Clinical trial results:
RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROLLED, MULTI-CENTER REGISTRATION TRIAL TO EVALUATE THE EFFICACY AND SAFETY OF TTP488 IN PATIENTS WITH MILD ALZHEIMER'S DISEASE RECEIVING ACETYLCHOLINESTERASE INHIBITORS AND/OR MEMANTINE

Summary

EudraCT number	2016-002005-19
Trial protocol	GB IE
Global end of trial date	01 June 2018

Results information

Result version number	v1 (current)
This version publication date	21 March 2021
First version publication date	21 March 2021

Trial information

Trial identification

Sponsor protocol code	TTP488-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02080364
WHO universal trial number (UTN)	-
Other trial identifiers	US IND : 68, 445, CTA Control #: 181266

Notes:

Sponsors

Sponsor organisation name	vTv Therapeutics LLC
Sponsor organisation address	3980 Premier Dr., High Point, United States, 27265
Public contact	Ann Gooch, vTv THERAPEUTICS LLC, 1 3368410300, AGOOCH@VTVTHERAPEUTICS.COM
Scientific contact	Ann Gooch, vTv THERAPEUTICS LLC, 1 3368410300, AGOOCH@VTVTHERAPEUTICS.COM

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 June 2018
Global end of trial reached?	Yes
Global end of trial date	01 June 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of azeliragon on cognitive [Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog)] and global function [Clinical Dementia Rating Scale Sum of Boxes (CDR-sb)] measures in patients with mild AD.

Protection of trial subjects:

Safety surveillance was performed regularly by the medical monitor (blinded) and the Independent Data Monitoring Committee as a protection for trial subjects. Safety surveillance of the accumulating safety data was performed by the medical monitors monthly in a blinded fashion. Safety surveillance review included review of adverse events, lab results and alerts, ECG results and alerts, MRI findings, and protocol deviations. In addition, an external Independent Data Monitoring Committee was responsible for the review of all available safety data. The primary function of the IDMC was to monitor the study and recommend to the Sponsor whether to amend safety monitoring procedures, modify the protocol or consent, terminate the study, or continue the study as designed in order to safeguard the well-being of subjects already in the study and those yet to be recruited.

Background therapy:

All subjects enrolled in TTP488-301 were required to be on a stable dose of a background cholinesterase inhibitor and/or memantine.

Evidence for comparator: -

Actual start date of recruitment	01 April 2015
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: 48
Country: Number of subjects enrolled	Ireland: 16
Country: Number of subjects enrolled	United States: 662
Country: Number of subjects enrolled	Canada: 84
Country: Number of subjects enrolled	Australia: 15
Country: Number of subjects enrolled	New Zealand: 9
Country: Number of subjects enrolled	South Africa: 46
Worldwide total number of subjects	880
EEA total number of subjects	64

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	115
From 65 to 84 years	654
85 years and over	111

Subject disposition

Recruitment

Recruitment details:

The A-Study was conducted from March 2015 through April 2018 in the United States and Canada. The B-Study was conducted from September 2016 through June 2018 in the United States, Canada, United Kingdom, Ireland, South Africa, Australia and New Zealand.

Pre-assignment

Screening details:

A total of 1733 subjects underwent screening procedures for determination of eligibility for participation across the A- and B- Studies.

Pre-assignment period milestones

Number of subjects started	1733[1]
Number of subjects completed	880

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen failure: 853

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 1733 subjects started the screening process worldwide; however, 880 subjects completed the screening process as eligible subjects to participate in the study. Therefore 880 subjects are captured as the worldwide enrollment number.

Period 1

Period 1 title	Baseline 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	Azeliragon - A Study

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Azeliragon
Investigational medicinal product code	
Other name	TTP488
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Drug supplies consisted of a 5 mg azeliragon and matching placebo formulation supplied as a Size 2 hard gelatin capsule in a double-blind fashion. Treatment began in the clinic at the baseline visit immediately following randomization. Participants were to be instructed to take one capsule per day by mouth for the duration of the treatment period.

Arm title	Placebo - A Study

Arm description: -

Arm type	Placebo

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

Dosage and administration details:

One capsule by mouth once daily. May be administered without regards to meals.

Arm title	Azeliragon - B Study

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Azeliragon
Investigational medicinal product code	
Other name	TTP488
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Drug supplies consisted of a 5 mg azeliragon and matching placebo formulation supplied as a Size 2 hard gelatin capsule in a double-blind fashion. Treatment began in the clinic at the baseline visit immediately following randomization. Participants were to be instructed to take one capsule per day by mouth for the duration of the treatment period.

Arm title	Placebo - B Study

Arm description: -

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

Dosage and administration details:

One capsule by mouth once daily. May be administered without regards to meals.

Number of subjects in period 1	Azeliragon - A Study	Placebo - A Study	Azeliragon - B Study
Started	197	208	247
Completed	195	206	246
Not completed	2	2	1
Other	-	1	1
Protocol deviation	2	1	-

Number of subjects in period 1	Placebo - B Study
Started	228
Completed	228
Not completed	0
Other	-
Protocol deviation	-

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Azeliragon - A Study

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Azeliragon
Investigational medicinal product code	
Other name	TTP488
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Drug supplies consisted of a 5 mg azeliragon and matching placebo formulation supplied as a Size 2 hard gelatin capsule in a double-blind fashion. Treatment began in the clinic at the baseline visit immediately following randomization. Participants were to be instructed to take one capsule per day by mouth for the duration of the treatment period.

Arm title	Placebo - A Study

Arm description: -

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

Dosage and administration details:

One capsule by mouth once daily. May be administered without regards to meals.

Arm title	Azeliragon - B Study

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Azeliragon
Investigational medicinal product code	
Other name	TTP488
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Drug supplies consisted of a 5 mg azeliragon and matching placebo formulation supplied as a Size 2 hard gelatin capsule in a double-blind fashion. Treatment began in the clinic at the baseline visit immediately following randomization. Participants were to be instructed to take one capsule per day by mouth for the duration of the treatment period.

Arm title	Placebo - B Study

Arm description: -

Arm type	Placebo

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

Dosage and administration details:

One capsule by mouth once daily. May be administered without regards to meals.

Arm title	Azeliragon- A+B Study

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Azeliragon
Investigational medicinal product code	
Other name	TTP488
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Drug supplies consisted of a 5 mg azeliragon and matching placebo formulation supplied as a Size 2 hard gelatin capsule in a double-blind fashion. Treatment began in the clinic at the baseline visit immediately following randomization. Participants were to be instructed to take one capsule per day by mouth for the duration of the treatment period.

Arm title	Placebo - A+B Study

Arm description: -

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

Dosage and administration details:

One capsule by mouth once daily. May be administered without regards to meals.

Number of subjects in period 2	Azeliragon - A Study	Placebo - A Study	Azeliragon - B Study
Started	195	206	246
Completed	148	157	9
Not completed	47	49	237
Consent withdrawn by subject	16	16	15
Adverse event, non-fatal	10	15	11
Other	14	12	21
Study Terminated by Sponsor	-	-	180
Lost to follow-up	2	3	5
Protocol deviation	5	3	5

Number of subjects in period 2	Placebo - B Study	Azeliragon- A+B Study	Placebo - A+B Study
Started	228	441	434
Completed	4	157	161
Not completed	224	284	273

Consent withdrawn by subject	10	31	26
Adverse event, non-fatal	14	21	29
Other	16	35	28
Study Terminated by Sponsor	183	180	183
Lost to follow-up	-	7	3
Protocol deviation	1	10	4

Baseline characteristics

Reporting groups	
Reporting group title	Azeliragon - A Study
Reporting group description: -	
Reporting group title	Placebo - A Study
Reporting group description: -	
Reporting group title	Azeliragon - B Study
Reporting group description: -	
Reporting group title	Placebo - B Study
Reporting group description: -	

Reporting group values	Azeliragon - A Study	Placebo - A Study	Azeliragon - B Study
Number of subjects	197	208	247
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
arithmetic mean	74.3	74.6	74.7
standard deviation	± 9.14	± 7.94	± 8.56
Gender categorical Units: Subjects			
Female	97	91	107
Male	98	115	139
Not recorded	2	2	1
Race Units: Subjects			
White	179	194	231
Black or African American	8	9	8
Asian	5	2	6
Hawaiian or other Pacific Islander	2	0	1
American Indian or Alaska Native	0	1	0
Multiple	1	0	0
Not recorded	2	2	1
Ethnicity Units: Subjects			
Hispanic or Latino	27	23	8
Not Hispanic or Latino	168	183	238

Not collected	2	2	1
Apo E4 status Units: Subjects			
Heterozygous	83	79	115
Homozygous	15	27	31
Non-carrier	95	98	96
Not collected	4	4	5
Education Level Units: Subjects			
High School	61	65	86
Other (trainings, certifications)	15	14	8
Some college	32	33	34
Associate's Degree	17	14	14
Bachelor's Degree	44	39	64
Master's Degree	21	26	29
Doctoral Degree	5	15	11
Not recorded	2	2	1
Background AD Medication Units: Subjects			
Memantine	12	16	19
Acetylcholinesterase inhibitor	117	124	156
Both Memantine and Acetylcholinesterase inhibitor	65	66	71
Not recorded	3	2	1
Years since AD diagnosis Units: years			
arithmetic mean	2.4	2.3	2.0
standard deviation	± 2.4	± 2.4	± 1.9
Baseline MMSE Units: points			
arithmetic mean	23.5	23.2	23.3
standard deviation	± 2.6	± 2.5	± 2.5
Baseline ADAS-cog Units: points			
arithmetic mean	15.3	15.6	17.0
standard deviation	± 5.2	± 5.5	± 5.6
Baseline CDR-Sum of Boxes Units: points			
arithmetic mean	4.1	4.1	4.6
standard deviation	± 1.7	± 1.6	± 1.6
Baseline ADCS-ADL Units: points			
arithmetic mean	67.8	67.5	66.3
standard deviation	± 7.3	± 8.4	± 8.2

Reporting group values	Placebo - B Study	Total	
Number of subjects	228	880	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	

Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous			
Units: years			
arithmetic mean	74.0		
standard deviation	± 8.53	-	
Gender categorical			
Units: Subjects			
Female	107	402	
Male	121	473	
Not recorded	0	5	
Race			
Units: Subjects			
White	220	824	
Black or African American	5	30	
Asian	3	16	
Hawaiian or other Pacific Islander	0	3	
American Indian or Alaska Native	0	1	
Multiple	0	1	
Not recorded	0	5	
Ethnicity			
Units: Subjects			
Hispanic or Latino	15	73	
Not Hispanic or Latino	213	802	
Not collected	0	5	
Apo E4 status			
Units: Subjects			
Heterozygous	105	382	
Homozygous	18	91	
Non-carrier	99	388	
Not collected	6	19	
Education Level			
Units: Subjects			
High School	79	291	
Other (trainings, certifications)	6	43	
Some college	31	130	
Associate's Degree	21	66	
Bachelor's Degree	55	202	
Master's Degree	25	101	
Doctoral Degree	11	42	
Not recorded	0	5	
Background AD Medication			
Units: Subjects			
Memantine	22	69	
Acetylcholinesterase inhibitor	145	542	

Both Memantine and Acetylcholinesterase inhibitor	60	262	
Not recorded	1	7	

Years since AD diagnosis			
Units: years			
arithmetic mean	1.9		
standard deviation	± 1.9	-	
Baseline MMSE			
Units: points			
arithmetic mean	23.4		
standard deviation	± 2.7	-	
Baseline ADAS-cog			
Units: points			
arithmetic mean	16.1		
standard deviation	± 5.3	-	
Baseline CDR-Sum of Boxes			
Units: points			
arithmetic mean	4.5		
standard deviation	± 1.6	-	
Baseline ADCS-ADL			
Units: points			
arithmetic mean	67.2		
standard deviation	± 7.6	-	

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) includes all randomized subjects who receive any study medication.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety set (SAF) includes all subjects who receive any study medication.	

Reporting group values	Full Analysis Set	Safety Analysis Set	
Number of subjects	829	875	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			

Age continuous Units: years			
arithmetic mean	74.4	74.7	
standard deviation	± 8.53	± 8.80	
Gender categorical Units: Subjects			
Female	380	402	
Male	449	473	
Not recorded			
Race Units: Subjects			
White	778	824	
Black or African American	30	30	
Asian	16	16	
Hawaiian or other Pacific Islander	3	3	
American Indian or Alaska Native	1	1	
Multiple	1	1	
Not recorded			
Ethnicity Units: Subjects			
Hispanic or Latino	69	73	
Not Hispanic or Latino	760	802	
Not collected			
Apo E4 status Units: Subjects			
Heterozygous	364	382	
Homozygous	84	91	
Non-carrier	368	388	
Not collected			
Education Level Units: Subjects			
High School	278	291	
Other (trainings, certifications)	39	43	
Some college	124	130	
Associate's Degree	60	66	
Bachelor's Degree	189	202	
Master's Degree	98	101	
Doctoral Degree	41	42	
Not recorded			
Background AD Medication Units: Subjects			
Memantine	313	331	
Acetylcholinesterase inhibitor	762	804	
Both Memantine and Acetylcholinesterase inhibitor	248	262	
Not recorded			
Years since AD diagnosis Units: years			
arithmetic mean	2.1	2.1	
standard deviation	± 2.2	± 2.2	
Baseline MMSE Units: points			

arithmetic mean	23.4	23.3	
standard deviation	± 2.6	± 2.6	
Baseline ADAS-cog			
Units: points			
arithmetic mean	16.0	16.0	
standard deviation	± 5.5	± 5.4	
Baseline CDR-Sum of Boxes			
Units: points			
arithmetic mean	4.3	4.3	
standard deviation	± 1.6	± 1.6	
Baseline ADCS-ADL			
Units: points			
arithmetic mean	67.0	67.4	
standard deviation	± 7.9	± 8.0	

End points

End points reporting groups

Reporting group title	Azeliragon - A Study
Reporting group description: -	
Reporting group title	Placebo - A Study
Reporting group description: -	
Reporting group title	Azeliragon - B Study
Reporting group description: -	
Reporting group title	Placebo - B Study
Reporting group description: -	
Reporting group title	Azeliragon - A Study
Reporting group description: -	
Reporting group title	Placebo - A Study
Reporting group description: -	
Reporting group title	Azeliragon - B Study
Reporting group description: -	
Reporting group title	Placebo - B Study
Reporting group description: -	
Reporting group title	Azeliragon- A+B Study
Reporting group description: -	
Reporting group title	Placebo - A+B Study
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) includes all randomized subjects who receive any study medication.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety set (SAF) includes all subjects who receive any study medication.	

Primary: Change from Baseline in the ADAS-cog

End point title	Change from Baseline in the ADAS-cog
End point description:	
Change from Baseline in ADAS-cog Total Score - MMRM	
End point type	Primary
End point timeframe:	
Baseline to Month 18 (Study A) Baseline to Month 12 (Study B) [B-study results reported for data collected through announcement of A-study results and termination of B-Study.]	

End point values	Azeliragon - A Study	Placebo - A Study	Azeliragon - B Study	Placebo - B Study
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	138	151	118[1]	121[2]
Units: Points				
least squares mean (standard error)	3.8 (± 0.51)	3.1 (± 0.49)	3.4 (± 0.46)	2.5 (± 0.46)

Notes:

[1] - Excludes data from visits after announcement of A-Study topline results and termination of B-Study
[2] - Excludes data from visits after announcement of A-Study topline results and termination of B-Study

Statistical analyses

Statistical analysis title	A-Study Change from Baseline in ADAS-cog

Statistical analysis description:

The primary analysis will be done on change from baseline in ADAS-cog and on change from baseline in CDR-sb.
The primary analysis will use the ITT methodology and a main-effects model with analysis of covariance (ANCOVA) at endpoint with multiple imputations (MI) for coping with missing data, with 100 invocations (acknowledging that more invocations are needed with more missing data). Monte Carlo methods are planned.

Comparison groups	Placebo - A Study v Azeliragon - A Study
Number of subjects included in analysis	289
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3386
Method	Mixed models analysis

Statistical analysis title	B-Study Change from Baseline in ADAS-cog
Comparison groups	Azeliragon - B Study v Placebo - B Study
Number of subjects included in analysis	239
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1992
Method	Mixed models analysis

Primary: Change from Baseline in the CDR-sb

End point title	Change from Baseline in the CDR-sb

End point description:

End point type	Primary

End point timeframe:

Baseline to Month 18 (Study A)
Baseline to Month 12 (Study B) [B-study results reported for data collected through announcement of A-study results and termination of B-Study.]

End point values	Azeliragon - A Study	Placebo - A Study	Azeliragon - B Study	Placebo - B Study
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	140	150	117	120
Units: points				
arithmetic mean (standard deviation)	1.4 (± 2.23)	1.4 (± 1.85)	1.3 (± 1.87)	0.7 (± 1.40)

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis

Statistical analysis description:

The primary analysis will be done on change from baseline in ADAS-cog and on change from baseline in CDR-sb.
The primary analysis will use the ITT methodology and a main-effects model with analysis of covariance (ANCOVA) at endpoint with multiple imputations (MI) for coping with missing data, with 100 invocations (acknowledging that more invocations are needed with more missing data). Monte Carlo methods are planned.

Comparison groups	Azeliragon - A Study v Placebo - A Study
Number of subjects included in analysis	290
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9394
Method	Mixed models analysis

Secondary: Change from Baseline in hippocampal volume at Month 18

End point title	Change from Baseline in hippocampal volume at Month 18

End point description:

Percent of Total Hippocampal Atrophy to Intracranial Volume

End point type	Secondary

End point timeframe:

Baseline to Month 18

End point values	Azeliragon-A+B Study	Placebo - A+B Study		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	116		
Units: Percent				
least squares mean (standard error)	-0.016 (± 0.001)	-0.014 (± 0.001)		

Statistical analyses

Statistical analysis title	Key Secondary

Statistical analysis description:

LS Means and standard errors are based on an ANCOVA model with change from baseline as the response variable and effects for treatment and baseline stratum and a covariate of baseline included in the model.

Comparison groups	Azeliragon- A+B Study v Placebo - A+B Study
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.1792
Method	ANCOVA

Notes:

[3] - LS Means and standard errors are based on an ANCOVA model with change from baseline as the response variable and effects for treatment and baseline stratum and a covariate of baseline included in the model.

Secondary: Change from Baseline in ADCS-ADL total score

End point title	Change from Baseline in ADCS-ADL total score

End point description:

End point type	Secondary

End point timeframe:

Baseline to Month 18 (Study A)
Baseline to Month 12 (Study B) [B-study results reported for data collected through announcement of A-study results and termination of B-Study.]

End point values	Azeliragon - A Study	Placebo - A Study	Azeliragon - B Study	Placebo - B Study
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	141	152	121	122
Units: points				
arithmetic mean (standard deviation)	-5.1 (± 8.63)	-3.2 (± 8.92)	-5.4 (± 8.85)	-2.8 (± 7.83)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in MMSE

End point title	Change from Baseline in MMSE

End point description:

End point type	Secondary

End point timeframe:

Baseline to Month 18 (Study A)
Baseline to Month 12 (Study B) [B-study results reported for data collected through announcement of A-study results and termination of B-Study.]

End point values	Azeliragon - A Study	Placebo - A Study	Azeliragon - B Study	Placebo - B Study
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	142	153	121	121
Units: points				
arithmetic mean (standard deviation)	-2.1 (± 3.55)	-2.0 (± 3.25)	-2.1 (± 3.25)	-1.8 (± 3.29)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in NPI total score

End point title	Change from Baseline in NPI total score

End point description:

End point type	Secondary

End point timeframe:

Baseline to Month 18 (Study A)
Baseline to Month 12 (Study B) [B-study results reported for data collected through announcement of A-study results and termination of B-Study.]

End point values	Azeliragon - A Study	Placebo - A Study	Azeliragon - B Study	Placebo - B Study
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	142	152	121	122
Units: points				
arithmetic mean (standard deviation)	-0.2 (± 9.77)	1.3 (± 11.53)	2.3 (± 11.24)	0 (± 10.67)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting will commence as soon as the study participant has been dosed and continue through their last study visit.

Adverse event reporting additional description:

Note: Non-serious adverse events reported here include all adverse events (including serious adverse events).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Azeliragon - Study A+B
Reporting group description: -	
Reporting group title	Placebo - Study A+B

Reporting group description: -

Serious adverse events	Azeliragon - Study A+B	Placebo - Study A+B	
Total subjects affected by serious adverse events			
subjects affected / exposed	70 / 441 (15.87%)	67 / 434 (15.44%)	
number of deaths (all causes)	4	5	
number of deaths resulting from adverse events	4	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 441 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer metastatic			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			

subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 441 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			

subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	2 / 441 (0.45%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	2 / 441 (0.45%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 441 (0.00%)	3 / 434 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 441 (0.45%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 441 (0.45%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthma			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Ischaemic stroke			

subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aggression			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Agitation			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	3 / 441 (0.68%)	3 / 434 (0.69%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	1 / 441 (0.23%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 441 (0.23%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaw fracture			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural inflammation			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			

subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 441 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 441 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns third degree			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			

subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	3 / 441 (0.68%)	5 / 434 (1.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 441 (0.45%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	1 / 441 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 441 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute myocardial infarction			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bundle branch block left			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			

subjects affected / exposed	0 / 441 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	4 / 441 (0.91%)	4 / 434 (0.92%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	2 / 441 (0.45%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	1 / 441 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 441 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	1 / 441 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nerve root compression			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Amyotrophic lateral sclerosis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive encephalopathy			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unresponsive to stimuli			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 441 (0.45%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 441 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric polyps			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal infarction			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			

subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 441 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Hyperparathyroidism			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 441 (1.13%)	4 / 434 (0.92%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 441 (0.45%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 441 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 441 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 441 (0.23%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 441 (0.00%)	2 / 434 (0.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal infection			
subjects affected / exposed	0 / 441 (0.00%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 441 (0.45%)	1 / 434 (0.23%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	1 / 441 (0.23%)	0 / 434 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Azeliragon - Study A+B	Placebo - Study A+B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	320 / 441 (72.56%)	324 / 434 (74.65%)	
Investigations			
Weight decreased			
subjects affected / exposed	17 / 441 (3.85%)	13 / 434 (3.00%)	
occurrences (all)	17	13	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	51 / 441 (11.56%)	58 / 434 (13.36%)	
occurrences (all)	62	62	
Laceration			
subjects affected / exposed	10 / 441 (2.27%)	11 / 434 (2.53%)	
occurrences (all)	10	13	
Contusion			

subjects affected / exposed	8 / 441 (1.81%)	9 / 434 (2.07%)	
occurrences (all)	9	13	
Vascular disorders			
Hypertension			
subjects affected / exposed	10 / 441 (2.27%)	14 / 434 (3.23%)	
occurrences (all)	10	14	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	8 / 441 (1.81%)	12 / 434 (2.76%)	
occurrences (all)	11	13	
Nervous system disorders			
Dizziness			
subjects affected / exposed	18 / 441 (4.08%)	15 / 434 (3.46%)	
occurrences (all)	19	15	
Headache			
subjects affected / exposed	15 / 441 (3.40%)	19 / 434 (4.38%)	
occurrences (all)	16	19	
Syncope			
subjects affected / exposed	11 / 441 (2.49%)	9 / 434 (2.07%)	
occurrences (all)	12	9	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 441 (2.95%)	14 / 434 (3.23%)	
occurrences (all)	16	15	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	17 / 441 (3.85%)	20 / 434 (4.61%)	
occurrences (all)	18	22	
Nausea			
subjects affected / exposed	14 / 441 (3.17%)	10 / 434 (2.30%)	
occurrences (all)	14	10	
Constipation			
subjects affected / exposed	10 / 441 (2.27%)	8 / 434 (1.84%)	
occurrences (all)	10	8	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	13 / 441 (2.95%)	9 / 434 (2.07%)	
occurrences (all)	13	9	
Psychiatric disorders			
Depression			
subjects affected / exposed	21 / 441 (4.76%)	20 / 434 (4.61%)	
occurrences (all)	21	20	
Agitation			
subjects affected / exposed	15 / 441 (3.40%)	17 / 434 (3.92%)	
occurrences (all)	17	18	
Anxiety			
subjects affected / exposed	11 / 441 (2.49%)	15 / 434 (3.46%)	
occurrences (all)	12	15	
Insomnia			
subjects affected / exposed	11 / 441 (2.49%)	7 / 434 (1.61%)	
occurrences (all)	11	7	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	10 / 441 (2.27%)	15 / 434 (3.46%)	
occurrences (all)	11	15	
Musculoskeletal pain			
subjects affected / exposed	10 / 441 (2.27%)	5 / 434 (1.15%)	
occurrences (all)	10	5	
Arthralgia			
subjects affected / exposed	9 / 441 (2.04%)	14 / 434 (3.23%)	
occurrences (all)	9	16	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	45 / 441 (10.20%)	35 / 434 (8.06%)	
occurrences (all)	47	36	
Upper respiratory tract infection			
subjects affected / exposed	20 / 441 (4.54%)	16 / 434 (3.69%)	
occurrences (all)	23	17	
Nasopharyngitis			
subjects affected / exposed	19 / 441 (4.31%)	23 / 434 (5.30%)	
occurrences (all)	19	24	

Bronchitis subjects affected / exposed occurrences (all)	10 / 441 (2.27%) 10	15 / 434 (3.46%) 15	
Pneumonia subjects affected / exposed occurrences (all)	9 / 441 (2.04%) 9	7 / 434 (1.61%) 7	
Sinusitis subjects affected / exposed occurrences (all)	9 / 441 (2.04%) 9	9 / 434 (2.07%) 9	
Influenza subjects affected / exposed occurrences (all)	7 / 441 (1.59%) 7	12 / 434 (2.76%) 12	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 441 (1.13%) 5	9 / 434 (2.07%) 9	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 September 2016	Investigator Brochure Version 10.1 dated 15 Aug 2016 included changes to the reference safety information based upon feedback from MHRA during CTA review.
21 February 2018	TTP488-301 Protocol Amendment 7 & IB Version 11 1. Remove restriction for drugs known to be strong CYP3A4 inhibitors based on completed drug drug interaction study showing no clinically relevant interaction between azeliragon and a strong CYP3A4 inhibitor. The recent Investigator's Brochure (IB) update (Version 11 dated 09 Aug 2017) includes the completed drug-drug interaction study justifying this change. 2. Add Follow-up visit to occur 3 months after last dose of study drug for those participants who discontinue the study early. This visit will allow a final safety follow-up assessment off treatment for participants who discontinue prior to the Month 18 Visit. 3. Modify the MRI and PET analyses to be unblinded to time sequence. MRI and PET trained technicians remain blinded to subject treatment assignment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
10 April 2018	On 10 April 2018, TTP488-301 Investigators were instructed to contact their STEADFAST Part B participants and caregivers as soon as possible to inform them that the study was being stopped due to lack of efficacy based upon Part A topline results. Part B Participants were informed to immediately discontinue dosing and return for an Early Termination Visit as soon as possible, and a Followup visit at 6 weeks following the last dose of study medication.	-

Notes:

Limitations and caveats

None reported