Clinical trial results:
A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-935 (OV935) as an Adjunctive Therapy in Pediatric Patients with Developmental and/or Epileptic Encephalopathies (ELEKTRA)

Summary

EudraCT number	2018-002484-25
Trial protocol	PT PL
Global end of trial date	20 July 2020

Results information

Result version number	v1 (current)
This version publication date	12 March 2021
First version publication date	12 March 2021

Trial information

Trial identification

Sponsor protocol code	TAK-935-2002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03650452
WHO universal trial number (UTN)	U1111-1206-5522

Notes:

Sponsors

Sponsor organisation name	Ovid Therapeutics Inc.
Sponsor organisation address	1460 Broadway, New York, NY, United States, 10036
Public contact	Medical Director, Clinical Science, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002572-PIP02-19
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	20 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect on the frequency of all seizures (convulsive and drop) in participants treated with TAK-935 as an adjunctive therapy compared to placebo in the Maintenance Period.

Protection of trial subjects:

All study participant’s parents, or their guardians were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 August 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	Australia: 4
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	China: 41
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Poland: 29
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	United States: 28
Worldwide total number of subjects	141
EEA total number of subjects	53

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)	94

Adolescents (12-17 years)	47
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 45 investigative sites globally from 8 August 2018 to 20 July 2020.

Pre-assignment

Screening details:

Participants with a diagnosis of Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS) were enrolled and randomized in a 1:1 ratio to double-blind treatment with TAK-935 or matching placebo for up to the 20-week Treatment Period (8-week Dose Optimization Period and 12-week Maintenance Period).

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

TAK-935 placebo-matching tablets, orally or via gastrostomy tube (G-tube)/percutaneous endoscopic gastrostomy (PEG), twice a day (BID) up to Week 20.

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

Dosage and administration details:

TAK-935 placebo-matching tablets or mini-tablets.

Arm title	TAK-935

Arm description:

TAK-935 tablets orally or via G-tube/PEG tube, BID. Participants weighing <60 kg received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20.

Arm type	Experimental
Investigational medicinal product name	TAK-935
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-935 tablets or mini-tablets.

Number of subjects in period 1	Placebo	TAK-935
Started	70	71
Completed	60	66
Not completed	10	5
Physician decision	1	-
Early Withdrawal from Study Treatment	3	-
Adverse event, non-fatal	3	4
Withdrawal by Parent/Guardian	3	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
TAK-935 placebo-matching tablets, orally or via gastrostomy tube (G-tube)/percutaneous endoscopic gastrostomy (PEG), twice a day (BID) up to Week 20.	
Reporting group title	TAK-935
Reporting group description:	
TAK-935 tablets orally or via G-tube/PEG tube, BID. Participants weighing <60 kg received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20.	

Reporting group values	Placebo	TAK-935	Total
Number of subjects	70	71	141
Age categorical Units: Subjects			
Children (2-11 years)	46	48	94
Adolescents (12-17 years)	24	23	47
Age Continuous Units: years			
arithmetic mean	9.5	9.6	
standard deviation	± 3.93	± 4.14	-
Sex: Female, Male Units: participants			
Female	28	22	50
Male	42	49	91
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	10	11	21
Not Hispanic or Latino	60	60	120
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	22	22	44
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	47	49	96
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Australia	2	2	4
Canada	3	3	6
China	20	21	41
Spain	11	8	19
Israel	5	4	9
Poland	12	17	29

Portugal	2	3	5
United States	15	13	28

Height			
Units: cm			
arithmetic mean		134.7	
standard deviation	±	± 21.34	-
Weight			
Units: kg			
arithmetic mean	32.8	33.3	
standard deviation	± 15.98	± 15.11	-
Body Mass Index (BMI)			
BMI= weight (km)/height (m^2)			
Units: (kg/m^2)			
arithmetic mean		17.43	
standard deviation	±	± 4.048	-
Clinical Global Impression of Severity (CGI-S) Responses of Investigator			
The CGI-Severity (CGI-S) focuses on clinicians' observations of the participant's cognitive, functional, and behavioral performance since the beginning of the study. The CGI-S is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill participants).			
Units: score on a scale			
arithmetic mean			
full range (min-max)			-

Subject analysis sets

Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-935 placebo-matching tablets, orally or via G-tube/PEG, BID up to Week 20. Number analyzed are the number of participants with data available for Height and BMI at Baseline.

Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-935 placebo-matching tablets, orally or via G-tube/PEG, BID up to Week 20. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2.

Subject analysis set title	TAK-935
Subject analysis set type	Sub-group analysis

Subject analysis set description:

TAK-935 tablets orally or via G-tube/PEG tube, BID. Participants weighing <60 kg received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2.

Reporting group values	Placebo	Placebo	TAK-935
Number of subjects	68	59	64
Age categorical			
Units: Subjects			
Children (2-11 years)			
Adolescents (12-17 years)			

Age Continuous Units: years arithmetic mean standard deviation	±	±	±
Sex: Female, Male Units: participants			
Female Male			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native Asian Native Hawaiian or Other Pacific Islander Black or African American White More than one race Unknown or Not Reported			
Region of Enrollment Units: Subjects			
Australia Canada China Spain Israel Poland Portugal United States			
Height Units: cm arithmetic mean standard deviation	132.4 ± 20.34	±	±
Weight Units: kg arithmetic mean standard deviation	±	±	±
Body Mass Index (BMI)			
BMI= weight (km)/height (m^2)			
Units: (kg/m^2) arithmetic mean standard deviation	17.63 ± 4.378	±	±
Clinical Global Impression of Severity (CGI-S) Responses of Investigator			
The CGI-Severity (CGI-S) focuses on clinicians' observations of the participant's cognitive, functional, and behavioral performance since the beginning of the study. The CGI-S is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill participants).			
Units: score on a scale			

arithmetic mean		4.8	4.5
full range (min-max)		3 to 7	2 to 7

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
TAK-935 placebo-matching tablets, orally or via gastrostomy tube (G-tube)/percutaneous endoscopic gastrostomy (PEG), twice a day (BID) up to Week 20.	
Reporting group title	TAK-935
Reporting group description:	
TAK-935 tablets orally or via G-tube/PEG tube, BID. Participants weighing <60 kg received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20.	
Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
TAK-935 placebo-matching tablets, orally or via G-tube/PEG, BID up to Week 20. Number analyzed are the number of participants with data available for Height and BMI at Baseline.	
Subject analysis set title	Placebo
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
TAK-935 placebo-matching tablets, orally or via G-tube/PEG, BID up to Week 20. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2.	
Subject analysis set title	TAK-935
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
TAK-935 tablets orally or via G-tube/PEG tube, BID. Participants weighing <60 kg received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2.	

Primary: Percent Change from Baseline in Seizure Frequency Per 28 Days During the Maintenance Period

End point title	Percent Change from Baseline in Seizure Frequency Per 28 Days During the Maintenance Period
End point description:	
Seizure frequency per 28 days is defined as total number of seizures reported during the period divided by number of days during the period seizures were assessed multiplied by 28. Percent change from Baseline is defined as (frequency of seizures per 28 days during maintenance period – frequency of seizures per 28 days at baseline) divided by frequency of seizures per 28 days at baseline multiplied by 100. Negative percent change from Baseline indicates improvement. Efficacy Analysis Set included all Modified Intent-to-Treat (mITT) participants whose efficacy assessments were compliant with Protocol Amendment 2. Number of participants analyzed is the number of participants with data available for analyses.	
End point type	Primary
End point timeframe:	
Baseline; Maintenance Period: Weeks 9 to 20	

End point values	Placebo	TAK-935		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56	64		
Units: percent change				
median (full range (min-max))	3.11 (-78.8 to 163.0)	-27.76 (-100.0 to 160.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TAK-935
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.0007 [2]
Method	Ranked ANCOVA
Parameter estimate	Hodges-Lehmann Estimation
Point estimate	-30.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	-46.99
upper limit	-13.19

Notes:

[1] - The location shift (TAK-935 - Placebo) and Asymptotic 95% confidence interval between TAK-935 and Placebo (TAK-935 - Placebo) were based on Hodges-Lehmann Estimation from un-adjusted rank statistics.
[2] - The p-value is 2-sided and it is for the difference of percent change from baseline between TAK-935 and Placebo were computed using Rank Transformed Analysis of Covariance (ANCOVA) adjusting for baseline seizure frequency and indication.

Secondary: Percent Change from Baseline in Seizure Frequency Per 28 Days During the Treatment period

End point title	Percent Change from Baseline in Seizure Frequency Per 28 Days During the Treatment period

End point description:

Seizure Frequency per 28 days is defined as total number of Seizures reported during the period divided by number of days during the period seizures were assessed multiplied by 28. Percent Change from Baseline is defined as (frequency of seizures per 28 days during treatment period – frequency of seizures per 28 days at baseline) divided by frequency of seizures per 28 days at baseline multiplied by 100. Negative percent change from Baseline indicates improvement. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2.

End point type	Secondary

End point timeframe:

Baseline; Treatment Period: Weeks 0 to 20

End point values	Placebo	TAK-935		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	64		
Units: percent change				
median (full range (min-max))	0.75 (-60.1 to 437.8)	-30.05 (-100.0 to 347.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TAK-935
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.0024 [4]
Method	Ranked ANCOVA
Parameter estimate	Hodges-Lehmann Estimate
Point estimate	-25.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.96
upper limit	-10.69

Notes:

[3] - The location shift (TAK-935 - Placebo) and Asymptotic 95% confidence interval between TAK-935 and Placebo (TAK-935 - Placebo) were based on Hodges-Lehmann Estimation from un-adjusted rank statistics.
[4] - The p-value is 2-sided and it is for the difference of percent change from baseline between TAK-935 and Placebo were computed using Rank Transformed ANCOVA adjusting for baseline seizure frequency and indication.

Secondary: Percent Change from Baseline in Convulsive Seizure Frequency Per 28 Days in Participants with Dravet Syndrome Stratum During the Maintenance Period

End point title	Percent Change from Baseline in Convulsive Seizure Frequency Per 28 Days in Participants with Dravet Syndrome Stratum During the Maintenance Period

End point description:

Convulsive seizure frequency per 28 days is defined as total number of convulsive seizures reported during the period divided by number of days during the period seizures were assessed multiplied by 28. Percent Change from Baseline (%) is defined as [(Maintenance Period Convulsive Seizure Frequency - Baseline Period Convulsive Seizure Frequency) divided by Baseline Convulsive Seizure Frequency] multiplied by 100. Negative percent change from Baseline indicates improvement. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2. Number of participants analyzed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline; Maintenance Period: Weeks 9 to 20

End point values	Placebo	TAK-935		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	24		
Units: percent change				
median (full range (min-max))	9.38 (-47.3 to 153.5)	-36.50 (-100.0 to 84.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TAK-935
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.0001 [6]
Method	Ranked ANCOVA
Parameter estimate	Hodges-Lehmann Estimate
Point estimate	-50
Confidence interval	
level	95 %
sides	2-sided
lower limit	-75.03
upper limit	-25.09

Notes:

[5] - The location shift (TAK-935 - Placebo) and Asymptotic 95% confidence interval between TAK-935 and Placebo (TAK-935 - Placebo) were based on Hodges-Lehmann Estimation from un-adjusted rank statistics.
[6] - The p-value is 2-sided and it is for the difference of percent change from baseline between TAK-935 and Placebo were computed using Rank Transformed ANCOVA adjusting for baseline seizure frequency.

Secondary: Percent Change from Baseline in Drop Seizure Frequency Per 28 Days in Participants with the Lennox-Gastaut Syndrome (LGS) Stratum During the Maintenance Period

End point title	Percent Change from Baseline in Drop Seizure Frequency Per 28 Days in Participants with the Lennox-Gastaut Syndrome (LGS) Stratum During the Maintenance Period

End point description:

Drop seizure frequency per 28 days is defined as total number of drop seizures reported during the period divided by number of days during the period seizures were assessed multiplied by 28. Percent Change from Baseline (%) is defined as [(Maintenance Period Drop Seizure Frequency - Baseline Period Drop Seizure Frequency) divided by Baseline Drop Seizure Frequency] multiplied by 100. Negative percent change from Baseline indicates improvement. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2. Number of participants analyzed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline; Maintenance Period: Weeks 9 to 20

End point values	Placebo	TAK-935		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	40		
Units: percent change				
median (full range (min-max))	-1.90 (-78.8 to 163.0)	-18.46 (-100.0 to 160.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TAK-935
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.147 [8]
Method	Ranked ANCOVA
Parameter estimate	Hodges-Lehmann Estimate
Point estimate	-16.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-39.5
upper limit	4.49

Notes:

[7] - The location shift (TAK-935 - Placebo) and Asymptotic 95% confidence interval between TAK-935 and Placebo (TAK-935 - Placebo) were based on Hodges-Lehmann Estimation from un-adjusted rank statistics.
[8] - The p-value is 2-sided and it is for the difference of percent change from baseline between TAK-935 and Placebo were computed using Rank Transformed ANCOVA adjusting for baseline seizure frequency.

Secondary: Percentage of Participants with LGS Stratum Considered Treatment Responders Throughout the Maintenance Period

End point title	Percentage of Participants with LGS Stratum Considered Treatment Responders Throughout the Maintenance Period

End point description:

Responders are defined as having over 50% drop seizure reduction compared to Baseline. Percent Reduction from Baseline (%) is defined as [(Maintenance Period Drop Seizure Frequency - Baseline Period Drop Seizure Frequency) divided by Baseline Drop Seizure Frequency] multiplied by 100. Data is reported as reduction of 25%, 50%, 75% and 100% or more in drop seizures from Baseline. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2. Only participants with LGS stratum indication were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline; Maintenance Period: Weeks 9 to 20

End point values	Placebo	TAK-935		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	40		
Units: percentage of participants				
number (confidence interval 95%)				
Reduction of >=25% in Drop Seizures from Baseline	29.7 (15.9 to 47.0)	42.5 (27.0 to 59.1)		
Reduction of >=50% in Drop Seizures from Baseline	16.2 (6.2 to 32.0)	27.5 (14.6 to 43.9)		
Reduction of >=75% in Drop Seizures from Baseline	2.7 (0.1 to 14.2)	10.0 (2.8 to 23.7)		
Reduction of 100% in Drop Seizures from Baseline	0 (0.0 to 9.5)	5.0 (0.6 to 16.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Dravet Syndrome Stratum Considered Treatment Responders Throughout the Maintenance Period

End point title	Percentage of Participants with Dravet Syndrome Stratum Considered Treatment Responders Throughout the Maintenance Period

End point description:

Responders are defined as having over 50% convulsive seizure reduction compared to Baseline. Percent Reduction from Baseline (%) is defined as [(Maintenance Period Convulsive Seizure Frequency - Baseline Period Convulsive Seizure Frequency) divided by Baseline Convulsive Seizure Frequency] multiplied by 100. Data is reported as reduction of 25%, 50%, 75% and 100% or more in drop seizures from Baseline. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2. Only participants with Dravet syndrome stratum indication were analyzed for this outcome measure.

End point type	Secondary

End point timeframe:

Maintenance Period: Weeks 9 to 20

End point values	Placebo	TAK-935		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	24		
Units: percentage of participants				
number (confidence interval 95%)				
Reduction of >=25% in Convulsive Seizures from BL	13.6 (2.9 to 34.9)	66.7 (44.7 to 84.4)		
Reduction of >=50% in Convulsive Seizures from BL	0 (0.0 to 15.4)	41.7 (22.1 to 63.4)		
Reduction of >=75% in Convulsive Seizures from BL	0 (0.0 to 15.4)	20.8 (7.1 to 42.2)		
Reduction of 100% in Convulsive Seizures from BL	0 (0.0 to 15.4)	8.3 (1.0 to 27.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Clinician's Clinical Global Impression of Severity (CGI-S) Responses of Investigator Reported Impression of Efficacy and Tolerability of Study Drug

End point title	Change from Baseline in Clinician's Clinical Global Impression of Severity (CGI-S) Responses of Investigator Reported Impression of Efficacy and Tolerability of Study Drug

End point description:

The CGI-Severity (CGI-S) focuses on clinicians' observations of the participant's cognitive, functional, and behavioral performance since the beginning of the study. The CGI-S is rated on a 7-point scale, with the severity of illness scale using a range of responses from 1 (normal) through to 7 (amongst the most severely ill participants). A negative change from Baseline indicates improvement. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2. Number of participants analyzed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 20

End point values	Placebo	TAK-935		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	58		
Units: score on scale				
least squares mean (standard deviation)	-0.3 (± 0.15)	-0.2 (± 0.14)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo v TAK-935
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6829 [9]
Method	Mixed-Model Repeated Measure (MMRM)
Parameter estimate	Least Square (LS) Mean
Point estimate	0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.49
Variability estimate	Standard deviation
Dispersion value	0.21

Notes:

[9] - The p-value is 2-sided and it is for the difference (TAK-935 - Placebo) of change from baseline between TAK-935 and Placebo was computed using MMRM.

Secondary: Percentage of Participants with Clinical Global Impression of Change (CGI-C) Responses as per the Investigator Reported Impression of Efficacy and Tolerability TAK-935

End point title	Percentage of Participants with Clinical Global Impression of Change (CGI-C) Responses as per the Investigator Reported Impression of Efficacy and Tolerability TAK-935

End point description:

CGI-Change (CGI-C) treatment response ratings should take account of both therapeutic efficacy and treatment-related AEs. Each component of the CGI is rated separately; the instrument does not yield a global score. The CGI-C is rated on a 7-point scale, where, 0 = Marked improvement and no side-effects, 1 = Marked improvement and minimal side-effects, 2 = No Change, 3 = Minimal improvement and marked side-effects and 4 = Unchanged or worse and side-effects outweigh the therapeutic effect. Lower scores indicated improvement. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2. Number of participants analyzed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Week 20

End point values	Placebo	TAK-935		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	58		
Units: percentage of participants				
number (not applicable)				
Week 20, Score 0	12.2	17.2		
Week 20, Score 1	2.0	15.5		
Week 20, Score 2	85.7	65.5		
Week 20, Score 3	0	0		
Week 20, Score 4	0	1.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Caregiver Global Impression of Change (Care GI-C) Responses as Per the Parent/Family Reported Impression of Efficacy and Tolerability of TAK-935

End point title	Percentage of Participants with Caregiver Global Impression of Change (Care GI-C) Responses as Per the Parent/Family

	Reported Impression of Efficacy and Tolerability of TAK-935

End point description:

The Care GI-C is rated on a 7-point scale, with the severity of illness scale where, 1 = Very much improved, 2 = Much improved, 3 = Slightly improved, 4 = No change, 5 = Slightly worse, 6 = Much worse and 7 = Very much worse. Lower scores indicated improvement. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2. Number of participants analyzed is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Week 20

End point values	Placebo	TAK-935		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	58		
Units: percentage of participants				
number (not applicable)				
Week 20, Score 1	2.0	13.8		
Week 20, Score 2	12.2	10.3		
Week 20, Score 3	18.4	32.8		
Week 20, Score 4	55.1	37.9		
Week 20, Score 5	8.2	3.4		
Week 20, Score 6	4.1	1.7		
Week 20, Score 7	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Plasma 24S-Hydroxycholesterol (24HC) Levels Participants Treated with TAK-935 as an Adjunctive Therapy

End point title	Change from Baseline in Plasma 24S-Hydroxycholesterol (24HC) Levels Participants Treated with TAK-935 as an Adjunctive Therapy

End point description:

A negative change from Baseline indicates improvement. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2, with available data. n=the number of participants with Baseline and Week 24 data available for analyses. 9999 indicated that the mean and standard deviation was not estimable as there were no evaluable participants for analyses. 99999 indicated that the standard deviation was not estimable for 1 participant.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	TAK-935		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	61		
Units: mg/dL				
arithmetic mean (standard deviation)				
Baseline (n=57, 61)	102.77 (± 50.385)	102.20 (± 62.332)		
Change from Baseline at Week 24 (n=0, 1)	9999 (± 9999)	-0.10 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Seizure Frequency in Participants Treated with TAK-935 as an Adjunctive Therapy

End point title	Change from Baseline in Seizure Frequency in Participants Treated with TAK-935 as an Adjunctive Therapy

End point description:

Seizure frequency was based on convulsive seizures for the participants in the Dravet Syndrome Indication and Drop Seizures for the participants in the LGS Indication. Seizure frequency per 28 days = (total number of seizures reported during the period) / (number of days during the period seizures were assessed) * 28. A negative change from Baseline indicates improvement. Efficacy Analysis Set included all mITT participants whose efficacy assessments were compliant with Protocol Amendment 2, with available data. n=the number of participants with Baseline and Week 24 data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Placebo	TAK-935		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	61		
Units: seizures per 28 days				
median (full range (min-max))				
Baseline (n=57, 61)	31.00 (3.1 to 1040.1)	32.12 (2.6 to 5187.7)		
Change from Baseline at Week 24 (n=33, 40)	0.30 (-84.9 to 520.4)	-6.29 (-1024.3 to 77.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose to 30 days post-last dose of study treatment (Up to 24 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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

TAK-935 placebo-matching tablets, orally or via G-tube/PEG, BID up to Week 20.

Reporting group title	TAK-935

Reporting group description:

TAK-935 tablets orally or via G-tube/PEG tube, BID. Participants weighing <60 kg received total daily dose of study drug calculated based on body weight. Participants weighing ≥60 kg at Baseline, were administered with 200 mg/day followed by 400 mg/day, then 600 mg/day, up to Week 20.

Serious adverse events	Placebo	TAK-935	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 70 (18.57%)	11 / 71 (15.49%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Foreign body in gastrointestinal tract			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Generalised tonic-clonic seizure			
subjects affected / exposed	2 / 70 (2.86%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	2 / 70 (2.86%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	1 / 2	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure cluster			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status epilepticus			
subjects affected / exposed	1 / 70 (1.43%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonic convulsion			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Hiatus hernia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 70 (1.43%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear infection			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 70 (1.43%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Septic shock			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	4 / 70 (5.71%)	2 / 71 (2.82%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Feeding disorder			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	TAK-935	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 70 (74.29%)	55 / 71 (77.46%)	
Vascular disorders			
Pallor			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	

General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 70 (11.43%)	11 / 71 (15.49%)	
occurrences (all)	13	13	
Asthenia			
subjects affected / exposed	1 / 70 (1.43%)	1 / 71 (1.41%)	
occurrences (all)	1	1	
Decreased activity			
subjects affected / exposed	1 / 70 (1.43%)	1 / 71 (1.41%)	
occurrences (all)	1	1	
Fatigue			
subjects affected / exposed	3 / 70 (4.29%)	4 / 71 (5.63%)	
occurrences (all)	3	4	
Influenza like illness			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Gait disturbance			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Peripheral swelling			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Erection increased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Adenoidal hypertrophy			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	3 / 70 (4.29%)	1 / 71 (1.41%)	
occurrences (all)	3	1	
Epistaxis			
subjects affected / exposed	0 / 70 (0.00%)	2 / 71 (2.82%)	
occurrences (all)	0	3	
Dysphonia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	2	
Rhinorrhoea			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Tonsillar hypertrophy			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract congestion			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Psychiatric disorders			
Affect lability			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Agitation			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Attention deficit hyperactivity disorder			

subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Apathy			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Impulsive behaviour			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Initial insomnia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	2	
Insomnia			
subjects affected / exposed	2 / 70 (2.86%)	1 / 71 (1.41%)	
occurrences (all)	2	1	
Middle insomnia			
subjects affected / exposed	1 / 70 (1.43%)	1 / 71 (1.41%)	
occurrences (all)	1	1	
Irritability			
subjects affected / exposed	2 / 70 (2.86%)	4 / 71 (5.63%)	
occurrences (all)	3	4	
Negativism			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Poverty of speech			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Restlessness			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Defiant behaviour			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Investigations			
Activated partial thromboplastin time prolonged			

subjects affected / exposed	3 / 70 (4.29%)	2 / 71 (2.82%)	
occurrences (all)	3	2	
Benzodiazepine drug level increased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Blood calcium decreased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Blood pressure diastolic increased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Blood urea increased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Blood urine present			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Drug level increased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Electrocardiogram P wave abnormal			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Electrocardiogram T wave amplitude decreased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Electrocardiogram abnormal			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	2 / 70 (2.86%)	0 / 71 (0.00%)	
occurrences (all)	2	0	
Gamma-glutamyltransferase increased			

subjects affected / exposed	1 / 70 (1.43%)	2 / 71 (2.82%)	
occurrences (all)	1	2	
Nitrite urine present			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Protein urine present			
subjects affected / exposed	1 / 70 (1.43%)	2 / 71 (2.82%)	
occurrences (all)	1	2	
Prothrombin time prolonged			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Red blood cells urine			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Urine output decreased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Vitamin D decreased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Blood bicarbonate decreased			
subjects affected / exposed	3 / 70 (4.29%)	0 / 71 (0.00%)	
occurrences (all)	3	0	
Injury, poisoning and procedural complications			
Arthropod bite			

subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	3	
Contusion			
subjects affected / exposed	3 / 70 (4.29%)	3 / 71 (4.23%)	
occurrences (all)	4	3	
Fall			
subjects affected / exposed	2 / 70 (2.86%)	0 / 71 (0.00%)	
occurrences (all)	2	0	
Head injury			
subjects affected / exposed	2 / 70 (2.86%)	0 / 71 (0.00%)	
occurrences (all)	4	0	
Joint injury			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Skin laceration			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Soft tissue injury			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Tibia fracture			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Cardiac disorders			

Bradycardia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Ventricular extrasystoles			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Nervous system disorders			
Seizure			
subjects affected / exposed	7 / 70 (10.00%)	4 / 71 (5.63%)	
occurrences (all)	8	4	
Somnolence			
subjects affected / exposed	3 / 70 (4.29%)	6 / 71 (8.45%)	
occurrences (all)	3	8	
Aphasia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Ataxia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Cerebellar ataxia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	2	
Change in seizure presentation			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Chorea			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Drooling			
subjects affected / exposed	1 / 70 (1.43%)	3 / 71 (4.23%)	
occurrences (all)	1	3	
Clonic convulsion			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Epilepsy			

subjects affected / exposed	2 / 70 (2.86%)	0 / 71 (0.00%)	
occurrences (all)	2	0	
Generalised tonic-clonic seizure			
subjects affected / exposed	4 / 70 (5.71%)	0 / 71 (0.00%)	
occurrences (all)	5	0	
Headache			
subjects affected / exposed	0 / 70 (0.00%)	3 / 71 (4.23%)	
occurrences (all)	0	3	
Hypotonia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Hypersomnia			
subjects affected / exposed	1 / 70 (1.43%)	2 / 71 (2.82%)	
occurrences (all)	1	2	
Myoclonic epilepsy			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Partial seizures			
subjects affected / exposed	2 / 70 (2.86%)	1 / 71 (1.41%)	
occurrences (all)	2	1	
Poor quality sleep			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 70 (0.00%)	3 / 71 (4.23%)	
occurrences (all)	0	4	
Seizure cluster			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Tonic convulsion			
subjects affected / exposed	4 / 70 (5.71%)	1 / 71 (1.41%)	
occurrences (all)	4	1	
Lethargy			
subjects affected / exposed	0 / 70 (0.00%)	5 / 71 (7.04%)	
occurrences (all)	0	5	
Blood and lymphatic system disorders			

Basophilia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Coagulopathy			
subjects affected / exposed	0 / 70 (0.00%)	3 / 71 (4.23%)	
occurrences (all)	0	3	
Granulocytopenia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Monocytosis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Lymphadenopathy			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Neutropenia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Eye disorders			
Amblyopia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Blepharitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Excessive eye blinking			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Ocular hyperaemia			

subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Periorbital swelling			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 70 (5.71%)	5 / 71 (7.04%)	
occurrences (all)	4	7	
Vomiting			
subjects affected / exposed	4 / 70 (5.71%)	6 / 71 (8.45%)	
occurrences (all)	5	7	
Aphthous ulcer			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	3	0	
Constipation			
subjects affected / exposed	0 / 70 (0.00%)	4 / 71 (5.63%)	
occurrences (all)	0	7	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Gingival pain			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Gingival swelling			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Mouth ulceration			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	

Salivary gland enlargement			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Lip swelling			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Umbilical hernia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Hepatomegaly			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	1 / 70 (1.43%)	2 / 71 (2.82%)	
occurrences (all)	1	3	
Pruritus			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Calculus bladder			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Hypercalciuria			

subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Pollakiuria			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	10 / 70 (14.29%)	12 / 71 (16.90%)	
occurrences (all)	11	20	
Nasopharyngitis			
subjects affected / exposed	6 / 70 (8.57%)	6 / 71 (8.45%)	
occurrences (all)	8	7	
Acute sinusitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Bronchiolitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Bronchitis viral			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	1 / 70 (1.43%)	2 / 71 (2.82%)	
occurrences (all)	1	2	
Conjunctivitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	2 / 70 (2.86%)	1 / 71 (1.41%)	
occurrences (all)	2	1	

Gastroenteritis viral			
subjects affected / exposed	2 / 70 (2.86%)	1 / 71 (1.41%)	
occurrences (all)	3	1	
Gingival abscess			
subjects affected / exposed	1 / 70 (1.43%)	1 / 71 (1.41%)	
occurrences (all)	1	1	
Gingivitis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Impetigo			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Infectious mononucleosis			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	4 / 70 (5.71%)	2 / 71 (2.82%)	
occurrences (all)	6	5	
Laryngitis			
subjects affected / exposed	1 / 70 (1.43%)	1 / 71 (1.41%)	
occurrences (all)	1	1	
Nail infection			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Otitis media acute			
subjects affected / exposed	3 / 70 (4.29%)	1 / 71 (1.41%)	
occurrences (all)	7	1	

Otitis media			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Peritonsillar abscess			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Pharyngitis			
subjects affected / exposed	1 / 70 (1.43%)	3 / 71 (4.23%)	
occurrences (all)	1	4	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	1 / 70 (1.43%)	3 / 71 (4.23%)	
occurrences (all)	1	3	
Pneumonia mycoplasmal			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Respiratory tract infection			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	0 / 70 (0.00%)	2 / 71 (2.82%)	
occurrences (all)	0	2	
Sepsis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Tonsillitis bacterial			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	

Urinary tract infection			
subjects affected / exposed	1 / 70 (1.43%)	1 / 71 (1.41%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	5 / 70 (7.14%)	6 / 71 (8.45%)	
occurrences (all)	5	6	
Abnormal loss of weight			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Dehydration			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Hypoglycaemia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	1 / 70 (1.43%)	0 / 71 (0.00%)	
occurrences (all)	1	0	
Hyponatraemia			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Malnutrition			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Metabolic acidosis			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Electrolyte imbalance			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	
Increased appetite			
subjects affected / exposed	0 / 70 (0.00%)	1 / 71 (1.41%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2018	Protocol Amendment 1: The primary purpose of this amendment was to make following changes. Removal of 'Non-Dravet patients with convulsive seizures". To change name of 'Drop seizure' stratum to 'LGS stratum'. To increase duration of maintenance period from 10 weeks to 12 weeks. To allow administration of TAK-935 via gastrostomy tube (G tube)/percutaneous endoscopic gastrostomy (PEG) tube. The total sample size was changed from 152 to 112. Remove exclusion criterion for status epilepticus (exclusion criterion #1). Remove exclusion criterion for inability to swallow study drug safety (exclusion criterion #3). Remove exclusion criterion for positive drug screen at screening. BMI assessment removed. Participants with Hepatitis B and C are excluded.
14 February 2019	Protocol Amendment 2: The primary purpose of this amendment was to make following changes. Clarified that iDMC will review the AE profiles of the first 12 patients aged ≥9 years completing 4 weeks of treatment. Renamed the Titration Period to the Dose Optimization Period and increased the period duration from 2 weeks to 8 weeks. Added additional phone calls to monitor dose optimization and safety. Removed hepatitis B and C serology panel. Changed the follow-up visit from a phone call to a clinic visit. Revised the PK collection timepoints and added sampling windows. Updated the approximate total blood volume collected. Revised the primary, secondary and exploratory objectives. Updated language regarding patient's legal representative. Clarified diagnosis of Dravet syndrome and Lennox-Gastaut syndrome for Inclusion. Clarified that convulsive status epilepticus requiring hospitalization is an exclusion criterion for this study. Revised the exclusion criterion related to ocular conditions. Added malignancy (including progressive tumors) as an exclusionary condition. Revised the primary, secondary and exploratory endpoints. Revised the pharmacokinetic endpoints. Revised and added analysis sets. Updated study rationale. Add new section to define end of the study. Clarified the handling of missed doses. Changed demographic collection from "date of birth" to "year of birth". Added a formula for assessment of seizure frequency. Clarified that the Exit survey is a separate questionnaire from the Care GI-C. Added statement about AEs or SAEs associated with overdose. Clarified reporting seizures as AEs/SAEs. Removed text that stated that expected SAEs were provided in the Investigators Brochure. Clarified SAE reporting process. Added text stating that TAK-935 should not be administered to pregnant or lactating females. Updated the schedule of assessments. Updated Appendix 2. Updated the Appendix 3 study sampling summary. Replaced table in Appendix 3.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported