1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

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

Vertex Study Number: VX19-814-101

[redacted]

EudraCT Number: 2019-003650-92

Date of Protocol: 21 May 2020 (Version 3.0)

Vertex Pharmaceuticals Incorporated
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2 PROTOCOL SYNOPSIS

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

Brief Title Evaluation of the Efficacy and Safety of VX-814 in Subjects With the *PiZZ* Genotype

Clinical Phase and Clinical Study Type Phase 2; efficacy and safety

Objectives

Primary Objectives

- To evaluate the efficacy of VX-814 in *PiZZ* subjects as measured by plasma functional alpha-1 antitrypsin (AAT) levels
- To evaluate the safety and tolerability of VX-814 in *PiZZ* subjects

Secondary Objectives

- To evaluate the efficacy of VX-814 in *PiZZ* subjects as measured by plasma antigenic AAT levels
- To evaluate the pharmacokinetics (PK) of VX-814 in *PiZZ* subjects

[redacted]

Endpoints

Primary Endpoints

- Change from baseline in plasma functional AAT levels at Day 28
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

Secondary Endpoints

- Change from baseline in plasma antigenic AAT levels at Day 28
- PK parameters of VX-814 derived from plasma concentration-time data

[redacted]

Number of Subjects Approximately 43 subjects with the *PiZZ* genotype

Study Population Male subjects and female subjects 18 through 80 years of age, inclusive, with the *PiZZ* genotype

Investigational Drug

Active substance: VX-814

Activity: AAT modulator

Strength and route of administration: 100-mg tablet and matching placebo for oral administration.

Study Duration

Excluding the Screening Period, each subject will participate in the study for approximately 56 days: 28 days for the Treatment Period and 28 days for the Safety Follow-up Period.

Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study of VX-814. Schematics of the study design are shown below.

Part A1: Approximately 15 subjects in total with the *PiZZ* genotype and antigenic AAT levels <8 µM at screening will be randomized (2:1:1:1) to 1 of 3 VX-814 groups or the placebo group.

Part A2: Approximately 8 subjects in total with the *PiZZ* genotype and antigenic AAT levels <8 µM at screening will be randomized (3:1) to a VX-814 group or the placebo group.

Enrollment may be adjusted to ensure approximately 12 subjects receive VX-814 400 mg q12h in Parts A1 and A2 combined.

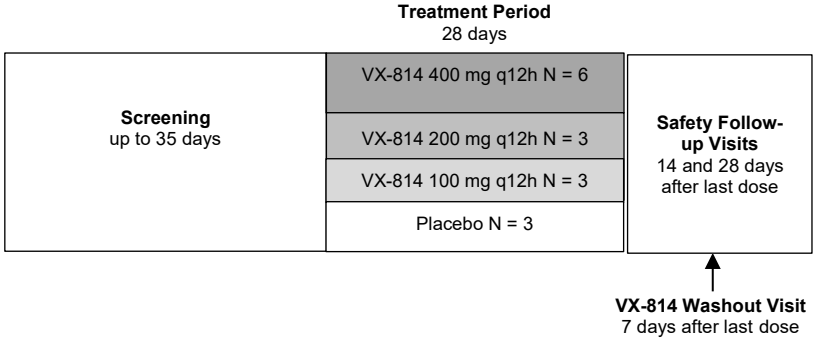
Part B: Approximately 20 subjects in total with the *PiZZ* genotype and antigenic AAT levels <8 µM at screening will be randomized (3:1) to a VX-814 group or the placebo group.

Enrollment in Parts A2 and B may be initiated before Part A1 completes the planned enrollment.

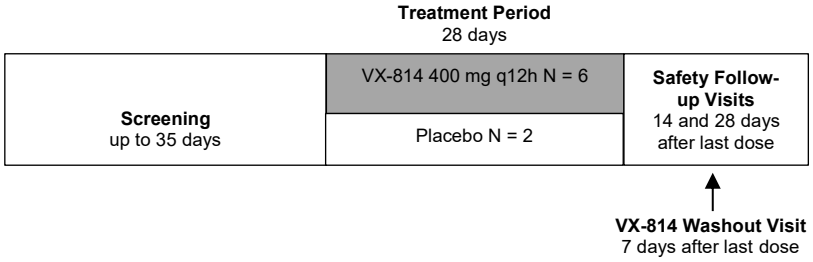
Randomization will be stratified by post-bronchodilator percent predicted forced expiratory volume in 1 second ($ppFEV_1$) obtained either during the Screening Period or from a historical post-bronchodilator $ppFEV_1$ value measured within 1 year before screening (<50% versus ≥50%).

Figure 2-1 Parts A1, A2, and B: Schematic of Study Design for Subjects Who Have Never Been on Augmentation Therapy

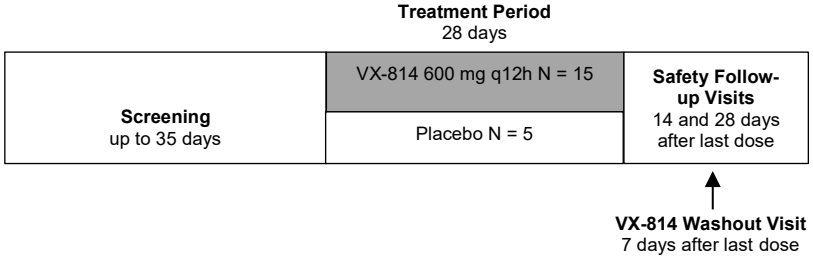
Part A1



Part A2



Part B



N: number of subjects; q12h: every 12 hours

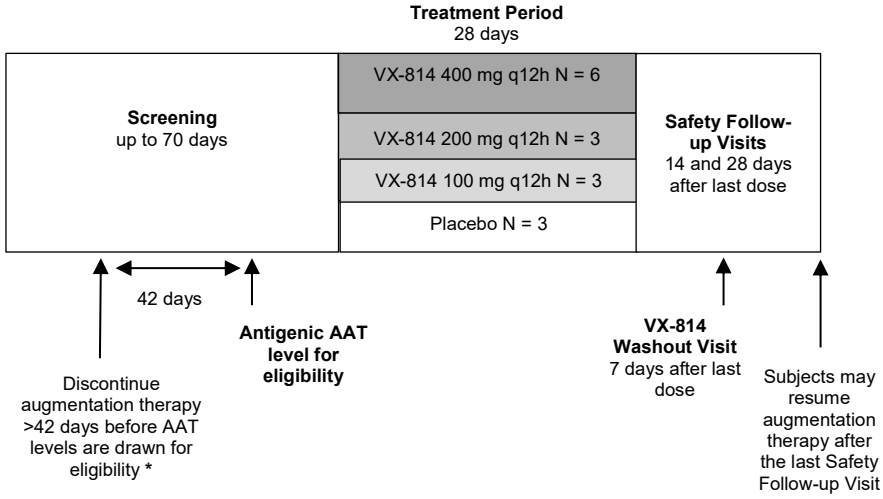
Note: Figure is not drawn to scale.

Subject numbers include subjects who have never been on augmentation therapy and subjects who have been on augmentation therapy at any time.

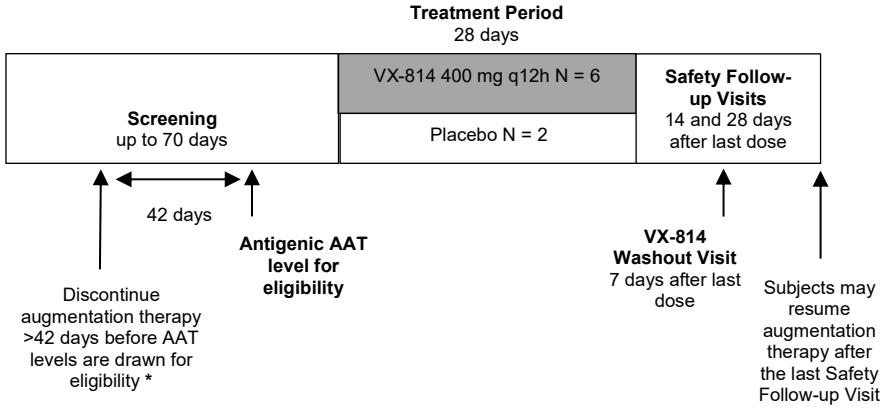
Antigenic AAT levels must be drawn to confirm eligibility and sent to the central laboratory; results must be obtained and confirmed to be <8 µM before randomization. Once antigenic AAT levels have been confirmed to meet this eligibility criterion, randomization and Day 1 can occur any time within the remaining screening window. **Sites should allow at least 14 days for sample processing and antigenic AAT level result reporting.**

Figure 2-2 Parts A1, A2, and B: Schematic of Study Design for Subjects Who Have Been on Augmentation Therapy at Any Time

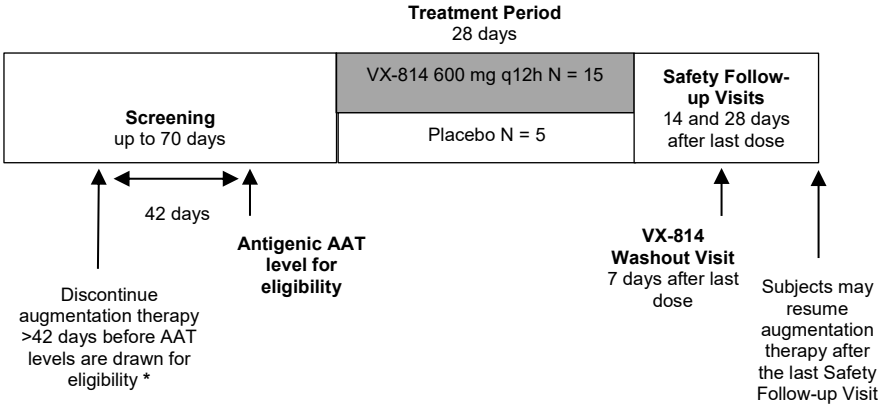
Part A1



Part A2



Part B



N: number of subjects; q12h: every 12 hours

Notes: Figure is not drawn to scale. Subject numbers include subjects who have never been on augmentation therapy and subjects who have been on augmentation therapy at any time. Subjects must discontinue augmentation therapy >42 days before antigenic AAT levels are drawn and sent to the central laboratory to confirm eligibility; results must be confirmed to be <8 μM before randomization. Once antigenic AAT levels have been confirmed to meet this eligibility criterion, randomization and Day 1 can occur any time within the remaining screening window. Sites should allow at least 14 days for sample processing and antigenic AAT level result reporting. Subjects can resume augmentation therapy after completion of assessments at the last Safety Follow-up Visit.

*Blood samples will be obtained for antigenic and functional AAT levels at the same time that the other screening laboratory assessments are performed. If the subject received the last dose of augmentation therapy >42 days prior, this sample can be used to measure antigenic AAT level for eligibility. If samples are obtained ≤42 days after the last dose of augmentation therapy, another sample must be drawn >42 days after the last dose of augmentation therapy and sent to the central laboratory to confirm eligibility.

Assessments

Efficacy:

Plasma functional and antigenic AAT levels

Safety:

AEs, clinical laboratory assessments, standard 12-lead ECGs, clinical evaluation of vital signs, pulse oximetry, spirometry, and physical examinations

Pharmacokinetics:

Plasma concentrations of VX-814

[redacted]

Statistical Analyses

In Part A1, subjects will be randomized 2:1:1:1 to receive VX-814 400 mg every 12 hours (q12h; n = 6), VX-814 200 mg q12h (n = 3), VX-814 100 mg q12h (n = 3), or placebo (n = 3). In Part A2, subjects will be randomized to receive VX-814 400 mg q12h (n = 6) or placebo (n = 2). In Part B, subjects will be randomized to receive VX-814 600 mg q12h (n = 15) or placebo (n = 5).

Assuming 10% of the randomized subjects have a missing value at Day 28, this sample size provides adequate precision to estimate the plasma functional AAT levels at Day 28 for the VX-814 600-mg q12h group in Part B.

The primary endpoint to assess efficacy is the change from baseline in plasma functional AAT levels at Day 28. [redacted]

3 SCHEDULE OF ASSESSMENTS

Schedules of assessments are in Table 3-1 (Parts A1, A2, and B Screening for subjects who have never been on augmentation therapy), Table 3-2 (Parts A1, A2, and B Screening for subjects who have been on augmentation therapy at any time), and Table 3-3 (Parts A1, A2, and B Treatment Period through Safety Follow-up).

Table 3-1 Study VX19‑814‑101 Parts A1, A2, and B: Screening for Subjects Who Have Never Been on Augmentation Therapy

Event/Assessment	Screening Period Day -35 through Day -1	Comments
Informed consent	X	
Inclusion and exclusion criteria review	X	Sections 8.1 and 8.2
Clinic visit	X	
Demographics	X	
Medical history	X	Section 11.1
Medications review	X	Section 9.6
Prior augmentation therapy review	X	Section 9.6
Antigenic AAT level	X	Antigenic AAT levels must be drawn and confirmed to be <8 µM to establish eligibility before randomization can occur. **Sites should allow at least 14 days for sample processing and antigenic AAT level result reporting.** Section 8.1, inclusion criterion #7 and Section 11.3.
Functional AAT level	X	Samples will be obtained for plasma functional AAT levels at the same time samples are obtained for antigenic AAT levels. Functional AAT level results will not be provided to site personnel. Section 11.3
Standard 12-lead ECG	X	Will be performed in triplicate after the subject has rested for at least 5 minutes. When ECGs, vital signs, and blood draws are done on the same day, they should be performed in said order. Section 11.5.4
Height and weight	X	Weight and height will be measured with shoes off.
Vital signs	X	Vital signs will be performed after the subject has rested for at least 5 minutes. Section 11.5.3
Pulse oximetry	X	Pulse oximetry will be performed after the subject has rested for at least 5 minutes. Section 11.5.3
Complete physical examination	X	Section 11.5.3
Serum FSH (postmenopausal female subjects only)	X	Section 11.5.2
Serum β-hCG (all female subjects)	X	Section 11.5.2
Serology (HBsAg, HCV Ab and RNA, HIV-1 and HIV-2 Abs)	X	Section 11.5.2
PiZZ genotype	X	*PiZZ* genotype must be performed at the central laboratory. Section 8.1, inclusion criterion #6
Serum chemistry	X	Section 11.5.2

Table 3-1 Study VX19‑814‑101 Parts A1, A2, and B: Screening for Subjects Who Have Never Been on Augmentation Therapy

Event/Assessment	Screening Period Day -35 through Day -1	Comments
Hematology	X	Section 11.5.2
Coagulation	X	Section 11.5.2
Urinalysis	X	Section 11.5.2
Spirometry	X	Spirometry will be performed post-bronchodilator and according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines. If spirometry cannot be performed, historical post-bronchodilator $ppFEV_1$ results measured within 1 year before screening can be used to determine eligibility. Section 8.2 exclusion criterion #7 and Section 11.5.5.
Urine cotinine	X	Section 11.5.2
AEs and SAEs	Continuous from signing of ICF through last Safety Follow-up Visit	Section 11.5.1

AAT: alpha-1 antitrypsin; AE: adverse event; β-hCG: beta-human chorionic gonadotropin; FSH: follicle-stimulating hormone; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV-1/HIV-2 Abs: antibodies against human immunodeficiency viruses 1 and 2; ICF: informed consent form; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SAE: serious adverse event

Note: Screening procedures (including informed consent) can be performed over more than 1 day. Informed consent must be obtained prior to any procedures. Repeat Screening assessments and Screening assessments that were not conducted at the initial visit during the Screening Period may be performed at the clinic or at home by a qualified visiting nurse, if permitted by ethical and regulatory authorities and agreed upon after investigator and subject consultation.

Table 3-2 Study VX19‑814‑101 Parts A1, A2, and B: Screening for Subjects Who Have Been on Augmentation Therapy at Any Time

Event/Assessment	Screening Period Day -70 through Day -1	Comments
Informed consent	X	
Inclusion and exclusion criteria review	X	Sections 8.1 and 8.2
Clinic visit	X	
Demographics	X	
Medical history	X	Section 11.1
Medications review	X	Section 9.6
Prior augmentation therapy review	X	**Subjects must discontinue augmentation therapy >42 days before the antigenic AAT levels are obtained to determine eligibility. Subjects can resume augmentation therapy after completion of the Safety Follow-up Assessments.** Section 9.6
Antigenic AAT level (up to 2 samples obtained during screening)	X	Samples will be obtained for plasma antigenic AAT level and sent to the central laboratory at the same time other screening laboratory assessments are done. If the subject received the last dose of augmentation therapy >42 days prior, these results can be used to determine eligibility. If this sample is obtained ≤42 days after the last dose of augmentation therapy, another sample **must** be drawn >42 days after the last dose of augmentation therapy to confirm eligibility. Results must be confirmed to be <8 μM before randomization. **This second sample can be drawn at a home or clinic visit. Sites should allow at least 14 days for sample processing and results reporting.** Section 8.1, inclusion criterion #7 and Section 11.3.
Functional AAT level (up to 2 samples obtained during screening)	X	Samples will be obtained for plasma functional AAT levels at the same time samples are obtained for antigenic AAT levels. **If a second sample is obtained, the second sample can be drawn at a home or clinic visit.** Results will not be provided to site personnel. Section 11.3
Standard 12-lead ECG	X	Will be performed in triplicate after the subject has rested for at least 5 minutes. When ECGs, vital signs, and blood draws are done on the same day, they should be performed in said order. Section 11.5.4
Height and weight	X	Weight and height will be measured with shoes off.
Vital signs	X	Vital signs will be performed after the subject has rested for at least 5 minutes. Section 11.5.3
Pulse oximetry	X	Pulse oximetry will be performed after the subject has rested for at least 5 minutes. Section 11.5.3
Complete physical examination	X	Section 11.5.3

Table 3-2 Study VX19‑814‑101 Parts A1, A2, and B: Screening for Subjects Who Have Been on Augmentation Therapy at Any Time

Event/Assessment	Screening Period Day -70 through Day -1	Comments
Serum FSH (postmenopausal female subjects only)	X	Section 11.5.2
Serum β-hCG (all female subjects)	X	Section 11.5.2
Serology (HBsAg, HCV Ab and RNA, HIV-1 and HIV-2 Abs)	X	Section 11.5.2
PiZZ genotype	X	*PiZZ* genotype must be performed at the central laboratory. Section 8.1, inclusion criterion #6
Serum chemistry	X	Section 11.5.2
Hematology	X	Section 11.5.2
Coagulation	X	Section 11.5.2
Urinalysis	X	Section 11.5.2
Spirometry	X	Spirometry will be performed post-bronchodilator and according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines. If spirometry cannot be performed, historical post-bronchodilator $ppFEV_1$ results within 1 year before screening can be used to determine eligibility. Section 8.2 exclusion criterion #7 and Section 11.5.5.
Urine cotinine	X	Section 11.5.2
AEs and SAEs	Continuous from signing of ICF through last Safety Follow-up Visit	Section 11.5.1

AAT: alpha-1 antitrypsin; AE: adverse event; β-hCG: beta-human chorionic gonadotropin; FSH: follicle-stimulating hormone; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; HIV-1/HIV-2 Abs: antibodies against human immunodeficiency viruses 1 and 2; ICF: informed consent form; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SAE: serious adverse event

Notes: Screening procedures (including informed consent) can be performed over more than 1 day. Informed consent must be obtained prior to any procedures. Repeat Screening assessments and Screening assessments that were not conducted at the initial visit during the Screening Period may be performed at the clinic or at home by a qualified visiting nurse, if permitted by ethical and regulatory authorities and agreed upon after investigator and subject consultation. If a second blood sample is required >42 days after the last dose of augmentation therapy to measure antigenic AAT levels to confirm eligibility, this second blood sample (and the second functional AAT level drawn at the same time) can be drawn at a home visit or clinic visit.

Table 3-3 Study VX19‑814-101 Parts A1, A2, and B: Treatment Period and Follow-up Visits

Event/ Assessment	Treatment Period: Day 1[a]	Day 7 (±1)[b]	Day 14 (±2)[b]	Day 21 (±2)[b]	Day 28 (-2)[c]	[redacted]	VX-814 Washout Visit 7 (±2) Days After Last Dose of Study Drug	ETT Visit[e]	Safety Follow-up Visit 14 (±2) Days After Last Dose of Study Drug	Safety Follow-up Visit 28 (±2) Days After Last Dose of Study Drug	Comments
Inclusion and exclusion criteria confirmation	X										
Randomization	X										Randomization may occur up to 7 days before Day 1 after all eligibility criteria including antigenic AAT levels <8 µM are confirmed. If randomization occurs before Day 1, eligibility must also be confirmed before the first dose of study drug on Day 1.
Clinic visit	X										

[a] **On Day 1, all assessments must be completed before the first dose of study drug except for the post dose PK sampling, which is done at 3 and 6 hours (±30 minutes) after dosing in the clinic.**

[b] **All assessments will be performed before administration of the morning or evening dose of study drug unless noted otherwise (Section 11).** These visits may be performed in the morning or the evening in the clinic or at home by a qualified visiting nurse. If the visit is performed at home, it must be followed by a consultation between the subject and investigator (i.e., in person, telephone, or telemedicine video conference) within 1 day and may also include a separate follow-up with the study coordinator.

[c] **On Day 28, all assessments will be performed before administration of the morning dose of study drug unless noted otherwise (Section 11).** The morning dose of study drug on the Day 28 Visit will be taken at home or in the clinic after the pre-dose PK sample has been drawn (within 60 minutes of dosing). Additional PK sampling will be done at 3 and 6 hours (±30 minutes) after dosing. The last dose of study drug will be taken at home in the evening on Day 28, regardless of whether the Day 28 Visit occurs on Day 26 or Day 27.

[redacted]

[e] If the subject prematurely discontinues study drug treatment, an ETT Visit should be scheduled as soon as possible after the decision to terminate study treatment. Subjects who prematurely discontinue treatment will be required to complete the Safety Follow-up Visits, approximately 14 (±2) and 28 (±2) days after their last dose of study drug. If the ETT Visit occurs between 12 and 21 days (inclusive) after the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit 14 days after the last dose of study drug, and a separate Safety Follow-up Visit 14 days after the last dose will not be required; the Safety Follow-up Visit 28 days after the last dose would still be required. If the ETT Visit occurs ≥22 days after the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit 28 days after the last dose, and a separate Safety Follow-up Visit 28 days after the last dose will not be required.

Table 3-3 Study VX19‑814-101 Parts A1, A2, and B: Treatment Period and Follow-up Visits

Event/ Assessment	Treatment Period: Day 1[a]	Day 7 (±1) [b]	Day 14 (±2)[b]	Day 21 (±2)[b]	Day 28 (-2)[c]	[redacted]	VX-814 Washout Visit 7 (±2) Days After Last Dose of Study Drug	ETT Visit[e]	Safety Follow-up Visit 14 (±2) Days After Last Dose of Study Drug	Safety Follow-up Visit 28 (±2) Days After Last Dose of Study Drug	Comments
Clinic or home health visit		X	X	X	X		X	X	X	X	Subjects will have the option to complete these visits in the clinic or to have a home health visit**. Home health visits are only an option if they receive approval from both ethical and regulatory authorities in the respective country.**
Telemedicine video conference or telephone contact		X	X	X	X		X	X	X	X	**Performed within 1 day after home health visit.** Required only for subjects who have a home health visit; not required for subjects who have a clinic visit.
Antigenic AAT level	X	X	X		X		X	X	X	X	Section 11.3
Functional AAT level	X	X	X		X		X	X	X	X	Section 11.3
[redacted]											

Table 3-3 Study VX19‑814-101 Parts A1, A2, and B: Treatment Period and Follow-up Visits

Event/ Assessment	Treatment Period: Day 1[a]	Day 7 (±1) [b]	Day 14 (±2)[b]	Day 21 (±2)[b]	Day 28 (-2)[c]	[redacted]	VX-814 Washout Visit 7 (±2) Days After Last Dose of Study Drug	ETT Visit[e]	Safety Follow-up Visit 14 (±2) Days After Last Dose of Study Drug	Safety Follow-up Visit 28 (±2) Days After Last Dose of Study Drug	Comments
[redacted]											
Weight and height	X										Weight and height will be measured with shoes off.
Standard 12-lead ECG	X	X			X			X	X	X	Performed in triplicate after the subject has rested for at least 5 minutes When ECGs, vital signs, and blood draws are done on the same day, they should be performed in said order. **Day 1**: predose and 6 hours (±15 min) after dosing. Section 11.5.4
Vital signs	X	X	X		X			X	X	X	Vital signs will be performed after the subject has rested for at least 5 minutes. Section 11.5.3
Pulse oximetry	X	X	X		X			X	X	X	Pulse oximetry will be performed after the subject has rested for at least 5 minutes. Section 11.5.3
Pregnancy test (premenopausal female subjects of childbearing potential only)	Urine and Serum		Serum		Urine			Serum	Serum	Serum	Subjects must have a negative urine pregnancy test result on Day 1 before starting dosing.

Table 3-3 Study VX19‑814-101 Parts A1, A2, and B: Treatment Period and Follow-up Visits

	Treatment Period									
Event/ Assessment	**Day 1[a]**	**Day 7 (±1) [b]**	**Day 14 (±2)[b]**	**Day 21 (±2)[b]**	**Day 28 (-2)[c]**	**VX-814 Washout Visit 7 (±2) Days After Last Dose of Study Drug**	**ETT Visit[e]**	**Safety Follow-up Visit 14 (±2) Days After Last Dose of Study Drug**	**Safety Follow-up Visit 28 (±2) Days After Last Dose of Study Drug**	**Comments**
Physical examination/ review of symptoms	Abbrev PE				Review of symptoms	Review of symptoms	Review of symptoms	Review of symptoms	Review of symptoms	If there are any abnormal findings in the review of symptoms, the subject will be instructed to have a complete PE in the clinic. Section 11.5.3
Spirometry (optional)	X				X					Spirometry will be performed post-bronchodilator and according to the American Thoracic Society Guidelines/European Respiratory Society Guidelines. Section 11.5.5
Sample for UGT1A1 genotype	X									A single sample will be collected at any time on Day 1. Section 11.2.2
[redacted]										
Serum chemistry	X	X	X	X	X	X	X	X	X	Section 11.5.2
Hematology	X	X	X	X	X	X	X	X	X	Section 11.5.2
Coagulation	X	X	X	X	X	X	X	X	X	Section 11.5.2
Urinalysis	X	X	X	X	X		X	X	X	Section 11.5.2

Table 3-3 Study VX19‑814-101 Parts A1, A2, and B: Treatment Period and Follow-up Visits

Event/ Assessment	Treatment Period: Day 1[a]	Day 7 (±1) [b]	Day 14 (±2)[b]	Day 21 (±2)[b]	Day 28 (-2)[c]	[redacted]	VX-814 Washout Visit 7 (±2) Days After Last Dose of Study Drug	ETT Visit[e]	Safety Follow-up Visit 14 (±2) Days After Last Dose of Study Drug	Safety Follow-up Visit 28 (±2) Days After Last Dose of Study Drug	Comments
Blood for PK sampling	X	X	X	X	X		X	X	X	X	**Day 1 and Day 28:** predose (within 60 minutes before dosing) and at 3 and 6 hours (±30 minutes) after dosing (relative to the morning dose**).** **Days 7, 14, and 21**: predose (within 60 minutes before dosing, relative to the morning or evening dose) **Safety Follow-up Visits:** collected at any time during the visit. Section 11.2.1
Study drug administration	Day 1 through Day 28										Section 9.7
AEs and SAEs	Continuous from signing of ICF through last Safety Follow-up Visit										Section 11.5.1
Medications review	Continuous from signing of ICF through last Safety Follow-up Visit										Section 9.6

AAT: alpha-1 antitrypsin; Abbrev: abbreviated; AE: adverse event; [redacted]; ETT: Early Termination of Treatment: ICF: informed consent form; [redacted] PK: pharmacokinetic; SAE: serious adverse event; [redacted]

4 TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
AAT	alpha-1 antitrypsin
AATD	alpha-1 antitrypsin deficiency
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
CD	compact disc
COPD	chronic obstructive pulmonary disease
CPAP	clinical pharmacology analysis plan
CRF	case report form
CRO	contract research organization
[redacted]	[redacted]
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
eGFR	estimated glomerular filtration rate
[redacted]	[redacted]
ETT	Early Termination of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLI	Global Lung Function Initiative
GLP	Good Laboratory Practice
GPP3	Good Publication Practices
GPS	Global Patient Safety
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV-1/HIV-2 Abs	antibodies against human immunodeficiency viruses 1 and 2
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
[redacted]	[redacted]
IMP	investigational medicinal product

Abbreviation	Definition
IRB	institutional review board
IUD	intrauterine device
IWRS	interactive web or voice response system
[redacted]	[redacted]
Max	maximum value
MCP-Mod	multiple-comparison procedures with modeling techniques
Min	minimum value
MMRM	mixed-effects model for repeated measures
[redacted]	[redacted]
N	size of subsample
PC	publication committee
PD	pharmacodynamics, pharmacodynamics
PE	physical examination
[redacted]	[redacted]
PIs	principal investigators
PiZZ	homozygous for the Z mutation in the *SERPINA1* gene that encodes the AAT protein
PK	pharmacokinetic, pharmacokinetics
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
q12h	every 12 hours
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SC	steering committee
SD	standard deviation
SERPINA1	serine (or cysteine) proteinase inhibitor, clade A (alpha-1antiproteinase, antitrypsin), member 1
SET	study execution team
[redacted]	[redacted]
SUSAR	suspected, unexpected, serious adverse reaction
TE	treatment-emergent
ULN	upper limit of normal
USA	United States of America
WHODrug	World Health Organization-Drug Dictionary

5 INTRODUCTION

5.1 Background

Alpha-1 antitrypsin deficiency (AATD) is a genetic disorder characterized by low circulating levels of alpha-1 antitrypsin (AAT). AAT is produced primarily in the liver and secreted into the blood, although other cell types, including lung epithelial cells, monocytes, macrophages, and neutrophils, produce the protein locally.[1, 2] AAT inhibits several serine proteinases secreted by inflammatory cells (most notably neutrophil elastase, cathepsin G, and proteinase-3) and thus protects organs such as the lung from damage by these proteinases, especially during periods of infection and increased inflammation.

A single point mutation in the *Z*-allele of *SERPINA1* (the gene encoding AAT) leads to protein misfolding, intracellular polymerization of misfolded mutant Z-AAT protein, and reduced secretion of active Z-AAT protein. Consequently, circulating AAT levels in individuals homozygous for the *Z*-allele (*PiZZ*) are markedly reduced; only approximately 15% of Z-AAT protein folds correctly and is secreted by the cell. The reduced levels of circulating, active AAT result in an imbalance between proteinase and antiproteinase activity, which has its greatest impact in the lung. Consequently, lung tissue is damaged over time, resulting in emphysema, a form of chronic obstructive pulmonary disease. This effect is most pronounced in *PiZZ* individuals and typically manifests in middle age, resulting in a decline in quality of life and shortened lifespan (mean 67 years of age).[3] *PiZZ* individuals account for the majority of those with clinically relevant AATD lung disease. The accumulation of polymerized Z-AAT protein within hepatocytes causes cytotoxicity that can result in neonatal liver disease or progressive liver disease in adulthood that can lead to cirrhosis or liver cancer.

VX-814 is being developed as a treatment for AATD. VX-814 has the potential to restore physiological levels of circulating AAT activity and thus reduce the risk of lung disease. By preventing Z-polymer formation in the liver, VX-814 may also reduce the risk of developing progressive liver disease (fibrosis and cirrhosis).

5.2 Study Rationale

The purpose of this study is to evaluate the efficacy and safety profile of VX-814, including identification of an optimal VX-814 dose, to support further clinical development as a treatment for AATD. [redacted]

6 STUDY OBJECTIVES

6.1 Primary Objectives

- To evaluate the efficacy of VX-814 in *PiZZ* subjects as measured by plasma functional AAT levels
- To evaluate the safety and tolerability of VX-814 in *PiZZ* subjects

6.2 Secondary Objectives

- To evaluate the efficacy of VX-814 in *PiZZ* subjects as measured by plasma antigenic AAT levels
- To evaluate the pharmacokinetics (PK) of VX-814 in *PiZZ* subjects

[redacted]

7 STUDY ENDPOINTS

7.1 Primary Endpoints

- Change from baseline in plasma functional AAT levels at Day 28
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

7.2 Secondary Endpoints

- Change from baseline in plasma antigenic AAT levels at Day 28
- PK parameters of VX-814 derived from plasma concentration-time data

[redacted]

8 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are randomized and will also be confirmed before the first dose of study drug on Day 1.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible.

8.1 Inclusion Criteria

1. Subject will sign and date an informed consent form (ICF).
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures.
3. Subjects will be 18 through 80 years of age, inclusive, at the time of signing of the ICF.
4. All female subjects must have a negative pregnancy test at screening (serum test). Premenopausal female subjects of child-bearing potential must also have a negative pregnancy test on Day 1 (urine test) and must not be nursing or planning to become pregnant during the study or within 90 days after the last study drug dose.
5. Body mass index (BMI) of 18.0 to 35.0 kg/m^2, inclusive.
6. Subjects must have a *PiZZ* genotype confirmed at screening.

   NOTE: *PiZZ* genotype must be tested at the central laboratory. Historical genotype results can be used to determine eligibility if they were obtained as part of a different Vertex study. In addition, if the screening *PiZZ* genotype result is not received before randomization, a previous non-Vertex *PiZZ* genotype laboratory report (approved by the medical monitor or designee) may be used to establish provisional eligibility. **Subjects who have been randomized and whose screening genotype subsequently does not confirm study eligibility must be discontinued from the study (Section 9.10).**
7. Plasma antigenic AAT level <8 μM during screening.

   For subjects who have been on augmentation therapy at any time, results used to confirm eligibility must be drawn >42 days after the last dose of augmentation therapy. Antigenic AAT levels must be obtained from the central laboratory and results confirmed before randomization.
8. Willing to remain off of augmentation therapy from >42 days before antigenic AAT levels are obtained for eligibility through the last Safety Follow-Up Visit

8.2 Exclusion Criteria

1. History or presence of any illness or clinical condition that, in the opinion of the investigator, might affect the subject's safety or compliance or confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This includes, but is not limited to, the following:
   - Solid organ, lung, or hematological transplantation or is currently on a transplant list
   - Subjects who have undergone gastrectomy or other gastrointestinal tract surgery, except appendectomy, cholecystectomy, and hemorrhoid surgery.
   - Cancer, except for squamous cell skin cancer, basal cell skin cancer, Stage 0 cervical carcinoma in situ, and stage 0 or 1 melanoma (all 4 with no recurrence during the last 5 years)

2. History of significant alcohol consumption for a period of more than 3 consecutive months within 1 year before screening, defined as more than 14 drinks/week for females or 21 drinks/week for males (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor).
3. Illegal drug use within 1 year before screening as deemed by the investigator, including but not limited to cocaine, heroin, and other opioids.
4. Ongoing or prior participation in a study of an investigational treatment within 28 days or 5 terminal half-lives (whichever is longer) before screening. The duration of the elapsed time may be longer if required by local regulations.
5. History of use of gene therapy or RNAi therapy at any time previously.
6. Use of oral corticosteroids (at any dose) for a duration of greater than 3 months at any time within the 3 months before screening.
7. A post-bronchodilator forced expiratory volume in 1 second (FEV_1) value <30% of predicted mean for age, sex, and height (equations of the Global Lung Function Initiative [GLI]) during screening. Post-bronchodilator spirometry measurements must meet American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for acceptability and repeatability.[4, 5, 6]

   NOTE: if spirometry cannot be performed at screening, historical post-bronchodilator percent predicted FEV_1 ($ppFEV_1$) results within 1 year before screening can be used to determine eligibility. Historical post-bronchodilator spirometry measurements are <30% of predicted mean for age, sex, and height (equations of the GLI) and must meet ATS/ERS criteria for acceptability and repeatability.
8. All clinically important pulmonary disease other than AATD-related COPD, including but not limited to physician-diagnosed COPD not related to AATD, interstitial lung disease, cystic fibrosis, pulmonary hypertension with or without cor pulmonale, history of pulmonary embolism, or malignant lung cancer.
9. Unstable AATD-related COPD as deemed by the investigator.
10. Documented chronic need for positive airway pressure therapy beyond nocturnal use.
11. Documented medical history or diagnosis of clinically evident liver disease including but not limited to a prior diagnosis of hepatitis of any etiology, cirrhosis, portal hypertension, or confirmed or suspected esophageal varices.
12. Any of the following abnormal laboratory values at screening:
    - Platelet count $<150 \times 10^9$/L.
    - Albumin ≤3.5 g/dL
    - International normalized ratio ≥1.2
    - Hemoglobin <10 g/dL
    - Total bilirubin > upper limit of normal (ULN)
    - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) >2 × ULN

- Estimated glomerular filtration rate (eGFR) ≤30 mL/min/1.73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)

13. Risk factors for Torsade de Pointes (e.g., familial long QT syndrome, chronic hypokalemia, heart failure) or concomitant medications that prolong the QT/QTc interval or any history of unstable cardiac disorder that, in the opinion of the investigator, might put the subject at risk or may confound the results of the study.
14. Any clinically significant ECG abnormality (as determined by the investigator) or median QTcF of triplicate standard 12-lead ECGs >450 msec at screening.
15. History of Gilbert's Syndrome.
16. Positive for HBsAg, HCV RNA, or HIV-1 and HIV-2 antibodies during screening.
17. Use of the substances, activities, or devices during the time periods indicated in Section 9.5.
18. Cigarette smoking during the past 6 months or a positive cotinine test at screening that is due to smoking or an electronic nicotine delivery system. Positive cotinine test due to nicotine replacement therapy for the purposes of smoking cessation, as attested by the investigator, is permitted.
19. Male subjects who plan to donate sperm or who have a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose.
20. The subject or a close relative of the subject is the investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study. An adult (18 years of age or older) who is a relative of a study staff member may be enrolled in the study provided that
    - the adult lives independently of and does not reside with the study staff member, and
    - the adult participates in the study at a site other than the site at which the family member is employed.
21. Hypersensitivity to any component of the investigational drug product or placebo (e.g., lactose).
22. Subjects for whom discontinuation of augmentation therapy is not considered to be in their best interest, based on the clinical judgement of the treating physician.

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 2, randomized, double-blind, placebo-controlled study of VX-814. Schematics of the study design are shown in Figure 9-1 and Figure 9-2.

Part A1: Approximately 15 subjects in total with the *PiZZ* genotype and antigenic AAT levels <8 µM at screening will be randomized (2:1:1:1) to 1 of 3 VX-814 groups or the placebo group.

Part A2: Approximately 8 subjects in total with the *PiZZ* genotype and antigenic AAT levels <8 µM at screening will be randomized (3:1) to the VX-814 group or the placebo group.

Enrollment may be adjusted to ensure approximately 12 subjects receive VX-814 400 mg q12h in Parts A1 and A2 combined.

Part B: Approximately 20 subjects in total with the *PiZZ* genotype and antigenic AAT levels <8 µM at screening will be randomized (3:1) to the VX-814 group or the placebo group.

Enrollment in Parts A2 and B may be initiated before Part A1 completes the planned enrollment.

Randomization will be stratified by $ppFEV_1$ obtained either during the Screening Period or from a historical $ppFEV_1$ value (<50% versus ≥50%).

Screening Visit assessments for subjects who have never been on augmentation therapy are listed in Table 3-1. Screening Visit assessments for subjects who have been on augmentation therapy at any time are listed in Table 3-2. Treatment Period assessments for all subjects are listed in Table 3-3.

Figure 9-1 Parts A1, A2, and B: Schematic of Study Design for Subjects Who Have Never Been on Augmentation Therapy

Part A1

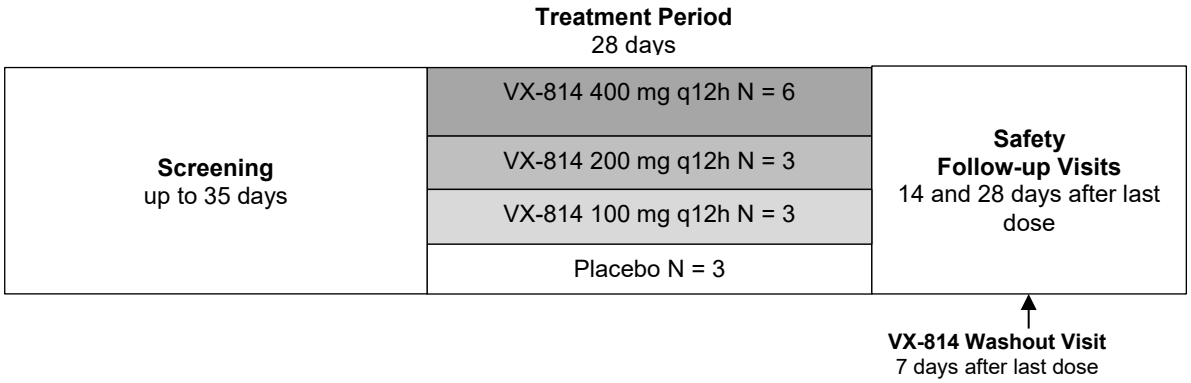
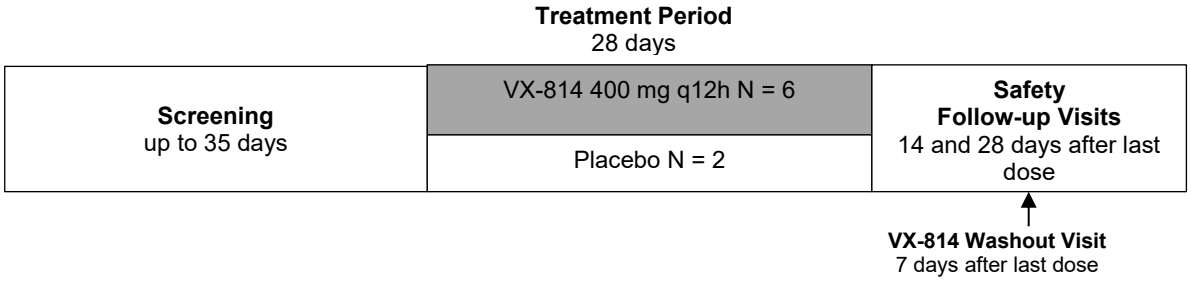
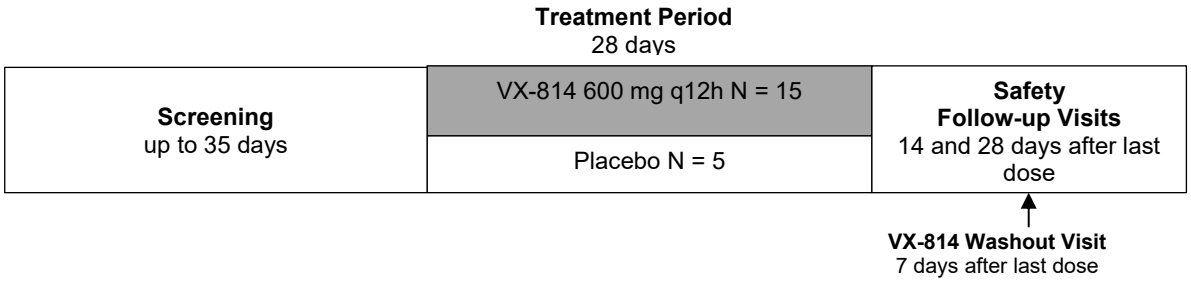


Figure 9-1 Parts A1, A2, and B: Schematic of Study Design for Subjects Who Have Never Been on Augmentation Therapy

Part A2



Part B



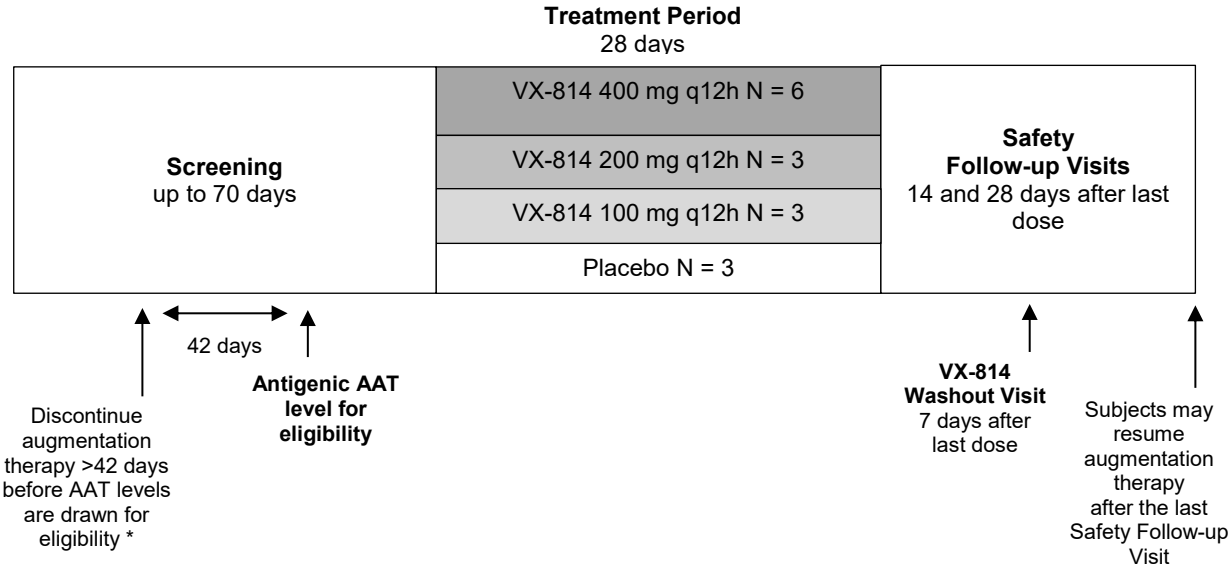
N: number of subjects; q12h: every 12 hours

Notes: Figure is not drawn to scale. Subject numbers include subjects who have never been on augmentation therapy and subjects who have been on augmentation therapy at any time.

Antigenic AAT levels must be drawn to confirm eligibility and sent to the central laboratory; results must be obtained and confirmed to be <8 µM before randomization. Once antigenic AAT levels have been confirmed to meet this eligibility criterion, randomization and Day 1 can occur any time within the remaining screening window. **Sites should allow at least 14 days for sample processing and antigenic AAT level result reporting.**

Figure 9-2 Parts A1, A2, and B: Schematic of Study Design for Subjects Who Have Been on Augmentation Therapy at Any Time

Part A



Part A2

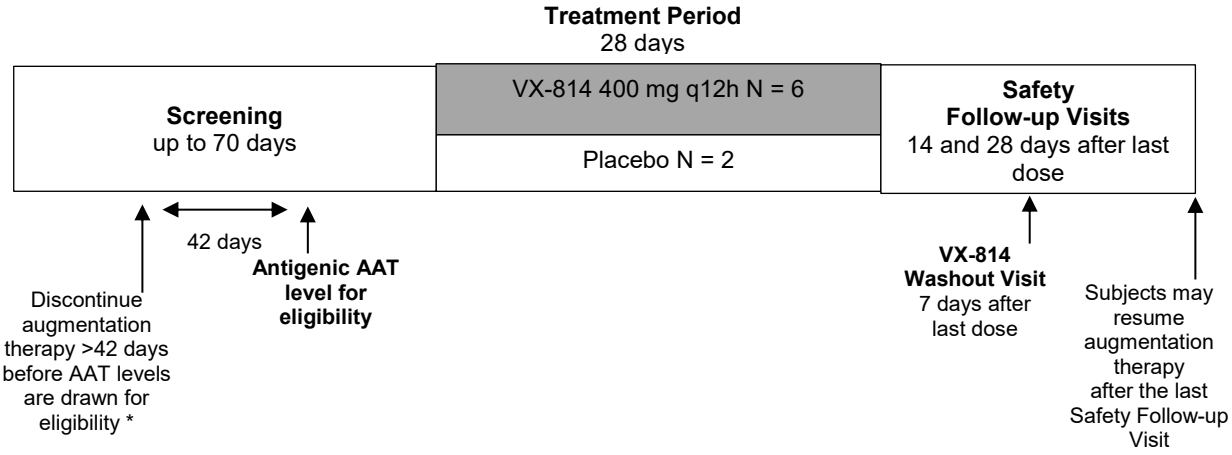
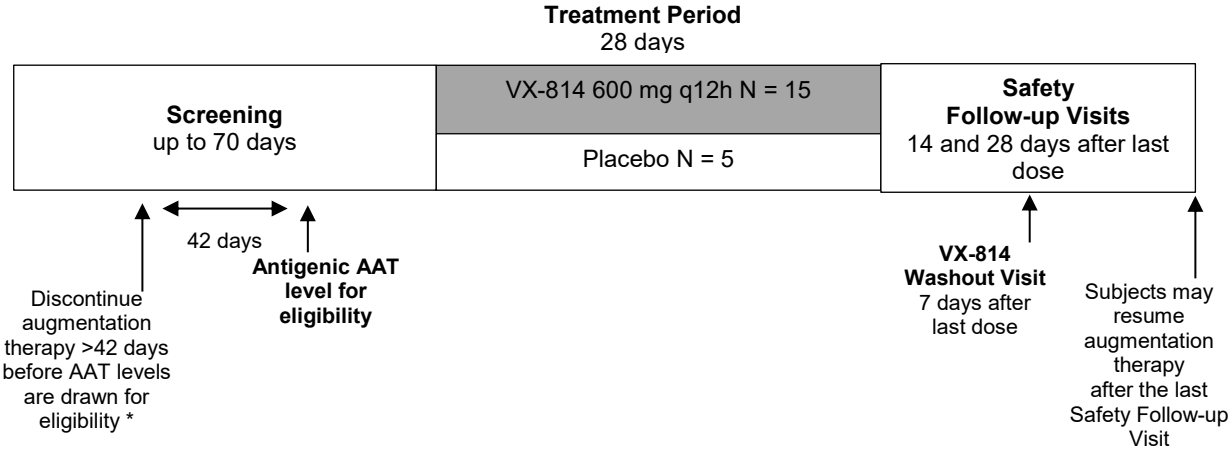


Figure 9-2 Parts A1, A2, and B: Schematic of Study Design for Subjects Who Have Been on Augmentation Therapy at Any Time

Part B



N: number of subjects; q12h: every 12 hours

Notes: Figure is not drawn to scale. Subject numbers include subjects who have never been on augmentation therapy and subjects who have been on augmentation therapy at any time. Subjects must discontinue augmentation therapy >42 days before antigenic AAT levels are drawn and sent to the central laboratory to confirm eligibility; results must be confirmed to be <8 μM before randomization. Once antigenic AAT levels have been confirmed to meet this eligibility criterion, randomization and Day 1 can occur any time within the remaining screening window. Sites should allow at least 14 days for sample processing and antigenic AAT level results reporting. Subjects can resume augmentation therapy after completion of assessments at the last Safety Follow-up Visit.

*Blood samples will be obtained for antigenic and functional AAT levels at the same time that the other screening laboratory assessments are performed. If the subject received the last dose of augmentation therapy >42 days prior, this sample can be used to measure antigenic AAT level for eligibility. If samples are obtained ≤42 days after the last dose of augmentation therapy, another sample **must** be drawn >42 days after the last dose of augmentation therapy and sent to the central laboratory to confirm eligibility.

9.1.1 Screening

For subjects who have never been on augmentation therapy, the Screening Period (Day -35 through Day -1) will occur up to 35 days before the first dose of study drug.

For subjects who have been on augmentation therapy at any time, the Screening Period (Day -70 through Day -1) will occur up to 70 days before the first dose of study drug. The last dose of augmentation therapy must have been given **>42 days before the antigenic AAT levels are obtained to confirm eligibility.** To establish eligibility, an antigenic AAT level must be drawn **>42 days after the last dose of augmentation therapy** and sent to the central laboratory**.** The antigenic AAT result must be reviewed to confirm eligibility before randomization. Subjects will remain off augmentation therapy thereafter until after the last Safety Follow-up Visit has been conducted.

Screening assessments will be used to confirm that subjects meet the eligibility criteria. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject before any study procedure takes place. Screening procedures (including informed consent) can be performed over more than 1 day. Informed consent must be obtained

prior to any procedures. Screening assessments that were not conducted at the initial visit during the Screening Period may be performed at home by a qualified visiting nurse or at the clinic (if permitted by ethical and regulatory authorities and agreed upon after investigator and subject consultation).

9.1.1.1 Repetition of Screening Assessment(s)

If screening spirometry measurements fail to meet acceptability and repeatability criteria as specified by American Thoracic Society/European Respiratory Society guidelines[4, 5, 6], repeat spirometry evaluation may be performed.

Otherwise, repeating individual screening assessment(s) that did not meet eligibility criteria is not permitted, with the following exceptions that require the approval of the medical monitor:

- If there is clear evidence of a damaged sample, laboratory error, or equipment malfunction, collection of a repeat sample for the appropriate laboratory test or assessment may be permitted.
- Exclusionary liver function, platelet, hemoglobin, albumin, or eGFR test results, which may be retested once.
- Exclusionary ECG tests results, which may be retested once.

The repeat screening assessment or blood sample may be conducted or drawn, respectively, at home by a qualified visiting nurse or at the clinic (if permitted by ethical and regulatory authorities and agreed upon after investigator and subject consultation). If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the screening window, then the subject is eligible for the study.

9.1.1.2 Rescreening

Subjects may be rescreened only once. If a subject is rescreened, all screening assessments will be repeated, except for:

- *PiZZ* genotyping
- Follicle-stimulating hormone (FSH) level (if serum FSH level was in the postmenopausal range as determined by the laboratory performing the test during prior screening)

If a subject is rescreened, a new screening window will begin when the first rescreening assessment has been initiated.

9.1.1.3 Extension of the Screening Period

A subject may have the Screening Period window extended by 2 weeks without medical monitor approval for the following reasons:

- Repetition of Screening Period assessments (Section 9.1.1.1)
- Unexpected operational or logistic delays, or to meet the eligibility criteria.

For subjects who have never been on augmentation therapy only, a subject may have the Screening Period window extended for an additional 2 weeks (total of 4 weeks extension) with medical monitor approval.

9.1.2 Treatment Period

The Treatment Period will be randomized, double-blind, and placebo-controlled. It will last approximately 28 days. Study drug administration details are provided in Section 9.7.

Subjects who prematurely discontinue study drug treatment will remain in the study from the time of discontinuation of study drug treatment through the last scheduled study visit and complete assessments for all study visits, as described in Section 9.1.4.

[redacted]

9.1.3 Follow-up

Subjects will have a VX-814 Washout Visit 7 (± 2) days after the last dose of study drug and Safety Follow-up Visits 14 (± 2) and 28 (± 2) days after the last dose of study drug.

9.1.4 Early Termination of Treatment

If a subject prematurely discontinues study treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the decision to terminate study treatment. Subjects who prematurely discontinue treatment will be required to complete the Safety Follow-up Visits 14 (± 2) and 28 (± 2) days after their last dose of study drug. The assessments performed at the ETT and Safety Follow-up Visits are listed in Table 3-3.

If the ETT Visit occurs between 12 and 21 days (inclusive) after the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visit 14 days after the last dose of study drug, and a separate Safety Follow-up Visit 14 days after the last dose will not be required; the Safety Follow-up Visit 28 days after the last dose will be required. If the ETT Visit occurs ≥22 days after the last dose of study drug, the ETT Visit will replace the Safety Follow-up Visit 28 days after the last dose, and a separate Safety Follow-up Visit 28 days after the last dose will not be required.

If a subject withdraws consent for the study, no further assessments will be performed. Vertex may retain and continue to use any data and samples collected before such withdrawal of consent.

9.2 Lost to Follow-up

A subject will be considered lost to follow up if both of the following occur:

- The subject misses 2 consecutive study visits (telephone contact, clinic, and/or home heath visit) and is subsequently unable to be contacted by telephone (3 documented attempts by telephone within 1 week following the second missed visit)
- The subject does not respond within 1 week to a registered letter sent after the 3 attempted telephone contacts.

9.3 Method of Assigning Subjects to Treatment Groups

In Part A1, subjects will be randomized (2:1:1:1) to 1 of 3 VX-814 groups or to the placebo group. In Part A2, subjects will be randomized (3:1) to the VX-814 group or to the placebo group. In Part B, subjects will be randomized (3:1) to the VX-814 group or to the placebo group. Each randomized subject will be assigned a unique subject number. Randomization will be stratified by $ppFEV_1$ obtained either during the Screening Period or from a historical $ppFEV_1$ value (<50% versus ≥50%).

An interactive web or voice response system (IWRS) will be used to assign subjects to treatment. The randomization code will be produced by Vertex Biostatistics or a qualified randomization vendor. The Vertex study biostatistician will review and approve the production of the final randomization list, which will be reviewed and approved by a designated unblinded biostatistician who is not a member of the study execution team (SET).

9.4 Rationale for Study Elements

9.4.1 Rationale for Study Design

A parallel-group, randomized, placebo-controlled design was selected to minimize the imbalance in the distribution of the baseline characteristics of the different dosing groups. A double-blind design was included to prevent bias in endpoint assessment by the investigator or subject.

The 28-day treatment duration is based on the estimated plasma half-life for AAT of approximately 5 days, indicating that plasma AAT levels will reach >95% of steady-state levels by the end of the treatment period. Therefore, it is expected that the 28-day treatment duration of VX-814 will be sufficient to evaluate the maximal effect of each dose level on plasma AAT.

9.4.2 Rationale for Study Population

The study population will be comprised of subjects with a confirmed *PiZZ* genotype. This patient population was selected based on the proposed mechanism of action of VX-814.

9.4.3 Rationale for Study Drug Dose

A total of 4 dose levels of VX-814 will be evaluated in this study (100 mg q12h, 200 mg q12h, 400 mg q12h, and 600 mg q12h). The doses will be administered orally. [redacted] The doses selected will provide an adequate assessment of the dose-response relationship and safety profile of VX-814 in the exposure range of interest, with an adequate safety margin at the highest dose (Section 6 in the VX-814 IB).

9.4.4 Rationale for Study Assessments

All safety and PK assessments are standard measurements for clinical studies in drug development.

Blood samples will be collected to evaluate the effect of VX-814 on plasma functional and antigenic AAT levels in *PiZZ* subjects based on the mechanism of action of VX-814.

UGT1A1 genotyping will be conducted to assess the impact of UGT1A1 polymorphism on PK exposure of VX-814, as UGT1A1 is the main enzyme metabolizing VX-814.

[redacted]

9.5 Study Restrictions

Study restrictions and timing of restrictions are summarized in Table 9-1. Subjects may enroll in the study if they are receiving acceptable concomitant medications (according to Table 9-1).

A non-exhaustive list of prohibited medications will be provided in the Study Reference Manual.

Table 9-1 Study Restrictions

Restricted Medication/Food/Activity[a]	Timing of Restriction	
	Start	Stop
Other investigational drugs or devices	28 days before screening, 5 half-lives before screening, or time determined by local requirements (whichever is longer)	Completion of the last Safety Follow-up Visit assessments
Augmentation therapy (human alpha-1 proteinase inhibitor)	More than 42 days before antigenic AAT level is obtained for eligibility	Completion of the last Safety Follow-up Visit assessments
[redacted]		
Sensitive CYP2C8 substrates	7 days or 5 half-lives (whichever is longer) before the first dose of study drug	Completion of the last Safety Follow-up Visit assessments
UGT1A1 moderate and strong inhibitors	7 days or 5 half-lives (whichever is longer) before the first dose of study drug	Completion of the last Safety Follow-up Visit assessments
UGT1A1 moderate and strong inducers	14 days before the first dose of study drug	Completion of the last Safety Follow-up Visit assessments
Tobacco products[c]	6 months before screening	Completion of the last Safety Follow-up Visit assessments
Alcohol: no more than 14 drinks/week for females or 21 drinks/week for males (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor)	Signing of ICF	Completion of the last Safety Follow-up Visit assessments

[a] See Section 9.6 for guidance on concomitant medications.

[redacted]

Nicotine replacement therapy under the direction of a physician is allowed.

9.5.1 Exposure to Sunlight

Subjects will take appropriate measures to minimize exposure to ultraviolet radiation (e.g., sunlight, tanning booths) from Day 1 through the last Safety Follow-up Visit.

9.6 Prior and Concomitant Medications

Subjects will follow restrictions described in Table 9-1.

[redacted]

In vitro data suggest that VX-814 acyl-glucuronide metabolite has the potential to inhibit CYP2C8, which may increase the exposure of medicinal products that are CYP2C8 substrates. Therefore, concomitant administration of sensitive CYP2C8 substrates is prohibited (Table 9-1).

All medications taken from the Screening Visit through the last Safety Follow-up Visit will be recorded with indication, route of administration, and start and stop dates of administration. For subjects who are screened but not subsequently randomized, details of prior medication will only be documented in the subjects' source documents.

Information about bronchodilator use during the study will be recorded for each subject. Use of short-acting and long-acting bronchodilators will be collected and documented in the source documents for each subject.

Information about prior augmentation therapy, as applicable, will be recorded for each subject, including dose, frequency of administration, start and stop dates of last infusion.

9.7 Administration

VX-814 will be administered orally, 2 times a day, approximately 12 hours apart. All subjects will receive the same number of tablets each day to maintain blinding. Additional information is provided in the Pharmacy Manual.

Study drug will be administered according to the following guidelines:

- Study drug will be taken **with a meal** (not a snack), preferably within 30 minutes of the start of the meal.
- Each subject should take the study drug approximately 12 hours apart (±1 hours). Subjects will swallow the tablet(s) whole without chewing or crushing the tablets with approximately 240 mL of water. Subjects may take additional water, as needed, to swallow tablets.
- The date, amount taken, and time of study drug administration, including whether a meal was taken with each dose, will be recorded for the 2 doses before PK sample collection and the dose associated with PK sample collection.

- If the subject's scheduled clinic or home visit is to occur in the morning (i.e., before noon), study drug will be administered after predose assessments have been completed. If the visit is a clinic visit, a meal will be provided by the site.
- If the subject's scheduled clinic or home visit is to occur in the afternoon, the following guidelines must be followed:
    - If the dose at the scheduled visit will be within 6 hours of the subject's scheduled morning dose, the subject should withhold the morning dose and the morning dose will be administered in the clinic with a meal provided by the site or witnessed by a home nurse at the home visit, with a meal.
    - If the dose at the scheduled visit will be more than 6 hours after the subject's scheduled morning dose, the subject should take the morning dose at home with a meal.
- If the subject's scheduled home visit is to occur in the evening, study drug will be administered with a meal after predose assessments have been completed.
- The morning dose of study drug on the Day 28 Visit will be taken in the clinic or at home with a meal provided by the site after the predose PK sample has been drawn. The last dose of study drug will be taken at home with a meal in the evening on Day 28, regardless of whether the Day 28 Visit occurs on Day 26 or Day 27.

Missed doses:

If a subject misses a dose, the subject can take the missed dose within 6 hours of the usual dosing time and should take the dose as soon as possible with a meal. If more than 6 hours have elapsed after the usual dosing time, the subject should skip that dose and resume the normal schedule for the following dose.

Morning and evening doses should not be taken at the same time.

9.8 Dose Modification for Toxicity

No dose modifications for toxicity are allowed or required. If any unacceptable toxicity arises in the opinion of the investigator individual subjects will discontinue dosing (Section 9.1.4).

9.9 Study Drug Interruption and Stopping Rules

The investigator has the discretion to discontinue study drug treatment at any time if the investigator feels that the subject's continued participation in the study jeopardizes their safety.

Any subject with worsening of AATD or disease progression that, in the judgement of the treating physician, requires (re)initiation of standard of care treatment (per local guidelines) that is prohibited in this study (including augmentation therapy) will discontinue study drug treatment.

Any subject with QTcF values above the threshold values as described in Section 11.5.4 will discontinue study drug treatment.

Study drug treatment may be interrupted for safety concerns at discretion of the investigator.

Study drug administration must be interrupted immediately (before confirmatory testing), and the medical monitor must be notified, if any of the following criteria are met:

- ALT or AST >5 × ULN
- Total bilirubin >3 × ULN
- ALT or AST >3 × ULN associated with total bilirubin >2 × ULN and/or clinical jaundice

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN, or total bilirubin >2 × ULN, must be followed closely, including confirmatory testing performed within 48 to 72 hours of the initial finding and there must be close monitoring of ALT, AST, and bilirubin levels thereafter, as clinically indicated.

If a subject cannot return to the site for confirmatory testing, a local laboratory may be used. Local laboratory results must be reported immediately to the medical monitor, and the subject must have the tests repeated and sent to the central laboratory as soon as possible (ideally within 48 to 72 hours).

In subjects who met above interruption criteria, a thorough investigation of potential causes should be conducted, and the subject must be followed closely for clinical progression. If an alternative, reversible cause of transaminase elevation and/or increased bilirubin has been identified, study drug administration may be resumed once transaminases and/or bilirubin return to baseline or are <ULN, whichever is higher. **Approval of the medical monitor is required before resumption of study drug.** Upon resumption of study drug, transaminases and bilirubin must be assessed weekly until 7 days after the last dose of study drug. If a protocol-defined transaminase and/or bilirubin elevation interruption threshold recurs, then study drugs must be permanently discontinued, regardless of the presumed etiology.

All subjects for whom treatment is discontinued for elevated transaminases and/or bilirubin should have these levels monitored closely until levels normalize or return to baseline.

9.10 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. A subject who withdraws from study drug treatment will continue to be followed unless the subject withdraws consent.

Subjects who are withdrawn from study drug dosing will complete assessments as described in Section 9.1.4.

Subjects who have been randomized and whose screening *PiZZ* genotype does not confirm study eligibility must be discontinued from the study, even if a previous *PiZZ* genotype laboratory report was used to establish eligibility.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject have a Safety Follow-up Visit, if applicable (see Section 9.1.4), and follow up with the subject regarding any unresolved AEs.

If a subject withdraws consent for the study, no further assessments will be performed. Vertex may retain and continue using the study data and samples after the study ends and may use the samples and information in the development of the study compound, for other drugs and diagnostics, in publications and presentations, and for education purposes. If a subject withdraws from the study, the study data and samples collected will remain part of the study. A subject will not be able to request the withdrawal of his/her information from the study data. A subject may request destruction of the samples collected from him/her during the study as long as those samples can be identified as his/her samples.

9.11 Replacement of Subjects

Subjects who withdraw or are withdrawn before the first dose of study drug may be replaced.

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug treatment period(s) may be replaced at Vertex's discretion.

10 STUDY DRUG INFORMATION AND MANAGEMENT

10.1 Preparation and Dispensing

Study drug may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects.

10.2 Packaging and Labeling

Vertex will supply the 100-mg VX-814 tablets and matching placebos. Study drug labeling will be in compliance with applicable local and national regulations. Additional details about packaging, labeling, and dispensing for VX-814 will be provided in the Pharmacy Manual.

10.3 Study Drug Supply, Storage, and Handling

The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for via the drug accountability forms as instructed by Vertex.

VX-814 and matching placebo will be supplied as tablets of similar size and appearance containing 100 mg VX-814 and 0 mg VX-814, respectively.

Detailed instructions regarding the storage, handling, and dispensation of the study drug will be provided in the Pharmacy Manual.

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information regarding the dates and amounts of study drug received, study drug dispensed to the subjects, and study drug returned by the subjects. Subjects will be instructed to return all used and unused materials associated with the study drug to the site. These materials will be retained at the site according to instructions provided by Vertex or its designee until inventoried by the study monitor. The study monitor will review study drug records and inventory throughout the study.

If a site uses a site-specific drug accountability system and/or process, including processes associated with the destruction of returned materials, the process must be documented and approved by Vertex. The study monitor must review the drug accountability documentation on a

regular basis. The study monitor will promptly communicate to Vertex any discrepancies he/she is unable to resolve with the site.

10.5 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. The investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

The principal investigator, study site staff, including pharmacy personnel will assist Vertex with any recall activities (as applicable) and place impacted investigational medicinal product (IMP) in quarantine when requested.

10.6 Compliance

To ensure treatment compliance, the investigator or designee will supervise all study drug dosing that occurs at the site. At each visit, site personnel or approved home nurse will review that the subject is compliant with study drug dosing and remind the subject of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count in the clinic or checked by home nurse for home visit.

If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator will contact the medical monitor to discuss discontinuing the subject from the study.

10.7 Blinding and Unblinding

This is a double-blind study.

10.7.1 Blinding

All subjects, site personnel (including the investigator, the site monitor, and the study team), and the Vertex study team will be blinded to the treatment codes with the exception of the following:

- Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency
- Any site personnel for whom this information is important to ensure the safety of the subject and her fetus in the event of a pregnancy
- Vertex GPS and Regulatory Affairs personnel to satisfy SAE processing and reporting regulations
- Unblinded statistician preparing the final (production) randomization list who is not part of the study team
- Vertex IWRS Manager
- Vertex Clinical Supply Chain
- The bioanalytical CRO analyzing PK samples and the Vertex Bioanalytical personnel who is not a member of the SET but analyzes and reviews raw data from Bioanalytical CRO. The Vertex Bioanalytical SET member will continue to be blinded.

Vertex medical monitor may, for matters relating to safety concerns, unblind individual subjects at any time.

A limited Vertex team not directly involved in the conduct of the study may be unblinded to individual subject treatment assignments and have access to plasma AAT levels, PK, and/or safety data (e.g., adverse events, clinical laboratory assessments) for continuous monitoring purposes. No unblinded data or results of unblinded analyses will be shared with the study sites or with the Vertex study team. All instances of unblinding by Vertex personnel will be documented.

Access to results of plasma functional and antigenic AAT data:

During the conduct of the study, the Vertex study team will not have access to the plasma AAT level results until the study is unblinded for full review, with the exception of the screening plasma antigenic AAT levels. Antigenic AAT levels obtained during screening will be provided to study sites in order to confirm the subject's eligibility to enroll in the study. Other AAT level results will not be disclosed to the study sites.

Shortly before any planned efficacy analysis related to plasma AAT levels is conducted, plasma AAT data will be reviewed for data cleaning purposes by a biostatistician who does not have access to the treatment codes.

Access to direct and indirect bilirubin results

After screening, direct and indirect bilirubin results will not be disclosed to the study sites. After screening, the Vertex study team will not have access to the direct and indirect bilirubin results until the study is unblinded for full review. Study sites and the Vertex study team will receive total bilirubin results.

Before the final data lock, direct and indirect bilirubin data will be reviewed for data cleaning purposes by a biostatistician who does not have access to the treatment codes.

10.7.2 Unblinding

At the initiation of the study, study site personnel will be instructed on the method for breaking the blind. The unblinding method will be either manual or electronic.

Unblinding of the individual subject's treatment by the investigator will be limited to medical emergencies or urgent clinical situations in which knowledge of the subject's study treatment is necessary for clinical management. In such cases, investigators will use their best judgment as to whether to unblind without first attempting to contact the medical monitor to discuss unblinding. If investigators deem it unnecessary to unblind immediately, they will first attempt to contact the medical monitor to discuss unblinding. If investigators have tried but are unable to reach the medical monitor, they will use their best judgment, based on the nature and urgency of the clinical situation, and may proceed with unblinding.

Contact information for the medical monitor (or appropriate backup) will be provided in a separate document.

If a subject's treatment assignment has been unblinded for a medical emergency or urgent clinical situation, the medical monitor will be notified within 24 hours of the unblinding event. The reason and the date of the unblinding will be documented clearly in the subject's study file. Information about the treatment assignment obtained from the unblinding will be maintained in a secure location with controlled access and will not be shared with Vertex, the CRO, or any site personnel (other than the physician treating the subject). In addition, the investigator will consider whether the clinical event that prompted unblinding will be considered an SAE, according to the regulatory definitions or criteria for SAEs, and if so, submit an SAE report to Vertex GPS or designee, per Section 13.1.2.

Vertex GPS or designee will also unblind any SAE reports in compliance with regulatory reporting requirements. In addition, Vertex may, for matters relating to safety, unblind individual subjects at any time.

11 ASSESSMENTS

The schedule of assessments is shown in Table 3-1, Table 3-2, and Table 3-3.

11.1 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, and weight. Cigarette and or e-cigarette smoking history (current smoker; ever smoker; never smoker) will be collected for each subject including time since quitting and pack-years and cartridge-years of smoking history (packs/day × number of years; cartridges/day × number of years).

11.2 Pharmacokinetics

11.2.1 Blood Sampling

Blood samples will be collected for the evaluation of plasma concentrations of VX-814. [redacted]

Plasma concentration samples collected from subjects treated with placebo study drug will not be routinely analyzed.

All efforts will be made to obtain the PK samples at the nominal time (±30 minutes) relative to dosing. Acceptable windows for sampling times are shown in Table 11-1. The exact time of the sample collection will be noted.

Table 11-1 Acceptable Pharmacokinetic Sampling Windows

Sampling Time	Time From Scheduled Sampling Allowed
Predose	Within 60 minutes before dosing
All other time points	± 30 minutes

The following details will be recorded in the source document: date and time of study drug and meal administration for the 2 doses before the dose on PK sampling days and date and time of each of the PK blood samples.

11.2.2 UGT1A1 Genotype

A single blood sample will be collected to assess the impact of UGT1A1 polymorphism on PK exposure of VX-814.

11.2.3 Processing and Handling of Pharmacokinetic Samples

Detailed procedures for the collection of blood samples and further procedures for processing and handling of samples for PK analysis will be in the PK Sample Handling Guidelines.

11.2.4 Bioanalysis

Samples will be analyzed using a validated analytical method in compliance with Vertex or designee standard operating procedures. A description of the assay and validation data will be provided in separate reports.

11.3 Efficacy

Detailed procedures for the collection, processing, handling, and storage of blood samples for functional and antigenic AAT levels will be provided in the Clinical Biomarker Sample Handling Guidelines.

Samples will be obtained for antigenic and functional AAT levels at the same time that other screening laboratory assessments are performed. These samples must be sent to the central laboratory. If the subject has never received augmentation therapy or if the subject received the last dose of augmentation therapy >42 days prior, this sample can be used to measure antigenic AAT level for eligibility. If samples are obtained ≤42 days after the last dose of augmentation therapy, another sample **must** be drawn >42 days after the last dose of augmentation therapy and sent to the central laboratory to determine eligibility. **Sites should allow at least 14 days for sample processing and results reporting**. Samples will be obtained for plasma functional AAT levels at the same time samples are obtained for antigenic AAT levels. Functional AAT level results will not be provided to site personnel.

[redacted]

11.5 Safety

Safety evaluations will include AEs, clinical laboratory assessments, standard 12-lead ECGs, clinical evaluation of vital signs, pulse oximetry, spirometry, and physical examinations (PEs).

11.5.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH GCP Guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs. A separate document that details AE CRF completion guidelines for investigators as well as training will be provided.

11.5.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory.

Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

The safety laboratory test panels are shown in Table 11-2.

Table 11-2 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis[a]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen[b]	Erythrocytes	Nitrite
Creatinine	Mean corpuscular volume	Urine protein
Sodium	Platelets	pH Urine
Potassium	Reticulocytes	Urine blood
Calcium	Leukocytes	Specific gravity
Chloride	Differential (absolute and percent):	Urine ketones
Magnesium	Eosinophils	Urine glucose
Bicarbonate	Basophils	Urine cotinine
Phosphate	Neutrophils	
Total bilirubin (direct bilirubin, indirect bilirubin)	Lymphocytes	
Alkaline phosphatase	Monocytes	
Aspartate transaminase	**Coagulation**	
Alanine transaminase	Activated partial thromboplastin time	
Amylase	Prothrombin time	
Lipase	Prothrombin time International Normalized Ratio	
Gamma-glutamyl transferase		
Protein		
Albumin		
Creatine kinase		
Urate		
Cholesterol		
Triglycerides		
Low-density lipoprotein		
High-density lipoprotein		

[a] If urinalysis results are positive for leukocyte esterase, nitrite, protein, or blood, microscopic examination of urine will be done, and results will be provided for leukocytes, erythrocytes, crystals, bacteria, and casts.

[b] If blood urea nitrogen cannot be collected, urea may be substituted.

Additional Tests at Screening:

- Serology test for HBsAg, HCV antibody and RNA, and HIV-1 and HIV-2 antibodies
- Serum beta-human chorionic gonadotropin (β-hCG) for all female subjects
- Serum FSH for postmenopausal female subjects with spontaneous amenorrhea for at least 12 consecutive months without another reason, except for those who have documented bilateral oophorectomy or hysterectomy. Levels will be within the laboratory's range for postmenopausal for subjects to be considered of non-childbearing potential.

Additional Evaluations: Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate for safety concerns.

For purposes of study conduct, only safety laboratory tests done at the central laboratory may be used; however, the investigator has the discretion to use local laboratory in the event of safety concerns. If a local laboratory is used, results must be reported immediately to the medical monitor. If a local laboratory test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a timely specimen to the central laboratory (e.g., the subject was hospitalized elsewhere), the investigator may base the assessment of an AE on the local laboratory value.

11.5.3 Physical Examinations, Vital Signs, and Pulse Oximetry

A PE of all body systems, vital signs and pulse oximetry assessment will be performed at screening. At other visits, symptom-directed PEs and symptom-directed vital signs assessments can be performed at the discretion of the investigator or healthcare provider.

A PE includes a review of the following systems: head, neck, and thyroid; eyes, ears, nose, and throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in PEs will be reported as AEs.

The abbreviated PE will include an assessment of the following body systems: head, neck, and thyroid; EENT; cardiovascular system; respiratory system; skin; and abdomen.

The review of symptoms will include a verbal review of symptoms by body system. If there are any abnormal findings, the subject will be instructed to have a complete PE in the clinic.

Vital signs include blood pressure (systolic and diastolic), temperature, pulse rate, and respiration rate. The subject will be instructed to rest for at least 5 minutes before vital signs are assessed.

The subject will be instructed to rest for at least 5 minutes before pulse oximetry is assessed.

11.5.4 Electrocardiograms

Standard 12-lead ECGs will be performed in triplicate. Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines. Detailed instructions are provided in the Study Reference Manual:

- The ECG will be done before any other procedures that may affect heart rate, such as blood draws.
- The subject will be instructed to rest for at least 5 minutes before having an ECG.
- The test should be performed in the supine position.

A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through the last Safety Follow-up Visit will be recorded as AEs.

To ensure safety of the subjects, a qualified individual at the study site or an approved home nurse at the home health visit will make comparisons of the QTcF value generated on the ECGs obtained at any time point after the first dose of drug administered in the treatment period to the pre-dose baseline QTcF value taken on Day 1 in the treatment period. If the median QTcF (of the safety ECGs performed in triplicate) is increased by >60 msec from the baseline (as defined in Section 12.3.1) or an absolute median QTcF value is ≥500 msec for any scheduled ECG assessment, triplicate ECGs will be repeated within 10 minutes of the initial assessment to confirm the original measurement. A subject with a confirmatory ECG that demonstrates a median QTcF (of the safety ECGs performed in triplicate) that has increased by >60 msec from the baseline or an absolute median QTcF value ≥500 msec will discontinue dosing. If the median QTcF (from the confirmatory ECGs repeated within 10 minutes of the initial assessment) falls below the threshold, the subject may continue dosing. If the confirmatory ECG is above the threshold then for safety monitoring, triplicate ECGs will be repeated at least every hour until the median QTcF value from 2 successive time points falls below the threshold value that triggered the repeat measurement.

11.5.5 Spirometry

Spirometry will be performed post-bronchodilator and will be performed according to the American Thoracic Society (ATS) Guidelines/European Respiratory Society Guidelines.[4, 5, 6] If spirometry cannot be performed at screening, historical post-bronchodilator ppFEV$_1$ results within 1 year before screening can be used to determine eligibility. This assessment is optional at all other study visits. Further details will be provided in the Study Reference Manual.

11.5.6 Contraception and Pregnancy

The effects of VX-814 on conception, pregnancy, and lactation in humans are not known. Refer to the VX-814 Investigator's Brochure for additional details.

11.5.6.1 Contraception

Participation in this study requires a commitment from subjects and their partners to use methods of contraception outlined below, which must be used correctly with every act of sexual intercourse.

Contraception for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from 28 days before Day 1 through 90 days after the last dose of study drug.
- If the male is infertile (e.g., bilateral orchiectomy). Infertility may be documented through examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound before the first dose of the study drug.
- If the female is of non-childbearing potential, per the following:
    - Documented hysterectomy or a bilateral oophorectomy/salpingo-oophorectomy.
    - Postmenopausal: continuous amenorrhea without another reason for at least 12 months and serum FSH levels within the laboratory's range for postmenopausal females.

- Same-sex relationships.

For subjects for whom contraception methods are not waived for one of the reasons cited above, the following are highly effective contraceptive methods (Table 11-3**) for male subjects and their female (non-study) partners and for female subjects and their male (non-study) partners. In addition to the subject or partner using 1 method from Table** 11-3**, all male (non-study) partners and male subjects must use a condom, with spermicide (if available), from 28 days before Day 1 until 90 days after the last dose of study drug. Acceptable methods of contraception are listed in Table** 11-3**.**

Table 11-3 Allowable Methods of Contraception

Male subjects and their female (non-study) partners	• Male vasectomy 6 months or more previously, with a documented negative post-vasectomy semen analysis for sperm • Female bilateral tubal ligation performed at least 6 months previously • Female continuous use of an intrauterine device for at least 90 days before the first dose of study drug, throughout study drug treatment, and until 90 days after the last dose of study drug. • Female hormonal contraceptives, if successfully used for at least 60 days before the first dose of study drug, throughout study drug treatment, and until 90 days after the last dose of study drug.
Female subjects and their male (non-study) partners	• Female bilateral tubal ligation performed at least 6 months previously • Female continuous use of an intrauterine device (non-hormone releasing) for at least 90 days before the first dose of study drug, throughout study drug treatment, and until 90 days after the last dose of study drug. • Male vasectomy 6 months or more previously, with a documented negative post-vasectomy semen analysis for sperm.

The effects of VX-814 on the PK of hormonal contraceptives are not known. Thus, hormonal contraception is NOT permitted as a highly effective method of contraception for female subjects.

Important notes:

- Male subjects must use a condom to avoid exposing a potential fetus to study drug via the seminal fluid. The female condom is not an acceptable method due to the increased risk of tearing when the female and male condoms are used at the same time.
- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active.
- Male subjects must not donate sperm after the first dose of study drug, throughout the study, and for 90 days following the last dose of study drug.
- Female subjects and female partners of male subjects should not plan to become pregnant during the study through 90 days following the last dose of study drug.
- Female subjects should not breastfeed a child from the start of study drug dosing through 90 days following the last dose of study drug.
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.

- Unique situations that may not fall within the above specifications may be discussed with the medical monitor on an individual basis.

11.5.6.2 Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study treatment and for 90 days after the last dose of study drug.

If a subject or the female partner of a male subject becomes pregnant while participating in the study, study drug will be permanently discontinued immediately. The investigator will notify the medical monitor and Vertex GPS within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy using the Pregnancy Information Collection Form.

A subject (or their partner, if relevant) who becomes pregnant while on study will be followed until the end of the pregnancy only if on blinded treatment, or if they have been unblinded and have received active drug. The infant will be followed for 1 year after birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself is not an AE.

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the principal features of the planned efficacy, safety, and PK analyses for the study. Safety and efficacy analysis details will be provided in the statistical analysis plan (SAP), and PK analysis details will be provided in the clinical pharmacology analysis plan (CPAP). Both the SAP and CPAP will be finalized before clinical data lock.

[redacted]

Final analyses will take place after all subjects have completed the study, all data have been entered in the clinical study database, and the clinical data have been locked.

12.1 Sample Size and Power

Approximately 43 subjects in total will be randomized to both parts of the study. In Part A1, subjects will be randomized to receive VX-814 400 mg q12h (n = 6), VX-814 200 mg q12h (n = 3), VX-814 100 mg q12h (n = 3), or placebo (n = 3). In Part A2, subjects will be randomized to receive VX-814 400 mg q12h (n = 6) or placebo (n = 2). In Part B, subjects will be randomized to receive VX-814 600 mg q12h (n = 15) or placebo (n = 5).

Assuming approximately 10% of the randomized subjects have a missing value at Day 28, this sample size provides adequate precision to estimate the plasma functional AAT levels at Day 28 for the VX-814 600 mg q12h group in Part B.

Information regarding the sample size assessments is provided below.

[redacted]

[redacted]

12.2 Analysis Set

The following analysis sets are defined: All Subjects Set, Full Analysis Set (FAS), and Safety Set.

The **All Subjects Set** will include all subjects who were randomized or received at least 1 dose of study drug. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

The **FAS** will include all randomized subjects who received at least 1 dose of study drug. The FAS will be used to summarize subject demographics and background characteristics, and for all efficacy analyses, unless otherwise specified. Subjects will be analyzed according to the treatment to which they were randomized.

The **Safety Set** will include all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses in which subjects will be analyzed according to the treatment they received, unless otherwise specified.

12.3 Statistical Analysis

The primary objective of this study is to characterize the efficacy and safety of VX-814 in *PiZZ* subjects. This section summarizes the statistical analysis of efficacy and safety data.

Methodological and related details (e.g., missing data) will be in the SAP.

12.3.1 General Considerations

All individual subject data for subjects who were randomized or received at least 1 dose of study drug will be presented in individual subject data listings. Data from Parts A and B will be pooled for analysis, unless specified otherwise.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, median, minimum value (min), and maximum value (max).

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug. For ECGs, the baseline value will be defined as the average of the non-missing pretreatment measurements (triplicate) before the first dose of study drug.

Change (absolute change) from baseline will be calculated as Post-baseline value – Baseline value.

Relative change from baseline will be calculated and expressed in percentage as 100% × (post-baseline value − Baseline value)/Baseline value.

Treatment-emergent (TE) Period will include the time period starting from the date of the first dose of study drug to either (1) Safety Follow-up Visit 28 days after the last dose of study drug, (2) ETT Visit if it replaces the Safety Follow-up Visit 28 days after the last dose of study drug, or (3) 28 days after the last dose date for subjects who do not have a Safety Follow-up Visit 28 days after the last dose or equivalent. The TE Period will be used for safety analyses unless specified otherwise.

Incomplete/missing data will not be imputed, unless specified otherwise.

12.3.2 Demographics and Background Characteristics

Subject disposition, e.g., completed treatment, prematurely discontinued the treatment and the reason for discontinuation, will be summarized by treatment group.

Demographic and other baseline characteristics (e.g., plasma AAT levels and $ppFEV_1$) will be summarized by treatment group. No statistical tests will be carried out to evaluate baseline imbalances between treatment groups.

Medications used will be coded using the World Health Organization-Drug Dictionary (WHODrug) and summarized descriptively. Exposure to study drug (i.e., duration of treatment) and dosing compliance (i.e., percentage of days being compliant to treatment) will be summarized descriptively.

Important protocol deviations will be provided in an individual subject data listing, and summarized, as appropriate.

Additional details will be provided in the SAP.

12.3.3 Efficacy Analysis

12.3.3.1 Analysis of the Primary Variable

The primary endpoint to assess efficacy is the change from baseline in plasma functional AAT levels at Day 28. [redacted]

Details will be provided in the SAP.

12.3.3.2 Multiplicity Adjustment

There is no multiplicity adjustment for the pairwise comparisons between different doses of VX-814 and placebo.

12.3.3.3 Missing Data Handling

For the primary analysis of the primary endpoint, missing data will be assumed to be missing at random conditional on the observed data and covariate; consequently, no imputation of missing data will be performed.

[redacted]

12.3.4 Safety Analysis

The overall safety profile of VX-814 will be assessed in terms of the following safety endpoints:

- Incidence of treatment emergent adverse events (TEAEs)
- Clinical laboratory values (i.e., hematology, serum chemistry, coagulation, and urinalysis)
- Standard 12-lead ECG outcomes
- Vital signs
- Pulse oximetry

For safety analyses, no statistical hypothesis testing will be conducted. Additional details will be provided in the SAP.

12.3.5 Interim and Independent Data Monitoring Committee Analyses

12.3.5.1 Interim Analysis

Interim analyses may be performed at any time at the discretion of the sponsor for internal decision-making. Interim analyses will be performed and reviewed by an unblinded Vertex team not involved in the conduct of the study.

12.3.5.2 Independent Data Monitoring Committee Analysis

Not applicable

12.4 Clinical Pharmacology Analysis

12.4.1 Pharmacokinetic Analysis

The PK of VX-814 will be described using summary statistics. Preliminary review and analyses of the drug concentrations may be done before data lock under the conditions of masked identifications of the subject concentrations.

Details of the analyses will be in the CPAP.

12.4.2 Pharmacokinetic/Pharmacodynamic Analyses

A population PK analysis of plasma concentration versus time data of VX-814 may be performed using a non-linear mixed-effects modeling approach. Population PK/PD models may also be developed to help understand the relationship between VX-814 exposure and PD endpoints. A more detailed description of the methodology will be included in a separate population analysis plan. Results of these analyses, if conducted, will be presented in standalone, separate documents and will not be included in the CSR.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

13.1 Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or worsening of a pre-existing condition (e.g., increase in its severity or frequency) after the ICF is signed.

An AE is considered serious if it meets the definition in Section 13.1.2.1.

13.1.1.2 Clinically Significant Assessments

Study assessments including clinical laboratory tests, ECGs, PEs, and vital signs will be assessed and those deemed to have clinically significant worsening from baseline will be documented as an AE. When possible, a clinical diagnosis for the study assessment will be provided, rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself will be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the subject has 1 or more of the following:

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant will be made by the investigator.

A laboratory value that is Grade 4 will not automatically be an SAE. A Grade 4 laboratory value will be an SAE if the subject's clinical status indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time the ICF is signed until the following times:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a Safety Follow-up Visit 28 days after the last dose: through the Safety Follow-up Visit 28 days after the last dose
- For enrolled subjects who do not have a Safety Follow-up Visit 28 days after the last dose, through the ETT visit if that visit is ≥22 days after the last dose of study drug (see Section 9.1.4) or 28 days after the last dose of study drug for subjects who do not have an ETT visit.

All subjects will be queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the CRF and source document. AEs for subjects who are screened but not subsequently enrolled will be recorded only in the subject's source documents. The following data will be documented for each AE:

- Description of the event
- Classification of "serious" or "nonserious"
- Date of first occurrence and date of resolution (if applicable)
- Severity
- Causal relationship to study drug(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed July 2018). AEs of CTCAE Grades 4 and 5 will be documented as "life-threatening." The severity of an AE described by a term that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

Classification	Definition
Mild (Grade 1)	Mild level of discomfort and does not interfere with regular activities
Moderate (Grade 2)	Moderate level of discomfort and significantly interferes with regular activities
Severe (Grade 3)	Significant level of discomfort and prevents regular activities
Life-threatening (Grade 4)	Any adverse drug event that places the subject, in the view of the investigator, at immediate risk of death

13.1.1.5 Adverse Event Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug(s). Causality will be classified using the categories in Table 13-2.

Table 13-2 Classifications for AE Causality

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the subject's medical record).

13.1.1.6 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the AE. The action taken will be classified according to the categories in Table 13-3.

Table 13-3 Classifications for Study Drug Action Taken With Regard to an AE

Classification	Definition
Dose not changed	Study drug dose not changed in response to an AE
Dose reduced	Study drug dose reduced in response to an AE
Drug interrupted	Study drug administration interrupted in response to an AE
Drug withdrawn	Study drug administration permanently discontinued in response to an AE
Not applicable	Action taken regarding study drug administration does not apply. "Not applicable" will be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

13.1.1.7 Adverse Event Outcome

An AE will be followed until the investigator has determined and provided the final outcome. The outcome will be classified according to the categories in Table 13-4.

Table 13-4 Classifications for Outcome of an AE

Classification	Definition
Recovered/resolved	Resolution of an AE with no residual signs or symptoms
Recovered/resolved with sequelae	Resolution of an AE with residual signs or symptoms
Not recovered/not resolved (continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing
Fatal	Outcome of an AE is death. "Fatal" will be used when death is at least possibly related to the AE.
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow up)

13.1.1.8 Treatment Given

The investigator ensures adequate medical care is provided to subjects for any AEs, including clinically significant laboratory values related to study drug. In addition, the investigator will describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE, and may include treatments such as other medications, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following outcomes:

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

Clarification will be made between the terms "serious" and "severe" because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious", which is based on subject/event outcome or action described above and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining expedited regulatory reporting obligations.

13.1.2.2 Reporting and Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the last Safety Follow-up Visit, regardless of causality, will be reported by the investigator to Vertex GPS **within 24 hours of identification**. In addition, all SAEs that occur after the last Safety Follow-up Visit and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours of identification**.

For SAEs that occur after obtaining informed consent and assent (where applicable) through the last Safety Follow-up Visit, the SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

Email: [redacted] (preferred choice)

Fax: [redacted]

For technical issues related to submitting the form, contact telephone: [redacted]

SAEs that occur after the last Safety Follow-up Visit and are considered related to study drug(s) will be recorded on the Vertex Clinical Trial Safety Information Collection Form (hereafter referred to as the "SAE Form") using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report the outcome to Vertex using the SAE Form.

13.1.2.3 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, IECs, and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central IECs.

It is the responsibility of the investigator or designee to promptly notify the local IRB/ IEC of all unexpected serious adverse drug reactions involving risk to human subjects.

13.2 Administrative Requirements

13.2.1 Product Complaints

A product complaint is defined as any verbal or written communication addressed to Vertex, or designee, of inquiry or dissatisfaction with the identity, strength, quality, or purity of a released drug product, IMP, or medical device. In addition, suspected counterfeit/falsified product is considered a product complaint.

Product complaints are to be reported to Vertex.

13.2.2 Ethical Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's

Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

13.2.3 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject or legal representative or guardian (if applicable) before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.4 Investigator Compliance

No modifications to the protocol will be made without the approval of both the investigator and Vertex. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., PD assessments) will require IRB/IEC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Vertex will submit all protocol modifications to the required regulatory authorities.

When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact will be made before the implementation of any changes. Any departures from the protocol will be fully documented in the source documentation and in a protocol deviation log.

13.2.5 Access to Records

The investigator will make the office and/or hospital records of subjects enrolled in this study available for inspection by Vertex or its representative at the time of each monitoring visit and for audits. The records will also be available for direct inspection, verification, and copying, as required by applicable laws and regulations, by officials of the regulatory health authorities (FDA and others). The investigator will comply with applicable privacy and security laws for use and disclosure of information related to the research set forth in this protocol.

13.2.6 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all CRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers, and access to subject names linked to such numbers will be limited to the site and the study physician and will not be disclosed to Vertex. As required by applicable laws and regulations in the countries in which the study is being conducted, the investigator will allow Vertex and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the CRFs/SAE Forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

For sites participating in the US, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations, an executed HIPAA authorization will be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization will comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

13.2.7 Record Retention

The investigator will maintain all study records according to ICH GCP Guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical Trial Agreement. If the investigator withdraws from the responsibility of keeping the study records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

13.2.8 Study Termination

At any time, Vertex may terminate this study in its entirety or may terminate this study at any particular site. In addition, for reasonable cause, either the investigators or their IRBs/IECs may terminate the study at their center.

Conditions that may lead to reasonable cause and warrant termination include, but are not limited to:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the FDA or other regulatory authority

Written notification that includes the reason for the clinical study termination is required.

13.2.9 End of Study

The end of study is defined as the last scheduled visit (or scheduled contact) of the last subject.

13.3 Data Quality Assurance

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each subject. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure,

validated, web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

Instances of missing, discrepant, or uninterpretable data will be queried with the investigator for resolution. Any changes to study data will be made to the CRF and documented in an audit trail, which will be maintained within the clinical database.

13.4 Monitoring

Monitoring and auditing procedures developed or approved by Vertex will be followed to comply with GCP Guidelines. On-site checking of the CRFs/SAE Forms for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by Vertex or its designee. Monitoring will be done by personal visits from a representative of Vertex or designee (study site monitor), who will review the CRFs/SAE Forms and source documents. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

13.5 Electronic Data Capture

Vertex will provide the study sites with secure access to and training on the EDC application sufficient to permit study site personnel to enter or correct information in the CRFs on the subjects for which they are responsible.

A CRF will be completed for each enrolled study subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data will indicate the subject's participation in the study and will document the dates and details of study procedures, AEs, other observations, and subject status.

The investigator, or designated representative, will complete the CRF as soon as possible after information is collected.

The audit trail entry will show the user's identification information and the date and time of any correction. The investigator will provide formal approval of all the information in the CRFs, including any changes made to them, to endorse the final submitted data for the subjects for whom the investigator is responsible.

Vertex will retain the CRF data and corresponding audit trails. A copy of the final archival CRF in the form of a compact disc (CD) or other electronic media will be placed in the investigator's study file.

13.6 Confidentiality and Disclosure

Any and all scientific, commercial, and technical information disclosed by Vertex in this protocol or elsewhere will be considered the confidential and proprietary property of Vertex. The investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The investigator understands that the information developed from this clinical study will be used by Vertex in connection with the development of the study drug and other drugs and diagnostics, and therefore may be disclosed as required to other clinical investigators, business partners and associates, the FDA, and other government agencies. The investigator also understands that, to allow for the use of the information derived from the clinical study, the investigator has the obligation to provide Vertex with complete test results and all data developed in the study.

13.7 Publications and Clinical Study Report

[redacted]

13.7.2 Clinical Study Report

A CSR, written in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

14 REFERENCES

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3 Piitulainen E, Tanash HA. The clinical profile of subjects included in the Swedish national register on individuals with severe alpha 1-antitrypsin deficiency. COPD. 2015;12(suppl 1):36-41.

4 Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40(6):1324-43.

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6 Culver BH, Graham BL, Coates AL, Wanger J, Berry CE, Clarke PK, et al. Recommendations for a standardized pulmonary function report. An official American Thoracic Society technical statement. Am J Respir Crit Care Med. 2017;196(11):1463-72.

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15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX19-814-101	Version #: 3.0	Version Date: 21 May 2020
Study Title: A Phase 2, Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of VX-814 in *PiZZ* Subjects		

This clinical study protocol has been reviewed and approved by the sponsor.

[redacted]

15.2 Investigator Signature Page

Protocol #: VX19-814-101	Version #: 3.0	Version Date: 21 May 2020
Study Title: A Phase 2, Randomized, Double-blind, Placebo-controlled Study of the Efficacy and Safety of VX-814 in *PiZZ* Subjects		

I have read Protocol VX19-814-101, Version 3.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-814 and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date