Clinical trial results:
Open-label, multiple dose study to evaluate the pharmacokinetics, safety and tolerability of ezogabine/retigabine as adjunctive treatment in subjects aged from 12 years to less than 18 years with partial onset seizures or Lennox-Gastaut syndrome

Summary

EudraCT number	2012-001132-60
Trial protocol	Outside EU/EEA
Global end of trial date	29 April 2013

Results information

Result version number	v1 (current)
This version publication date	27 February 2016
First version publication date	27 February 2016

Trial information

Trial identification

Sponsor protocol code	RTG113284

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01494584
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000116-PIP01-07
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	31 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 April 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To characterize the pharmacokinetic (PK) profile of repeat doses of ezogabine/retigabine IR tablet in subjects aged 12 to less than 18 years old.

Protection of trial subjects:

This pediatric PK study used minimum-volume venipuncture tubes for the PK collections in an effort to minimize blood volume sampled, and distress due to a child's visual perspective of tube size. Efforts were also made to obtain capillary blood at the time of venipuncture for validation of a PK assay to mitigate future need for venipuncture.

Subjects had standard safety testing, i.e. clinical laboratory tests, vital signs, and physical examinations; to monitor for the known retigabine/ezogabine pharmacologic effects, baseline and post-dose testing of post-void residual ultrasounds (urinary retention) and electrocardiogram (ECG) (QT prolongation) were required.

The suicidality risk with anti-epileptic drugs was assessed using the Columbia Suicide Severity Rating Scale (CSSR-S).

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	25 July 2012
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 States: 5
Worldwide total number of subjects	5
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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	5
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Enrolled participants (par.) were aged 12 years to less than 18 years with partial onset seizures or Lennox-Gastaut syndrome (LGS), and were required to be on at least 1 but not more than 3 anti-epileptic therapies without achieving complete control of their seizures.

Pre-assignment

Screening details:

A total of 5 par. who met the eligibility criteria were assigned to Regimen A (>50 kilograms [kg]) or B (30 to <=50 kg) based on body weight and entered a 2-week Screening phase, followed by a dosing phase (up to 5 weeks). Upon completion of the dosing phase, par. either entered a follow-up phase or a separate extension study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Ezogabine/Retigabine

Arm description:

Participants received an initial dose of ezogabine/retigabine 300 milligrams (mg) per day administered as 100 mg immediate release (IR) tablets three times a day (TID) orally and underwent weekly up-titration at Weeks 1, 3, and 5. Dose titration occurred no more than once per week, with participants receiving up-titrated daily doses of 450 mg (150 mg TID), 600 mg (200 mg TID), 750 mg (250 mg TID), and 900 mg (300 mg TID) at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

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

Dosage and administration details:

Initial dose of 300 milligrams (mg) per day administered as 100 mg immediate release (IR) tablets three times a day (TID) orally and underwent weekly up-titration at Weeks 1, 3, and 5. Dose titration occurred no more than once per week, with participants receiving up-titrated daily doses of 450 mg (150 mg TID), 600 mg (200 mg TID), 750 mg (250 mg TID), and 900 mg (300 mg TID) at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Number of subjects in period 1	Ezogabine/Retigabine
Started	5
Completed	4
Not completed	1
Study Closed/Terminated	1

Baseline characteristics

Reporting groups	
Reporting group title	Ezogabine/Retigabine
Reporting group description:	
Participants received an initial dose of ezogabine/retigabine 300 milligrams (mg) per day administered as 100 mg immediate release (IR) tablets three times a day (TID) orally and underwent weekly up-titration at Weeks 1, 3, and 5. Dose titration occurred no more than once per week, with participants receiving up-titrated daily doses of 450 mg (150 mg TID), 600 mg (200 mg TID), 750 mg (250 mg TID), and 900 mg (300 mg TID) at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.	

Reporting group values	Ezogabine/Retigabine	Total	
Number of subjects	5	5	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 14.6 ± 1.34	 -	
Gender categorical Units: Subjects			
Female	1	1	
Male	4	4	
Race, Customized Units: Subjects			
White-White/Caucasian/European Heritage	5	5	

End points

End points reporting groups

Reporting group title	Ezogabine/Retigabine

Reporting group description:

Participants received an initial dose of ezogabine/retigabine 300 milligrams (mg) per day administered as 100 mg immediate release (IR) tablets three times a day (TID) orally and underwent weekly up-titration at Weeks 1, 3, and 5. Dose titration occurred no more than once per week, with participants receiving up-titrated daily doses of 450 mg (150 mg TID), 600 mg (200 mg TID), 750 mg (250 mg TID), and 900 mg (300 mg TID) at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Subject analysis set title	Regimen A: Ezogabine/Retigabine (E/R) 300 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants (par.) with a body weight of >50 kilograms (kg) received a starting dose of 300 milligrams per day (mg/day) ezogabine/retigabine administered as 100 mg immediate release (IR) tablets three times a day (TID) orally and underwent weekly up-titration at a frequency of no more than once per week. The TID dosing regimen was administered at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Subject analysis set title	Regimen A: E/R 300/450 mg then 600 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Par. with a body weight of >50 kg received a starting dose of 300 mg/day ezogabine/retigabine administered as 100 mg IR tablets TID orally and underwent weekly up-titration at a frequency of no more than once per week. At week two (Day 14), par. received 450 mg/day administered as 150 mg IR tablets TID orally.At week 3 (Day 21), par. received 600 mg/day administered as 200 mg IR tablets TID orally. The TID dosing regimen was administered at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Subject analysis set title	Regimen A: E/R 300/450/ 600/750 mg then 900 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Par. with a body weight of >50 kg received a starting dose of 300 mg/day ezogabine/retigabine administered as 100 mg IR tablets TID orally and underwent weekly up-titration at a frequency of no more than once per week. At week two (Day 14), par. received 450 mg/day administered as 150 mg IR tablets TID orally. At week 3 (Day 21), par. received 600 mg/day administered as 200 mg IR tablets TID orally. At week 4 (Day 28), par. received 750 mg/day administered as 250 mg IR tablets TID orally. At week 5 (Day 35), par. received 900 mg/day administered as 300 mg IR tablets TID orally. The TID daily dosing regimen was administered at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Subject analysis set title	Regimen A: Ezogabine/Retigabine 300 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with a body weight of >50 kg received a starting dose of 300 mg/day ezogabine/retigabine administerd as 100 mg IR tablets TID orally and underwent weekly up-titration at a frequency of no more than once per week. The TID dosing regimen was administered at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Subject analysis set title	Regimen A: Ezogabine/Retigabine 300 mg, then 450 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with a body weight of >50 kg received a starting dose of 300 mg/day ezogabine/retigabine administered as 100 mg IR tablets TID orally and underwent weekly up-titration at a frequency of no more than once per week. These participants then received an uptitrated dose of 450 mg/day ezogabine/retigabine as 150 mg IR tablets TID orally. The TID daily dosing regimen was administered at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Subject analysis set title	Regimen A: Ezogabine/Retigabine 300/450 mg, then 600 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with a body weight of >50 kg received a starting dose of 300 mg/day ezogabine/retigabine administered as 100 mg IR tablets TID orally and underwent weekly up-titration at a frequency of no more than once per week. These participants received an up-titrated dose of 450 mg/day ezogabine/retigabine (as 150 mg IR tablets TID orally) initially, then received an up-titrated dose of 600

mg/day ezogabine/retigabine as 200 mg IR tablets TID orally. The TID daily dosing regimen was administered at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Subject analysis set title	Regimen A: Ezogabine/Retigabine 300/450/600 mg, then 750 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with a body weight of >50 kg received a starting dose of 300 mg/day ezogabine/retigabine as 100 mg IR tablets TID orally and underwent weekly up-titration at a frequency of no more than once per week. These participants received up-titrated doses of ezogabine/retigabine 450 mg and 600 mg (as 150 mg IR and 200 mg IR tablets, respectively, TID orally) initially, then received an up-titrated dose of 750 mg/day ezogabine/retigabine as 250 mg IR tablets TID orally. The TID daily dosing regimen was administered at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Subject analysis set title	Regimen A: Ezogabine/Retigabine 300/450/600/750, then 900 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with a body weight of >50 kg received a starting dose of 300 mg/day ezogabine/retigabine as 100 mg IR tablets TID orally and underwent weekly up-titration at a frequency of no more than once per week. These participants received up-titrated doses of ezogabine/retigabine 450 mg, 600 mg, and 750 mg (as 150 mg IR, 200 mg IR, and 250 mg IR tablets, respectively, TID orally) initially, then received an up-titrated dose of 900 mg/day ezogabine/retigabine as 300 mg IR tablets TID orally. The TID daily dosing regimen was administered at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Primary: The area under the plasma concentration-time curve over the dosing interval (AUC[0-tau]) following oral administration of ezogabine/retigabine

End point title	The area under the plasma concentration-time curve over the dosing interval (AUC[0-tau]) following oral administration of ezogabine/retigabine[1]

End point description:

The steady state pharmacokinetic profile following oral administration of ezogabine/retigabine included determining the area under the curve over the dosing interval (AUC[0-tau]). The area under the plasma concentration-time curve over the dosing interval (AUC[0-tau]) was determined using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations. Blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35 to estimate AUC(0-tau). Pharmacokinetic Population: all participants in the All Subjects Population (defined as all participants who received at least one dose of study medication) for whom a pharmacokinetic sample was obtained and analyzed.

End point type	Primary

End point timeframe:

Pre-dose and 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35

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: No statistical analysis was conducted for this end point.

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5[2]	4[3]	3[4]	
Units: hour*nanograms/milliliter (h.ng/mL)				
geometric mean (confidence interval 95%)	1680 (1162.4 to 2428.2)	2558.8 (1873.4 to 3494.8)	3783.8 (1059.6 to 13512)	

Notes:

[2] - Pharmacokinetic Population

[3] - Pharmacokinetic Population

[4] - Pharmacokinetic Population

Statistical analyses

No statistical analyses for this end point

Primary: Apparent clearance (CL/F) following oral administration of ezogabine/retigabine

End point title	Apparent clearance (CL/F) following oral administration of ezogabine/retigabine[5]

End point description:

Clearance (CL/F) is defined as dose/AUC(0-tau). Blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35 to estimate CL/F.

End point type	Primary

End point timeframe:

Pre-dose and 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35

Notes:

[5] - 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: No statistical analysis was conducted for this end point.

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5[6]	4[7]	3[8]	
Units: Liters/Hour				
geometric mean (confidence interval 95%)	178.6 (123.5 to 258.1)	234.5 (171.7 to 320.3)	237.9 (66.6 to 849.4)	

Notes:

[6] - Pharmacokinetic Population

[7] - Pharmacokinetic Population

[8] - Pharmacokinetic Population

Statistical analyses

No statistical analyses for this end point

Primary: Maximum observed concentration (Cmax) and pre-dose (trough) concentration at the end of the dosing interval (Ctau) following oral administration of ezogabine/retigabine

End point title	Maximum observed concentration (Cmax) and pre-dose (trough) concentration at the end of the dosing interval (Ctau) following oral administration of ezogabine/retigabine[9]

End point description:

Cmax is defined as the first occurrence of the maximum observed plasma concentration. Ctau refers to the pre-dose (trough) concentration after the dosing interval which is equal to the minimum observed concentration (Cmin) at Steady State. Blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35 to estimate Cmax and Ctau.

End point type	Primary

End point timeframe:

Pre-dose and 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35

Notes:

[9] - 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: No statistical analysis was conducted for this end point.rmed.

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5[10]	4[11]	3[12]	
Units: Nanograms/milliliter (ng/mL)				
geometric mean (confidence interval 95%)				
Cmax	370 (260.9 to 524.7)	535.9 (344.4 to 833.8)	750.9 (289.8 to 1945.3)	
Ctau	105.32 (58.7 to 188.98)	199.77 (140.67 to 283.72)	287.48 (44.38 to 1862.12)	

Notes:

[10] - Pharmacokinetic Population

[11] - Pharmacokinetic Population

[12] - Pharmacokinetic Population

Statistical analyses

No statistical analyses for this end point

Primary: Apparent volume of distribution (Vd/F) following oral administration of ezogabine/retigabine

End point title	Apparent volume of distribution (Vd/F) following oral administration of ezogabine/retigabine[13]

End point description:

The volume of distribution (Vd/F) is defined as MRT*CL/F, where MRT is the mean residence time (calculated as AUMC[0-tau]/AUC[0-tau], where AUMC[0-tau] is the area under the first moment curve determined as the area under the concentration*time versus time curve). Blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35 to estimate the apparent volume of distribution. “Not Applicable (NA)” data is presented as “99999".

End point type	Primary

End point timeframe:

Pre-dose and 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35

Notes:

[13] - 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: No statistical analysis was conducted for this end point.

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3[14]	3[15]	1[16]	
Units: Liters				
geometric mean (confidence interval 95%)	1130.9 (511.1 to 2502.1)	2118 (539.4 to 8315.8)	1934.3 (-99999 to 99999)	

Notes:

[14] - Pharmacokinetic Population. Only those par. available at the specified time points were analyzed.

[15] - Pharmacokinetic Population. Only those par. available at the specified time points were analyzed.

[16] - Pharmacokinetic Population. Only those par. available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any adverse event (AE)

End point title	Number of participants with any adverse event (AE)

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product.

End point type	Secondary

End point timeframe:

From the start of the first titration until follow-up (assessed up to 46 days)

End point values	Regimen A: Ezogabine/Retigabine 300 mg	Regimen A: Ezogabine/Retigabine 300 mg, then 450 mg	Regimen A: Ezogabine/Retigabine 300/450 mg, then 600 mg	Regimen A: Ezogabine/Retigabine 300/450/600 mg, then 750 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[17]	5[18]	4[19]	4[20]
Units: Participants	1	1	1	0

Notes:

[17] - All Subjects Population: all participants who received at least one dose of study medication

[18] - All Subjects Population: all participants who received at least one dose of study medication

[19] - All Subjects Population: all participants who received at least one dose of study medication

[20] - All Subjects Population: all participants who received at least one dose of study medication

End point values	Regimen A: Ezogabine/Retigabine 300/450/600/750, then 900 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	3[21]			
Units: Participants	0			

Notes:

[21] - All Subjects Population: all participants who received at least one dose of study medication

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in albumin and total protein at Day 7 post each up-titration

End point title	Change from baseline in albumin and total protein at Day 7 post each up-titration

End point description:

Change from baseline was calculated 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 35 for up-titration to 900 mg/day dose) by subtracting the baseline value from the individual post-dose values. Baseline is defined as the Screening visit. Only those participants available at the specified time points were analyzed (represented by n=X, X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Baseline (Screening), Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5[22]	4[23]	3[24]	
Units: Grams per Liter (G/L)				
arithmetic mean (standard deviation)				
Albumin, n=4, 4, 3	-3.8 (± 0.96)	-3 (± 3.46)	-0.7 (± 3.06)	
Total protein, n=4, 4, 3	-4 (± 2.94)	-3.5 (± 3.79)	-0.7 (± 5.03)	

Notes:

[22] - All Subjects Population

[23] - All Subjects Population

[24] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in alkaline phosphatase, alanine amino transferase, aspartate amino transferase, and gamma glutamyl Transferase at Day 7 post each up-titration

End point title	Change from baseline in alkaline phosphatase, alanine amino transferase, aspartate amino transferase, and gamma glutamyl Transferase at Day 7 post each up-titration

End point description:

Change from baseline was calculated 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 35 for up-titration to 900 mg/day dose) by subtracting the baseline value from the individual post-dose values. Baseline is defined as the Screening visit. Only those participants available at the specified time points were analyzed (represented by n=X, X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Baseline (Screening), Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5[25]	4[26]	3[27]	
Units: International Units per Liter (IU/L)				
arithmetic mean (standard deviation)				
Alkaline phosphatase, n=4, 4, 3	-5.8 (± 16.17)	10.3 (± 35.93)	5 (± 6.93)	
Alanine amino transferase, n=4, 4, 3	-2 (± 2.16)	35 (± 74.02)	-1 (± 2)	
Aspartate amino transferase, n=4, 4, 3	-0.8 (± 2.5)	10.8 (± 17.75)	1.7 (± 3.21)	
Gamma glutamyl transferase, n=3, 3, 2	-1.3 (± 0.58)	111 (± 181.06)	50.5 (± 47.38)	

Notes:

[25] - All Subjects Population

[26] - All Subjects Population

[27] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in direct bilirubin, total bilirubin, creatinine, and uric acid at Day 7 post each up-titration

End point title	Change from baseline in direct bilirubin, total bilirubin, creatinine, and uric acid at Day 7 post each up-titration

End point description:

Change from baseline was calculated 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 35 for up-titration to 900 mg/day dose) by subtracting the baseline value from the individual post-dose values. Baseline is defined as the Screening visit. Only those participants available at the specified time points were analyzed (represented by n=X, X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population. "Not Applicable (NA)" data is presented as "99999".

End point type	Secondary

End point timeframe:

Baseline (Screening), Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5[28]	4[29]	3[30]	
Units: Micromoles per liter (UMOL/L)				
arithmetic mean (standard deviation)				
Direct bilirubin, n=1, 2, 1	2.736 (± 99999)	2.736 (± 3.86929)	-0.855 (± 99999)	
Total bilirubin, n=4, 4, 3	0.855 (± 2.2076)	2.138 (± 2.565)	4.56 (± 0.9873)	

Creatinine, n=4, 4, 3	1.326 (± 1.14124)	-4.199 (± 5.02015)	0.5893 (± 3.34677)	
Uric acid, n=4, 3, 1	16.357 (± 19.04289)	15.8613 (± 36.34288)	23.792 (± 99999)	

Notes:

[28] - All Subjects Population

[29] - All Subjects Population

[30] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in calcium, chloride, carbon dioxide content/bicarbonate, glucose, potassium, sodium, inorganic phosphorus, and urea/blood urea nitrogen (BUN) at Day 7 post each up-titration

End point title	Change from baseline in calcium, chloride, carbon dioxide content/bicarbonate, glucose, potassium, sodium, inorganic phosphorus, and urea/blood urea nitrogen (BUN) at Day 7 post each up-titration

End point description:

Change from baseline was calculated 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 35 for up-titration to 900 mg/day dose) by subtracting the baseline value from the individual post-dose values. Baseline is defined as the Screening visit. Only those participants available at the specified time points were analyzed (represented by n=X, X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population. "Not Applicable (NA)" data is presented as "99999".

End point type	Secondary

End point timeframe:

Baseline (Screening), Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5[31]	4[32]	3[33]	
Units: Millimoles per liter (MMOL/L)				
arithmetic mean (standard deviation)				
Calcium, n=4, 4, 3	0.00624 (± 0.062375)	-0.04366 (± 0.117689)	0.02495 (± 0.194866)	
Chloride, n=4, 4, 3	1.8 (± 0.96)	3 (± 0.82)	3 (± 1.73)	
Carbon dioxide content/bicarbonate, n=4, 4, 3	0.8 (± 3.5)	-1.5 (± 1.73)	-2.7 (± 2.08)	
Glucose, n=4, 4, 3	0.69388 (± 1.184069)	0.15265 (± 0.821317)	0.29605 (± 0.279394)	
Potassium, n=4, 4, 3	0.08 (± 0.206)	0.17 (± 0.574)	0.2 (± 0.624)	
Sodium, n=4, 4, 3	1.8 (± 0.5)	2 (± 1.83)	2.3 (± 3.06)	
Inorganic phosphorus, n=4, 3, 1	-0.39555 (± 0.727481)	-0.04305 (± 0.189202)	0.09687 (± 99999)	
Urea/BUN, n=4, 4, 3	-0.357 (± 1.23668)	0.714 (± 0.714)	1.309 (± 0.74315)	

Notes:

[31] - All Subjects Population

[32] - All Subjects Population

[33] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in basophils, eosinophils, lymphocytes, monocytes, total neutrophils (total ANC [total absolute neutrophil count]), platelet count, and white blood cell count at Day 7 post each up-titration

End point title	Change from baseline in basophils, eosinophils, lymphocytes, monocytes, total neutrophils (total ANC [total absolute neutrophil count]), platelet count, and white blood cell count at Day 7 post each up-titration

End point description:

Change from baseline was calculated 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 35 for up-titration to 900 mg/day dose) by subtracting the baseline value from the individual post-dose values. Baseline is defined as the Screening visit. Only those participants available at the specified time points were analyzed (represented by n=X, X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Baseline (Screening), Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5[34]	4[35]	3[36]	
Units: Giga (10^9) per liter (GI/L)				
arithmetic mean (standard deviation)				
Basophils, n=3, 3, 2	0.03 (± 0.062)	0.04 (± 0.053)	0 (± 0.006)	
Eosinophils, n=3, 3, 2	0.07 (± 0.059)	0.09 (± 0.2)	0.1 (± 0.005)	
Lymphocytes, n=3, 3, 2	14.77 (± 26.358)	-0.45 (± 0.654)	-0.65 (± 0.918)	
Monocytes, n=3, 3, 2	-0.04 (± 0.347)	0.09 (± 0.101)	0.05 (± 0.065)	
Total neutrophils, n=3, 3, 2	14.9 (± 24.176)	-0.11 (± 0.37)	0.61 (± 0.263)	
Platelet count, n=4, 4, 3	-17 (± 40.12)	-15.8 (± 34.32)	-1.3 (± 17.16)	
White blood cell count, n=4, 4, 3	0.393 (± 1.2125)	-0.6 (± 0.6272)	-0.583 (± 1.3345)	

Notes:

[34] - All Subjects Population

[35] - All Subjects Population

[36] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in hemoglobin and mean corpuscle hemoglobin concentration at Day 7 post each up-titration

End point title	Change from baseline in hemoglobin and mean corpuscle hemoglobin concentration at Day 7 post each up-titration

End point description:

Change from baseline was calculated 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 35 for up-titration to 900 mg/day dose) by subtracting the baseline value from the individual post-dose values. Baseline is defined as the Screening visit. Only those participants available at the specified time points were analyzed (represented by n=X, X, X in the category titles). Different participants may have been analyzed for different parameters, so the overall number of participants analyzed reflects everyone in the All Subjects Population.

End point type	Secondary

End point timeframe:

Baseline (Screening), Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5[37]	4[38]	3[39]	
Units: Grams per liter (G/L)				
arithmetic mean (standard deviation)				
Hemoglobin, n=4, 4, 3	-3 (± 4.9)	-10.3 (± 6.85)	-2 (± 4.36)	
Mean corpuscle hemoglobin concentration, n=4, 4, 3	-2.5 (± 2.38)	0.3 (± 10.59)	-6.7 (± 4.93)	

Notes:

[37] - All Subjects Population

[38] - All Subjects Population

[39] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in hematocrit at Day 7 post each up-titration

End point title	Change from baseline in hematocrit at Day 7 post each up-titration

End point description:

Change from baseline was calculated 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 35 for up-titration to 900 mg/day dose) by subtracting the baseline value from the individual post-dose values. Baseline is defined as the Screening visit.

End point type	Secondary

End point timeframe:

Baseline (Screening), Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4[40]	4[41]	3[42]	
Units: Fraction of one unit (1)				
arithmetic mean (standard deviation)	-0.0057 (± 0.01452)	-0.0303 (± 0.02198)	0.0017 (± 0.1201)	

Notes:

[40] - All Subjects Population. Only those participants available at the specified time point were analyzed

[41] - All Subjects Population. Only those participants available at the specified time point were analyzed

[42] - All Subjects Population. Only those participants available at the specified time point were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean corpuscle hemoglobin at Day 7 post each up-titration

End point title	Change from baseline in mean corpuscle hemoglobin at Day 7 post each up-titration

End point description:

Change from baseline was calculated 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 35 for up-titration to 900 mg/day dose) by subtracting the baseline value from the individual post-dose values. Baseline is defined as the Screening visit.

End point type	Secondary

End point timeframe:

Baseline (Screening), Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4[43]	4[44]	3[45]	
Units: Picograms per cell (PG/cell)				
arithmetic mean (standard deviation)	-0.07 (± 0.126)	0.15 (± 0.569)	-0.23 (± 0.153)	

Notes:

[43] - All Subjects Population. Only those participants available at the specified time point were analyzed

[44] - All Subjects Population. Only those participants available at the specified time point were analyzed

[45] - All Subjects Population. Only those participants available at the specified time point were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in mean corpuscle volume at Day 7 post each up-titration

End point title	Change from baseline in mean corpuscle volume at Day 7 post each up-titration

End point description:

Change from baseline was calculated 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 35 for up-titration to 900 mg/day dose) by subtracting the baseline value from the individual post-dose values. Baseline is defined as the Screening visit.

End point type	Secondary

End point timeframe:

Baseline (Screening), Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4[46]	4[47]	3[48]	
Units: Femtoliters (FL)				
arithmetic mean (standard deviation)	0.52 (± 1.056)	0.45 (± 1.034)	1 (± 1)	

Notes:

[46] - All Subjects Population. Only those participants available at the specified time point were analyzed

[47] - All Subjects Population. Only those participants available at the specified time point were analyzed

[48] - All Subjects Population. Only those participants available at the specified time point were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in red blood cell count at Day 7 post each up-titration

End point title	Change from baseline in red blood cell count at Day 7 post each up-titration

End point description:

Change from baseline was calculated 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 35 for up-titration to 900 mg/day dose) by subtracting the baseline value from the individual post-dose values. Baseline is defined as the Screening visit.

End point type	Secondary

End point timeframe:

Baseline (Screening), Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	4[49]	4[50]	3[51]	
Units: 10^12 cells/L (TI/L)				
arithmetic mean (standard deviation)	-0.09 (± 0.1463)	-0.357 (± 0.2304)	-0.03 (± 0.1136)	

Notes:

[49] - All Subjects Population. Only those participants available at the specified time point were analyzed
[50] - All Subjects Population. Only those participants available at the specified time point were analyzed
[51] - All Subjects Population. Only those participants available at the specified time point were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated urinalysis parameter dipstick test results from Screening to Follow-up

End point title	Number of participants with the indicated urinalysis parameter dipstick test results from Screening to Follow-up

End point description:

Urinalysis parameters analyzed included: urine occult blood (UOB), urine glucose (UG), urine ketones (UK), and urine protein (UP). The dipstick was a strip used to detect the presence or absence of these parameters in the urine sample. The dipstick test provides results in a semi-quantitative manner, and results can be read as negative (Neg), Trace, and 80, indicating proportional concentrations in the urine sample. Urinalysis parameters were assessed at Titration 1 (T1; 300 mg/day), Titration 2 (T2; 450 mg/day), Titration 3 (T3; 600 mg/day), Titration 4 (T4; 750 mg/day), and Titration 5 (T5; 900 mg/day). Only those participants available at the specified time points were analyzed (represented by n=X, X, X, X, X in the category titles). Different participants may have been analyzed at different time points and for different parameters, so the overall number of participants analyzed reflects everyone in the ASP.

End point type	Secondary

End point timeframe:

Screening, Day 1 (D1), Day 7 (D7), Day 14 (D14), Day 21 (D21), Day 28 (D28), Day 35 (D35), and at the Follow-up Visit (up to Day 46)

End point values	Regimen A: Ezogabine/Retigabine 300 mg	Regimen A: Ezogabine/Retigabine 300 mg, then 450 mg	Regimen A: Ezogabine/Retigabine 300/450 mg, then 600 mg	Regimen A: Ezogabine/Retigabine 300/450/600 mg, then 750 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[52]	5[53]	4[54]	4[55]
Units: Participants				
UOB, T1, D1, 80, n=5, 0, 0, 0, 0	0	0	0	0
UOB, T1, D1, Negative, n=5, 0, 0, 0, 0	4	0	0	0
UOB, T1, D1, Trace, n=5, 0, 0, 0, 0	1	0	0	0
UOB, T1, D7, 80, n=5, 0, 0, 0, 0	0	0	0	0
UOB, T1, D7, Negative, n=5, 0, 0, 0, 0	4	0	0	0
UOB, T1, D7, Trace, n=5, 0, 0, 0, 0	1	0	0	0
UOB, T2, D7, 80, n=0, 5, 0, 0, 0	0	0	0	0
UOB, T2, D7, Negative, n=0, 5, 0, 0, 0	0	5	0	0
UOB, T2, D7, Trace, n=0, 5, 0, 0, 0	0	0	0	0
UOB, T3, D7, 80, n=0, 0, 4, 0, 0	0	0	0	0
UOB, T3, D7, Negative, n=0, 0, 4, 0, 0	0	0	3	0
UOB, T3, D7, Trace, n=0, 0, 4, 0, 0	0	0	1	0
UOB, T3, D14, 80, n=0, 0, 1, 0, 0	0	0	0	0
UOB, T3,D14, Negative, n=0, 0, 1, 0, 0	0	0	1	0
UOB, T3, D14, Trace, n=0, 0, 1, 0, 0	0	0	0	0

Urine Occult Blood, T4, D7, 80, n=0,0,0,3,0	0	0	0	0
UOB, T4, D7, Negative, n=0, 0, 0, 3, 0	0	0	3	0
Urine Occult Blood, T4, D7, Trace, n=0,0,0,3,0	0	0	0	0
UOB, T5, D7, 80, n=0, 0, 0, 0, 3	0	0	0	0
UOB, T5, D7, Negative, n=0, 0, 0, 0, 3	0	0	0	0
UOB, T5, D7, Trace, n=0, 0, 0, 0, 3	0	0	0	0
UG, T1, D1, 80, n=5, 0, 0, 0, 0	0	0	0	0
UG, T1, D1, Negative, n=5, 0, 0, 0, 0	5	0	0	0
UG, T1, D1, Trace, n=5, 0, 0, 0, 0	0	0	0	0
UG, T1, D7, 80, n=5, 0, 0, 0, 0	0	0	0	0
UG, T1, D7, Negative, n=5, 0, 0, 0, 0	5	0	0	0
UG, T1, D7, Trace, n=5, 0, 0, 0, 0	0	0	0	0
UG, T2, D7, 80, n=0, 5, 0, 0, 0	0	0	0	0
UG, T2, D7, Negative, n=0, 5, 0, 0, 0	0	5	0	0
UG, T2, D7, Trace, n=0, 5, 0, 0, 0	0	0	0	0
UG, T3, D7, 80, n=0, 0, 4, 0, 0	0	0	0	0
UG, T3, D7, Negative, n=0, 0, 4, 0, 0	0	0	4	0
UG, T3, D7, Trace, n=0, 0, 4, 0, 0	0	0	0	0
UG, T3, D14, 80, n=0, 0,1,0,0	0	0	0	0
UG, T3, D14, Negative, n=0, 0, 1, 0, 0	0	0	1	0
UG, T3, D14, Trace, n=0, 0, 1, 0, 0	0	0	0	0
UG, T4, D7, 80, n=0, 0, 0, 4, 0	0	0	0	0
UG, T4, D7, Negative, n=0, 0, 0, 4, 0	0	0	0	4
UG, T4, D7, Trace, n=0, 0, 0, 4, 0	0	0	0	0
UG, T5, D7, 80, n=0, 0, 0, 0, 3	0	0	0	0
UG, T5, D7, Negative, n=0, 0, 0, 0, 3	0	0	0	0
UG, T5, D7, Trace, n=0, 0, 0, 0, 3	0	0	0	0
UK, T1, D1, 80, n=5, 0, 0, 0, 0	0	0	0	0
UK, T1, D1, Negative, n=5, 0, 0, 0, 0	5	0	0	0
UK, T1, D1, Trace, n=5, 0, 0, 0, 0	0	0	0	0
UK, T1, D7, 80, n=5, 0, 0, 0, 0	0	0	0	0
UK, T1, D7, Negative, n=5, 0, 0, 0, 0	5	0	0	0
UK, T1, D7, Trace, n=5, 0, 0, 0, 0	0	0	0	0
UK, T2, D7, 80, n=0, 5, 0, 0, 0	0	1	0	0
UK, T2, D7, Negative, n=0, 5, 0, 0, 0	0	3	0	0
UK, T2, D7, Trace, n=0, 5, 0, 0, 0	0	1	0	0
UK, T3, D7, 80, n=0, 0, 4, 0, 0	0	0	0	0
UK, T3, D7, Negative, n=0, 0, 4, 0, 0	0	0	4	0
UK, T3, D7, Trace, n=0, 0, 4, 0, 0	0	0	0	0
UK, T3, D14, 80, n=0, 0, 1, 0, 0	0	0	0	0
UK, T3, D14, Negative, n=0, 0, 1, 0, 0	0	0	1	0
UK, T3, D14, Trace, n=0, 0, 1, 0, 0	0	0	0	0
UK, T4, D7, 80, n=0, 0, 0, 4, 0	0	0	0	0
UK, T4, D7, Negative, n=0, 0, 0, 4, 0	0	0	0	4
UK, T4, D7, Trace, n=0, 0, 0, 4, 0	0	0	0	0
UK, T5, D7, 80, n=0, 0, 0, 0, 3	0	0	0	0
UK, T5, D7, Negative, n=0, 0, 0, 0, 3	0	0	0	0
UK, T5, D7, Trace, n=0, 0, 0, 0, 3	0	0	0	0
UP, T1, D1, 80, n=5, 0, 0, 0, 0	0	0	0	0
UP, T1, D1, Negative, n=5, 0, 0, 0, 0	4	0	0	0

UP, T1, D1, Trace, n=5, 0, 0, 0, 0	1	0	0	0
UP, T1, D7, 80, n=5, 0, 0, 0, 0	0	0	0	0
UP, T1, D7, Negative, n=5, 0, 0, 0, 0	5	0	0	0
UP, T1, D7, Trace, n=5, 0, 0, 0, 0	0	0	0	0
UP, T2, D7, 80, n=0, 5, 0, 0, 0	0	0	0	0
UP T2, D7, Negative, n=0, 5, 0, 0, 0	0	4	0	0
UP, T2, D7, Trace, n=0, 5, 0, 0, 0	0	1	0	0
UP, T3, D7, 80, n=0, 0, 4, 0,0	0	0	0	0
UP, T3, D7, Negative, n=0, 0, 4, 0, 0	0	0	3	0
UP, T3, D7, Trace, n=0, 0, 4, 0, 0	0	0	1	0
UP, T3, D14, 80, n=0, 0, 1, 0, 0	0	0	0	0
UP, T3, D14, Negative, n=0, 0, 1, 0, 0	0	0	1	0
UP, T3, D14, Trace, n=0, 0, 1, 0, 0	0	0	0	0
UP, T4, D7, 80, n=0, 0, 0, 4, 0	0	0	0	0
UP, T4, D7, Negative, n=0, 0, 0, 4, 0	0	0	0	4
UP, T4, D7, Trace, n=0, 0, 0, 4, 0	0	0	0	0
UP, T5, D7, 80, n=0, 0, 0, 0, 3	0	0	0	0
UP, T5, D7, Negative, n=0, 0, 0, 0, 3	0	0	0	0
UP, T5, D7, Trace, n=0, 0, 0, 0, 3	0	0	0	0

Notes:

[52] - All Subjects Population (ASP)

[53] - All Subjects Population (ASP)

[54] - All Subjects Population (ASP)

[55] - All Subjects Population (ASP)

End point values	Regimen A: Ezogabine/Retigabine 300/450/600/750, then 900 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	3[56]			
Units: Participants				
UOB, T1, D1, 80, n=5, 0, 0, 0, 0	0			
UOB, T1, D1, Negative, n=5, 0, 0, 0, 0	0			
UOB, T1, D1, Trace, n=5, 0, 0, 0, 0	0			
UOB, T1, D7, 80, n=5, 0, 0, 0, 0	0			
UOB, T1, D7, Negative, n=5, 0, 0, 0, 0	0			
UOB, T1, D7, Trace, n=5, 0, 0, 0, 0	0			
UOB, T2, D7, 80, n=0, 5, 0, 0, 0	0			
UOB, T2, D7, Negative, n=0, 5, 0, 0, 0	0			
UOB, T2, D7, Trace, n=0, 5, 0, 0, 0	0			
UOB, T3, D7, 80, n=0, 0, 4, 0, 0	0			
UOB, T3, D7, Negative, n=0, 0, 4, 0, 0	0			
UOB, T3, D7, Trace, n=0, 0, 4, 0, 0	0			
UOB, T3, D14, 80, n=0, 0, 1, 0, 0	0			
UOB, T3,D14, Negative, n=0, 0, 1, 0, 0	0			
UOB, T3, D14, Trace, n=0, 0, 1, 0, 0	0			
Urine Occult Blood, T4, D7, 80, n=0,0,0,3,0	0			
UOB, T4, D7, Negative, n=0, 0, 0, 3, 0	0			
Urine Occult Blood, T4, D7, Trace, n=0,0,0,3,0	0			

UOB, T5, D7, 80, n=0, 0, 0, 0, 3	0			
UOB, T5, D7, Negative, n=0, 0, 0, 0, 3	2			
UOB, T5, D7, Trace, n=0, 0, 0, 0, 3	1			
UG, T1, D1, 80, n=5, 0, 0, 0, 0	0			
UG, T1, D1, Negative, n=5, 0, 0, 0, 0	0			
UG, T1, D1, Trace, n=5, 0, 0, 0, 0	0			
UG, T1, D7, 80, n=5, 0, 0, 0, 0	0			
UG, T1, D7, Negative, n=5, 0, 0, 0, 0	0			
UG, T1, D7, Trace, n=5, 0, 0, 0, 0	0			
UG, T2, D7, 80, n=0, 5, 0, 0, 0	0			
UG, T2, D7, Negative, n=0, 5, 0, 0, 0	0			
UG, T2, D7, Trace, n=0, 5, 0, 0, 0	0			
UG, T3, D7, 80, n=0, 0, 4, 0, 0	0			
UG, T3, D7, Negative, n=0, 0, 4, 0, 0	0			
UG, T3, D7, Trace, n=0, 0, 4, 0, 0	0			
UG, T3, D14, 80, n=0, 0,1,0,0	0			
UG, T3, D14, Negative, n=0, 0, 1, 0, 0	0			
UG, T3, D14, Trace, n=0, 0, 1, 0, 0	0			
UG, T4, D7, 80, n=0, 0, 0, 4, 0	0			
UG, T4, D7, Negative, n=0, 0, 0, 4, 0	0			
UG, T4, D7, Trace, n=0, 0, 0, 4, 0	0			
UG, T5, D7, 80, n=0, 0, 0, 0, 3	0			
UG, T5, D7, Negative, n=0, 0, 0, 0, 3	3			
UG, T5, D7, Trace, n=0, 0, 0, 0, 3	0			
UK, T1, D1, 80, n=5, 0, 0, 0, 0	0			
UK, T1, D1, Negative, n=5, 0, 0, 0, 0	0			
UK, T1, D1, Trace, n=5, 0, 0, 0, 0	0			
UK, T1, D7, 80, n=5, 0, 0, 0, 0	0			
UK, T1, D7, Negative, n=5, 0, 0, 0, 0	0			
UK, T1, D7, Trace, n=5, 0, 0, 0, 0	0			
UK, T2, D7, 80, n=0, 5, 0, 0, 0	0			
UK, T2, D7, Negative, n=0, 5, 0, 0, 0	0			
UK, T2, D7, Trace, n=0, 5, 0, 0, 0	0			
UK, T3, D7, 80, n=0, 0, 4, 0, 0	0			
UK, T3, D7, Negative, n=0, 0, 4, 0, 0	0			
UK, T3, D7, Trace, n=0, 0, 4, 0, 0	0			
UK, T3, D14, 80, n=0, 0, 1, 0, 0	0			
UK, T3, D14, Negative, n=0, 0, 1, 0, 0	0			
UK, T3, D14, Trace, n=0, 0, 1, 0, 0	0			
UK, T4, D7, 80, n=0, 0, 0, 4, 0	0			
UK, T4, D7, Negative, n=0, 0, 0, 4, 0	0			
UK, T4, D7, Trace, n=0, 0, 0, 4, 0	0			
UK, T5, D7, 80, n=0, 0, 0, 0, 3	0			
UK, T5, D7, Negative, n=0, 0, 0, 0, 3	3			
UK, T5, D7, Trace, n=0, 0, 0, 0, 3	0			
UP, T1, D1, 80, n=5, 0, 0, 0, 0	0			
UP, T1, D1, Negative, n=5, 0, 0, 0, 0	0			
UP, T1, D1, Trace, n=5, 0, 0, 0, 0	0			
UP, T1, D7, 80, n=5, 0, 0, 0, 0	0			
UP, T1, D7, Negative, n=5, 0, 0, 0, 0	0			
UP, T1, D7, Trace, n=5, 0, 0, 0, 0	0			
UP, T2, D7, 80, n=0, 5, 0, 0, 0	0			

UP T2, D7, Negative, n=0, 5, 0, 0, 0	0			
UP, T2, D7, Trace, n=0, 5, 0, 0, 0	0			
UP, T3, D7, 80, n=0, 0, 4, 0,0	0			
UP, T3, D7, Negative, n=0, 0, 4, 0, 0	0			
UP, T3, D7, Trace, n=0, 0, 4, 0, 0	0			
UP, T3, D14, 80, n=0, 0, 1, 0, 0	0			
UP, T3, D14, Negative, n=0, 0, 1, 0, 0	0			
UP, T3, D14, Trace, n=0, 0, 1, 0, 0	0			
UP, T4, D7, 80, n=0, 0, 0, 4, 0	0			
UP, T4, D7, Negative, n=0, 0, 0, 4, 0	0			
UP, T4, D7, Trace, n=0, 0, 0, 4, 0	0			
UP, T5, D7, 80, n=0, 0, 0, 0, 3	0			
UP, T5, D7, Negative, n=0, 0, 0, 0, 3	3			
UP, T5, D7, Trace, n=0, 0, 0, 0, 3	0			

Notes:

[56] - All Subjects Population (ASP)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in 28-day seizure frequency rate

End point title	Percent change from baseline in 28-day seizure frequency rate

End point description:

Participants or their caregivers recorded the number of seizures experienced by the participant, by seizure type (e.g., simple partial seizure [seizure that affects only a small region of the brain; consciousness is unaffected], complex partial seizure [seizure associated with unilateral cerebral hemisphere involvement and causing impairment of awareness or responsiveness], etc.), as well as by duration of episodes of innumerable seizure activity, in their daily diaries during all phases of this study. Percent change from baseline (BL) is defined as 100 * (rate in a given period minus the baseline rate) / (baseline rate). baseline seizures are defined as those seizures that occurred after Screening and before the start of the treatment. Post-baseline seizures are defined as those seizures that occurred from the start of the treatment until the start of Follow-up. Seizure frequency rate was computed as: 28 * (number of seizures during given period / number of days in given period).

End point type	Secondary

End point timeframe:

Baseline (Screening) and until Follow-up or early discontinuation (assessed up to 46 days)

End point values	Regimen A: Ezogabine/Retigabine 300/450/600/750, then 900 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	5[57]			
Units: Percent change				
arithmetic mean (standard deviation)	-41.5 (± 29.95)			

Notes:

[57] - All Subjects Population. Only par. with BL and post-BL seizure measurements were included.

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable concentration (AUC [0-t]) for the n-acetyl metabolite of ezogabine/retigabine

End point title	Area under the concentration-time curve from time zero (pre-dose) to the last time of quantifiable concentration (AUC [0-t]) for the n-acetyl metabolite of ezogabine/retigabine

End point description:

The area under the curve was determined using the linear trapezoidal rule for increasing concentrations and the logarithmic trapezoidal rule for decreasing concentrations. Blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35 to assess the plasma n-acetyl metabolite (NAMR) of ezogabine/retigabine following oral administration of ezogabine/retigabine.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5[58]	4[59]	3[60]	
Units: h*ng/mL				
geometric mean (confidence interval 95%)	2222.1 (1531.4 to 3224.4)	3479.2 (2374 to 5099)	5000.6 (1528.9 to 16355.7)	

Notes:

[58] - PK Population

[59] - PK Population

[60] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose (trough) concentration at the end of the dosing interval (Ctau) for the n-acetyl metabolite of ezogabine/retigabine

End point title	Pre-dose (trough) concentration at the end of the dosing interval (Ctau) for the n-acetyl metabolite of ezogabine/retigabine

End point description:

Ctau refers to the pre-dose (trough) concentration at the end of the dosing interval which is equivalent to the minimum observed concentration (Cmin) at Steady State. Blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35 to assess the Ctau for n-acetyl metabolite (NAMR) of ezogabine/retigabine following oral administration of ezogabine/retigabine.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5[61]	4[62]	3[63]	
Units: ng/mL				
geometric mean (confidence interval 95%)	170.51 (86.32 to 336.82)	307.85 (190.25 to 498.14)	415.66 (120.74 to 1430.93)	

Notes:

[61] - PK Population

[62] - PK Population

[63] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum concentration (Tmax) following oral administration of ezogabine/retigabine

End point title	Time to maximum concentration (Tmax) following oral administration of ezogabine/retigabine

End point description:

Blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35 to assess plasma Tmax.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	5[64]	4[65]	3[66]	
Units: hours				
median (full range (min-max))	1 (0.5 to 1.08)	1.55 (0.5 to 8)	2 (0.5 to 6)	

Notes:

[64] - PK Population

[65] - PK Population

[66] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma half life at steady state (t1/2) following oral administration of ezogabine/retigabine

End point title	Plasma half life at steady state (t1/2) following oral administration of ezogabine/retigabine

End point description:

Blood samples were collected at pre-dose and at 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35 to assess plasma t1/2. Steady-state t1/2 is derived as (Vd/F) / (CL/F), where Vd/F is defined as the apparent volume of distribution after extravascular (e.g., oral) administration, and CL/F is defined as the apparent clearance following oral dosing. "Not Applicable (NA)" data is presented as "99999".

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 1.5, 2, 4, 6, and 8 hours post-dose on Day 7, Day 21, and Day 35

End point values	Regimen A: Ezogabine/Retigabine (E/R) 300 mg	Regimen A: E/R 300/450 mg then 600 mg	Regimen A: E/R 300/450/600/750 mg then 900 mg	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	3[67]	3[68]	1[69]	
Units: hours				
geometric mean (confidence interval 95%)	4.168 (2.363 to 7.35)	5.897 (0.962 to 36.16)	3.473 (-99999 to 99999)	

Notes:

[67] - PK Population. Only those participants available at the indicated time point were analyzed.

[68] - PK Population. Only those participants available at the indicated time point were analyzed.

[69] - PK Population. Only those participants available at the indicated time point were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal electrocardiogram (ECG) findings

End point title	Number of participants with abnormal electrocardiogram (ECG) findings

End point description:

An ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QT interval corrected for heart rate (QTc intervals) was used. Measurements were taken 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 14 for up-titration to 450 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 28 for up-titration to 750 mg/day dose; Day 35 for up-titration to 900 mg/day dose). ECG parameters were assessed at Titration 1 (T1; 300 mg/day): Day 1 pre-dose, Day 1 at 3 hours (h), pre-dose, and 3 h post-dose. Titration 2 (T2; 450 mg/day): Day 7. Titration 3 (T3; 600 mg/day): pre-dose and 3 h post-dose. Titration 3 Dose Held (T3DH): pre-dose. Titration 4 (T4; 750 mg/day): Day 7. Titration 5 (T5; 900 mg/day): pre-dose and 3 h post-dose. The number of participants with abnormal (Abn) clinically significant (CS) and not clinically significant (NCS) ECG findings was recorded. The investigator determined if an ECG finding was CS or NCS.

End point type	Secondary

End point timeframe:

Baseline (Screening) and Day 7 post up-titration, up to Day 35

End point values	Regimen A: Ezogabine/Retigabine 300 mg	Regimen A: Ezogabine/Retigabine 300 mg, then 450 mg	Regimen A: Ezogabine/Retigabine 300/450 mg, then 600 mg	Regimen A: Ezogabine/Retigabine 300/450/600 mg, then 750 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[70]	5[71]	4[72]	4[73]
Units: Participants				
T1, Day 1 pre-dose, Abn NCS, n=5, 0, 0, 0, 0	0	0	0	0
T1, Day 1 pre-dose, Abn CS, n=5, 0, 0, 0, 0	0	0	0	0
T1, Day 1, 3 h, Abn NCS, n=5, 0, 0, 0, 0	0	0	0	0
T1, Day 1, 3 h, Abn CS, n=5, 0, 0, 0, 0	0	0	0	0
T1, pre-dose, Abn NCS, n=5, 0, 0, 0, 0	0	0	0	0
T1, pre-dose, Abn CS, n=5, 0, 0, 0, 0	0	0	0	0
T1, 3 h, Abn NCS, n=5, 0, 0, 0, 0	0	0	0	0
T1, 3 h, Abn CS, n=5, 0, 0, 0, 0	0	0	0	0
T2, Day 7, Abn NCS, n=0, 5, 0, 0, 0	0	1	0	0
T2, Day 7, Abn CS, n=0, 5, 0, 0, 0	0	0	0	0
T3, pre-dose, Abn NCS, n=0, 0, 4, 0, 0	0	0	0	0
T3, pre-dose, Abn CS, n=0, 0, 4, 0, 0	0	0	0	0
T3, 3 h, Abn NCS, n=0, 0, 4, 0, 0	0	0	0	0
T3, 3 h, Abn CS, n=0, 0, 4, 0, 0	0	0	0	0
T3DH, pre-dose, Abn NCS, n=0, 0, 1, 0, 0	0	0	0	0
T3DH, pre-dose, Abn CS, n=0, 0, 1, 0, 0	0	0	0	0
T4, Day 7, Abn NCS, n=0, 0, 0, 4, 0	0	0	0	0
T4, Day 7, Abn CS, n=0, 0, 0, 4, 0	0	0	0	0
T5, pre-dose, Abn NCS, n=0, 0, 0, 0, 3	0	0	0	0
T5, pre-dose, Abn CS, n=0, 0, 0, 0, 3	0	0	0	0
T5, 3 h, Abn NCS, n=0, 0, 0, 0, 2	0	0	0	0
T5, 3 h, Abn CS, n=0, 0, 0, 0, 2	0	0	0	0

Notes:

[70] - All Subjects Population. Only those par. available at the specified time points were analyzed.

[71] - All Subjects Population. Only those par. available at the specified time points were analyzed.

[72] - All Subjects Population. Only those par. available at the specified time points were analyzed.

[73] - All Subjects Population. Only those par. available at the specified time points were analyzed.

End point values	Regimen A: Ezogabine/Retigabine 300/450/600/750, then 900 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	3[74]			
Units: Participants				
T1, Day 1 pre-dose, Abn NCS, n=5, 0, 0, 0, 0	0			
T1, Day 1 pre-dose, Abn CS, n=5, 0, 0, 0, 0	0			
T1, Day 1, 3 h, Abn NCS, n=5, 0, 0, 0, 0	0			
T1, Day 1, 3 h, Abn CS, n=5, 0, 0, 0, 0	0			

T1, pre-dose, Abn NCS, n=5, 0, 0, 0, 0	0			
T1, pre-dose, Abn CS, n=5, 0, 0, 0, 0	0			
T1, 3 h, Abn NCS, n=5, 0, 0, 0, 0	0			
T1, 3 h, Abn CS, n=5, 0, 0, 0, 0	0			
T2, Day 7, Abn NCS, n=0, 5, 0, 0, 0	0			
T2, Day 7, Abn CS, n=0, 5, 0, 0, 0	0			
T3, pre-dose, Abn NCS, n=0, 0, 4, 0, 0	0			
T3, pre-dose, Abn CS, n=0, 0, 4, 0, 0	0			
T3, 3 h, Abn NCS, n=0, 0, 4, 0, 0	0			
T3, 3 h, Abn CS, n=0, 0, 4, 0, 0	0			
T3DH, pre-dose, Abn NCS, n=0, 0, 1, 0, 0	0			
T3DH, pre-dose, Abn CS, n=0, 0, 1, 0, 0	0			
T4, Day 7, Abn NCS, n=0, 0, 0, 4, 0	0			
T4, Day 7, Abn CS, n=0, 0, 0, 4, 0	0			
T5, pre-dose, Abn NCS, n=0, 0, 0, 0, 3	1			
T5, pre-dose, Abn CS, n=0, 0, 0, 0, 3	0			
T5, 3 h, Abn NCS, n=0, 0, 0, 0, 2	0			
T5, 3 h, Abn CS, n=0, 0, 0, 0, 2	0			

Notes:

[74] - All Subjects Population. Only those par. available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the indicated time points

End point title	Change from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at the indicated time points

End point description:

Vital sign assessment included the measurement of systolic and diastolic blood pressure at Titration 1 (T1; 300 mg/day): Day 1 pre-dose, Day 1 at 3 hours (h), Day 7 pre-dose, and 3 h post dose. Titration 2 (T2; 450 mg/day): Day 7. Titration 3 (T3; 600 mg/day): Day 21 pre-dose and 3 h post-dose. Titration 3 Dose Held (T3DH): pre-dose. Titration 4 (T4; 750 mg/day): Day 7. Titration 5 (T5; 900 mg/day): Day 35 pre-dose and 3 h post-dose. Measurements were taken 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 14 for up-titration to 450 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 28 for up-titration to 750 mg/day dose; Day 35 for up-titration to 900 mg/day dose). Change from baseline was calculated by subtracting the baseline value from the individual post-dose values. Baseline is defined as as the Day 1 pre-dose value. “Not Applicable (NA)” data is presented as “99999".

End point type	Secondary

End point timeframe:

Baseline (Screening) and Day 7 post up-titration, up to Day 35

End point values	Regimen A: Ezogabine/Retigabine 300 mg	Regimen A: Ezogabine/Retigabine 300 mg, then 450 mg	Regimen A: Ezogabine/Retigabine 300/450 mg, then 600 mg	Regimen A: Ezogabine/Retigabine 300/450/600 mg, then 750 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[75]	5[76]	4[77]	4[78]
Units: Millimeters of Mercury (mmHg)				

arithmetic mean (standard deviation)				
SBP, T1, Day 1 3h, n=5, 0, 0, 0, 0	2.8 (± 6.02)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
SBP, T1, Day 7 Pre-dose, n=5, 0, 0, 0, 0	2.6 (± 5.18)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
SBP, T1, Day 7 3h, n=5, 0, 0, 0, 0	-1.2 (± 8.81)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
SBP, T2, Day 7, n=0, 5, 0, 0, 0	99999 (± 99999)	5.4 (± 4.39)	99999 (± 99999)	99999 (± 99999)
SBP, T3, Day 21 Pre-dose, n=0, 0, 4, 0, 0	99999 (± 99999)	99999 (± 99999)	11.3 (± 11.62)	99999 (± 99999)
SBP, T3, Day 21 3h, n=0, 0, 4, 0, 0	99999 (± 99999)	99999 (± 99999)	3 (± 10.68)	99999 (± 99999)
SBP, T3DH, Pre-dose, n=0, 0, 1, 0, 0	99999 (± 99999)	99999 (± 99999)	13 (± 99999)	99999 (± 99999)
SBP, T4, Day 28, n=0, 0, 0, 4, 0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	3 (± 3.27)
SBP, T5, Day 35 Pre-dose, n=0, 0, 0, 0, 3	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
SBP, T5, Day 35 3h, n=0, 0, 0, 0, 3	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
DBP, T1, Day 1 3h, n=5, 0, 0, 0, 0	1.4 (± 7.92)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
DBP, T1, Pre-dose, n=5, 0, 0, 0, 0	0.2 (± 4.6)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
DBP, T1, 3h, n=5, 0, 0, 0, 0	4.4 (± 5.81)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
DBP, T2, Day 7, n=0, 5, 0, 0, 0	99999 (± 99999)	-0.2 (± 15.55)	99999 (± 99999)	99999 (± 99999)
DBP, T3, Pre-dose, n=0, 0, 4, 0, 0	99999 (± 99999)	99999 (± 99999)	1.8 (± 4.65)	99999 (± 99999)
DBP, T3, 3h, n=0, 0, 4, 0, 0	99999 (± 99999)	99999 (± 99999)	3.8 (± 12.89)	99999 (± 99999)
DBP, T3DH, Pre-dose, n=0, 0, 1, 0, 0	99999 (± 99999)	99999 (± 99999)	23 (± 99999)	99999 (± 99999)
DBP, T4, Day 7, n=0, 0, 0, 4, 0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	-0.3 (± 2.99)
DBP, T5, Pre-dose, n=0, 0, 0, 0, 3	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
DBP, T5, 3h, n=0, 0, 0, 0, 3	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Notes:

[75] - All Subjects Population. Only those par. available at the specified time points were analyzed.

[76] - All Subjects Population. Only those par. available at the specified time points were analyzed.

[77] - All Subjects Population. Only those par. available at the specified time points were analyzed.

[78] - All Subjects Population. Only those par. available at the specified time points were analyzed.

End point values	Regimen A: Ezogabine/Retigabine 300/450/600/750, then 900 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	3[79]			
Units: Millimeters of Mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP, T1, Day 1 3h, n=5, 0, 0, 0, 0	99999 (± 99999)			

SBP, T1, Day 7 Pre-dose, n=5, 0, 0, 0, 0	99999 (± 99999)			
SBP, T1, Day 7 3h, n=5, 0, 0, 0, 0	99999 (± 99999)			
SBP, T2, Day 7, n=0, 5, 0, 0, 0	99999 (± 99999)			
SBP, T3, Day 21 Pre-dose, n=0, 0, 4, 0, 0	99999 (± 99999)			
SBP, T3, Day 21 3h, n=0, 0, 4, 0, 0	99999 (± 99999)			
SBP, T3DH, Pre-dose, n=0, 0, 1, 0, 0	99999 (± 99999)			
SBP, T4, Day 28, n=0, 0, 0, 4, 0	99999 (± 99999)			
SBP, T5, Day 35 Pre-dose, n=0, 0, 0, 0, 3	8.7 (± 13.32)			
SBP, T5, Day 35 3h, n=0, 0, 0, 0, 3	5.3 (± 10.97)			
DBP, T1, Day 1 3h, n=5, 0, 0, 0, 0	99999 (± 99999)			
DBP, T1, Pre-dose, n=5, 0, 0, 0, 0	99999 (± 99999)			
DBP, T1, 3h, n=5, 0, 0, 0, 0	99999 (± 99999)			
DBP, T2, Day 7, n=0, 5, 0, 0, 0	99999 (± 99999)			
DBP, T3, Pre-dose, n=0, 0, 4, 0, 0	99999 (± 99999)			
DBP, T3, 3h, n=0, 0, 4, 0, 0	99999 (± 99999)			
DBP, T3DH, Pre-dose, n=0, 0, 1, 0, 0	99999 (± 99999)			
DBP, T4, Day 7, n=0, 0, 0, 4, 0	99999 (± 99999)			
DBP, T5, Pre-dose, n=0, 0, 0, 0, 3	7.3 (± 12.7)			
DBP, T5, 3h, n=0, 0, 0, 0, 3	3.7 (± 16.77)			

Notes:

[79] - All Subjects Population. Only those par. available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate (HR)

End point title	Change from Baseline in heart rate (HR)

End point description:

Vital sign assessment included heart rate measurement and was assessed at Titration 1 (T1; 300 mg/day): Day 1 pre-dose, Day 1 at 3 hours (h), pre-dose and 3 h post-dose. Titration 2 (T2; 450 mg/day): Day 7. Titration 3 (T3; 600 mg/day): pre-dose and 3 h post-dose. Titration 3 Dose Held (T3DH): pre-dose. Titration 4 (T4; 750 mg/day): Day 7. Titration 5 (T5; 900 mg/day): pre-dose and 3 h post-dose. Measurements were taken 7 days after each up-titration (Day 7 for 300 mg/day dose; Day 14 for up-titration to 450 mg/day dose; Day 21 for up-titration to 600 mg/day dose; Day 28 for up-titration to 750 mg/day dose; Day 35 for up-titration to 900 mg/day dose). Change from baseline was calculated by subtracting the baseline value from the individual post-dose values. Baseline is defined as as the Day 1 pre-dose value. “Not Applicable (NA)” data is presented as “99999".

End point type	Secondary

End point timeframe:

Baseline (Screening) and Day 7 post up-titration, up to Day 35

End point values	Regimen A: Ezogabine/Retigabine 300 mg	Regimen A: Ezogabine/Retigabine 300 mg, then 450 mg	Regimen A: Ezogabine/Retigabine 300/450 mg, then 600 mg	Regimen A: Ezogabine/Retigabine 300/450/600 mg, then 750 mg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	5[80]	5[81]	4[82]	4[83]
Units: Beats per Minute (BPM)				
arithmetic mean (standard deviation)				
HR, T1, Day 1 3h, n=5, 0, 0, 0, 0	3.6 (± 11.26)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
HR, T1, Pre-dose, n=5, 0, 0, 0, 0	-0.8 (± 7.22)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
HR, T1, 3h, n=5, 0, 0, 0, 0	2.8 (± 5.89)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
HR, T2, Day 7, n=0, 5, 0, 0, 0	99999 (± 99999)	8.2 (± 11.67)	99999 (± 99999)	99999 (± 99999)
HR, T3, Pre-dose, n=0, 0, 4, 0, 0	99999 (± 99999)	99999 (± 99999)	0.5 (± 7.51)	99999 (± 99999)
HR, T3, 3h, n=0, 0, 4, 0, 0	99999 (± 99999)	99999 (± 99999)	6 (± 5.48)	99999 (± 99999)
HR, T3DH, Pre-dose, n=0, 0, 1, 0, 0	99999 (± 99999)	99999 (± 99999)	8 (± 99999)	99999 (± 99999)
HR, T4, Day 7, n=0, 0, 0, 4, 0	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	1.8 (± 6.18)
HR, T5, Pre-dose, n=0, 0, 0, 0, 3	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)
HR, T5, 3h, n=0, 0, 0, 0, 3	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)	99999 (± 99999)

Notes:

[80] - All Subjects Population. Only those par. available at the specified time points were analyzed.

[81] - All Subjects Population. Only those par. available at the specified time points were analyzed.

[82] - All Subjects Population. Only those par. available at the specified time points were analyzed.

[83] - All Subjects Population. Only those par. available at the specified time points were analyzed.

End point values	Regimen A: Ezogabine/Retigabine 300/450/600/750, then 900 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	3[84]			
Units: Beats per Minute (BPM)				
arithmetic mean (standard deviation)				
HR, T1, Day 1 3h, n=5, 0, 0, 0, 0	99999 (± 99999)			
HR, T1, Pre-dose, n=5, 0, 0, 0, 0	99999 (± 99999)			
HR, T1, 3h, n=5, 0, 0, 0, 0	99999 (± 99999)			
HR, T2, Day 7, n=0, 5, 0, 0, 0	99999 (± 99999)			
HR, T3, Pre-dose, n=0, 0, 4, 0, 0	99999 (± 99999)			

HR, T3, 3h, n=0, 0, 4, 0, 0	99999 (± 99999)			
HR, T3DH, Pre-dose, n=0, 0, 1, 0, 0	99999 (± 99999)			
HR, T4, Day 7, n=0, 0, 0, 4, 0	99999 (± 99999)			
HR, T5, Pre-dose, n=0, 0, 0, 0, 3	1.7 (± 4.16)			
HR, T5, 3h, n=0, 0, 0, 0, 3	2.3 (± 4.16)			

Notes:

[84] - All Subjects Population. Only those par. available at the specified time points were analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in post void residual ultrasound at Day 21

End point title	Change from baseline in post void residual ultrasound at Day 21

End point description:

A post void residual (PVR) bladder ultrasound was carried out as a measure of bladder function. PVR was clinically indicated following the occurrence of adverse events relating to the lower urinary tract (e.g., micturition difficulties, including urinary hesitancy or urinary retention). These assessments were also repeated following drug withdrawal following such events. A prompt follow-up PVR was recommended if a high score was obtained from a participant on the Pediatric Lower Urinary Tract Symptom scale (the PLUTS scale is a clinician-rated scale used to assess lower urinary tract symptoms, including urinary retention) and if the clinician felt that the participant was at risk or had symptoms of urinary retention. PVR was measured at Day 7 of Titration 3 (600 mg/day). Baseline is defined as the Screening visit.

End point type	Secondary

End point timeframe:

Screening and Day 7 of Titration 3 (Day 21)

End point values	Regimen A: E/R 300/450 mg then 600 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	4[85]			
Units: Milliliters (ML)				
arithmetic mean (standard deviation)	14.4 (± 21)			

Notes:

[85] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated neurological abnormality

End point title	Number of participants with the indicated neurological abnormality

End point description:

Abnormal Central Nervous System (CNS) symptoms were assessed by a full and brief neurological examination. A full neurological examination included assessment of mental status, cranial nerves, gait,

coordination, sensation, speech/language, muscle strength, muscle tone, and reflexes. A brief neurological examination included assessment of mental status, cranial nerves, gait, coordination, reflexes, and speech/language. Neurological parameters assessed were memory impairment, impaired intellect, decreased attention, psychomotor slowing, decreased muscle strength, hypertonia, somnolence, right and left biceps, right and left brachioradialis, right and left knee, right and left ankle, and right and left planter response. Neurological examination was performed at Day 7 of Titration 3 (600 mg/day). "Not Applicable (NA)" data is presented as "99999".

End point type	Secondary

End point timeframe:

Screening and Day 7 of Titration 3 (Day 21)

End point values	Regimen A: E/R 300/450 mg then 600 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	4[86]			
Units: Participants				
Memory impairment	0			
Impaired intellect	0			
Decreased attention	0			
Psychomotor slowing	0			
Decreased muscle strength	0			
Hypertonia	0			
Somnolence	1			
Bicep right	99999			
Bicep left	99999			
Brachioradialis right	99999			
Brachioradialis left	99999			
Knee right	99999			
Knee left	99999			
Ankle right	99999			
Ankle left	99999			
Planter response right	99999			
Planter response left	99999			

Notes:

[86] - All Subjects Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data, volunteered by the participant, discovered by the investigator, or detected by other means, were collected from the start of study treatment until the Follow-up contact (maximum of 46 days).

Adverse event reporting additional description:

Serious adverse events (SAEs) and non-serious AEs were collected in members of the All Subjects Population, compromised of all participants who received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Regimen A: Ezogabine/Retigabine 300 mg

Reporting group description:

Participants with a body weight of >50 kg received a starting dose of 300 mg/day ezogabine/retigabine administerd as 100 mg IR tablets TID orally and underwent weekly up-titration at a frequency of no more than once per week. The TID dosing regimen was administered at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Reporting group title	Regimen A: Ezogabine/Retigabine 300 mg, then 450 mg

Reporting group description:

Participants with a body weight of >50 kg received a starting dose of 300 mg/day ezogabine/retigabine administered as 100 mg IR tablets TID orally and underwent weekly up-titration at a frequency of no more than once per week. These participants then received an up-titrated dose of 450 mg/day ezogabine/retigabine as 150 mg IR tablets TID orally. The TID daily dosing regimen was administered at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Reporting group title	Regimen A: Ezogabine/Retigabine 300/450 mg, then 600 mg

Reporting group description:

Participants with a body weight of >50 kg received a starting dose of 300 mg/day ezogabine/retigabine administered as 100 mg IR tablets TID orally and underwent weekly up-titration at a frequency of no more than once per week. These participants received an up-titrated dose of 450 mg/day ezogabine/retigabine (as 150 mg IR tablets TID orally) initially, then received an up-titrated dose of 600 mg/day ezogabine/retigabine as 200 mg IR tablets TID orally. The TID daily dosing regimen was administered at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Reporting group title	Regimen A: Ezogabine/Retigabine 300/450/600 mg, then 750 mg

Reporting group description:

Participants with a body weight of >50 kg received a starting dose of 300 mg/day ezogabine/retigabine as 100 mg IR tablets TID orally and underwent weekly up-titration at a frequency of no more than once per week. These participants received up-titrated doses of ezogabine/retigabine 450 mg and 600 mg (as 150 mg IR and 200 mg IR tablets, respectively, TID orally) initially, then received an up-titrated dose of 750 mg/day ezogabine/retigabine as 250 mg IR tablets TID orally. The TID daily dosing regimen was administered at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Reporting group title	Regimen A: Ezogabine/Retigabine 300/450/600/750, then 900 mg

Reporting group description:

Participants received an initial dose of ezogabine/retigabine 300 mg/day administered as 100 mg IR tablets TID orally and underwent weekly up-titration at Weeks 1, 3, and 5. Dose titration occurred no more than once per week, with participants receiving up-titrated daily doses of 450 mg (150 mg TID), 600 mg (200 mg TID), 750 mg (250 mg TID), and 900 mg (300 mg TID) at an 8-hour dosing interval or a 6-, 6-, 12-hour dosing interval.

Serious adverse events	Regimen A: Ezogabine/Retigabine 300 mg	Regimen A: Ezogabine/Retigabine 300 mg, then 450 mg	Regimen A: Ezogabine/Retigabine 300/450 mg, then 600 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Regimen A: Ezogabine/Retigabine 300/450/600 mg, then 750 mg	Regimen A: Ezogabine/Retigabine 300/450/600/750, then 900 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Regimen A: Ezogabine/Retigabine 300 mg	Regimen A: Ezogabine/Retigabine 300 mg, then 450 mg	Regimen A: Ezogabine/Retigabine 300/450 mg, then 600 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	1 / 5 (20.00%)	1 / 4 (25.00%)
Nervous system disorders			
Somnolence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 5 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Urinary hesitation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Regimen A: Ezogabine/Retigabine 300/450/600 mg, then 750 mg	Regimen A: Ezogabine/Retigabine 300/450/600/750, then 900 mg	
Total subjects affected by non-serious			

adverse events subjects affected / exposed	0 / 4 (0.00%)	0 / 3 (0.00%)	
Nervous system disorders Somnolence subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	
Renal and urinary disorders Urinary hesitation subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 3 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2011	Amendment No. 1: Addition of microsampling technique for pediatric volume assay validation and change of Sponsor IND holder.
10 October 2012	Amendment No. 2: Clarification of exclusion criteria, laboratory parameters; and removal of urine PK.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported