Clinical trial results:
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

Summary

EudraCT number	2018-003318-42
Trial protocol	DE BE
Global end of trial date	27 May 2022

Results information

Result version number	v1 (current)
This version publication date	11 June 2023
First version publication date	11 June 2023

Trial information

Trial identification

Sponsor protocol code	TAK-954-2004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03827655
WHO universal trial number (UTN)	U1111-1222-4784

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 May 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to assess the efficacy and safety of intravenous (IV) TAK-954 for accelerating the recovery of gastrointestinal (GI) function postsurgery in participants undergoing open or laparoscopic-assisted partial small- or large-bowel resection.

Protection of trial subjects:

Study participants were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 36
Country: Number of subjects enrolled	United States: 173
Worldwide total number of subjects	209
EEA total number of subjects	36

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	152
From 65 to 84 years	56
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 20 investigative sites in Germany and the United States from 07 March 2019 to 27 May 2022.

Pre-assignment

Screening details:

Participants with a diagnosis of postoperative gastrointestinal dysfunction were enrolled in a 1:1:1:1:1 ratio into one of the five treatment groups to receive TAK-954 and/or placebo before and after surgery.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Assessor, Carer, Investigator, Data analyst, Subject

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

TAK-954 placebo-matching, 60-minute infusion, intravenously (IV), once presurgery on Day 1 and once daily postsurgery until return of upper and lower gastrointestinal (GI) function or for up to 10 days.

Arm type	Placebo
Investigational medicinal product name	TAK-954 Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

TAK-954 placebo-matching intravenous infusion.

Arm title	TAK-954 0.1 mg/100 mL

Arm description:

TAK-954 0.1 milligrams per 100 milliliters (mg/100 mL), 60-minute infusion, IV, once presurgery on Day 1 and once daily postsurgery until return of upper and lower GI function or for up to 10 days.

Arm type	Experimental
Investigational medicinal product name	TAK-954
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

TAK-954 intravenous infusion.

Arm title	TAK-954 0.5 mg/100 mL

Arm description:

TAK-954 0.5 mg/100 mL, 60-minute infusion, IV, once presurgery on Day 1 and once daily postsurgery until return of upper and lower GI function or for up to 10 days.

Arm type	Experimental

Investigational medicinal product name	TAK-954
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

TAK-954 intravenous infusion.

Arm title	TAK-954 0.1 mg/100 mL + Placebo

Arm description:

TAK-954 0.1 mg/100 mL, 60-minute infusion, IV, once presurgery on Day 1 and once daily placebo infusions postsurgery up to Day 10 or until resolution of upper and lower GI function.

Arm type	Experimental
Investigational medicinal product name	TAK-954
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

TAK-954 intravenous infusion.

Investigational medicinal product name	TAK-954 Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

TAK-954 placebo-matching intravenous infusion.

Arm title	TAK-954 0.5 mg/100 mL + Placebo

Arm description:

TAK-954 0.5 mg/100 mL, 60-minute infusion, IV, once presurgery on Day 1 and once daily placebo infusions postsurgery up to Day 10 or until resolution of upper and lower GI function.

Arm type	Experimental
Investigational medicinal product name	TAK-954
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

TAK-954 intravenous infusion.

Investigational medicinal product name	TAK-954 Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

TAK-954 placebo-matching intravenous infusion.

Number of subjects in period 1	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL
Started	52	27	51
Safety Set	49	26	48
Full Analysis Set (FAS)	45	23 [1]	42 [2]
Pharmacokinetic (PK) Analysis Set	0 [3]	26	47
Completed	45	24	47
Not completed	7	3	4
Adverse event, serious fatal	-	-	-
Consent withdrawn by subject	3	2	2
Protocol Deviation	1	-	1
Reason not Specified	3	1	1

Number of subjects in period 1	TAK-954 0.1 mg/100 mL + Placebo	TAK-954 0.5 mg/100 mL + Placebo
Started	27	52
Safety Set	25	50
Full Analysis Set (FAS)	21 [4]	44 [5]
Pharmacokinetic (PK) Analysis Set	24 [6]	50
Completed	25	49
Not completed	2	3
Adverse event, serious fatal	-	1
Consent withdrawn by subject	-	1
Protocol Deviation	1	-
Reason not Specified	1	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Safety Set included all participants who were randomized and received at least 1 dose of double-blind study medication.
FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).
PK Analysis Set included all participants who were randomized, received at least 1 dose and had at least 1 measurable post-dose plasma for TAK-954.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Safety Set included all participants who were randomized and received at least 1 dose of double-blind study medication.
FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).
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Justification: Safety Set included all participants who were randomized and received at least 1 dose of double-blind study medication.

FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).
PK Analysis Set included all participants who were randomized, received at least 1 dose and had at least 1 measurable post-dose plasma for TAK-954.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Safety Set included all participants who were randomized and received at least 1 dose of double-blind study medication.
FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).
PK Analysis Set included all participants who were randomized, received at least 1 dose and had at least 1 measurable post-dose plasma for TAK-954.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Safety Set included all participants who were randomized and received at least 1 dose of double-blind study medication.
FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).
PK Analysis Set included all participants who were randomized, received at least 1 dose and had at least 1 measurable post-dose plasma for TAK-954.
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Safety Set included all participants who were randomized and received at least 1 dose of double-blind study medication.
FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).
PK Analysis Set included all participants who were randomized, received at least 1 dose and had at least 1 measurable post-dose plasma for TAK-954.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
TAK-954 placebo-matching, 60-minute infusion, intravenously (IV), once presurgery on Day 1 and once daily postsurgery until return of upper and lower gastrointestinal (GI) function or for up to 10 days.	
Reporting group title	TAK-954 0.1 mg/100 mL
Reporting group description:	
TAK-954 0.1 milligrams per 100 milliliters (mg/100 mL), 60-minute infusion, IV, once presurgery on Day 1 and once daily postsurgery until return of upper and lower GI function or for up to 10 days.	
Reporting group title	TAK-954 0.5 mg/100 mL
Reporting group description:	
TAK-954 0.5 mg/100 mL, 60-minute infusion, IV, once presurgery on Day 1 and once daily postsurgery until return of upper and lower GI function or for up to 10 days.	
Reporting group title	TAK-954 0.1 mg/100 mL + Placebo
Reporting group description:	
TAK-954 0.1 mg/100 mL, 60-minute infusion, IV, once presurgery on Day 1 and once daily placebo infusions postsurgery up to Day 10 or until resolution of upper and lower GI function.	
Reporting group title	TAK-954 0.5 mg/100 mL + Placebo
Reporting group description:	
TAK-954 0.5 mg/100 mL, 60-minute infusion, IV, once presurgery on Day 1 and once daily placebo infusions postsurgery up to Day 10 or until resolution of upper and lower GI function.	

Reporting group values	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL
Number of subjects	52	27	51
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57.9	55.9	57.3
standard deviation	± 11.99	± 13.83	± 14.10
Gender categorical Units: Subjects			
Female	32	10	21
Male	20	17	30
Ethnicity Units: Subjects			
Hispanic or Latino	1	1	3
Not Hispanic or Latino	43	21	37
Unknown or Not Reported	8	5	11
Race Units: Subjects			
American Indian or Alaska Native	1	0	0
Asian	1	1	0
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	5	2	0
White	37	18	42

More than one race	0	0	0
Unknown or Not Reported	8	5	9
Region of Enrollment Units: Subjects			
Germany	8	5	9
United States	44	22	42
Height Units: centimeters (cm)			
arithmetic mean	170.83	173.01	172.30
standard deviation	± 10.991	± 9.273	± 9.335
Weight Units: kilograms (kg)			
arithmetic mean	87.25	82.92	87.26
standard deviation	± 19.317	± 18.066	± 15.995
Body Mass Index (BMI)			
BMI=[weight(kg)]/[height(m^2)]			
Units: kilograms per square meter (kg/m^2)			
arithmetic mean	29.84	27.80	29.45
standard deviation	± 5.920	± 6.492	± 5.465

Reporting group values	TAK-954 0.1 mg/100 mL + Placebo	TAK-954 0.5 mg/100 mL + Placebo	Total
Number of subjects	27	52	209
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	53.7	53.2	
standard deviation	± 12.15	± 15.28	-
Gender categorical Units: Subjects			
Female	12	26	101
Male	15	26	108
Ethnicity Units: Subjects			
Hispanic or Latino	2	3	10
Not Hispanic or Latino	21	39	161
Unknown or Not Reported	4	10	38
Race Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	1
Black or African American	4	3	14
White	18	38	153
More than one race	0	0	0
Unknown or Not Reported	5	11	38
Region of Enrollment Units: Subjects			

Germany	4	10	36
United States	23	42	173

Height			
Units: centimeters (cm)			
arithmetic mean	172.23	172.60	
standard deviation	± 10.972	± 9.603	-
Weight			
Units: kilograms (kg)			
arithmetic mean	82.84	85.64	
standard deviation	± 26.018	± 20.416	-
Body Mass Index (BMI)			
BMI=[weight(kg)]/[height(m^2)]			
Units: kilograms per square meter (kg/m^2)			
arithmetic mean	27.60	28.76	
standard deviation	± 6.904	± 6.652	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
TAK-954 placebo-matching, 60-minute infusion, intravenously (IV), once presurgery on Day 1 and once daily postsurgery until return of upper and lower gastrointestinal (GI) function or for up to 10 days.	
Reporting group title	TAK-954 0.1 mg/100 mL
Reporting group description:	
TAK-954 0.1 milligrams per 100 milliliters (mg/100 mL), 60-minute infusion, IV, once presurgery on Day 1 and once daily postsurgery until return of upper and lower GI function or for up to 10 days.	
Reporting group title	TAK-954 0.5 mg/100 mL
Reporting group description:	
TAK-954 0.5 mg/100 mL, 60-minute infusion, IV, once presurgery on Day 1 and once daily postsurgery until return of upper and lower GI function or for up to 10 days.	
Reporting group title	TAK-954 0.1 mg/100 mL + Placebo
Reporting group description:	
TAK-954 0.1 mg/100 mL, 60-minute infusion, IV, once presurgery on Day 1 and once daily placebo infusions postsurgery up to Day 10 or until resolution of upper and lower GI function.	
Reporting group title	TAK-954 0.5 mg/100 mL + Placebo
Reporting group description:	
TAK-954 0.5 mg/100 mL, 60-minute infusion, IV, once presurgery on Day 1 and once daily placebo infusions postsurgery up to Day 10 or until resolution of upper and lower GI function.	

Primary: Time From End of the Surgery to Resolution of Upper and Lower Gastrointestinal (GI) Function Postsurgery as Assessed by the Investigator

End point title	Time From End of the Surgery to Resolution of Upper and Lower Gastrointestinal (GI) Function Postsurgery as Assessed by the Investigator
End point description:	
The time from end of surgery to tolerance of solid food, without first occurrence of vomiting or clinically significant nausea for 1 calendar day after a solid meal (upper GI function) and first spontaneous bowel movement (lower GI function), whichever occurred later up to 10 days postsurgery was observed. Kaplan-Meier survival analysis method was used. FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).	
End point type	Primary
End point timeframe:	
Day 1 (surgery) up to Day 10 postsurgery	

End point values	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL	TAK-954 0.1 mg/100 mL + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	23	42	21
Units: days				
median (full range (min-max))	1.89 (1.41 to 5.79)	2.76 (1.51 to 7.85)	2.59 (0.85 to 4.97)	2.62 (1.13 to 7.59)

End point values	TAK-954 0.5 mg/100 mL + Placebo			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: days				
median (full range (min-max))	2.58 (1.46 to 7.74)			

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.649 [1]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.63
upper limit	1.33

Notes:

[1] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL + Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.505 [2]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	1

Confidence interval	
level	90 %
sides	2-sided
lower limit	0.69
upper limit	1.43

Notes:

[2] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Secondary: Time From the End of the Surgery (Time the Incision is Closed) Until Ready for Discharge as Assessed by the Investigator

End point title	Time From the End of the Surgery (Time the Incision is Closed) Until Ready for Discharge as Assessed by the Investigator

End point description:

The time from the end of surgery (time the incision is closed) until ready for discharge was defined as time from end of surgery until the participant presented effective intestinal transit (spontaneous bowel movement), tolerated solids without vomiting or clinically significant nausea for 1 calendar day after a solid meal, had satisfactory pain control with oral analgesics, and was medically stable/free of complications. Kaplan-Meier survival analysis method was used. FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).

End point type	Secondary

End point timeframe:

Day 1 (surgery) up to Day 24

End point values	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL	TAK-954 0.1 mg/100 mL + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	23	42	21
Units: days				
median (full range (min-max))	2.03 (1.41 to 16.83)	2.82 (1.51 to 9.68)	2.69 (0.85 to 8.79)	2.94 (1.47 to 7.73)

End point values	TAK-954 0.5 mg/100 mL + Placebo			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: days				
median (full range (min-max))	2.77 (1.51 to 7.74)			

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only

independent variable.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.449 [3]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.71
upper limit	1.49

Notes:

[3] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL + Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.507 [4]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.69
upper limit	1.44

Notes:

[4] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Secondary: Time From the End of Surgery Until the Discharge Order is Written

End point title	Time From the End of Surgery Until the Discharge Order is Written

End point description:

Kaplan-Meier survival analysis method was used. FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).

End point type	Secondary

End point timeframe:

Day 1 (surgery) up to Day 24

End point values	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL	TAK-954 0.1 mg/100 mL + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	23	42	21
Units: days				
median (full range (min-max))	2.86 (1.62 to 16.72)	3.95 (1.88 to 10.89)	2.81 (0.89 to 11.09)	2.94 (1.47 to 7.81)

End point values	TAK-954 0.5 mg/100 mL + Placebo			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: days				
median (full range (min-max))	3.33 (1.56 to 14.74)			

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.406 [5]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.73
upper limit	1.52

Notes:

[5] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL + Placebo

Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.88 [6]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.54
upper limit	1.11

Notes:

[6] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Secondary: Time From the End of Surgery to Discharge From Hospital

End point title	Time From the End of Surgery to Discharge From Hospital

End point description:

Kaplan-Meier survival analysis method was used. FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).

End point type	Secondary

End point timeframe:

Day 1 (surgery) up to Day 24

End point values	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL	TAK-954 0.1 mg/100 mL + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	23	42	21
Units: days				
median (full range (min-max))	2.96 (1.72 to 16.76)	4.06 (1.97 to 10.89)	2.89 (1.00 to 11.11)	3.05 (1.58 to 7.83)

End point values	TAK-954 0.5 mg/100 mL + Placebo			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: days				
median (full range (min-max))	3.39 (1.70 to 14.77)			

Statistical analyses

Statistical analysis title	Satistical Analysis 1

Statistical analysis description:

Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.446 [7]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.72
upper limit	1.48

Notes:

[7] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL + Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.892 [8]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.53
upper limit	1.09

Notes:

[8] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Secondary: Time From End of Surgery to Tolerance of Solid Food as Assessed by the Investigator

End point title	Time From End of Surgery to Tolerance of Solid Food as Assessed by the Investigator

End point description:

The time from end of surgery to tolerance of solid food was defined as intake of solids without vomiting or clinically significant nausea for 1 calendar day after a solid meal. Kaplan-Meier survival analysis method was used. FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).

End point type	Secondary

End point timeframe:

Day 1 (surgery) up to Day 10 postsurgery

End point values	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL	TAK-954 0.1 mg/100 mL + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	23	42	21
Units: days				
median (full range (min-max))	1.82 (1.41 to 5.79)	2.76 (1.51 to 7.85)	2.36 (0.74 to 4.97)	2.15 (1.13 to 7.59)

End point values	TAK-954 0.5 mg/100 mL + Placebo			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: days				
median (full range (min-max))	2.55 (1.32 to 7.74)			

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.76 [9]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.6
upper limit	1.23

Notes:

[9] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL + Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81 [10]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.58
upper limit	1.18

Notes:

[10] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Secondary: Time From End of Surgery to First Spontaneous Bowel Movement as Assessed by the Investigator

End point title	Time From End of Surgery to First Spontaneous Bowel Movement as Assessed by the Investigator

End point description:

The time from end of surgery to first spontaneous bowel movement was defined as a stool not induced by the use of enemas or laxatives. Kaplan-Meier survival analysis method was used. FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).

End point type	Secondary

End point timeframe:

Day 1 (surgery) up to Day 10 postsurgery

End point values	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL	TAK-954 0.1 mg/100 mL + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	23	42	21
Units: days				
median (full range (min-max))	1.56 (0.16 to 7.89)	1.73 (0.11 to 3.81)	1.11 (0.08 to 4.82)	1.72 (0.20 to 3.23)

End point values	TAK-954 0.5 mg/100 mL + Placebo			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: days				
median (full range (min-max))	1.74 (0.53 to			

4.94)

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.	
Comparison groups	Placebo v TAK-954 0.5 mg/100 mL + Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.453 [11]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.72
upper limit	1.47

Notes:

[11] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.	
Comparison groups	Placebo v TAK-954 0.5 mg/100 mL
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.288 [12]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.78
upper limit	1.64

Notes:

[12] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Secondary: Percentage of Participants with Postoperative Gastrointestinal

Dysfunction (POGD) >= 5 Days as Assessed by the Investigator	
End point title	Percentage of Participants with Postoperative Gastrointestinal Dysfunction (POGD) >= 5 Days as Assessed by the Investigator

End point description:

Participants unable to tolerate solid foods, take anything by mouth, or requiring insertion or reinsertion of nasogastric (NG) tube at or after 5 days post-surgery. Percentages are rounded off to whole number at the nearest single decimal. Stratified Miettinen and Nurminen approach was used for analysis. FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).

End point type	Secondary

End point timeframe:

Day 1 (surgery) up to Day 10

End point values	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL	TAK-954 0.1 mg/100 mL + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	23	42	21
Units: percentage of participants				
number (not applicable)	8.9	8.7	2.4	4.8

End point values	TAK-954 0.5 mg/100 mL + Placebo			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: percentage of participants				
number (not applicable)	9.1			

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The p-values, risk differences and corresponding 90% CIs were obtained using a stratified Miettinen and Nurminen approach with strata weighting by sample size.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL + Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.516 [13]
Method	Stratified Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.11
upper limit	0.11

Notes:

[13] - P-value was derived using a one-sided test with Ha: Risk Difference<0.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The p-values, risk differences and corresponding 90% CIs were obtained using a stratified Miettinen and Nurminen approach with strata weighting by sample size.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046 [14]
Method	Stratified Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	-0.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.17
upper limit	0

Notes:

[14] - P-value was derived using a one-sided test with Ha: Risk Difference<0.

Secondary: Percentage of Participants Requiring Insertion of Nasogastric (NG) Tube Postsurgery

End point title	Percentage of Participants Requiring Insertion of Nasogastric (NG) Tube Postsurgery

End point description:

Participants who required insertion of NG tube postsurgery for drainage and symptom relief in case of persistent nausea and vomiting postsurgery were observed. Percentages are rounded off to whole number at the nearest single decimal. Stratified Miettinen and Nurminen approach was used for analysis. FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).

End point type	Secondary

End point timeframe:

Day 1 (surgery) up to Day 24 postsurgery (10 days of treatment period postsurgery plus 14-day observation period post last dose for recurrence of symptoms)

End point values	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL	TAK-954 0.1 mg/100 mL + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	23	42	21
Units: percentage of participants				
number (not applicable)	8.9	0.0	4.8	4.8

End point values	TAK-954 0.5 mg/100 mL + Placebo			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: percentage of participants				
number (not applicable)	11.4			

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The p-values, risk differences and corresponding 90% CIs were obtained using a stratified Miettinen and Nurminen approach with strata weighting by sample size.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL + Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.677 [15]
Method	Stratified Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	0.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.07
upper limit	0.13

Notes:

[15] - P-value was derived using a one-sided test with Ha: Risk Difference<0.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The p-values, risk differences and corresponding 90% CIs were obtained using a stratified Miettinen and Nurminen approach with strata weighting by sample size.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL

Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.296 [16]
Method	Stratified Miettinen and Nurminen
Parameter estimate	Risk difference (RD)
Point estimate	-0.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.12
upper limit	0.06

Notes:

[16] - P-value was derived using a one-sided test with Ha: Risk Difference<0.

Secondary: Time From End of Surgery to First Flatus

End point title	Time From End of Surgery to First Flatus

End point description:

Kaplan-Meier survival analysis method was used. FAS included all participants who were randomized, received at least 1 dose of study drug, and had at least 1 valid postbaseline on-treatment primary efficacy evaluation (bowel movement or tolerating solid food).

End point type	Secondary

End point timeframe:

Day 1 (surgery) up to first flatus (up to Day 10 postsurgery)

End point values	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL	TAK-954 0.1 mg/100 mL + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	23	42	21
Units: days				
median (full range (min-max))	1.21 (0.06 to 6.22)	1.26 (0.28 to 7.62)	0.96 (0.08 to 3.04)	1.18 (0.20 to 2.82)

End point values	TAK-954 0.5 mg/100 mL + Placebo			
Subject group type	Reporting group			
Number of subjects analysed	44			
Units: days				
median (full range (min-max))	1.12 (0.02 to 3.88)			

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL
Number of subjects included in analysis	87
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.338 [17]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.76
upper limit	1.57

Notes:

[17] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Hazard ratios, 90% CIs and associated Wald Chi-square p-values between TAK-954 dose levels and placebo are obtained using a stratified Cox proportional hazard model with treatment as the only independent variable.

Comparison groups	Placebo v TAK-954 0.5 mg/100 mL + Placebo
Number of subjects included in analysis	89
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.422 [18]
Method	Wald chi-square test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.73
upper limit	1.49

Notes:

[18] - P-values were derived using a one-sided test with alternative hypothesis (Ha): Hazard Ratio>1.

Secondary: Observed Plasma Concentration of TAK-954 at the End of Infusion on Day 1

End point title	Observed Plasma Concentration of TAK-954 at the End of Infusion on Day 1[19]

End point description:

PK Analysis Set included all participants who were randomized, received at least 1 dose and had at least 1 measurable post-dose plasma for TAK-954. Overall number analyzed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Day 1 (surgery): postinfusion

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As pre-specified in the statistical analysis plan, only drug-treated arms were to be analysed in this endpoint.

End point values	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL	TAK-954 0.1 mg/100 mL + Placebo	TAK-954 0.5 mg/100 mL + Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	20	33	20	35
Units: picograms per milliliter (pg/mL)				
arithmetic mean (standard deviation)	1190 (± 480)	5220 (± 1810)	2500 (± 4140)	12000 (± 28500)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to Day 100

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

TAK-954 placebo-matching, 60-minute infusion, intravenously (IV), once presurgery on Day 1 and once daily postsurgery until return of upper and lower gastrointestinal (GI) function or for up to 10 days.

Reporting group title	TAK-954 0.1 mg/100 mL

Reporting group description:

TAK-954 0.1 milligrams per 100 milliliters (mg/100 mL), 60-minute infusion, IV, once presurgery on Day 1 and once daily postsurgery until return of upper and lower GI function or for up to 10 days.

Reporting group title	TAK-954 0.5 mg/100 mL + Placebo

Reporting group description:

TAK-954 0.5 mg/100 mL, 60-minute infusion, IV, once presurgery on Day 1 and once daily placebo infusions postsurgery up to Day 10 or until resolution of upper and lower GI function.

Reporting group title	TAK-954 0.1 mg/100 mL + Placebo

Reporting group description:

TAK-954 0.1 mg/100 mL, 60-minute infusion, IV, once presurgery on Day 1 and once daily placebo infusions postsurgery up to Day 10 or until resolution of upper and lower GI function.

Reporting group title	TAK-954 0.5 mg/100 mL

Reporting group description:

TAK-954 0.5 mg/100 mL, 60-minute infusion, IV, once presurgery on Day 1 and once daily postsurgery until return of upper and lower GI function or for up to 10 days.

Serious adverse events	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL + Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 49 (16.33%)	9 / 26 (34.62%)	11 / 50 (22.00%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 49 (2.04%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Anastomotic leak			
subjects affected / exposed	2 / 49 (4.08%)	1 / 26 (3.85%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound evisceration			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative ileus			
subjects affected / exposed	1 / 49 (2.04%)	1 / 26 (3.85%)	5 / 50 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative delirium			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Dehiscence			
subjects affected / exposed	1 / 49 (2.04%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	1 / 49 (2.04%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenitis			
subjects affected / exposed	1 / 49 (2.04%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	1 / 49 (2.04%)	0 / 26 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal fluid collection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 49 (0.00%)	1 / 26 (3.85%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intra-abdominal haemorrhage			

subjects affected / exposed	0 / 49 (0.00%)	1 / 26 (3.85%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mechanical ileus			
subjects affected / exposed	0 / 49 (0.00%)	1 / 26 (3.85%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal perforation			
subjects affected / exposed	0 / 49 (0.00%)	1 / 26 (3.85%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 49 (0.00%)	1 / 26 (3.85%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 49 (0.00%)	1 / 26 (3.85%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prerenal failure			
subjects affected / exposed	1 / 49 (2.04%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinoma			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 49 (2.04%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 49 (0.00%)	1 / 26 (3.85%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	TAK-954 0.1 mg/100 mL + Placebo	TAK-954 0.5 mg/100 mL	
Total subjects affected by serious adverse events			

subjects affected / exposed	2 / 25 (8.00%)	8 / 48 (16.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic leak			
subjects affected / exposed	0 / 25 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 25 (4.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound evisceration			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative ileus			
subjects affected / exposed	0 / 25 (0.00%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative delirium			
subjects affected / exposed	0 / 25 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 25 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Dehiscence			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal fluid collection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal perforation			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 25 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 25 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 25 (4.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinoma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 25 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			

subjects affected / exposed	0 / 25 (0.00%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	TAK-954 0.1 mg/100 mL	TAK-954 0.5 mg/100 mL + Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 49 (93.88%)	23 / 26 (88.46%)	41 / 50 (82.00%)
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 49 (2.04%)	1 / 26 (3.85%)	4 / 50 (8.00%)
occurrences (all)	1	1	4
Urine output decreased			
subjects affected / exposed	1 / 49 (2.04%)	0 / 26 (0.00%)	3 / 50 (6.00%)
occurrences (all)	1	0	3
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	6 / 49 (12.24%)	1 / 26 (3.85%)	5 / 50 (10.00%)
occurrences (all)	6	1	5
Postoperative ileus			
subjects affected / exposed	3 / 49 (6.12%)	1 / 26 (3.85%)	1 / 50 (2.00%)
occurrences (all)	3	1	1
Procedural complication			
subjects affected / exposed	3 / 49 (6.12%)	1 / 26 (3.85%)	0 / 50 (0.00%)
occurrences (all)	3	1	0
Procedural hypotension			
subjects affected / exposed	15 / 49 (30.61%)	0 / 26 (0.00%)	10 / 50 (20.00%)
occurrences (all)	16	0	10
Procedural hypertension			
subjects affected / exposed	5 / 49 (10.20%)	0 / 26 (0.00%)	1 / 50 (2.00%)
occurrences (all)	5	0	1
Procedural nausea			

subjects affected / exposed	3 / 49 (6.12%)	1 / 26 (3.85%)	2 / 50 (4.00%)
occurrences (all)	3	1	2
Procedural pain			
subjects affected / exposed	4 / 49 (8.16%)	5 / 26 (19.23%)	4 / 50 (8.00%)
occurrences (all)	4	5	4
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 49 (12.24%)	1 / 26 (3.85%)	7 / 50 (14.00%)
occurrences (all)	7	1	7
Hypotension			
subjects affected / exposed	3 / 49 (6.12%)	0 / 26 (0.00%)	4 / 50 (8.00%)
occurrences (all)	3	0	4
Cardiac disorders			
Bradycardia			
subjects affected / exposed	3 / 49 (6.12%)	0 / 26 (0.00%)	2 / 50 (4.00%)
occurrences (all)	4	0	3
Tachycardia			
subjects affected / exposed	5 / 49 (10.20%)	1 / 26 (3.85%)	3 / 50 (6.00%)
occurrences (all)	7	1	3
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 49 (14.29%)	1 / 26 (3.85%)	4 / 50 (8.00%)
occurrences (all)	7	1	4
Leukocytosis			
subjects affected / exposed	6 / 49 (12.24%)	1 / 26 (3.85%)	4 / 50 (8.00%)
occurrences (all)	6	1	5
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 49 (6.12%)	3 / 26 (11.54%)	0 / 50 (0.00%)
occurrences (all)	4	3	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 49 (4.08%)	0 / 26 (0.00%)	1 / 50 (2.00%)
occurrences (all)	3	0	1
Abdominal distension			

subjects affected / exposed	5 / 49 (10.20%)	1 / 26 (3.85%)	5 / 50 (10.00%)
occurrences (all)	5	1	5
Constipation			
subjects affected / exposed	1 / 49 (2.04%)	2 / 26 (7.69%)	1 / 50 (2.00%)
occurrences (all)	1	2	1
Diarrhoea			
subjects affected / exposed	7 / 49 (14.29%)	3 / 26 (11.54%)	7 / 50 (14.00%)
occurrences (all)	7	3	7
Dyspepsia			
subjects affected / exposed	0 / 49 (0.00%)	4 / 26 (15.38%)	1 / 50 (2.00%)
occurrences (all)	0	4	1
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 49 (4.08%)	0 / 26 (0.00%)	2 / 50 (4.00%)
occurrences (all)	2	0	2
Nausea			
subjects affected / exposed	22 / 49 (44.90%)	14 / 26 (53.85%)	19 / 50 (38.00%)
occurrences (all)	35	16	24
Vomiting			
subjects affected / exposed	14 / 49 (28.57%)	8 / 26 (30.77%)	11 / 50 (22.00%)
occurrences (all)	20	9	11
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	2 / 49 (4.08%)	1 / 26 (3.85%)	3 / 50 (6.00%)
occurrences (all)	2	1	3
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	4 / 49 (8.16%)	3 / 26 (11.54%)	1 / 50 (2.00%)
occurrences (all)	4	3	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 49 (0.00%)	0 / 26 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	4 / 49 (8.16%)	0 / 26 (0.00%)	3 / 50 (6.00%)
occurrences (all)	4	0	3

Hypocalcaemia			
subjects affected / exposed	10 / 49 (20.41%)	1 / 26 (3.85%)	7 / 50 (14.00%)
occurrences (all)	10	1	7
Hypophosphataemia			
subjects affected / exposed	3 / 49 (6.12%)	5 / 26 (19.23%)	4 / 50 (8.00%)
occurrences (all)	3	5	4
Hypomagnesaemia			
subjects affected / exposed	2 / 49 (4.08%)	4 / 26 (15.38%)	7 / 50 (14.00%)
occurrences (all)	2	4	7
Hypokalaemia			
subjects affected / exposed	6 / 49 (12.24%)	5 / 26 (19.23%)	5 / 50 (10.00%)
occurrences (all)	6	5	5

Non-serious adverse events	TAK-954 0.1 mg/100 mL + Placebo	TAK-954 0.5 mg/100 mL	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 25 (84.00%)	39 / 48 (81.25%)	
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 25 (4.00%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Urine output decreased			
subjects affected / exposed	0 / 25 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	2 / 25 (8.00%)	9 / 48 (18.75%)	
occurrences (all)	2	9	
Postoperative ileus			
subjects affected / exposed	1 / 25 (4.00%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Procedural complication			
subjects affected / exposed	0 / 25 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Procedural hypotension			
subjects affected / exposed	0 / 25 (0.00%)	9 / 48 (18.75%)	
occurrences (all)	0	9	

Procedural hypertension			
subjects affected / exposed	0 / 25 (0.00%)	4 / 48 (8.33%)	
occurrences (all)	0	4	
Procedural nausea			
subjects affected / exposed	1 / 25 (4.00%)	1 / 48 (2.08%)	
occurrences (all)	1	1	
Procedural pain			
subjects affected / exposed	4 / 25 (16.00%)	2 / 48 (4.17%)	
occurrences (all)	4	2	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 25 (0.00%)	7 / 48 (14.58%)	
occurrences (all)	0	7	
Hypotension			
subjects affected / exposed	0 / 25 (0.00%)	4 / 48 (8.33%)	
occurrences (all)	0	4	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 25 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Tachycardia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 25 (8.00%)	6 / 48 (12.50%)	
occurrences (all)	2	6	
Leukocytosis			
subjects affected / exposed	0 / 25 (0.00%)	4 / 48 (8.33%)	
occurrences (all)	0	4	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 25 (8.00%)	2 / 48 (4.17%)	
occurrences (all)	2	2	
Abdominal distension			
subjects affected / exposed	1 / 25 (4.00%)	5 / 48 (10.42%)	
occurrences (all)	1	6	
Constipation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 48 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 25 (8.00%)	11 / 48 (22.92%)	
occurrences (all)	3	11	
Dyspepsia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 48 (4.17%)	
occurrences (all)	0	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 25 (12.00%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Nausea			
subjects affected / exposed	12 / 25 (48.00%)	20 / 48 (41.67%)	
occurrences (all)	15	23	
Vomiting			
subjects affected / exposed	9 / 25 (36.00%)	8 / 48 (16.67%)	
occurrences (all)	10	9	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 48 (2.08%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	2 / 25 (8.00%)	0 / 48 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 48 (0.00%)	
occurrences (all)	1	0	

Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 25 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Hypocalcaemia			
subjects affected / exposed	1 / 25 (4.00%)	10 / 48 (20.83%)	
occurrences (all)	1	10	
Hypophosphataemia			
subjects affected / exposed	1 / 25 (4.00%)	3 / 48 (6.25%)	
occurrences (all)	1	3	
Hypomagnesaemia			
subjects affected / exposed	1 / 25 (4.00%)	3 / 48 (6.25%)	
occurrences (all)	1	3	
Hypokalaemia			
subjects affected / exposed	4 / 25 (16.00%)	2 / 48 (4.17%)	
occurrences (all)	4	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 July 2019	Following changes were implemented with Protocol Amendment 4: -Incorporated 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. -Added 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-hydroxytryptamine receptor 4 (5-HT4) agonist and serotonin syndrome. -Clarified end of the surgery. -Corrected of the collection of a peak nausea severity score. -Clarified the maximum dose that will be used for this study. -Added the justification for a maximum dose of 1.0 mg TAK-954. -Added definition for the end of the study. -Deleted "subject's legally acceptable representative". -Clarified who can review an electrocardiogram (ECG) for inclusion into the study. -Revised the timeframe for excluded medications. -Clarified laxative use. -Removed medications associated with serotonin syndrome. -Clarified drug dosing in relation to surgery delays. -Clarified the use of the interactive response technology (IRT). -Clarified the procedure for clinically significant physical examination changes. -Added collection of approximate length of bowel removed during surgery. -Clarified the clinical assessments.
22 March 2021	Following changes were implemented with Protocol Amendment 5: -Revised to reflect the total sample size for the study. -Added new figure to indicate study design. -Clarified the secondary objective. -Specified time window for study drug dosing for the secondary objective. -Refined the definition of the primary efficacy endpoint time. -Clarified the timing for participants requiring NG tubes postsurgery and clarified plasma TAK-954 concentrations will be measured. -Removed minimum percentage of participants required for each surgery type. -Revised sample size of remaining arms based on blinded assessments. -Revised the language. -Modified protocol for impact of coronavirus disease-19 (COVID-19). -Defined time assessment windows for the follow-up visit. -Revised inclusion and exclusion criteria. -Revised study withdrawal. -Revised liver function tests to liver tests. -Added the possibility that the participant may withdraw from the study or study drug. -Updated wording. - Added definitions. -Clarified primary and secondary efficacy analyses. -Added clarification and specification that sites should make every effort to conduct follow-up assessments. -Revised to clarify that all medications are to be collected and not just excluded medications. -Clarified timing of assessments. -Defined timing of study procedure. -Clarified study procedures.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported