



Clinical trial results:

A Phase 2, Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of VX-814 in PiZZ Subjects

Summary

EudraCT number	2019-003650-92
Trial protocol	DE SE GB IE
Global end of trial date	14 November 2020

Results information

Result version number	v1 (current)
This version publication date	23 January 2022
First version publication date	23 January 2022

Trial information

Trial identification

Sponsor protocol code	VX19-814-101
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04167345
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, United States,
Public contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617 341 6777, medicalinfo@vrtx.com
Scientific contact	Medical Monitor, Vertex Pharmaceuticals Incorporated, +1 617 341 6777, medicalinfo@vrtx.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	22 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 November 2020
Global end of trial reached?	Yes
Global end of trial date	14 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy, safety and pharmacokinetics (PK) of VX-814 in PiZZ subjects.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Council on Harmonization (ICH) Guideline for Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2020
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	Canada: 3
Country: Number of subjects enrolled	United States: 30
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Ireland: 6
Worldwide total number of subjects	48
EEA total number of subjects	15

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)	38
From 65 to 84 years	10

Subject disposition

Recruitment

Recruitment details:

There were 3 parts in study: Parts A1, A2 and B. As specified in SAP, data from placebo group for Parts A1, A2 and B were pooled and reported as a combined arm (Parts A1, A2 and B Combined: Placebo) and data from VX-814 400 mg for Parts A1 and A2 were pooled and reported as a combined arm (Parts A1 and A2 Combined: VX-814 400 mg) in below results.

Pre-assignment

Screening details:

This study was conducted in subjects 18 through 80 of years of age, inclusive with the PiZZ genotype.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Carer, Assessor, Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Parts A1, A2 and B Combined: Placebo

Arm description:

Subjects received placebo matched to VX-814 in the treatment period for 28 days.

Arm type	Placebo
Investigational medicinal product name	Placebo (matched to VX-814)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to VX-814 daily in morning and evening.

Arm title	Part A1: VX-814 100 milligrams (mg)
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Arm description:

Subjects received VX-814 100 mg once every 12 hours (q12h) in the treatment period for 28 days.

Arm type	Experimental
Investigational medicinal product name	VX-814
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-814 100 mg daily in the morning and evening.

Arm title	Part A1: VX-814 200 mg
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Arm description:

Subjects received VX-814 200 mg q12h in the treatment period for 28 days.

Arm type	Experimental
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Investigational medicinal product name	VX-814
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-814 200 mg daily in the morning and evening.

Arm title	Parts A1 and A2 Combined: VX-814 400 mg
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Arm description:

Subjects received VX-814 400 mg q12h in the treatment period for 28 days.

Arm type	Experimental
Investigational medicinal product name	VX-814
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-814 400 mg daily in the morning and evening.

Arm title	Part B: VX-814 600 mg
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Arm description:

Subjects received VX-814 600 mg q12h in the treatment period for 28 days.

Arm type	Experimental
Investigational medicinal product name	VX-814
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-814 600 mg daily in the morning and evening.

Number of subjects in period 1	Parts A1, A2 and B Combined: Placebo	Part A1: VX-814 100 milligrams (mg)	Part A1: VX-814 200 mg
Started	10	4	3
Completed	9	3	3
Not completed	1	1	0
Other	1	1	-

Number of subjects in period 1	Parts A1 and A2 Combined: VX-814 400 mg	Part B: VX-814 600 mg
Started	13	18
Completed	13	18
Not completed	0	0
Other	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Parts A1, A2 and B Combined: Placebo
Reporting group description: Subjects received placebo matched to VX-814 in the treatment period for 28 days.	
Reporting group title	Part A1: VX-814 100 milligrams (mg)
Reporting group description: Subjects received VX-814 100 mg once every 12 hours (q12h) in the treatment period for 28 days.	
Reporting group title	Part A1: VX-814 200 mg
Reporting group description: Subjects received VX-814 200 mg q12h in the treatment period for 28 days.	
Reporting group title	Parts A1 and A2 Combined: VX-814 400 mg
Reporting group description: Subjects received VX-814 400 mg q12h in the treatment period for 28 days.	
Reporting group title	Part B: VX-814 600 mg
Reporting group description: Subjects received VX-814 600 mg q12h in the treatment period for 28 days.	

Reporting group values	Parts A1, A2 and B Combined: Placebo	Part A1: VX-814 100 milligrams (mg)	Part A1: VX-814 200 mg
Number of subjects	10	4	3
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	54.6 ± 11.3	51.8 ± 14.8	55.5 ± 7.8
Gender categorical Units: Subjects			
Female	5	3	0
Male	5	1	3
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	1	0
Not Hispanic or Latino	9	3	3
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	10	4	3
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Plasma Functional Alpha-1 Antitrypsin (AAT) Levels Units: micromole per liter arithmetic mean standard deviation	4.2 ± 1.2	5.1 ± 2.3	3.9 ± 0.4
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Reporting group values	Parts A1 and A2 Combined: VX-814 400 mg	Part B: VX-814 600 mg	Total
Number of subjects	13	18	48
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	57.9 ± 13.2	57.9 ± 9.1	-
Gender categorical Units: Subjects			
Female	7	12	27
Male	6	6	21
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	2
Not Hispanic or Latino	12	14	41
Unknown or Not Reported	1	4	5
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	13	18	48
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Plasma Functional Alpha-1 Antitrypsin (AAT) Levels Units: micromole per liter arithmetic mean standard deviation	3.9 ± 0.7	4.5 ± 1.0	-

End points

End points reporting groups

Reporting group title	Parts A1, A2 and B Combined: Placebo
Reporting group description:	Subjects received placebo matched to VX-814 in the treatment period for 28 days.
Reporting group title	Part A1: VX-814 100 milligrams (mg)
Reporting group description:	Subjects received VX-814 100 mg once every 12 hours (q12h) in the treatment period for 28 days.
Reporting group title	Part A1: VX-814 200 mg
Reporting group description:	Subjects received VX-814 200 mg q12h in the treatment period for 28 days.
Reporting group title	Parts A1 and A2 Combined: VX-814 400 mg
Reporting group description:	Subjects received VX-814 400 mg q12h in the treatment period for 28 days.
Reporting group title	Part B: VX-814 600 mg
Reporting group description:	Subjects received VX-814 600 mg q12h in the treatment period for 28 days.

Primary: Change in Plasma Functional Alpha-1 Antitrypsin (AAT) Levels

End point title	Change in Plasma Functional Alpha-1 Antitrypsin (AAT) Levels
End point description:	Full analysis set (FAS) included all randomized subjects who received at least 1 dose of study drug. The "number of subjects analysed" signifies subjects who were evaluable at the specified time point. As pre-specified in SAP, statistical comparisons with placebo were planned only for VX-814 400 mg and 600 mg treatment arms.
End point type	Primary
End point timeframe:	From Baseline at Day 28

End point values	Parts A1, A2 and B Combined: Placebo	Part A1: VX-814 100 milligrams (mg)	Part A1: VX-814 200 mg	Parts A1 and A2 Combined: VX-814 400 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	2	3	8
Units: micromole per liter				
arithmetic mean (standard deviation)	-0.4 (± 0.3)	0.2 (± 0.1)	0.3 (± 0.5)	1.4 (± 0.6)

End point values	Part B: VX-814 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: micromole per liter				
arithmetic mean (standard deviation)	1.6 (± 1.0)			

Statistical analyses

Statistical analysis title	Statistical analysis VX-814 400 mg versus placebo
Comparison groups	Parts A1 and A2 Combined: VX-814 400 mg v Parts A1, A2 and B Combined: Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean Difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	2.3

Statistical analysis title	Statistical analysis VX-814 600 mg versus placebo
Comparison groups	Part B: VX-814 600 mg v Parts A1, A2 and B Combined: Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean Difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	2.9

Primary: Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Safety and Tolerability as Assessed by Number of Subjects With Treatment Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) ^[1]
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End point description:

The safety set included all subjects who received at least 1 dose of study drug.

End point type	Primary
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End point timeframe:

Day 1 up to Week 8

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Only descriptive data were planned for this primary safety endpoint. No statistical comparison were planned.

End point values	Parts A1, A2 and B Combined: Placebo	Part A1: VX-814 100 milligrams (mg)	Part A1: VX-814 200 mg	Parts A1 and A2 Combined: VX-814 400 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	4	3	13
Units: subjects				
Subjects With AEs	4	3	1	10
Subjects With SAEs	0	2	1	1

End point values	Part B: VX-814 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: subjects				
Subjects With AEs	14			
Subjects With SAEs	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Plasma Antigenic AAT Levels

End point title	Change in Plasma Antigenic AAT Levels
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End point description:

FAS. The "number of subjects analysed" signifies subjects who were evaluable at the specified time point. As pre-specified in SAP, statistical comparisons with placebo were planned only for VX-814 400 mg and 600 mg treatment arms.

End point type	Secondary
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End point timeframe:

From Baseline at Day 28

End point values	Parts A1, A2 and B Combined: Placebo	Part A1: VX-814 100 milligrams (mg)	Part A1: VX-814 200 mg	Parts A1 and A2 Combined: VX-814 400 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	2	3	8
Units: micromole per liter				
arithmetic mean (standard deviation)	0.4 (± 1.3)	0.1 (± 0.2)	0.7 (± 0.7)	2.4 (± 1.2)

End point values	Part B: VX-814 600 mg			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: micromole per liter				
arithmetic mean (standard deviation)	2.6 (± 1.1)			

Statistical analyses

Statistical analysis title	Statistical analysis VX-814 400 mg versus placebo
Comparison groups	Parts A1 and A2 Combined: VX-814 400 mg v Parts A1, A2 and B Combined: Placebo
Number of subjects included in analysis	14
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0114
Method	t-test, 2-sided
Parameter estimate	Mean Difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	3.4

Statistical analysis title	Statistical analysis VX-814 600 mg versus placebo
Comparison groups	Part B: VX-814 600 mg v Parts A1, A2 and B Combined: Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0009
Method	t-test, 2-sided
Parameter estimate	Mean Difference
Point estimate	2.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	3.5

Secondary: Observed Pre-dose Plasma Concentration of VX-814

End point title	Observed Pre-dose Plasma Concentration of VX-814 ^[2]
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End point description:

Pharmacokinetic analysis included all randomized subjects who received at least 1 dose of study drug. Here "n" signifies subjects who were evaluable at the specified time point and "99999" represents "not reported" because the number evaluable subject was 1 at the specified time point.

End point type	Secondary
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End point timeframe:

Pre-dose at Day 7, Day 14, Day 21, and Day 28

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Pharmacokinetic analysis was not applicable for Placebo arm.

End point values	Part A1: VX-814 100 milligrams (mg)	Part A1: VX-814 200 mg	Parts A1 and A2 Combined: VX-814 400 mg	Part B: VX-814 600 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	13	18
Units: micrograms per milliliter				
arithmetic mean (standard deviation)				
Day 7 (n=2, 3, 9, 14)	0.476 (± 0.375)	0.948 (± 0.512)	3.53 (± 1.72)	10.3 (± 6.55)
Day 14 (n=2, 3, 8, 17)	0.244 (± 0.0919)	1.07 (± 0.152)	3.25 (± 2.23)	8.53 (± 11.8)
Day 21 (n=1, 1, 6, 16)	0.700 (± 99999)	1.45 (± 99999)	3.68 (± 3.40)	7.20 (± 6.05)
Day 28 (n=3, 3, 7, 15)	0.326 (± 0.0282)	0.993 (± 0.0300)	3.23 (± 2.82)	5.80 (± 3.73)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to Week 8

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Part A1: VX-814 100 mg
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Reporting group description:

Subjects received VX-814 100 mg q12h in the treatment period for 28 days.

Reporting group title	Parts A1, A2 and B Combined: Placebo
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Reporting group description:

Subjects received placebo matched to VX-814 in the treatment period for 28 days.

Reporting group title	Parts A1 and A2 Combined: VX-814 400 mg
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Reporting group description:

Subjects received VX-814 400 mg q12h in the treatment period for 28 days.

Reporting group title	Part B: VX-814 600 mg
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Reporting group description:

Subjects received VX-814 600 mg q12h in the treatment period for 28 days.

Reporting group title	Part A1: VX-814 200 mg
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Reporting group description:

Subjects received VX-814 200 mg q12h in the treatment period for 28 days.

Serious adverse events	Part A1: VX-814 100 mg	Parts A1, A2 and B Combined: Placebo	Parts A1 and A2 Combined: VX-814 400 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 4 (50.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	1 / 13 (7.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B: VX-814 600 mg	Part A1: VX-814 200 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 18 (0.00%)	1 / 3 (33.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	0 / 18 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastrointestinal infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part A1: VX-814 100 mg	Parts A1, A2 and B Combined: Placebo	Parts A1 and A2 Combined: VX-814 400 mg
Total subjects affected by non-serious adverse events subjects affected / exposed	1 / 4 (25.00%)	4 / 10 (40.00%)	9 / 13 (69.23%)
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Dyspnoea exertional subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Respiration abnormal subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0 0 / 4 (0.00%) 0	1 / 10 (10.00%) 1 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0	0 / 13 (0.00%) 0 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 1 / 13 (7.69%) 1 0 / 13 (0.00%) 0 0 / 13 (0.00%) 0
Psychiatric disorders			

Nightmare subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	2 / 13 (15.38%) 2
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	2 / 13 (15.38%) 2
Blood cholesterol increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 2
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Blood pressure increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Crystal urine present subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Eosinophil count increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
International normalised ratio increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Protein urine present subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1

Prothrombin time prolonged subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Injury, poisoning and procedural complications Dental restoration failure subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	2 / 13 (15.38%) 2
Restless legs syndrome subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Abdominal pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	2 / 10 (20.00%) 2	1 / 13 (7.69%) 1
Dyspepsia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Frequent bowel movements subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Nausea			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Skin and subcutaneous tissue disorders Rash pruritic subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Bone pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 10 (10.00%) 1	0 / 13 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Infections and infestations Ear infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Rhinitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	1 / 13 (7.69%) 1
Tooth abscess subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 10 (0.00%) 0	0 / 13 (0.00%) 0

Urinary tract infection subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Vulvovaginal candidiasis subjects affected / exposed	0 / 4 (0.00%)	0 / 10 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part B: VX-814 600 mg	Part A1: VX-814 200 mg	
Total subjects affected by non-serious adverse events subjects affected / exposed	14 / 18 (77.78%)	0 / 3 (0.00%)	
Vascular disorders Hot flush subjects affected / exposed	0 / 18 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions Fatigue subjects affected / exposed	2 / 18 (11.11%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders Chronic obstructive pulmonary disease subjects affected / exposed	1 / 18 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Dyspnoea subjects affected / exposed	0 / 18 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Dyspnoea exertional subjects affected / exposed	1 / 18 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Epistaxis subjects affected / exposed	0 / 18 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain subjects affected / exposed	1 / 18 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Respiration abnormal			

subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 3 (0.00%) 0	
Psychiatric disorders Nightmare subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 3 (0.00%) 0	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	6 / 18 (33.33%) 6	0 / 3 (0.00%) 0	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	6 / 18 (33.33%) 6	0 / 3 (0.00%) 0	
Blood cholesterol increased subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 3 (0.00%) 0	
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 3 (0.00%) 0	
Blood pressure increased subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2	0 / 3 (0.00%) 0	
Crystal urine present subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 3 (0.00%) 0	
Eosinophil count increased subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 3 (0.00%) 0	
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 3 (0.00%) 0	
International normalised ratio increased subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 3 (0.00%) 0	

Protein urine present subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 3 (0.00%) 0	
Prothrombin time prolonged subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 3 (0.00%) 0	
Injury, poisoning and procedural complications Dental restoration failure subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 3 (0.00%) 0	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 3 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all) Restless legs syndrome subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2 0 / 18 (0.00%) 0	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Frequent bowel movements	0 / 18 (0.00%) 0 3 / 18 (16.67%) 3 3 / 18 (16.67%) 3 0 / 18 (0.00%) 0	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	

subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 3 (0.00%) 0	
Nausea subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 4	0 / 3 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 3 (0.00%) 0	
Skin and subcutaneous tissue disorders Rash pruritic subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 3 (0.00%) 0	
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 3 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 3 (0.00%) 0	
Bone pain subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 3 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 3 (0.00%) 0	
Infections and infestations Ear infection subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1	0 / 3 (0.00%) 0	
Respiratory tract infection subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 3 (0.00%) 0	
Rhinitis subjects affected / exposed occurrences (all)	0 / 18 (0.00%) 0	0 / 3 (0.00%) 0	

Tooth abscess			
subjects affected / exposed	1 / 18 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	2 / 18 (11.11%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 3 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 March 2020	Amended to update inclusion criteria.
21 May 2020	Amended to add Parts A2 and B.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
20 March 2020	Vertex Pharmaceuticals temporarily paused screening and enrollment in the VX19-814-101 study due to the outbreak of the COVID-19 pandemic.	28 April 2020

Notes:

Limitations and caveats

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

Based on elevated AST/ALT and low achieved VX-814 exposures, Vertex concluded to terminate study early as it was not feasible to safely reach VX-814 targeted exposure level. Therefore, data are incomplete and result should be interpreted with caution

Notes: