1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

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

Vertex Study Number: VX22-864-108

IND Number: [redacted]

EudraCT Number: 2022-002746-40

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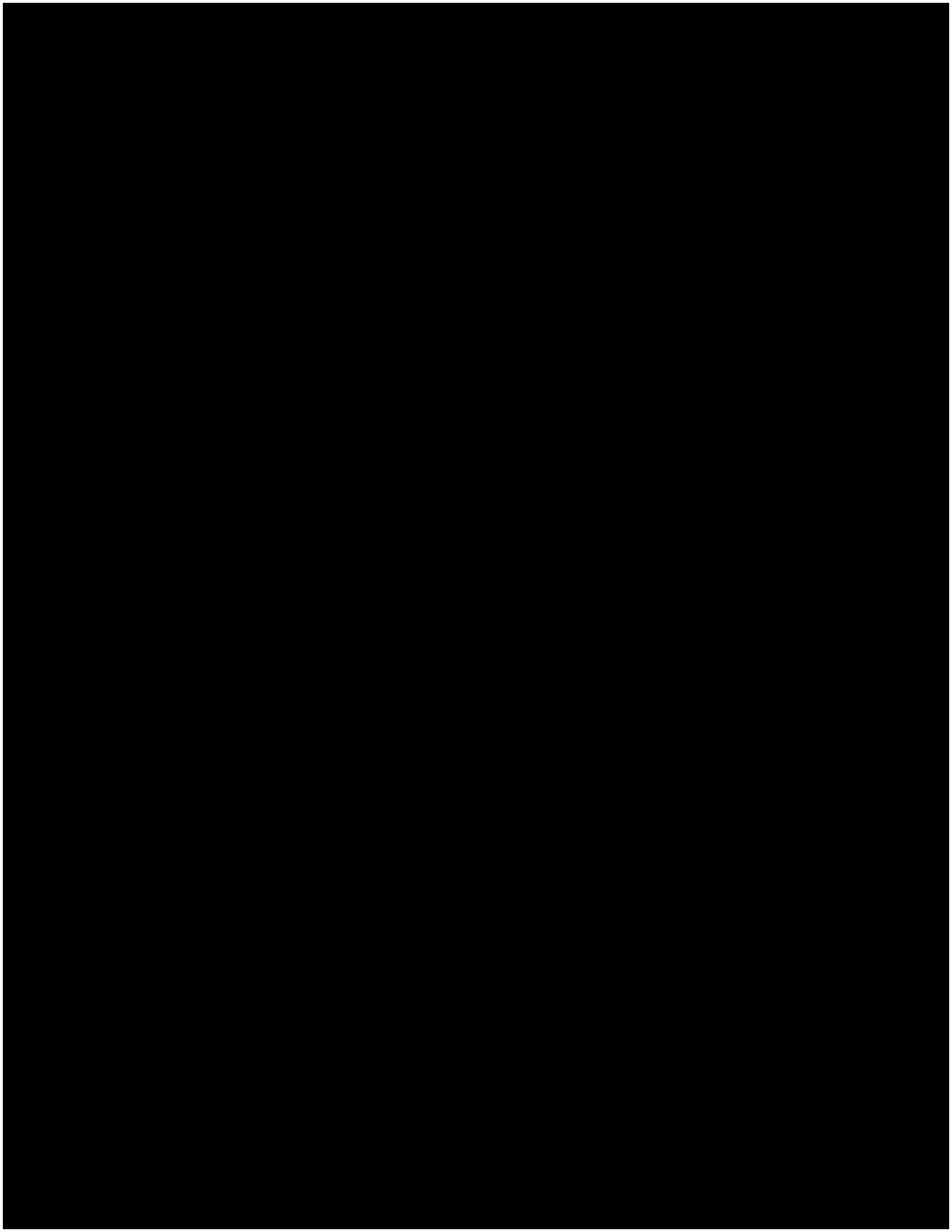


2 PROTOCOL SYNOPSIS

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

Brief Title A Study to Evaluate Efficacy and Safety of VX-864 in Subjects With the PiZZ Genotype

Clinical Phase and Clinical Study Type Phase 2 efficacy and safety

Objectives

Primary Objective

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

Secondary Objectives

- To evaluate the efficacy of VX-864 on blood levels of antigenic AAT in individuals with the PiZZ genotype
- To evaluate the efficacy of VX-864 on blood levels of Z-polymer in individuals with PiZZ genotype
- To evaluate the efficacy of VX-864 on liver Z-polymer in individuals with the PiZZ genotype (in Group B only)
- To evaluate the safety and tolerability of VX-864 in individuals with the PiZZ genotype

[redacted]

Endpoints

Primary Endpoint

- Change from baseline in blood levels of functional AAT at Week 48

Secondary Endpoints

- Change from baseline in blood levels of functional AAT over time
- Change from baseline in blood levels of antigenic AAT over time
- Change from baseline in blood levels of Z-polymer over time
- Change from baseline in Z-polymer accumulation in the liver over time (in Group B only)
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead ECGs, and vital signs

[redacted]

Number of Subjects

Approximately 20 subjects with the PiZZ genotype will be enrolled: Groups A and B will enroll approximately 10 subjects each.

Study Population

Group A: Male and female subjects 18 through 80 years of age, inclusive, with the PiZZ genotype

Group B: Male and female subjects 18 through 70 years of age, inclusive, with the PiZZ genotype

Investigational Drug

Active substance: VX-864

Activity: AAT modulator

Strength and route of administration: 100-mg or 250-mg tablets for oral administration

Study Duration

Excluding the Screening Period, each subject will participate in the study for approximately 52 weeks (48-week Treatment Period and 28-day Safety Follow-up Period). In subjects who consent to the posttreatment Telemedicine Visit(s), the total duration for study participation will increase by approximately 24 weeks (i.e., approximately 76 weeks total, from Screening Period through posttreatment Telemedicine Visit).

Study Design

This is a Phase 2, open-label, multicenter study. Approximately 20 subjects with the PiZZ genotype will be enrolled. Groups A and B will enroll approximately 10 subjects each. All subjects will receive VX-864 500 mg every 12 hours (q12h) for 48 weeks. Figure 2-1 displays the study design.

Group A subjects will not have a liver biopsy.

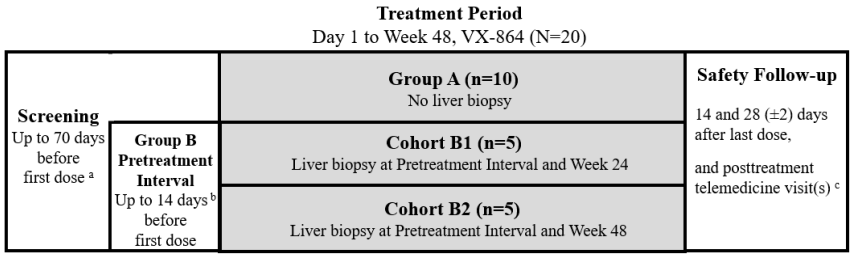
Subjects in Group B will have 2 liver biopsies performed over the course of the study. All liver biopsies will be performed percutaneously. All subjects in Group B (approximately 10 subjects) will have a liver biopsy during the Pretreatment Interval (Figure 2-1). Approximately 5 subjects (Cohort B1) will have a second liver biopsy at Week 24. Approximately 5 subjects (Cohort B2) will have a second liver biopsy at Week 48.

The pretreatment liver biopsy must be performed at least 7 days before Day 1 dosing, after all eligibility criteria have been met. Local laboratory hematology and coagulation results must be collected and reviewed by investigator within approximately 48 hours prior to the liver biopsy being performed. The Week 24 and Week 48 liver biopsies will be performed 3 hours (±30 minutes) postdose relative to the morning dose.

The Safety Follow-up Visits are required for all subjects. In subjects who terminate their participation early, the ETT visit, which may be conducted at the site or by telephone or video interview, replaces the Safety Follow-up Visit, if the

ETT Visit occurs 3 weeks or later following the last dose of study drug. All subjects may also consent to the posttreatment Telemedicine Visit(s) following final dose of study drug, to monitor for development of AEs of rash (for up to 6 months) and to monitor any ongoing AEs of rash (for up to 6 months following resolution of AEs of rash; see Section 9.1.6).

Figure 2-1 VX22-864-108 Study Design



n: size of subsample; N: number of subjects
Note: Figure is not drawn to scale.

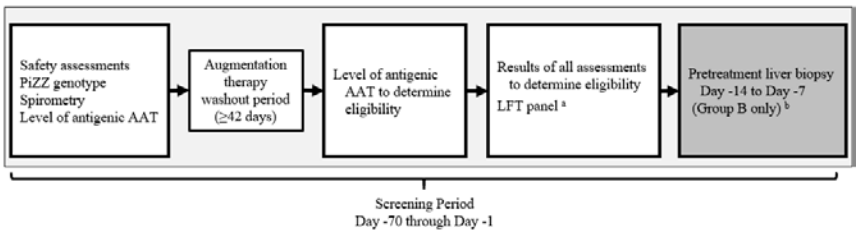
[a] In subjects not requiring augmentation therapy washout, the Screening Period will be up to 28 days. In subjects requiring augmentation therapy washout, the Screening Period will be up to 70 days.

[b] Day -14 to Day -7; pretreatment liver biopsy must be performed at least 7 days before Day 1 dosing.

[c] There will be no further dosing in this study as of 25 September 2023. All subjects may consent to the posttreatment Telemedicine Visit(s) following final dose of study drug, to monitor for development of AEs of rash (for up to 6 months) and monitor any ongoing AEs of rash (for up to 6 months following resolution of AEs of rash; see Section 9.1.6).

Figure 2-2 displays the general recommended order of key screening assessments for subjects who have received augmentation therapy within 42 days before the initial screening visit.

Figure 2-2 Recommended Order of Key Screening Assessments for Subjects Who Have Received Augmentation Therapy Within 42 Days Before the Initial Screening Visit



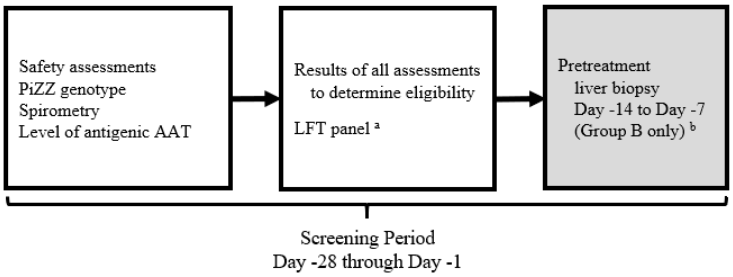
AAT: alpha-1 antitrypsin; LFT: liver function test
Note: Figure is not drawn to scale.

[a] If serum chemistry was completed more than 28 (+7) days before Day 1 dosing, the LFT panel must be completed within 28 (+7) days before Day 1 dosing.

[b] Pretreatment liver biopsy must be performed at least 7 days before Day 1 dosing.

Figure 2-3 displays the general recommended order of key screening assessments for subjects who have not received augmentation therapy within 42 days before the initial screening visit.

Figure 2-3 Recommended Order of Key Screening Assessments for Subjects Who Have Not Received Augmentation Therapy Within 42 Days Before the Initial Screening Visit



AAT: alpha-1 antitrypsin; LFT: liver function test
Note: Figure is not drawn to scale.
[a] If serum chemistry was completed more than 28 (+7) days before Day 1 dosing, the LFT panel must be completed within 28 (+7) days before Day 1 dosing.
[b] Pretreatment liver biopsy must be performed at least 7 days before Day 1 dosing.

Assessments

Efficacy: Blood samples for levels of functional AAT, antigenic AAT, and Z-polymer, and liver biopsy (to evaluate Z-polymer accumulation in the liver)

Safety: AEs, clinical laboratory assessments, standard 12-lead ECGs, clinical evaluation of vital signs, and physical examinations

[redacted]

Statistical Analyses

The primary efficacy endpoint is the change from baseline in blood levels of functional AAT at Week 48.

Assuming (1) the mean of blood levels of functional AAT at baseline is 4.1 µM (SD of 0.6 µM); (2) post-baseline blood levels of functional AAT have a constant coefficient of variation of 0.25; and (3) an intra-subject correlation of 0.8 between baseline and post-baseline measurements, the 95% CI for the change from baseline in blood levels of functional AAT at Week 48 has a half-width between 0.59 and 1.24 if the observed change from baseline is between 2 and 7 µM with a sample size of 16 evaluable subjects (combining Groups A and B). To account for up to a 20% dropout rate, 20 subjects will be enrolled.

The primary analysis will be based on a mixed-effects model for repeated measures (MMRM) with change from baseline in blood levels of functional AAT as the dependent variable. The model will include visit as a fixed effect.

Interim analyses may be conducted at the discretion of the sponsor.

3 SCHEDULE OF ASSESSMENTS

Please note, as of 25 September 2023 this study is no longer screening or enrolling subjects.

Schedules of assessments are in Table 3-1 (Screening for subjects who have received augmentation therapy within 42 days before the initial screening visit), Table 3-2 (Screening for subjects who have not received augmentation therapy within 42 days before the initial screening visit), Table 3-3 (Treatment Period, Day 1 through Week 24), and Table 3-4 (Treatment Period, Week 25 through Safety Follow-up). All visits will be scheduled relative to the Day 1 Visit in this study.

Except where specified otherwise, assessments may be performed in any order when more than 1 assessment is required at a particular time point. All assessments will be performed before study drug dosing (Section 9.6), unless noted otherwise.

Table 3-1 Study VX22-864-108: Screening for Subjects Who Have Received Augmentation Therapy Within 42 Days Before the Initial Screening Visit

Event/Assessment	Screening Period[a] Day -70 through Day -1	Comments
Informed consent	X	
Demographics	X	Section 11.2
Medical history	X	
Medications review	X	Section 9.5
Prior augmentation therapy review	X	Subjects must discontinue augmentation therapy >42 days before the levels of antigenic AAT are obtained to determine eligibility. Section 9.1.1.1 and Figure 9-2
Height and weight	X	Height and weight will be measured with shoes off. Section 11.6.6
Vital signs	X	Complete before blood draws after subject has rested for ≥5 minutes. Sections 11.6.3 and 11.6.4
Pulse oximetry	X	
Physical examination	X	Section 11.6.3
Standard 12-lead ECG	X	Performed in triplicate, with subject in supine position after resting for ≥5 minutes. Performed prior to blood draws. Section 11.6.5
Spirometry	X	To be performed according to ATS/ERS guidelines. A historical $ppFEV_1$ result within 1 year prior to the first Screening Visit can be used to establish eligibility. Section 11.6.7
Urine β-hCG	X	All female subjects; Section 11.6.2

[a] The Screening Period may require multiple visits to complete assessments and to enable scheduling and completion of the pretreatment liver biopsy before Day 1 dosing (Table 3-3). Screening Period may be extended as described in Section 9.1.1.6.

Table 3-1 Study VX22-864-108: Screening for Subjects Who Have Received Augmentation Therapy Within 42 Days Before the Initial Screening Visit

Event/Assessment	Screening Period[a] Day -70 through Day -1	Comments
Serum FSH	X	Obtained to confirm postmenopausal status in female subjects who have spontaneous amenorrhea for ≥12 months without an alternative cause and do not have a history of bilateral oophorectomy or hysterectomy. If a subject has a previous documented FSH result within the performing laboratory's range for postmenopausal females, this assessment does not need to be repeated. Section 11.6.2
Serum chemistry	X	All subjects must complete a safety laboratory test panel (Table 11-2) at the first screening visit to establish eligibility. If serum chemistry (Table 11-2) was completed more than 28 (+7) days before Day 1 dosing, the LFT panel (Table 11-3) must be completed within 28 (+7) days before Day 1 dosing (Section 9.1.1.3). Section 11.6.2
Hematology	X	
Coagulation	X	
Drug test (urine or blood), including cotinine	X	Section 11.6.2
Alcohol test (urine, blood, or breath)	X	
Serology (HbsAg, HCV RNA, and HIV-1/HIV-2 Abs)	X	
Urinalysis	X	
PiZZ genotyping	X	• Sample must be collected and tested at the central laboratory for all subjects, except subjects with historical evidence provided from another Vertex study. • A historical genotype (not from another Vertex study) may be used to establish eligibility with medical monitor approval. Subjects who have been enrolled, and whose screening genotype from the central laboratory does not confirm study eligibility, must be discontinued from the study. • PiZZ genotype must be confirmed in all subjects. In Group A subjects, it must be confirmed before Day 1 dosing. In Group B subjects, it must be confirmed prior to the pretreatment liver biopsy. See Section 8.1, Inclusion Criterion #4 **Sites should allow at least 14 days for sample processing and results reporting.**
Blood sample for antigenic AAT	X	Samples for antigenic and functional AAT will be obtained at the same time.

Table 3-1 Study VX22-864-108: Screening for Subjects Who Have Received Augmentation Therapy Within 42 Days Before the Initial Screening Visit

Event/Assessment	Screening Period[a] Day -70 through Day -1	Comments
Blood sample for functional AAT	X	Blood samples will be obtained for antigenic AAT and sent to the central laboratory at the initial screening visit. 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 in all subjects. In Group A subjects, it must be confirmed before Day 1 dosing. In Group B subjects, it must be confirmed prior to the pretreatment liver biopsy. **Sites should allow at least 14 days for sample processing and results reporting.** See Figure 9-2 and Sections 11.1 and 11.4.1 for details.
Blood sample for Z-polymer	X	Section 11.4.1
Adverse events	Continuous from signing of ICF through completion of study participation	Section 11.6.1

AAT: alpha-1 antitrypsin; ATS: American Thoracic Society; β-hCG: beta-human chorionic gonadotropin; ERS: European Respiratory Society; FSH: follicle-stimulating hormone; HbsAg: hepatitis B surface antigen; HCV RNA: hepatitis C virus ribonucleic acid; HIV-1/HIV-2 Abs: antibodies against human immunodeficiency viruses 1 and 2; ICF: informed consent form; LFT: liver function test; $ppFEV_1$: percent predicted forced expiratory volume in 1 second

Table 3-2 Study VX22-864-108: Screening for Subjects Who Have Not Received Augmentation Therapy Within 42 Days Before the Initial Screening Visit

Event/Assessment	Screening Period[a] Day -28 through Day -1	Comments
Informed consent	X	
Demographics	X	Section 11.2
Medical history	X	
Medications review	X	Section 9.5
Prior augmentation therapy review	X	Section 9.1.1.2 and Figure 9-3
Height and weight	X	Height and weight will be measured with shoes off. Section 11.6.6
Vital signs	X	Complete before blood draws after subject has rested for ≥5 minutes. Sections 11.6.3 and 11.6.4
Pulse oximetry	X	
Physical examination	X	Section 11.6.3
Standard 12-lead ECG	X	Performed in triplicate, with subject in supine position after resting for ≥5 minutes. Performed prior to blood draws. Section 11.6.5
Spirometry	X	To be performed according to ATS/ERS guidelines. A historical ppFEV$_1$ result within 1 year prior to the first Screening Visit can be used to establish eligibility. Section 11.6.7
Urine β-hCG	X	All female subjects; Section 11.6.2
Serum FSH	X	Obtained to confirm postmenopausal status in female subjects who have spontaneous amenorrhea for ≥12 months without an alternative cause and do not have a history of bilateral oophorectomy or hysterectomy. If a subject has a previous documented FSH result within the performing laboratory's range for postmenopausal females, this assessment does not need to be repeated. Section 11.6.2
Serum chemistry	X	All subjects must complete a safety laboratory test panel (Table 11-2) at the first screening visit to establish eligibility. If serum chemistry (Table 11-2) was completed more than 28 (+7) days before Day 1 dosing, the LFT panel (Table 11-3) must be completed within 28 (+7) days before Day 1 dosing (Section 9.1.1.3). Section 11.6.2
Hematology	X	
Coagulation	X	
Drug test (urine or blood), including cotinine	X	Section 11.6.2
Alcohol test (urine, blood, or breath)	X	
Serology (HbsAg, HCV RNA, and HIV-1/HIV-2 Abs)	X	

[a] The Screening Period may require multiple visits to complete assessments, and to enable scheduling and completion of the pretreatment liver biopsy before Day 1 dosing (Table 3-3). Screening Period may be extended as described in Section 9.1.1.6.

Table 3-2 Study VX22-864-108: Screening for Subjects Who Have Not Received Augmentation Therapy Within 42 Days Before the Initial Screening Visit

Event/Assessment	Screening Period[a] Day -28 through Day -1	Comments
Urinalysis	X	
PiZZ genotyping	X	• Sample must be collected and tested at the central laboratory for all subjects, except subjects with historical evidence provided from another Vertex study. • A historical genotype (not from another Vertex study) may be used to establish eligibility with medical monitor approval. Subjects who have been enrolled, and whose screening genotype from the central laboratory does not confirm study eligibility, must be discontinued from the study. • PiZZ genotype must be confirmed in all subjects. In Group A subjects, it must be confirmed before Day 1 dosing. In Group B subjects, it must be confirmed prior to the pretreatment liver biopsy. See Section 8.1, Inclusion Criterion #4 **Sites should allow at least 14 days for sample processing and results reporting.**
Blood sample for antigenic AAT	X	Samples for antigenic and functional AAT will be obtained at the same time. Blood sample(s) for level of antigenic AAT will be obtained to determine eligibility in all subjects. In Group A subjects, it must be confirmed before Day 1 dosing. In Group B subjects, it must be confirmed prior to the pretreatment liver biopsy. **Sites should allow at least 14 days for sample processing and results reporting.** See Figure 9-3 and Sections 11.1 and 11.4.1 for details.
Blood sample for functional AAT	X	
Blood sample for Z-polymer	X	Section 11.4.1
Adverse events	Continuous from signing of ICF through completion of study participation	Section 11.6.1

AAT: alpha-1 antitrypsin; ATS: American Thoracic Society; β-hCG: beta-human chorionic gonadotropin; ERS: European Respiratory Society; FSH: follicle-stimulating hormone; HbsAg: hepatitis B surface antigen; HCV RNA: hepatitis C virus ribonucleic acid; HIV-1/HIV-2 Abs: antibodies against human immunodeficiency viruses 1 and 2; ICF: informed consent form; LFT: liver function test; $ppFEV_1$: percent predicted forced expiratory volume in 1 second

Table 3-3 Study VX22-864-108: Treatment Period, Day 1 through Week 24

Event/ Assessment[a]	Treatment Period												ETT[b]	Comments
	Day -14 to Day -7	Day 1	Day 7 (±1 d)	Day 15 (±2 d)	Day 21 (±2 d)	Day 28 (±2 d)	Wk 6 (±7 d)	Wk 8 (±7 d)	Wk 12 (±7 d)	Wk 16 (±7 d)	Wk 20 (±7 d)	Wk 24 (±14 d)		
Study Visit	Group B only	X	X	X	X	X	X	X	X	X	X	X	X	**The Day -14 to Day -7 (in Group B only), Day 1, and Week 24 Visits, must occur at the clinic.** All other visits may occur at the clinic or at home (if permitted by local regulations) as outlined in Section 9.1.3. If the visit occurs at home, then a home health follow-up consultation with the investigator or qualified designee (i.e., telemedicine video conference, telephone contact, or in person) must be performed within 5 business days after any home visit. The home health follow-up consultation with the investigator or qualified designee can occur outside the visit window, and may also include a separate follow-up with the study coordinator. Section 9.1.3.1
Weight		X										X		Weight will be measured with shoes off.

[a] There will be no further dosing in this study.

[b] ETT Visit may be conducted remotely by telephone or video (Section 9.1.5).

Table 3-3 Study VX22-864-108: Treatment Period, Day 1 through Week 24

Event/ Assessment[a]	Treatment Period												ETT[b]	Comments
	Day -14 to Day -7	Day 1	Day 7 (±1 d)	Day 15 (±2 d)	Day 21 (±2 d)	Day 28 (±2 d)	Wk 6 (±7 d)	Wk 8 (±7 d)	Wk 12 (±7 d)	Wk 16 (±7 d)	Wk 20 (±7 d)	Wk 24 (±14 d)		
Standard 12-lead ECG		X	X			X			X			X		All ECGs will be performed in triplicate, with subject in supine position after resting for ≥5 minutes. Performed prior to blood draws when on same day. **Days 1 and 7:** predose and at 3 hours (± 15 minutes) postdose Section 11.6.5
Vital signs		X	X	X	X	X	X	X	X	X	X	X		Complete before blood draws after subject has rested for ≥5 minutes. Sections 11.6.3 and 11.6.4
Pulse oximetry		X	X	X	X	X	X	X	X	X	X	X		
Physical examination/ review of symptoms	PE, Group B only	PE	X	X	X	X	X	X	X	X	X	PE		A complete PE will be conducted on the Pretreatment Interval (**Day -14 to Day -7**), **Day 1**,**Week 24**, and **ETT** Visits; a review of symptoms will be conducted at all other times. 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 11.6.3

Table 3-3 Study VX22-864-108: Treatment Period, Day 1 through Week 24

Event/ Assessment[a]	Treatment Period												ETT[b]	Comments
	Day -14 to Day -7	Day 1	Day 7 (±1 d)	Day 15 (±2 d)	Day 21 (±2 d)	Day 28 (±2 d)	Wk 6 (±7 d)	Wk 8 (±7 d)	Wk 12 (±7 d)	Wk 16 (±7 d)	Wk 20 (±7 d)	Wk 24 (±14 d)		
Urine β-hCG		X				X		X	X	X	X	X		All female subjects of childbearing potential. Section 11.6.8
Serum β-hCG		X												On Day 1, study drug must not be administered until after a negative result is confirmed by the urine pregnancy test. At study visits, the urine pregnancy test should be administered and reported by a health professional (e.g., home health nurse, study coordinator). Section 11.6.2
Serum chemistry		X	X	X	X	X	X	X	X	X	X	X		Complete before dosing and before biopsy, when applicable. Section 11.6.2 In Group B, local lab hematology and coagulation results must be collected and reviewed by investigator within approximately 48 hours prior to performing the liver biopsy.
Hematology	Group B only	X	X	X	X	X	X	X	X	X	X	X		
Coagulation	Group B only	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis		X	X	X	X	X	X		X			X		
Blood sample for antigenic AAT		X	X	X	X	X	X	X	X	X	X	X		Section 11.4.1
Blood sample for functional AAT		X	X	X	X	X	X	X	X	X	X	X		
Blood sample for Z-polymer		X	X	X	X	X	X	X	X	X	X	X		

[redacted]

Table 3-3 Study VX22-864-108: Treatment Period, Day 1 through Week 24

Event/ Assessment[a]	Treatment Period												ETT[b]	Comments
	Day -14 to Day -7	Day 1	Day 7 (±1 d)	Day 15 (±2 d)	Day 21 (±2 d)	Day 28 (±2 d)	Wk 6 (±7 d)	Wk 8 (±7 d)	Wk 12 (±7 d)	Wk 16 (±7 d)	Wk 20 (±7 d)	Wk 24 (±14 d)		
Percutaneous liver biopsy	Group B only											Cohort B1		On **Week 24**, liver biopsy will be performed after all other assessments (unless otherwise stated). The liver biopsy will be performed 3 hours (±30 minutes) postdose relative to the morning dose. Local lab hematology and coagulation results must be collected and reviewed by investigator within approximately 48 hours prior to performing the liver biopsy. Section 11.4.2
[redacted]														

Table 3-3 Study VX22-864-108: Treatment Period, Day 1 through Week 24

Event/ Assessment[a]	Treatment Period												ETT[b]	Comments
	Day -14 to Day -7	Day 1	Day 7 (±1 d)	Day 15 (±2 d)	Day 21 (±2 d)	Day 28 (±2 d)	Wk 6 (±7 d)	Wk 8 (±7 d)	Wk 12 (±7 d)	Wk 16 (±7 d)	Wk 20 (±7 d)	Wk 24 (±14 d)		
[redacted]														
Study drug dosing [c]	No further dosing will be administered as of 25 September 2023													Section 9.6
Adverse events	Continuous from signing of ICF through completion of study participation													Section 11.6.1

Table 3-3 Study VX22-864-108: Treatment Period, Day 1 through Week 24

Event/ Assessment[a]	Treatment Period												ETT[b]	Comments
	Day -14 to Day -7	Day 1	Day 7 (±1 d)	Day 15 (±2 d)	Day 21 (±2 d)	Day 28 (±2 d)	Wk 6 (±7 d)	Wk 8 (±7 d)	Wk 12 (±7 d)	Wk 16 (±7 d)	Wk 20 (±7 d)	Wk 24 (±14 d)		
Medications review	Continuous from signing of ICF through completion of study participation													Section 9.5

Note: Shaded columns represents visits required to be performed in clinic.
AAT: alpha-1 antitrypsin; β-hCG: beta-human chorionic gonadotropin; d: day; ETT: early termination of treatment; ICF: informed consent form; PE: physical examination; [redacted] wk: week

[c] There will be no further dosing in this study. All subjects may consent to the posttreatment Telemedicine Visit(s) following final dose of study drug, to monitor for development of AEs of rash (for up to 6 months) and monitor any ongoing AEs of rash (for up to 6 months following resolution of AEs of rash; see Section 9.1.6 and Posttreatment Telemedicine Visit column in Table 3-4).

Table 3-4 Study VX22-864-108: Treatment Period, Week 25 through Safety Follow-Up

Event/ Assessment[a]	Treatment Period						ETT[b]	SFU Visits, 14 and 28 (± 2d) Days After Last Dose of Study Drug	Posttreatment Telemedicine Visit(s) [c]	Comments
	Wk 28 (±7 d)	Wk 32 (±7 d)	Wk 36 (±7 d)	Wk 40 (±7 d)	Wk 44 (±7 d)	Wk 48 (±14 d)				
Study Visit		X		X		X		X		**The Week 48, and Safety Follow-up Visits must occur at the clinic.** All other visits may occur at the clinic or at home (if permitted by local regulations) as outlined in Section 9.1.3. If the visit occurs at home, then a home health follow-up consultation with the investigator or qualified designee (i.e., telemedicine video conference, telephone contact, or in person) must be performed within 5 business days after any home visit. The home health follow-up consultation with the investigator or qualified designee can occur outside the visit window, and may also include a separate follow-up with the study coordinator. Section 9.1.3.1
Telephone (or video as appropriate) visit	X		X		X		X		X	Female subjects of childbearing potential only will report the results of their home pregnancy tests. Section 9.1.2.1 **Posttreatment Telemedicine Visit(s)** to be only conducted in subjects who consent to it. Urine pregnancy testing does not need to be performed during the posttreatment Telemedicine Visit(s). Section 9.1.6
Weight						X		X		Weight will be measured with shoes off.
Standard 12-lead ECG						X		X		All ECGs will be performed in triplicate, with subject in supine position after resting for ≥5 minutes. Performed prior to blood draws when on same day. Section 11.6.5

[a] There will be no further dosing in this study.
[b] ETT Visit may be conducted remotely by telephone or video (Section 9.1.5).

Table 3-4 Study VX22-864-108: Treatment Period, Week 25 through Safety Follow-Up

Event/ Assessment[a]	Treatment Period						ETT[b]	SFU Visits, 14 and 28 (± 2d) Days After Last Dose of Study Drug	Posttreatment Telemedicine Visit(s) [c]	Comments
	Wk 28 (±7 d)	Wk 32 (±7 d)	Wk 36 (±7 d)	Wk 40 (±7 d)	Wk 44 (±7 d)	Wk 48 (±14 d)				
Vital signs		X		X		X		X		Complete before blood draws after subject has rested for ≥5 minutes. Sections 11.6.3 and 11.6.4
Pulse oximetry		X		X		X		X		
Physical examination/review of symptoms		X		X		PE		PE		A complete PE will be conducted on **Week 48**, and **SFU** Visits; a review of symptoms will be conducted at all other times. If any findings in the review of symptoms are considered abnormal by the investigator, the subject will be instructed to have a complete PE in the clinic. Section 11.6.3
Urine β-hCG	Home kit	X	Home kit	X	Home kit	X		X		All female subjects of childbearing potential. Section 11.6.8 At study visits, the urine pregnancy test should be administered and reported by a health professional (e.g., home health nurse, study coordinator). At indicated telephone visits, a urine pregnancy test will be performed with a home kit provided by the study site. Results will be reported to the site by telephone. Section 11.6.2
Serum chemistry		X		X		X		X		Complete before dosing and before biopsy on Week 48 (Cohort B2 only), when applicable. Section 11.6.2 Local lab hematology and coagulation results must be collected and reviewed by investigator within approximately 48 hours prior to performing the liver biopsy.
Hematology		X		X		X		X		
Coagulation		X		X		X		X		
Urinalysis						X				
Blood sample for antigenic AAT		X		X		X		X		Section 11.4.1
Blood sample for functional AAT		X		X		X		X		
Blood sample for Z-polymer		X		X		X		X		

Table 3-4 Study VX22-864-108: Treatment Period, Week 25 through Safety Follow-Up

Event/ Assessment[a]	Treatment Period						ETT[b]	SFU Visits, 14 and 28 (± 2d) Days After Last Dose of Study Drug	Posttreatment Telemedicine Visit(s) [c]	Comments
	Wk 28 (±7 d)	Wk 32 (±7 d)	Wk 36 (±7 d)	Wk 40 (±7 d)	Wk 44 (±7 d)	Wk 48 (±14 d)				
[redacted]										
Percutaneous liver biopsy						Cohort B2				On **Week 48**, liver biopsy will be performed after all other assessments (unless otherwise stated). The liver biopsy will be performed 3 hours (±30 minutes) postdose relative to the morning dose. Local lab hematology and coagulation results must be collected and reviewed by investigator within approximately 48 hours prior to performing the liver biopsy. Section 11.4.2
[redacted]										

Table 3-4 Study VX22-864-108: Treatment Period, Week 25 through Safety Follow-Up

Event/ Assessment[a]	Treatment Period						ETT[b]	SFU Visits, 14 and 28 (± 2d) Days After Last Dose of Study Drug	Posttreatment Telemedicine Visit(s) [c]	Comments
	Wk 28 (±7 d)	Wk 32 (±7 d)	Wk 36 (±7 d)	Wk 40 (±7 d)	Wk 44 (±7 d)	Wk 48 (±14 d)				
[redacted]										
Study drug dosing	No further dosing will be administered as of 25 September 2023									Section 9.6
Adverse events	Continuous from signing of ICF through completion of study participation									Section 11.6.1
Medications review	Continuous from signing of ICF through completion of study participation									Section 9.5

Note: Shaded columns represents visits required to be performed in clinic.
AAT: alpha-1 antitrypsin; β-hCG: beta-human chorionic gonadotropin; d: day; ETT: early termination of treatment; ICF: informed consent form; PE: physical examination; [redacted] SFU: Safety Follow-up; wk: week

[c] There will be no further dosing in this study. All subjects may consent to the posttreatment Telemedicine Visit(s) following final dose of study drug, to monitor for development of AEs of rash (for up to 6 months) and monitor any ongoing AEs of rash (for up to 6 months following resolution of AEs of rash (Section 9.1.6).

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List of Abbreviations

Abbreviation	Definition
AAT	alpha-1 antitrypsin
AATD	alpha-1 antitrypsin deficiency
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ASMA	anti-smooth muscle antibody
AST	aspartate transaminase
ATS	American Thoracic Society
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
CCP	cyclic citrullinated peptide
CI	confidence interval
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus-19 pandemic
CPAP	clinical pharmacology analysis plan
CPK	creatine phosphokinase
CRF	case report form
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A	cytochrome P450 3A
d	Day
DNA	deoxyribonucleic acid
EBV	Epstein-Barr virus
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
eGFR	estimated glomerular filtration rate
ERS	European Respiratory Society
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
GPS	Global Patient Safety
HbsAg	hepatitis B surface antigen
HCV	hepatitis C virus

Abbreviation	Definition
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
IgA/G/M	immunoglobulin A/G/M
IMP	investigational medicinal product
IND	Investigational New Drug (application) (US)
INR	international normalized ratio
IRB	institutional review board
LFT	liver function test
LKM-1	liver-kidney microsomal type 1
[redacted]	
max	maximum value
min	minimum value
MMRM	mixed-effects model for repeated measures
n	size of subsample
N	total sample size (e.g., number of subjects treated)
NSAIDs	nonsteroidal anti-inflammatory drug
OATP1B1	organic anion transporting polypeptide 1B1
P	probability
PD	pharmacodynamic, pharmacodynamics
PE	physical examination
Pex	pulmonary exacerbation
PI	principal investigator
PiZZ	homozygous for the Z mutation of the *SERPINA1* gene that encodes the AAT protein
[redacted]	
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
q12h	every 12 hours
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
RNA	ribonucleic acid
RNAi	ribonucleic acid interference
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SS	Safety Set
SUSAR	suspected, unexpected, serious adverse reaction
TE	treatment-emergent

Abbreviation	Definition
TEAE	treatment-emergent adverse event
UGT1A1/A4	uridine diphosphate glucuronosyltransferase family 1 member A1/A4
ULN	upper limit of normal
wk	Week

5 INTRODUCTION

5.1 Background

Alpha-1 antitrypsin deficiency (AATD) is an inheritable genetic disorder characterized by a protein folding defect causing 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]

A single amino acid substitution in the AAT protein, E342K, (a lysine for a glutamic acid residue; the Z-AAT variant) results in misfolding of the protein, intracellular polymerization of misfolded mutant Z-AAT protein, and reduced secretion of Z-AAT protein by hepatocytes. Circulating levels of AAT in individuals homozygous for the *Z* allele (PiZZ) are markedly reduced; approximately 15% of Z-AAT protein folds correctly and is secreted by hepatocytes. The deficiency of circulating AAT increases the risk of developing pulmonary emphysema in subjects with the PiZZ genotype due to unopposed neutrophil-derived serine proteinase activity in the lungs. However, individuals with the PiZZ genotype may also develop severe hepatic disease due to the toxic gain-of-function associated with Z-AAT protein accumulation in the liver. Z-polymer accumulates within hepatocytes leading to endoplasmic reticular stress, hepatocyte cytotoxicity, and cell death, [redacted] The majority of individuals with severe AATD-associated hepatic disease have the PiZZ genotype.

VX-864 targets the underlying cause of this genetic disorder by repairing the protein folding defect to increase levels of functionally active Z-AAT in the circulation. Based on available clinical data, VX-864 has been generally well tolerated by participants of Phase 1 and Phase 2 clinical studies conducted by the Sponsor, which included healthy subjects and subjects with AATD and the PiZZ genotype (these studies are detailed in the VX-864 Investigator's Brochure [IB]). Based on exploratory data from previous trials, VX-864 warrants further evaluation over a longer duration.

5.2 Study Rationale

The purpose of this study is to evaluate the efficacy and safety of VX-864 in individuals with the PiZZ genotype. VX-864 is theorized to prevent intracellular Z-AAT protein polymerization and increase secretion of functionally active AAT, potentially addressing unmet medical need in this population. Clinical data in individuals with the PiZZ genotype in the Phase 1 study VX21-864-008 and in the Phase 2 study VX19-864-101 demonstrate that VX-864 is generally safe and well tolerated in generally healthy subjects with the PiZZ genotype (refer to the VX-864 IB).

A small but statistically significant increase in blood levels of functional and antigenic AAT was demonstrated in the Phase 2 study VX19-864-101 over 28 days in subjects with the PiZZ genotype. In addition, in generally healthy subjects with the PiZZ genotype receiving multiple doses of VX-864 over 14 days in the recently completed Phase 1 open-label study VX21-864-008, evaluation of the concentration of VX-864 in the liver demonstrated adequate levels of study drug were distributed effectively to the target organ. The results of these 14-day and 28-day studies suggest further evaluation of VX-864 over a longer period is warranted, with the hypothesis that a longer period of VX-864 dosing may result in in higher blood levels of functional and antigenic AAT compared with 28 days of dosing. The study results may also

inform future development of potential new small molecules in AATD. Hence, this study will evaluate VX-864 over a longer period than prior studies, i.e., 48 weeks in subjects with the PiZZ genotype.

6 STUDY OBJECTIVES

6.1 Primary Objective

- To evaluate the efficacy of VX-864 on blood levels of functional AAT in individuals with the PiZZ genotype

6.2 Secondary Objectives

- To evaluate the efficacy of VX-864 on blood levels of antigenic AAT in individuals with the PiZZ genotype
- To evaluate the efficacy of VX-864 on blood levels of Z-polymer in individuals with PiZZ genotype
- To evaluate the efficacy of VX-864 on liver Z-polymer in individuals with the PiZZ genotype (in Group B only)
- To evaluate the safety and tolerability of VX-864 in individuals with the PiZZ genotype

[redacted]

7 STUDY ENDPOINTS

7.1 Primary Endpoint

- Change from baseline in blood levels of functional AAT at Week 48

7.2 Secondary Endpoints

- Change from baseline in blood levels of functional AAT over time
- Change from baseline in blood levels of antigenic AAT over time
- Change from baseline in blood levels of Z-polymer over time
- Change from baseline in Z-polymer accumulation in the liver over time (in Group B only)
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, standard 12-lead ECGs, and vital signs

8 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled.

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 (Section 11.6.8.1), and other study procedures.
3. In subjects not undergoing liver biopsies (Group A):
   - Subjects between the ages of 18 and 80 years, inclusive, at the time of ICF signing.

   In subjects undergoing liver biopsies (Group B):
   - Subjects between the ages of 18 and 70 years, inclusive at the time of the ICF signing.
4. Subjects must have a PiZZ genotype confirmed during screening.
   - All subjects must have PiZZ genotype tested at the central laboratory, except for subjects who have had historical genotype results obtained via the central laboratory as part of another Vertex study.
   - A historical genotype (not from another Vertex study) may be used to establish eligibility with medical monitor approval. Subjects who have been enrolled, and whose screening genotype from the central laboratory does not confirm study eligibility, must be discontinued from the study.
   - In Group A subjects, the PiZZ genotype must be confirmed before Day 1 dosing. In Group B subjects, the PiZZ genotype must be confirmed prior to the pretreatment liver biopsy.

5. In subjects not undergoing biopsies (Group A)

   - A 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 or a historical result within 1 year before the initial Screening Visit. Post-bronchodilator spirometry measurements must meet American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria for acceptability and repeatability.

   In subjects undergoing biopsies (Group B)

   - An FEV_1 value ≥40% of predicted mean for age, sex, and height (equations of the GLI) during screening or a historical result within 1 year before the initial Screening Visit. Post-bronchodilator spirometry measurements must meet ATS/ ERS criteria for acceptability and repeatability.

6. Body mass index (BMI) of 18.0 to 35 kg/m^2, inclusive.
7. Screening antigenic AAT <8 μM. For subjects who have received augmentation therapy within 42 days before the initial screening visit, results used to confirm eligibility must be drawn >42 days after the last dose of augmentation therapy. Levels of antigenic AAT must be obtained from the central laboratory and results confirmed in all subjects. In Group A subjects, it must be confirmed prior to Day 1. In Group B subjects, it must be confirmed prior to the pretreatment liver biopsy.

8.2 Exclusion Criteria

1. History of any illness or any clinical condition that, in the opinion of the investigator or the subject's general practitioner, might confound the results of the study or pose an additional risk in administering study drug to the subject. This may include, but is not limited to, history of relevant drug or food allergies; history of cardiovascular or central nervous system disease; history or presence of clinically significant pathology; history of mental disease; and history of cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years).
2. Solid organ or hematological transplantation or is currently on a transplant list.
3. Subjects who have undergone gastrectomy or major resection of the small bowel or proximal colon.
4. All clinically important pulmonary disease as deemed by investigator, including but not limited to unstable AATD-related chronic obstructive pulmonary disease (COPD), interstitial lung disease, cystic fibrosis, pulmonary hypertension with or without cor pulmonale, history of pulmonary embolism, or malignant lung cancer.
5. 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.
6. Only in subjects undergoing liver biopsies (in Group B), any contraindication to a percutaneous liver biopsy including a bleeding diathesis, ascites, or chronic need for treatment with anti-coagulants or anti-platelet agents.
7. Current diagnosis of active hepatitis and/or significant chronic liver disease of any etiology other than AATD-associated non-cirrhotic liver disease including, but not limited to hepatic cirrhosis, portal hypertension, or confirmed or suspected esophageal varices.

8. History of Gilbert's Syndrome.
9. History of use of gene therapy or RNAi therapy at any time previously.
10. Hypersensitivity to any component of the investigational drug product.
11. History of significant alcohol consumption within 3 months before screening, defined as more than 1 drink/day for females or 2 drinks/day 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), or alcohol consumption during the study that is not compliant with the protocol-defined restriction (Table 9-1).
12. Use of oral corticosteroids (at any dose) for a duration of greater than 3 months at any time within the 3 months before screening.
13. Use of inhaled cannabis within the 6 months before screening, or illegal drugs within 1 year before screening as deemed by the investigator (use of non-inhaled, ingestible forms of cannabis-containing products are not exclusionary if legal in the subject's region).
14. 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.
15. Any clinically significant ECG abnormality (as determined by the investigator) or median QTcF of triplicate standard 12-lead ECGs >450 msec at screening.
16. Any of the following abnormal laboratory values at screening:
    - Platelet count $<150 \times 10^9$/L
    - Albumin <3.5 g/dL
    - International normalized ratio (INR) ≥1.2
    - Hemoglobin <10 g/dL for women and <12 g/dL for men
    - Total bilirubin >upper limit of normal (ULN)
    - Aspartate transaminase (AST), alanine transaminase (ALT), or alkaline phosphatase (ALP) >2 × ULN
    - Gamma-glutamyl transferase (GGT) >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)
17. Positive for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) RNA, or antibodies against human immunodeficiency viruses 1 and 2 (HIV-1/HIV-2 Abs) during screening.
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. Use of the substances, activities, or devices during the time periods indicated in Section 9.4.

20. 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. For subjects who have participated in a prior Vertex study, approval of the medical monitor is required.
21. All female subjects must have a negative pregnancy test at screening. Premenopausal female subjects of child-bearing potential must also have a negative pregnancy test (urine or serum test) on Day 1 and must not be breastfeeding or planning to become pregnant during the study or within 90 days after the last study drug dose.

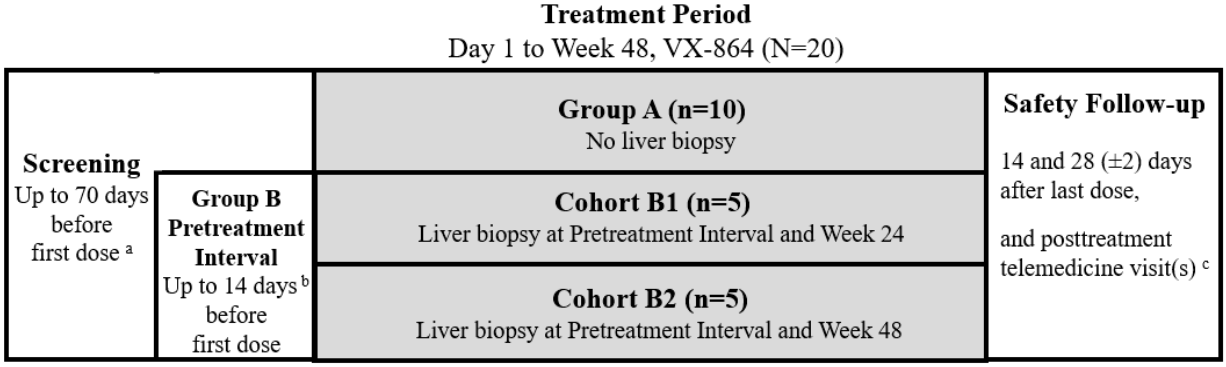
    Male subjects who plan to donate sperm or who have a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose.
22. Subject or close relative of the subject is the investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a Phase 2, open-label, multicenter study. A schematic of the study design is shown in Figure 9-1. Approximately 20 subjects with the PiZZ genotype will be enrolled. Groups A and B will enroll approximately 10 subjects each. All subjects will receive VX-864 500 mg every 12 hours (q12h) for 48 weeks. Group A subjects will not have a liver biopsy. Subjects in Group B will have 2 liver biopsies performed over the course of the study. All liver biopsies will be performed percutaneously. All subjects in Group B (approximately 10 subjects) will have a liver biopsy during the Pretreatment Interval (Figure 9-1). Approximately 5 subjects (Cohort B1) will have a second liver biopsy at Week 24. Approximately 5 subjects (Cohort B2) will have a second liver biopsy at Week 48. The pretreatment liver biopsy must be performed at least 7 days before Day 1 dosing, after all eligibility criteria have been met. Local laboratory hematology and coagulation results must be collected and reviewed by investigator within approximately 48 hours prior to the liver biopsy being performed. The Week 24 and Week 48 liver biopsies will be performed 3 hours (±30 minutes) postdose relative to the morning dose. The Safety Follow-up Visits are required for all subjects. In subjects who terminate their participation early, the ETT visit, which may be conducted at the site or by telephone or video interview, replaces the Safety Follow-up Visits, if the ETT Visit occurs 3 weeks or later following the last dose of study drug. All subjects may also consent to the posttreatment Telemedicine Visit(s) following final dose of study drug, to monitor for development of AEs of rash (for up to 6 months) and monitor any ongoing AEs of rash (for up to 6 months following resolution of AEs of rash; see Section 9.1.6).

Figure 9-1 VX22-864-108 Study Design



n: size of subsample; N: number of subjects
Note: Figure is not drawn to scale.

[a] In subjects not requiring augmentation therapy washout, the Screening Period will be up to 28 days. In subjects requiring augmentation therapy washout, the Screening Period will be up to 70 days.

[b] Day -14 to Day -7; pretreatment liver biopsy must be performed at least 7 days before Day 1 dosing.

[c] There will be no further dosing in this study as of 25 September 2023. All subjects may consent to the posttreatment Telemedicine Visit(s) following final dose of study drug, to monitor for development of AEs of rash (for up to 6 months) and monitor any ongoing AEs of rash (for up to 6 months following resolution of AEs of rash; see Section 9.1.6).

9.1.1 Screening

The Screening Period may require multiple visits to complete assessments, and to enable evaluation of eligibility (Table 3-1 and Table 3-2). Please note, there will be no further enrollment of subjects in this study.

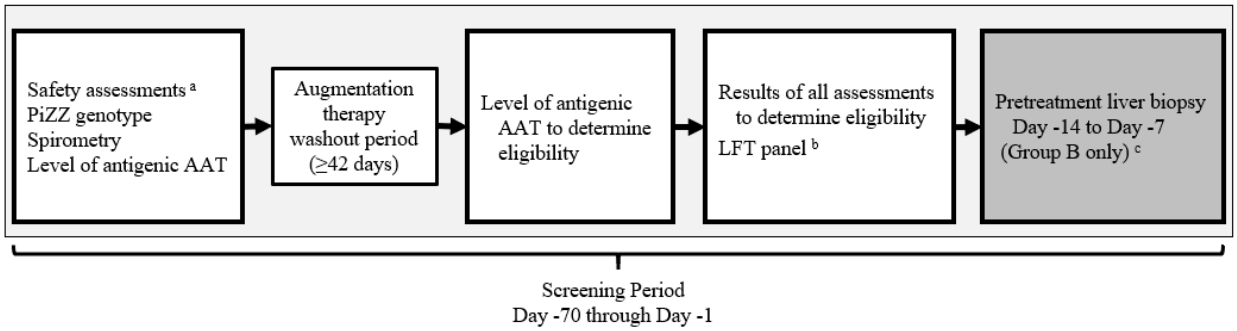
9.1.1.1 Screening for Subjects Who Have Received Augmentation Therapy Within 42 Days Before the Initial Screening Visit

The Screening Period may be up to 70 days in duration (Day -70 through Day -1) for subjects who are discontinuing augmentation therapy. This is to accommodate an appropriate washout of augmentation therapy that is ≥42 days in duration, enable enough time to perform all required screening assessments which will require multiple visits during screening, and to enable scheduling of the pretreatment liver biopsy (Table 3-1).

Figure 9-2 displays the general recommended order of key screening assessments for subjects who are discontinuing augmentation therapy for subjects screening for enrollment in Groups A or B.

Blood samples will be obtained for antigenic AAT at the initial Screening Visit. If the subject received the last dose of augmentation therapy >42 days prior to sample collection, 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.

Figure 9-2 Recommended Order of Key Screening Assessments for Subjects Who Have Received Augmentation Therapy Within 42 Days Before the Initial Screening Visit



AAT: alpha-1 antitrypsin; β-hCG: beta-human chorionic gonadotropin; FSH: follicle-stimulating hormone; LFT: liver function test

Note: Figure not drawn to scale. **Sites should allow at least 14 days for sample processing and results reporting for level of antigenic AAT and the PiZZ genotype.**

[a] Safety assessments include height and weight, vital signs, pulse oximetry, physical examination, ECG, FSH, β-hCG, serology, serum chemistry, hematology, coagulation, and urinalysis.

[b] If serum chemistry (Table 11-2) was completed more than 28 (+7) days before Day 1 dosing, the LFT panel (Table 11-3) must be completed within 28 (+7) days before Day 1 dosing (Section 9.1.1.3).

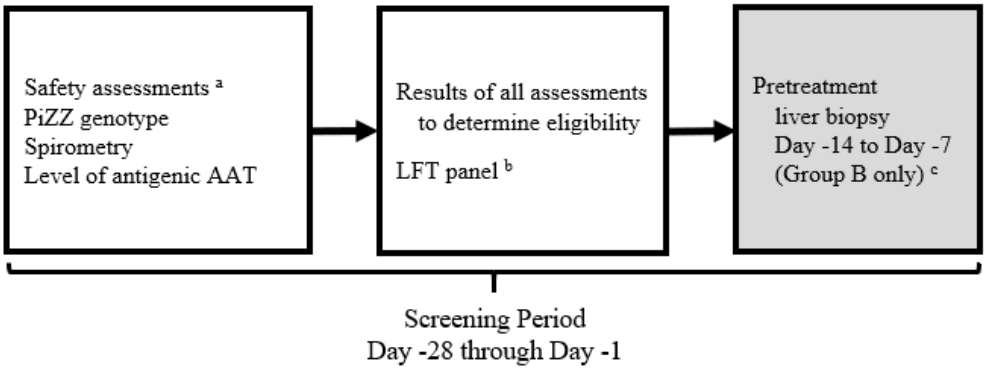
[c] In Group B only, the pretreatment liver biopsy must be performed at least 7 days before Day 1 dosing, after all eligibility criteria have been met. Local laboratory hematology and coagulation results must be collected and reviewed by investigator within approximately 48 hours prior to the liver biopsy being performed.

9.1.1.2 Screening for Subjects Who Have Not Received Augmentation Therapy Within 42 Days Before the Initial Screening Visit

For subjects who were not on augmentation therapy and hence do not require a washout period, the Screening Period will be up to 28 days in duration (Day -28 through Day -1).

Figure 9-3 displays the general recommended order of screening assessments for subjects who are not discontinuing augmentation therapy for subjects screening for enrollment in Groups A or B.

Figure 9-3 Recommended Order of Screening Assessments for Subjects Who Have Not Received Augmentation Therapy Within 42 Days Before the Initial Screening Visit



AAT: alpha-1 antitrypsin; β-hCG: beta-human chorionic gonadotropin; FSH: follicle-stimulating hormone; LFT: liver function test

Note: Figure not drawn to scale. **Sites should allow at least 14 days for sample processing and results reporting for level of antigenic AAT and the PiZZ genotype.**

[a] Safety assessments include height and weight, vital signs, pulse oximetry, physical examination, ECG, FSH, β-hCG, serology, serum chemistry, hematology, coagulation, and urinalysis.

[b] If serum chemistry (Table 11-2) was completed more than 28 (+7) days before Day 1 dosing, the LFT panel (Table 11-3) must be completed within 28 (+7) days before Day 1 dosing (Section 9.1.1.3).

[c] In Group B only, the pretreatment liver biopsy must be performed at least 7 days before Day 1 dosing, after all eligibility criteria have been met. Local laboratory hematology and coagulation results must be collected and reviewed by investigator within approximately 48 hours prior to the liver biopsy being performed.

9.1.1.3 LFT Panel Before Day 1 Dosing

If serum chemistry (Table 11-2) was completed more than 28 (+7) days before Day 1 dosing, the liver function test (LFT) panel (Table 11-3) must be completed within 28 (+7) days before Day 1 dosing. If an LFT panel is completed, the following results must be met before the subject may proceed to dosing on Day 1:

- ALT and AST ≤2 × ULN
- Total bilirubin ≤ULN

If the LFT panel results preclude the subject from proceeding to Day 1 dosing, the LFT panel may be repeated every 3 to 4 days until the above criteria are met.

9.1.1.4 Repetition of Screening Assessment(s)

Repeating individual screening assessment(s) that did not meet eligibility criteria is not permitted, with the following exceptions:

- If there is clear evidence of a damaged sample, laboratory error, equipment malfunction, or if the investigator believes the result is not consistent with the subject's current medical condition or historic result, collection of a repeat sample for the appropriate laboratory test or assessment may be permitted.
- Spirometry, which may be retested once.
- Exclusionary ALT, AST, GGT, total bilirubin, ALP, INR, platelet, hemoglobin, albumin, or eGFR test results, which may be retested once.

- Exclusionary ECG test results, which may be retested once.
- Screening levels of antigenic AAT performed to determine eligibility may be repeated.

The repeat screening assessment or blood sample may be conducted or drawn, respectively, at the clinic or at home by a qualified visiting nurse, where permitted by local regulations. 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.

9.1.1.5 Rescreening

Subjects may be rescreened only once for non-safety assessments, except if subject experiences a pulmonary exacerbation (PEx) during the first rescreening, or in the event the clinical site closes or becomes not operational during the first rescreening due to unforeseen reasons (e.g., COVID-19 associated shutdown of site) in which case the subjects may be rescreened more than 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.

9.1.1.6 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 9.1.1.4)
- A PEx during the Screening Period
- Unexpected operational or logistic delays, or to meet the eligibility criteria.

Subjects who have not received augmentation therapy within 42 days before the initial Screening Visit 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

Treatment Period assessments are listed in Table 3-3 and Table 3-4 (Day 1 through Week 48 Visit).

Completion of study participation is defined in Section 9.1.9.

9.1.2.1 Telephone Visits

For female subjects of childbearing potential only, the result from the urine home pregnancy test kit will be reported by the subject to the study site at these telephone visits.

In subjects who consent to the posttreatment Telemedicine Visit(s), this visit may be conducted as a telephone or video interview, as detailed in Section 9.1.6. Urine pregnancy tests will not be required for these visits.

9.1.3 Use of Remote Measures

The initial Screening Visit and study visits on Day -14 to Day -7 (in Group B only), Day 1, Weeks 24, 48, and Safety Follow-up must be performed in the clinic, even under extenuating circumstances. However, at Screening Visits (other than the initial visit) when the assessments are feasible to conduct in the home setting, and at other study visits as specified in Table 3-3 and Table 3-4 where permitted by local regulations, study assessments may be performed remotely (i.e., home visit). The decision to conduct study visits remotely or in clinic will be at the discretion of the investigator after consultation with the subject.

Early Termination of Treatment (ETT) visit may be performed by telephone or video.

If local regulations or site practice do not allow remote measures, all study visits will be performed in the clinic.

9.1.3.1 Home Health Follow-up Consultation With the Investigator

Following all home visits, the investigator or qualified designee will review all source documentation associated with the assessments performed at the home visit. The investigator or qualified designee will then engage the subject in a telephone call, telemedicine video conference, or in person within 5 business days after the home visit. This consultation may occur outside the visit window. The home health follow-up consultation with the investigator or qualified designee may include, but is not limited to, verbal confirmation of safety assessments and study compliance information as appropriate. The investigator or qualified designee will follow up on any assessments that were not performed as scheduled. Additional details will be provided in the Study Reference Manual.

9.1.4 Safety Follow-up

The Safety Follow-up Visits are scheduled to occur 14 and 28 (± 2) days after the last dose of study drug. The Safety Follow-up Visit assessments are listed in Table 3-4.

The Safety Follow-up Visits are required for all subjects.

9.1.5 Early Termination of Treatment

If a subject prematurely discontinues study treatment, an ETT Visit should be scheduled as soon as possible after the decision to discontinue study drug treatment. Subjects who prematurely discontinue study drug treatment will also be required to complete the Safety Follow-up Visits, approximately 14 and 28 (± 2) days after their last dose of study drug.

If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the Safety Follow-up Visits, and a separate Safety Follow-up Visit will not be required. The ETT visit may be performed at the site or by telephone or video.

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 (Section 9.9), the study data and samples collected will remain part of the study.

9.1.6 Posttreatment Telemedicine Visit(s)

In subjects who consent to the posttreatment Telemedicine Visit(s), current status of symptoms from resolved or ongoing AEs of rash will be discussed via a telephone or video interview, which may consist of multiple telemedicine visits, if necessary according to AE resolution status.

This telemedicine visit will be 6 months after last dose or AE of rash resolution as follows:

- subjects with no AEs of rash are to be followed for up to 6 months after the last dose of study drug
- subjects with AEs of rash are to be followed for up to 6 months following resolution of their respective AE(s) of rash

Recommended precautions for exposure to sunlight (Section 9.4.1) should be followed through the final posttreatment Telemedicine Visit. Subjects should also be instructed to contact the investigational site if they develop new or worsening rash.

9.1.7 Timing Under Extenuating Circumstances

In the event that extenuating circumstances (e.g., events related to COVID-19) or unforeseen conditions (e.g., natural disasters or unforeseen external factors impacting clinical site) alter the timing of a scheduled visit being conducted, the investigator should notify the medical monitor, and the visit window specified in the Schedule of Assessments during the Treatment Period may be expanded by up to ± 7 days upon consultation with the investigator and medical monitor.

For study visits requiring a liver biopsy, the visit will be rescheduled upon consultation with the investigator and medical monitor.

9.1.8 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 visit) and is subsequently unable to be contacted by telephone (3 documented attempts by telephone within 2 weeks following the second missed visit)
- The subject does not respond within 2 weeks to a registered letter sent after the 3 attempted telephone contacts.

9.1.9 Completion of Study Participation

Completion of study participation for each individual subject is defined as one of the following:

- For subjects who complete the Treatment Period: the last Safety Follow-up Visit.
- For subjects who prematurely discontinue study drug treatment but do not withdraw consent, the latest of the following: the Week 48 Visit, ETT Visit, or the last Safety Follow-up Visit (if required), or the last posttreatment Telemedicine Visit.
- For subjects who withdraw consent: the date of withdrawal of consent (Section 9.9).

If subjects are lost to follow-up (Section 9.1.8), the date of completion of study participation will be defined as the date of last contact.

The end of study is defined in Section 13.2.9.

9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study.

9.3 Rationale for Study Elements

9.3.1 Study Population

This Phase 2 study will enroll consented subjects who meet the eligibility criteria. Results from this study will provide information on the efficacy, safety, tolerability, [redacted] of the orally administered VX-864 in male and female subjects with AATD who are aged 18 to 80 years, inclusive (Group A), and aged 18 to 70 years, inclusive (Group B), and have the PiZZ genotype.

9.3.2 Study Drug Dose and Duration

Up to the time of dosing suspension, subjects received VX-864 q12h for 48 weeks. The dose of VX-864 was 500mg q12h. As of 25 September 2023 all dosing has been suspended.

9.3.3 Rationale for Study Assessments

All safety assessments are standard parameters for clinical studies in drug development. The efficacy parameters being evaluated are widely accepted and generally recognized as reliable, accurate, and relevant to the study of individuals with AATD. Similar parameters were measured in Phase 1 and Phase 2 studies of VX-864 in healthy subjects and in subjects with AATD who have the PiZZ genotype.

Blood samples will be collected to evaluate the effect of VX-864 on blood levels of functional AAT, antigenic AAT, and Z-polymer, and based on the mechanism of action of VX-864 and its anticipated effect in this population.

A key histologic change in AATD-related hepatic disease is Z-polymer accumulation in the liver (Group B subjects only). [redacted]

9.4 Study Restrictions

Study restrictions are summarized in Table 9-1. A non-exhaustive list of study prohibitions and cautions for medication will be provided in the Study Reference Manual.

Table 9-1 Study Restrictions

	Timing of Restriction	
Restricted Medication/Food/Activity [a]	**Start**	**Stop**
Depo-Provera®	6 months before first dose of study drug	28 days after final dose of study drug
Hormonal methods of contraception (oral or patch)	28 days before first dose of study drug	28 days after final dose of study drug
Sensitive CYP3A substrates except inhaled and topical formulations [b, c]	7 days or 5 half-lives (whichever is longer) before the first dose of study drug	28 days after final dose of study drug

Table 9-1 Study Restrictions

Restricted Medication/Food/Activity [a]	Timing of Restriction	
	Start	**Stop**
UGT1A1/UGT1A4 moderate and strong inhibitors	7 days or 5 half-lives (whichever is longer) before the first dose of study drug	28 days after final dose of study drug
UGT1A1/UGT1A4 moderate and strong inducers	14 days before the first dose of study drug	
Prescription or nonprescription NSAIDs, anti-coagulants, or anti-platelet agents (e.g., warfarin, clopidogrel, aspirin, ibuprofen)	10 days before liver biopsy [e]	28 days after final dose of study drug
Other investigational drugs or devices	28 days before screening, 5 half-lives before screening, or time determined by local requirements (whichever is longer)	28 days after final dose of study drug
Augmentation therapy (human alpha-1 proteinase inhibitor)	More than 42 days before level of antigenic AAT is obtained for eligibility	28 days after final dose of study drug
Tobacco products, including use of electronic tobacco devices, e.g., e-cigarettes [d]	6 months before screening	28 days after final dose of study drug
Inhaled cannabis	6 months before screening	28 days after final dose of study drug
Alcohol: no more than 1 drink/day for females or 2 drinks/day 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	28 days after final dose of study drug

AAT: alpha-1 antitrypsin; ICF: informed consent form; NSAID: nonsteroidal anti-inflammatory drug; UGT1A1/A4: uridine diphosphate glucuronosyltransferase family 1 member A1/A4

[a] See Section 9.5 for guidance on concomitant medications.

[b] Chronic use of corticosteroids is prohibited with the exception that subjects may receive doses of prednisone or prednisolone of up to 5 mg/day chronically. Use of rosuvastatin at doses of up to 10 mg/day, and atorvastatin at doses of up to 20 mg/day is permitted. Also, an acute course of corticosteroids (as described in Section 9.5) as standard of care to treat a pulmonary exacerbation is permitted (dose and duration per investigator judgment in consultation with the Sponsor). In addition, use of inhaled fluticasone propionate and inhaled salmeterol are prohibited.

[c] In Group B only, sedation and local anesthesia (e.g., midazolam, fentanyl, local lidocaine) used for the liver biopsy procedure are allowed. Low-dose non-NSAID pain medications (e.g., acetaminophen with codeine, oxycodone, acetaminophen with oxycodone) are allowed for post-procedure pain. VX-864 may cause increased exposure of sensitive CYP3A4 substrates. When utilizing sensitive CYP3A4 substrates for sedation, local anesthesia, or acute pain management, caution should be utilized and dose adjustments may be considered.

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

[e] During the Treatment Period, occasional, limited ibuprofen (≤1200 mg/day) use for pain is allowed in both Groups A and B. In Group B only, limited ibuprofen use for pain is allowed until 10 days before the liver biopsy, at which time all ibuprofen use is prohibited until 2 weeks after the liver biopsy.

9.4.1 Exposure to Sunlight

Subjects will take appropriate measures to minimize exposure to UVA/UVB radiation from Day 1 through the final posttreatment Telemedicine Visit. As a precaution, subjects should avoid being in strong direct sunlight and/or UVA/UVB exposure or use protective clothing, broad spectrum sunscreen (UVA + UVB coverage), and sunglasses from first dose until the final posttreatment Telemedicine Visit (Section 9.1.6).

9.5 Prior and Concomitant Medications

Information regarding prior and concomitant medications, including any AATD medications or therapies, other medications, and herbal and naturopathic remedies, will be collected in each subject's source documentation for medications taken within the 70 days before the first dose of study drug in this study through completion of study participation, as defined in Section 9.1.9.

- Subjects should stop augmentation therapy regimen for at least 42 days prior to level of antigenic AAT sample collection used to determine eligibility, and refrain from restarting augmentation therapy until 28 days after final dose of study drug.
- Subjects may receive doses of prednisone or prednisolone up to 5 mg/day chronically.
- Subjects may receive an acute course of corticosteroids (prednisone, prednisolone, hydrocortisone, or triamcinolone only) as standard of care to treat a PEx (dose and duration per investigator judgement in consultation with the Sponsor).
- Sedation and local anesthesia (e.g., midazolam, fentanyl, local lidocaine) used for the liver biopsy procedure (Group B only) are allowed. Low-dose non-nonsteroidal anti-inflammatory drug (NSAID) pain medications (e.g., acetaminophen with codeine, oxycodone, acetaminophen with oxycodone) are allowed for post-procedure pain. VX-864 may cause increased exposure of sensitive CYP3A4 substrates. When utilizing sensitive CYP3A4 substrates for sedation, local anesthesia, or acute pain management, caution should be utilized and dose adjustments may be considered.

Clinical experience suggests that VX-864 strongly inhibits CYP3A4 and may increase exposure of sensitive CYP3A4 substrates. Therefore, concomitant administration of sensitive CYP3A4 substrates are prohibited (Table 9-1). VX-864 is a mild inhibitor of organic anion transporting polypeptide 1B1 (OATP1B1) and as such use of OATP1B1 substrates are permitted (except when also a substrate of CYP3A4).

9.6 Administration

9.6.1 Dosing

There will be no further dosing in this study as of 25 September 2023.

9.7 Dose Modification for Toxicity

No dose modifications for toxicity are allowed. Treatment may be interrupted as outlined in Section 9.8. If any unacceptable toxicity arises, individual subjects will discontinue dosing (Section 9.1.5).

9.8 Study Drug Interruption and Stopping Rules

The medical monitor should be notified of an interruption of study drug for any reason and of the resumption of study drug after such interruption.

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 the subject's 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 AAT augmentation therapy) will discontinue study drug treatment, and will be discontinued from the study.

Any subject with QTcF values above the threshold values as described in Section 11.6.5 will discontinue study drug treatment.

On Day 1, urine and serum beta-human chorionic gonadotropin (β-hCG) tests will be performed and subsequently every 4 weeks, continuing through completion of study participation, a urine β-hCG test will be performed. If a urine pregnancy test is positive, all study drug dosing will stop, and the pregnancy will be confirmed with a serum β-hCG test. If pregnancy is confirmed, the procedures outlined in Section 11.6.8.2 will be followed.

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 2 to 3 days 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 2 to 3 days).

In subjects who met the interruption criteria listed above, transaminase and/or bilirubin levels must be assessed at a frequency of every 3 to 4 days until the elevations return to normal limits or the subject's baseline levels, whichever is higher, and the subject must be followed closely for clinical progression. A thorough investigation of potential causes must be conducted. The investigation will include (but will not be limited to) the following: clinical chemistry, hematology and coagulation panels as described in Table 11-2 (including bilirubin measured with the BILT3 assay), additional clinical laboratory tests as described in Table 11-4, a liver ultrasound scan, and a consultation with a hepatologist. The liver ultrasound scan, consultation with a hepatologist, and/or other tests may be waived with approval from medical monitor.

- If an alternative, reversible cause of transaminase elevation and/or increased bilirubin has <u>not</u> been identified, study drug must be permanently discontinued.

- If an alternative, reversible cause of transaminase elevation and/or increased bilirubin has been identified, study drug administration may be resumed after 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, for the following 2 weeks, transaminases and bilirubin should be monitored every 3 to 4 days, and then weekly for another 2 weeks.

If a protocol-defined transaminase and/or bilirubin elevation interruption threshold recurs, then study drug must be permanently discontinued, regardless of the presumed etiology.

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9.9 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. If a subject has been withdrawn from study drug treatment, the reason for withdrawal should be documented and every effort should be made to continue to follow the subject until the end of the study.

In addition, a subject must be discontinued from study drug treatment if the subject meets any of the following criteria:

- Has a screening PiZZ genotype from the central laboratory that does not confirm study eligibility after a historical PiZZ genotype or was used to establish eligibility. These subjects must be discontinued from the study (Section 8.1).
- Meets any of the stopping (discontinuation) criteria (Section 9.8)
- Becomes pregnant (the subject or the female partner of a male subject; Section 11.6.8.2)

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 return for a Safety Follow-up Visit, if applicable (see Section 9.1.5), 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.

9.10 Replacement of Subjects

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug treatment period 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 or 250-mg VX-864 tablets. Study drug labeling will be in compliance with applicable local and national regulations. Additional details about packaging, labeling, and dispensing for VX-864 will be 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.

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 (1) study drug received; (2) study drug dispensed to the subjects; and (3) study drug returned by the subjects. A central pharmacy will be used for subjects opting to have home health visits. Subjects will be instructed to return all used and unused materials associated with the study drug to the home health nurse or site. These materials will be retained at the site or central pharmacy according to instructions provided by Vertex or its designee. The study monitor will review study drug records and inventory throughout the study. If a site or central pharmacy 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 (PI), 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 or in the subject's home at required study visits. At each visit, site

personnel/home healthcare nurses 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.

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 an open-label study; however, subjects should not be informed of their study-related levels of functional and antigenic AAT, levels of blood Z-polymer, liver biopsy results, or [redacted] during the Treatment Period, regardless if the subject permanently discontinues.

Levels of antigenic AAT obtained during screening will be provided to study sites in order to confirm the subject's eligibility to enroll in the study. All subsequent antigenic AAT results will not be disclosed to the study sites. Levels of functional AAT, levels of blood Z-polymer, and liver biopsy results will not be disclosed to the study sites.

Access to restricted data:

Levels of functional and antigenic AAT, levels of blood Z-polymer, and liver biopsy results (excluding quality control) will be considered as restricted data. During the conduct of the study, the Vertex study team will not have access to restricted data until the final analysis, with the exception of the screening levels of antigenic AAT. Shortly before any planned efficacy analysis of restricted data is conducted, the data will be reviewed for data cleaning purposes by a biostatistician who is not part of the study team.

A limited Vertex team not directly involved in the conduct of the study may have access to levels of functional and antigenic AAT, levels of blood Z-polymer, liver biopsy results, [redacted] safety data (e.g., AEs, clinical laboratory assessments) for continuous monitoring purposes. No results of analyses of restricted data will be shared with the study sites or with the Vertex study team.

11 ASSESSMENTS

The schedule of assessments are shown in Table 3-1 through Table 3-4.

11.1 Timing of Assessments

The initial screening visit and study visits on Day -14 to Day -7 (Pretreatment Interval), Day 1, Weeks 24, 48, and Safety Follow-up, must be performed in the clinic, even under extenuating circumstances. At all other visits, remote measures may be used. Rescreening and screening assessments that were not conducted at the initial visit may be conducted remotely when the assessments are feasible to conduct in the home setting, if agreed upon after investigator and subject consultation (Section 9.1.3), and only where permitted by local regulations.

Early Termination of Treatment (ETT) may be performed by telephone or video visit.

Repetition of eligibility assessments during the Screening Period is permitted per conditions described in Section 9.1.1.4.

11.2 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).

[redacted]

11.4 Efficacy

Blood levels of functional AAT, antigenic AAT, and Z-polymer, and the liver biopsy (Group B) will be performed to evaluate efficacy. The purpose of the liver biopsy is to enable evaluation of the efficacy of VX-864 on Z-polymer in the liver, [redacted] Each of these assessments are detailed below.

11.4.1 Blood Samples for Levels of Functional and Antigenic AAT and Z-polymer

Detailed procedures for the collection, processing, handling, and storage of blood samples for functional AAT, antigenic AAT, and Z-polymer levels will be provided [redacted].

11.4.2 Percutaneous Liver Biopsy in Group B Only

Liver biopsies will be performed percutaneously. All subjects in Group B will have 2 liver biopsies performed during the study, including the first biopsy during the Pretreatment Interval (Day -14 to Day -7), and the second biopsy at either Week 24 or Week 48 of the Treatment Period. Specifically, approximately 5 subjects (Cohort B1) will have their second liver biopsy at Week 24, and approximately 5 subjects (Cohort B2) will have their second liver biopsy at Week 48.

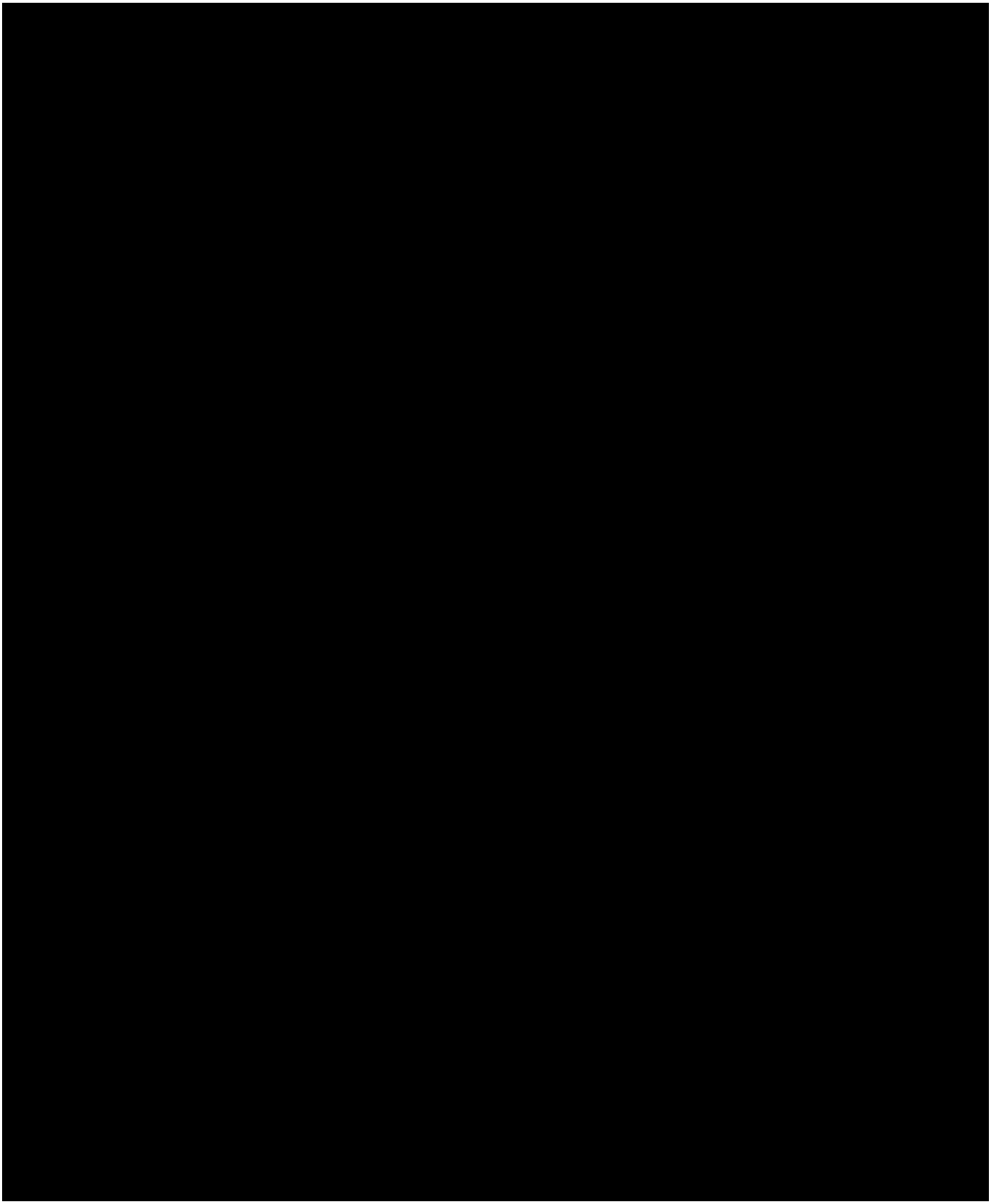
Biopsies will be used to evaluate Z-polymer accumulation in the liver, [redacted].

[redacted]

The timing of the biopsy relative to the last dose of study drug will be recorded. The liver biopsy should be performed 3 (±30 minutes) hours postdose relative to the morning dose.

Detailed procedures for the collection of liver biopsy and further procedures for processing and handling of liver samples will be described in the Liver Biopsy Manual and [redacted].

[redacted]



11.6 Safety

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

11.6.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with current ICH E6 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.

11.6.2 Clinical Laboratory Assessments

Blood and urine samples will be analyzed at a central laboratory, with the exception of the urine pregnancy tests in all subjects, and hematology and coagulation laboratory assessments as appropriate for liver biopsies in Group B subjects. As described below, urine pregnancy tests will either be analyzed by the site or at home using a home kit. On Day 1, blood samples will be collected before the first dose of the study drug. At all other scheduled visits, these samples will be collected at any time during the visit.

For purposes of study conduct, only laboratory tests done in the central laboratory may be used. Local laboratories may be used at the discretion of the local investigator for management of urgent medical issues, safety concerns, or under extenuating circumstances. 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.

The investigator will have access to all laboratory results for subjects from their site through the central laboratory portal. The central laboratory will additionally provide laboratory alerts to notify the investigator by email in the event of a laboratory result of potential clinical significance.

Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1.1.2).

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	Urine blood
Potassium	Reticulocytes	
Calcium	Leukocytes	
Chloride	Differential (absolute and percent):	
Magnesium	Eosinophils	
Bicarbonate	Basophils	
Phosphate	Neutrophils	
Total bilirubin (direct bilirubin, indirect bilirubin)	Lymphocytes	
	Monocytes	
Alkaline phosphatase	**Coagulation**	
Aspartate transaminase	Activated partial thromboplastin time	
Alanine transaminase	Prothrombin time	
Amylase	Prothrombin time International Normalized Ratio	
Lipase		
Gamma-glutamyl transferase		
Protein		
Albumin		
Creatine kinase		
Urate		
Cholesterol		
Triglycerides		
Low-density lipoprotein		
High-density lipoprotein		
C-reactive protein		

[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:

If serum chemistry (Table 11-2) was completed more than 28 (+7) days before Day 1 dosing, the LFT panel (Table 11-3) must be completed within 28 (+7) days before Day 1 dosing (Section 9.1.1.3).

Table 11-3 Liver Function Test Panel

Serum Chemistry
Total bilirubin (direct bilirubin, indirect bilirubin)
Alkaline phosphatase
Aspartate transaminase
Alanine transaminase
Gamma-glutamyl transferase

The following additional tests will be performed during screening to assess eligibility:

- Serology test for HBsAg, HCV RNA, and HIV-1/HIV-2 Abs
- Urine β-hCG for all female subjects
- FSH: Blood samples for FSH will be obtained to confirm postmenopausal status in female subjects who have spontaneous amenorrhea for ≥12 months without an alternative cause and do not have a history of bilateral oophorectomy or hysterectomy. Serum FSH levels within the laboratory's range for postmenopausal women can be used to confirm whether female subjects are of non-childbearing potential. If a subject has a previous documented FSH result within the performing laboratory's range for postmenopausal females, this assessment does not need to be repeated.

Pregnancy Testing for Female Subjects of Childbearing Potential (as defined in Section 11.6.8):

- On Day 1, urine and serum β-hCG tests will be performed and subsequently every 4 weeks, continuing through completion of study participation, a urine β-hCG test will be performed. Urine home pregnancy test kits will be provided by the study site.
- If a urine pregnancy test is positive, all study drug dosing will stop and the pregnancy will be confirmed with a serum β-hCG test. If pregnancy is confirmed, the procedures outlined in Section 11.6.8.2 will be followed.

Drug and Alcohol Screening: Opiates, methadone, cannabinoids, cocaine, amphetamines/methamphetamines, barbiturates, benzodiazepines, cotinine, and alcohol levels will be assessed by a blood or urine test; alcohol breath tests are acceptable alternatives for alcohol testing. Subjects may undergo random urine drug screen and alcohol testing if deemed appropriate by the investigator. Drug screen results must be negative for a subject to receive study drug.

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

Additional Tests to be Performed Following Transaminases Elevations:

As outlined under conditions described in Study Drug Interruption and Stopping Rules in Section 9.8, additional tests to be performed in subjects with transaminases elevations are shown in Table 11-4.

Table 11-4 Safety Laboratory Tests to Investigate Transaminases Elevations

Auto-immunology	Other Tests	Urinalysis
Anti-DNA (double-stranded) antibodies Antinuclear antibodies Complement C3 ASMA LKM-1 antibody Rheumatoid factor anti-CCP Serum immunoglobulin IgA, IgG (and IgG subclasses), and IgM	Blood CPK Blood alcohol levels SARS-CoV2[a] Serology for hepatitis A, B, C, D[b], E Serology for EBV Serology for CMV	Urine drug screen (including acetaminophen or paracetamol)

ASMA: anti-smooth muscle antibody; CCP: cyclic citrullinated peptide; CMV: cytomegalovirus; CPK: creatine phosphokinase; EBV: Epstein-Barr virus; IgA/G/M: immunoglobulin A/G/M; LKM-1: liver-kidney microsomal type 1; SARS-CoV2: severe acute respiratory syndrome coronavirus 2

[a] Where permitted by local regulations.

[b] Hepatitis D testing will only be performed if hepatitis B test result is positive.

11.6.3 Physical Examinations and Vital Signs

A complete PE of all body systems and vital signs assessment will be performed at screening and select study visits. At home visits, a qualified nurse will perform a review of symptoms. The review of symptoms will include a verbal review of symptoms by body system. If there are any findings from the verbal review that are considered abnormal by the investigator, the subject will be instructed to have a complete PE in the clinic.

A complete 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 (see Section 13.1.1.2).

Vital signs include blood pressure (systolic and diastolic), temperature (oral), pulse rate, and respiration rate. The subject will be instructed to rest for at least 5 minutes before vital signs are assessed. After screening, any clinically significant abnormal findings in vital signs will be reported as AEs (see Section 13.1.1.2).

11.6.4 Pulse Oximetry

Pulse oximetry is a noninvasive measure of oxygen delivery to the tissues and has been correlated with clinical status and lung function. Arterial oxygen saturation by pulse oximetry will be assessed following at least a 5-minute rest and before study drug dosing. At visits when study drug is taken at the site, pulse oximetry will be collected before study drug dosing.

11.6.5 Electrocardiograms

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

- 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.

ECG traces will be made available for safety review by the investigator and maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through completion of study participation will be recorded as AEs.

To ensure safety of the subjects, a qualified individual at the study site or a qualified home nurse at home health visits (Section 9.1.3) 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 predose 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.

11.6.6 Height and Weight

Height and weight will be measured and with shoes off.

11.6.7 Spirometry

Spirometry will be performed according to the ATS/ERS guidelines.[3, 4, 5] A historical percent predicted forced expiratory volume in 1 liter ($ppFEV_1$) results within 1 year before the first Screening Visit can be used to determine eligibility. Further details are provided in the Study Reference Manual.

11.6.8 Contraception and Pregnancy

The effects of VX-864 on pregnancy, and lactation in humans are not known. No new safety concerns were identified when female subjects received VX-864 in combination with the oral contraceptives levonorgestrel and ethinyl estradiol. VX-864 did not show genotoxic potential in a standard battery of in vitro and in vivo studies. Reproductive toxicology studies of VX-864 have not shown teratogenicity in rats and rabbits. Refer to the VX-864 IB for additional details.

11.6.8.1 Contraception

Study participation requires compliance with the contraception guidelines outlined below:

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, and post-ovulation

methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from the Screening Visit through 90 days after the dose of study drug.

- If the male is infertile (e.g., bilateral orchiectomy). If a male subject is assumed to have complete bilateral absence of the vas deferens, infertility must be documented before the dose of study drug (e.g., examination of a semen specimen or by demonstration of the absence of the vas deferens by ultrasound).
- If the female is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
  - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females
  - Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy

  Note: All other females (including females with tubal ligations and females who do not have a documented bilateral oophorectomy/salpingo-oophorectomy) will be considered to be of childbearing potential.
- Exclusive same-sex relationships.

For subjects for whom the contraception requirement is not waived, study participation requires a commitment from the subject that at least 1 acceptable method of contraception will be used as a couple. Methods of contraception must be in successful use from signing of consent, approximately 28 days before study drug administration (unless otherwise noted), and until 90 days following study drug administration. Additional contraception requirements may need to be followed according to local regulations and/or requirements. Acceptable methods of contraception are listed in Table 11-5.

Table 11-5 Acceptable Methods of Contraception

Method	Male Subjects and Their Female (Non-study) Partners	Female Subjects and Their Male (Non-study) Partners
Vasectomy 6 months or more previously, with a documented negative postvasectomy semen analysis for sperm	Yes	Yes
Documented bilateral tubal ligation performed at least 6 months previously	Yes	Yes
Male or female condom with or without spermicide[a]	Yes	Yes
Female barrier contraception (such as diaphragm, cervical cap, or sponge) with spermicide	Yes	Yes

Table 11-5 Acceptable Methods of Contraception

Method	Male Subjects and Their Female (Non-study) Partners	Female Subjects and Their Male (Non-study) Partners
Continuous use of a non-hormone releasing intrauterine device for at least 90 days before the dose of study drug	Yes	Yes
Oral, patch, implanted, injected hormonal contraceptives, if used consistently and correctly for at least 60 days before the dose of study drug	Yes	No

Note: At least 1 acceptable method of contraception must be used by couples not exempt from the contraception requirement.

[a] A female condom cannot be used with a male condom due to risk of tearing.

Additional notes:

- 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 with a partner of the opposite sex.
- Male subjects must not donate sperm during the period starting from the dose of study drug until 90 days after the dose of study drug.
- Female subjects of childbearing potential should not plan to become pregnant during the study or within 90 days after the dose of study drug. For male subjects with a female partner of childbearing potential, the couple should not plan to become pregnant during the study or within 90 days after the dose of study drug, with the exception of couples who plan to become pregnant by artificial insemination using sperm banked by the male subject before the dose of study drug or sperm from another source.
- Male subjects whose female partner becomes pregnant through well-documented in vitro fertilization (donated sperm) or banked sperm (collected before the subject received study drug), or is otherwise already pregnant before the male subject's dose of study drug, must be compliant with the contraception requirements. In this scenario, the male subject and his female partner must commit to using a male condom (to ensure there is no exposure of the fetus to study drug) from signing consent through 90 days after the dose of study drug.
- Female subjects should not nurse a child from signing consent through 90 days following the study drug administration.
- Unique situations that may not fall within the above specifications may be discussed with the Vertex medical monitor or authorized designee on an individual basis.

11.6.8.2 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 Global Patient Safety (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 within 90 days after the last dose of study drug will be followed until the end of the pregnancy. 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 ANALYSIS

This section presents a summary of the principal features of the planned efficacy and safety analyses for the study. Efficacy and safety analysis details will be provided in the statistical analysis plan (SAP), and [redacted] Both the SAP and [redacted] will be finalized before the 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.

[redacted]

12.2 Analysis Sets

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

The **Full Analysis Set (FAS)** is defined as all enrolled subjects who have received at least 1 dose of study drug. The FAS will be used to summarize background characteristics and for all efficacy analyses unless otherwise specified.

The **Safety Set (SS)** is defined as all subjects who have received at least 1 dose of study drug. The SS will be used for all safety analyses unless otherwise specified.

12.3 Statistical Analysis

12.3.1 General Considerations

All individual subject data for subjects who were enrolled or received at least 1 dose of study drug will be presented in individual subject data listings. Data from Groups A and B will be pooled for the analysis of endpoints collected in both groups, 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) on Day 1.

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

Treatment-emergent (TE) Period will include the time from the first dose of study drug to 28 days after the last dose of study drug or to the completion of study participation (as defined in Section 9.1.9), whichever occurs first.

12.3.2 Background Characteristics

Subject disposition (e.g., enrolled, completed treatment, discontinued treatment) will be summarized based on the All Subjects Set.

Demographics (e.g., age) and background characteristics (e.g., blood levels of antigenic AAT at screening, prior augmentation therapy, Z-polymer accumulation in the liver at baseline in Group B), will be summarized. Also, medical history and medication use will be summarized descriptively.

Exposure to study drug (i.e., duration of treatment) will be summarized based on the SS. Study drug compliance (i.e., percentage of days without study drug interruption) will be summarized based on the FAS.

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

Only the principal features of the efficacy analysis will be presented in this section. For more details, refer to the SAP.

12.3.3.1 Analysis of Primary Endpoint

The primary efficacy endpoint is the change from baseline in blood levels of functional AAT at Week 48.

The primary analysis will be based on a mixed-effects model for repeated measures (MMRM) with change from baseline in blood levels of functional AAT as the dependent variable. The

model will include visit as a fixed effect. The model will be estimated using restricted maximum likelihood. Denominator degrees of freedom for the *F*-test for fixed effects will be estimated using the Kenward-Roger approximation. An unstructured covariance structure will be used to model the within-subject errors. If the model estimation does not converge, a compound symmetry covariance structure will be used instead.

The primary result obtained from the model will be the estimated change from baseline in blood levels of functional AAT at Week 48 and the corresponding 95% CI and *P* value for the within-group comparison.

12.3.3.2 Analysis of Secondary Efficacy Endpoints

The change from baseline in blood levels of functional AAT at additional visits will be reported based on a similar model to that used for the analysis of the primary endpoint. The change from baseline in blood levels of antigenic AAT and blood levels of Z-polymer will be analyzed in a similar manner to the change from baseline in blood levels of functional AAT.

The change from baseline in Z-polymer accumulation in the liver at Weeks 24 and 48 will be summarized descriptively. In addition, the change from baseline in Z-polymer accumulation in the liver combining both cohorts within Group B (i.e., Week 24 for Cohort B1 and Week 48 for Cohort B2) will be summarized descriptively.

12.3.3.3 Multiplicity Adjustment

There will be no multiplicity adjustment performed in the analysis of this study.

12.3.3.4 Missing Data Handling

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

12.3.4 Safety Analysis

The overall safety profile of VX-864 will be assessed in terms of the following safety and tolerability endpoints:

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

For safety analyses, no statistical hypothesis testing will be conducted. All safety data will be presented in individual subject data listings. Additional details will be provided in the SAP.

12.4 Interim Analysis

Interim analyses may be conducted at the discretion of the sponsor.

12.5 Data Monitoring Committee Analysis

Not applicable.

[redacted]

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 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 a serious adverse event (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: time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects: completion of study participation, as defined in Section 9.1.9

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 2022). 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	Description
Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 (Moderate)	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]

Table 13-1 Grading of AE Severity

Classification	Description
Grade 4 (Life-threatening)	Life-threatening consequences; urgent intervention indicated
Grade 5 (Death)	Death related to adverse event

Source: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed July 2022)
ADL: activities of daily living; AE: adverse event
Note: A semi-colon indicates 'or' within the description of the grade.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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).

AE: adverse event

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[a]	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.

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

Classification[a]	Definition

AE: adverse event

[a] Refer to Sections 9.7 and 9.8 for directions regarding what drug actions are permitted per protocol.

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)

AE: adverse event

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 completion of study participation, regardless of causality, will be reported by the investigator to Vertex GPS **within 24 hours of identification**. In addition, all SAEs that occur after completion of study participation 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 completion of study participation, 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: globalpatientsafety@vrtx.com (preferred choice)

Fax: +1-617-341-6159

For technical issues related to submitting the form, contact telephone: +1-617-341-6677

SAEs that occur after completion of study participation 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, IEC, and participating investigators in accordance with current ICH E2A 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 E6 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, IB, 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), and assent will be obtained from the subject (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 current ICH E6 GCP Guidelines and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

ICFs for reconsent may be provided electronically or by post mail to subjects or legal representatives or guardians (if applicable), where permitted by local regulations. The subject and/or legal representative or guardian will review the ICF with an appropriately qualified member of the investigator's team via telephone contact or video call. After this review, the subject and/or legal representative or guardian will reconsent verbally and by signing and dating the ICF and returning it to the site via post mail. The signed and dated ICF will then be signed and dated by the investigator.

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., efficacy 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 data provided to Vertex, 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 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 current ICH E6 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 on-site or remote (as applicable by local regulation) 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 per current ICH E6 GCP Guidelines.

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

The study will be monitored by Vertex or its designee in accordance with written procedures. Monitoring and auditing procedures developed or approved by Vertex for these activities comply with GCP regulatory requirements and guidelines. The monitoring strategy may include onsite, remote, and central monitoring activities, in accordance with local regulations. 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 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 current ICH E3 Guideline, will be submitted in accordance with local regulations.

14 REFERENCES

1 Bergin DA, Reeves EP, Hurley K, Wolfe R, Jameel R, Fitzgerald S, et al. The circulating proteinase inhibitor alpha-1 antitrypsin regulates neutrophil degranulation and autoimmunity. Sci Transl Med. 2014;6(217):217ra1.

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3 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.

4 Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

5 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.

6 Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good publication practice for communicating company-sponsored medical research: GPP3. Ann Intern Med. 2015;163(6):461-4.

7 International Committee of Medical Journal Editors (ICMJE). December 2017. Recommendations for conduct, reporting, editing, and publication of scholarly work in medical journals. Available at: http://www.icmje.org/recommendations/. Accessed 22 July 2022.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX22-864-108	Version #: 2.0	Version Date: 02 November 2023
Study Title: A Phase 2, Open-label Study Evaluating Efficacy and Safety of VX-864 in Subjects With Alpha-1 Antitrypsin Deficiency Who Have the PiZZ Genotype, Over 48 Weeks		

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

Printed Name	Title
Signature	Date

15.2 Investigator Signature Page

Protocol #: VX22-864-108	Version #: 2.0	Version Date: 02 November 2023
Study Title: A Phase 2, Open-label Study Evaluating Efficacy and Safety of VX-864 in Subjects With Alpha-1 Antitrypsin Deficiency Who Have the PiZZ Genotype, Over 48 Weeks		

I have read Protocol VX22-864-108, Version 2.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-864 and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date