Statistical Analysis Plan: AVTX-002-NEA-201

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of AVTX-002 for the Treatment of Poorly Controlled Non-Eosinophilic Asthma
Study Number:	AVTX-002-NEA-201
Study Phase:	2
Sponsor:	Avalo Therapeutics, Inc. 1500 Liberty Ridge Drive, Suite 321 Wayne, PA 19087
NCT #:	NCT05288504
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Confidentiality Statement

Version History	
Version: Final 1.0	Initial version
Version: Final 2.0	Updates resulting from Protocol Amendment No. 4 (ie, Protocol Version 5.0, 17 Oct 2022) Updates made to baseline definitions as well as post-baseline calculations for diary data Updates made to reflect programmatically determined derivation of the occurrence of asthma related events, in addition to the Investigator assessment in the eCRF Updates made to reflect repeat analysis of the primary endpoint based on different baseline values for daily number of SABA puffs/inhalations and peak flow rate. Updates made to include calculation of an annual asthma related event rate for each treatment group Added production of figures to display results for peak flow rate and number of SABA puffs/inhalations recorded by subjects in their diary Addition of a Per Protocol Analysis Set Added clarification on handling of clinical laboratory results reported as not fully numeric Addition of PCI criteria for vital signs
Version: Final 3.0	Addition of statistical comparison between treatment groups for time to first asthma related event, as well as addition of a Kaplan-Meier plot of the time to asthma related event curves of the two treatment groups. Addition of repeat of the primary efficacy analysis for subjects with an asthma related event in the period of time from date of first administration of study drug through 28 days after final dose of study drug Update to wording for further clarity on the start date of an asthma related event Addition of clarification of asthma related event criterion related to use of systemic corticosteroids Minor corrections to formatting
Version: Final 4.0	Update to Section 6.2.4 for imputation of missing values and derivation of overall score for the Asthma Control Questionnaire Update to Section 10.3 to add that the screening eosinophil level will be part of the subject listing as well as table summary for demographics and baseline characteristics Update to Section 10.6.1 to add that Wald Ztest will be performed including and without continuity correction Update to Table 4 (Appendix 2) to clarify imputation of missing start date for prior and concomitant medications Update to Table 9 (Appendix 5) to add CTCAE grading for laboratory parameters analyzed per protocol

1 TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

2 SIGNATURE PAGE

A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety and Efficacy of AVTX-002 for the Treatment of Poorly Controlled Non-Eosinophilic Asthma

Study Number: AVTX-002-NEA-201

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACQ	Asthma Control Questionnaire
ADA	anti-drug antibody
AE	adverse event
AQLQ(S)+12	Standardized Asthma Quality of Life Questionnaire for 12 to 70 years
ASD	Asthma Symptom Diary
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CFB	change from baseline
CFB%	percentage change from baseline
CGI-I	Clinician Global Impression of Improvement
CGI-I/S	Clinician Global Impression of Improvement/Severity
CGI-S	Clinician Global Impression of Severity
CSR	Clinical Study Report
CTCAE	common terminology criteria for adverse events
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	European Quality of Life – 5 dimension 5 level questionnaire
EQ VAS	European Quality of Life visual analogue scale
ET	Early Termination
FAS	Full Analysis Set
FEV_1	forced expiratory volume in 1 second
FeNO	fractional exhaled nitric oxide
ICS	inhaled corticosteroid

IFN-γ	interferon gamma
IL-6	interleukin 6
LABA	long-acting beta agonist
LIGHT	Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator, a receptor expressed by T lymphocytes
LFT	liver function test
MedDRA	Medical Dictionary for Regulatory Activities
NEA	non-eosinophilic asthma
PCI	potentially clinically important
PD	pharmacodynamic(s)
PGI-C	Patient Global Impression of Change
PGI-C/S	Patient Global Impression of Change/Severity
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PT	preferred term
ppb	parts per billion
RAS	Randomized Analysis Set
SABA	short-acting beta agonist
SAP	statistical analysis plan
SAS	Safety Analysis Set
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation
SG	Specific Gravity
SOC	system organ class

TEAE	treatmentemergent adverse event
TNF-α	tumor necrosis factor alpha
US	United States
VAS	visual analogue scale
WHO	World Health Organization
WHO-DD	World Health Organization Drug Dictionary

4 INTRODUCTION

The purpose of this SAP is to describe the framework for the reporting, summarization, and statistical analysis methodology of the safety and efficacy parameters measured throughout the study, applying principles and methodology per International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines [1, 2]. It is based on Protocol AVTX-002-NEA-201, Version 5.0, dated 17 Oct 2022.

5 STUDY OBJECTIVES AND ENDPOINTS

Table 1. Study Objectives and Associated Endpoints

Objectives	Endpoints
Primary	
To assess the ability of AVTX-002 to improve asthma control in subjects with poorly controlled NEA	Primary Endpoint: Proportion of subjects who experience any of the following asthma related events: • ≥ 6 additional reliever puffs of SABA (compared to baseline) in a 24-hour period on 2 consecutive days (where baseline SABA use is the average daily number of individual SABA puffs/inhalations taken by the subject during the 7 days preceding Visit 2) or, • increase in ICS dose ≥ 4 times than the dose at baseline (where baseline ICS dose is the dosage the subject received during the 30-day run-in period) or, • a decrease in peak flow of ≥ 30% (compared to baseline) on 2 consecutive days of treatment (where baseline peak flow is the average of measurements in the 7 days preceding Visit 2) or, • an asthma exacerbation requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or, • a hospitalization or emergency room visit because of an asthma exacerbation. Secondary Endpoints: Change from baseline in FEV_1 at Weeks 2, 4, 6, 8, 12, and 14 Time to asthma related event Change from baseline in FeNO at Weeks 2, 4, 6, 8, 12, and 14 Change from baseline in ACQ at Weeks 2, 4, 6, 8, 12, and 14 Change from baseline in AQLQ(S)+12 at Weeks 2, 4, 6, 8, 12, and 14 Change from baseline in ASD score at Weeks 2, 4, 6, 8, 12, and 14 Change from baseline in EQ-5D-5L at Weeks 2, 4, 6, 8, 12, and 14 Change from baseline in PGI-C/S at Weeks 2, 4, 6, 8, 12, and 14 Change from baseline in CGI-I/S at Weeks 2, 4, 6, 8, 12, and 14 Incidence of SABA puffs/inhalations at Weeks 2, 4, 6, 8, 12, and 14
Secondary	
To assess the safety and tolerability of AVTX-002	Incidence of AEs, and changes from baseline in clinical laboratory tests, vital signs measurements, and physical examinations at Weeks 2, 4, 6, 8, 12, and 14
To evaluate biomarkers of PD activity and mechanism of action of AVTX-002	Change from baseline in serum soluble LIGHT levels at Weeks 2, 4, 6, 8, 12, and 14
To evaluate the immunogenicity of AVTX-002	Incidence of ADAs at Weeks 2, 4, 6, 8, 12, and 14
Exploratory	
To assess the ability of AVTX002 to improve asthma control in subjects with poorly controlled NEA who also have < 150 eosinophils/μL	Occurrence of an asthma related event in subjects with < 150 eosinophils/μL

Objectives	Endpoints
Exploratory (continued)	
To assess sputum soluble LIGHT levels and gene expression in a select subset of subjects	Change from baseline in sputum soluble LIGHT and gene expression (select subset of site/subjects only)
To evaluate inflammatory proteins including but not limited to: IL-6, IFN-γ, and TNF-α	Change from baseline in inflammatory proteins including but not limited to: IL-6, IFN- γ, and TNF-α
To evaluate the PK/PD relationship	PK/PD assessments

ACQ = Asthma Control Questionnaire; ADA = anti-drug antibody; AE = adverse event; AQLQ(S)+12 = Standardized Asthma Quality of Life Questionnaire for 12 to 70 years; ASD = Asthma Symptom Diary; CGI-I/S = Clinician Global Impression of Improvement/Severity; EQ-5D-5L = European Quality of Life – 5 dimension 5 level questionnaire; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; IFN-γ = interferon gamma; IL-6 = interleukin 6; LIGHT = Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator, a receptor expressed by T lymphocytes; NEA = non-eosinophilic asthma; PD = pharmacodynamic(s); PGI-C/S = Patient Global Impression of Change/Severity; PK = pharmacokinetic(s); TNF-α = tumor necrosis factor alpha; SABA = short-acting beta agonist

6 STUDY DESIGN CONSIDERATIONS

6.1 Study Design

This is a randomized, double-blind, placebo-controlled, Phase 2 study to evaluate the safety and efficacy of AVTX002 for the treatment of poorly controlled NEA. Upon confirmation of eligibility, subjects will complete a 30-day, stable therapy, run-in period with a LABA (salmeterol 50 µg twice daily) and an ICS (fluticasone, with starting dose at Investigator discretion). After the 30-day run-in is complete, subjects will be randomly assigned at the Baseline visit to receive either AVTX002 or placebo (1:1 ratio).

Fourteen days after randomization, subjects will discontinue salmeterol therapy (ie, at Visit 4). After an additional 14 days (ie, at Visit 5), subjects will taper fluticasone dose to 50%. After another 14 days (ie, at Visit 6), fluticasone use will be completely discontinued. The final visit will be Visit 9 (98 days after randomization).

Subjects will receive 3 doses of either AVTX002 or placebo (ie, at Visit 2, Visit 5, and Visit 7). AVTX002 or placebo will be administered by SC injection in the abdomen in a zone of 4 to 10 cm from the umbilicus, with the injection site rotated based on the number of syringes used. AVTX002 will be administered at a dose of 600 mg.

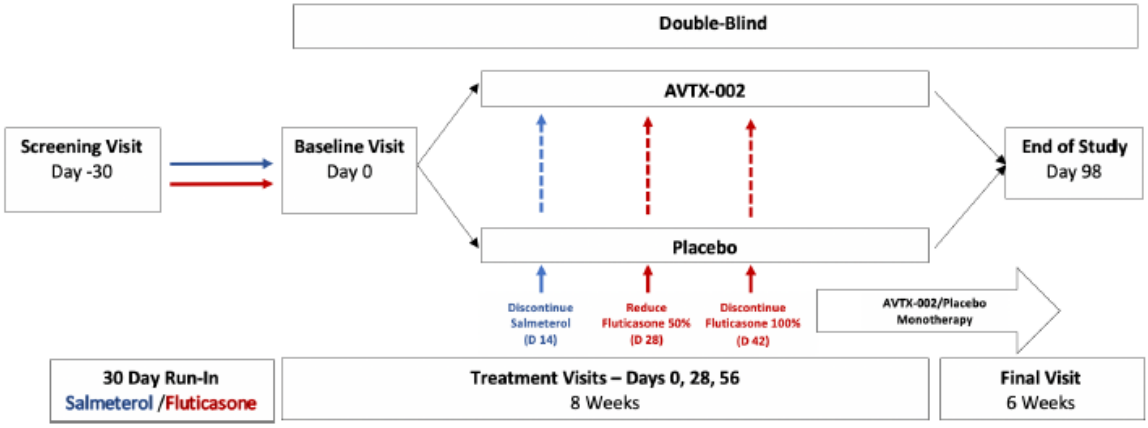
An adequate number of subjects will be enrolled to ensure approximately 80 subjects complete the study. Subjects who withdraw or are discontinued from the study or have poor study compliance may be replaced. The study will take place at approximately 25 study sites in the US.

All subjects will undergo efficacy, safety, PK/PD, and immunogenicity assessments as described in Section 6.2, Section 6.3, Section 6.4, and Section 6.5, respectively. Time points for all assessments are summarized in Table 2.

The study schema is presented in Figure 1 below.

Figure 1. Study Schema

Note: refer to Section 8 for changes to numbering of assessment day, for purposes of reporting of study results. The assessment day as presented in Figure 1 below, reflects the numbering as presented in the study protocol.



There is no interim analysis of data planned for this study.

6.1.1 Justification of Sample Size

The sample size in this study will be approximately 80 subjects, ie, 40 subjects per treatment arm, randomized in a 1:1 ratio.

The sample size estimate was based on the estimated proportions of subjects in the 2 treatment groups expected to have an asthma related event as defined by the primary endpoint. In a study of similar design with another asthma controller therapy, rates of 6% in the active group and 44% in the placebo group were observed [3]. If these estimates were used as is, then a study with 40 subjects per group would have over 95% power. Considering likely variations from the cited study, estimates of sample were assessed assuming a Type I error of 5% and the proportion of subjects with an asthma related event ranging from 30% to 50% in the placebo group and 5% to 8% in the active group. In the 20 such scenarios examined, only in the cases in which the difference between treatments gets below 23% does the power fall slightly below 80%. In the vast majority of cases examined the power is greater than 90%.

The overall event rate may be assessed in a blinded fashion when an adequate amount of subject followup has occurred. If this event rate is found to be much lower than assumed, a sample size reestimation may be performed.

6.2 Efficacy Measures

Time points for all assessments are summarized in Table 2.

6.2.1 Asthma Related Events

The following are considered asthma related events:

- ≥ 6 additional reliever puffs of SABA (compared to baseline) in a 24-hour period on 2 consecutive days (where baseline SABA use is the average daily number of individual SABA puffs/inhalations taken by the subject during the 7 days preceding Visit 2)
- increase in ICS dose ≥ 4 times than the dose at baseline at any time post-baseline (where baseline ICS dose is the dosage the subject received during the 30-day run-in period)
- a decrease in peak flow of ≥ 30% (compared to baseline) on 2 consecutive days of treatment (where baseline peak flow is the average of measurements in the 7 days preceding Visit 2)
- an asthma exacerbation requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days
- a hospitalization or emergency room visit because of an asthma exacerbation

The occurrence of each of the above asthma related events will be derived programmatically using different baseline definitions (where applicable), and from the source data as specified below:

Criterion to Meet for Asthma Related Event	Applicable Source Data	Baseline Definition
≥ 6 additional reliever puffs of SABA (compared to baseline) in a 24-hour period on 2 consecutive days *	ePRO Asthma Symptom Diary, ASD Morning and ASD Evening pages	The derivation whether a subject meets this criterion for an asthma related event will be performed using each of the 4 baseline values for mean daily number of SABA puffs/inhalations calculated according to Definitions 1 to 4 in Section 9.2
Increase in ICS dose ≥ 4 times than the dose at baseline at any time post-baseline	Prior and Concomitant Medications page of eCRF, coded appropriately so that ICS can be identified	ICS dose which the subject received during the 30-day run-in period
A decrease in peak flow of ≥ 30% (compared to baseline) on 2 consecutive days of treatment	ePRO Asthma Symptom Diary, Peak Flow Diary page (before Peak Flow Diary page was available, this was collected as part of ASD Morning page)	The derivation whether a subject meets this criterion for an asthma related event will be performed using each of the 4 baseline values for mean peak flow rate calculated according to Definitions 1 to 4 in Section 9.2
An asthma exacerbation requiring the use of systemic corticosteroids (tablets, suspension, or injection) for ≥ 3 days **	Prior and Concomitant Medications page of eCRF, coded appropriately so that systemic corticosteroids can be identified	Not applicable
A hospitalization or emergency room visit because of an asthma exacerbation	Asthma exacerbation reported as SAE; in case SAE was not reported (ie, in case asthma exacerbation required only emergency room visit which consequently is not reported as SAE), the Investigator assessment in the eCRF of occurrence of an asthma related event is to be utilized as the source data	Not applicable

ICS = inhaled corticosteroid; SABA = short-acting beta agonist

* This criterion may be met via 2 consecutive calendar days of assessments (ie, morning and evening diary entries for calendar date 1 plus morning and evening diary entries for the calendar date 2) or over a span of 3 consecutive calendar days (ie, evening diary entry for calendar date 1 and morning diary entry for calendar date 2 plus evening diary entry for calendar date 2 and morning diary entry for calendar date 3).

** In the case which use of systemic corticosteroids being administered for an asthma exacerbation is ongoing at the end of the study, the duration will be considered to be ≥ 3 days – as in clinical practice corticosteroid prescription including tapering usually last more than 3 days – and therefore the subject will be considered to have met this criterion for an asthma related event.

** Subjects being administered systemic corticosteroids for ≥ 3 days for a nonasthma event, will be considered to have met this criterion for an asthma related event, provided they have corresponding signs and symptoms of an asthma exacerbation. Also, subjects being administered a single dose of a longterm acting systemic corticosteroid (eg, dexamethasone) with a dose equivalent to a treatment of ≥ 3 days with other short to midterm systemic corticosteroids will be considered to have met this criterion for an asthma related event. Such cases will be confirmed by the sponsor as having met the criterion for an asthma related event or not.

In addition, an Investigator assessment of the occurrence of an asthma related event is recorded in the eCRF at each visit during the course of the study.

Time to first asthma related event will be measured in days as follows:

- Subjects with an asthma related event (censor = 0): the first day of the event above denotes the first day the protocol defined criteria associated with the asthma related event occurred (eg, for peak flow, the first of 2 days a decrease of ≥ 30% occurred, or for systemic corticosteroid use, the start of the qualifying medication), ie, time to event is calculated as follows:

$$(start\ date\ of\ first\ asthma\ related\ event - date\ of\ first\ administration\ of\ study\ drug) + 1$$

For subjects that do NOT have an asthma related event (censor = 1), the day of the last subject visit denotes the day of censoring, ie, time to censoring is calculated as follows:

$$(date\ of\ last\ subject\ visit - date\ of\ first\ administration\ of\ study\ drug) + 1$$

Furthermore, an annual asthma related event rate will be calculated for each treatment group as follows (for exploratory reasons):

$$365.25 * \left(\frac{total\ number\ of\ asthma\ related\ events\ within\ the\ treatment\ group}{total\ duration\ of\ study\ participation\ with\ the\ treatment\ group\ [days]}\right)$$

where total duration of study participation within treatment group (days) is the sum of $(date\ of\ last\ subject\ visit - date\ of\ first\ administration\ of\ study\ drug) + 1$ for all subjects.

6.2.2 Forced Expiratory Volume in 1 second

FEV_1 is the volume of air that can be forcibly exhaled from the lungs in the first second, measured in liters by a spirometer. FEV_1 (L) will be reported in the study results.

6.2.3 Fractional Exhaled Nitric Oxide

A FeNO test measures the levels of nitric oxide during exhalation, measured in ppb. A FeNO test will be done by breathing into a tube attached to a handheld monitor.

6.2.4 Asthma Control Questionnaire

The ACQ is a questionnaire to measure the adequacy of asthma control and change in asthma control. The questionnaire has a multidimensional construct assessing symptoms (5 items, selfadministered, looking back at the past week), rescue bronchodilator use (1 item, selfadministered, looking back at the past week), and FEV_1 (1 item, completed by study staff). For each of the self-administered questions (items), scoring is done on a 7point scale, ranging between 0 (totally controlled) and 6 (extremely poorly controlled).

All the items in the questionnaire are equally weighted and so the overall score for each assessment is the mean of the responses to the 7 items. The overall score also ranges between 0 (totally controlled) and 6 (extremely poorly controlled) [4].

The aim is not to have any missing data on the questionnaire. If there is more than one missing value per completed questionnaire, the data for that questionnaire will not be used (ie, will be set to missing). The following interpolation method will be used to impute a missing value, in case of a single missing value other than Item 1 or Item 7 on the ACQ questionnaire (values from either previous or subsequent completions of the questionnaire for the same subject can be used to impute a missing value) – the method is explained by means of an example [4]:

For the following example data (note that in the example the previous visit is used to impute the missing value at Visit 2; as a rule the closest complete previous visit will be used to impute a missing value, and if no complete previous visit is available, the closest complete subsequent visit's data will be used to impute a missing value from an incomplete visit):

	Visit 1	Visit 2
Item 1	4	6
Item 2	3	5
Item 3	4	4
Item 4	5	6
Item 5	2	Missing
Item 6	4	3
Item 7	3	5

Total Visit 1 score for items answered on both visits: $4 + 3 + 4 + 5 + 4 + 3 = 23\ (A)$

Total Visit 2 score for items answered on both visits: $6 + 5 + 4 + 6 + 3 + 5 = 29\ (B)$

Item 5 (item for which there is missing value at Visit 2) score at Visit $1 = 2\ (C)$

Imputed Item 5 score at Visit 2: $\frac{B}{A} \times C = \frac{29}{23} \times 2 = 2.52$

After imputation of the missing value, the overall score for each of Visit 1 and Visit 2 therefore will be:

Visit 1: $\frac{(4+3+4+5+2+4+3)}{7} = 3.57$

Visit 2: $\frac{(6+5+4+6+2.52+3+5)}{7} = 4.50$

Imputed values will be flagged in subject listings.

The overall score will be derived as the mean of the responses to the 7 items on the completed questionnaire when there is no missing data for a questionnaire or when a single missing value (ie, other than Item 1 or Item 7) was imputed according to the method above (in this case, the imputed value is used when calculating the mean). In the case where the only missing result for the completed questionnaire is either Item 1 or Item 7, the overall score will be derived using the

responses of the 6 completed items on the questionnaire (ie, the denominator when calculating the mean is 6 in this case). If there is more than one missing value per completed questionnaire, an overall score is not calculated (ie, will be set to missing).

6.2.5 Standardized Asthma Quality of Life Questionnaire for Ages 12 to 70 years

The AQLQ(S)+12 includes 32 questions (items) in 4 domains (symptoms, activity limitation, emotional function, and environmental stimuli) [5].

The questionnaire is selfadministered. Subjects will be asked to recall their experiences during the previous 2 weeks and score each of the questions on a 7point scale, where 7=not at all limited and 1=totally limited.

The 32 questions (items) are assigned as follows to the 4 domains:

Symptoms: Items 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 29, 30

Activity limitation: Items 1, 2, 3, 4, 5, 11, 19, 25, 28, 31, 32

Emotional function: Items 7, 13, 15, 21, 27

Environmental stimuli: Items 9, 17, 23, 26

Individual items are equally weighted. The overall score of the AQLQ(S)+12 will be derived as the average of the 32 items; thus, the overall score ranges from 1 ("total impairment") to 7 ("no impairment"). The domains are summarized in exactly the same way – each domain score will be derived as the average score of the items for the specific domain. Each domain score thus also ranges from 1 ("total impairment") to 7 ("no impairment").

The aim is not to have any missing data on the questionnaire. The data for a completed questionnaire will not be used (ie, will be set to missing) in the following cases:

- For calculation of overall score: if > 3 missing responses in total or > 1 missing response in any domain
- For calculation of symptom or activity limitation domain scores: if > 1 missing response in the domain, or
- For calculation of emotional function and environmental stimuli domain scores: if any missing response in the domain.

In case the number of missing values does not exceed the specifications listed above, imputation of missing values will be performed using the same method as described for the ACQ questionnaire in Section 6.2.4 [5].

Imputed values will be flagged in subject listings.

6.2.6 Asthma Symptom Diary

For the data collected by subjects in their diaries, if any data are recorded after the subject end of study date, this will not be used for any of the presentations described in this SAP; ie, only diary data collected up to the earlier of the end of study date or the diary deactivation date will be used for study data analysis.

6.2.6.1 Symptom Scores

The ASD is a 6item daily measure of asthma symptom severity that assesses 3 core categories of asthma symptoms: breathing symptoms (difficulty breathing; wheezing; shortness of breath), chest symptoms (chest tightness; chest pain), and cough. The ASD is intended for twice daily completion and comprises a morning diary (for completion upon waking and referring to asthma symptoms during the nighttime) and an evening diary (for completion before going to bed and referring to asthma symptoms during the day).

Subjects are required to rate the 6 symptoms at their worst during the respective timeframes using an 11-point numeric rating scale ranging from 0 ('None') to 10 ('As bad as you can imagine') [6].

Individual morning and evening ASD symptom scores for the 6 symptoms of difficulty breathing, wheezing, shortness of breath, chest tightness, chest pain, cough will be reported for each symptom as recorded in the diary. If the assessment of a particular symptom is missing for either the morning or evening diary, then that symptom's score for that diary timepoint will be missing.

Mean symptom scores will be calculated for each symptom as the mean of the available scores for the applicable symptom for each week, as follows:

$$\frac{sum\ of\ available\ entries\ for\ the\ week, for\ each\ symptom}{number\ of\ available\ entries\ for\ the\ week, for\ each\ symptom}$$

A mean ASD score will be calculated as the mean of all available symptom scores for each week, as follows:

$$\frac{sum\ of\ available\ entries\ for\ the\ week, for\ all\ symptoms}{number\ of\ available\ entries\ for\ the\ week, for\ all\ symptoms}$$

The first week post-baseline will start with the morning diary on Day 1 and will end with the evening diary 1 week later on Day 7 (ie, if there are no missing entries, a week will comprise 14 entries for each symptom). If Day 1 entries are utilized to calculate a baseline value (see Section 9.2), these Day 1 entries will not be part of the first week post-baseline (ie, in this case the first week post-baseline will start with the morning diary on Day 2 and will end with the evening diary on Day 7). For the mean symptom scores, if a subject has > 3 missing morning diary entries or > 3 missing evening diary entries for the applicable symptom in a week, then the mean symptom score for that week will be missing. For the mean ASD score, if a subject has > 3 missing morning diary entries or > 3 missing evening diary entries for any of the 6 symptoms

in a week, then the mean ASD score for that week will be missing. Mean scores for all subsequent weeks will be defined similarly, with the same rule for handling missing data. Baseline is defined in Section 9.2.

6.2.6.2 Additional Endpoints from Diary Data

A peak flow meter measures how well the lungs are able to expel air. Subjects will measure peak flow daily on a device provided by the sponsor and record the results in their diary. The daily peak flow rate as well as the use of SABA, which will also be recorded in the diary, will be used to assess the occurrence of asthma related events (see Section 6.2.1).

Peak flow rate is recorded daily by the subject. Mean peak flow rate will be calculated as the mean of all available recordings for each week, as follows:

$$\frac{sum\ of\ available\ entries\ for\ the\ week}{number\ of\ available\ entries\ for\ the\ week}$$

The first week post-baseline will start with the recording in the diary on Day 1 and will end with the recording in the diary on Day 7 (ie, if there are no missing entries, a week will comprise 7 entries). If the Day 1 entry is utilized as baseline (see Section 9.2, Definition 1 for mean peak flow rate), the Day 1 entry will not be part of the first week post-baseline (ie, in this case the first week post-baseline will start with the Day 2 diary recording and will end with the Day 7 diary recording). If a subject has > 3 missing entries in a week, then the mean score for that week will be missing. Mean values for all subsequent weeks will be defined similarly, with the same rule for handling missing entries. Baseline is defined in Section 9.2 (Definition 1 for mean peak flow rate).

The number of times (number of puffs/inhalations) a SABA is used will be assessed by reviewing the diary maintained by the subject. The number of puffs/inhalations of SABA is entered by the subject in their diary twice daily, ie, the morning diary is used to record number of SABA puffs/inhalations during the nighttime and the evening diary is used to record number of SABA puffs/inhalations during the day. For analysis of the SABA use data, beginning with the day on which the diary is activated through the earlier of the end of study date or the diary deactivation date, all missing entries will be considered 0 for analysis. Daily sums of SABA puffs/inhalations will be calculated as the sum of the morning diary and evening diary entries for the same calendar date. Mean daily number of puffs/inhalations over weekly periods will be calculated from the daily sums, as follows:

$$\frac{sum\ of\ daily\ sums\ for\ the\ week}{number\ of\ days\ the\ diary\ was\ available\ for\ the\ week}$$

For the first mean daily number of puffs/inhalations post-baseline, the week will start with the morning diary on Day 1 and will end with the evening diary 1 week later on Day 7 (ie, a week will comprise 14 entries). If Day 1 entries are utilized as baseline (see Section 9.2, Definition 1 for mean daily number of SABA puffs/inhalations), the Day 1 entries will not be part of the first week post-baseline (ie, in this case the first week post-baseline will start with the morning diary on Day 2 and will end with the evening diary on Day 7). Mean daily number of SABA

puffs/inhalations for all subsequent weeks will be defined similarly, with the same rule for handling missing entries. Baseline is defined in Section 9.2 (Definition 1 for mean daily number of SABA puffs/inhalations).

6.2.7 European Quality of Life – 5 Dimension 5 Level Questionnaire

The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ VAS. The descriptive system includes 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the subject's self-rated health on a vertical VAS, where the endpoints are labelled 'The best health you can imagine' (100) and 'The worst health you can imagine' (0) [7].

6.2.8 Patient Global Impression of Change/Severity

The PGI-C/S scale is a global index that can be used to rate the severity of a specific condition (a single-state scale) from the patient's perspective.

The PGI-S for this study is a single question asking the subject to rate the current state of their overall asthma severity on a 7-point scale (normal, borderline, mild, moderate, marked, severe, extreme). The PGI-C for this study is a single question asking the subject to rate their overall asthma status since the start of the study, (ie, since baseline [Visit 2]) on a 7-point scale (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse).

6.2.9 Clinician Global Impression of Improvement/Severity

The CGI-I/S is a global index that can be used to rate the severity of a specific condition (a single-state scale) from the clinician's perspective.

The CGIS for this study is a single question asking the clinician to rate the current state of the subject's overall asthma severity on a 7point scale (normal, borderline, mild, moderate, marked, severe, extreme). The CGII for this study is a single question asking the clinician to rate the subject's overall asthma status since the start of the study (ie, since baseline [Visit 2]) on a 7point scale (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse).

6.3 Safety Measures

Safety and tolerability assessments will include the frequency and severity of AEs as well as the evaluation of changes in clinical laboratory values and vital signs.

Time points for all assessments are summarized in Table 2.

6.4 Pharmacodynamic and Biomarker, and Pharmacokinetic Assessments

Time points for all assessments are summarized in Table 2.

6.4.1 Pharmacodynamics and Biomarkers

Serum samples will be analyzed for soluble LIGHT levels.

For a selected subset of sites or subjects, sputum samples will be analyzed for soluble LIGHT levels. Sputum samples may be evaluated for gene expression in the future. Biomarkers associated with inflammation will be collected and may be evaluated in the future, and samples for immunophenotyping of immune cell subsets in circulation will be collected and may be analyzed in the future.

6.4.2 Pharmacokinetics

Blood samples will be collected for measurement of AVTX-002 in plasma. Time points for collection are indicated in Table 2.

6.5 Immunogenicity Measures

Immunogenicity will be evaluated by means of the incidence of measured ADAs. Time points for all assessments are summarized in Table 2.

7 STUDY POPULATIONS

7.1 Analysis Populations

7.1.1 Randomized Analysis Set

The RAS will include all subjects who are randomized in the study. Subjects will be categorized according to their randomized treatment group. The RAS will be used for all disposition, protocol deviations, and demographic and other baseline characteristics analyses.

7.1.2 Safety Analysis Set

The SAS will include all subjects who are randomized in the study and receive at least one dose of investigational product. Subjects will be categorized according to their actual treatment group. The SAS will be used for all exposure, safety, and immunogenicity analyses.

7.1.3 Full Analysis Set

The FAS will include all subjects who receive at least one dose of investigational product and have a baseline and at least one post-baseline value of any of the efficacy assessments. Subjects will be categorized according to their randomized treatment group. The FAS will be used for all efficacy and PD analyses.

7.1.4 Per Protocol Analysis Set

The Per Protocol analysis set will include all subjects in the FAS who do not have significant protocol violations as determined by the sponsor as exclusionary from this analysis set prior to database lock (including, but not limited to, lack of compliance with study drug).

7.1.5 Pharmacokinetic Analysis Set

The PK Analysis Set will include all subjects who receive at least one dose of investigational product and have at least one postdose measurable plasma AVTX002 concentration. Subjects will be categorized according to their actual treatment group. The PK Analysis Set will be used for all PK analyses.

7.2 Subgroups

Occurrence of asthma related events will be evaluated in subjects with < 150 eosinophils/μL at baseline.

Sputum soluble LIGHT levels will be assessed in a select subset of subjects. Inclusion of subjects in this subset will be presented (as recorded in the eCRF as a subject consented to sputum sample collection and with at least one sputum sample being collected), although any results from sputum samples do not form part of the statistical analysis described in this SAP (see Section 10.9).

8 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

The following changes from protocol conventions are applied:

1.
According to the Schedule of Assessments (Table 1 in study protocol), numbering of assessment day starts at Day 0 at Visit 2, Baseline; ie:

Procedure	**Screening**	**…**	**Baseline**	**Doubleblind Treatment Period**						
Visit	**V 1**	**…**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9/ET**
Assessment Week	**-4**	**…**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**14**
Assessment Day	**Appr -37**	**…**	**0**	**7**	**14**	**28**	**42**	**No later than 56**	**84**	**98**

Appr = approximately; ET = early termination; V = Visit

For the purpose of presentation of the study results however, the first day of dosing will be denoted Day 1 (ie, there will be no Day 0). This results in the following changes to numbering of assessment day, according to which the study results will be reported:

Procedure	**Screening**	**…**	**Baseline**	**Doubleblind Treatment Period**						
Visit	**V 1**	**…**	**V 2**	**V 3**	**V 4**	**V 5**	**V 6**	**V 7**	**V 8**	**V 9/ET**
Assessment Week	**-4**	**…**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**14**
Assessment Day	**Appr -37**	**…**	**1**	**8**	**15**	**29**	**43**	**No later than 57**	**85**	**99**

Appr = approximately; ET = early termination; V = Visit

2.
According to protocol Section 11.1.1, an AE will be considered treatmentemergent if it occurs after the first dose of investigational product and within 28 days after a subject's last dose of investigational product. However, since the start time for AEs are collected in this study only if AE duration is < 24 hours, the definition for an AE to be considered treatmentemergent will be as follows:

- If AE start time is recorded: an AE will be considered treatmentemergent if it occurs on or after the time of first dose of investigational product and within 28 days after a subject's last dose of investigational product.
- If AE start time is not recorded: an AE will be considered treatmentemergent if it occurs on or after the date of first dose of investigational product and within 28 days after a subject's last dose of investigational product.

9 OVERALL STATISTICAL CONSIDERATIONS

9.1 General Conventions

Efficacy, safety, PK, PD, and immunogenicity variables will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, SD, median, minimum, and maximum. Summaries of change from baseline variables will include only subjects who have both a baseline value and corresponding value at the time point of interest. Descriptive statistics for categorical data will include frequency and percentage. Data will be summarized by treatment group (AVTX-002 and placebo) and overall (where applicable).

Descriptive statistics for continuous data will be displayed with applicable decimal precision as follows in relation to the source data (N: number of decimals for source parameter value, with $0 \leq N \leq 3$):

- Number (n)
- Mean, Median: N + 1
- SD: N + 2
- Minimum, Maximum: N + 0

Statistical hypothesis testing is planned to be performed on only the primary endpoint (see Section 10.6.1).

Listings will be provided for all collected study data.

Although the protocol defines the first day of administration of study drug as Day 0 (Visit 2, Baseline), for datasets and the study results reporting, the first day of administration of study drug is defined as Day 1. All other study days will be computed relative to Day 1. The study day for a particular event or visit will be calculated as $Date_{event} - Date_{first\ dose} + 1$ (for event occurring on or after first dose), and $Date_{event} - Date_{first\ dose}$ (for events occurring prior to first dose). For concomitant medications, AEs, clinical laboratory and vital signs assessments, as well as efficacy, PK, and PD assessments which occurred or were performed on or after the date of last administration of study drug, the study day relative to last study drug dose will also be displayed, ie, $Daylast = Date_{event} - Date_{last\ dose}$. In case of missing or partial dates being recorded for an event, the study day will not be calculated and will appear as missing in the subject listings.

9.2 Baseline and Related Changes Definition

In general and unless otherwise specified, baseline is defined as the last available assessment prior to the first dose of the study drug.

CFB is calculated as: $CFB = observed\ value - baseline\ value$

CFB% is calculated as: $CFB\% = \left({}^{CFB}/_{baseline\ value}\right) \times 100$ (if the baseline value is 0, CFB% cannot be calculated)

Where unscheduled/repeat assessments are relevant and exist for any subject at a particular visit they will also be considered in the baseline definitions, provided they remain prior to the first dose of study drug.

Visit 1a (Day 7 [2 days]) with diary activation was added to the protocol Schedule of Assessments in Protocol Version 4.0 (Amendment 3), 05 May 2022. Therefore, subjects enrolled prior to this amendment did not have a diary activated until the day of randomization (ie, they will not have diary entries during the 7 days preceding Visit 2). A baseline value cannot be calculated for subjects with no diary entries before the day of randomization. To include such subjects in analyses, additional definitions of baseline have been included in which Day 1 entries or Day 1 through Day 7 entries may be used for calculation of baseline when a subject does not have sufficient diary entries prior to Day 1. This approach has been taken given that all subjects have received a 30day regimen of stable asthma medications leading up to Day 1 which will be maintained until Day 14 per protocol; therefore, a Day 1 (or Day 1 through Day 7) diary entry is a reasonable representation of their baseline. The baseline definitions are detailed below for each of the following subject diary assessments:

Asthma Symptom Diary Assessment	Baseline Definition
Mean symptom score	Subjects with at least 1 morning diary entry and at least 1 evening diary entry from Day -7 through Day -1 for the applicable symptom, will have their baseline value calculated as: $\frac{sum\ of\ available\ entries\ from\ Day\ -7\ through\ Day\ -1}{number\ of\ available\ entries\ from\ Day\ -7\ through\ Day\ -1}$ When the above criteria are not met, subjects with at least 1 morning diary entry and at least 1 evening diary entry from Day -7 through Day 1 for the applicable symptom, will have their baseline value calculated as: $\frac{sum\ of\ available\ entries\ from\ Day\ -7\ through\ Day\ 1}{number\ of\ available\ entries\ from\ Day\ -7\ through\ Day\ 1}$ Otherwise, subjects who do not have at least 1 morning diary entry and at least 1 evening diary entry from Day -7 through Day 1 for the applicable symptom will have a missing baseline value.
Mean ASD score	Subjects with at least 1 morning diary entry and at least 1 evening diary entry from Day -7 through Day -1 for each of the 6 symptoms, will have their baseline value calculated as: $\frac{sum\ of\ available\ entries\ from\ Day\ -7\ through\ Day\ -1}{number\ of\ available\ entries\ from\ Day\ -7\ through\ Day\ -1}$ When the above criteria are not met, subjects with at least 1 morning diary entry and at least 1 evening diary entry from Day -7 through Day 1 for each of the 6 symptoms, will have their baseline value calculated as: $\frac{sum\ of\ available\ entries\ from\ Day\ -7\ through\ Day\ 1}{number\ of\ available\ entries\ from\ Day\ -7\ through\ Day\ 1}$

	Otherwise, subjects who do not have at least 1 morning diary entry and at least 1 evening diary entry from Day -7 through Day 1 for each of the 6 symptoms will have a missing baseline value.
Mean daily number of SABA puffs/inhalations	Baseline values will be calculated by the following 4 separate definitions. The primary baseline definition (Definition 1) will be used for all output that requires a comparison of SABA use to baseline. Definition 2 through 4 will only be used for the primary endpoint summary in the FAS and associated listings (ie, occurrence of an asthma related event; see Section 6.2.1). Definition 1 (primary baseline definition): • Subjects whose diary was activated no later than Day -1, will have their baseline value calculated as: $$\frac{sum\ of\ daily\ sums\ from\ Day\ -7\ through\ Day\ -1}{number\ of\ days\ the\ diary\ was\ available\ from\ Day\ -7\ through\ Day\ -1}$$ • Subjects for whom their diary was not activated by Day -1 but for whom the diary was activated on Day 1 and ≥ 1 Day 1 entry is available, will have their baseline value calculated as: $$sum\ of\ entries\ on\ Day\ 1$$ • Subjects for whom their diary was not activated by Day 1, will have a null baseline. Definition 2: • Subjects whose diary was activated no later than Day -1, will have their baseline value calculated as defined in Definition 1 above. • Subjects for whom their diary was not activated by Day -1 but for whom the diary was activated for ≥ 1 day between Day 1 and Day 7, will have their baseline value calculated as: $$\frac{sum\ of\ daily\ sums\ from\ Day\ 1\ through\ Day\ 7}{number\ of\ days\ the\ diary\ was\ available\ from\ Day\ 1\ through\ Day\ 7}$$ • Subjects for whom their diary was not activated by Day 7, will have a null baseline. Definition 3: • Subjects whose diary was activated no later than Day -1, will have their baseline value calculated as defined in Definition 1 above. • Subjects for whom their diary was not activated by Day -1, will have a null baseline. Definition 4: • Subjects whose diary was activated no later than Day -4, will have their baseline value calculated as defined in Definition 1 above. • Subjects for whom their diary was not activated by Day -4, will have a null baseline. **Note: for the days the diary was available (ie, any day from diary activation through deactivation), all missing entries will be considered 0 for calculation of the baseline value**
Mean peak flow rate	Baseline values will be calculated by the following 4 separate definitions. The primary baseline definition (Definition 1) will be used for all output that requires a comparison of peak flow rate to baseline. Definition 2 through 4 will only be used for the primary endpoint summary in the FAS and associated listings (ie, occurrence of an asthma related event; see Section 6.2.1).

Definition 1 (primary baseline definition):

- Subjects with ≥ 1 of the expected 7 entries from Day -7 through Day -1, will have their baseline value calculated as:

$$\frac{sum\ of\ available\ entries\ from\ Day\ \text{-}7\ through\ Day\ \text{-}1}{number\ of\ available\ entries\ from\ Day\ \text{-}7\ through\ Day\ \text{-}1}$$

- Subjects with no entries from Day -7 through Day -1 but for whom the Day 1 entry is available, will have their baseline value calculated as:

$$Day\ 1\ entry$$

- For subjects with no entries from Day -7 through Day 1, the baseline value will be missing.

Definition 2:

- Subjects with ≥ 1 of the expected 7 entries from Day -7 through Day -1, will have their baseline value calculated as defined in Definition 1 above.
- Subjects with no entries from Day -7 through Day -1 but for whom ≥ 1 entry between Day 1 and Day 7 is available, will have their baseline value calculated as:

$$\frac{sum\ of\ available\ entries\ from\ Day\ 1\ through\ Day\ 7}{number\ of\ available\ entries\ from\ Day\ 1\ through\ Day\ 7}$$

- For subjects with no entries from Day -7 through Day 7, the baseline value will be missing.

Definition 3:

- Subjects with ≥ 1 of the expected 7 entries from Day -7 through Day -1, will have their baseline value calculated as defined in Definition 1 above.
- For subjects with no entries from Day -7 through Day -1, the baseline value will be missing.

Definition 4:

- Subjects with ≥ 4 of the expected 7 entries from Day -7 through Day -1, will have their baseline value calculated as defined in Definition 1 above.
- For subjects with < 4 entries from Day -7 through Day -1, the baseline value will be missing.

ASD = Asthma Symptom Diary; FAS = Full Analysis Set; SABA = short-acting beta agonist

9.3 Handling of Partial Dates

Rules for imputation of missing or partial dates to enable background calculation/classification of AEs and prior/concomitant medication/procedures are presented in Appendix 2.

Listings will display the dates as collected on the eCRF.

9.4 Interim Analysis

No interim analyses are applicable.

9.5 Pooling Strategy for Study Sites

Data from all subjects will be pooled across study sites.

9.6 Visit Windows / Unscheduled Visits

A schedule of assessments is included in Table 2. Additional visit windowing, beyond the protocol-defined windows, will not be applied.

Unscheduled measurements will be classified as unscheduled visits at the site. Unscheduled visits will not be included in by-visit summaries or analysis, but will be included in summaries of PCI values and will also be considered when the baseline assessment and worst overall post-baseline values are defined.

10 STATISTICAL ANALYSIS METHODS

10.1 Subject Disposition

The following subject listings will be provided, using the analysis set indicated:

- Screen failures (all subjects)
- Randomized subjects (RAS)
- Subject completion/discontinuation information (RAS)
- Inclusion/exclusion of subjects from analysis sets (RAS)

Summary tables will be provided using the RAS/all subjects (as applicable), including the following information: number of subjects who completed the study, number of subjects who discontinued the study early (including reason for early discontinuation), number of subjects who completed study drug treatment, number of subjects who discontinued study drug treatment early (including reason for early discontinuation), and number of subjects in each analysis set. The number of subjects screened and number of screen failures (including reason for screen failures) will also be summarized for all subjects screened. These summaries will be presented by treatment group and overall.

10.2 Protocol Deviations

Reported protocol deviations will be categorized to a deviation category and will also be categorized as significant/not significant prior to unblinding of data.

All deviations will be included in a subject listing, using the RAS.

Significant deviations will be summarized by treatment group and overall, using counts and percentages by deviation category (as applicable) for the RAS. Subjects will only be counted once within each deviation category.

10.3 Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be included in a subject listing, using the RAS:

- Age
- Sex
- If female, whether of childbearing potential
- Race
- Ethnicity
- Baseline height, body weight, and BMI
- Screening and Baseline eosinophil level
- Part of sputum subset of subjects

The demographic and baseline characteristics will be summarized by treatment group and overall using descriptive statistics, for the RAS (including screening eosinophil level [< 150 eosinophils/μL, ≥ 150 eosinophils/μL] and sputum subset [Yes, No] as categorical variables).

BMI will be derived as:

$$BMI = \frac{baseline\ weight\ (kg)}{[baseline\ height\ (m)]^2}$$

10.3.1 Medical History

Medical history terms will be coded using MedDRA, version 24, 01 Sep 2021.

Medical history items will be included in a subject listing, using the RAS.

The number and percentage of subjects reporting any medical history will be summarized by SOC and PT, by treatment group and overall, for the RAS. A subject with multiple medical conditions will be counted once per SOC and PT. For computing percentages, the denominator will be the number of subjects in the RAS for each treatment group. The summary table will be sorted alphabetically for SOC, then by descending frequency of PT (for AVTX-002) within each SOC (then alphabetically for ties).

10.4 Prior and Concomitant Medications and Procedures

A prior medication or procedure is defined as having been received before the date of first study drug. A concomitant medication or procedure is defined as having been received on or after the date of the first dose of study drug (ie, either stops on/after the date of the first dose of study drug or is ongoing). Hence, a recorded medication may be both prior and concomitant.

Prior medications are captured from the screening visit, with the exception of ICS and LABA, which should also be recorded for the 3 months immediately prior to screening.

All prior and concomitant medications will be coded using the WHO-DD, version Sep 2021.

All prior and concomitant medications and procedures will be included in a subject listing, using the SAS. Any record/s where criteria for an asthma related event were met (see Section 6.2.1), will be flagged in the listing.

The number and percentage of subjects reporting prior and concomitant medications will be summarized by WHO-DD ATC Level 3 and preferred name, by treatment group, for the SAS. The same convention as detailed above for medical history (see Section 10.3.1) will be applied to the table summaries.

Prior/concomitant status (according to the definition provided at the start of this section) will be derived using the medication/procedure start and stop dates. For partial dates, see imputation rules in Appendix 2 (Table 4).

10.4.1 Salmeterol/Fluticasone Run-in

A separate subject listing will be provided detailing the administration of salmeterol and fluticasone during the 30day runin period prior to randomization, for the SAS. The listing will display for each subject whether the 30day runin period was started, completed without interruption, and whether the dose was tapered and discontinued as per protocol, for salmeterol and fluticasone use during the runin period, as applicable. Reason/s for not receiving salmeterol and/or fluticasone per protocol specifications will also be presented, as applicable.

10.5 Treatment Exposure

Based upon the PK of the study drug (halflife of 18.0 to 27.0 days) and dosage administered, each dose will count as 28 days of exposure to study drug. Therefore, days of exposure to study drug will be calculated as:

$$(last\ study\ drug\ dose\ date - first\ study\ drug\ dose\ date) + 28$$

A subject listing of treatment exposure will be presented, using the SAS, including the date and time of each study drug administration, reason for a dose not administered, location of each injection for each study drug administration, confirmation whether the injections were administered 4-10 cm from the umbilicus (with reason if not), and whether the complete dose was administered (with reason if not). The study drug exposure (days) will also be included in the listing.

Exposure to study drug (days) will be summarized by treatment group and overall using descriptive statistics, for the SAS. The number and percentage of subjects receiving 3, 2, 1, and 0 doses of study drug, respectively, will also be presented.

10.6 Efficacy

The following subject listings will be provided, using the FAS (observed as well as change from baseline values will be included as applicable):

- Occurrence of asthma related events – based on programmatic derivations from raw data (including the specification that constitutes the asthma related event – see Section 6.2.1, date of first administration of study drug, first date of asthma related event/date of last subject visit, the applicable baseline definition – see Section 9.2, time to first asthma related event/time to censoring in days)
- Individual daily recordings for peak flow measurements and number of SABA reliever puffs for subjects with an asthma related event; record/s where criteria for an asthma related event were met, will be flagged in this listing
- Occurrence of asthma related events – based on Investigator assessment (including the specification that constitutes the asthma related event – see Section 6.2.1, date of first administration of study drug, first date of asthma related event/date of last subject visit)
- Discordance between programmatic derivation from raw data and Investigator assessment in occurrence of asthma related events

- FEV_1 (FEV_1 [L]) and FeNO (nitric oxide level [ppb]) results
- ACQ results (results for each individual item as well as the overall score – see Section 6.2.4)
- AQLQ(S)+12 results (results for each individual item as well as the domain and overall scores – see Section 6.2.5)
- ASD results (see Section 6.2.6) – this will include the following:
  - mean symptom scores for each symptom separately, as well as mean ASD scores, for each 1-week period
  - number of SABA reliever puffs (mean daily puffs/inhalations over each 1-week period)
  - peak flow measurements (mean measurement over each 1-week period)

  Note: Only the weekly mean data are presented by subject in these subject listings; all individual daily recordings are however available in the submission datasets.
- EQ-5D-5L results (results for each of the 5 dimensions as well as for the EQ VAS – see Section 6.2.7)
- PGI-C/S and CGI-I/S results (results for each question – see Section 6.2.8 and Section 6.2.9)

10.6.1 Primary Endpoint Analysis

The primary endpoint analysis is performed using the assessments for the occurrence of asthma related events based on programmatic derivations from raw data.

The proportion of subjects who experience any asthma related event will be summarized by treatment group, also including the proportion of subjects who experience each of the 5 separate criteria for an asthma related event (as identified in Section 6.2.1). A subject who experienced multiple asthma related events will be counted once in each of the applicable criteria categories and once for having an asthma related event.

Summary statistics showing the number and percentage of subjects with and without asthma related events in each treatment group will be provided via a 2x2 table. Comparison of the proportions of subjects who had an asthma related event will be via a Wald Z-test (including and without continuity correction). The test statistic, its associated p-value and a 95% confidence interval for the treatment difference will also be provided.

The summary table and associated statistical analysis of the occurrence of asthma related events will be repeated for results obtained using each of the 4 baseline values for mean daily number of SABA puffs/inhalations and mean peak flow rate calculated according to Definitions 1 to 4 in Section 9.2, for all subjects in the FAS. In addition, the results for occurrence of asthma related events using the baseline values for mean daily number of SABA puffs/inhalations and mean peak flow rate calculated according to Definition 1 in Section 9.2, for subjects in the Per Protocol Analysis Set, will also be presented.

Figures (one per subject) will display the % change from baseline in peak flow rate and change from baseline in daily number of SABA puffs/inhalations over time. Baseline values calculated according to Definition 1 in Section 9.2 will apply. Occurrence of the following will also be

indicated on the figure for each subject: administration of each dose of study drug, reduction of fluticasone dose, discontinuation of salmeterol and fluticasone, end of study participation. As part of the figure, information on subject disposition (whether the subject completed the study or reason for early discontinuation from the study) and whether any criteria for occurrence of an asthma related event were met, will also be displayed.

10.6.2 Secondary Endpoints Summaries

The following results will be summarized descriptively, using the FAS:

- Time to first asthma related event/censoring (in days) will be summarized descriptively by treatment group as well as by a Kaplan-Meier plot of the time to asthma related event curves of the two treatment groups. A statistical comparison between treatment groups will be accomplished with the log rank test, for which the test statistic and associated p-value will be provided. For exploratory reasons, annual asthma related event rate will also be summarized descriptively by treatment group. As above for the primary endpoint analysis, this summary is performed using the assessments for the occurrence of asthma related events based on programmatic derivations from raw data and using the results from applying baseline Definition 1 where applicable (see Section 9.2).
- FEV_1 (FEV_1 [L]) and FeNO (nitric oxide level [ppb]) results – summary statistics for observed as well as change from baseline values, by visit for each treatment group
- ACQ results (overall score – see Section 6.2.4) – summary statistics for observed as well as change from baseline values, by visit for each treatment group
- AQLQ(S)+12 results (4 domain scores and overall score - see Section 6.2.5) – summary statistics for observed as well as change from baseline values, by visit for each treatment group
- Mean symptom score (each symptom separately) and mean ASD score (see Section 6.2.6.1) – summary statistics for observed as well as change from baseline values, by week for each treatment group
- Mean daily number of SABA puffs/inhalations over 1-week period (see Section 6.2.6.2) – summary statistics for observed as well as change from baseline values, by week for each treatment group; the summary will present the results applying calculation of baseline values according to Definition 1 for mean daily number of SABA puffs/inhalations (see Section 9.2)
- Mean peak flow rate (see Section 6.2.6.2) – summary statistics for observed as well as change from baseline values, by week for each treatment group; the summary will present the results applying calculation of baseline values according to Definition 1 for mean peak flow rate (see Section 9.2)
- EQ-5D-5L results (VAS score – see Section 6.2.7) – summary statistics for observed as well as change from baseline values, by visit for each treatment group
- EQ-5D-5L results (each of the 5 dimensions – see Section 6.2.7) – the shift from baseline to each post-baseline visit will be presented by treatment group
- Patient and Clinician Global Impression Questionnaires (see Section 6.2.8 and Section 6.2.9)

- for numeric scores: summary statistics for observed as well as change from baseline values (change from baseline values only applicable for PGIS and CGIS), by visit for each treatment group;
- for categorical result for each question: number and percentage of subjects for each rating for each visit by treatment group

10.6.3 Exploratory Endpoint Analyses

The primary efficacy analysis (see Section 10.6.1) will be repeated for subjects in the FAS, for the subgroup of subjects with < 150 eosinophils/μL at the baseline visit. When evaluating SABA use and peak flow for this analysis, mean daily number of SABA puffs/inhalations and mean peak flow rate will be calculated according to baseline Definition 1 in Section 9.2.

In addition, the primary efficacy analysis (see Section 10.6.1) will be repeated for subjects who experience an asthma related event in the period of time from date of first administration of study drug through 28 days after final dose of study drug. When evaluating SABA use and peak flow for this analysis, mean daily number of SABA puffs/inhalations and mean peak flow rate will be calculated according to baseline Definition 1 in Section 9.2.

10.6.4 Interim Analysis

No formal interim analysis is planned for this study.

10.7 Safety and Tolerability

Safety analyses will be conducted using data from the SAS (as defined in Section 7.1.2). Safety variables will include TEAEs, clinical laboratory values, vital signs, and ECG results. No formal inferential analyses will be conducted for any safety variables, unless otherwise noted.

10.7.1 Adverse Events

All AEs are collected from the time that the informed consent is signed until the end of study.

The definition for an AE to be considered treatmentemergent is as follows:

- If AE start time is recorded: an AE will be considered treatmentemergent if it occurs on or after the time of first dose of investigational product and within 28 days after a subject's last dose of investigational product.
- If AE start time is not recorded: an AE will be considered treatmentemergent if it occurs on or after the date of first dose of investigational product and within 28 days after a subject's last dose of investigational product.

Additionally, an AE that occurred prior to the date of first study drug dosing and increased in severity after start of first dosing and within 28 days of a subject's last dose of investigational product will also be considered treatment-emergent. An AE that occurred prior to first study drug dose and then again after first study drug dose at the same severity is NOT considered treatment-emergent.

AE verbatim terms will be coded to a SOC and PT using MedDRA, version 24, 01 Sep 2021.

For incidence of AEs by treatment group, SOC and PT, a subject will be counted only once per SOC and PT.

For AE incidence presented as the number and percentage of subjects with a specific AE, if there is more than one occurrence of an event, the event with the worst severity or the highest rated causality category will be summarized.

Summaries of AEs by SOC and PT will be sorted alphabetically for SOC, then by descending order of frequency of PT (for AVTX-002) within each SOC (then alphabetically for ties). Summaries of AEs by PT will be sorted by descending order of frequency of PT (for AVTX-002), then alphabetically for ties.

Missing assessments of seriousness, intensity and relationship to study drug that have been queried and remain missing, will be treated 'worst case' for presentation filtering purposes as follows:

- Missing seriousness assessment: AE will be regarded as serious.
- Missing relationship to study drug: AE will be regarded probably related to study drug, except when start date is prior to first dose of study drug (in which case the AE will be regarded not related to study drug).
- Missing intensity assessment:
  - If subject has died, AE will be regarded Grade 5 intensity.
  - If subject has not died but subject had intervention indicated for the AE, AE will be regarded Grade 4 intensity.
  - If none of the previous conditions are met, AE will be regarded Grade 3 intensity.

The following subject listings will be provided, using the SAS:

- All AEs (including TEAEs and nonTEAEs)
- All serious AEs (including serious TEAEs and serious nonTEAEs)
- All AEs leading to death
- All AEs leading to discontinuation of study drug

An overall summary of AEs will be provided, containing the number and percentage of subjects by treatment group with:

- any AEs
- any serious AEs
- any TEAEs
- any study drug related TEAEs

- any TEAEs leading to study drug discontinuation
- any study drug related TEAEs leading to study drug discontinuation
- any TEAEs by maximum CTCAE grade (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5)
- any serious TEAEs
- any study drug related serious TEAEs
- any TEAEs leading to death
- any serious TEAEs by maximum CTCAE grade (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5)

The following summary tables will be provided by SOC and PT, by treatment group:

- Incidence of TEAEs
- Incidence of study drug related TEAEs
- Incidence of TEAEs leading to study drug discontinuation.
- Incidence of study drug related TEAEs leading to study drug discontinuation
- Incidence of TEAEs by maximum CTCAE grade (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5)
- Incidence of serious AEs (only if incidence of serious AEs and serious TEAEs differs)
- Incidence of serious TEAEs
- Incidence of study drug related serious TEAEs
- Incidence of serious TEAEs by maximum CTCAE grade (Grade 1, Grade 2, Grade 3, Grade 4, Grade 5)

10.7.2 Clinical Laboratory Values

Subject listings, using the SAS, will be provided for all clinical laboratory tests, ie, hematology, clinical chemistry, urinalysis, and pregnancy tests.

Observed values of hematology and clinical chemistry parameters, and continuous urinalysis parameters (SG, pH) at selected time points, and change from baseline in these parameters at each post-baseline time point, will be summarized descriptively by treatment group. The overall worst value post-baseline (which includes results from unscheduled visits) will also be included in the summaries. Table 10 provides the directionality of the worst values for each laboratory parameter.

Shift tables for hematology and clinical chemistry laboratory parameters, using laboratory CTCAE version 5.0 grading (see Table 9) showing changes from baseline to post-baseline values will be summarized using counts and percentages. For a specific laboratory parameter, subjects with both baseline and a post-baseline value will be included for shift summaries. For computing percentages, the denominator will be the total number of subjects with non-missing baseline and post-baseline values for the respective post-baseline visit point and treatment group.

The number and percentage of subjects meeting criteria for abnormal LFTs (see Table 6) will be summarized by treatment group and time point (including results from unscheduled visits). For computing percentages, the denominator will be the number of subjects with a post-baseline value for the specific laboratory parameter and the respective time point. Only subjects with newly occurring values (at least one post-baseline measurement meeting the criterion but not meeting the criterion at baseline) will be counted.

The number and percentage of subjects meeting PCI criteria for laboratory values (see Table 7) post-baseline will be presented by treatment group (including results from unscheduled visits). For computing percentages, the denominator will be the number of subjects with a post-baseline value for the specific laboratory parameter and time point; the exception is for hemoglobin where the denominator will be the number of subjects with both a baseline and a post-baseline value at the respective time point, given that the criteria for hemoglobin includes both an absolute value as well as change from baseline criteria. Only subjects with newly occurring values (at least one post-baseline measurement meeting the criterion but not meeting the criterion at baseline) will be counted. Subjects with laboratory values meeting PCI criteria will be included in a subject listing; all values for the laboratory parameter meeting PCI criteria will be included in the listing.

For results reported as not fully numeric (eg, result is reported as < 3.5 mmol/L), the numeric portion of the result (ie, 3.5 in this case) will be used in case calculations/derivations need to be performed (eg, when summary statistics or change from baseline values are calculated, or toxicity grading is derived).

10.7.3 Electrocardiograms

All ECG results will be listed by subject.

10.7.4 Vital Signs

A subject listing, using the SAS, will be provided for all vital signs results. Results meeting PCI criteria (see Table 8) will be flagged in the listing.

Observed values of SBP, DBP, pulse rate, respiratory rate, temperature, and body weight at baseline and at selected postbaseline time points, and change from baseline in these parameters at each postbaseline time point, will be summarized descriptively by treatment group.

10.7.5 Physical Examinations

Any clinically significant findings during physical examinations are to be reported as medical history or AEs, depending on timing. No separate listing will be provided for physical examination results.

10.8 Pharmacokinetics

AVTX-002 plasma concentrations will be listed by subject (using the PK Analysis Set), and will be summarized by visit and treatment group, for the PK Analysis Set.

10.9 Pharmacodynamics

Results from sputum soluble LIGHT levels and gene expression, inflammatory biomarkers, and immunophenotyping of immune cell subsets are reported separately (as applicable) and will not form part of the statistical analysis described in this SAP.

Results from serum soluble LIGHT levels will be listed by subject in a subject listing, and descriptive statistics for actual as well as change from baseline values will be presented by treatment group and time point, using the FAS.

10.10 Immunogenicity

For the immunogenicity variables (ie, ADA), results will be listed by subject in a subject listing, and descriptive statistics for actual as well as change from baseline values will be presented by treatment group and time point, using the SAS.

11 REFERENCES

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12 APPENDICES

Appendix 1. Schedule of Assessments and Procedures

Note: refer to Section 8 for changes to numbering of assessment day, for purposes of reporting of study results. The assessment day as presented in Table 2 below, reflects the numbering as presented in the study protocol.

Table 2. Schedule of Assessments (as per V4 study protocol)

Procedure	**Screening**	**30day Runin Period**		**Baseline**	**Doubleblind Treatment Period**						
Visit	**Visit 1**		**Visit 1a**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9/ ET[2]**
Assessment Week	**-4**			**0**	**1**	**2**	**4**	**6**	**8**	**12**	**14**
Assessment Day	**Appr -37[1]**	**-30 through -1**	**-7**	**0**	**7**	**14**	**28**	**42**	**No later than 56[3]**	**84**	**98**
Visit Window[4]	**NA**		**-2 days**	**+3 days[5]**	**±1 day**	**±1 day**	**±3 days**	**±3 days**	**-3 days**	**±3 days**	**±3 days**
Phone visit			X[6]								
Informed consent	X										
Inclusion/exclusion review	X			X							
Demographics	X										
Medical history	X										
Prior medications	X	X	X								
Randomization				X							
Concomitant medications				X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X[8]			X[7]		X	X[7]	X	X[7]	X	X
Physical examination	X			X		X	X	X	X	X	X
12-lead ECG	X										
FEV_1	X			X		X	X	X	X	X	X
FeNO	X			X		X	X	X	X	X	X
Peak Flow Test (daily)[9, 17]			X	X	X	X	X	X	X	X	X
ACQ	X			X		X	X	X	X	X	X
AQLQ(S)+12				X		X	X	X	X	X	X
ASD (2x daily)[17]			X	X	X	X	X	X	X	X	X
Record SABA use (2x daily)[18]			X	X	X	X	X	X	X	X	X
EQ-5D-5L				X		X	X	X	X	X	X

Procedure	**Screening**	**30day Runin Period**		**Baseline**	**Doubleblind Treatment Period**						
Visit	**Visit 1**		**Visit 1a**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9/ ET[2]**
Assessment Week	**-4**			**0**	**1**	**2**	**4**	**6**	**8**	**12**	**14**
Assessment Day	**Appr -37[1]**	**-30 through -1**	**-7**	**0**	**7**	**14**	**28**	**42**	**No later than 56[3]**	**84**	**98**
Visit Window[4]	**NA**		**-2 days**	**+3 days[5]**	**±1 day**	**±1 day**	**±3 days**	**±3 days**	**-3 days**	**±3 days**	**±3 days**
PGI-C/S				X		X	X	X	X	X	X
CGI-I/S				X		X	X	X	X	X	X
ADA[10]				X		X	X	X	X	X	X
Serum: soluble LIGHT				X		X	X	X	X	X	X
Inflammatory proteins	X						X		X	X	X
Immunophenotyping of circulating immune cells				X						X	X[16]
Sputum: soluble LIGHT and gene expression[11]				X						X	
Plasma AVTX-002 level				X	X	X	X	X	X	X	X[16]
Clinical laboratory tests (hematology, clinical chemistries)	X			X		X	X	X	X	X	X
Urinalysis	X			X		X			X	X	X
Serum pregnancy test[12]	X									X	X
Urine pregnancy test[12]				X			X		X		
Study drug administration (onsite)[13, 14, 15]				X			X		X		
Salmeterol/Fluticasone runin		X	X								
Discontinue salmeterol						X					
Taper/discontinue fluticasone							X	X			

ACQ = Asthma Control Questionnaire; ADA = anti-drug antibody; AE = adverse event; AQLQ(S)+12 = Standardized Asthma Quality of Life Questionnaire for 12 to 70 years; ASD = Asthma Symptom Diary; CGI-I/S = Clinician Global Impression of Improvement/Severity; ECG = electrocardiogram; EQ-5D-5L = European Quality of Life – 5 dimension 5 level questionnaire; ET = early termination; FeNO = fractional exhaled nitric oxide; FEV_1 = forced expiratory volume in 1 second; LIGHT = Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator, a receptor expressed by T lymphocytes; PGI-C/S = Patient Global Impression of Change/Severity; SABA = short-acting beta agonist

1. Documentation of eligibility on all inclusion and exclusion criteria is required before a subject can enter the study 30-day run-in period prior to Visit 2 (randomization) when the subject is switched to stand alone salmeterol and fluticasone. Confirmation of eligibility should take place within a reasonable amount of time after the Screening Visit. If confirmation of eligibility is not available within 14 days from the date of screening, the study sponsor should provide approval for the subject to continue.
2. If a subject discontinues from the study/study drug, the Visit 9/ET procedures will be performed 4 weeks post last dose (±3 days).
3. A subject must be dosed with the Visit 7 (Week 8) dose no later than Day 56.

Procedure	Screening	30day Runin Period		Baseline	Doubleblind Treatment Period						
Visit	**Visit 1**		**Visit 1a**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9/ ET[2]**
Assessment Week	**-4**			**0**	**1**	**2**	**4**	**6**	**8**	**12**	**14**
Assessment Day	**Appr -37[1]**	**-30 through -1**	**-7**	**0**	**7**	**14**	**28**	**42**	**No later than 56[3]**	**84**	**98**
Visit Window[4]	**NA**		**-2 days**	**+3 days[5]**	**±1 day**	**±1 day**	**±3 days**	**±3 days**	**-3 days**	**±3 days**	**±3 days**

4. After Visit 2 (Day 0), visits should be scheduled relative to Visit 2 (Day 0). Visit 7 (Week 8) must not be performed later than Day 56.
5. Baseline visit to occur the day following completion of the 30-day run-in period with a window of an additional 3 days.
6. Visit 1a (Day -7) may be completed either by telephone or may be completed as an in-clinic visit, depending on the needs of the site and/or each individual subject. Visit 1a should occur with 7 days remaining in the 30-day run-in (-2 day window for Visit 1a). During this phone call/onsite visit, the subject should be reminded to begin daily peak flow testing, and daily completion of their diary to capture asthma symptoms, SABA use, and daily peak flow values.
7. At Visit 2 (Day 0), Visit 5 (Day 28), and Visit 7 (Day 56), pre and postdose vital signs will be measured: predose vital signs should be taken within 60 minutes before dosing; postdose vital signs should be taken at least 60 minutes after dosing, prior to discharge.
8. Height will only be recorded at the Screening Visit.
9. Subject should record the best result of 3 attempts daily at home. Subject should perform daily peak flow at approximately the same time each day between 10:00 AM and 2:00 PM. Subject should also bring peak flow meter to clinic visits. If peak flow has not been completed at home by the subject on the day of a clinic visit it should be completed at the clinic during the visit.
10. In addition to ADA collection time points per the schedule of events, an ADA sample will be collected when an immunologically related AE is reported (eg, a skin reaction, lupuslike syndrome, unexplained thrombocytopenia).
11. Select subset of sites/subjects only.
12. For females of childbearing potential. A subject is not considered to be of childbearing potential if at least 6 weeks have passed since sterilization, defined as females having undergone one of the following surgeries: hysterectomy, bilateral tubal ligation or occlusion, bilateral oophorectomy, or bilateral salpingectomy; and males who are vasectomized. Contraception is not required where females are postmenopausal (defined as 12 consecutive months of spontaneous amenorrhea and age ≥51 years).
13. On the day of randomization when the first dose of study drug is administered (Visit 2/Day 0), all visit procedures should be completed prior to study drug administration. At the other study drug administration days (Visit 5/Day 28 and Visit 7/Day 56), only the PK, ADA, serum soluble LIGHT, inflammatory proteins and immunophenotyping samples must be collected prior to study drug dosing. Other procedures can be performed as needed in the clinic on the visit day.
14. Subjects will be required to remain in the clinic for at least 60 minutes after study drug administration for AE monitoring.
15. Investigational product will be prepared by an unblinded pharmacist or appropriately qualified individual.
16. Immunophenotyping and PK only required if an ET visit is completed. Immunophenotyping and PK not required at Visit 9/Day 98.
17. Site regular assessment of diary completion for compliance.
18. SABA use is defined as the number of individual puffs or inhalations taken by the subject.

Appendix 2. Imputation of Partial Dates

Table 3. Imputation Rules for Partial Dates – Adverse Events

Parameter	Missing	Additional Condition	Imputation
Start Date	D only	M and Y are prior to first study drug dose	First day of indicated month
		M and Y is same as first study drug dose	Date of first study drug dose
		M and Y are after first study drug dose	First day of indicated month
	M and D	Y is prior to first study drug dose	01 Jan of indicated year
		Y is same as first study drug dose	Date of first study drug dose
		Y is after first study drug dose	01 Jan of indicated year
	M, D, and Y	---	assumed to be TEAE
End Date	D only	M and Y are prior to last study drug dose	Last day of indicated month
		M and Y is same as last study drug dose	Date of last observation if within indicated M and Y; if date of last observation extends after indicated M and Y, then use last day of indicated month
		M and Y are after last study drug dose	First day of indicated month
	M and D	Y is prior to last study drug dose	31 Dec of indicated year
		Y is same as last study drug dose	Date of last observation if within indicated Y; if date of last observation extends after indicated Y, then use 31 Dec of indicated year
		Y is after last study drug dose	01 Jan of indicated year
	M, D, and Y	---	TEAE is ongoing
	---	Estimated end date is before a complete or imputed AE start date	Last day of the month of AE start date

AE = adverse event; D = day; M = month; TEAE = treatmentemergent adverse event; Y= year
Note: The imputation of end date must be later than start date

Table 4. Imputation Rules for Partial Dates – Prior and Concomitant Medications and Procedures

Parameter	Missing	Additional Condition	Imputation
Start Date	D only	M and Y same as M and Y of first study drug dosing	Date of first study drug dose
		M and/or Y not the same as M and Y of first study drug dosing	First day of indicated month
	M and D	Y same as Y of first study drug dosing	Date of first study drug dose
		Y not the same as Y of first study drug dosing	01 Jan of indicated year
	M, D, and Y	---	Date of first study drug dose
		End date < date of first study drug dose	End date
End Date	D only	M and Y same as M and Y of last study drug dosing	Date of last study drug dose
		M and/or Y not the same as M and Y of last study drug dosing	Last day of indicated month
	M and D	Y same as Y of last study drug dosing	Date of last study drug dose
		Y not the same as Y of last study drug dosing	31 Dec of indicated year
	M, D, and Y	---	Date of last study drug dose

D = day; M = month; Y= year

Appendix 3. Planned Laboratory Assays

Table 5. Planned Laboratory Assays

Laboratory Category	Assay Grouping	Assay
Chemistry		Sodium
		Potassium
		Chloride
		Bicarbonate
		Glucose
		BUN
		Creatine
		Creatinine phosphokinase
		ALT
		AST
		GGT
		ALP
		TBL
		Calcium
		Magnesium
		Phosphorous
		LDH
		Uric acid
		Total protein
		Albumin
		CRP
		Total cholesterol
		HDL cholesterol
		LDL cholesterol
		Triglycerides
Hematology		Hemoglobin
		Hematocrit
		RBC count
		Platelet count
	RBC indices	MCV
		MCH
		MCHC
	WBC count with differentials	Neutrophils – absolute and percent
		Lymphocytes – absolute and percent
		Monocytes – absolute and percent
		Eosinophils – absolute and percent
		Basophils – absolute and percent
Urinalysis	Dipstick	pH
		SG
		Protein
		Blood

		Glucose Ketones
		Microscopic examination if blood or protein is present
Serum/urine pregnancy tests		Highly sensitive hCG pregnancy test*
Other tests	Immunogenicity	ADA
	PD and biomarker assessments	Serum: soluble LIGHT
		Serum: Inflammatory proteins** PBMC: Immunophenotyping** Sputum: soluble LIGHT**
	PK assessments	Plasma: AVTX-002

ADA = anti-drug antibody; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = Creactive protein; GGT = gamma glutamyl transferase; hCG = human chorionic gonadotropin; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LIGHT = Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator, a receptor expressed by T lymphocytes; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamic/s; PK = pharmacokinetic/s; RBC = red blood cell; SAP = statistical analysis plan; SG = Specific Gravity; TBL = total bilirubin; WBC = white blood cell

* For women of childbearing potential

** Samples for these analyses are collected as per the Schedule of Assessments (Table 2); however, these results are reported separately (as applicable), and will not form part of the statistical analysis described in this SAP

Appendix 4. Potentially Clinically Important Criteria

Table 6. Liver Function PCI Criteria

Laboratory Parameter	PCI Criteria
ALT	> 3 × ULN; > 5 × ULN; > 10 × ULN
AST	> 3 × ULN; > 5 × ULN; > 10 × ULN
TBL	> 1.5 × ULN
ALT and TBL	ALT > 3 × ULN and TBL > 2 × ULN
AST and TBL	AST > 3 × ULN and TBL > 2 × ULN
ALT/AST and TBL and ALP	ALT/AST > 3 × ULN and TBL > 2 × ULN and ALP < 2 × ULN (Hy's Law Criteria)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; PCI = potentially clinically important; TBL = total bilirubin; ULN = upper limit of normal

Table 7. Safety Laboratory PCI Criteria

Laboratory Parameter	SI Unit	Lower Limit	Upper Limit
Creatinine	µmol/L		> 150
Sodium	mmol/L	≤ 130	> 150
Potassium	mmol/L	< 3.0	> 5.5
TBL	µmol/L		> 1.5 × ULN
ALT	U/L		> 3 × ULN
AST	U/L		> 3 × ULN
Hemoglobin	g/L	< 0.8 × LLN and > 20% decrease from baseline	> 1.3 × ULN and > 30% increase from baseline
Leukocytes	× 10^9/L	≤ 2.8	≥ 16.0
Lymphocytes	× 10^9/L	< 0.5	> 20
Neutrophils	× 10^9/L	< 1.0	
Platelets	× 10^9/L	≤ 75	≥ 500

ALT = alanine aminotransferase; AST = aspartate aminotransferase; LLN = lower limit of normal; PCI = potentially clinically important; TBL = total bilirubin; ULN = upper limit of normal

Table 8. Vital Signs PCI Criteria

Vital Signs Parameter	PCI Criteria
SBP	≤ 90 mmHg and decrease of ≥ 20 mmHg from baseline
	≥ 180 mmHg and increase of ≥ 25 mmHg from baseline
DBP	≤ 50 mmHg and decrease of ≥ 15 mmHg from baseline
	≥ 105 mmHg and increase of ≥ 15 mmHg from baseline
Pulse rate	≤ 40 bpm
	≥ 100 bpm

DBP = diastolic blood pressure; PCI = potentially clinically important; SBP = systolic blood pressure

Appendix 5. Laboratory CTCAE Criteria

Table 9. Laboratory CTCAE Grade Version 5.0 Criteria

		CTCAE Grade v5.0				
Lab Parameter	**SI Unit**	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Hemoglobin decreased (Anemia)	g/L	≥ LLN	100 – < LLN	80 – < 100	< 80	
Hemoglobin increased	g/L	≤ ULN	> ULN – 2 × ULN	> 2 × ULN – 4 × ULN	> 4 × ULN	
Hypoglycemia (Glucose decreased)	mmol/L	≥ LLN	3.0525 – < LLN	2.22 – < 3.0525	1.665 – < 2.22	< 1.665
Glucose (hyperglycemia)	mmol/L	LLN – ULN	> ULN – 8.88	> 8.88 – 13.875	> 13.875 – 27.75	> 27.75
Albumin	g/L	≥ LLN	< LLN – 30	< 30 – 20	< 20	Life-threatening consequences; urgent intervention indicated*
ALP		≤ ULN	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
ALT increased	U/L	≤ULN	> ULN – 3 × ULN	> 3 × ULN – 5 × ULN	> 5 × ULN – 20 × ULN	> 20 × ULN
AST increased	U/L	≤ULN	> ULN – 3 × ULN	> 3 × ULN – 5 × ULN	> 5 × ULN – 20 × ULN	> 20 × ULN
Blood bilirubin increased	umol/L	≤ULN	> ULN – 1.5 × ULN	> 1.5 × ULN – 3 × ULN	> 3 × ULN – 10 × ULN	> 10 × ULN
Creatinine increased	umol/L	≤ULN	> ULN – 1.5 × ULN	> 1.5 × ULN – 3 × ULN	> 3 × ULN – 6 × ULN	> 6 × ULN
Calcium (hypocalcemia)	mmol/L	LLN – ULN	< LLN – 2.0	< 2.0 – 1.8	< 1.8 – 1.5	< 1.5
Calcium (hypercalcemia)	mg/dL	LLN – ULN	> ULN – 2.9	> 2.9 – 3.1	> 3.1 – 3.4	> 3.4
Eosinophils increased	× 10^9/L	≤ ULN	> ULN and > Baseline			
Lymphocyte count decreased	× 10^9/L	≥ LLN	0.8 – < LLN	0.5 – < 0.8	0.2 – < 0.5	< 0.2
Lymphocyte count increased	× 10^9/L	≤ 4		> 4 – 20	> 20	
Neutrophil count decreased	× 10^9/L	≥ LLN	1.5 – < LLN	1 – < 1.5	0.5 – < 1.0	< 0.5
Platelet count decreased	× 10^9/L	≥ LLN	75 – < LLN	50 – < 75	25 – < 50	< 25

		CTCAE Grade v5.0				
Lab Parameter	**SI Unit**	**Grade 0**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
WBC count decreased	$\times 10^9$/L	≥ LLN	3 – < LLN	2 – < 3	1 – < 2	< 1
WBC count increased (leukocytosis)	$\times 10^9$/L	≤ 10			> 10	
Hyperkalemia (Potassium increased)	mmol/L	≤ ULN	> ULN – 5.5	> 5.5 – 6.0	> 6.0 – 7.0	> 7.0
Hypokalemia (Potassium decreased)	mmol/L	≥ LLN	3.0 – < LLN	Symptomatic with 3.0 – < LLN**	2.5 – < 3.0	< 2.5
Hypernatremia (Sodium increased)	mmol/L	≤ ULN	> ULN – 150	> 150 – 155	> 155 – 160	> 160
Hyponatremia (Sodium decreased)	mmol/L	≥ LLN	130 – < LLN	125 – < 130	120 – < 125	< 120
Bicarbonate decreased		≥ LLN	< LLN			
CPK increased		≤ ULN	> ULN – 2.5 × ULN	> 2.5 × ULN – 5 × ULN	> 5 × ULN – 10 × ULN	> 10 × ULN
GGT increased		≤ ULN if baseline was normal; ≤ 2.0 × baseline if baseline was abnormal	> ULN – 2.5 × ULN if baseline was normal; 2.0 – 2.5 × baseline if baseline was abnormal	> 2.5 – 5.0 × ULN if baseline was normal; > 2.5 – 5.0 × baseline if baseline was abnormal	> 5 – 20.0 × ULN if baseline was normal; > 5 – 20.0 × baseline if baseline was abnormal	> 20.0 × ULN if baseline was normal; > 20.0 × baseline if baseline was abnormal
Hypermagnesemia (magnesium increased)	mmol/L	≤ ULN	> ULN – 1.23		> 1.23 – 3.30	> 3.30
Hypomagnesemia (magnesium decreased)	mmol/L	≥ LLN	< LLN – 0.5	< 0.5 – 0.4	< 0.4 – 0.3	< 0.3
LDH increased		≤ ULN	> ULN			
Total cholesterol high	mmol/L	≤ ULN	> ULN – 7.75	> 7.75 – 10.34	> 10.34 – 12.92	> 12.92
Hypertriglyceridemia (triglycerides increased)	mmol/L	≤ 1.71	1.71 – 3.42	> 3.42 – 5.7	> 5.7 – 11.4	> 11.4

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = common terminology criteria for adverse events; CPK = creatinine phosphokinase; GGT = gamma glutamyl transferase; LDH = lactate dehydrogenase; LLN = lower limit of normal; ULN = upper limit of normal; WBC = white blood cell

* Any albumin < 20 g/L will be categorized as Grade 3

** Any potassium 3.0 – < LLN will be categorized as Grade 1

Appendix 6. Directionality of Worst Laboratory Parameters

Table 10. Directionality of Worst Laboratory Parameters

Laboratory Parameter	Worst Value
Hematology:	
Hemoglobin	Both highest and lowest value
Hematocrit	Both highest and lowest value
RBC count	Both highest and lowest value
Platelet count	Lowest value
MCV	Both highest and lowest value
MCH	Both highest and lowest value
MCHC	Both highest and lowest value
WBC count	Both highest and lowest value
Neutrophils	Lowest value
Lymphocytes	Both highest and lowest value
Monocytes	Both highest and lowest value
Eosinophils	Both highest and lowest value
Basophils	Both highest and lowest value
Chemistry:	
Sodium	Both highest and lowest value
Potassium	Both highest and lowest value
Chloride	Both highest and lowest value
Bicarbonate	Both highest and lowest value
Glucose	Both highest and lowest value
BUN	Highest value
Creatine	Highest value
Creatinine phosphokinase	Highest value
ALT	Highest value
AST	Highest value
GGT	Highest value
ALP	Highest value
TBL	Highest value
Calcium	Both highest and lowest value
Magnesium	Both highest and lowest value
Phosphorous	Both highest and lowest value
LDH	Highest value
Uric acid	Highest value
Total protein	Both highest and lowest value
Albumin	Lowest value
CRP	Highest value
Total cholesterol	Highest value
HDL cholesterol	Highest value
LDL cholesterol	Highest value
Triglycerides	Highest value

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = Creactive protein; GGT = gamma glutamyl transferase; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; TBL = total bilirubin; WBC = white blood cell