



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Six-Month Study to Evaluate the Efficacy, Safety and Tolerability of Sarizotan in Patients with Rett Syndrome with Respiratory Symptoms

Summary

EudraCT number	2015-004448-20
Trial protocol	GB IT
Global end of trial date	04 May 2020

Results information

Result version number	v1 (current)
This version publication date	28 May 2021
First version publication date	28 May 2021

Trial information

Trial identification

Sponsor protocol code	Sarizotan/001/II/2015
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02790034
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Newron Pharmaceuticals S.p.A.
Sponsor organisation address	Via Meucci 3, Bresso (MI) , Italy, 20091
Public contact	Ravi Anand, Newron Pharmaceuticals S.p.A., +41 793741364, ravi@anand.ch
Scientific contact	Ravi Anand, Newron Pharmaceuticals S.p.A., +41 793741364, ravi@anand.ch

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001808-PIP03-17
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	04 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 August 2019
Global end of trial reached?	Yes
Global end of trial date	04 May 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of sarizotan high dose (5 and 10 mg bid), compared to placebo, on reducing the number of apnea episodes, during awake time, in patients with RTT with respiratory abnormalities.

Protection of trial subjects:

There was no specific patient support therapy implemented by the sponsor.

Background therapy:

No background therapy was involved.

Evidence for comparator:

There are currently no approved treatments for the key symptoms, including respiratory dysfunction, in RTT patients; therefore, a placebo control, rather than an active control, was used in this study.

Actual start date of recruitment	26 October 2016
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	United Kingdom: 21
Country: Number of subjects enrolled	Italy: 30
Country: Number of subjects enrolled	India: 34
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	129
EEA total number of subjects	30

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)	58
Adolescents (12-17 years)	27

Adults (18-64 years)	44
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in 5 countries (Italy, UK, India, Australia, US) with recruitment period October 2016 to February 2019 - for the double-blind period. Patients without safety and tolerability issues continued with open label sarizotan for up to an additional 168 weeks.

Pre-assignment

Screening details:

198 patients were screened; 69 (34.8%) were screen failures

Reason for SF:

Did not meet entry criteria - 53 (76.8%)

Major protocol deviation - 0

Pretreatment Event/Adverse Event - 1 (1.4%)

Lost to follow-up - 1 (1.4%)

Voluntary withdrawal - 14 (20.3%)

Study termination - 0

Other reason; specify - 0

Period 1

Period 1 title	Double Blind Low dose/ High Dose/Placebo (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sarizotan Low Dose

Arm description:

2 mg or 5 mg bid based on age and weight criteria for 24 wks DB

2 mg bid (4 to <13 years; ≥13 years of age and weighing <25 kg)

5 mg bid (≥13 years of age and weighing ≥25 kg)

Assessment of safety, tolerability and efficacy on reducing the respiratory symptoms in patients.

Arm type	Experimental
Investigational medicinal product name	Sarizotan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Gastric use, Oral use

Dosage and administration details:

- Patients of age 4 to <13 years were randomized to 1:1:1 sarizotan 2 mg bid (low dose sarizotan group), sarizotan 5 mg bid (high dose sarizotan group), or placebo bid.
- Patients of age ≥13 years and weight <25 kg were randomized to 1:1:1 sarizotan 2 mg bid (low dose sarizotan group), sarizotan 5 mg bid (high dose sarizotan group), or placebo bid.

Arm title	Sarizotan High Dose
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Arm description:

5 mg or 10 mg bid based on age and weight criteria for 24 wks DB

5 mg bid (4 to <13 years; ≥13 years of age and weighing <25 kg)

10 mg bid (≥13 years of age and weighing ≥25 kg)

Assessment of safety, tolerability and efficacy on reducing the respiratory symptoms in patients.

Arm type	Experimental
Investigational medicinal product name	Sarizotan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Gastric use, Oral use

Dosage and administration details:

- Patients of age ≥ 13 years and weight ≥ 25 kg were randomized to 1:1:1 sarizotan 5 mg bid (low dose sarizotan group), sarizotan 10 mg bid (high dose sarizotan group), or placebo bid.

Arm title	Placebo
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Arm description:

Placebo bid for 24 wks DB
age 4 and above

Placebo: placebo BID followed by assessment of safety, tolerability and efficacy on reducing the respiratory symptoms in patients.

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

Dosage and administration details:

- Patients of age 4 to <13 years were randomized to 1:1:1 sarizotan 2 mg bid (low dose sarizotan group), sarizotan 5 mg bid (high dose sarizotan group), or placebo bid.
- Patients of age ≥ 13 years and weight <25 kg were randomized to 1:1:1 sarizotan 2 mg bid (low dose sarizotan group), sarizotan 5 mg bid (high dose sarizotan group), or placebo bid.
- Patients of age ≥ 13 years and weight ≥ 25 kg were randomized to 1:1:1 sarizotan 5 mg bid (low dose sarizotan group), sarizotan 10 mg bid (high dose sarizotan group), or placebo bid.

Number of subjects in period 1	Sarizotan Low Dose	Sarizotan High Dose	Placebo
Started	33	56	40
Completed	27	46	36
Not completed	6	10	4
Consent withdrawn by subject	1	4	1
Adverse event, non-fatal	4	6	2
No matching reasons found	1	-	1

Baseline characteristics

Reporting groups

Reporting group title	Sarizotan Low Dose
Reporting group description:	
2 mg or 5 mg bid based on age and weight criteria for 24 wks DB	
2 mg bid (4 to <13 years; ≥13 years of age and weighing <25 kg)	
5 mg bid (≥13 years of age and weighing ≥25 kg)	
Assessment of safety, tolerability and efficacy on reducing the respiratory symptoms in patients.	
Reporting group title	Sarizotan High Dose
Reporting group description:	
5 mg or 10 mg bid based on age and weight criteria for 24 wks DB	
5 mg bid (4 to <13 years; ≥13 years of age and weighing <25 kg)	
10 mg bid (≥13 years of age and weighing ≥25 kg)	
Assessment of safety, tolerability and efficacy on reducing the respiratory symptoms in patients.	
Reporting group title	Placebo
Reporting group description:	
Placebo bid for 24 wks DB	
age 4 and above	
Placebo: placebo BID followed by assessment of safety, tolerability and efficacy on reducing the respiratory symptoms in patients.	

Reporting group values	Sarizotan Low Dose	Sarizotan High Dose	Placebo
Number of subjects	33	56	40
Age categorical			
All the patients enrolled in the study were female. The mean (SD) age was 14.51 (8.780) years and ranged between 3.7 years to 44.4 years. Approximately half of the patients (67 [51.9%]) were 4 to 12 years of age and 44 (34.1%) patients were adults (≥18 years). 18 (14.0%) were in the 13-17 years old category.			
Units: Subjects			
Children (4-12 years)	17	26	24
Adolescents (13-17 years)	6	9	3
Adults (≥18 years)	10	21	13
Gender categorical			
All the patients enrolled in the study were female.			
Units: Subjects			
Female	33	56	40
Male	0	0	0
Race			
The majority of patients (82 [63.6%]) were White, and most (89.9%) were not Hispanic or Latino. Overall, 37 (28.7%) patients were Asian.			
Units: Subjects			
Black or African American	1	1	3
Native Hawaiian or other Pacific Islanders	0	1	0
White	23	37	22
Asian	8	16	13
Other	0	1	2

Multiple	1	0	0
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Baseline disease characteristic			
Summary of duration of Rett syndrome by treatment group: The mean (SD) duration of Rett syndrome was numerically higher in sarizotan groups (87.90 [72.536] months in low dose sarizotan group and 97.18 [72.922] months in high dose sarizotan group) compared with placebo group (73.94 [65.800] months).			
Units: Months			
arithmetic mean	87.90	97.18	73.94
standard deviation	± 72.536	± 72.922	± 65.800

Reporting group values	Total		
Number of subjects	129		
Age categorical			
All the patients enrolled in the study were female. The mean (SD) age was 14.51 (8.780) years and ranged between 3.7 years to 44.4 years. Approximately half of the patients (67 [51.9%]) were 4 to 12 years of age and 44 (34.1%) patients were adults (≥18 years). 18 (14.0%) were in the 13-17 years old category.			
Units: Subjects			
Children (4-12 years)	67		
Adolescents (13-17 years)	18		
Adults (≥18 years)	44		
Gender categorical			
All the patients enrolled in the study were female.			
Units: Subjects			
Female	129		
Male	0		
Race			
The majority of patients (82 [63.6%]) were White, and most (89.9%) were not Hispanic or Latino. Overall, 37 (28.7%) patients were Asian.			
Units: Subjects			
Black or African American	5		
Native Hawaiian or other Pacific Islanders	1		
White	82		
Asian	37		
Other	3		
Multiple	1		
Baseline disease characteristic			
Summary of duration of Rett syndrome by treatment group: The mean (SD) duration of Rett syndrome was numerically higher in sarizotan groups (87.90 [72.536] months in low dose sarizotan group and 97.18 [72.922] months in high dose sarizotan group) compared with placebo group (73.94 [65.800] months).			
Units: Months			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Sarizotan Low Dose
Reporting group description:	
2 mg or 5 mg bid based on age and weight criteria for 24 wks DB	
2 mg bid (4 to <13 years; ≥13 years of age and weighing <25 kg)	
5 mg bid (≥13 years of age and weighing ≥25 kg)	
Assessment of safety, tolerability and efficacy on reducing the respiratory symptoms in patients.	
Reporting group title	Sarizotan High Dose
Reporting group description:	
5 mg or 10 mg bid based on age and weight criteria for 24 wks DB	
5 mg bid (4 to <13 years; ≥13 years of age and weighing <25 kg)	
10 mg bid (≥13 years of age and weighing ≥25 kg)	
Assessment of safety, tolerability and efficacy on reducing the respiratory symptoms in patients.	
Reporting group title	Placebo
Reporting group description:	
Placebo bid for 24 wks DB	
age 4 and above	
Placebo: placebo BID followed by assessment of safety, tolerability and efficacy on reducing the respiratory symptoms in patients.	

Primary: Percent reduction (change) from baseline in the number of apnea episodes (each ≥10 seconds in duration) per hour, during awake time

End point title	Percent reduction (change) from baseline in the number of apnea episodes (each ≥10 seconds in duration) per hour, during awake time
End point description:	
The primary efficacy outcome was the percent reduction (change) from baseline in the number of apnea episodes (each ≥10 seconds in duration) per hour, during awake time obtained from the BioRadioTM. The percent change from baseline was calculated as follows: %Change from Baseline at Visit X = ([Value at Post-baseline Visit X – Baseline Value]/Baseline value)*100.	
End point type	Primary
End point timeframe:	
24 Weeks	

End point values	Sarizotan Low Dose	Sarizotan High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	56	40	
Units: percentage change in mean counts per hr				
least squares mean (standard error)	1.54 (± 10.1228)	13.211 (± 7.5075)	18.503 (± 8.441)	

Statistical analyses

Statistical analysis title	Primary efficacy analysis
Statistical analysis description:	
Primary inferential comparison between treatment groups used a restricted maximum likelihood (REML)-based, mixed-effects repeated measures model approach (MMRM) with 95% CI for the difference between treatment groups for % change from baseline in the number of apnea episodes.	
Model included % change from baseline as response, the fixed, categorical effects of treatment group, visit, treatment group-by-visit interaction, and the continuous terms age and baseline value as covariate.	
Comparison groups	Sarizotan High Dose v Placebo
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≥ 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-5.292
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.741
upper limit	17.157
Variability estimate	Standard error of the mean
Dispersion value	11.3184

Secondary: Difference between sarizotan and placebo on the mean rating of the CIC at Week 24/endpoint

End point title	Difference between sarizotan and placebo on the mean rating of the CIC at Week 24/endpoint
End point description:	
The key secondary efficacy outcome was the difference between sarizotan and placebo on the CIC from baseline, a 7-point Likert-type scale for which ratings range from 1 = very much improved to 7 = very much worse, with 4 = no change. This caregiver-rated measure considered activities, behavior, mood and functioning. This rating was performed in consultation with the study Investigator but was based largely on the caregivers' evaluation during the reporting period. The rating of the CIC was to be based on changes in the following domains:	
• Activities (watching TV, interest in conversations around her, cooperation during toileting, dressing/bathing, etc.), • Communication (verbal or by eye movements, hand movements, or head movements), • Behavior (agitation, refusal to feed, scratching, social avoidance), • Participation in family/outdoor/social events, etc.	
End point type	Secondary
End point timeframe:	
24 weeks	

End point values	Sarizotan Low Dose	Sarizotan High Dose	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	56	40	
Units: number				
arithmetic mean (standard deviation)	3.6 ($\pm$ 0.67)	3.5 ($\pm$ 1.12)	3.4 ($\pm$ 0.79)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs will be collected, from the time of signing of Informed Consent to the end of the safety follow-up period (14 days after last dose of study medication). In addition, all subjects will be followed up for 30 days after last dose for SAEs.

Adverse event reporting additional description:

Analysis population = safety

Classification of the Event: Classify the event as either serious or non-serious

Description of Signs or Symptoms: Whenever possible, record a specific diagnosis for the event

Start/stop date

Intensity (mild, moderate, severe)

Causality

Action taken with IMP

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Sarizotan Low Dose
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Reporting group description:

2 mg or 5 mg bid based on age and weight criteria for 24 wks DB

2 mg bid (4 to <13 years; ≥13 years of age and weighing <25 kg)

5 mg bid (≥13 years of age and weighing ≥25 kg)

Assessment of safety, tolerability and efficacy on reducing the respiratory symptoms in patients.

Reporting group title	Sarizotan High Dose
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Reporting group description:

5 mg or 10 mg bid based on age and weight criteria for 24 wks DB

5 mg bid (4 to <13 years; ≥13 years of age and weighing <25 kg)

10 mg bid (≥13 years of age and weighing ≥25 kg)

Assessment of safety, tolerability and efficacy on reducing the respiratory symptoms in patients.

Reporting group title	Placebo
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Reporting group description:

Placebo bid for 24 wks DB

(age 4 to <13 years; age ≥13 years and weight <25 kg; age ≥13 years and weight ≥25 kg)

Placebo: placebo BID followed by assessment of safety, tolerability and efficacy on reducing the respiratory symptoms in patients.

Serious adverse events	Sarizotan Low Dose	Sarizotan High Dose	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 33 (6.06%)	10 / 56 (17.86%)	5 / 39 (12.82%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 33 (0.00%)	1 / 56 (1.79%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Medication error			
subjects affected / exposed	0 / 33 (0.00%)	1 / 56 (1.79%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Accidental overdose			
subjects affected / exposed	0 / 33 (0.00%)	0 / 56 (0.00%)	2 / 39 (5.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 33 (0.00%)	0 / 56 (0.00%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 33 (0.00%)	2 / 56 (3.57%)	1 / 39 (2.56%)
occurrences causally related to treatment / all	0 / 0	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Change in seizure presentation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 56 (1.79%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 33 (0.00%)	1 / 56 (1.79%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			

subjects affected / exposed	1 / 33 (3.03%)	0 / 56 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 56 (1.79%)	0 / 39 (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
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 33 (0.00%)	1 / 56 (1.79%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival hypertrophy			
subjects affected / exposed	1 / 33 (3.03%)	0 / 56 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 33 (0.00%)	1 / 56 (1.79%)	0 / 39 (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
Asthma			
subjects affected / exposed	0 / 33 (0.00%)	1 / 56 (1.79%)	0 / 39 (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
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)	1 / 56 (1.79%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection bacterial			

subjects affected / exposed	0 / 33 (0.00%)	1 / 56 (1.79%)	0 / 39 (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
Pneumonia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 56 (1.79%)	0 / 39 (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
Gingivitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 56 (0.00%)	0 / 39 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 56 (1.79%)	0 / 39 (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
Hypophagia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 56 (1.79%)	0 / 39 (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	Sarizotan Low Dose	Sarizotan High Dose	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 33 (75.76%)	46 / 56 (82.14%)	30 / 39 (76.92%)
Nervous system disorders			
Seizure			
subjects affected / exposed	8 / 33 (24.24%)	15 / 56 (26.79%)	5 / 39 (12.82%)
occurrences (all)	8	15	5
Somnolence			
subjects affected / exposed	2 / 33 (6.06%)	10 / 56 (17.86%)	6 / 39 (15.38%)
occurrences (all)	2	10	6
Psychomotor hyperactivity			

subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	1 / 56 (1.79%) 1	3 / 39 (7.69%) 3
Dystonia subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	3 / 56 (5.36%) 3	1 / 39 (2.56%) 1
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	4 / 33 (12.12%) 4	3 / 56 (5.36%) 3	0 / 39 (0.00%) 0
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	4 / 56 (7.14%) 4	4 / 39 (10.26%) 4
Constipation subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	5 / 56 (8.93%) 5	2 / 39 (5.13%) 2
Vomiting subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 5	2 / 56 (3.57%) 2	2 / 39 (5.13%) 2
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1	3 / 56 (5.36%) 3	4 / 39 (10.26%) 4
Psychiatric disorders Sleep disorder subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	4 / 56 (7.14%) 4	1 / 39 (2.56%) 1
Insomnia subjects affected / exposed occurrences (all)	3 / 33 (9.09%) 3	2 / 56 (3.57%) 2	2 / 39 (5.13%) 2
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 2	3 / 56 (5.36%) 3	3 / 39 (7.69%) 3
Upper respiratory tract infection			

subjects affected / exposed	1 / 33 (3.03%)	5 / 56 (8.93%)	1 / 39 (2.56%)
occurrences (all)	1	5	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 March 2017	The 24-week, double blind, extension treatment period of the study was converted into an open-label, extension period. Appropriate changes were made throughout the protocol related to the conversion of the double-blind extension treatment period into an open-label period, including modification of the schedule of evaluations and revision of the dose titration paradigm.
29 March 2017	• Allowed inclusion of RTT patients who were 6 to <13 years of age and weigh at least 10 kg. • Implemented a weight-based dosing paradigm for these younger patients (6 to <13 years of age) in the initial double-blind treatment period. • Allowed inclusion of patients ≥13 years of age and weighing <25 kg in the study. These patients were included with the younger patients and randomized (2:1) to sarizotan 5 mg bid (High Dose) or placebo. • Implemented a weight-based dosing paradigm for younger patients (6 to <13 years of age), as well as patients ≥13 years of age and weighing <25 kg, in the open-label extension treatment period.
02 October 2017	• The randomization scheme for patients 6 to <13 years of age was modified, to balance the randomization (1:1:1) across the 3 treatment groups (sarizotan 2 mg bid, sarizotan 5 mg bid, or placebo bid). • The CIC was modified to eliminate the inclusion of respiratory symptoms in the overall assessment of the change in the patient's condition from baseline.
02 November 2017	The primary purpose of this amendment was to allow patients who were benefitting from open label treatment with sarizotan to continue to benefit long-term. This amendment extended open-label treatment by an additional 48 weeks, for a total of 72 weeks of open label treatment.
11 February 2018	The purpose of this amendment was to allow patients older than 4 years of age, and weighing at least 10 kg, to be enrolled in the study. Previously, the lower age limit for inclusion was set at 6 years.
29 November 2018	The primary purpose of this amendment was to allow patients benefitting from open-label treatment with sarizotan for up to 72 weeks under the current protocol, to extend the treatment by another 48 weeks to a total of 120 weeks of open-label treatment.
10 December 2019	The primary purpose of this amendment was to allow patients who were benefitting from treatment with sarizotan for up to 144 weeks to continue to benefit with longer-term treatment. This amendment extended open-label treatment of 120 weeks by an additional 48 weeks, to have a total of 168 weeks of open-label treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

109 patients completed the initial 24 week double-blind placebo-controlled phase; 97 patients entered the open-label extension study. The extension period was later terminated, as the primary efficacy endpoint in the initial phase was not met
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Notes: