV administration. Based on the principle of superposition, the predicted maximum concentration during a dosing interval, at steady state ($C_{max,ss}$) and area under the concentration-time curve from time 0 to 24 hours, at steady state ($AUC_{24,ss}$) for TAK-954 1.0 mg QD IV dosing provides an approximately 41-fold/851-fold margin relative to total/free C_{max} at the no-observed-effect level in the dog cardiovascular (CV) study, 468-fold margin relative to AUC_{24} in the rat 13-week repeat-dose study at the no-observed-adverse-effect level (NOAEL), and 250-fold margin relative to AUC_{24} in the rabbit embryo-fetal-development study at the NOAEL, respectively. These exposures are approximately one-third to one-half of the exposures that were achieved with 5 mg QD oral dosing for 10 days in healthy subjects (maximum tolerated dose).

Rationale for Endpoints

All patients undergoing an abdominal surgical procedure will inevitably develop a transient episode of impaired GI motility (traditionally referred to as POI) and stasis of the intraluminal contents [14]. In some cases, this may result in nausea, vomiting, bloating, delayed passage of stool and inability to tolerate liquid or solid foods. Normally, inhibition of small bowel motility is transient and the stomach recovers within 24 to 48 hours, whereas colonic function takes 48 to 72 hours to return [14]. The duration of this impaired motility reflects the clinical recovery of the patient. Determination of the end of POGD (or POI) has been somewhat controversial as different studies have tried to identify the return of normal bowel motility with unreliable and poorly specific clinical endpoints such as time to first flatus or return of bowel sounds. Using scintigraphy, van Bree et al [15] have shown that the return of gastric emptying is reflective of the ability to tolerate solid food, and that the occurrence of the first solid stool reflects return of lower GI motility. The combined outcome measure of tolerance of solid food and having had defecation (area under the concentration-time curve = 0.9, SE = 0.04, 95% CI = 0.79-0.95, $p < 0.001$) best indicated recovery of GI transit with a positive predictive value of 93% (95% CI = 78-99). They further validated this endpoint using data from a multicenter trial of 320 segmental colectomy patients in which multiple regression analysis revealed that time to first stool and solid food tolerance best predicted the duration of hospital stay. Therefore, the primary endpoint in this study will assess the duration of time to tolerance of solid food and time to the first spontaneous bowel movement (whichever occurs later) which reflects a clinically meaningful return of GI function/motility.

6.3 End of the Study

The overall study ends when the last subject completes the last planned or follow-up visit/interaction associated with a planned visit (this can be a phone contact), discontinues from the study, or is lost to follow-up (ie, the investigator is unable to contact the subject).

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6.4 Premature Termination or Suspension of Study or Study Site

6.4.1 Criteria for Premature Termination or Suspension of the Study

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

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

6.4.2 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 enrollment or performance of the study, or as otherwise permitted by the contractual agreement.

6.4.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

1. In the opinion of the investigator, the subject is capable of understanding and complying with protocol requirements.
2. The subject signs and dates a written, informed consent form and any required privacy authorization prior to the initiation of any study procedures.
3. The subject is scheduled to undergo a laparoscopic-assisted, or open partial small- or large-bowel, resection.
4. The subject is male or female and is at least 18 years old.
5. The subject's ASA physical status classification is ASA 1 to 3.

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6. A female subject of childbearing potential* who is sexually active with a nonsterilized* male partner agrees to use a highly effective method of contraception* from signing of informed consent throughout the duration of the study and for up to 30 days posttreatment.

> *Definitions and highly effective methods of contraception are defined in Section 9.1.13 and reporting responsibilities are defined in Section 9.1.14.

7.2 Exclusion Criteria

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

1. The subject has received any investigational compound within 30 days prior to screening.
2. The subject has received TAK-954 in a previous clinical study or as a therapeutic agent.
3. The subject is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.
4. The subject has significant mechanical bowel obstruction that is not expected to resolve after the surgery, short bowel syndrome, pre-existing clinically significant GI motility disorder (eg, gastroparesis, scleroderma, chronic intestinal pseudo-obstruction), uncontrolled diabetes (glycosylated hemoglobin [HbA1c] >10%), has an active gastric pacemaker, or requires parenteral nutrition.
5. The subject had previous major abdominal surgery (eg, gastrectomy, gastric bypass, gastric sleeve, lap banding, Whipple, pancreatic resection, total/subtotal colectomy, hemicolectomy, extensive bowel resection).
6. The subject has a history of radiation therapy to the abdomen or pelvis.
7. The subject is scheduled to undergo any of the following surgeries: low anterior resection, total or subtotal colectomy, colostomy, ileostomy, or reversal of stoma or has a diagnosis that requires rectal resection (eg, tumors in the anorectum) and will likely require lower anterior resection surgery. Subjects with planned surgery for which there is no anticipated significant rectal resection and is, therefore, likely to preserve anorectal function and continence postsurgery, will likely be eligible for inclusion in the study if they meet all the study inclusion/exclusion criteria (eg, subjects with lesions not involving the rectum [sigmoid colon and above]).
8. The subject has pre-existing hepatic disease that meets Child-Pugh Class B (moderate; total score 7 to 9 points) or C (severe; total score 10 to 15 points).
9. The subject has alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN), or total bilirubin >2 × ULN.
10. The subject has an estimated glomerular filtration rate <30 mL/min.

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11. The subject has received alvimopan, erythromycin, prucalopride, metoclopramide, domperidone, cisapride, mosapride, renzapride, or azithromycin in the 24 hours prior to starting study drug.
12. The subject has a resting heart rate of <50 beats per minute (bpm).
13. The subject has clinically significant ECG abnormalities indicative of cardiac conduction abnormality or acute cardiac instability as determined by the investigator at screening; more than first degree atrioventricular (AV) block; >5 beats of nonsustained ventricular tachycardia (VT) at a rate >120 bpm; or ECG changes consistent with acute myocardial ischemia or infarction.
14. The subject has a QT interval with Fridericia correction method (QTcF) ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events at screening. The records of subjects with bundle branch block and a prolonged QTcF should be reviewed by a medically qualified person in consultation with the medical monitor and the sponsor for potential inclusion.
15. The subject has known COVID-19 infection, or suspected COVID-19 infection (as assessed by the investigator).
16. The subject has any other significant uncontrolled organic or systemic medical condition or social circumstance that, in the investigator's opinion, would mean it was not appropriate for the subject to participate in this clinical study.
17. The subject is scheduled for abdominal surgery that is classified as emergency.
18. The subject had acute myocardial infarction or ischemia within the past 12 months. Subjects with increased cardiac risks for surgery including coronary artery disease or prior myocardial infarction and evidence of reduced left ventricular function or history of angina should be assessed by the investigator for stability and control of their cardiac condition and risk of surgery, and excluded if in the investigator's opinion, participation in the study is not considered appropriate. The sponsor should be consulted if subjects with these conditions are considered by the investigator to be acceptable.
19. The subject had pulmonary embolism, deep venous thrombosis, or mechanical ventilation for any medical condition within the past 12 months. Subjects with a history of multiple venous thrombosis or pulmonary embolic events, history of a hypercoagulable condition, history of severe exacerbation for chronic obstructive pulmonary disease or evidence of pulmonary hypertension should be assessed by the investigator for stability and control of their conditions and risk of surgery, and excluded if in the investigator's opinion, participation in the study is not considered appropriate. The sponsor should be consulted if subjects with these conditions are considered by the investigator to be acceptable.

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7.3 Excluded Medications

The following medications are excluded from 24 hours prior to starting study drug to 5 days post last dose of study drug.

Laxatives (preoperative bowel preparations are not excluded).

Prokinetic agents: domperidone, erythromycin, azithromycin, and 5-HT_4 agonists (cisapride, mosapride, prucalopride, renzapride, and metoclopramide).

μ-Opioid antagonist: Alvimopan.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.19.

1. Treatment discontinuations due to an AE: The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE. Specific events that require treatment discontinuation (see Section 10.1.6) include:
   - Prolonged QT: Second episode of Grade 2 (QTcF >480 and ≤500 msec), any occurrence of Grade 3 (QTcF >500 msec, or >60 msec change from baseline) or Grade 4 (Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia).
   - Second or third-degree heart block: Treatments with study drug may be continued in second-degree heart block Mobitz I (Wenckebach) after medical monitor review.
   - Any occurrence of Grade 4 (life-threatening) supraventricular tachycardia (SVT) that is considered related by the investigator.
   - Suspected serotonin syndrome.
   - Liver test abnormalities: Treatment with study drug should be discontinued in subjects who develop ALT or AST >3 × ULN concurrently with total bilirubin >2 × ULN while on treatment with study drug. These findings should be reported to the sponsor as a serious adverse events of special interest (AESI). The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies, such as acute viral hepatitis, other acute liver disease, or medical history/concurrent medical conditions. In addition, the investigator should contact the medical monitor for any increase in liver tests without clear etiology.
   - Known COVID-19 infection.
2. Significant protocol deviation. The discovery postrandomization 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. Subject did not receive 2 or more doses of the assigned randomized treatment.
4. If the subject, due to intraoperative circumstances, has surgery that results in a significant resection of rectal tissue, a >50% resection of colon tissue, or an ostomy, study drug dosing should be discontinued.

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5. Voluntary withdrawal. The subject wishes to withdraw from the study or study drug. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category). Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category. Additional efforts should be made and documented to encourage subject to participate in the follow-up portion of the study.

6. Study termination. The sponsor, IRB, IEC, or regulatory agency terminates the study.

7. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.14.

8. 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.

9. Other.

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

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study drug participation at any time during the study when the subject meets the study drug termination criteria described in Section 7.4. 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 study drug termination must be recorded by the investigator.

In addition, efforts should be made to perform all procedures scheduled for the early termination visit. Every effort should be made to perform the follow-up visits at 14, 30, and 90 days post last dose for every dosed subject, as noted in the Schedule of Study Procedures (Appendix A). For subjects who did not receive study drug, the follow-up visits do not need to be completed.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

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

8.1.1.1 TAK-954

The drug product, TAK-954 Injection (Concentrate for Solution for Infusion), consists of a clear colorless solution of TAK-954 free base in clear Type I glass vials fitted with a rubber stopper and sealed with an aluminum cap. The drug product is formulated as 0.1 mg/mL of TAK-954 free base

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equivalent dissolved in water for injection, adjusted to pH 5.0 with hydrochloric acid and/or sodium hydroxide. Each glass vial contains 5.5 mL of sterile TAK-954 solution designed to deliver nominally 5.0 mL of the solution. The drug product solution is intended to be diluted to the required concentration with normal saline (0.9% sodium chloride for injection), for IV infusion. Normal saline is used as placebo.

TAK-954 cartons and vials will be affixed with labels that are in accordance with regulatory requirements.

8.1.1.2 Ancillary Materials

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

8.1.2 Storage

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

8.1.3 Dose and Regimen

Subjects will be randomized 1:1:1:1:1 into 1 of 5 treatment groups. Adjustments to the treatment groups may be made based on IA results.

Following the discontinuation of 2 treatment groups (see Section 6.1), subjects will be randomized to 1:1:1 into 1 of 3 remaining treatment groups by Protocol Amendment 5 (see Section 6.1).

Additional information regarding the dosing instructions for TAK-954 can be found in the pharmacy manual.

Table 8.a describes the dosing regimens in the protocol and Table 8.b describes the dosing regimens remaining after discontinuing 2 dosing groups as clarified in this protocol amendment.

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Table 8.a Dose and Regimen Prior to Protocol Amendment 5

Treatment Group	Dose	Treatment Description
1	Placebo (100 mL saline infusion over 60 minutes)	Given preoperation and daily postoperation for up to 10 days or until return of upper and lower GI function.
2	TAK-954 (0.1 mg/100 mL infusion over 60 minutes)	Given preoperation and daily postoperation for up to 10 days or until return of upper and lower GI function.
3	TAK-954 (0.5 mg/100 mL infusion over 60 minutes)	Given preoperation and daily postoperation for up to 10 days or until return of upper and lower GI function.
4	TAK-954 (0.1 mg/100 mL infusion over 60 minutes)	Given preoperation and daily placebo infusions postoperation for up to 10 days or until return of upper and lower GI function.
5	TAK-954 (0.5 mg/100 mL infusion over 60 minutes)	Given preoperation and daily placebo infusions postoperation for up to 10 days or until return of upper and lower GI function.

Abbreviations: GI, gastrointestinal.

Table 8.b Dose and Regimen as a Result of Protocol Amendment 5

Treatment Group	Dose	Treatment Description
1	Placebo (100 mL saline infusion over 60 minutes)	Given preoperation and daily postoperation for up to 10 days or until return of upper and lower GI function.
3	TAK-954 (0.5 mg/100 mL infusion over 60 minutes)	Given preoperation and daily postoperation for up to 10 days or until return of upper and lower GI function.
5	TAK-954 (0.5 mg/100 mL infusion over 60 minutes)	Given preoperation and daily placebo infusions postoperation for up to 10 days or until return of upper and lower GI function.

Abbreviations: GI, gastrointestinal.

On Day 1, the completion of the infusion should occur within 3 hours of the start of surgery (induction of anesthesia). Subsequent doses (Days 2 to 10, if required) should be approximately 24 hours (±5 hours) from the start of the prior infusion. If a subsequent dose cannot be administered during this window, it should be skipped.

8.1.4 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 on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database.

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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.

TAK-954 has been investigated in clinical studies up to 20 mg orally. AEs observed at 5 mg orally (with a mean exposure approximately 4-fold higher than that for IV dosing at 0.5 mg) or higher included mild orthostatic hypotension in 1 subject after they received a single oral 5 mg dose and mild AV dissociation in 2 subjects after they received a single oral 10 mg dose. In the event of an IV overdose, discontinue the treatment of study drug, treat the subject symptomatically and provide supportive care as needed.

8.2 Study Drug Assignment and Dispensing Procedures

In order to maintain the blind, all study site personnel except the investigational pharmacist or designee will be blinded to subject treatment assignments for the duration of the study. A member of the investigator staff will utilize the IRT to randomize the subject into the study. During this contact, the staff member will provide the necessary subject-identifying information, including the subject number assigned at screening. Subjects will be assigned in a 1:1:1:1:1 ratio to receive the treatments or placebo, TAK-954 0.1 or 0.5 mg preoperation, or TAK-954 0.1 or 0.5 mg preoperation and postoperation daily for up to 10 days or until the return of upper and lower GI function. By Protocol Amendment 5, subjects will be assigned in a 1:1:1 ratio to receive the treatments or placebo, TAK-954 0.5 mg preoperation, or TAK-954 0.5 mg preoperation and postoperation daily for up to 10 days or until the return of upper and lower GI function. The study drug assignment will be emailed to the unblinded pharmacist only. Unblinded investigator staff should not be involved with any study procedures or assessments other than those related to study drug management (eg, dispensing, preparation, accountability, etc.). Similarly, blinded investigational staff should not have access to pharmacy documentation or interact with pharmacy staff in a manner which could unblind them to subject treatment assignment.

Subject randomization will be stratified by laparoscopic and open surgery procedures.

Subjects will be assigned to receive their treatment according to the randomization schedule allocated to each study site.

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

8.3 Randomization Code Creation and Storage

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

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8.4 Study Drug Blind Maintenance

The study drug blind will be maintained using the IRT.

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

8.5 Unblinding Procedure

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 assessments 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.

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

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

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

Placebo PK samples will not be analyzed; therefore, the randomization code will be sent to the analyzing laboratory.

8.6 Accountability and Destruction of Sponsor-Supplied Drugs

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

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

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment as instructed per the documentation accompanying the shipment. If there are any discrepancies between the packing list versus the

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actual product received, the sponsor or its designee must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

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

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

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

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

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

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

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

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

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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 prior to the subject entering into the study, and before any protocol-directed procedures are performed. Informed consent may be performed in clinic or remotely using electronic signature where allowed by site IRBs/IECs.

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 to be obtained will include date of birth or age, sex, ethnicity (as described by the subject or subject's representative), height, weight, and smoking status of the subject at screening.

Medical history to be obtained will include determining whether the subject has any significant conditions or diseases relevant to the disease under study that resolved at or prior to signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the screening examination, according the judgment of the investigator. History of chronic obstructive pulmonary disease, chronic kidney and liver disease, diabetes, and CV comorbidity should be documented.

Medication history information to be obtained includes all medication and any medication relevant to eligibility criteria stopped at or within 24 hours prior to signing of informed consent.

9.1.3 Physical Examination Procedure (Including Neurology Examination)

A baseline physical examination (defined as the assessment before first dose of study drug) will consist of the following body systems: (1) CV system; (2) respiratory system; (3) GI system; (4) nervous system looking mainly for hypertonicity, reflexes, and clonus; and (5) other. Physical examinations collected as standard of care (SOC) within 21 days of randomization may be used for study screening purposes. If physical examinations are collected as SOC on the day of surgery but before informed consent, they may be used for screening/baseline purposes as long as the results are assessed for eligibility before randomization. Any clinically significant changes from the baseline examination will be recorded as an AE.

A targeted neurological examination looking for hypertonicity, reflexes, and clonus will be performed by medically qualified personnel at screening, baseline (preinfusion Day 1), on Days 2

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and 5, on the last day of study treatment or early termination (as applicable), and at the follow-up visit (14 days post last dose).

During the COVID-19 public health emergency, the follow-up visit at 14 days (±4 days) post last dose may be conducted at the clinic or via phone call (eg, collection of AEs, concomitant medications, and monitoring), to extend flexibility to study subjects. In the case of a phone call, a physical examination (including neurology examination) would not be collected; however, AEs will be assessed, including a safety check on any emerging clinical signs or symptoms. Subjects may be requested to return to the site for further safety assessment, due to reported AEs, at the investigator's discretion. The type of visit (whether clinic visit or phone call) must be recorded in the study records.

9.1.4 Weight, Height, and BMI

A subject should have weight and height collected as per the SOC. BMI will be derived from the subject's height and weight.

9.1.5 Vital Sign Procedure

Vital signs will include blood pressure (systolic and diastolic) and pulse (bpm). Subjects should have rested for at least 5 minutes before vital sign assessment. Vital signs collected as SOC within 21 days of randomization may be used for study screening purposes. If vital signs are collected as SOC on the day of surgery but before informed consent, they may be used for screening/baseline purposes as long as the results are assessed for eligibility before randomization.

Vital signs will be collected at the following time points: screening, presurgery before and at the end of study drug infusion on Day 1 on Days 2 to 10 (ie, at the end of study drug infusion in the morning and in the evening), and at the follow-up visit (14 days post last dose). The time window will be 12 hours ±4 hours. On the day of surgery, vital signs will be monitored as part of the SOC. Clinically abnormal vital signs will be captured as an AE as per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

During the COVID-19 public health emergency, the follow-up visit at 14 days post last dose may be conducted at the clinic or via phone call (eg, collection of AEs, concomitant medications, and monitoring), to extend flexibility to study subjects. In the case of a phone call, vital signs would not be collected; however, AEs will be assessed, including a safety check on any emerging clinical signs or symptoms. Subjects may be requested to return to the site for further safety assessment, due to reported AEs, at the investigator's discretion. The type of visit (whether clinic visit or phone call) must be recorded in the study records.

9.1.6 Primary Efficacy Measurement

The length of time from the end of the surgery to the occurrence of the toleration of solid foods (defined as first occurrence of no vomiting or no clinically significant nausea for 1 calendar day after a solid meal) and time to first spontaneous bowel movement, whichever occurs later.

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If a subject meets the primary endpoint after midnight, the study procedures outlined in the Schedule of Study Procedures (Appendix A) can be completed the next day. If a subject meets the primary endpoint in morning and is discharged later that day, this is considered a minor protocol deviation. Note that the exact times of first spontaneous bowel movement and tolerance to solid food should be documented in source file and reported in the eCRF.

9.1.7 Study Surgery

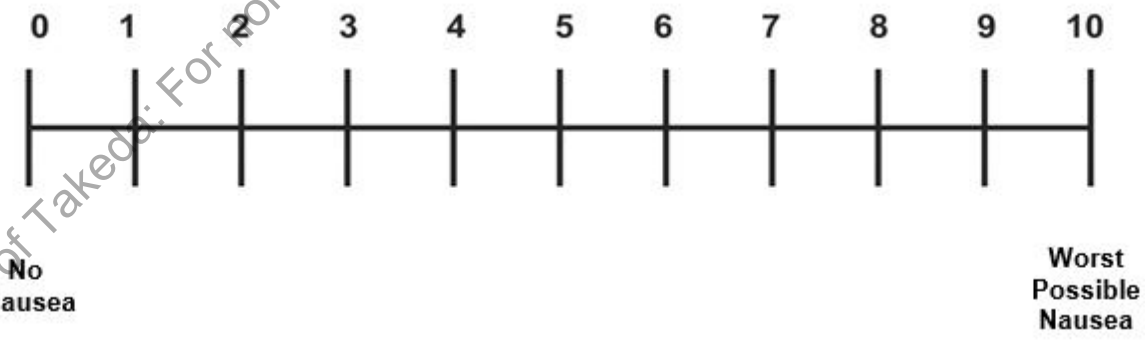
The reason for surgery, the type of surgery, ASA scores, start and stop times, approximate length of bowel removed (cm), and the duration of the surgery will be documented.

9.1.8 Clinical Assessments

The investigator is responsible for assessing the following on a daily basis from Day 1 to discharge:

- Time to first spontaneous bowel movement and the approximate number of bowel movements each day.
- Tolerance to fluid intake (only until tolerance is achieved).
- Tolerance to soft food (only until tolerance is achieved).
- Tolerance to solid food (only until tolerance is achieved).
- Presence of vomiting/retching with the number of episodes in previous 24 hours, approximate volume, and if bilious.
- Presence and severity of nausea measured through a numerical rating scale from 0 (no nausea) to 10 (worst possible nausea) as in Figure 9.a.

Figure 9.a Numerical Rating Scale



- Assessment of abdominal distension, including tympany if present.
- Presence of flatus (only until first episode of flatus).

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- Need for reinsertion of nasogastric tube in the postoperative period for NG suction.
- Readiness for hospital discharge.

9.1.9 Documentation of Concurrent Medical Procedures

All procedures (eg, computed tomography scan, biopsy, insertion of the NG tube, aspiration of fluid) conducted after signing the informed consent form and up to Day 10 of study drug administration are to be recorded on the eCRF.

9.1.10 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug, including antiemetics used for prophylaxis or treatment of PONV, anesthetics, analgesia, or treatment for postoperative complications. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. All concomitant medications received from the time of obtaining informed consent will be recorded. During the follow-up visit 14 days (±4 days) post last dose, subjects will be asked whether they have taken any medication, including vitamin supplements, over-the-counter medications, and oral herbal preparations, and this must be recorded in the eCRF.

9.1.11 Documentation of Core ERP

Sites will document that they are following core ERP for each randomized subject. Adherence to core ERP will be evaluated based on the Core ERP criteria outlined in Section 6.1.

9.1.12 Procedures for Clinical Laboratory Samples

All samples will be collected in accordance with acceptable laboratory procedures. Results of clinical laboratory assessments collected as SOC within 21 days of randomization or HbA1c collected within 30 days of informed consent may be used for study screening purposes. If clinical laboratory samples are collected as SOC on the day of surgery but before informed consent, they may be used for screening/baseline purposes as long as the results are assessed for eligibility before randomization. Details of these procedures and required safety monitoring will be given in the site operations manual.

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

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Table 9.a Clinical Laboratory Tests

Hematology	**Serum Chemistry**
RBC	ALT
WBC	Albumin
Hemoglobin	Alkaline phosphatase
Hematocrit	AST
Platelets	Total bilirubin
Prothrombin time	Total protein
INR	Creatinine
Erythrocyte sedimentation rate	Blood urea nitrogen
	Chloride
	Creatine kinase
	GGT
	Potassium
	Sodium
	CRP
Other:	
Serum	**Serum or urine**
HbA1c [a]	Beta hCG (for pregnancy, female subjects only) [a]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; C-reactive protein, CRP; GGT, γ-glutamyl transferase; HbA1c, glycosylated hemoglobin, hCG, human chorionic gonadotropin; INR, international normalized ratio; RBC, red blood cell; WBC, white blood cell.

[a] Collected at screening only. An HbA1c collected within 30 days of screening is adequate for screening purposes.

The local laboratory will perform all tests found in Table 9.a, as per the Schedule of Study Procedures (Appendix A). The results of laboratory tests will be returned to the investigator, who is responsible for reviewing and filing these results.

Any clinically significant laboratory result will be captured as an AE as per the NCI CTCAE v5.0.

Treatment with study drug should be discontinued in subjects who develop liver test elevation as described in Section 10.1.6.4.

9.1.13 Contraception and Pregnancy Avoidance Procedure

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

Given that TAK-954 did not exhibit genotoxic potential in the standard battery of genotoxicity assays and the terminal disposition phase half-life of TAK-954, the duration of contraception for 30 days after the last dose is considered acceptable. This is in line with the Clinical Trials Facilitation Group "Recommendations related to contraception and pregnancy testing in clinical trials."

Females of reproductive potential, as well as fertile men and their partners who are female of reproductive potential, must agree to abstain from sexual intercourse or to use a highly effective

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form of contraception from the time of giving informed consent, during the study, and for 30 days (females and males) following the last dose of study drug. A highly effective form of contraception is defined as follows:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral.
  - Intravaginal.
  - Transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral.
  - Injectable.
  - Implantable.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner.
- Sexual abstinence.

The following definitions apply for contraception and pregnancy avoidance procedures:

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

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

9.1.14 Pregnancy

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

If the female subject and/or female partner of a male subject agree to the primary care physician being informed, the investigator should notify the primary care physician that the female

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subject/female partner of the subject was participating in a clinical study at the time she became pregnant and provide details of the study drug the subject received.

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

9.1.15 ECG Procedure

ECG assessments collected as SOC within 21 days of randomization may be used for study screening purposes. If an ECG is collected as SOC on the day of surgery but prior to informed consent, it may be used for screening/baseline purposes as long as the results are assessed for eligibility prior to randomization. A standard 12-lead ECG will be performed as follows:

- Screening (Days -21 to 1) (to be reviewed by a medically qualified person).
- Day 1: prior to and at the end of the 60-minute IV infusion (+20 minutes).
- Day 2: At the end of the 60-minute IV infusion (+20 minutes) and approximately 2 hours (+20 minutes) after the start of the 60-minute infusion.
- Days 4, 6, 8, and 10: at the end of the 60-minute IV infusion (+20 minutes) on every other day of treatment.
- Early termination (as applicable).

Subjects should have rested in a supine or semisupine position for at least 5 minutes before ECG. The same position (either supine or semisupine) should be used for the same individual throughout the study.

When ECG, vital signs, and blood draw coincide at the same nominal time point, the sequence of procedures will be safety ECG, vital signs assessment, and blood draw.

In addition, a 12-lead ECG will be performed if a subject develops symptoms suggestive of CV origin (eg, dizziness, chest pain, lightheadedness, chest pain, chest heaviness, palpitations, shortness of breath, tachycardia).

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. The time that a 12-lead ECG was performed will be recorded. The following parameters will be recorded on the eCRF from the subject's ECG trace: heart rate, RR interval, PR interval, QRS, and QT interval. The sponsor will derive QTcF. Heart-rate corrected QT interval will be calculated using Fridericia formula ($QTcF = QT/RR^{1/3}$). This same formula should be used for assessing eligibility.

New onset or changes in ECG findings (compared with baseline Day 1 preinfusion values) are considered to be AEs only if they are judged to be clinically significant as per CTCAE v5.0 (ie, if some action or intervention is required or if the investigator judges the change to be beyond the

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range of normal physiologic fluctuation). If abnormal ECG findings are the result of pathology for which there is an overall diagnosis, the diagnosis should be reported appropriately as an AE (Section 10.1).

9.1.16 Biomarker Sample Collection

Biomarkers samples will be taken for exploratory analysis as shown in Table 9.b.

Biomarkers associated with inflammation, nausea, or intestinal motility including but not limited to cortisol, IL-6, IL-10, MCP-1, and CRP will be measured depending on assay feasibility.

Subjects will have serum biomarker samples collected prior to and at the end of the infusion (+10 minutes) and after surgery on Day 1; on Day 2, prior to and at 4 hours (+10 minutes) after the start of the infusion; on Day 3 up to Day 10, a predose sample will be obtained every other day. Sample collection instructions for circulating biomarkers will be explained in detail in the laboratory manual to be provided to the site. The samples will be stored at site/commercial vendor, and analyzed as needed.

9.1.17 PK Sample Collection

9.1.17.1 Collection of Plasma for PK Sampling

Subjects will have PK samples collected as follows:

- Day 1: Collect 1 sample prior (within 30 minutes) to the start of the infusion, 1 sample at the end of the 60-minute infusion (+10 minutes), and another sample within the 1- to 3-hour window after the surgery, for a total of 3 samples.
- Day 2: Collect 1 sample prior (within 30 minutes) to the start of the infusion, 1 sample at the end of the 60-minute infusion (+10 minutes), and an additional sample within the 3- to 5-hour window after the end of the infusion, for a total of 3 samples.
- Day 3 up to Day 10 while on study drug: a trough (predose, within 30 minutes of the start of the infusion) sample obtained every other day starting on Day 3.

Times indicated are relative to the start of the infusion. It is important that the date and time of each sample collection be accurately recorded on the eCRF. The date and time of start and end of infusion should also be accurately recorded on the eCRF. All blood samples, except the sample collected at the end of infusion, 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 eCRF. Placebo PK samples will not be analyzed; therefore, the randomization code will be sent to the analyzing laboratory. If indicated, collected TAK-954 samples may also be assayed in an exploratory manner for metabolites if deemed necessary for interpretation of the data and these data will be reported in PK listings only.

When ECG, vital signs, and blood draw coincide at the same nominal time point, the sequence of procedures will be safety ECG, vital signs assessment, and blood draw.

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9.1.18 Primary Specimen Collection

Primary specimen collections are provided in Table 9.b.

Table 9.b Primary Specimen Collection

Specimen Name	Primary Specimen	Description of Intended Use	Sample Collection
Serum sample for circulating biomarkers	Serum	Biomarker measurement	Mandatory
Plasma sample for TAK-954 PK	Plasma	PK measurements	Mandatory

Abbreviations: PK, pharmacokinetic.

9.1.19 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

If the subject is withdrawn at the screening visit after signing the informed consent, the investigator should complete the required screening eCRFs. The IRT should be contacted as a notification of screen failure. No follow-up visits are expected.

The primary reason for screen failure is recorded in the subject source documents and eCRF using the following categories:

- AE.
- Did not meet inclusion criteria or did meet exclusion criteria (specify reason).
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other study-specific reason.
- Other (specify reason).

Subject identification numbers assigned to subjects who fail screening should not be reused. Subjects may be rescreened 1 time and will be given a new subject ID.

9.1.20 Documentation of Randomization

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

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

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9.1.21 Quality of Life Assessment

Quality of life will be assessed by subjects completing the following questionnaires at baseline, last day of treatment, and the follow-up visit at 14 days (±4 days) post last dose:

- SF-12.
- EQ-5D.

At discharge, a printed copy of SF-12 and EQ-5D (with pre-addressed envelopes) will be provided to subjects as part of their discharge packages. If the Day 14 visit is done via phone follow-up, the study coordinator will remind subjects to complete the quality of life scales on the same day as the follow-up phone call and completed questionnaires will be mailed to the clinic.

9.2 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).

9.2.1 Post Study Care

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

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment SAEs

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

10.1.2 AEs

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

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

10.1.3 Additional Points to Consider for AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered AEs.)
- Necessitate therapeutic intervention.

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- 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.

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

Diagnoses vs 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 an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG retest 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 an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as AEs. If the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a 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 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…").

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Worsening of AEs:

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

Changes in intensity of AEs:

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

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered 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 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 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 AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered AEs and will be recorded on the AE page of the eCRF.

10.1.4 SAEs

An SAE is defined as any untoward medical occurrence:

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.

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5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT based on the opinion of either the investigator or sponsor that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life-threatening or fatal or does not result in hospitalization.

10.1.5 Severity of AEs

All AEs, including clinically significant treatment-emergent laboratory abnormalities, will be graded according to CTCAE v5.0. AEs not listed by the NCI CTCAE will be graded displayed in Table 10.a.

Table 10.a 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 [a].
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	Life-threatening consequences; urgent intervention indicated.
5	Fatal AE; an event that results in the death of the subject.

Abbreviations: ADL: activities of daily living; AE, adverse event; NCICAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

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

10.1.6 Management of Specific AEs

10.1.6.1 CV Disorders

CV Events:

Subjects with clinically significant ECG abnormalities indicative of acute cardiac instability or acute myocardial ischemia or infarction, as determined by the investigator at screening will be excluded from the study.

Suspected CV events that include ischemic heart disease, cerebrovascular accident (eg, transient ischemic attack and stroke), venous or arterial thromboembolic events, and heart failure, should be reported as an AESI to the sponsor within 24 hours irrespective of the seriousness. These events will be adjudicated by a cardiovascular endpoint committee (CEC).

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QT prolongation

Subjects with >5 beats of nonsustained VT at a rate >120 bpm or have QTcF ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events at screening will be excluded from the study. Subjects with bundle branch block and a prolonged QTcF should be reviewed by a cardiologist for potential inclusion.

Any QT prolongation event assessed as Grade 2 or worse (QTcF longer than 480 msec), irrespective of the seriousness, should be reported as an AESI to the sponsor within 24 hours and managed according to the guidelines below.

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

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

Abbreviations: ECG, electrocardiogram; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; QTcF, QT interval with Fridericia correction method; VT, ventricular tachycardia.
[a] Heart rate-corrected QT interval will be calculated using Fridericia's formula ($QTcF=QT/RR^{1/3}$).

AV Dissociation/Heart Block

Patients with AV block other than first degree heart block will be excluded from the study.

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

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

SVT

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

Table 10.c Management of SVT by NCI CTCAE Grade

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

Abbreviations: NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; SVT, supraventricular tachycardia.

Hypotension/Orthostatic Hypotension

If the subject has orthostatic hypotension prior to dosing, the treatment should be delayed and the case should be discussed with the medical monitor.

If any subject develops Grade 3 hypotension or orthostatic hypotension, the medical monitor should be contacted and the hypotensive event should be investigated and managed as per institutional guidelines.

For Grade 4 hypotension, treatment with study drug should be discontinued.

10.1.6.2 Serotonin Syndrome

Neurological examinations looking for hypertonicity, reflexes, and clonus will be performed at screening and during treatment with study drug as per the Schedule of Study Procedures (Appendix A).

Treatment with study drug should be discontinued if a subject develops any of the following clinical features (Hunter's criteria):

- Spontaneous clonus.
- Inducible clonus PLUS agitation or diaphoresis.

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- Ocular clonus PLUS agitation or diaphoresis.
- Tremor PLUS hyperreflexia.
- Hypertonia PLUS temperature above 38ºC PLUS ocular clonus or inducible clonus.

In case of a suspected serotonin syndrome, treatment with TAK-954 and/or other potential serotoninergic drugs will be immediately interrupted and other supportive and therapeutic measures will be initiated as clinically indicated. Any suspected case of serotonin syndrome will be reported to the sponsor as a serious AESI within 24 hours.

10.1.6.3 Diarrhea

AEs of diarrhea (new onset or change from baseline) should be investigated for underlying etiology and graded for severity as per the NCI CTCAE grading system, as follows:

- Grade 1: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.
- Grade 2: Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline.
- Grade 3: Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care of activities of daily living.
- Grade 4: Life-threatening consequences; urgent intervention indicated.
- Grade 5: Death.

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

10.1.6.4 Abnormal Liver Tests

Treatment with study drug should be discontinued in subjects who develop ALT and/or AST >3 × ULN concurrently with total bilirubin >2 × ULN while on treatment with study drug. These findings should be reported to the sponsor as a serious AESI. The investigator must contact the medical monitor for discussion of the relevant subject details and possible alternative etiologies such as acute viral hepatitis, other acute liver disease, or medical history/concurrent medical conditions. In addition, the investigator should contact the medical monitor for any increase in liver tests without clear etiology.

10.1.6.5 AESI

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

The following events will be reported as AESI:

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- Suspected CV events (ischemic heart disease, cerebrovascular accident [eg, transient ischemic attack and stroke], venous or arterial thromboembolic events, and heart failure).
- QT prolongation G2 or above.
- 2nd or 3rd degree heart block.
- SVT G2 or above with heart rate over 130 bpm.
- Suspected serotonin syndrome.
- Diarrhea Grade 3 or higher.
- Liver test elevations as defined in Section 10.1.6.4.

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

10.1.10 Stop Date

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

10.1.11 Frequency

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

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10.1.12 Action Concerning Study Drug

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

10.1.13 Outcome

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

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 AE Collection Period

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

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Collection of AEs and SAEs (treatment-emergent) will commence from the time that the subject is first administered study drug (Day 1). Routine collection of AEs and SAEs will continue until the final follow-up visit (90 days post last dose).

10.2.1.2 AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

All subjects experiencing AEs or SAEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All AEs will be documented in the AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

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

10.2.1.3 AESI

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

10.2.2 Collection and Reporting of SAEs

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

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

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

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

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

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

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

10.3 Follow-up of SAEs

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

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

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

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

11.0 STUDY-SPECIFIC COMMITTEES

11.1 Independent CEC

An independent CEC consisting of 2 CV experts and 1 neurologist will review and adjudicate all suspected CV events in a blinded fashion to determine if the reported event meets the criteria for

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major adverse cardiac event. Details of the independent CEC, including meeting frequency, will be captured in a charter prior to the start of the trial.

11.2 Internal Monitoring Committee

An IMC within Takeda composed of a senior clinician, a senior statistician, and a senior pharmacovigilance physician not involved in the study will perform ongoing reviews of the serious AEs, conduct periodic scheduled reviews of safety, and conduct reviews of IA results. The IMC is responsible for making recommendations for changes to the study after the IA, if appropriate.

Details of the IMC, including meeting frequency, will be captured in a charter prior to 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, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs (Electronic and Paper)

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

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

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

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

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

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

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

12.2 Record Retention

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

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

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

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13.1.1 Analysis Sets

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

The per-protocol set (PPS) will include all FAS subjects who had no major protocol deviation that could confound the interpretation of the primary analyses based on the FAS. The major protocol deviations that lead to a subject's exclusion from the FAS to form the PPS will be specified in the SAP. The PPS will be used to perform sensitivity analysis for the efficacy endpoints.

The safety set will include all subjects who were randomized and received at least 1 dose of double-blind study medication. In safety summaries, subjects will be analyzed according to the treatment they received.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

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

13.1.3 Efficacy Analysis

The primary efficacy endpoint is time from the end of surgery to resolution of upper and lower GI function (ie, time to first tolerance of solid food [defined as first occurrence of no vomiting or no clinically significant nausea for 1 calendar day after a solid meal] and first spontaneous bowel movement, whichever occurs later) up to Day 10 postsurgery.

The primary endpoint will be analyzed using the Cox proportional hazard model with treatment group as a single covariate, with Efron's method of tie handling, stratified by randomization stratification factor. Hazard ratios between TAK-954 doses/regimens and placebo and their 90% CIs based on the Cox model will be presented. P-values for the comparisons of TAK-954 doses/regimens and placebo will be calculated using Wald chi-square test based on the Cox model and presented. Median time to resolution of upper and lower GI function will be estimated by Kaplan-Meier survival analysis. The hazard ratios and median time differences between TAK-954 doses/regimens and placebo will be used to express the magnitude of treatment effects. The statistical tests will be 1-sided comparing TAK-954 doses/regimens to placebo. As a sensitivity analysis, the primary endpoint will be analyzed using the same method above based on PPS.

In the final analyses of efficacy endpoints, for the 2 discontinued treatment arms, only the summary statistics (n, mean, SD, median, minimum, and maximum for continuous endpoints; number and percentage of subjects for categorical data; the number and percentages of events and censoring, median, minimum, and maximum for time to event endpoint) will be provided; for the remaining treatment groups after IA, the inferential statistics (point estimates of interest and 90%

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CIs and 1-sided p-values) for each treatment group and the TAK-954 doses/regimens in comparison with placebo will be provide along with summary statistics.

The secondary endpoints time to tolerance of solid food from the end of surgery, time to first spontaneous bowel movement from the end of surgery, time from the end of surgery until ready for discharge, time from the end of surgery until the discharge order is written, time from the end of surgery to discharge from hospital, and time from the end of surgery to first flatus will be analyzed using similar statistical methods described for the primary efficacy analysis.

The comparisons of TAK-954 dose levels and placebo in percent of subjects with POGD ≥5 days and the percent of subjects requiring insertion of NG tube postsurgery will be based on the Miettinen and Nurminen's method stratified by randomization stratification factor for risk difference.

13.1.4 PK Analysis

No formal noncompartmental PK analyses will be performed on concentration-time data. The observed plasma concentrations of TAK-954 will be summarized by dose/regimen at study scheduled day/time point where appropriate. Individual concentration-time data for TAK-954 and its metabolites will be included in listings.

A population PK analysis may be conducted 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 Safety Analysis

AEs will be summarized using the safety analysis set.

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

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

Clinical Evaluations:

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

13.2 IA and Criteria for Early Termination

The first IA will be conducted after approximately 125 subjects (25 per arm) have completed or withdrawn from the study. The second IA is removed. Following the IA, bayesian approach for

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decision making will be implemented for the potential study modification including futility, regimen decision, and sample size adjustment.

The IMC will review the IA results and make recommendations for changes to the study, if appropriate. All members of the study team and the investigative team will remain blinded to treatment arm assignment and treatment arm results until the completion of the study.

13.3 Determination of Sample Size

Assuming 80% of subjects will have resolution of POGD at the end of study in the placebo group and 92.5% of subjects will have resolution of POGD at the end of study in the active TAK-954 doses, a total of approximately 300 subjects (100 per treatment group) will provide 80% power with a 0.05 2-sided significance level under Protocol Amendment 4.

In order to mitigate the statistical, clinical, and operational risks to this study in light of the COVID-19 pandemic, the probability of success of the study is re-estimated by blinded assessments using efficacy assumptions of Protocol Amendment 4. Specifically, by the removal of the second IA per this amendment and changing the statistical significance level from 2-sided 5% to 1-sided 5%, the resulting sample size is an overall total of 50 subjects for each remaining arm (Figure 6.b). Under these revised assumptions and the dropping of 2 arms, an overall total of approximately 180 subjects for the study will provide approximately 80% probability, for at least 1 remaining TAK-954 treatment arm, that TAK-954 is superior to placebo in time to resolution of upper and lower GI function at a 1-sided 5% significance level for the final analysis.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

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

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

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14.2 Protocol Deviations

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

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

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 study drug is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and study sites 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 B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

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

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Assurance Number or comparable number assigned by the Department of Health and Human Services.

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

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

Subject reimbursements should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC 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 prior to use.

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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 or IEC.

The subject 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 prior to subject entering into the study.

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 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 sample for DNA analysis can withdraw their consent and request disposal of a stored sample at any time prior to analysis.

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, and subject initials may be used to verify the subject and accuracy of the subject's unique identification number.

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

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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 eCRF).

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

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.

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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

1. Venara A, Neunlist M, Slim K, Barbieux J, Colas PA, Hamy A, et al. Postoperative ileus: Pathophysiology, incidence, and prevention. J Visc Surg 2016;153(6):439-46.
2. Colorectal Writing Group for the Scoap-Certain Collaborative, Ehlers AP, Simianu VV, Bastawrous AL, Billingham RP, Davidson GH, et al. Alvimopan use, outcomes, and costs: A report from the surgical care and outcomes assessment program comparative effectiveness research translation network collaborative. J Am Coll Surg 2016;222(5):870-7.
3. Ahmed Ali U, Dunne T, Gurland B, Vogel JD, Kiran RP. Actual versus estimated length of stay after colorectal surgery: which factors influence a deviation? Am J Surg 2014;208(4):663-9.
4. The FO, Bennink RJ, Ankum WM, Buist MR, Busch OR, Gouma DJ, et al. Intestinal handling-induced mast cell activation and inflammation in human postoperative ileus. Gut 2008;57(1):33-40.
5. Sloots CE, Rykx A, Cools M, Kerstens R, De Pauw M. Efficacy and safety of prucalopride in patients with chronic noncancer pain suffering from opioid-induced constipation. Dig Dis Sci 2010;55(10):2912-21.
6. Gong J, Xie Z, Zhang T, Gu L, Yao W, Guo Z, et al. Randomised clinical trial: prucalopride, a colonic pro-motility agent, reduces the duration of post-operative ileus after elective gastrointestinal surgery. Aliment Pharmacol Ther 2016;43(7):778-89.
7. Pedziwiatr M, Kisialeuski M, Wierdak M, Stanek M, Natkaniec M, Matlok M, et al. Early implementation of Enhanced Recovery After Surgery (ERAS(R)) protocol - Compliance improves outcomes: A prospective cohort study. Int J Surg 2015;21:75-81.
8. Keller DS, Bankwitz B, Woconish D, Champagne BJ, Reynolds HL, Jr., Stein SL, et al. Predicting who will fail early discharge after laparoscopic colorectal surgery with an established enhanced recovery pathway. Surg Endosc 2014;28(1):74-9.
9. Grass F, Slieker J, Jurt J, Kummer A, Sola J, Hahnloser D, et al. Postoperative ileus in an enhanced recovery pathway-a retrospective cohort study. Int J Colorectal Dis 2017;32(5):675-81.

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10. Hussain Z, Lee YJ, Yang H, Jeong EJ, Sim JY, Park H. YH12852, a potent and highly selective 5-HT4 receptor agonist, significantly improves both upper and lower gastrointestinal motility in a guinea pig model of postoperative ileus. Neurogastroenterol Motil 2017;29(10):1-6.
11. Tsuchida Y, Hatao F, Fujisawa M, Murata T, Kaminishi M, Seto Y, et al. Neuronal stimulation with 5-hydroxytryptamine 4 receptor induces anti-inflammatory actions via alpha7nACh receptors on muscularis macrophages associated with postoperative ileus. Gut 2011;60(5):638-47.
12. Maca J, Peteja M, Reimer P, Jor O, Sedenkova V, Panackova L, et al. Surgical injury: comparing open surgery and laparoscopy by markers of tissue damage. Ther Clin Risk Manag 2018;14:999-1006.
13. Kenward H, Elliott J, Lee T, Pelligand L. Anti-nausea effects and pharmacokinetics of ondansetron, maropitant and metoclopramide in a low-dose cisplatin model of nausea and vomiting in the dog: a blinded crossover study. BMC Vet Res 2017;13(1):244.
14. Luckey A, Livingston E, Tache Y. Mechanisms and treatment of postoperative ileus. Arch Surg 2003;138(2):206-14.
15. van Bree SH, Bemelman WA, Hollmann MW, Zwinderman AH, Matteoli G, El Temna S, et al. Identification of clinical outcome measures for recovery of gastrointestinal motility in postoperative ileus. Ann Surg 2014;259(4):708-14.

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Appendix A Schedule of Study Procedures

	Days -21 to 1 [a]	Baseline/Day 1 (Preinfusion) [b]	Day 1 (Postinfusion)	Day 2 to up Day 10	Early Termination (ET)	Days 16 to 24 Interim Follow-up (14 Days [±4 Days] Post Last Dose) [c]	Days 32 to 40 Follow-up (30 days [±3 days] Post Last Dose) (Phone Call)	Days 92 to 100 (90 days [±7 days]) Post Last Dose Final Follow-up (Phone Call)
Informed consent [d]	X							
Inclusion/exclusion criteria	X	X [e]						
Demographics and medical history	X	X						
Medication history	X	X						
Physical examination (including neurology examination) [f]	X	X		X	X	X		
Height, weight, and BMI	X							
Vital signs [g]	X	X	X	X		X		
Clinical assessment			X	X	X			
Concurrent medical procedures	X	X	X	X	X			
Concomitant medications	X	X	X	X	X	X		
ERP assessment			X	X [h]				
Clinical laboratory evaluations [i]	X	X		X	X			
Serum or urine pregnancy test (hCG) [j]	X				X	X		
12-lead ECG [k]	X	X	X	X	X			
Study drug dosing [l]			X	X				
Surgery [m]			X					
Plasma sample for TAK-954 PK [n]		X	X	X				

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	Days -21 to 1 [a]	Baseline/Day 1 (Preinfusion) [b]	Day 1 (Postinfusion)	Day 2 to up Day 10	Early Termination (ET)	Days 16 to 24 Interim Follow-up (14 Days [±4 Days] Post Last Dose) [c]	Days 32 to 40 Follow-up (30 days [±3 days] Post Last Dose) (Phone Call)	Days 92 to 100 (90 days [±7 days]) Post Last Dose Final Follow-up (Phone Call)
Serum sample for circulating biomarkers [o]		X	X	X				
Ready for discharge [p]				X				
Discharge papers written				X				
Discharge from hospital [q]				X				
EQ-5D [r]		X		X		X		
SF-12 [r]		X		X		X		
AE assessment [s]		X	X	X	X	X	X	X

Abbreviations: AE, adverse event; BMI, body mass index; COVID-19, coronavirus disease 2019; ECG, electrocardiogram; EQ-5D, EuroQol 5-dimensional questionnaire; ERP, enhanced recovery pathway; GI, gastrointestinal; HbA1c, glycosylated hemoglobin; PK, pharmacokinetics; SF-12, 12-Item Short Form Health Survey; SOC, standard of care.

[a] All screening procedures need to be reviewed before randomization if done on Day -1. These screening procedures may be used as baseline parameters on Day 1.

[b] The day of first study drug administration for the treatment period is Day 1. Baseline evaluations are defined as the assessment before first dose of study drug.

[c] During the COVID-19 public health emergency, every attempt should be made to perform the follow-up visit at 14 days post last dose in clinic however, it may be conducted at the clinic or via phone call (eg, collection of AEs, concomitant medications, and monitoring) to extend flexibility to study subjects. In the case of a phone call follow-up, physical examination (including neurology examination), vital signs, or pregnancy test would not be collected; however, AEs will be assessed, including a safety check on any emerging clinical sign or symptoms. Subjects may be requested to return to the site for further safety assessment, due to reported AEs, at the investigator's discretion. The type of visit (whether clinic visit or phone call) must be recorded in the study records.

[d] Informed consent will be signed before any study-specific procedures are performed. Informed consent may be performed in clinic or remotely using electronic signature where allowed by site institutional review boards/ethics committees.

[e] Excluded medications should be reassessed during the 24 hours prior to surgery.

[f] Physical examination includes a neurology examination. A targeted neurological examination looking for hypertonicity, reflexes, and clonus will be performed by medically qualified personnel at screening, baseline (preinfusion on Day 1), on Days 2 and 5, on the last day of treatment, at the early termination visit (as applicable), and at the safety follow-up visit (14 days post last dose). Physical examinations collected as SOC within 21 days of randomization may be used for study screening purposes. If physical examinations are collected as SOC on the day of surgery but before informed consent, they may be used for screening/baseline purposes as long as the results are assessed for eligibility before randomization.

[g] Vital signs will include blood pressure (systolic and diastolic) and pulse (beats per minute). Vital signs collected as SOC within 21 days of randomization may be used for study screening purposes. If vital signs are collected as SOC on the day of surgery but before informed consent, they may be used for screening/baseline purposes as long as the results are assessed for eligibility before randomization. Vital signs will be collected at the following time points: screening, presurgery before and at the end of infusion on Day 1, on Days 2 to

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10 (ie, at the end of infusion in the morning and in the evening), and at the safety follow-up visit (on 14 days post last dose visit). Vital signs on day of surgery will be monitored according to SOC. Clinically abnormal vital signs will be captured as an AE as per NCI CTCAE v5.0. Subjects should have rested for at least 5 minutes before vital signs are assessed. When ECG, vital signs, and blood draw coincide at the same nominal time point, the sequence of procedures will be safety ECG, vital signs assessment, and blood draw.

[h] Assessment of ERP will be during the perioperative period on Day 1 and 2 only.

[i] Laboratory samples will be collected at screening, preinfusion Day 1 (Baseline) (note: it is not required that Day 1 laboratory assessments are reviewed before study drug administration) and Day 2. Results of clinical laboratory assessments collected as SOC within 21 days of randomization may be used for study screening purposes. If laboratory assessments are collected as SOC on the day of surgery but before informed consent, they may be used for screening/baseline purposes as long as the results are assessed for eligibility before randomization. In addition, liver test parameters (ie, ALT, AST, total bilirubin, alkaline phosphatase) will be tested on the last day of study dosing and early termination (as applicable). Clinical laboratory samples will be collected as per SOC and will not be duplicated. HbA1c to be collected at screening only (or collected as SOC within 30 days of informed consent may be used for screening purposes). Any clinically significant laboratory result will be captured as an AE as per NCI CTCAE v5.0.

[j] For women of childbearing potential. Beta hCG will be collected at screening, early termination (if applicable), and the follow-up visit (ie, 14 days post last dose).

[k] ECGs will be collected at screening; prior to and at the end of the infusion (+20 minutes) on Day 1; at the end of the 60-minute IV infusion (+20 minutes) and approximately 2 hours (+20 minutes) after the start of the 60-minute infusion on Day 2; at the end of the infusion (+20 minutes) on every other day of treatment (Days 4, 6, 8, and 10), and early termination (as applicable). Subjects should have rested in a supine or semisupine position for at least 5 minutes before ECG assessment. The same position (either supine or semisupine) should be used for the same individual throughout the study. ECG assessments collected as SOC within 21 days of randomization may be used for study screening purposes. If an ECG is collected as SOC on the day of surgery but before informed consent, it may be used for screening/baseline purposes as long as the results are assessed for eligibility before randomization. When ECG, vital signs, and blood draw coincide at the same nominal time point, the sequence of procedures will be safety ECG, vital signs assessment, and blood draw.

[l] On Day 1, the completion of the infusion should occur within 3 hours of the start of the surgery (induction of anesthesia). Subsequent doses (Days 2 to 10, if required) should be approximately 24 hours (±5 hours) from the start of the prior infusion. If a subsequent dose cannot be administered during this window, it should be skipped.

[m] The start and stop times of the surgery must be recorded. The start time of surgery is the start of general anesthesia.

[n] Subjects will have PK samples collected as follows: Day 1: Collect 1 sample prior (within 30 minutes) to the start of the infusion, 1 sample at the end of the 60-minute infusion (+10 minutes), and another sample within the 1- to 3-hour window after the surgery, for a total of 3 samples. Day 2: Collect 1 sample prior (within 30 minutes) to the start of the infusion, 1 sample at the end of the 60-minute infusion (+10 minutes), and an additional sample within the 3- to 5-hour window after the end of the infusion, for a total of 3 samples; Day 3 up to Day 10 while on study drug: a trough (predose, within 30 minutes of the start of the infusion) sample obtained every other day starting on Day 3. For the PK samples that correlate with the end of study drug infusion, the sample should always be collected from the arm opposite to the arm in which study drug is infused. When ECG, vital signs, and blood draw coincide at the same nominal time point, the sequence of procedures will be safety ECG, vital signs assessment, and blood draw.

[o] Subjects will have serum biomarker samples collected prior to and at the end of the infusion (+10 minutes) on Day 1 and after surgery; on Day 2, prior to and at 4 hours (+10 minutes) after the start of the infusion; on Day 3 up to Day 10, and a predose sample will be obtained every other day.

[p] Ready for discharge is defined as the time when the subject presents effective intestinal transit (spontaneous bowel movement), tolerates solids without clinically significant nausea and vomiting for 1 calendar day, has satisfactory pain control with oral analgesics, and is medically stable/free of complications.

[q] Discharge cannot occur prior to the occurrence of the primary endpoints. If a subject meets the primary endpoint after midnight, discharge procedures can be completed the next day. This would not be considered a protocol deviation. If a subject meets the primary endpoint in the morning and is discharged later that day, this is considered a minor protocol deviation.

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[r] EQ-5D and SF-12 questionnaires will be conducted at baseline, last day of treatment, and at the Day 14 post last dose follow-up visit. At discharge, printed copy of SF-12 and EQ-5D (with pre-addressed envelopes), will be provided to subjects as part of their discharge packages. If the Day 14 visit is done via phone follow-up, the study coordinator will remind subjects to complete the quality of life scales on the same day as the follow-up phone call and completed questionnaires will be mailed to the clinic.

[s] After informed consent, but before initiation of study drugs, only SAEs caused by a protocol-mandated intervention will be collected (eg, SAEs related to invasive procedures). All AEs and SAEs (treatment-emergent) will be collected from study drug start until 90 days post last dose. Serious and nonserious CV events (suspected ischemic heart disease, cerebrovascular accident [eg, transient ischemic attack and stroke], venous or arterial thromboembolic events, or heart failure), SVT/arrhythmias and death will be collected.

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Appendix B Responsibilities of the Investigator

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

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

1. Conduct the study in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that study related procedures, including study specific (nonroutine/nonstandard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the study are informed of these obligations.
5. Secure prior approval of the study and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the study to the IRB/IEC, and issue a final report within 3 months of study completion.
7. Ensure that requirements for informed consent, as outlined, 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.
9. Prepare and maintain adequate case histories of all persons entered into the study, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied drugs, and return all unused sponsor-supplied drugs to the sponsor.

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12. Report adverse reactions to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

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Appendix C 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 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.

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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

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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 the last dose. If a subject is found to be pregnant during study, study drug will be discontinued and the investigator will offer the subject the choice to receive unblinded treatment information.
26. Male subjects must use highly effective contraception (as defined in the informed consent) from signing the informed consent throughout the duration of the study, and for 30 days after the 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.

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Appendix D Investigator Consent to Use of Personal Information

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

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

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

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

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

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

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Appendix E Protocol History

Date	Amendment Number	Amendment Type	Region
23 March 2021	Amendment 5	Substantial	Global
09 July 2019	Amendment 4	Substantial	Global
13 May 2019	Amendment 3	Substantial	Local (Germany)
23 April 2019	Amendment 2	Nonsubstantial	Local (Belgium)
19 December 2018	Amendment 1	Not applicable	Global
15 October 2018	Initial protocol	Not applicable	Global

Rationale for Amendment 4

The primary reason for this amendment is to produce 1 common international protocol by incorporating individual country amendments (Germany's Bundesinstitut für Arzneimittel und Medizinprodukte [BfArM] and Belgium's Federal Agency for Medicines and Health Products) containing responses to their regulatory reviews. In addition, the amendment contains changes to address operational issues and an updated list of prohibited medicines as a consequence of new data supporting the absence of direct evidence suggesting a relationship between selective 5-HT_4 agonist and serotonin syndrome.

Changes in Amendment 4

1. Clarification of the end of the surgery.
2. Correction of the collection of a peak nausea severity score.
3. Clarification of the maximum dose that will be used for this study.
4. Addition of the justification for a maximum dose of 1.0 mg TAK-954.
5. Added definition for the end of the study.
6. Deleted "subject's legally acceptable representative".
7. Clarification of who can review an electrocardiogram (ECG) for inclusion into the study.
8. Revised the timeframe for excluded medications.
9. Clarification of laxative use.
10. Removal of medications associated with serotonin syndrome.
11. Clarification of drug dosing in relation to surgery delays.
12. Clarification of the use of the interactive response technology (IRT).
13. Clarification of the procedure for clinically significant physical examination changes.
14. Addition of the collection of approximate length of bowel removed during surgery.
15. Clarification of the clinical assessments.

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16. Revised highly effective forms of contraception.
17. Clarification of ECG procedures.
18. Clarification of the quality of life assessment.
19. Clarification of specific adverse events (AEs) related to cardiovascular (CV) events.
20. Correction of the management of QT prolongation.
21. Clarification of the procedure for suspected serotonin syndrome.
22. Correction of action concerning study drug.
23. Correction of the members of the internal monitoring committee (IMC).
24. Correction of the analysis of the primary endpoint.
25. Addition of a pregnancy test at the Days 16 to 24 follow-up visit.
26. Correction and clarification of laboratory sample collection.
27. Clarification of pharmacokinetic (PK) sample collection.
28. Correction of plasma and serum biomarker sample collection.
29. Correction of ERP assessments.

Rationale for Amendment 3

The primary reason for this amendment is in response to the Bundesinstitut für Arzneimittel und Medizinprodukte responses.

Changes in Amendment 3:

1. Added definition for the end of the study.
2. Deleted "subject's legally acceptable representative".
3. Revised the timeframe for excluded medications.
4. Revised highly effective forms of contraception.
5. Added a pregnancy test at the Days 16 to 24 follow-up visit.

Rationale for Amendment 2

The primary reason for this amendment is in response to the Federal Agency for Medicines and Health Products.

Changes in Amendment 2

1. Clarification of the maximum dose that will be used for this study.
2. Addition of the justification for a maximum dose of 1.0 mg TAK-954.
3. Addition of a pregnancy test at the Days 16 to 24 follow-up visit.

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Rationale for Amendment 1

The primary reason for this amendment is clarification following initial discussion with investigators.

Changes in Amendment 1

1. Revision and addition of exploratory objectives.
2. Clarification of primary endpoint.
3. Addition and clarification of secondary endpoints.
4. Addition and clarification of exploratory endpoints.
5. Deletion and clarification of core enhanced recovery pathway (ERP).
6. Removal of subject daily diary and clarification of bowel movement.
7. Revision of exclusion criteria regarding glycosolated hemoglobin requirements and addition of exclusion criteria regarding radiation.
8. Revised and added criterion for discontinuation or withdrawal of a subject regarding study drug dosing.
9. Additional instructions related to timing of dosing and the surgery.
10. Addition and clarification of vital sign measurements.
11. Revision of POGD assessment.
12. Added section for documentation of concurrent medical procedures.
13. Clarification of concomitant medications.
14. Clarification of concurrent medical conditions.
15. Revised pregnancy test to allow for serum or urine and added glycosylated hemoglobin (HbA1c) to the clinical laboratory table.
16. Clarification of ECG procedures.
17. Clarification of PK sampling.
18. Added a quality of life assessment at hospital discharge.
19. Correction of SAE or AESI reporting to the safety database.
20. Addition of Baseline column to Schedule of Assessments table and corrections throughout.
21. Correction of the documentation of clinically significant changes for physical examinations.
22. Added laxatives to the excluded medications list.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
[redacted]	Biostatistics Approval	25-Mar-2021 17:23 UTC
[redacted]	Clinical Science Approval	25-Mar-2021 19:11 UTC
[redacted]	Clinical Pharmacology Approval	25-Mar-2021 20:31 UTC

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