Clinical trial results:
A Phase 2, Open-label Study Evaluating Efficacy and Safety of VX-864 in Subjects With Alpha-1 Antitrypsin Deficiency Who Have the PiZZ Genotype, Over 48 Weeks

Summary

EudraCT number	2022-002746-40
Trial protocol	IE
Global end of trial date	19 August 2024

Results information

Result version number	v1 (current)
This version publication date	04 September 2025
First version publication date	04 September 2025

Trial information

Trial identification

Sponsor protocol code	VX22-864-108

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05643495
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Vertex Pharmaceuticals Incorporated
Sponsor organisation address	50 Northern Avenue, Boston, Massachusetts, India,
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	09 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 August 2024
Global end of trial reached?	Yes
Global end of trial date	19 August 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of VX-864 on blood levels of functional alpha-1 antitrypsin (AAT) in individuals with the PiZZ genotype

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 February 2023
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: 14
Worldwide total number of subjects	14
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	11
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study had 2 Groups: Group A subjects did not have a liver biopsy and Group B subjects have 2 liver biopsies performed over the course of the study.

Pre-assignment

Screening details:

A total of 14 subjects were enrolled from 23 February 2023 to 03 November 2023 in this study. Study drug dosing and efficacy assessments were terminated early due to Sponsor decision, therefore evaluation of efficacy endpoint was not completed.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A VX-864 500 mg

Arm description:

Subjects received VX-864 every 12 hours (q12h) for 48 weeks or until study drug dosing was terminated.

Arm type	Experimental
Investigational medicinal product name	VX-864
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-864 tablets orally every 12 hours (q12h).

Arm title	Group B VX-864 500 mg

Arm description:

Subjects undergo a liver biopsy before receiving VX-864 q12h for 48 weeks or until study drug dosing was terminated and undergo a second liver biopsy at either Week 24 or Week 48.

Arm type	Experimental
Investigational medicinal product name	VX-864
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received VX-864 tablets orally every 12 hours (q12h).

Number of subjects in period 1	Group A VX-864 500 mg	Group B VX-864 500 mg
Started	10	4
Completed	9	2
Not completed	1	2
Adverse event	-	1
Withdrawal of consent (not due to adverse event)	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Group A VX-864 500 mg
Reporting group description:	
Subjects received VX-864 every 12 hours (q12h) for 48 weeks or until study drug dosing was terminated.	
Reporting group title	Group B VX-864 500 mg
Reporting group description:	
Subjects undergo a liver biopsy before receiving VX-864 q12h for 48 weeks or until study drug dosing was terminated and undergo a second liver biopsy at either Week 24 or Week 48.	

Reporting group values	Group A VX-864 500 mg	Group B VX-864 500 mg	Total
Number of subjects	10	4	14
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	52.8	50.8	
standard deviation	± 14.2	± 10.4	-
Gender categorical Units: Subjects			
Female	8	3	11
Male	2	1	3
Race Units: Subjects			
White	10	4	14
Ethnicity Units: Subjects			
Not Hispanic or Latino	10	4	14

End points

End points reporting groups

Reporting group title	Group A VX-864 500 mg

Reporting group description:

Subjects received VX-864 every 12 hours (q12h) for 48 weeks or until study drug dosing was terminated.

Reporting group title	Group B VX-864 500 mg

Reporting group description:

Subjects undergo a liver biopsy before receiving VX-864 q12h for 48 weeks or until study drug dosing was terminated and undergo a second liver biopsy at either Week 24 or Week 48.

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

End point title	Change in Blood Functional Alpha-1 Antitrypsin (AAT) Levels[1]

End point description:

Data was not collected for this endpoint as the study drug dosing was terminated prior to any subject reaching Week (wk) 48.

End point type	Primary

End point timeframe:

From Baseline at Week 48

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 planned for this endpoint.

End point values	Group A VX-864 500 mg	Group B VX-864 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: µM				
median (full range (min-max))	(to)	(to)		

Notes:

[2] - Data was not collected as the study drug dosing was terminated prior to any subject reaching Week 48
[3] - Data was not collected as the study drug dosing was terminated prior to any subject reaching wk 48.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Blood Functional AAT Levels

End point title	Change in Blood Functional AAT Levels

End point description:

Data was not collected for this endpoint as the study drug dosing was terminated prior to any subject reaching Week 48.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Group A VX-864 500 mg	Group B VX-864 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: µM				
median (full range (min-max))	(to)	(to)		

Notes:

[4] - Data was not collected as the study drug dosing was terminated prior to any subject reaching wk 48.
[5] - Data was not collected as the study drug dosing was terminated prior to any subject reaching wk 48.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Blood Antigenic AAT Levels

End point title	Change in Blood Antigenic AAT Levels

End point description:

Data was not collected for this endpoint as the study drug dosing was terminated prior to any subject reaching Week 48.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Group A VX-864 500 mg	Group B VX-864 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: µM				
median (full range (min-max))	(to)	(to)		

Notes:

[6] - Data was not collected as the study drug dosing was terminated prior to any subject reaching wk 48.
[7] - Data was not collected as the study drug dosing was terminated prior to any subject reaching wk 48.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Blood Z-polymer Levels

End point title	Change in Blood Z-polymer Levels

End point description:

Data was not collected for this endpoint as the study drug dosing was terminated prior to any subject reaching Week 48.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Group A VX-864 500 mg	Group B VX-864 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: mg/L				
median (full range (min-max))	(to)	(to)		

Notes:

[8] - Data was not collected as the study drug dosing was terminated prior to any subject reaching wk 48.

[9] - Data was not collected as the study drug dosing was terminated prior to any subject reaching wk 48.

Statistical analyses

No statistical analyses for this end point

Secondary: Group B: Change in Z-polymer Accumulation in the Liver

End point title	Group B: Change in Z-polymer Accumulation in the Liver

End point description:

No subjects in Group B underwent a second liver biopsy at week 24 or week 48 as the study drug dosing was terminated prior to any subject reaching week 24 or week 48. Therefore no data was not collected for this end point.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Group A VX-864 500 mg	Group B VX-864 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: mg/L				
median (full range (min-max))	(to)	(to)		

Notes:

[10] - Data was not collected as the study drug dosing was terminated prior to any subject reaching wk 48.

[11] - Data was not collected as the study drug dosing was terminated prior to any subject reaching wk 48.

Statistical analyses

No statistical analyses for this end point

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

End point title	Safety and Tolerability as Assessed by Number of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

Safety set included all subjects who had received at least 1 dose of study drug in this study.

End point type	Secondary

End point timeframe:
Day 1 up to Week 52

End point values	Group A VX-864 500 mg	Group B VX-864 500 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	4		
Units: Subjects				
Subjects with TEAEs	10	4		
Subjects with SAEs	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 up to Week 52	
Adverse event reporting additional description:	
Safety set included all subjects who had received at least 1 dose of study drug in this study.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	Group A VX-864 500 mg
Reporting group description:	
Subjects received VX-864 q12h for 48 weeks or until study drug dosing was terminated.	
Reporting group title	Group B VX-864 500 mg
Reporting group description:	
Subjects undergo a liver biopsy before receiving VX-864 q12h for 48 weeks or until study drug dosing was terminated and undergo a second liver biopsy at either Week 24 or Week 48.	

Serious adverse events	Group A VX-864 500 mg	Group B VX-864 500 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Infections and infestations			
Diverticulitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (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: 5 %

Non-serious adverse events	Group A VX-864 500 mg	Group B VX-864 500 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	4 / 4 (100.00%)	
Investigations			
Blood creatine phosphokinase increased			

subjects affected / exposed	1 / 10 (10.00%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Congenital, familial and genetic disorders			
Porphyria non-acute			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Dysgeusia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Hyperaesthesia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	2 / 10 (20.00%)	2 / 4 (50.00%)	
occurrences (all)	2	2	
Mouth ulceration			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 10 (30.00%)	2 / 4 (50.00%)	
occurrences (all)	3	2	
Paraesthesia oral			

subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	2 / 10 (20.00%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Dermatitis contact			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Drug eruption			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction			
subjects affected / exposed	3 / 10 (30.00%)	0 / 4 (0.00%)	
occurrences (all)	3	0	
Dyshidrotic eczema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Post inflammatory pigmentation change			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	2	0	
Pseudoporphyria			

subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 4 (25.00%)	
occurrences (all)	1	1	
Joint swelling			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 4 (25.00%)	
occurrences (all)	0	1	
Diverticulitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 4 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 November 2023	Amended to stop all enrollment and study drug dosing at Vertex's discretion due to the occurrence of non-serious AEs of rash in several subjects. Therefore, all efficacy, pharmacokinetic, and exploratory biomarker assessments scheduled for subjects on or after the date of this amendment, 02 November 2023, will not be performed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Study drug dosing was permanently discontinued at the Sponsor's discretion based on frequency and nature of skin and subcutaneous tissue disorders.

Notes: