Clinical trial results:
A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2b Study to Evaluate the Efficacy and Safety of Twice-Daily Oral Administration of a Peripherally Acting Dopamine Receptor D2/D3 Antagonist, TAK-906 for the Treatment of Adult Subjects With Symptomatic Idiopathic or Diabetic Gastroparesis

Summary

EudraCT number	2018-001275-21
Trial protocol	BE PL IT
Global end of trial date	15 July 2021

Results information

Result version number	v1 (current)
This version publication date	30 June 2022
First version publication date	30 June 2022

Trial information

Trial identification

Sponsor protocol code	TAK-906-2002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03544229
WHO universal trial number (UTN)	U1111-1211-2779

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	15 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to assess the efficacy of treatment with various dose levels of TAK-906 in adult participants with gastroparesis compared with placebo during 12 weeks of treatment.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 October 2018
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	Japan: 35
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	United States: 192
Worldwide total number of subjects	242
EEA total number of subjects	15

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)	167
From 65 to 84 years	75
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants with symptomatic idiopathic or diabetic gastroparesis took part in the study at 73 investigative sites in Belgium, Poland, Japan and the United States from 14 October 2018 to 15 July 2021.

Pre-assignment

Screening details:

Participants receive TAK-906 5 mg, 25 mg, 50 mg Maleate or placebo in 1:1:1:1 ratio until protocol amendment 8 was implemented. As pre-specified in protocol amendment 8 further randomization TAK-906 5 mg arm was discontinued and remaining enrolled participants were randomized into TAK-906 25 mg, TAK-906 50 mg Maleate or placebo in 1:1:1 ratio.

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	Subject, Investigator, Data analyst, Carer

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

TAK-906 maleate placebo-matching capsules, orally, twice daily (BID) for up to 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

TAK-906 maleate placebo-matching capsules.

Arm title	TAK-906 Maleate 5 mg

Arm description:

TAK-906 maleate 5 mg, capsules, orally, BID for up to 12 weeks.

Arm type	Experimental
Investigational medicinal product name	TAK-906 Maleate
Investigational medicinal product code	
Other name	TAK-906
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

TAK-906 maleate 5 mg capsules.

Arm title	TAK-906 Maleate 25 mg

Arm description:

TAK-906 maleate 25 mg, capsules, orally, BID for up to 12 weeks.

Arm type	Experimental

Investigational medicinal product name	TAK-906 Maleate
Investigational medicinal product code	
Other name	TAK-906
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

TAK-906 maleate 25 mg capsules.

Arm title	TAK-906 Maleate 50 mg

Arm description:

TAK-906 maleate 50 mg, capsules, orally, BID for up to 12 weeks.

Arm type	Experimental
Investigational medicinal product name	TAK-906 Maleate
Investigational medicinal product code	
Other name	TAK-906
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

TAK-906 maleate 50 mg capsules.

Number of subjects in period 1	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg
Started	73	23	72
Completed	67	21	67
Not completed	6	2	5
Adverse event, non-fatal	1	-	1
Voluntary Withdrawal	2	1	3
Protocol Deviation	-	-	1
Lost to follow-up	3	-	-
Lack of efficacy	-	1	-

Number of subjects in period 1	TAK-906 Maleate 50 mg
Started	74
Completed	72
Not completed	2
Adverse event, non-fatal	-
Voluntary Withdrawal	-
Protocol Deviation	-
Lost to follow-up	2
Lack of efficacy	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
TAK-906 maleate placebo-matching capsules, orally, twice daily (BID) for up to 12 weeks.	
Reporting group title	TAK-906 Maleate 5 mg
Reporting group description:	
TAK-906 maleate 5 mg, capsules, orally, BID for up to 12 weeks.	
Reporting group title	TAK-906 Maleate 25 mg
Reporting group description:	
TAK-906 maleate 25 mg, capsules, orally, BID for up to 12 weeks.	
Reporting group title	TAK-906 Maleate 50 mg
Reporting group description:	
TAK-906 maleate 50 mg, capsules, orally, BID for up to 12 weeks.	

Reporting group values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg
Number of subjects	73	23	72
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	57.1	56.3	56.4
standard deviation	± 14.22	± 14.32	± 13.31
Gender categorical Units: Subjects			
Male	19	4	11
Female	54	19	61
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	30	14	38
Not Hispanic or Latino	42	9	34
Unknown or Not Reported	1	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	8	4	12
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	10	1	4
White	54	18	55
More than one race	0	0	0
Unknown or Not Reported	1	0	1
Region of Enrollment Units: Subjects			
Belgium	3	0	3
Japan	8	4	10
Poland	2	0	2

United States	60	19	57
Smoking Classification Units: Subjects			
Participant has Never Smoked	51	18	57
Participant is a Current Smoker	10	1	7
Participant is an Ex-smoker	12	4	8
Height Units: centimetres (cm)			
arithmetic mean	164.17	164.43	161.32
standard deviation	± 10.238	± 9.178	± 7.313
Weight Units: kilograms (kg)			
arithmetic mean	79.35	82.62	71.97
standard deviation	± 16.383	± 17.021	± 16.261
Body Mass Index (BMI)			
BMI was calculated as weight (kg) divided by square of height (m^2).			
Units: kg/m^2			
arithmetic mean	29.35	30.48	27.61
standard deviation	± 5.003	± 5.606	± 5.835
ANMS GCSI-DD Composite Score			
American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary(ANMS GCSI-DD): patient-reported outcome instrument for symptom-based clinical trial endpoint in gastroparesis. The daily score was calculated by summing scores on 4 symptoms(nausea, early satiety, postprandial fullness, and upper abdominal pain)/4 (number of items within score), ranged from 0 to 4 with higher scores=symptom severity. FAS=all participants who were randomized, received at least 1 dose of study drug, and have baseline and at least 1 valid postbaseline value for assessment.			
Units: score on a scale			
arithmetic mean	2.59	2.77	2.57
full range (min-max)	2.0 to 4.0	2.0 to 3.8	2.0 to 4.0
ANMS GCSI-DD Nausea Symptom Score at Week 12 of the Treatment Period			
ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity score calculated from a 5-point Likert scale. The ANMS GCSI-DD nausea symptom score ranged from 0 to 4 with higher scores reflecting greater symptom severity. FAS: all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale			
arithmetic mean	2.80	2.85	2.70
full range (min-max)	1.6 to 4.0	1.7 to 4.0	1.6 to 4.0
ANMS GCSI-DD Early Satiety Symptom Score at Week 12 of the Treatment Period			
ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity score calculated from a 5-point Likert scale. The ANMS GCSI-DD early satiety symptom score ranged from 0 to 4 with higher scores reflecting greater symptom severity. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale			
arithmetic mean	2.80	2.97	2.82
full range (min-max)	1.3 to 4.0	2.0 to 4.0	1.3 to 4.0
ANMS GCSI-DD Postprandial Fullness Symptom Score at Week 12 of the Treatment Period			
ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity score calculated from a 5-point Likert scale. The ANMS GCSI-DD			

postprandial fullness symptom score ranged from 0 to 4 with higher scores reflecting greater symptom severity. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale			
arithmetic mean	2.99	3.16	2.98
full range (min-max)	2.0 to 4.0	2.1 to 4.0	2.0 to 4.0
ANMS GCSI-DD Upper Abdominal Pain Symptom Score at Week 12 of the Treatment Period			
ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity score calculated from a 5-point Likert scale. The ANMS GCSI-DD upper abdominal pain symptom score ranged from 0 to 4 with higher scores reflecting greater symptom severity. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale			
arithmetic mean	1.76	2.11	1.77
full range (min-max)	0.0 to 4.0	0.1 to 4.0	0.0 to 4.0
ANMS GCSI-DD Recorded Vomiting Frequency at Week 12 of the Treatment Period			
The vomiting frequency was scored from 0 to 4 (where 0 = no vomiting and 4 = four or more episodes of vomiting). The maximum core symptom score could be (5 symptoms × maximum score 4 divided by 5) = 20/5 = 4. The weekly recorded vomiting frequency for each postbaseline week was the average of the 7 daily scores within the targeted week relative to the first dose date. The ANMS GCSI-DD daily vomiting frequency score ranged from 0 to 4 with higher scores reflecting greater symptom severity.			
Units: score on a scale			
arithmetic mean	1.41	0.73	1.25
full range (min-max)	0.0 to 11.4	0.0 to 1.9	0.0 to 7.9
ANMS GCSI-DD Overall Severity of Gastroparesis Symptoms Score in Treatment Period			
The maximum total symptom score could be (6 symptoms × maximum score 4 divided by 6) = 24/6 = 4. The ANMS GCSI-DD overall severity of gastroparesis symptoms score can range from 0 to 4 with higher scores reflecting greater symptom severity. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale			
arithmetic mean	2.90	3.07	2.86
full range (min-max)	2.0 to 4.0	2.0 to 4.0	1.4 to 4.0
Bloating Severity Scale Score at Week 12 of the Treatment Period			
The bloating severity scale was scored from 0 to 4 (where 0 = no symptom and 4 = severe symptom). The maximum total symptom score could be (6 symptoms × maximum score 4 divided by 6)= 24/6 = 4. The ANMS GCSI-DD daily total score can range from 0 to 4 with higher scores reflecting greater symptom severity. FAS: all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale			
arithmetic mean	2.86	3.13	2.89
full range (min-max)	2.0 to 4.0	2.0 to 4.0	1.1 to 4.0
ANMS GCSI-DD Total Score at Week 12 of the Treatment Period			
The daily total score is calculated by summing the scores on each of the 5 symptom items in ANMS GCSI-DD (nausea, early satiety, postprandial fullness, upper abdominal pain, and vomiting) plus the bloating severity item and then dividing by 6. The maximum total symptom score could be (6 symptoms × maximum score 4 divided by 6) = 24/6 = 4. The ANMS GCSI-DD daily total score can range from 0 to 4 with higher scores reflecting greater symptom severity. FAS population.			
Units: score on a scale			
arithmetic mean	2.40	2.49	2.37
full range (min-max)	1.7 to 3.6	1.7 to 3.4	1.5 to 4.0
PAGI-SYM Total Score at Week 12 of the			

Treatment Period			
The patient assessment of upper gastrointestinal disorders-symptom severity index (PAGI-SYM) total score is defined as the mean of 6 PAGI-SYM subscale scores from 20 items. A 6-point Likert response scale, ranging from 0 (none) to 5 (very severe), is used to measure symptom severity in patients with upper GI disorders. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale			
arithmetic mean	3.13	3.33	3.05
full range (min-max)	0.1 to 4.9	2.1 to 4.7	1.7 to 4.7

Reporting group values	TAK-906 Maleate 50 mg	Total	
Number of subjects	74	242	
Age Categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	53.4		
standard deviation	± 15.09	-	
Gender categorical			
Units: Subjects			
Male	25	59	
Female	49	183	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	28	110	
Not Hispanic or Latino	45	130	
Unknown or Not Reported	1	2	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	1	1	
Asian	15	39	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	11	26	
White	45	172	
More than one race	0	0	
Unknown or Not Reported	2	4	
Region of Enrollment			
Units: Subjects			
Belgium	3	9	
Japan	13	35	
Poland	2	6	
United States	56	192	
Smoking Classification			
Units: Subjects			
Participant has Never Smoked	54	180	
Participant is a Current Smoker	5	23	
Participant is an Ex-smoker	15	39	

Height			
Units: centimetres (cm)			
arithmetic mean	166.12		
standard deviation	± 8.841	-	
Weight			
Units: kilograms (kg)			
arithmetic mean	78.77		
standard deviation	± 15.201	-	
Body Mass Index (BMI)			
BMI was calculated as weight (kg) divided by square of height (m^2).			
Units: kg/m^2			
arithmetic mean	28.52		
standard deviation	± 4.934	-	
ANMS GCSI-DD Composite Score			
American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary(ANMS GCSI-DD): patient-reported outcome instrument for symptom-based clinical trial endpoint in gastroparesis. The daily score was calculated by summing scores on 4 symptoms(nausea, early satiety, postprandial fullness, and upper abdominal pain)/4 (number of items within score), ranged from 0 to 4 with higher scores=symptom severity. FAS=all participants who were randomized, received at least 1 dose of study drug, and have baseline and at least 1 valid postbaseline value for assessment.			
Units: score on a scale			
arithmetic mean	2.64		
full range (min-max)	2.0 to 4.0	-	
ANMS GCSI-DD Nausea Symptom Score at Week 12 of the Treatment Period			
ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity score calculated from a 5-point Likert scale. The ANMS GCSI-DD nausea symptom score ranged from 0 to 4 with higher scores reflecting greater symptom severity. FAS: all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale			
arithmetic mean	2.72		
full range (min-max)	1.9 to 4.0	-	
ANMS GCSI-DD Early Satiety Symptom Score at Week 12 of the Treatment Period			
ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity score calculated from a 5-point Likert scale. The ANMS GCSI-DD early satiety symptom score ranged from 0 to 4 with higher scores reflecting greater symptom severity. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale			
arithmetic mean	2.82		
full range (min-max)	1.9 to 4.0	-	
ANMS GCSI-DD Postprandial Fullness Symptom Score at Week 12 of the Treatment Period			
ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity score calculated from a 5-point Likert scale. The ANMS GCSI-DD postprandial fullness symptom score ranged from 0 to 4 with higher scores reflecting greater symptom severity. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale			
arithmetic mean	3.08		
full range (min-max)	2.0 to 4.0	-	
ANMS GCSI-DD Upper Abdominal Pain			

Symptom Score at Week 12 of the Treatment Period			
ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity score calculated from a 5-point Likert scale. The ANMS GCSI-DD upper abdominal pain symptom score ranged from 0 to 4 with higher scores reflecting greater symptom severity. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale arithmetic mean full range (min-max)	 1.94 0.0 to 3.9	 -	
ANMS GCSI-DD Recorded Vomiting Frequency at Week 12 of the Treatment Period			
The vomiting frequency was scored from 0 to 4 (where 0 = no vomiting and 4 = four or more episodes of vomiting). The maximum core symptom score could be (5 symptoms × maximum score 4 divided by 5) = 20/5 = 4. The weekly recorded vomiting frequency for each postbaseline week was the average of the 7 daily scores within the targeted week relative to the first dose date. The ANMS GCSI-DD daily vomiting frequency score ranged from 0 to 4 with higher scores reflecting greater symptom severity.			
Units: score on a scale arithmetic mean full range (min-max)	 1.18 0.0 to 11.0	 -	
ANMS GCSI-DD Overall Severity of Gastroparesis Symptoms Score in Treatment Period			
The maximum total symptom score could be (6 symptoms × maximum score 4 divided by 6) = 24/6 = 4. The ANMS GCSI-DD overall severity of gastroparesis symptoms score can range from 0 to 4 with higher scores reflecting greater symptom severity. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale arithmetic mean full range (min-max)	 2.86 1.4 to 4.0	 -	
Bloating Severity Scale Score at Week 12 of the Treatment Period			
The bloating severity scale was scored from 0 to 4 (where 0 = no symptom and 4 = severe symptom). The maximum total symptom score could be (6 symptoms × maximum score 4 divided by 6)= 24/6 = 4. The ANMS GCSI-DD daily total score can range from 0 to 4 with higher scores reflecting greater symptom severity. FAS: all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale arithmetic mean full range (min-max)	 2.91 1.7 to 4.0	 -	
ANMS GCSI-DD Total Score at Week 12 of the Treatment Period			
The daily total score is calculated by summing the scores on each of the 5 symptom items in ANMS GCSI-DD (nausea, early satiety, postprandial fullness, upper abdominal pain, and vomiting) plus the bloating severity item and then dividing by 6. The maximum total symptom score could be (6 symptoms × maximum score 4 divided by 6) = 24/6 = 4. The ANMS GCSI-DD daily total score can range from 0 to 4 with higher scores reflecting greater symptom severity. FAS population.			
Units: score on a scale arithmetic mean full range (min-max)	 2.41 1.7 to 3.8	 -	
PAGI-SYM Total Score at Week 12 of the Treatment Period			
The patient assessment of upper gastrointestinal disorders-symptom severity index (PAGI-SYM) total score is defined as the mean of 6 PAGI-SYM subscale scores from 20 items. A 6-point Likert response scale, ranging from 0 (none) to 5 (very severe), is used to measure symptom severity in patients with upper GI disorders. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.			
Units: score on a scale			

arithmetic mean	3.14		
full range (min-max)	1.0 to 4.9	-	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
TAK-906 maleate placebo-matching capsules, orally, twice daily (BID) for up to 12 weeks.	
Reporting group title	TAK-906 Maleate 5 mg
Reporting group description:	
TAK-906 maleate 5 mg, capsules, orally, BID for up to 12 weeks.	
Reporting group title	TAK-906 Maleate 25 mg
Reporting group description:	
TAK-906 maleate 25 mg, capsules, orally, BID for up to 12 weeks.	
Reporting group title	TAK-906 Maleate 50 mg
Reporting group description:	
TAK-906 maleate 50 mg, capsules, orally, BID for up to 12 weeks.	

Primary: Change From Baseline in the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS GCSI-DD) Composite Score at Week 12 of the Treatment Period

End point title	Change From Baseline in the American Neurogastroenterology and Motility Society Gastroparesis Cardinal Symptom Index-Daily Diary (ANMS GCSI-DD) Composite Score at Week 12 of the Treatment Period

End point description:

ANMS GCSI-DD:a patient-reported outcome instrument for symptom-based clinical trial endpoint in gastroparesis, its composite score included score of nausea, early satiety, upper abdominal pain, and postprandial fullness. Severity scores ranged from 0(none) to 4(very severe). Daily composite score was calculated by summing the scores on 4 symptom items (nausea,early satiety,postprandial fullness,and upper abdominal pain)/4, that is number of items within the composite score, maximum daily composite score was (4 symptoms×maximum score 4 divided by 4)=16/4=4. ANMS GCSI-DD daily composite score ranged from 0 to 4 with higher scores reflecting greater symptom severity.Negative change from baseline indicates improvement. Mixed-effects Model for Repeated Measures (MMRM) was used for analysis. FAS:all participants randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy, available for analysis.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg	TAK-906 Maleate 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	15	55	58
Units: score on a scale				
least squares mean (standard error)	-1.19 (± 0.120)	-1.11 (± 0.219)	-1.17 (± 0.120)	-1.21 (± 0.116)

Statistical analyses

Statistical analysis title	ANMS GCSI-DD Composite Score
Comparison groups	Placebo v TAK-906 Maleate 5 mg
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.618 [2]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.34
upper limit	0.49
Variability estimate	Standard error of the mean
Dispersion value	0.25

Notes:

[1] - Mixed-effects Model for Repeated Measures (MMRM) included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.
[2] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD composite score was <0.

Statistical analysis title	ANMS GCSI-DD Composite Score
Comparison groups	Placebo v TAK-906 Maleate 25 mg
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.533 [4]
Method	MMRM
Parameter estimate	Least Square Mean Difference
Point estimate	0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.27
upper limit	0.29
Variability estimate	Standard error of the mean
Dispersion value	0.17

Notes:

[3] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.
[4] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD composite score was <0.

Statistical analysis title	ANMS GCSI-DD Composite Score
Comparison groups	Placebo v TAK-906 Maleate 50 mg

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.447 [6]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.3
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.167

Notes:

[5] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[6] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD composite score was <0.

Secondary: Percentage of Participants with at Least 50% Reduction from Baseline in ANMS GCSI-DD Composite Score at Week 12

End point title	Percentage of Participants with at Least 50% Reduction from Baseline in ANMS GCSI-DD Composite Score at Week 12

End point description:

ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis . The ANMS GCSI-DD composite score included score of nausea, early satiety, upper abdominal pain and postprandial fullness. The severity scores of these symptoms range from 0 (none) to 4 (very severe). The daily composite score was calculated by summing the scores on the 4 symptom items (nausea, early satiety, postprandial fullness, and upper abdominal pain) and then dividing by 4, that is the number of items within the composite score. Thus, the maximum daily composite score was (4 symptoms × maximum score 4 divided by 4) = 16/4 = 4. The ANMS GCSI-DD daily composite score ranged from 0 to 4 with higher scores reflecting greater symptom severity. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg	TAK-906 Maleate 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73	23	72	74
Units: percentage of participants				
number (not applicable)	42.5	39.1	47.2	41.9

Statistical analyses

Statistical analysis title	Statistical Analysis: At Least 50% Reduction
Comparison groups	Placebo v TAK-906 Maleate 5 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.607
Method	Logistic Regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.87
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.39
upper limit	1.96

Notes:

[7] - Comparisons of TAK-906 to Placebo was based on logistic regression with at least 50% reduction of participants from baseline in weekly composite score with baseline composite score, disease population at randomization, and treatment as covariates.

Statistical analysis title	Statistical Analysis: At Least 50% Reduction
Comparison groups	Placebo v TAK-906 Maleate 25 mg
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.283
Method	Logistic Regression
Parameter estimate	Odds ratio (OR)
Point estimate	1.21
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.7
upper limit	2.1

Notes:

[8] - Comparisons of TAK-906 to Placebo was based on logistic regression with at least 50% reduction of participants from baseline in weekly composite score with baseline composite score, disease population at randomization, and treatment as covariates.

Statistical analysis title	Statistical Analysis: At Least 50% Reduction
Comparison groups	Placebo v TAK-906 Maleate 50 mg
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.527
Method	Logistic Regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.98
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.56
upper limit	1.69

Notes:

[9] - Comparisons of TAK-906 to Placebo was based on logistic regression with at least 50% reduction of participants from baseline in weekly composite score with baseline composite score, disease population at randomization, and treatment as covariates.

Secondary: Change from Baseline in the ANMS GCSI-DD Nausea Symptom Score at Week 12 of the Treatment Period

End point title	Change from Baseline in the ANMS GCSI-DD Nausea Symptom Score at Week 12 of the Treatment Period

End point description:

ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity score calculated from a 5-point Likert scale. The ANMS GCSI-DD nausea symptom score ranged from 0 to 4 with higher scores reflecting greater symptom severity. Negative change from baseline indicates improvement. MMRM was used for analyses. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy. Number analysed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg	TAK-906 Maleate 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	15	55	58
Units: score on a scale				
least squares mean (standard error)	-1.42 (± 0.134)	-1.36 (± 0.245)	-1.36 (± 0.133)	-1.40 (± 0.129)

Statistical analyses

Statistical analysis title	ANMS GCSI-DD Nausea Symptom Score
Comparison groups	Placebo v TAK-906 Maleate 5 mg
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.584 [11]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.4
upper limit	0.52
Variability estimate	Standard error of the mean
Dispersion value	0.279

Notes:

[10] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[11] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD nausea symptom score was <0.

Statistical analysis title	ANMS GCSI-DD Nausea Symptom Score
Comparison groups	Placebo v TAK-906 Maleate 25 mg
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[12]
P-value	= 0.625 [13]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.25
upper limit	0.37
Variability estimate	Standard error of the mean
Dispersion value	0.189

Notes:

[12] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[13] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD nausea symptom score was <0.

Statistical analysis title	ANMS GCSI-DD Nausea Symptom Score
Comparison groups	Placebo v TAK-906 Maleate 50 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 0.54
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.29
upper limit	0.33
Variability estimate	Standard error of the mean
Dispersion value	0.187

Notes:

[14] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

Secondary: Change from Baseline in the ANMS GCSI-DD Early Satiety Symptom Score at Week 12 of the Treatment Period

End point title	Change from Baseline in the ANMS GCSI-DD Early Satiety

	Symptom Score at Week 12 of the Treatment Period

End point description:

ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity score calculated from a 5-point Likert scale. The ANMS GCSI-DD early satiety symptom score ranged from 0 to 4 with higher scores reflecting greater symptom severity. The negative change from Baseline indicated improvement. MMRM was used for the analysis. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy. Number analysed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg	TAK-906 Maleate 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	15	55	58
Units: score on a scale				
least squares mean (standard error)	-1.26 (± 0.136)	-1.25 (± 0.248)	-1.17 (± 0.135)	-1.33 (± 0.131)

Statistical analyses

Statistical analysis title	ANMS GCSI-DD Early Satiety Symptom Score
Comparison groups	Placebo v TAK-906 Maleate 5 mg
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 0.51 [16]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.46
upper limit	0.47
Variability estimate	Standard error of the mean
Dispersion value	0.283

Notes:

[15] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[16] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD early satiety symptom score was <0.

Statistical analysis title	ANMS GCSI-DD Early Satiety Symptom Score
Comparison groups	Placebo v TAK-906 Maleate 25 mg

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.674 [18]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.09
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.23
upper limit	0.4
Variability estimate	Standard error of the mean
Dispersion value	0.192

Notes:

[17] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[18] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD early satiety symptom score was <0.

Statistical analysis title	ANMS GCSI-DD Early Satiety Symptom Score
Comparison groups	Placebo v TAK-906 Maleate 50 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.367 [20]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.38
upper limit	0.25
Variability estimate	Standard error of the mean
Dispersion value	0.189

Notes:

[19] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[20] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD early satiety symptom score was <0.

Secondary: Change from Baseline in the ANMS GCSI-DD Postprandial Fullness Symptom Score at Week 12 of the Treatment Period

End point title	Change from Baseline in the ANMS GCSI-DD Postprandial Fullness Symptom Score at Week 12 of the Treatment Period

End point description:

ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity score calculated from a 5-point Likert scale. The ANMS GCSI-DD postprandial fullness symptom score ranged from 0 to 4 with higher scores reflecting greater symptom severity. The negative change from baseline indicates improvement. MMRM was used for the analysis. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a

baseline value and at least 1 valid postbaseline value for assessment of primary efficacy. Number analysed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg	TAK-906 Maleate 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	15	55	58
Units: score on a scale				
least squares mean (standard error)	-1.32 (± 0.139)	-1.26 (± 0.253)	-1.27 (± 0.138)	-1.35 (± 0.134)

Statistical analyses

Statistical analysis title	ANMS GCSI-DD Postprandial Fullness Symptom Score
Comparison groups	Placebo v TAK-906 Maleate 5 mg
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.587 [22]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.41
upper limit	0.54
Variability estimate	Standard error of the mean
Dispersion value	0.289

Notes:

[21] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[22] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD postprandial fullness symptom score was <0.

Statistical analysis title	ANMS GCSI-DD Postprandial Fullness Symptom Score
Comparison groups	Placebo v TAK-906 Maleate 25 mg
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.6 [24]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.05

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.27
upper limit	0.37
Variability estimate	Standard error of the mean
Dispersion value	0.196

Notes:

[23] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[24] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD postprandial fullness symptom score was <0.

Statistical analysis title	ANMS GCSI-DD Postprandial Fullness Symptom Score
Comparison groups	Placebo v TAK-906 Maleate 50 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[25]
P-value	= 0.446 [26]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.03
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.34
upper limit	0.29
Variability estimate	Standard error of the mean
Dispersion value	0.193

Notes:

[25] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[26] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD postprandial fullness symptom score was <0.

Secondary: Change from Baseline in the ANMS GCSI-DD Upper Abdominal Pain Symptom Score at Week 12 of the Treatment Period

End point title	Change from Baseline in the ANMS GCSI-DD Upper Abdominal Pain Symptom Score at Week 12 of the Treatment Period

End point description:

ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The ANMS GCSI-DD assesses nausea, early satiety, postprandial fullness, and upper abdominal pain on a severity score calculated from a 5-point Likert scale. The ANMS GCSI-DD upper abdominal pain symptom score ranged from 0 to 4 with higher scores reflecting greater symptom severity. The negative change from baseline indicates improvement. MMRM was used for the analysis. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy. Number analysed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg	TAK-906 Maleate 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	15	55	58
Units: score on a scale				
least squares mean (standard error)	-0.72 (± 0.118)	-0.68 (± 0.214)	-0.90 (± 0.117)	-0.76 (± 0.114)

Statistical analyses

Statistical analysis title	ANMS GCSI-DD Upper Abdominal Pain Symptom Score
Comparison groups	Placebo v TAK-906 Maleate 5 mg
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[27]
P-value	= 0.562 [28]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.37
upper limit	0.44
Variability estimate	Standard error of the mean
Dispersion value	0.245

Notes:

[27] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[28] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD upper abdominal pain symptom score was <0.

Statistical analysis title	ANMS GCSI-DD Upper Abdominal Pain Symptom Score
Comparison groups	Placebo v TAK-906 Maleate 25 mg
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[29]
P-value	= 0.138 [30]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.46
upper limit	0.09

Variability estimate	Standard error of the mean
Dispersion value	0.166

Notes:

[29] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.
[30] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD upper abdominal pain symptom score was <0.

Statistical analysis title	ANMS GCSI-DD Upper Abdominal Pain Symptom Score
Comparison groups	Placebo v TAK-906 Maleate 50 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.394 [32]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.32
upper limit	0.23
Variability estimate	Standard error of the mean
Dispersion value	0.164

Notes:

[31] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.
[32] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD upper abdominal pain symptom score was <0.

Secondary: Change from Baseline in the ANMS GCSI-DD Recorded Vomiting Frequency at Week 12 of the Treatment Period

End point title	Change from Baseline in the ANMS GCSI-DD Recorded Vomiting Frequency at Week 12 of the Treatment Period

End point description:

ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The vomiting frequency was scored from 0 to 4 (where 0 = no vomiting and 4 = four or more episodes of vomiting). The maximum core symptom score could be (5 symptoms × maximum score 4 divided by 5) = 20/5 = 4. The weekly recorded vomiting frequency for each postbaseline week was the average of the 7 daily scores within the targeted week relative to the first dose date. The ANMS GCSI-DD daily vomiting frequency score ranged from 0 to 4 with higher scores reflecting greater symptom severity. The negative change from baseline indicates improvement. MMRM was used for the analysis. FAS: all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy. Number analysed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg	TAK-906 Maleate 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	15	55	57
Units: score on a scale				
least squares mean (standard error)	-0.71 (± 0.236)	-0.44 (± 0.421)	-0.48 (± 0.234)	-0.63 (± 0.231)

Statistical analyses

Statistical analysis title	ANMS GCSI-DD Recorded Vomiting Frequency
Statistical analysis description: ANMS	
Comparison groups	Placebo v TAK-906 Maleate 5 mg
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.709
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.27
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.53
upper limit	1.07
Variability estimate	Standard error of the mean
Dispersion value	0.484

Notes:

[33] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

Statistical analysis title	ANMS GCSI-DD Recorded Vomiting Frequency
Comparison groups	Placebo v TAK-906 Maleate 25 mg
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[34]
P-value	= 0.76 [35]
Method	MMRM
Parameter estimate	Least-Sqaures Mean Difference
Point estimate	0.24
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.31
upper limit	0.78
Variability estimate	Standard error of the mean
Dispersion value	0.332

Notes:

[34] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[35] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD recorded vomiting frequency was <0.

Statistical analysis title	ANMS GCSI-DD Recorded Vomiting Frequency
Comparison groups	Placebo v TAK-906 Maleate 50 mg
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority[36]
P-value	= 0.591 [37]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.47
upper limit	0.62
Variability estimate	Standard error of the mean
Dispersion value	0.33

Notes:

[36] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[37] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD recorded vomiting frequency was <0.

Secondary: Change from Baseline in the ANMS GCSI-DD Overall Severity of Gastroparesis Symptoms Score at Week 12 of the Treatment Period

End point title	Change from Baseline in the ANMS GCSI-DD Overall Severity of Gastroparesis Symptoms Score at Week 12 of the Treatment Period

End point description:

ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The maximum total symptom score was (6 symptoms × maximum score 4 divided by 6) = 24/6 = 4. The ANMS GCSI-DD overall severity of gastroparesis symptoms score can range from 0 to 4 with higher scores reflecting greater symptom severity. The negative change from baseline indicates improvement. MMRM was used for analysis. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy. Number analysed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg	TAK-906 Maleate 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	15	55	58
Units: score on a scale				
least squares mean (standard error)	-1.20 (± 0.130)	-1.02 (± 0.237)	-1.22 (± 0.129)	-1.25 (± 0.125)

Statistical analyses

Statistical analysis title	ANMS GCSI-DD Overall Severity of Gastroparesis
Comparison groups	Placebo v TAK-906 Maleate 5 mg
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.742 [39]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.27
upper limit	0.62
Variability estimate	Standard error of the mean
Dispersion value	0.27

Notes:

[38] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[39] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD overall severity of gastroparesis symptoms score was <0.

Statistical analysis title	ANMS GCSI-DD Overall Severity of Gastroparesis
Comparison groups	Placebo v TAK-906 Maleate 25 mg
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.461 [41]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.32
upper limit	0.28
Variability estimate	Standard error of the mean
Dispersion value	0.183

Notes:

[40] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[41] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD overall severity of gastroparesis symptoms score was <0.

Statistical analysis title	ANMS GCSI-DD Overall Severity of Gastroparesis
Comparison groups	Placebo v TAK-906 Maleate 50 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[42]
P-value	= 0.376 [43]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.36
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.181

Notes:

[42] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[43] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD overall severity of gastroparesis symptoms score was <0.

Secondary: Change from Baseline in the Bloating Severity Scale Score at Week 12 of the Treatment Period

End point title	Change from Baseline in the Bloating Severity Scale Score at Week 12 of the Treatment Period

End point description:

ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The bloating severity scale was scored from 0 to 4 (where 0 = no symptom and 4 = severe symptom). The maximum total symptom score could be (6 symptoms × maximum score 4 divided by 6)= 24/6 = 4. The ANMS GCSI-DD daily total score can range from 0 to 4 with higher scores reflecting greater symptom severity. The negative change from baseline indicates improvement. MMRM was used for analyses. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy. Number analysed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg	TAK-906 Maleate 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	15	55	58
Units: score on a scale				
least squares mean (standard error)	-1.15 (± 0.137)	-1.09 (± 0.250)	-1.26 (± 0.136)	-1.16 (± 0.132)

Statistical analyses

Statistical analysis title	Bloating Severity Scale Score
Comparison groups	Placebo v TAK-906 Maleate 5 mg
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[44]
P-value	= 0.591 [45]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.41
upper limit	0.54
Variability estimate	Standard error of the mean
Dispersion value	0.286

Notes:

[44] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[45] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD bloating severity scale score was <0.

Statistical analysis title	Bloating Severity Scale Score
Comparison groups	Placebo v TAK-906 Maleate 50 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[46]
P-value	= 0.476 [47]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.33
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.191

Notes:

[46] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[47] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD bloating severity scale score was <0.

Statistical analysis title	Bloating Severity Scale Score
Comparison groups	Placebo v TAK-906 Maleate 25 mg
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[48]
P-value	= 0.291 [49]
Method	MMRM
Parameter estimate	Least-Squares mean Difference
Point estimate	-0.11
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.43
upper limit	0.21
Variability estimate	Standard error of the mean
Dispersion value	0.193

Notes:

[48] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[49] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD bloating severity scale score was <0.

Secondary: Change from Baseline in the ANMS GCSI-DD Total Score at Week 12 of the Treatment Period

End point title	Change from Baseline in the ANMS GCSI-DD Total Score at Week 12 of the Treatment Period

End point description:

ANMS GCSI-DD is a patient-reported outcome instrument for a symptom-based clinical trial endpoint in gastroparesis. The daily total score is calculated by summing the scores on each of the 5 symptom items in ANMS GCSI-DD (nausea, early satiety, postprandial fullness, upper abdominal pain, and vomiting) plus the bloating severity item and then dividing by 6. The maximum total symptom score could be (6 symptoms × maximum score 4 divided by 6) = 24/6 = 4. The ANMS GCSI-DD daily total score can range from 0 to 4 with higher scores reflecting greater symptom severity. The negative change from baseline indicates improvement. MMRM was used for analyses. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy. Number analysed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg	TAK-906 Maleate 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	50	15	55	58
Units: score on a scale				
least squares mean (standard error)	-1.10 (± 0.108)	-1.00 (± 0.196)	-1.09 (± 0.107)	-1.11 (± 0.104)

Statistical analyses

Statistical analysis title	ANMS GCSI-DD Total Score
Comparison groups	Placebo v TAK-906 Maleate 5 mg
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	superiority[50]
P-value	= 0.675 [51]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.27
upper limit	0.47
Variability estimate	Standard error of the mean
Dispersion value	0.224

Notes:

[50] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[51] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD total score was <0.

Statistical analysis title	ANMS GCSI-DD Total Score
Comparison groups	Placebo v TAK-906 Maleate 25 mg
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority[52]
P-value	= 0.531 [53]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.24
upper limit	0.26
Variability estimate	Standard error of the mean
Dispersion value	0.152

Notes:

[52] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[53] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD total score was <0.

Statistical analysis title	ANMS GCSI-DD Total Score
Comparison groups	Placebo v TAK-906 Maleate 50 mg
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority[54]
P-value	= 0.473 [55]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.01
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.26
upper limit	0.24
Variability estimate	Standard error of the mean
Dispersion value	0.15

Notes:

[54] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[55] - 1-sided p-values were obtained using MMRM Model. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in ANMS GCSI-DD total score was <0.

Secondary: Percentage of Symptomatic Weeks

End point title	Percentage of Symptomatic Weeks

End point description:

Symptomatic weeks are weeks with average composite symptom score assessed as >mild [ANMS GCSI-DD score ≥2] during 12 weeks of treatment. Analysis of variance (ANOVA) was used for the analysis. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy.

End point type	Secondary

End point timeframe:

Up to 12 weeks

End point values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg	TAK-906 Maleate 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73	23	72	74
Units: percentage of weeks				
least squares mean (standard error)	54.89 (± 4.746)	46.42 (± 8.474)	50.03 (± 4.781)	51.31 (± 4.714)

Statistical analyses

Statistical analysis title	Statistical Analysis: Symptomatic Weeks
Comparison groups	Placebo v TAK-906 Maleate 5 mg
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.192 [56]
Method	ANOVA
Parameter estimate	Least-Squares Mean Difference
Point estimate	-8.47
Confidence interval	
level	90 %
sides	2-sided
lower limit	-24.5
upper limit	7.57
Variability estimate	Standard error of the mean
Dispersion value	9.71

Notes:

[56] - The 1-sided p-value was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 -Placebo) in symptomatic weeks was <0.

Statistical analysis title	Statistical Analysis: Symptomatic Weeks
Comparison groups	Placebo v TAK-906 Maleate 25 mg
Number of subjects included in analysis	145
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.236 [57]
Method	ANOVA
Parameter estimate	Least-Squares Mean Difference
Point estimate	-4.85
Confidence interval	
level	90 %
sides	2-sided
lower limit	-15.98
upper limit	6.27
Variability estimate	Standard error of the mean
Dispersion value	6.736

Notes:

[57] - The 1-sided p-value was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 -
Placebo) in symptomatic weeks was <0.

Statistical analysis title	Statistical Analysis: Symptomatic Weeks
Comparison groups	Placebo v TAK-906 Maleate 50 mg
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.297 [58]
Method	ANOVA
Parameter estimate	Least-Squares Mean Difference
Point estimate	-3.58

Confidence interval	
level	90 %
sides	2-sided
lower limit	-14.62
upper limit	7.47
Variability estimate	Standard error of the mean
Dispersion value	6.689

Notes:

[58] - The 1-sided p-value was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 -
Placebo) in symptomatic weeks was <0.

Secondary: Change from Baseline in the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) Total Score at Week 12 of the Treatment Period

End point title	Change from Baseline in the Patient Assessment of Upper Gastrointestinal Disorders-Symptom Severity Index (PAGI-SYM) Total Score at Week 12 of the Treatment Period

End point description:

The PAGI-SYM total score is defined as the mean of 6 PAGI-SYM subscale scores from 20 items. A 6-point Likert response scale, ranging from 0 (none) to 5 (very severe), is used to measure symptom severity in participants with upper GI disorders. The negative change from baseline indicates improvement. MMRM was used for analysis. FAS included all participants who were randomized, received at least 1 dose of study drug, and have a baseline value and at least 1 valid postbaseline value for assessment of primary efficacy. Number analyzed is the number of participants with data available for analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Placebo	TAK-906 Maleate 5 mg	TAK-906 Maleate 25 mg	TAK-906 Maleate 50 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	16	54	60
Units: score on a scale				
least squares mean (standard error)	-1.33 (± 0.141)	-1.25 (± 0.265)	-1.51 (± 0.142)	-1.57 (± 0.136)

Statistical analyses

Statistical analysis title	Statistical Analysis: PAGI-SYM Total Score
Comparison groups	Placebo v TAK-906 Maleate 5 mg
Number of subjects included in analysis	73
Analysis specification	Pre-specified
Analysis type	superiority[59]
P-value	= 0.601 [60]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	0.08

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.42
upper limit	0.57
Variability estimate	Standard error of the mean
Dispersion value	0.3

Notes:

[59] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.
[60] - 1-sided p-values were obtained using MMRM of PAGI-SYM total score. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in PAGI-SYM total score was <0.

Statistical analysis title	Statistical Analysis: PAGI-SYM Total Score
Comparison groups	Placebo v TAK-906 Maleate 50 mg
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority[61]
P-value	= 0.114 [62]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.24
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.56
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.196

Notes:

[61] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.
[62] - 1-sided p-values were obtained using MMRM of PAGI-SYM total score. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in PAGI-SYM total score was <0.

Statistical analysis title	Statistical Analysis: PAGI-SYM Total Score
Comparison groups	Placebo v TAK-906 Maleate 25 mg
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority[63]
P-value	= 0.181 [64]
Method	MMRM
Parameter estimate	Least-Squares Mean Difference
Point estimate	-0.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.51
upper limit	0.15
Variability estimate	Standard error of the mean
Dispersion value	0.2

Notes:

[63] - MMRM model included week, treatment, participant disease population (DG/IG), treatment-by-week interaction as fixed effects, baseline and baseline score-by-week interaction as covariates, with an unstructured working covariance matrix as default.

[64] - 1-sided p-values were obtained using MMRM of PAGI-SYM total score. It was based on the one-sided alternative hypothesis testing that the treatment difference (TAK-906 - Placebo) in PAGI-SYM total score was <0.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the study start up to 30 days after end of treatment (up to approximately 16 weeks)

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. Safety data was collected for all participants evaluable for response.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Placebo

Reporting group description:

TAK-906 maleate placebo-matching capsules, orally, BID for up to 12 weeks.

Reporting group title	TAK-906 25 mg

Reporting group description:

TAK-906 maleate 25 mg, capsules, orally, BID for up to 12 weeks.

Reporting group title	TAK-906 5 mg

Reporting group description:

TAK-906 maleate 5 mg, capsules, orally, BID for up to 12 weeks.

Reporting group title	TAK-906 50 mg

Reporting group description:

TAK-906 maleate 50 mg, capsules, orally, BID for up to 12 weeks.

Serious adverse events	Placebo	TAK-906 25 mg	TAK-906 5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 73 (2.74%)	2 / 72 (2.78%)	0 / 23 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal carcinoma			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 23 (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
Vascular disorders			
Intermittent claudication			

subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	0 / 23 (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			
Diabetic foot			
subjects affected / exposed	1 / 73 (1.37%)	0 / 72 (0.00%)	0 / 23 (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
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 23 (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
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	0 / 23 (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
Hypoglycaemia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 72 (1.39%)	0 / 23 (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-906 50 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 74 (2.70%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Oesophageal carcinoma			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Intermittent claudication			

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19 pneumonia			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Placebo	TAK-906 25 mg	TAK-906 5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 73 (0.00%)	4 / 72 (5.56%)	2 / 23 (8.70%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 73 (0.00%)	4 / 72 (5.56%)	0 / 23 (0.00%)
occurrences (all)	0	4	0
Gastrointestinal disorders			
Nausea			

subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 72 (0.00%)	2 / 23 (8.70%)
occurrences (all)	0	0	2

Non-serious adverse events	TAK-906 50 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 74 (5.41%)		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2018	Amendment 1.0: The primary purpose of this amendment was to make following changes: • Updated the biomarkers to be analyzed and rationales. • Clarified the objective and endpoint for the gastric emptying breath test (GEBT) and the timing of GEBT relative to dosing of study drug. • Clarified the criteria for use of rescue medication for nausea and vomiting. • Updated the participant eligibility criteria. • Updated the list of excluded medications. • Updated the safety section with guidance to investigators for management of extrapyramidal symptoms (EPS) and central nervous system (CNS)/neuropsychiatric AEs. • Clarified the primary efficacy analysis.
06 August 2018	Amendment 2.0: The primary purpose of this amendment was to make following changes: • Updated the secondary endpoints. • Updated the biomarkers to be analysed.
08 August 2019	Amendment 6.0: The primary purpose of this amendment was to make following changes: • Added text about the effects of estimated glomerular filtration rate (eGFR) on exposure of TAK-906 and the effects of the co-administration of esomeprazole on area under the concentration-time curve from time 0 to infinity (AUC∞) and maximum observed concentration (Cmax) of TAK-906. • Deleted the requirement for medication to be taken on an empty stomach (at least 2 hours of fasting except for water). • Revised the interim analysis by adding a futility analysis. • Clarified the use of rescue medication. • Revised exclusion criterion #26 to define prolonged corrected QT interval (QTcF) as ≥450 milliseconds and to exclude participants with risk factors for QT interval prolongation. • Revised exclusion criterion #31 to exclude participants who have any signs and/or symptoms or history of extrapyramidal system disease or history of suicide attempt. • Changed exclusion criterion #37 to exclude participants with renal impairment, defined as a lower limit of eGFR <30 mL/min at screening visit and deleted the formulas for calculating eGFR in various participant populations. • Revised the list of excluded medications. • Removed the stipulation that participants who had taken <80% of study drug in the previous 4-week period would be withdrawn from the study because of noncompliance with study drug. • Added the criteria that participants who were <80% compliant or who missed ≥6 consecutive doses since the last study visit would be re-educated about the importance of being consistent with their dosing per the protocol.

13 July 2020	Amendment 8.0: The primary purpose of this amendment was to make following changes: • Updated the period of evaluation from 17 to 22 weeks from screening to follow-up. • Removed GEBT at Visits 5 and 7; GEBT may still have been performed at Visit 2 if it was required for diagnostic confirmation of delayed gastric emptying. • Removed exploratory biomarker sample collection. • Discontinued randomization into the 5 mg dose arm. • Reduced the planned sample size by 10 participants per arm to 60 participants per treatment groups of placebo, TAK-906M 25 mg, and TAK-906M 50 mg. • Removed the minimum number of DG and IG participants in each dose arm. • Revised the statistical testing from 2-sided (with a significance level of 5%) to 1-sided (with a significance level of 5%). • Shortened the safety follow-up phone call from 40 to 30 days. • Added exclusion criterion #41 for any participant with suspected or known COVID-19 infection and addressed possible changes to study procedures necessitated by the COVID-19 pandemic. • Added OATP1B1/1B3 inhibitors and otilonium bromide (Spasmomen) to excluded medications. • Removed the planned interim efficacy analysis. • Updated the patient global impression of severity (PGI-S) scale; replaced the patient global impression of improvement (PGI-I) scale with the patient global impression of change (PGI-C) scale.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported