Clinical trial results:
A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-935 as an Adjunctive Therapy in Adult Subjects With Chronic Complex Regional Pain Syndrome

Summary

EudraCT number	2018-004750-21
Trial protocol	GB
Global end of trial date	28 October 2020

Results information

Result version number	v1 (current)
This version publication date	04 November 2021
First version publication date	04 November 2021

Trial information

Trial identification

Sponsor protocol code	TAK-935-2008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03990649
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, MA, United States, 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	28 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective this study is to investigate the effect of soticlestat (TAK-935) on calculated 24-hour average pain intensity by the numeric pain scale (NPS).

Protection of trial subjects:

All the participants were required to read and sign the informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 July 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 24
Worldwide total number of subjects	24
EEA total number of subjects	0

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)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at three investigative sites in United Kingdom (UK) from 23 July 2019 to 28 October 2020.

Pre-assignment

Screening details:

Participants with a diagnosis of chronic complex regional pain syndrome (CRPS) were enrolled to receive soticlestat or placebo in Part A (Double-blind [DB] Treatment Period) and soticlestat in Part B (Open-label [OL] Treatment Period). Following completion of the Part A, participants had an option to continue into Part B.

Period 1

Period 1 title	Part A: DB Treatment Period (15 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Double-Blind Treatment Period - Part A: Placebo

Arm description:

Soticlestat matching placebo tablets, orally, twice daily (BID) for Weeks 1, 2 and 3 in Double blind Titration Period. Soticlestat matching placebo tablets, orally BID for 12 weeks in Double blind Maintenance Period. Taper period (if participant did not continue to Part B): Dose of soticlestat matching placebo tablets was reduced to next lower dose every 3 days (maximum 6 days) until discontinuation.

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

Dosage and administration details:

Soticlestat matching placebo tablets

Arm title	Double-Blind Treatment Period - Part A: Soticlestat

Arm description:

Soticlestat, tablet, orally, 100 mg BID for Week 1, followed by 2×100 mg tablets, soticlestat, orally BID for Week 2, further followed by 3×100 mg tablets, soticlestat, orally BID for Week 3. Dose was uptitrated every week based on safety and tolerability. Part A (Double blind Maintenance Period): 3×100 mg tablets, soticlestat, orally BID for 12 weeks. Dose was adjusted during Maintenance Period due to safety and tolerability. Taper Period (if participant did not continue to Part B): Dose of soticlestat was reduced to next lower dose every 3 days (maximum 6 days) until soticlestat was discontinued.

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

Dosage and administration details:

Soticlestat tablets

Number of subjects in period 1	Double-Blind Treatment Period - Part A: Placebo	Double-Blind Treatment Period - Part A: Soticlestat
Started	9	15
Completed	6	12
Not completed	3	3
Adverse event, non-fatal	-	1
Withdrawal by Subject	2	-
Lost to follow-up	-	1
Reason not Specified	1	1

Period 2

Period 2 title	Part B: OL Extension Period (14 weeks)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Open-Label Extension Period - Part B: Soticlestat

Arm description:

Soticlestat, 2x100 mg tablets, orally, BID for Week 1, followed by 3x100 mg tablets, soticlestat, orally, BID for Week 2. Dose was uptitrated every week based on safety and tolerability. Part B (Open label extension: Maintenance Period): 3x100 mg tablets, soticlestat, orally, BID for 12 weeks. Dose was adjusted during Maintenance Period due to safety and tolerability. Taper Period: Dose of soticlestat was reduced to next lower dose every 3 days (maximum 6 days) until soticlestat was discontinued.

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

Dosage and administration details:

Soticlestat tablets

Number of subjects in period 2	Open-Label Extension Period - Part B: Soticlestat
Started	18
Completed	14
Not completed	4
Adverse event, non-fatal	1

Withdrawal by Subject	2
Reason not Specified	1

Baseline characteristics

Reporting groups	
Reporting group title	Double-Blind Treatment Period - Part A: Placebo
Reporting group description:	
Soticlestat matching placebo tablets, orally, twice daily (BID) for Weeks 1, 2 and 3 in Double blind Titration Period. Soticlestat matching placebo tablets, orally BID for 12 weeks in Double blind Maintenance Period. Taper period (if participant did not continue to Part B): Dose of soticlestat matching placebo tablets was reduced to next lower dose every 3 days (maximum 6 days) until discontinuation.	
Reporting group title	Double-Blind Treatment Period - Part A: Soticlestat
Reporting group description:	
Soticlestat, tablet, orally, 100 mg BID for Week 1, followed by 2×100 mg tablets, soticlestat, orally BID for Week 2, further followed by 3×100 mg tablets, soticlestat, orally BID for Week 3. Dose was uptitrated every week based on safety and tolerability. Part A (Double blind Maintenance Period): 3×100 mg tablets, soticlestat, orally BID for 12 weeks. Dose was adjusted during Maintenance Period due to safety and tolerability. Taper Period (if participant did not continue to Part B): Dose of soticlestat was reduced to next lower dose every 3 days (maximum 6 days) until soticlestat was discontinued.	

Reporting group values	Double-Blind Treatment Period - Part A: Placebo	Double-Blind Treatment Period - Part A: Soticlestat	Total
Number of subjects	9	15	24
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	39.0	42.1	
standard deviation	± 13.51	± 10.27	-
Gender categorical Units: Subjects			
Female	6	11	17
Male	3	4	7
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	1	1
Not Hispanic or Latino	7	13	20
Unknown or Not Reported	2	1	3
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	9	15	24
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
United Kingdom	9	15	24

Numeric Pain Scale (NPS) Score			
The 24-hour average pain intensity was calculated from current pain intensity scores collected three times a day as measured by the electronic pain diary daily using NPS. NPS is an 11-point scale, where scores range from 0-10, 0= no pain to 10 = most pain imaginable.			
Units: scores on a scale			
arithmetic mean	6.33	6.33	
full range (min-max)	4.9 to 7.8	4.5 to 7.6	-
CRPS Severity Score (CSS) Total Score			
Signs and symptoms reflecting the sensory, vasomotor, sudomotor/edema, and motor/trophic disturbances of CRPS had been incorporated into a clinically feasible CSS. Total CSS is a 16-point score which was calculated by the number of "yes" answers to the questions on the 8 symptoms and 8 signs when all 16 questions were answered.			
Units: scores on a scale			
arithmetic mean	12.7	12.9	
standard deviation	± 1.73	± 1.87	-
Patient-Reported Outcomes Measurement Information System v2.1 Domain (Physical Function) Score			
Patient-Reported Outcomes Measurement Information System (PROMIS-29) v2.1 assess health-related quality of life for 7 domains with T-scores of reference population: Physical function:1=unable to do-5=without any difficulty;T-scores:22.5-57.03. Higher scores=more of domain being measured.			
Units: score on a scale			
arithmetic mean	35.83	34.65	
standard deviation	± 5.607	± 4.743	-
PROMIS-29 v2.1 Domain (Anxiety) Score			
PROMIS-29 (v2.1) assess health-related quality of life for 7 domains with T-scores of reference population: Anxiety:1=never-5=always;T-scores:40.3-81.6. Higher scores=more of domain being measured.			
Units: score on a scale			
arithmetic mean	46.30	51.94	
standard deviation	± 11.906	± 8.873	-
PROMIS-29 v2.1 Domain (Depression) Score			
Measure Description: PROMIS-29 (v2.1) assess health-related quality of life for 7 domains with T-scores of reference population: Depression:1=never-5=always;T-scores:41.0-79.4. Higher scores=more of domain being measured.			
Units: score on a scale			
arithmetic mean	47.31	47.27	
standard deviation	± 12.523	± 8.868	-
PROMIS-29 v2.1 Domain (Fatigue) Score			
PROMIS-29 (v2.1) assess health-related quality of life for 7 domains with T-scores of reference population: Fatigue:1=not at all-5=very much;T-scores:33.7-75.8. Higher scores=more of domain being measured.			
Units: score on a scale			
arithmetic mean	57.17	60.55	
standard deviation	± 8.427	± 8.280	-
PROMIS-29 v2.1 Domain (Sleep Disturbance) Score			
PROMIS-29 (v2.1) assess health-related quality of life for 7 domains with T-scores of reference population: Sleep disturbance:1=very much-5=not at all;T-scores:32.0-73.3. Higher scores=more of domain being measured.			
Units: score on a scale			
arithmetic mean	54.63	54.99	
standard deviation	± 3.854	± 2.390	-
PROMIS-29 v2.1 Domain (Ability to Participate in Social Roles and Activities) Score			

PROMIS-29 (v2.1) assess health-related quality of life for 7 domains with T-scores of reference population: Ability to participate in social roles and activities:1=always-5=never;T-scores:27.5-64.2 Higher scores=more of domain being measured.			
Units: score on a scale			
arithmetic mean	40.03	39.11	
standard deviation	± 6.205	± 4.723	-
PROMIS-29 v2.1 Domain (Pain Interference) Score			
PROMIS-29 (v2.1) assess health-related quality of life for 7 domains with T-scores of reference population: Pain interference: 1=not at all-5=very much;T-scores:41.6-75.6. Higher scores=more of domain being measured.			
Units: score on a scale			
arithmetic mean	66.37	64.22	
standard deviation	± 6.710	± 8.039	-

End points

End points reporting groups

Reporting group title	Double-Blind Treatment Period - Part A: Placebo

Reporting group description:

Soticlestat matching placebo tablets, orally, twice daily (BID) for Weeks 1, 2 and 3 in Double blind Titration Period. Soticlestat matching placebo tablets, orally BID for 12 weeks in Double blind Maintenance Period. Taper period (if participant did not continue to Part B): Dose of soticlestat matching placebo tablets was reduced to next lower dose every 3 days (maximum 6 days) until discontinuation.

Reporting group title	Double-Blind Treatment Period - Part A: Soticlestat

Reporting group description:

Soticlestat, tablet, orally, 100 mg BID for Week 1, followed by 2×100 mg tablets, soticlestat, orally BID for Week 2, further followed by 3×100 mg tablets, soticlestat, orally BID for Week 3. Dose was uptitrated every week based on safety and tolerability. Part A (Double blind Maintenance Period): 3×100 mg tablets, soticlestat, orally BID for 12 weeks. Dose was adjusted during Maintenance Period due to safety and tolerability. Taper Period (if participant did not continue to Part B): Dose of soticlestat was reduced to next lower dose every 3 days (maximum 6 days) until soticlestat was discontinued.

Reporting group title	Open-Label Extension Period - Part B: Soticlestat

Reporting group description:

Soticlestat, 2x100 mg tablets, orally, BID for Week 1, followed by 3x100 mg tablets, soticlestat, orally, BID for Week 2. Dose was uptitrated every week based on safety and tolerability. Part B (Open label extension: Maintenance Period): 3x100 mg tablets, soticlestat, orally, BID for 12 weeks. Dose was adjusted during Maintenance Period due to safety and tolerability. Taper Period: Dose of soticlestat was reduced to next lower dose every 3 days (maximum 6 days) until soticlestat was discontinued.

Primary: Change From Baseline in Mean 24-Hour Pain Intensity as Assessed by NPS Score to the End of Part A

End point title	Change From Baseline in Mean 24-Hour Pain Intensity as Assessed by NPS Score to the End of Part A[1]

End point description:

The 24-hour average pain intensity was calculated from current pain intensity scores collected three times a day as measured by the electronic pain diary daily using NPS. NPS is an 11-point scale, where scores range from 0-10, 0=no pain to 10=most pain imaginable. Negative change from Baseline indicated improvement. Full Analysis Set (FAS) included all participants who were randomised, received at least 1 dose of study drug, and had at least one valid post-baseline value for the assessment of average 24-hour pain score. The data is reported for Part A in this outcome measure. Overall number of participants analysed are the number of participants with data available for analyses.

End point type	Primary

End point timeframe:

Baseline and Week 15

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive analysis are reported for this endpoint.

End point values	Double-Blind Treatment Period - Part A: Placebo	Double-Blind Treatment Period - Part A: Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: scores on scale				
arithmetic mean (standard deviation)	-0.74 (± 1.614)	-1.05 (± 1.310)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Mean 24-Hour Pain Intensity as Assessed by NPS Score to the End of Part A

End point title	Percent Change From Baseline in Mean 24-Hour Pain Intensity as Assessed by NPS Score to the End of Part A

End point description:

The 24-hour average pain intensity was calculated from current pain intensity scores collected three times a day as measured by the electronic pain diary daily using NPS. NPS is an 11-point scale, where scores range from 0-10, 0=no pain to 10=most pain imaginable. Negative percent change from Baseline indicated improvement. FAS included all participants who were randomised, received at least 1 dose of study drug, and had at least one valid post-baseline value for the assessment of average 24-hour pain score. The data is reported for Part A in this outcome measure. Overall number of participants analysed are the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 15

End point values	Double-Blind Treatment Period - Part A: Placebo	Double-Blind Treatment Period - Part A: Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	12		
Units: percent change				
arithmetic mean (standard deviation)	-12.20 (± 29.108)	-18.35 (± 23.699)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Considered Responders at the End of Part A

End point title	Percentage of Participants Considered Responders at the End of Part A

End point description:

Response was defined as >=30% improvement on the 24-hour pain intensity as assessed by the NPS score. The 24-hour average pain intensity was calculated from current pain intensity scores collected three times a day as measured by the electronic pain diary daily using NPS during Part A. NPS is an 11-point scale, where scores range from 0- 10, 0=no pain to 10 = most pain imaginable. FAS included all participants who were randomised, received at least 1 dose of study drug, and had at least one valid post-baseline value for the assessment of average 24-hour pain score. The data is reported for Part A in this outcome measure.

End point type	Secondary
End point timeframe: Week 15	

End point values	Double-Blind Treatment Period - Part A: Placebo	Double-Blind Treatment Period - Part A: Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	15		
Units: percentage of participants				
number (not applicable)	22.2	26.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline (CFB) in Domain Score of PROMIS-29 Version 2.1 at the End of Part A

End point title	Change From Baseline (CFB) in Domain Score of PROMIS-29 Version 2.1 at the End of Part A

End point description:

PROMIS-29(v2.1): assessed 7 domains with 4 questions on 5-point Likert scale.Total raw domain scores are converted into Tscores(TS):Depression and Anxiety:1 =never to S=always,TS:41.0-79.4 and 40.3-81.6; Physical function:1 =unable to do to S=without any difficulty,TS:22.5-57.0; Pain interference and Fatigue:1 =not at all to S=very much,TS:41.6-75.6 and 33.7-75.B; Sleep disturbance:1 =very much to 5=not at all,TS:32.0-73.3; Ability to participate in social activities:1 =always to S=never,TS:27.5-64.2. High scores(HS):more of domain being measured. On symptom-oriented domains,HS=worse symptomatology and negative CFB indicates improvement.On function oriented domains, HS=better functioning and positive CFB indicates improvement. FAS:all randomised, received at least 1 dose of study drug, and had at least one valid post-baseline value for assessment of average 24-hour pain score. Data is reported for part A. Here 'n' is number analysed are participants with data available for analyses.

End point type	Secondary
End point timeframe: Baseline and Week 15	

End point values	Double-Blind Treatment Period - Part A: Placebo	Double-Blind Treatment Period - Part A: Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	15		
Units: t-score				
arithmetic mean (standard deviation)				
Physical Function (n =8, 12) Anxiety (n=8, 13)	1.53 (± 2.207) 3.29 (± 10.348)	2.39 (± 4.042) -1.99 (± 9.567)		

Depression (n=8, 13)	1.15 (± 10.011)	-0.78 (± 6.902)		
Fatigue (n=8, 13)	0.45 (± 12.126)	-3.66 (± 10.456)		
Sleep Disturbance (n=8, 13)	2.13 (± 5.110)	2.55 (± 1.927)		
Ability to Participate in Social Roles (n=7, 13)	1.66 (± 6.051)	2.74 (± 5.147)		
Pain Interference (n=7, 13)	-1.53 (± 6.257)	-0.38 (± 7.597)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Domain Score of PROMIS-29 Version 2.1 at the End of Part A

End point title	Percent Change From Baseline in Domain Score of PROMIS-29 Version 2.1 at the End of Part A

End point description:

PROMIS-29(v2.1):assessed 7 domains with 4 questions on 5-point Likert scale. Total raw domain scores are converted into T-scores(TS): Depression and Anxiety:1=never to 5=always,TS:41.0-79.4 and 40.3-81.6; Physical function:1 =unable to do to 5=without any difficulty,TS:22.5-57.0; Pain interference and Fatigue:1=not at all to 5=very much,TS:41.6-75.6 and 33.7-75.8;Sleep disturbance:1=very much to 5=not at all,TS: 32.0-73.3;Ability to participate in social activities:1=always to 5=never,TS:27.5-64.2. High scores(HS):more of domain being measured. On symptom-oriented domains, HS=worse symptomatology and negative CFB indicates improvement. On function-oriented domains, HS=better functioning and positive CFB indicates improvement. FAS:all randomised, received at least 1 dose of study drug, and had at least one valid post-baseline value for assessment of average 24-hour pain score. Data is reported for part A. 'n' indicates number analysed are participants with data available for analyse.

End point type	Secondary

End point timeframe:

Baseline and Week 15

End point values	Double-Blind Treatment Period - Part A: Placebo	Double-Blind Treatment Period - Part A: Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	15		
Units: percent change				
arithmetic mean (standard deviation)				
Physical Function (n =8, 12)	4.27 (± 6.197)	8.00 (± 14.106)		
Anxiety (n=8, 13)	9.35 (± 24.153)	-2.43 (± 16.584)		
Depression (n=8, 13)	4.51 (± 21.864)	0.04 (± 13.494)		
Fatigue (n=8, 13)	2.42 (± 22.902)	-4.62 (± 16.045)		
Sleep Disturbance (n=8, 13)	4.46 (± 9.611)	4.75 (± 3.600)		
Ability to Participate in Social Roles (n=7, 13)	4.39 (± 15.195)	7.42 (± 13.796)		

Pain Interference (n=7, 13)	-1.88 (± 9.149)	0.82 (± 15.571)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants in Each Category of the Patient Global Impression of Change (PGIC) Scale at the End of Part A

End point title	Percentage of Participants in Each Category of the Patient Global Impression of Change (PGIC) Scale at the End of Part A

End point description:

The PGIC is a 7-point Likert scale to address the following question: Since beginning treatment at this clinic would you describe any changes (if any) in activity, limitations, symptoms, emotions and overall quality of life related to your painful condition compared to before treatment Participants select from scale range of 1-7: very much improved (1); much improved (2); minimally improved (3); no change (4); minimally worse (5); much worse (6); very much worse (7). Only categories with at least 1 participant were reported. FAS included all participants who were randomised, received at least 1 dose of study drug, and had at least one valid post-baseline value for the assessment of average 24- hour pain score. The data is reported for Part A in this outcome measure.

End point type	Secondary

End point timeframe:

Week 15

End point values	Double-Blind Treatment Period - Part A: Placebo	Double-Blind Treatment Period - Part A: Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	15		
Units: percentage of participants				
number (not applicable)				
Much Improved	33.33	33.33		
Minimally Improved	11.1	13.3		
No Change	22.2	33.3		
Minimally Worse	11.1	0		
Missing	22.2	20.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Complex Regional Pain Syndrome (CSS) at the End of Part A

End point title	Change From Baseline in Complex Regional Pain Syndrome (CSS) at the End of Part A

End point description:

Signs and symptoms reflecting the sensory, vasomotor, sudomotor/edema, and motor/trophic disturbances of CRPS had been incorporated into a clinically feasible CSS. Total CSS is a 16-point score which was calculated by the number of "yes" answers to the questions on the 8 symptoms and 8 signs when all 16 questions were answered. Negative change from Baseline indicates improvement. FAS included all participants who were randomised, received at least 1 dose of study drug, and had at least one valid post-baseline value for the assessment of average 24-hour pain score. The data is reported for Part A in this outcome measure. Overall number of participants analysed are the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 15

End point values	Double-Blind Treatment Period - Part A: Placebo	Double-Blind Treatment Period - Part A: Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	13		
Units: scores on scale				
arithmetic mean (standard deviation)	-2.2 (± 2.48)	-3.1 (± 3.12)		

Statistical analyses

Statistical analysis title	Statistical Analysis for CSS
Comparison groups	Double-Blind Treatment Period - Part A: Placebo v Double-Blind Treatment Period - Part A: Soticlestat
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.54 [2]
Method	t-test, 2-sided

Notes:

[2] - The p-values were estimated using a two-sample t-test.

Secondary: Percent Change From Baseline in CSS at the End of Part A

End point title	Percent Change From Baseline in CSS at the End of Part A

End point description:

Signs and symptoms reflecting the sensory, vasomotor, sudomotor/edema, and motor/trophic disturbances of CRPS had been incorporated into a clinically feasible CSS. Total CSS is a 16-point score which was calculated by the number of "yes" answers to the questions on the 8 symptoms and 8 signs when all 16 questions were answered. Negative percent change from Baseline indicates improvement. FAS included all participants who were randomised, received at least 1 dose of study drug, and had at least one valid post-baseline value for the assessment of average 24-hour pain score. The data is reported for Part A in this outcome measure. Overall number of participants analysed are the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline and Week 15

End point values	Double-Blind Treatment Period - Part A: Placebo	Double-Blind Treatment Period - Part A: Soticlestat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	13		
Units: percent change				
arithmetic mean (standard deviation)	-16.1 (± 18.89)	-23.8 (± 26.29)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of the informed consent up to 15 days after last dose of the study drug (Up to approximately Week 32)

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	23.0

Reporting groups

Reporting group title	Double-Blind Treatment Period - Part A: Placebo

Reporting group description:

Soticlestat matching placebo tablets, orally, twice daily (BID) for Weeks 1, 2 and 3 in Double blind Titration Period. Soticlestat matching placebo tablets, orally BID for 12 weeks in Double blind Maintenance Period. Taper period (if participant did not continue to Part B): Dose of soticlestat matching placebo tablets was reduced to next lower dose every 3 days (maximum 6 days) until discontinuation.

Reporting group title	Double-Blind Treatment Period - Part A: Soticlestat

Reporting group description:

Soticlestat, tablet, orally, 100 mg BID for Week 1, followed by 2×100 mg tablets, soticlestat, orally BID for Week 2, further followed by 3×100 mg tablets, soticlestat, orally BID for Week 3. Dose was uptitrated every week based on safety and tolerability. Part A (Double blind Maintenance Period): 3×100 mg tablets, soticlestat, orally BID for 12 weeks. Dose was adjusted during Maintenance Period due to safety and tolerability. Taper Period (if participant did not continue to Part B): Dose of soticlestat was reduced to next lower dose every 3 days (maximum 6 days) until soticlestat was discontinued.

Reporting group title	Open-Label Extension Period - Part B: Soticlestat

Reporting group description:

Soticlestat, 2×100 mg tablets, orally, BID for Week 1, followed by 3×100 mg tablets, soticlestat, orally, BID for Week 2. Dose was uptitrated every week based on safety and tolerability. Part B (Open label extension: Maintenance Period): 3×100 mg tablets, soticlestat, orally, BID for 12 weeks. Dose was adjusted during Maintenance Period due to safety and tolerability. Taper Period: Dose of soticlestat was reduced to next lower dose every 3 days (maximum 6 days) until soticlestat was discontinued.

Serious adverse events	Double-Blind Treatment Period - Part A: Placebo	Double-Blind Treatment Period - Part A: Soticlestat	Open-Label Extension Period - Part B: Soticlestat
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	3 / 15 (20.00%)	0 / 18 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	2 / 15 (13.33%)	0 / 18 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 15 (6.67%)	0 / 18 (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

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

Non-serious adverse events	Double-Blind Treatment Period - Part A: Placebo	Double-Blind Treatment Period - Part A: Soticlestat	Open-Label Extension Period - Part B: Soticlestat
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)	12 / 15 (80.00%)	10 / 18 (55.56%)
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 9 (0.00%)	0 / 15 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Procedural pain			
subjects affected / exposed	1 / 9 (11.11%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	1	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 9 (22.22%)	4 / 15 (26.67%)	0 / 18 (0.00%)
occurrences (all)	2	5	0
Headache			
subjects affected / exposed	4 / 9 (44.44%)	2 / 15 (13.33%)	5 / 18 (27.78%)
occurrences (all)	7	3	7
Lethargy			
subjects affected / exposed	1 / 9 (11.11%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	1	2	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 9 (0.00%)	2 / 15 (13.33%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Influenza like illness			
subjects affected / exposed	0 / 9 (0.00%)	2 / 15 (13.33%)	0 / 18 (0.00%)
occurrences (all)	0	2	0

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	1	1	1
Constipation			
subjects affected / exposed	1 / 9 (11.11%)	2 / 15 (13.33%)	1 / 18 (5.56%)
occurrences (all)	1	3	1
Dry mouth			
subjects affected / exposed	0 / 9 (0.00%)	2 / 15 (13.33%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	3 / 15 (20.00%)	1 / 18 (5.56%)
occurrences (all)	1	4	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 9 (33.33%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	3	1	1
Oropharyngeal pain			
subjects affected / exposed	0 / 9 (0.00%)	2 / 15 (13.33%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	2 / 9 (22.22%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Insomnia			
subjects affected / exposed	1 / 9 (11.11%)	2 / 15 (13.33%)	1 / 18 (5.56%)
occurrences (all)	1	2	1
Suicidal ideation			
subjects affected / exposed	0 / 9 (0.00%)	0 / 15 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	0 / 15 (0.00%)	2 / 18 (11.11%)
occurrences (all)	0	0	2
Musculoskeletal pain			

subjects affected / exposed	0 / 9 (0.00%)	2 / 15 (13.33%)	0 / 18 (0.00%)
occurrences (all)	0	2	0
Neck pain			
subjects affected / exposed	1 / 9 (11.11%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 15 (6.67%)	2 / 18 (11.11%)
occurrences (all)	0	1	2
Lower respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 9 (22.22%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	2	1	1
Oral candidiasis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 15 (6.67%)	1 / 18 (5.56%)
occurrences (all)	0	1	1
Oral herpes			
subjects affected / exposed	1 / 9 (11.11%)	0 / 15 (0.00%)	1 / 18 (5.56%)
occurrences (all)	2	0	1
Urinary tract infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 15 (6.67%)	0 / 18 (0.00%)
occurrences (all)	2	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 9 (0.00%)	2 / 15 (13.33%)	0 / 18 (0.00%)
occurrences (all)	0	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2019	Amendment 1: -Updated the language regarding unblinding procedures.
01 July 2019	Amendment 2: - Corrected a typographical error -Updated the language regarding contraception procedures -Updated the language regarding pharmacogenomics sample collection -Corrected the 29-item Patient-Reported Outcomes Measurement Information System (PROMIS-29) scale to version 2.1.
16 December 2019	Amendment 3: - Updated the dose selection rationale -Clarified the schematic of study design -Moved a secondary objective to an exploratory objective to align with endpoints -Modified Figure 4.a. -Clarified the rationale for the study -Moved the detail on pharmacogenomic analysis -Revised contraceptive requirements -Modified the detail regarding blood volumes collected during the study -Clarified the ECG procedures for specific visits -Clarified the efficacy analysis, the exploratory analysis and the interim analysis -Clarified when blood samples for plasma protein binding assessment will be collected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported