PROTOCOL

PRODUCT NAME:	AVTX-002
PROTOCOL NUMBER:	**AVTX-002-NEA-201**
IND NUMBER:	[redacted]
DEVELOPMENT PHASE:	Phase 2
PROTOCOL 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
PROTOCOL VERSION AND DATE:	Version 5.0, 17 October 2022
COORDINATING/PRINCIPAL INVESTIGATOR:	[redacted]
SPONSOR:	Avalo Therapeutics, Inc. 1500 Liberty Ridge Drive, Suite 321 Wayne, PA 19087 Phone: 610-254-4201 Fax: 443-304-8001
CONTRACT RESEARCH ORGANIZATION:	[redacted]

This study will be performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents.

CONFIDENTIAL

1 APPROVAL SIGNATURES

PROTOCOL NUMBER:	**AVTX-002-NEA-201**
PROTOCOL 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
FINAL PROTOCOL:	17 October 2022

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study.

2 EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must e-mail the Serious Adverse Event Form within 24 hours to the CRO Pharmacovigilance Department using the email address noted below. For questions on SAE reporting, contact the drug safety mailbox noted below.

- [redacted]

In the event of an SAE, the Investigator should also notify the Medical Monitor. All medical personnel and their contact details can be found in the site study documentation (study binder). For protocol safety-related issues, please first contact the Medical Monitor using the contact information below:

[redacted]

[redacted]

3 Protocol Version History

Document	Date
Original, Version 1.0	28 September 2021
Amendment 1, Version 2.0	08 November 2021
Amendment 2, Version 3.0	05 January 2022
Amendment 3, Version 4.0	05 May 2022
Amendment 4, Version 5.0	17 October 2022

Note: Administrative changes to the protocol have been made throughout the document to reflect change in version number and date of issue. Corrections of minor typographical errors and inconsistencies, grammar, improvement for comprehension, or corrections of abbreviations are not listed within the summary of changes. Major changes are reflected below:

Summary of Changes, Amendment 4, Version 5.0 (17 October 2022):

Section Number and Name	Description of Change	Brief Rationale
4 SYNOPSIS, ENDPOINTS, Primary Endpoints 7.2.1 Primary Endpoints 10.2.2.1 Asthma Related Events	Added text in bold: o Baseline SABA use **(defined as the number of individual puffs or inhalations taken by the subject)** will be determined by the average use in the 7 days preceding Visit 2, o **An asthma exacerbation requiring use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days** o **a hospitalization or emergency room visit because of an asthma exacerbation**	Additions made based upon a prior protocol clarification letter as well as to align the definition of an asthma related event with the American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice (Reddel, 2009).
4 SYNOPSIS, Study Entry Criteria 8.5.1 Inclusion Criteria	Added text in bold: 5. Subjects must have had at least one asthma exacerbation in the last 24 months prior to Screening **An asthma exacerbation is defined as follows:** o **a course of oral corticosteroids because of worsening asthma symptoms, and/or** o **at least a doubling of the subject's inhaled corticosteroids for at least 14 days because of worsening asthma symptoms.** **If a subject's medical experience satisfies either or both statements, the**	Additions made based upon a prior protocol clarification letter.

	subject has experienced an asthma exacerbation.	
SYNOPSIS, Study Entry Criteria 8.5.2 Exclusion Criteria	Added text in bold: 3. Subjects who: • Are current smokers, **users of inhaled cannabis and/or e-cigarettes/vaping devices** or,	Wording updated to clarify that inhaled cannabis and e-cigarettes/vaping are also under the umbrella of smoking and are prohibited during study based on their ability to be an airway irritant.
Table 1. Schedule of Assessments	Added: • Footnote 17: Site regular assessment of diary completion for compliance • Footnote 18: SABA use is defined as the number of individual puffs or inhalations taken by the subject. • Requirement for AVTX-002 Plasma (PK blood draw) at the Early Termination Visit. This has been added to the table as well as Footnote 16.	Additional footnotes made based upon a prior protocol clarification letter as well as to ensure regular review of diary data by sites. PK blood draw added as part of Early Termination visit in order to ensure information is available on AVTX-002 drug levels post last dose in subjects who discontinue from study early.
Table 1. Schedule of Assessments	Updated (change noted in bold): Footnote 1 If confirmation of eligibility is not available within **7 days** from the date of Screening, the study Sponsor should provide approval for the subject to continue. TO 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.	Widened window for confirmation of eligibility to allow time to receive and review all screening visit data.
Table 1. Schedule of Assessments 8.2 Discussion of Study Design	Clarified that: Visit 1a may be completed either by telephone or as an in-clinic visit, depending upon the needs of the site or subject.	Additions made based upon a prior protocol clarification letter.
8.5 Study Entry Criteria	Added: Subjects are to be enrolled based on the inclusion and exclusion criteria below. The diagnosis of NEA is determined at Screening Visit 1 based upon Inclusion Criteria 2 through 5. At Baseline Visit 2, a review of all Inclusion/Exclusion criteria should be done to ensure continued eligibility prior to randomization and dosing the subject. As long as the subject qualifies as having NEA per protocol at the Screening Visit, there is no expectation that their diagnosis be re-confirmed at Baseline Visit 2, and therefore changes in eosinophil count and/or ACQ score within the period of time between Screening Visit 1 and Baseline Visit 2	Additions made based upon a prior protocol clarification letter.

	would not reverse their diagnosis and would not disqualify the subject. Although chemistry and hematology labs must be drawn as part of Baseline Visit 2 procedures, there is not an expectation that these test results be available during the visit to re-confirm eligibility (Exclusion Criteria 12 and 13). Per the schedule of assessments, a urine pregnancy test must be completed and show negative results at Baseline Visit 2 prior to randomization and dosing. Subjects with a positive urine pregnancy test should NOT be randomized and dosed with AVTX-002.	
8.7 Premature Subject Withdrawal 12.3.1.1 Disposition and Withdrawals	Added: Any subject who receives three doses of AVTX-002 or placebo by definition is considered as completing study therapy. Subjects who require systemic corticosteroids or other non-study drug for treatment of their asthma should be considered to have lack of efficacy and withdrawn from study drug. Subjects who meet one of the other protocol definitions of an asthma related event should also be considered to have lack of efficacy and be considered for withdraw from study drug. Instances where the Investigator feels that a subject meeting these criteria should continue receiving study drug should be discussed on a case-by-case basis with the medical monitor. Subjects who are prematurely withdrawn from study drug should be followed up as instructed in the schedule of assessments.	Given each dose of study drug equates to 4 weeks of therapy, clarified that subjects who receive all 3 doses are considered as completing study therapy. Also provided requirements for study drug discontinuation based upon meeting criteria for an asthma related event.
9.11.4 Prohibited Therapies	Added: Subjects who require systemic corticosteroids or another non-study asthma medication to treat an asthma exacerbation should be withdrawn from the study. If a subject receives a systemic corticosteroid for another reason (e.g., bee sting), the Medical Monitor should be consulted regarding the subject's continuation in the study.	Additions made for clarification of withdrawal criteria previously omitted.
10 STUDY PROCEDURES	Added: In the event a subject cannot be in-clinic for a study visit after randomization due to pandemic, natural disaster, or other kinds of unforeseeable situations, sites should attempt to complete as many visit procedures as possible that can be done remotely, by phone or telehealth/video, on time and per protocol windows. This	Additions made based upon a prior protocol clarification letter.

	includes completion of study-required questionnaires which should be provided to the subject or reviewed via phone prior to the visit, if possible, so that the subject can be prepared with appropriate responses. The medical monitor should be consulted for decisions regarding dosing, laboratory testing, and other protocol procedures which are unable to be done remotely. If a visit is done remotely, it should be documented as such in subject source records.	
10.2.2.4 Peak Flow Meter 10.2.2.7 Asthma Symptom Diary 10.2.2.11 Short-Acting Beta Agonist Use	Added: The site will monitor the diary entries closely to assess subject compliance. Subjects who are not compliant with the diary will be counseled by the site and will be considered protocol deviations if an overall compliance rate of less than 80% is reached.	Additions made for clarification of diary compliance previously omitted.
11.1.1 Adverse Event Collection	Updated: Previous wording: Lack of effect, including worsening of symptoms, disease progression, or lack of improvement, should not be recorded as an AE unless it meets the definition of the criteria for an SAE. New Wording: Events that meet the protocol definition of an asthma related event are captured as part of the primary efficacy endpoint for the study, and therefore need not be recorded as an AE unless they meet the definition of an SAE. Asthma exacerbations that do not meet the protocol definition of an asthma related event should be captured as AEs.	Clarifications of AE capture related to primary endpoint events.
16 REFERENCES	Added: Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, Chanez P, Enright PL, Gibson PG, Jongste JC, Kerstjens HAM, Lazarus SC, Levy ML, O'Byrne PM, Partridge MR, Pavord ID, Sears MR, Sterk PJ, Stoloff SW, Sullivan SD, Szefler SJ, Thomas MD, Wenzel SE. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. Am J Respir Crit Care Med. 2009;180:59–99.	Addition made to add American Thoracic Society/European Respiratory Society statement to references.

4 SYNOPSIS

PRODUCT NAME	AVTX-002 (formerly known as MDGN-002, SAR252067)
PROTOCOL NUMBER	AVTX-002-NEA-201
DEVELOPMENT PHASE	Phase 2
PROTOCOL 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
OBJECTIVES	**Primary Objective:** • To assess the ability of AVTX-002 to improve asthma control in subjects with poorly controlled non-eosinophilic asthma (NEA). **Secondary Objectives**: • To assess the safety and tolerability of AVTX-002. • To evaluate biomarkers of pharmacodynamic (PD) activity and mechanism of action of AVTX-002. • To evaluate the immunogenicity of AVTX-002. **Exploratory Objectives:** • To assess the ability of AVTX-002 to improve asthma control in subjects with poorly controlled NEA who also have <150 eosinophils/ μL • To assess sputum soluble LIGHT levels and gene expression in a select subset of subjects • To evaluate inflammatory proteins including but not limited to: interleukin (IL)-6, interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) • To evaluate the PK/PD relationship
ENDPOINTS	**Primary Endpoint:** • Proportion of patients who experience any of the following asthma-related events: o ≥6 additional reliever puffs of SABA (compared to baseline) in a 24-hour period on 2 consecutivedays or, • Baseline SABA use (defined as the number of individual puffs or inhalations taken by the subject) will be determined by the average use in the 7 days preceding Visit 2, o increase in ICS dose ≥4 times than the dose at baseline or, • Baseline ICS dose is defined as the dosage the subject received during the 30-day run-in period, o a decrease in peak flow of 30% or more (compared to baseline) on 2 consecutive days of treatment or, • Baseline peak flow will be determined by the average of measurements in the 7 days preceding Visit 2 o An asthma exacerbation requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or, o a hospitalization or emergency room visit because of an asthma exacerbation. **Secondary Endpoints:** • Change from baseline in forced expiratory volume in 1 second (FEV1) at Weeks 2, 4, 6, 8, 12, and 14. • Time to asthma related event • Change from baseline in fractional exhaled nitric oxide (FeNO) at Weeks 2, 4, 6, 8, 12, and 14. • Change from baseline in Asthma Control Questionnaire (ACQ) at Weeks 2, 4, 6, 8, 12, and 14.

	• Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12) at Weeks 2, 4, 6, 8, 12, and 14. • Change from baseline in Asthma Symptom Diary Score at Weeks 2, 4, 6, 8, 12, and 14. • Change from baseline in European Quality of Life – 5 Dimension 5 level Questionnaire at Weeks 2, 4, 6, 8, 12, and 14. • Change from baseline in Patient Global Impression of Change/Severity at Weeks 2, 4, 6,8, 12, and 14. • Change from baseline in Clinician Global Impression of Improvement/Severity at Weeks 2, 4, 6, 8, 12, and 14. • Incidence of SABA use at Weeks 2, 4, 6, 8, 12, and 14. • Change from baseline in serum soluble LIGHT (Lymphotoxin like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator) levels at Weeks 2, 4, 6, 8, 12, and 14. • Incidence of adverse events (AE), and changes from baseline in clinical laboratory tests, vital signs measurements,and physical examinations at Weeks 2, 4, 6, 8, 12, and 14. • Incidence of anti-drug antibodies (ADAs) at Weeks 2, 4, 6, 8, 12, and 14.
	Exploratory Endpoints: • Occurrence of asthma related events in subjects with <150 eosinophils/μL • Change from baseline in sputum soluble LIGHT and gene expression (select subset of sites/subjects only) • Change from baseline in inflammatory proteins including but not limited to: interleukin (IL)-6, interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α) • PK/PD assessments
STUDY DESIGN	Subjects will be screened for the study and complete a 30-day, stable therapy, run-in period with a long-acting beta agonist (LABA) (salmeterol 50 mcg twice daily) and an inhaled corticosteroid (ICS) (fluticasone starting dose at investigator discretion). After the 30-day run-in is complete, at the Baseline Visit (Day 0), subjects will be randomly assigned (1:1) to AVTX-002 or placebo. Fourteen days after randomization, subjects in each treatment group will discontinue salmeterol therapy at Visit 4 (Day 14). After an additional 14 days, at Visit 5 (Day 28), all subjects will taper fluticasone dose to 50%. At Visit 6 (Day 42), all subjects will discontinue the use of fluticasone therapy completely. AVTX-002 or placebo will be administered at Visit 2 (Day 0), Visit 5 (Day 28) and Visit 7 (Day 56). AVTX-002 will be administered at a dose of 600 mg. The final visit will be on Day 98.
PLANNED NUMBER OF SUBJECTS	Approximately 80 completed subjects
PLANNED NUMBER OF STUDY SITES	Approximately 25 sites from the United States will participate
STUDY ENTRY CRITERIA	**Inclusion criteria:** 1. Subject is ≥18 years of age at the time of informed consent. 2. Documented non-eosinophilic asthma diagnosis (<300 eosinophils/μL). 3. Symptoms consistent with a diagnosis of asthma that is poorly controlled as determined by an ACQ score ≥ 1.5. 4. Poorly controlled asthma despite the use of a LABA and ICS for at least 3 consecutive months immediately prior to screening. 5. Subjects must have had at least one asthma exacerbation in the last 24 months prior to Screening. An asthma exacerbation is defined as follows: o a course of oral corticosteroids because of worsening asthma symptoms, and/or o at least a doubling of the subject's inhaled corticosteroids for at least 14 days because of worsening asthma symptoms.

If a subject's medical experience satisfies either or both statements, the subject has experienced an asthma exacerbation.

6. Non-pregnant, non-lactating female subjects of childbearing potential who are heterosexually active and non-sterile male subjects with female sexual partners of childbearing potential agree to use a highly effective method of contraception during the treatment period and for 28 days following the last dose of study medication. A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as oral/injectable/inserted/implanted/transdermal contraceptives, condom with diaphragm, condom with spermicide, diaphragm with spermicide, intrauterine hormone-releasing system, or intrauterine device (IUD), or sexual abstinence. Contraception is not required where 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). Females of childbearing potential must have a negative pregnancy test as part of the screening assessment.
7. Subject can understand and provide informed consent to participate in this study.

Exclusion criteria:

1. Pulmonary disease other than asthma.
2. Currently on biologic therapy. Previous biologic therapy is permitted with adequate washout (12 weeks or 5 half-lives, whichever is longer).
3. Subjects who:
    - Are current smokers, users of inhaled cannabis and/or e-cigarettes/vaping devices or
    - Have a history of smoking >/=10 pack years or
    - Have a history of inhaled cannabis >4 days/week for the most recent 3 months prior to screening or
    - Use e-cigarettes or vaping devices >4 days/week for the most recent 3 months prior to screening.
4. Current suspected drug or alcohol abuse.
5. Use of systemic immunosuppressants within the last 6 months.
6. Use of systemic corticosteroids within 6 weeks prior to Screening or use of antibiotics within 4 weeks prior to Screening.
7. Subjects that are pregnant or breastfeeding.
8. Subject has a history of neoplasia (except for a curatively treated non-melanomaskin tumor or carcinoma of the cervix treated in situ with no indication of recurrence) within the 10 years prior to Visit 1.
9. Subject has a chronic, active infection or another disease, which entails a tendency towards infection.
10. Subject has a chronic severe or uncontrolled medical disorder that might confound the results of safety assessments conducted in this study.
11. Subject has a history of unresolved latent tuberculosis.
12. Subject has alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) >5 upper limit of normal (ULN) and/or serum creatinine concentration >1.5 mg/dL.
13. Subject has hemoglobin ≤10 g/dL, neutrophils ≤1,500/µl, and/or platelets ≤75,000/µl.
14. Subject has received a live vaccine within 12 weeks prior to Visit 2.
15. Subject has used an investigational product, including Emergency Use Authorization (EUA) vaccines, within 30 days of Visit 1.
16. Subject has known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any ingredients of the investigational product.
17. There is any concern on the part of the investigator regarding the subject's safety, compliance, or suitability with respect to his/her participation in the study.

CONCOMITANT TREATMENT	During the study, new initiation of investigational compounds or concomitant treatment with other asthma therapy is not permitted.
INVESTIGATIONAL PRODUCT, DOSE AND MODE OF ADMINISTRATION	AVTX-002 will be supplied in single-use vials containing 300-mg AVTX- 002 (concentration 150 mg/mL). AVTX-002 will be administered by a subcutaneous (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.
REFERENCE PRODUCT	Placebo will be sourced locally and provided as volume matched normal saline for injection and will be administered by an 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.
TREATMENT REGIMEN AND DURATION	600 mg of AVTX-002 or placebo will be administered at Visit 2 (Day 0), Visit 5 (Day 28), and Visit 7 (Day 56). **A subject must be dosed with the Week 8 dose no later than Day 56.** The investigational product will be prepared by an unblinded pharmacist or appropriately qualified individual. Fourteen days after randomization (Day 0), subjects in each treatment group will discontinue salmeterol therapy at Visit 4 (Day 14). After an additional 14 days, at Visit 5 (Day 28), all subjects will taper fluticasone dose to 50%. At Visit 6 (Day 42), all subjects will discontinue the use of fluticasone therapy completely.
COORDINATING PRINCIPAL INVESTIGATOR / PRINCIPAL INVESTIGATOR	[redacted]

CRITERIA FOR EVALUATION	**Efficacy:** • The efficacy of AVTX-002 will be determined by the occurrence of asthma related events (primary endpoint), time to asthma related events, and change from baseline in the following parameters: FEV1; FeNO; ACQ; AQLQ(S)+12; Asthma Symptom Diary Score; European Quality of Life – 5 Dimension 5 level Questionnaire; Patient Global Impression of Change/Severity (PGI-C/S); Clinician Global Impression ofImprovement/Severity (CGI-I/S); and incidence of short-acting beta agonist (SABA) use. **Safety:** The safety of AVTX-002 will be determined by monitoring of AEs, clinical laboratory tests, vital signs measurements, and physical examinations. **Pharmacodynamics:** The PD of AVTX-002 will be determined by measuring the serum levels of LIGHT biomarker patterns. **Immunogenicity:** The immunogenicity of AVTX-002 will be determined by measuring ADA levels. **Exploratory:** • Evaluation of the primary endpoint in subjects with <150 eosinophils/μL • Sputum soluble LIGHT and gene expression (select subset of sites/subjects only) • Inflammatory proteins including but not limited to: IL-6, INF-γ, and TNF-α • AVTX-002 plasma concentrations at select timepoints

STATISTICAL METHODS	For the primary variable, comparison of the proportions of subjects that had an asthma-related event will be via a Wald Z-test (continuity corrected). Summary statistics will be provided via a 2x2 table showing the number and percentage with and without asthma-related events in each treatment group. The test statistic, its associated p-value and a 95% confidence interval for the treatment difference will also be provided. All other efficacy variables will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, 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 timepoint of interest. Descriptive statistics for categorical data will include frequencies and percentages. AE data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The overall incidence of subjects having at least one AE will be summarized. The incidence of treatment-emergent adverse events (TEAEs) will be summarized by treatment group, system organ class (SOC), and preferred term (PT). Each subject will be counted only once per SOC and PT. For all continuous safety variables (e.g., laboratory and vital sign measures), descriptive statistics for all reported values and change from baseline values will be summarized by treatment group.
SAMPLE SIZE DETERMINATION	The sample size in this study will be approximately 80 with 40 subjects per treatment arm, randomized in a 1:1 ratio. The sample size estimate was based on the estimated proportions of patients in the two treatment groups expected to have an asthma related event as defined by the primary endpoint. In a study with another product, rates of 6% in the active group and 44% in the placebo group were observed (Wenzel, 2013). 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%.
STUDY AND TREATMENT DURATION	After the Screening visit, subjects will complete a 30-day, stable therapy, run-in until randomization at the Baseline Visit (Day 0). AVTX-002 or placebo will be administered at Visit 2 (Day 0), Visit 5 (Day 28), and Visit 7 (Day 56). The final visit will be on Day 98. The overall study duration will be up to approximately 135 days.

Table 1: Schedule of Assessments

Procedure	**Screening**	**30-Day Run-In Period**		**Baseline**	**Double-Blind 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**		**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**14**
Assessment Day	**Approxi-mately -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										
FEV1	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
Asthma Symptom Diary (2xDaily)[17]			X	X	X	X	X	X	X	X	X
Record SABA Use (2xDaily)[18]			X	X	X	X	X	X	X	X	X
EQ-5D-5L				X		X	X	X	X	X	X
Patient Global Impression of Change/Severity				X		X	X	X	X	X	X
Clinician Global Impression of Improvement/Severity				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

Procedure	**Screening**	**30-Day Run-In Period**		**Baseline**	**Double-Blind 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**		**-1**	**0**	**1**	**2**	**4**	**6**	**8**	**12**	**14**
Assessment Day	**Approxi-mately -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**
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 Run-In		X	X								
Discontinue salmeterol						X					
Taper/discontinue fluticasone							X	X			

Abbreviations: ACQ=Asthma Control Questionnaire; ADA=anti-drug antibody; AQLQ(S)+12=Standardized Asthma Quality of Life Questionnaire for 12 years and older; ECG=electrocardiogram; European Quality of Life – 5 Dimension 5 Level; Questionnaire ET=early termination; FeNO=fractional exhaled nitric oxide; FEV1=forced expiratory volume in 1 second; LIGHT= Lymphotoxin like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator.

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.**
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 post-dose vital signs will be measured: Pre-dose vital signs should be taken within 60 minutes before dosing. Post-dose 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. Subjects should record the best result of 3 attempts daily at home. Subjects 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 timepoints per the schedule of events, an ADA sample will be collected if an immunologically related adverse event is reported (e.g., a skin reaction, lupus-like 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 IP administration is required (Visit 2/Day 0), all visit procedures should be completed prior to IP administration. At the other IP administration Visit dates (Visit 5/Day 28 and Visit 7/Day 56), only the pharmacokinetic (PK), anti-drug antibody (ADA), Serum soluble LIGHT, inflammatory proteins and immunophenotyping samples must be collected prior to 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 adverse event monitoring.
15. Investigational product will be prepared by an unblinded pharmacist or appropriately qualified individual.
16. Immunophenotyping and PK only required if an Early Termination 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.

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LIST OF ABBREVIATIONS

ACQ	asthma control questionnaire
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AQLQ (S)+12	standardized asthma quality of life questionnaire for 12 years and older
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{last}	area under the serum concentration versus time curve from time zero to the last observed concentration
AUC_{0-t}	area under the plasma concentration time curve from time zero to the last observed concentration
AUC_{0-tau}	area under the curve from time zero to the time of the end of dosing interval
CGI-I	clinician global impression of improvement
CGI-S	clinician global impression of severity
COVID-19	coronavirus disease 2019
C_{max}	maximum observed concentration
CRA	clinical research associate
CRO	contract research organization
ECG	Electrocardiogram
eCRF	electronic case report form
EC	Ethics committee
ET	early termination
EU	European Union
EUA	Emergency Use Authorization
FeNO	fractional exhaled nitric oxide
FEV1	forced expiratory volume in 1 second
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICS	inhaled corticosteroid
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonization

IFN	interferon
IFN-γ	Interferon gamma
IgG4	immunoglobulin G subclass 4
IL	interleukin
IL- 6	Interleukin 6
IRB	Institutional Review Board
IUD	intrauterine device
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
Mab	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Affairs
NEA	non-eosinophilic asthma
PGI-C	patient global impression of change
PGI-S	patient global impression of severity
PBMC	peripheral blood mononuclear cells
PK	pharmacokinetic
PD	pharmacodynamic
PT	preferred term
SABA	short-acting beta agonist
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SD	standard deviation
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment emergent adverse event
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor alpha
$t_{1/2}$	terminal half-life
t_{max}	time to maximum observed concentration
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WHO	World Health Organization

6 INTRODUCTION

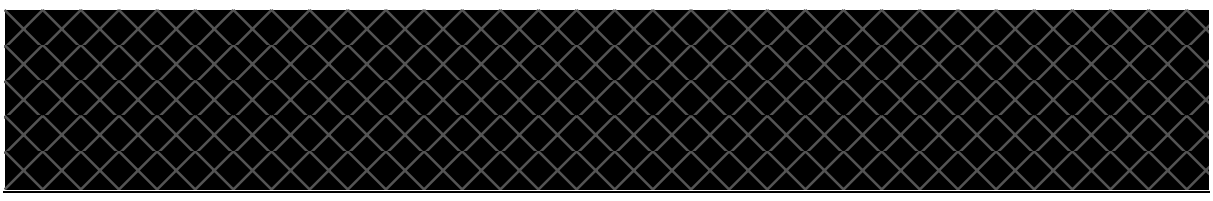
6.1 Background and Rationale in Non-Eosinophilic Asthma

Asthma is a chronic disease of the lungs characterized by airway inflammation causing swelling and excess mucous production, and as a result, patients experience difficulty breathing which can be life threatening in severe cases (Boulet et al. 2000). Asthma affects approximately 25 million patients in the US and over 300 million globally (Centers for Disease Control, 2021, IHME, 2019). There are classifications of asthma based on the inciting factors (allergic versus non-allergic) and the nature of the immune-inflammatory response (Th2 or low/no Th2) (Ray and Kolls 2017, Wenzel et al., 1999, Woodruff et al., 2009). An allergic or Th2 biased response is associated with eosinophilic classifications and related to type 2 cytokines IL-4, IL-5, and IL-13 (Lambrecht, Hammad, and Fahy 2019). Non-allergic or low/absent Th2 response is associated with neutrophilic and pauci-granulocytic classifications, which as a group are called non-eosinophilic asthma and account for 40% - 50% of all asthma patients (Douwes et al. 2002, Stokes et al., 2016).

The long-term control of asthma is typically accomplished through the use of long-acting bronchodilators in combination with inhaled corticosteroids as needed. For patients specifically with severe allergic asthma, biologic agents have been approved for treatment which target IgE (omalizumab) or the Th2-related cytokine pathways of IL-4 and IL-5 (mepolizumab, resilizumab, benralizumab, and dupilumab). The cytokine pathways identified as contributing to NEA include IL-6, IL-8, IL-17, IFNγ, TNFα, and G-CSF (Lambrecht, Hammad, and Fahy 2019). For NEA patients with severe disease, there are no approved agents related to these pathways and, as such, there remains a significant unmet medical need for these patients. Previously it was demonstrated that human bronchial epithelial cells express receptors for LIGHT (LTbR) and upon LIGHT stimulation of BEC there is a resulting broad gene expression of proinflammatory mediators, with these proinflammatory changes in gene expression being resistant to corticosteroid treatment; consistent with the clinical presentation of NEA (da Silva Antunes et al. 2015).

Human BEC cells express receptors for LIGHT (LTβR) and upon LIGHT stimulation of BECs in vitro there is a resulting broad gene expression of proinflammatory mediators (da Silva Antunes et al. 2015), which are resistant to corticosteroid treatment, consistent with the clinical presentation of NEA. Soluble proinflammatory mediators such as IL-6, IL-8, OSM, and MCP-1 were also detected in this in vitro system. In the clinic, administration of an oral CXCR2 antagonist resulted in lowered sputum neutrophil counts and fewer mild exacerbations (Nair et al. 2012). Separately, sputum levels of soluble LIGHT positively correlated with increased sputum Th1 cytokine levels and neutrophil counts and negatively correlated with lung function (Romeo 2013). Along with soluble LIGHT detected in sputum, others have observed elevated serum levels of DcR3 in asthma patients, which are even greater during asthma exacerbations suggesting a response to elevated LIGHT levels in relation to asthma and disease activity (Kowal et al., 2019).

6.2 Nonclinical Experience



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6.3 Clinical Experience

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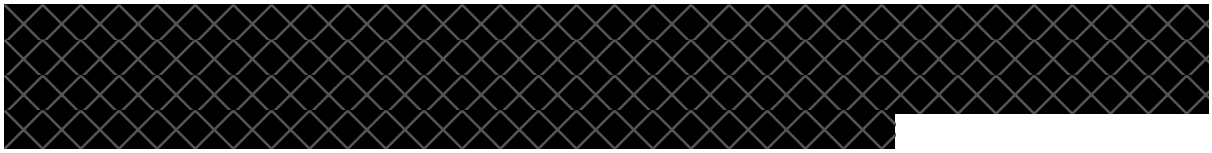
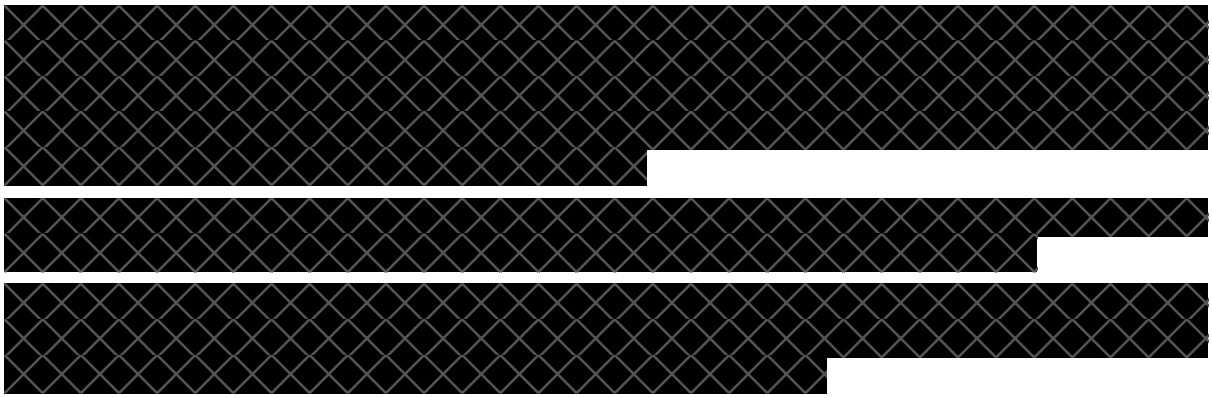


6.4 Summary of Potential Risks and Benefits



7 STUDY OBJECTIVES AND ENDPOINTS

7.1 Study Objectives

7.1.1 Primary Objective

- To assess the ability of AVTX-002 to improve asthma control in subjects with poorly controlled NEA

7.1.2 Secondary Objectives

- To assess the safety and tolerability of AVTX-002
- To evaluate biomarkers of pharmacodynamic (PD) activity and mechanism of action of AVTX-002
- To evaluate the immunogenicity of AVTX-002

7.1.3 Exploratory Objectives

- To assess the ability of AVTX-002 to improve asthma control in subjects with poorly controlled NEA who also have <150 eosinophils/ μL
- To assess sputum soluble LIGHT levels and gene expression in a select subset of subjects
- To evaluate inflammatory proteins including but not limited to: interleukin (IL)-6, interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α)
- To evaluate the PK/PD relationship

7.2 Study Endpoints

7.2.1 Primary Endpoints

- Proportion of patients 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 consecutivedays or,
    - Baseline SABA use (defined as the number of individual puffs or inhalations

taken by the subject) will be determined by the average use in the 7 days preceding Visit 2,
- increase in ICS dose ≥4 times than the dose at baseline or,
  - Baseline ICS dose is defined as the dosage the subject received during the 30-day run-in period,
- a decrease in peak flow of 30% or more (compared to baseline) on 2 consecutive days of treatment or,
  - Baseline peak flow will be determined by 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 or,
- a hospitalization or emergency room visit because of an asthma exacerbation.

7.2.2 Secondary Endpoints

- Change from baseline in forced expiratory volume in 1 second (FEV1) at Weeks 2, 4, 6, 8, 12, and 14.
- Time to asthma related event.
- Change from baseline in fractional exhaled nitric oxide (FeNO) at Weeks 2, 4, 6, 8, 12, and 14.
- Change from baseline in Asthma Control Questionnaire (ACQ) at Weeks 2, 4, 6, 8, 12, and14.
- Change from baseline in Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12) at Weeks 2, 4, 6, 8, 12, and14.
- Change from baseline in Asthma Symptom Diary Score at Weeks 2, 4, 6, 8, 12, and14.
- Change from baseline in European Quality of Life – 5 Dimension 5 level Questionnaire at Weeks 2, 4, 6, 8, 12, and14.
- Change from baseline in Patient Global Impression of Change/Severity at Weeks 2, 4, 6, 8, 12, and14.
- Change from baseline in Clinician Global Impression of Improvement/Severity at Weeks 2, 4, 6, 8, 12, and14.
- Incidence of short-acting beta agonist (SABA) use at Weeks 2, 4, 6, 8, 12, and14.
- Change from baseline in serum soluble LIGHT levels at Weeks 2, 4, 6, 8, 12, and14.
- Incidence of adverse events (AEs), and changes from baseline in clinical laboratory tests, vital signs measurements, and physical examinations at Weeks 2, 4, 6, 8, 12, and14.
- Incidence of ADAs at Weeks 2, 4, 6, 8, 12, and14.

7.2.3 Exploratory Endpoints

- Occurrence of asthma related events in subjects with <150 eosinophils/μL
- Change from baseline in sputum soluble LIGHT and gene expression (select subset of site/subjects only)
- Change from baseline in inflammatory proteins including but not limited to: IL-6, IFN-γ, and tumor necrosis factor alpha (TNF-α)
- PK/PD assessments

8 STUDY DESIGN

8.1 Overall Study Design and Plan

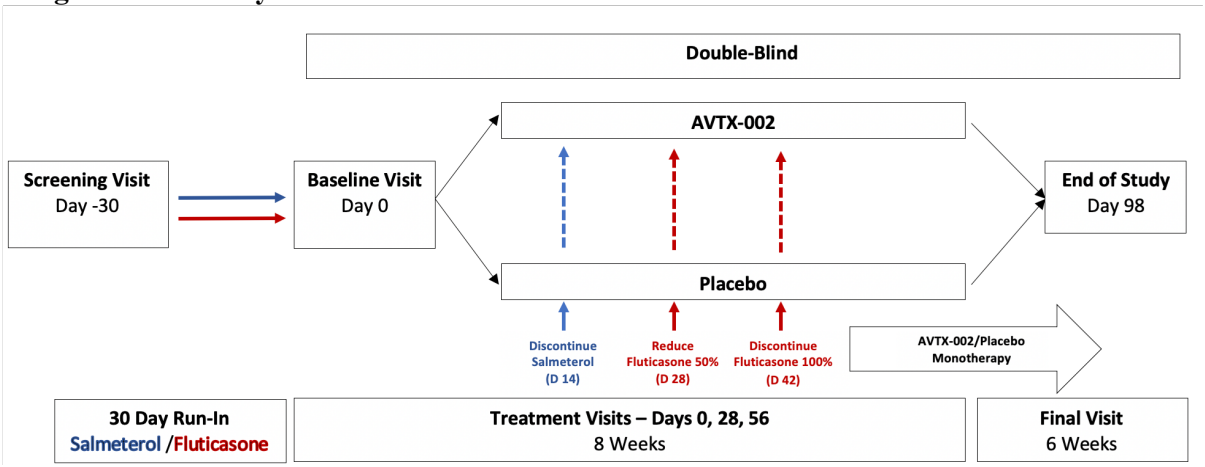
This is a randomized, double-blind, placebo-controlled, Phase 2 study to evaluate the safety and efficacy of AVTX-002 for the treatment of poorly controlled NEA. Upon confirmation of eligibility, subjects will complete a 30-day, salmeterol and fluticasone stable dose, run-in prior to randomization. At Baseline subjects will be randomized to receive either three doses of AVTX-002 at 600 mg (Days 0, 28 and 56) or they will receive 3 doses of placebo at the same time points. Subjects will then begin a withdrawal of salmeterol and fluticasone therapies. Subjects will discontinue salmeterol at Day 14 and then taper fluticasone use to 50% dose at Day 28. Fluticasone use will be completely discontinued at Day 42. Subjects will be followed until Day 98.

An adequate number of subjects will be enrolled to ensure approximately 80 subjects complete the study.

All subjects will undergo efficacy, safety, PK/PD, and immunogenicity assessments. The efficacy of AVTX-002 will be determined by the occurrence of an asthma related event (primary endpoint), time to asthma related event, and change from baseline in the following parameters: FEV1; FeNO; ACQ; AQLQ(S)+12); Asthma Symptom Diary Score; European Quality of Life – 5 Dimension 5 level Questionnaire; Patient Global Impression of Change/Severity (PGI-C/S); Clinician Global Impression of Improvement/Severity (CGI-I/S); and Incidence of short-acting beta agonist (SABA) use. All subjects will be monitored for AEs and will undergo physical exams, vital signs, and routine safety laboratory tests. The PK/PD of AVTX-002 will be determined by measuring the levels of AVTX-002 and LIGHT in addition to other biomarkers of NEA. Finally, the immunogenicity of AVTX-002 will be determined by measuring ADA levels.

The study schema is displayed in Figure 1.

Figure 1: Study Schema



8.2 Discussion of Study Design

This study will assess safety and efficacy of AVTX-002 in subjects with poorly controlled non-eosinophilic asthma.

Subjects will be evaluated for enrollment at the Screening visit. If considered eligible for enrollment, subjects will undergo a 30-day, stable dose, run-in period with a LABA (salmeterol) and an ICS

(fluticasone). 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.

During the 30-day run-in, a visit (Visit 1a) should occur 7 days prior to Baseline, at Day -7 (-2 day window). Visit 1a may be completed either by telephone or as an in-clinic visit, depending upon the needs of the site or subject. During this visit, the subject should be reminded to begin daily peak flow measurements as well as completion of the daily diary to capture ASD, SABA use and daily peak flow values.

After the run-in period, subjects will be randomized at the Baseline Visit (Day 0) to either AVTX-002 administered at 600 mg or placebo. Subjects will receive AVTX-002 or placebo at Visit 2 (Day 0), Visit 5 (Day 28) and Visit 7 (Day 56). Over the course of the first 42 days after randomization subjects will taper or discontinue use of products administered during their run-in period. Salmeterol will be discontinued at Visit 4 (Day 14), fluticasone use will be tapered to 50% dose at Visit 5 (Day 28) and fluticasone will be discontinued completely at Visit 6 (Day 42). All subjects will proceed on AVTX-002 or placebo monotherapy until Visit 9 (Day 98), which is also the end of study visit. Efficacy will be assessed from Baseline Visit (Day 0) through Visit 9 (Day 98) per the schedule outlined in schedule of assessments (Table1).

The run-in period after Screening and before Baseline must be completed with a stand-alone LABA (salmeterol) and an ICS (fluticasone). Principal investigators will ensure subjects are transitioned to these stand-alone products at Run-In if the subject is not already on these products.

If a subject must discontinue the study prior to Visit 9 (Day 98) for any reason, the subject will be required to complete an Early Termination Visit (Day 98 procedures).

8.3 Study Sites

The study will take place at approximately 25 study sites in the US.

8.4 Selection of Study Population

Subjects diagnosed with NEA (<300 eosinophils/μL) will be randomized into the study. An adequate number of subjects will be enrolled to ensure approximately 80 subjects complete the study.

A screening log of study candidates will be maintained at each study site.

8.5 Study Entry Criteria

Subjects are to be enrolled based on the inclusion and exclusion criteria below. The diagnosis of NEA is determined at Screening Visit 1 based upon Inclusion Criteria 2 through 5. At Baseline Visit 2, a review of all Inclusion/Exclusion criteria should be done to ensure continued eligibility prior to randomization and dosing the subject. As long as the subject qualifies as having NEA per protocol at the Screening Visit, there is no expectation that their diagnosis be re-confirmed at Baseline Visit 2, and therefore changes in eosinophil count and/or ACQ score within the period of time between Screening Visit 1 and Baseline Visit 2 would not reverse their diagnosis and would not disqualify the subject.

Although chemistry and hematology labs must be drawn as part of Baseline Visit 2 procedures,

there is not an expectation that these test results be available during the visit to re-confirm eligibility (Exclusion Criteria 12 and 13).

Per the schedule of assessments, a urine pregnancy test must be completed and show negative results at Baseline Visit 2 prior to randomization and dosing. Subjects with a positive urine pregnancy test should NOT be randomized and dosed with AVTX-002.

8.5.1 Inclusion Criteria

Subjects must fulfill the following requirements to be randomized into the study:

1. Subject is ≥18 years of age at the time of informed consent.
2. Documented non-eosinophilic asthma diagnosis (<300 eosinophils/µL).
3. Symptoms consistent with a diagnosis of asthma that is poorly controlled as determined by an ACQ score ≥ 1.5.
4. Poorly controlled asthma despite the use of a LABA and ICS for at least 3 consecutive months immediately prior to the Screening Visit.
5. Subjects must have had at least one asthma exacerbation in the last 24 months prior to Screening. An asthma exacerbation is defined as follows:
    - a course of oral corticosteroids because of worsening asthma symptoms, and/or
    - at least a doubling of the subject's inhaled corticosteroids for at least 14 days because of worsening asthma symptoms.

    If a subject's medical experience satisfies either or both statements, the subject has experienced an asthma exacerbation.
6. Non-pregnant, non-lactating female subjects of childbearing potential who are heterosexually active and non-sterile male subjects with female sexual partners of childbearing potential agree to use a highly effective method of contraception during the treatment period and for 28 days following the last dose of study medication. A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as oral/injectable/inserted/implanted/transdermal contraceptives, condom with diaphragm, condom with spermicide, diaphragm with spermicide, intrauterine hormone-releasing system, or intrauterine device (IUD), or sexual abstinence. Contraception is not required where 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). Females of childbearing potential must have a negative pregnancy test as part of the screening assessment.
7. Subject can understand and provide informed consent to participate in this study.

8.5.2 Exclusion Criteria

The presence of any of the following criteria excludes a subject from the study:

1. Pulmonary disease other than asthma.
2. Currently on biologic therapy. Previous biologic therapy is permitted with adequate washout(12 weeks or 5 half-lives, whichever is longer).

3. Subjects who:
    - Are current smokers, users of inhaled cannabis and/or e-cigarettes/vaping devices or,
    - Have a history of smoking >/=10 pack years or,
    - Have a history of inhaled cannabis >4 days/week for the most recent 3 months prior to screening or,
    - Use e-cigarettes or vaping devices >4 days/week for the most recent 3 months prior to screening.
4. Current suspected drug or alcohol abuse.
5. Use of systemic immunosuppressants within the last 6 months.
6. Use of systemic corticosteroids within 6 weeks prior to Screening or use of antibiotics within 4 weeks prior to Screening.
7. Subjects that are pregnant or breastfeeding.
8. Subject has a history of neoplasia (except for a curatively treated non-melanoma skin tumor or carcinoma of the cervix treated in situ with no indication of recurrence) within the10 years prior to Visit 1.
9. Subject has a chronic, active infection or another disease, which entails a tendency towards infection.
10. Subject has a chronic severe or uncontrolled medical disorder that might confound the results of safety assessments conducted in this study.
11. Subject has a history of unresolved latent tuberculosis.
12. Subject has alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) >5 upper limit of normal (ULN) and/or serum creatinine concentration >1.5 mg/dL.
13. Subject has hemoglobin ≤10 g/dL, neutrophils ≤1,500/µl, and/or platelets ≤75,000/µl.
14. Subject has received a live vaccine within 12 weeks prior to Visit 2.
15. Subject has used an investigational product, including Emergency Use Authorization (EUA) vaccines, within 30 days of Visit 1.
16. Subject has known or suspected intolerance or hypersensitivity to the investigational product(s), closely related compounds, or any ingredients of the investigational product.
17. There is any concern on the part of the investigator regarding the subject's safety, compliance, or suitability with respect to his/her participation in the study.

8.6 Screen Failures

Subjects who fail inclusion and/or exclusion criteria may be rescreened for the study with Sponsor approval.

8.7 Premature Subject Withdrawal

All subjects will be advised that they are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Every reasonable attempt should be made by the investigator to keep subjects in the study; however, subjects must be withdrawn from the study if they withdraw consent to participate. Investigators must attempt to contact subjects who fail to attend scheduled visits by telephone or other means to exclude the possibility of an AE being the cause of withdrawal. Should this be the cause, the AE must be documented, reported, and followed as described in Section 11.1.1.

Subjects can decline to continue receiving study drug at any time during the study. If this occurs, the investigator is to discuss with the subject the completion of the Early Termination Visit to occur 4 weeks (±3 days) post last dose. If the subject refuses this visit/procedures associated with this visit, data on concomitant medications and AEs will be collected if the subject agrees. Data on concomitant medications and AEs can be collected via a telephone call if the subject refuses an in-person visit.

Withdrawal of consent for a study means the subject does not wish to receive further protocol-required treatment or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publicly available data can be included after withdrawal of consent.

Any subject who receives three doses of AVTX-002 or placebo by definition is considered as completing study therapy.

The Sponsor reserves the right to request the withdrawal of a subject due to protocol deviations or other reasons.

The investigator also has the right to withdraw subjects from the study at any time for any reason. If a subject is withdrawn before completing the study, the subject should be followed-up as instructed in the schedule of assessments (Table 1). The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the electronic case report form (eCRF) as well as the date of discontinuation. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF.

Reasons for discontinuation include but are not limited to:

- Lack of efficacy
- Adverse event
- Death
- Protocol deviation
- Physician decision
- Sponsor request
- Withdrawal by subject
- Lost to follow-up
- Other (specify). For example, pregnancy.

Subjects who require systemic corticosteroids or other non-study drug for treatment of their asthma should be considered to have lack of efficacy and withdrawn from study drug.

Subjects who meet one of the other protocol definitions of an asthma related event should also be considered to have lack of efficacy and be considered for withdraw from study drug. Instances where the Investigator feels that a subject meeting these criteria should continue receiving study drug should be discussed on a case-by-case basis with the medical monitor.

Subjects who are prematurely withdrawn from study drug should be followed up as instructed in the schedule of assessments.

9 TREATMENTS

9.1 Identification of Investigational Product(s), Dose and Mode of Administration

The following investigational product will be used in this study:

- AVTX-002 will be supplied in single-use vials containing 300 mg AVTX-002 (concentration 150 mg/mL).
- Placebo will be sourced locally and provided as volume-matched normal saline for injection.
- AVTX-002 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.
- AVTX-002 or placebo will be administered at Visit 2 (Day 0), Visit 5 (Day 28), and Visit 7 (Day 56). AVTX-002 will be administered at a dose of 600 mg.

9.2 Labeling and Packaging

All packaging and labeling operations will be performed by the Sponsor or designee per Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP). The investigational product willbe sent to the study site by the Sponsor or designee. Labeling will be in local language and dependent upon local regulations.

9.2.1 Labeling

The AVTX-002 vials will have affixed a label that meets the applicable regulatory requirements and may include the following: name of compound, dosage strength, medication identifier, protocol number, caution statement (“New Drug – Limited by Federal (or United States) Law to Investigational Use”), storage conditions, and Sponsor identification.

The investigator will be asked to save all used or unused vials for final disposition by the Sponsor. Syringes used for dosing must be treated as biologic waste and disposed of properly.

9.2.2 Packaging

AVTX-002 will be supplied in single-use, 2.0 mL vials containing 300 mg AVTX-002 (concentration 150 mg/mL). Vials will be packaged separately into bulk, open-labeled cartons. Placebo will be sourced locally and supplied as volume-matched normal saline for injection.

9.3 Treatment Preparation

Preparation of syringes will be described in the pharmacy manual.

9.4 Treatments Administered

Eligible subjects will receive 600 mg AVTX-002 or placebo SC on Visit 2 (Day 0), Visit 5 (Day 28), andVisit 7 (Day 56).

9.5 Dispensing and Storage

AVTX-002 supplied by the Sponsor is to be used exclusively in this clinical study per the instructions of this protocol. Placebo will be sourced locally and provided as volume-matched injection of normal saline. The investigator is responsible for dispensing the investigational product per the dosage scheme and for ensuring proper storage of the investigational product.

The unblinded pharmacist or appropriately qualified individual must confirm the receipt of the investigational product with his/her signature. A copy of this receipt must be kept by the unblinded pharmacist or appropriately qualified individual, and another copy will be stored at the Sponsor and/or designee. Until the investigational product is dispensed to the subjects, it must be stored at 2°C to 8°C (35.6 °F to 46.4 °F) and protected from light. Investigators or other authorized persons (e.g., pharmacists) are responsible for storing the investigational product provided by the Sponsor in a secure and safe place in accordance with local regulations, labeling specifications, institutional policies, and procedures.

Control of storage conditions for the investigational product provided by the Sponsor, especially control of temperature (e.g., refrigerated storage) and daily temperature monitoring, and information on in-use stability and instructions for handling the investigational product must be managed according to the rules provided by the Sponsor in the pharmacy manual.

9.6 Blinding and Unblinding Treatment Assignment

This is a double-blind study. All subjects, investigators, and study personnel involved in the conduct of the study will be blinded to treatment assignment except as outlined in study specific blind management plans.

Treatment unblinding is discouraged if knowledge of the treatment assignment will not materially change the planned management of a medical emergency. Unblinding is permitted in a medical emergency that requires immediate knowledge of the subject's treatment assignment. Whenever possible unblinding should be discussed with the medical monitor. For emergency unblinding, the investigator can unblind in the IRT/eCRF. If the investigator is not able to discuss treatment unblinding with the medical monitor in advance of theunblinding, then they should notify the medical monitor as soon as possible about the unblinding incident without revealing the subject's treatment assignment. The investigator or designee must record the date and reason for study discontinuation on the appropriate eCRF for that subject. In all cases that are not emergencies, the investigator should discuss the event with the medical monitor prior to unblinding the subject's treatment assignment.

If the treatment assignment is unblinded for an individual subject, the investigator will be notified of that subject's treatment assignment without unblinding the treatment assignments for the remaining subjects in the study.

9.7 Selection of Doses in the Study

[redacted] Based on the PK data and favorable

safety profile of [redacted], the AVTX-002 dose in AVTX-002-NEA-201 will be 600 mg once monthly for a total of 3 doses. This dosing regimen is expected to provide higher serum AVTX-002 concentrations prior to discontinuation of salmeterol at study day 14 with the 28-day dosing interval limiting the potential for accumulation with the 2 subsequent doses.

9.8 Dose Adjustment Criteria

No dose adjustments are allowed.

9.9 Drug Accountability

The investigator must ensure that adequate records showing the receipt, dispensing, or other disposition of the investigational product including the date, lot identifier, dosage, volume administered to each subject, and identification of subjects (subject number and initials) who received the investigational product are maintained by an unblinded pharmacist. The investigator will not supply the investigational product to any person except those named as sub-investigators on the US Food and Drug Administration (FDA) Form FDA 1572 and designated study personnel, and subjects in this study. The investigator will not dispense the investigational product from any study locations other than those listed on Form FDA 1572. If any of the investigational product is not dispensed, is lost, stolen, spilled, unusable, or received in a damaged container, this information must be documented and reported to the Sponsor and appropriate regulatory agencies, as required.

Upon completion of the study, unused investigational product, partially used investigational product and all empty packaging (e.g., vials) must be left in the original packaging for return and final disposition by the Sponsor or their designee or destroyed locally per the site's standard practice after receiving approval from the Sponsor.

9.10 Handling and Disposal

Investigational product reconciliation must be performed at the site by the unblinded pharmacist(s) or appropriately qualified individual(s) using treatment log forms or within the IRT system. After reconciliation authorization by the Sponsor, all used, partially used, and unused vials and all original packaging will be disposed of by the Sponsor or per the site's standard practice. This process will be provided to the site by the Sponsor's designee.

9.11 Permitted and Prohibited Therapies

All non-study therapies including but not limited to over the counter and non-pharmacological treatments from the time of Screening (Visit 1) and through the end of study must be recordedon the appropriate eCRF page. Record of ICS and LABA use should be captured for the three months immediately prior to Screening.

9.11.1 Prior Therapies

Prior therapies include all therapies received from the Screening Visit (Visit 1) to just prior to 1st dose of study drug, with the exception of ICS and LABA which should also be recorded for the 3 months immediately prior to Screening (Visit 1). Prior therapy information must be recorded on the appropriate eCRF page.

9.11.2 Concomitant Therapies

Concomitant therapies refer to all therapies taken on or after the first dose of study drug through

the last visit. Concomitant therapy information must be recorded on the appropriate eCRF page.

9.11.3 Permitted Therapies

Medications considered necessary for the subject's welfare, may be administered at the discretion of the investigator. The medical monitor should be contacted in the event the site is in a situation where further clarity is needed.

Acceptable methods of birth control considered to be highly effective (e.g., results in a low failure rate [i.e., <1% per year]) when used consistently and correctly, include oral/injectable/inserted/implanted/ transdermal contraceptives, condom with diaphragm, condom with spermicide, diaphragm with spermicide, intrauterinehormone-releasing system or IUD, or sexual abstinence.

9.11.4 Prohibited Therapies

During the study, new initiation of investigational compounds or concomitant treatment with other asthma therapy is not permitted. The use of systemic corticosteroids, biologics, immunosuppressants and inhaled anticholinergics is not permitted. Subjects who require systemic corticosteroids or another non-study asthma medication to treat an asthma exacerbation should be withdrawn from the study. If a subject receives a systemic corticosteroid for another reason (e.g., bee sting), the Medical Monitor should be consulted regarding the subject's continuation in the study.

Leukotriene inhibitors are not allowed to be added to a subject's treatment regimen after they are screened for the study. Subjects who are on leukotriene inhibitors as part of their prior therapy at Screening (Visit 1) may continue on leukotriene inhibitors during the course of study participation.

9.12 Treatment after End of Study

Subjects will be treated per standard clinical practice following completion of participation in the study.

10 STUDY PROCEDURES

Subjects will provide written informed consent before any study-related procedures are initiated.

For the timing of assessments and procedures throughout the study, refer to the schedule of assessments (Table 1). Throughout the study, every reasonable effort should be made by study personnel to follow the timing of assessments and procedures in the schedule of events for each subject. Visits performed after Visit 2 should be scheduled relative to Visit 2. If a subject misses a study visit for any reason, the visit should be rescheduled as soon as possible. Permitted visit windows are noted in the schedule of assessments (Table 1).

In the event a subject cannot be in-clinic for a study visit after randomization due to pandemic, natural disaster, or other kinds of unforeseeable situations, sites should attempt to complete as many visit procedures as possible that can be done remotely, by phone or telehealth/video, on time and per protocol windows. This includes completion of study-required questionnaires which should be provided to the subject or reviewed via phone prior to the visit, if possible, so that the subject can be prepared with appropriate responses.

The medical monitor should be consulted for decisions regarding dosing, laboratory testing, and other protocol procedures which are unable to be done remotely.

If a visit is done remotely, it should be documented as such in subject source records.

10.1 Study Duration

AVTX-002 and placebo treatment will be administered at Visit 2 (Day 0), Visit 5 (Day 28), and Visit 7 (Day 56). **A subject may not be dosed after Day 56.** The duration of the treatment period is considered 84 days, with each dose of study drug considered to be 28 days of treatment. The overall study period is approximately 135 days, including Screening and the 30-day, stabledose, run-in period.

10.2 Assessments

10.2.1 Medical History

A medical and surgical history will be taken at Screening. All significant medical history findings that have been present or active within the 5 years prior to screening will be entered into the eCRF. Medical history findings that have not been present within the 5 years prior to screening will be recorded if deemed clinically relevant by the investigator to the conduct of the study.

Additionally, the subject's overall NEA history will be captured at Screening. This includes but is not limited to the approximate date of diagnosis and prior treatment including approximate start and stop dates.

10.2.2 Efficacy

Efficacy response will be assessed by the procedures listed below at the time points mentioned in the schedule of assessments (Table 1).

10.2.2.1 Asthma Related Events

The proportion of patients who experience any of the following asthma related events and time to the asthma related event will be determined:

- ≥6 additional reliever puffs of SABA (compared to baseline) in a 24-hour period on 2 consecutivedays or,
  - Baseline SABA use (defined as the number of individual puffs or inhalations taken by the subject) will be determined by the average use in the 7 days preceding Visit 2,
- increase in ICS dose ≥4 times than the dose at baseline or,
  - Baseline ICS dose is defined as the dosage the subject received during the 30-day run-in period,
- a decrease in peak flow of 30% or more (compared to baseline) on 2 consecutive days of treatment or,
  - Baseline peak flow will be determined by 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 or
- a hospitalization or emergency room visit because of an asthma exacerbation.

Time to event will be measured in days using the first day of the event above to denote the day of the overallasthma related event occurrence.

Subjects meeting any of the above criteria for an asthma related event will be permitted to restart background (pre-study) therapy, or alternate asthma therapy. If background/alternate therapy is reinitiated/started, the patient must be withdrawn from the study.

10.2.2.2 Forced Expiratory Volume in 1 Second (FEV1)

The FEV1 is the volume of air that can be forcibly exhaled from the lungs in the first second, measured in liters by a spirometer and reported as a percent of expected volume.

10.2.2.3 Fractional Exhaled Nitric Oxide (FeNO)

A FeNO test measures the levels of nitric oxide during exhalation. A FeNO test will be done by breathing into a tube attached to a hand-held monitor.

10.2.2.4 Peak Flow Meter

A peak flow meter measures how well 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 site will monitor the diary entries closely to assess subject compliance. Subjects who are not compliant with the diary will be counseled by the site and will be considered protocol deviations if an overall compliance rate of less than 80% is reached.

10.2.2.5 Asthma Control Questionnaire (ACQ)

This is a simple questionnaire to measure the adequacy of asthma control and change in asthma control. ACQ has a multidimensional construct assessing symptoms (5 items, self-administered), rescue bronchodilator use (1 item, self-administered), and FEV1 (1 item, completed by study staff). Scores range between 0 (totally controlled) and 6 (severely uncontrolled) (Juniper et al, 2005).

10.2.2.6 Standardized Asthma Quality of Life Questionnaire for 12 years and older (AQLQ(S)+12)

The AQLQ(S)+12 is a modified version of the standardized AQLQ, which was developed to measure functional impairments experienced by adults aged ≥17 years. The AQLQ(S)+12 is valid for patients aged 12 to 70 years and includes 32 questions in 4 domains (symptoms, activity limitation, emotional function, and environmental stimuli) (Juniper et al, 1992; Wyrwich et al, 2011).

Subjects will be asked to recall their experiences during the previous 2 weeks and score each of the questions on a 7-point scale, where 7=not at all limited and 1=totally limited. The overall score of the AQLQ +12 will be derived as the average of the 32 questions; thus, the total score ranges from 1 (indicates "total impairment") to 7 (indicates "no impairment").

10.2.2.7 Asthma Symptom Diary

The Asthma Symptom Diary is a 6-item daily measure of asthma symptom severity that assesses three core categories of asthma symptoms: breathing symptoms (difficulty breathing; wheezing; shortness of breath), chest symptoms (chest tightness; chest pain), and cough. The Asthma Symptom Diary 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 eveningdiary (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 usingan 11-point numeric rating scale ranging from 0 (‘None’) to 10 (‘As bad as you can imagine’) (FDA, n.d.). The site will monitor the diary entries closely to assess subject compliance. Subjects who are not compliant with the diary will be counseled by the site and will be considered protocol deviations if an overall compliance rate of less than 80% is reached.

10.2.2.8 European Quality of Life – 5 Dimension 5 level Questionnaire (EQ-5D-5L)

The EQ-5D-5L consists of the EQ-5D descriptive system and the EQ visual analogue scale (EQ

VAS). The descriptive system comprises five 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' and 'The worst health you can imagine' (EuroQol, 2017).

10.2.2.9 Patient Global Impression of Change/Severity

The Patient Global Impression of Change or Severity (PGI-C, PGI-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-C is a single question scale asking the patient to rate the overall status of their specific condition on a 7-point scale. The PGI-S is a single questionscale asking the patient to rate current state of their specific condition on a 7-point scale.

10.2.2.10 Clinician Global Impression of Improvement/Severity

The Clinician Global Impression of Improvement or Severity (CGI-I, CGI-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 CGI-I is a single question scale asking clinician to rate the overall status of the patient's specific condition on a 7-point scale since the beginning of the research study. The CGI-S is a single question scale asking the clinician to rate current state of the patient's specific condition on a 7-point scale.

10.2.2.11 Short-Acting Beta Agonist Use

The number of times a short-acting beta agonist (number of inhalations/puffs) is used will be assessed by reviewing the diary maintained by the subject. The site will monitor the diary entries closely to assess subject compliance. Subjects who are not compliant with the diary will be counseled by the site and will be considered protocol deviations if an overall compliance rate of less than 80% is reached.

10.2.3 Safety

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

10.2.3.1 Clinical Laboratory Safety Assessments

10.2.3.1.1 Clinical Laboratory Tests to be Performed

Samples for the following clinical laboratory tests will be collected at the time points specified in the schedule of assessments (Table 1).

Hematology	Hemoglobin, hematocrit, red blood cell count, red blood cell indices, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count (or estimate), and white bloserum od cell count including differential
Serum chemistry	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatine, creatinine phosphokinase, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, calcium, magnesium, phosphorous, lactate dehydrogenase, uric acid, total protein, albumin, C-reactive protein, total cholesterol, high density lipoprotein, LDL, and triglycerides

Serum/urine pregnancy	For females of childbearing potential.
Urinalysis	pH, specific gravity, dipstick determinations of protein, blood, glucose, and ketones
Other	Anti-drug antibody (ADA), serum: soluble LIGHT, inflammatory proteins, immunophenotyping, sputum: soluble LIGHT, Plasma AVTX-002 Pharmacokinetics

Fasting is not required for any study-specific lab sample.

Laboratory specimens will be collected and analyzed at the laboratories specified in the study Laboratory Manual(s) or guidelines.

10.2.3.1.2 Sampled Blood Volume

The sampled blood volume for this study is shown in Table 2.

Table 2: Sampled Blood Volume per Subject

Assessment	Sample Volume (mL)	Number of samples	Total Volume (mL)
Chemistry	3.5	8	28.0
Hematology	2.0	8	16.0
ADA	4.5	7	31.5
Serum LIGHT	3.5	7	24.5
Inflammatory proteins	3.5	5	17.5
Immunophenotyping of circulating immune cells	10.0	3	30.0
Plasma AVTX-002	4.5	7	31.5
Total (approximate)	**31.5**	**45**	**179**

ADA=anti-drug antibody; LIGHT=Lymphotoxin-like, exhibits Inducible expression, and competes with Herpes Virus Glycoprotein D for Herpesvirus Entry Mediator, a receptor expressed by T lymphocytes.

10.2.3.1.3 Specimen Handling Requirements

The transmission of infectious agents may occur through contact with contaminated needles and blood or blood products. Consequently, appropriate blood and body fluid precautions should be employed by all study personnel involved in the collection of blood and handling of specimens in both the clinic and laboratory settings. Refer to current recommendations of the appropriate authorities.

In addition to appropriate handling of subject samples, specific regulations exist regarding the shipment of biologic samples. Procedures and regulations for the packaging and shipping of infectious samples are outlined in the site and/or study laboratory manual. The investigator is responsible for ensuring that all study samples that are to be transported to another location are appropriately packed and shipped per the applicable regulations.

10.2.3.1.4 Evaluation of Laboratory Values

The normal ranges of values for the central laboratory assessments in this study will be provided to each site as part of the lab manual. For assessments performed locally, the normal ranges of values for the local laboratory will be provided to the Sponsor's designee. They will be regarded as the reference ranges on which decisions will be made for the specific site.

If a laboratory value is out of the reference range, it is not necessarily clinically relevant. The investigator must evaluate the out-of-range values and record his/her assessment of the clinical relevance in the subject's source documentation.

All laboratory values which, in the investigator's opinion, show clinically relevant or pathological changes during or after termination of the treatment are to be discussed with the medical monitor, as necessary, and reported as AEs and followed, as described in Section 11.1.1.

All measurements described in this section are recognized standard methods.

10.2.3.2 Clinical Examinations

10.2.3.2.1 Blood Pressure, Pulse Rate, Respiratory Rate, and Temperature

Vital signs, including systolic and diastolic blood pressure, temperature, pulse, respiration rate, height, and bodyweight, will be collected as shown in the schedule of assessments (see Table 1).

Pre-dose vital signs should be taken within 60 minutes before dosing. Post-dose vital signs should be taken at least 60 minutes after dosing, prior to discharge. Additional blood pressure and pulse measurements may be performed, as determined by the investigator, to ensure appropriate monitoring of subject safety and accurate recording of vital sign measurements. Any changes from baseline deemed clinically significant by the investigator are to be recorded as AEs.

10.2.3.2.2 Electrocardiogram

A standard 12 lead ECG will be performed after the subject has been supine for approximately 5 minutes, at time points shown in the schedule of assessments (see Table 1). All ECG recordings will be identified with the subject number, date, and time of the recording and a copy will be included with the subject's source documentation.

All ECG values which, in the investigator's opinion, show clinically relevant or pathological changes during or after termination of the treatment are to be discussed with the medical monitor and reported as AEs and followed, as described in Section 11.1.1.

10.2.3.2.3 Physical Examination, Weight, and Height

A complete physical examination, including measurements of height and weight, will be conducted by a qualified licensed physician, physician's assistant, or a nurse practitioner at Visit 1 through Visit 9/ET (see Table 1). Any clinically significant physical examination findings are to be reported as AEs and followed, as described in Section 11.1.1. Height will be measured only at Visit 1.

10.2.3.3 Adverse Events

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE described below. At each visit, the subject will be allowed time to spontaneously report any issues since the last visit or evaluation.

Any clinically relevant observations made during each visit will also be considered AEs. AEs will

be collected from the time of informed consent through the last study visit.

10.2.4 Immunogenicity Analyses

Blood samples for ADA analysis will be collected at time points shown in the schedule of assessments (see Table 1). The Visit 2 sample is to be collected prior to dosing. Additionally, an ADA sample will be collected if an immunologically related AE is reported. Samples for ADAwill be processed according to the methods and directions set forward in the laboratory manual(s)and guidance(s). ADA sample analysis will be performed by a laboratory defined in the laboratory manual(s) and guidance(s), according to their standard operating procedures (SOPs) using a validated method. Assay and analysis details will be described in the method validation and bioanalytical information.

10.2.5 Pharmacokinetic, Pharmacodynamic and Biomarker Assessments

Blood samples will be collected for assessment of PK, PD activity and mechanism of action of AVTX-002 in NEA.

Blood samples will be used to isolate serum, which will be subjected to analysis of soluble LIGHT levels in circulation using a relevant immunoassay for PD activity measures. Additionally, for a selected subset of sites or subjects, sputum samples will be analyzed for soluble LIGHT levels and gene expression. Biomarkers associated with inflammation such as (including but not limited to) IL-6, IFN-γ, and TNF-α may be evaluated using relevant immunoassays. Serum may be also used for novel biomarkers analyses as the rationale evolves.

Blood samples collected for PBMC isolation may be used for comprehensive immunophenotyping of immune cell subsets in circulation by flow cytometry or CyTOF to study the effects of AVTX-002 on these cell types. Furthermore, transcriptomic analysis may be performed in PBMC as needed.

All these exploratory biomarkers as listed in Table 1 will be performed at the laboratories specified in the laboratory manual(s) and/or guidance(s).

11 ADVERSE EVENTS

11.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

11.1.1 Adverse Event Collection

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the product. An AE can therefore be any unfavorable and unintended sign (including a new, clinically important abnormal laboratory finding), symptom, or disease, temporally associated with the product, whether related to the product. An AE will be considered treatment-emergent if it occurs after the first dose of investigational product and within 28 days of a subject's last dose of investigational product. Additionally, an AE that occurred prior to dosing with study medication and increased in severity after start of dosing and within 28 days of a subject's last dose of investigational product will also be considered treatment emergent.

All AEs are collected from the time of the informed consent is signed until the end of study (Day 98/ET). This includes events occurring regardless of whether investigational product is administered. Note: Clinically significant observations noted during screening procedures (labs, physical examination, vital signs, etc.) should be entered as medical history. Only if the clinically

significant observation is clearly related to the performance of a screening procedure should it be entered as an AE (e.g., a hematoma because of drawing blood for screening labs). Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually.

All AEs must be followed to closure, regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached or stabilization achieved (i.e. the investigator does not expect any further improvement or worsening of the event).When appropriate, medical tests and examinations are performed so that resolution of an event(s)can be documented.

Events that meet the protocol definition of an asthma related event are captured as part of the primary efficacy endpoint for the study, and therefore need not be recorded as an AE unless they meet the definition of an SAE. Asthma exacerbations that do not meet the protocol definition of an asthma related event should be captured as AEs.

An AE that changes in severity over time should be recorded in the eCRF once at the highest severity with two exceptions:

- Worsening of non-NEA-related pre-treatment events after initiation of investigational product must be recorded as new AEs. E.g., if the subject experiences mild, intermittent headachesprior to dosing with investigational product; however, the headache intensity increases to moderate after the first dose of investigational product, a new AE of moderate intermittentheadaches is to be recorded in the source documents and eCRF.
- An AE which begins as a non-serious event, which later meets the definition of an SAE, should be entered once for the non-serious portion of the AE, and then be re-recorded as a new event with the start date the day it became serious.

11.2 Severity of Adverse Events

The medical assessment of clinical severity of an AE will be determined using the definitions outlined in Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 (Published November 27, 2017, by the US Department of Health and Human Services, National Institutes of Health, National Cancer Institute):

Grade 1 Mild; asymptomatic or mild symptoms; or clinical or diagnostic observations only; or intervention not indicated

Grade 2 Moderate; or minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living (ADL)

Grade 3 Severe or medically significant but not immediately life-threatening; or hospitalization or prolongation of hospitalization indicated; or disabling; or limiting self-care ADL

Grade 4 Life-threatening consequences; or urgent intervention indicated

Grade 5 Death related to AE

The above grading guidelines should be used whenever possible. For AEs that cannot be graded using CTCAE, the severity should be graded using mild (Grade 1), moderate (Grade 2), severe (Grade 3), life threatening (Grade 4), and fatal (Grade 5).

Please refer to the above-referenced CTCAE document for full description of CTCAE terms and instrumental and self-care ADLs. It is important to distinguish between severe AEs and SAEs. Severity is a classification of intensity whereas an SAE is an AE that meets serious criteria, as

described in Section 11.2.2.3.

11.2.1 Relationship Categorization

A physician investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related".

Otherwise, the AE should be categorized per the guidelines below. The causality assessment must be documented in the source document and the eCRF (Table 3).

Table 3: Assessment of Relationship to Investigational Product

Relationship	Description
Not Related	Exposure to investigational product has not occurred. *OR* The administration of investigational product and the occurrence of the AE are not reasonably related in time *OR* The AE is considered likely to be related to an etiology other than the use of the investigational product, that is, there are no facts/evidence or arguments to suggest a causal relationship to the investigational product.
Possibly Related	The administration of the investigational product and the occurrence of the AE are reasonably related in time. *AND* The AE could not be explained equally well by factors or causes other than exposure to investigational product
Probably Related	The administration of investigational product and the occurrence of the AE are reasonably related in time. *AND* The AE is more likely explained by exposure to investigational product than by other factors or causes.

AE = adverse event.

11.2.1.1 Outcome at the Time of Last Observation

The outcome at the time of last observation will be classified as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved
- Fatal*
- Unknown

*See Section 11.2.3.

11.2.2 Serious Adverse Events

11.2.2.1 Investigational Product Safety Information

The IB is the reference document for safety information pertaining to this study. The IB is provided separately.

11.2.2.2 Reporting of Serious Adverse Events

Initial and follow-up SAE reports must be completed by the investigator or designee and sent to

the CRO within 24 hours of the first awareness of an SAE. The investigator or designee must complete, sign and date the appropriate SAE form and verify the accuracy of the information against corresponding source documents. This information is to be sent to the CRO Pharmacovigilance Department by e-mail as noted below. For questions on SAE reporting, please e-mail the drug safety mailbox noted below.

- [redacted]

11.2.2.3 Serious Adverse Event Definition

An SAE **is any untoward medical** occurrence, whether considered to be related to investigational product or not, that at any dose:

- **Results in death.**
- **Is life-threatening.**
  NOTE: *The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*
- **Requires inpatient hospitalization or prolongation of existing hospitalization.** NOTE: *Inpatient hospitalization is defined as 24 hours in a hospital or an overnight stay. An elective hospital admission to treat a condition present before exposure to the test drug, or a hospital admission for a diagnostic evaluation of an AE, does not qualify the condition or event as an SAE. Further, an overnight stay in the hospital that is only due to transportation, organization, or accommodation problems and without medical background does not need to be considered an SAE.*
- Results in persistent or significant disability/incapacity.
- **Is a congenital anomaly.**
  NOTE: *A congenital anomaly in an infant born to a mother who was exposed to the investigational product during pregnancy is an SAE. However, a newly diagnosed pregnancy in a subject that has received an investigational product is not considered an SAE unless it is suspected that the investigational product(s) interacted with a contraceptive method and led to the pregnancy.*
- **Is an important medical event.**
  NOTE: *Medical and scientific judgment should be exercised in deciding whether it is appropriate to consider other situations serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.*

11.2.2.4 Serious Adverse Event Collection Time Frame

All SAEs, regardless of the relationship to study, are collected from the time the subject signs the informed consent until the End of Study/Early Termination Visit. The investigator or designee must report all SAEspromptly to CRO within 24 hours of first becoming aware of the event.

Any SAE(s), regardless of relationship to study, which occurred during the study but is not discovered by the site until after the study has been completed must be reported to CRO within 24 hours of the first awareness of the event.Please see individual study site documentation (study binder) for forms and contact details.

11.2.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date an outcome is reached or stabilization is achieved (i.e. the investigator does not expect any further improvement or worsening of the event).

Any signs or symptoms experienced by the subject after signing the informed consent form and assent form (if applicable) or leading up to the onset date of the SAE or following the resolution date of the SAE must be recorded as an AE.

11.2.3 Fatal Outcome

Fatal should only be selected as an outcome when the AE results in death. If more than 1 AE is possibly related to the subject's death, the outcome of death should be indicated for each such AE.

Any AE that results in the subject's death must have fatal checked as an outcome with the date of death recorded as the resolution date. AEs resulting in death must be reported within 24 hours as a SAE, if not already reported as such. In the event of a subject's death, data should be collected on whether the death occurred after the withdrawal of care and, if so, the reason for the withdrawal of care.

For other AEs, ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

11.3 Special Considerations

11.3.1 Pregnancy

All females of childbearing potential, and males with female partners of childbearing potential, who participate in the study should be counseled on the need to utilize a highly effective method of birth control throughout the study and for 28 days following the last dose of study drug, and on the importance of avoiding pregnancy during study participation. A highly effective method of birth control is defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as oral/injectable/inserted/implanted/ transdermal contraceptives, condom with diaphragm, condom with spermicide, diaphragm with spermicide, intrauterine hormone-releasing system or IUD, or sexual abstinence. Contraception is not required where 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 (12 consecutive months of spontaneous amenorrhea and age ≥51 years).

Females and males with female partners should be instructed to contact the investigator or study staff immediately if pregnancy occurs or is suspected.

Pregnancy testing will be conducted on every female as per the schedule of assessments (Table 1). A female who is found to be pregnant at screening will be excluded from the study and considered to be a screening failure. A female who is found to be pregnant after receiving investigational product is required to be discontinued from the study and the end of study visit assessments performed as soon as possible after learning of the pregnancy.

The investigator must report the pregnancy of any female (study participant or female partner of male study participant) who becomes pregnant during investigational product treatment or within 28 days of discontinuing the investigational product (permission must be obtained from the pregnant female partner of a male subject to follow the pregnancy to conclusion and report the results). The pregnancy must be reported within 24 hours of learning of the pregnancy to the CRO

using the Pregnancy Data Collection Form via the same email address as for SAE reporting. The investigator should contact the designated individual(s) who receive pregnancy notification and record information related to the pregnancy on the Pregnancy Form/other designated form provided by the Sponsor or its designee.

The investigator is also responsible for following the pregnancy until delivery or termination. These findings must be reported on the Pregnancy Data Collection Form and forwarded to the designated individual(s). The event meets the SAE criterion only if it results in a spontaneous abortion or a congenital anomaly.

11.3.2 Reporting to Regulatory Agency, Institutional Review Board/Ethics Committee (EC) and Site

The Sponsor or its designee is responsible for notifying the relevant regulatory authorities and if applicable, US central institutional review board (IRB) of related, unexpected SAEs.

In addition, the Sponsor and the CRO are responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the development program.

The investigator is responsible for notifying the local IRB, local ethics committee (EC), or the relevant local regulatory authority of all SAEs that occur at his/her site, as required.

12 STATISTICS

12.1 Sample Size Determination

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

The sample size estimate was based on the estimated proportions of patients in the two treatment groups expected to have an asthma related event as defined by the primary endpoint. In a study with another product, rates of 6% in the active group and 44% in the placebo group were observed (Wenzel, 2013). 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%.

A sample size re-estimation may be performed at a point in time when an adequate number of subjects has been enrolled to provide meaningful data. Details will be provided in the statistical analysis plan.

12.2 Analysis Populations

This study will have the following populations of interest:

- The Randomized Analysis Set will include all subjects who are randomized in the study. Subjects will be categorized according to their randomized treatment group. The Randomized Analysis Set will be used for all disposition, protocol deviations, and demographic and other baseline characteristics analyses.
- The Safety Analysis Set 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 Safety Analysis Set will be used for all exposure and safety analyses and immunogenicity analysis.

- The Full Analysis Set will include all subjects who receive at least one dose of investigational product and have a baseline and at least one post-baseline efficacy assessment. Subjects will be categorized according to their randomized treatment group. The Full Analysis Set will be used for all efficacy and pharmacodynamic analyses.

12.3 Statistical Analyses

This section presents a summary of the planned statistical analyses. Additional details regarding data handling, analytical methods, and presentation of results will be described in the Statistical Analysis Plan (SAP) for this study. The SAP will be finalized prior to database lock.

All efficacy, safety, PD, and ADA variables will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, 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 timepoint of interest. Descriptive statistics for categorical data will include frequency and percentage.

Listings will be provided for all collected study data.

12.3.1 Study Subjects and Demographics

12.3.1.1 Disposition and Withdrawals

The study medication and study disposition of all subjects randomized in this study will be summarized by treatment group and completion/discontinuation status. Subjects who discontinue the study medication and/or study prematurely will be summarized by treatment group and reason for discontinuation. The number of subjects in each analysis set will also be summarized by treatment group. Any subject who receives three doses of AVTX-002 or placebo by definition is considered as completing therapy.

12.3.1.2 Protocol Deviations

All subject data will be reviewed for the occurrence of protocol deviations. Prior to database lock, all protocol deviations will be reviewed and classified with respect to the potential to influence experimental outcomes. Protocol deviations will be summarized by treatment group.

12.3.1.3 Demographics and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by treatment group using descriptive statistics.

12.3.2 Prior and Concomitant Medications

All prior and concomitant medications will be coded using the WHO Drug Dictionary. Prior and concomitant medications will be summarized by treatment group using descriptive statistics.

12.3.3 Exposure and Compliance

Exposure to investigational product will be summarized by treatment group using descriptive statistics.

12.3.4 Safety and Tolerability Analyses

Safety analyses will be conducted using data from the Safety Analysis Set (as defined in Section 12.2). 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.

12.3.4.1 Adverse Events

Adverse event verbatim terms will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The overall incidence of subjects having at least one AE will be summarized by treatment group. The incidence of TEAEs will be summarized by treatment group, system organ class (SOC) and preferred term (PT). Each subject will be counted only once per SOC and preferred term. An AE will be considered treatment-emergent if it occurs after the first dose of investigational product and within 28 days after a subject's last dose of investigational product.

12.3.4.2 Clinical Laboratory Evaluations

For all continuous laboratory test variables, descriptive statistics for all reported values and change from baseline values will be summarized by treatment group and visit.

12.3.4.3 Vital Signs

For all continuous vital sign variables, descriptive statistics for all reported values and change from baseline values will be summarized by treatment group and visit.

12.3.5 Efficacy Analyses

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

All other efficacy variables will be summarized using descriptive statistics. Descriptive statistics for continuous data will include number of subjects (n), mean, standard deviation, 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 timepoint of interest. Descriptive statistics for categorical data will include frequencies and percentages.

Further details regarding all statistical analysis can be found in the study Statistical Analysis Plan (SAP).

12.3.6 Pharmacokinetic, Pharmacodynamic and Biomarker Analyses

For all PK, PD and biomarker variables, descriptive statistics will be presented by treatment group andtime point.

12.3.7 Immunogenicity Analyses

For all immunogenicity variables, descriptive statistics will be presented by treatment group and time point.

12.3.8 Interim Analysis

No formal interim analysis is planned for this study.

13 STUDY CONDUCT

Steps to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study sites, review of protocol procedures with the investigator and associated personnel prior to the study, periodic monitoring visits, and meticulous data management.

13.1 Sponsor and Investigator Responsibilities

13.1.1 Sponsor Responsibilities

The Sponsor is obligated to conduct the study in accordance with strict ethical principles (Section 15). The Sponsor reserves the right to withdraw a subject from the study (Section 8.7), to terminate participation of a study site at any time (Section 13.5), and/or to discontinue the study (Section 13.4).

The Sponsor agrees to provide the investigator with sufficient material and support to permit the investigator to conduct the study per the study protocol.

13.1.2 Investigator Responsibilities, Protocol Adherence, and Investigator Agreement

By signing the Investigator's Agreement, the investigator indicates that she/he has carefully read the protocol, fully understands the requirements, and agrees to adhere to the protocol as detailed in this document.

The investigator also agrees to conduct this study in accordance with all laws, regulations, and guidelines of the pertinent regulatory authorities, including and in accordance with the April 1996 International Council for Harmonisation (ICH) Guidance for Industry E6 GCP and in agreement with the 1996 Version of the Declaration of Helsinki. While delegation of certain aspects of the study to sub-investigators and study coordinators is appropriate, the investigator will remain personally accountable for closely overseeing the study and for ensuring compliance with the protocol and all applicable regulations and guidelines. The investigator is responsible for maintaining a list of all persons that have been delegated study-related responsibilities (e.g., sub-investigators and study coordinators) and their specific study-related duties.

Investigators should ensure that all persons who have been delegated study-related responsibilities are adequately qualified and informed about the protocol, investigational products, and their specific duties within the context of the study. Investigators are responsible for providing the Sponsor with documentation of the qualifications, GCP training, and research experience for themselves and their staff as required by the Sponsor and the relevant governing authorities.

To ensure compliance with the guidelines, the study may be audited by an independent person. The investigator agrees, by written consent to this protocol, to cooperate fully with compliance checks by allowing access to all study documentation by authorized individuals.

Per local laws and regulations, the investigator, Sponsor, or designee will communicate with the IRB/EC to ensure accurate and timely information is provided throughout the study.

13.2 Study Documents

All documentation and material provided by the Sponsor for this study are to be retained in a secure location and treated as confidential material.

13.2.1 Case Report Forms

By signing the Investigator's Agreement, the investigator agrees to complete the eCRFs and maintain source documentation as part of the case histories for all subjects who sign an ICF.

Case report forms are considered confidential documents and should be handled and stored accordingly. The Sponsor or its designee will provide the necessary training on the use of the specific eCRFs used during the study to ensure that the study information is captured accurately and appropriately.

To ensure data accuracy, eCRF data for individual subject visits should be completed as soon as possible after the visit. All requested information must be entered in the eCRF per the completion guidelines provided by the Sponsor or its designee. All data will have separate source documentation; no data will be recorded directly into the eCRF.

The eCRFs will be signed by the investigator or a sub-investigator to whom this authority has been delegated. These signatures serve to attest that the information contained in the eCRF is accurate and true.

13.2.2 Recording and Retention of Source Data and Study Documents

All study information must be recorded in the subject's medical records and no data will be recorded directly onto the eCRF. Data recorded in the eCRF must be supported by corresponding source documentation. Examples of acceptable source documentation include, but are not limited to, hospital records, clinic and office charts, laboratory reports and notes, and recorded data from automated instruments, memoranda, and pharmacy dispensing records.

13.3 Data Quality Control

The Sponsor and its designees will perform quality control checks on this clinical study.

13.3.1 Access to Study and Source Documents

The Sponsor and/or designee will conduct site visits to monitor the study and ensure compliance with the protocol, GCP, and applicable regulations and guidelines. The consent form includes a statement by which the subject agrees to the monitor/auditor from the Sponsor or its representatives, national or local authorities, or the IRB/EC, having access to the source data (for example, subject's medical records, appointment books, original laboratory reports, radiographic exams, and reports, etc.)

The assigned CRA(s) will visit the investigator and study site at periodic intervals and maintain periodic communication. The investigator agrees to allow the CRA(s) and other authorized Sponsor personnel access. The CRA(s) will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. While on site, the CRA(s) will review:

- Regulatory documents, directly comparing entries in the eCRF with the source documents.
- Consenting procedures.
- Adverse event procedures.
- Storage and accountability of study materials.
- Storage and accountability of investigational product (performed by the unblinded CRA).

The CRA will ask for clarification and/or correction of any noted inconsistencies. Procedures for correcting eCRFs will be described for the study personnel as part of training. As representatives of the Sponsor, CRAs are responsible for notifying project management of any noted protocol deviations.

By signing the Investigator's Agreement, the investigator agrees to meet with the CRA(s) during

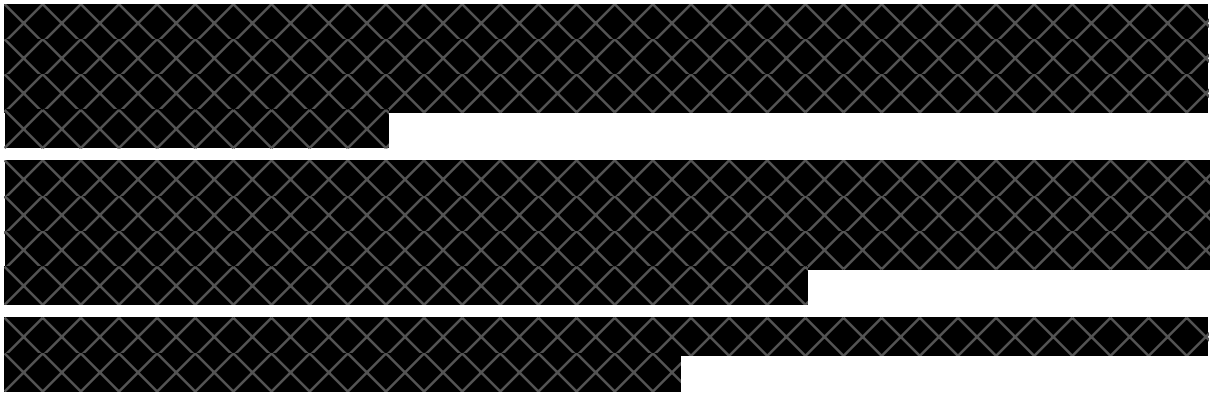
study site visits; to ensure that study staff is available to the CRA(s) as needed, to provide the CRA(s) access to all study documentation, to the clinical supplies dispensing and storage area, and to assist the monitors in their activities, if requested. Further, the investigator agrees to allow the Sponsor or designee auditors or inspectors from IRBs/ECs or regulatory agencies to review records and to assist the inspectors in their duties, if requested.

13.3.2 Data Management

The Sponsor or designee will be responsible for activities associated with the data management of this study. The standard procedures for handling and processing records will be followed per GCP and the designee's SOPs. Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. A comprehensive data management plan will be developed including a data management overview, database contents, annotated eCRF, self-evident correction conventions, and consistency checks.

Study site personnel will be responsible for providing resolutions to all data queries. The investigator will be required to document electronic data review to ensure the accuracy of the corrected and/or clarified data. Procedures for soliciting and documenting resolution to data queries will be described.

13.3.3 Quality Assurance Audit / Inspection



13.4 Study Termination

The study may be terminated at the Sponsor's discretion at any time and for any reason.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the Sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will return all investigational product, containers, and other study materials to the Sponsor.

13.5 Study Site Closure

At the end of the study, all study sites will be closed. The Sponsor may terminate participation of a study site at any time. Examples of conditions that may require premature termination of a study site include, but are not limited to, the following:

- Noncompliance with the protocol and/or applicable regulations and guidelines.
- Inadequate subject enrollment.

13.5.1 Record Retention

It is the investigator's responsibility for maintaining adequate and accurate study and medical records. The investigator shall retain and preserve 1 copy of all data generated during the study, specifically including, but not limited to, those defined by ICH GCP as essential until:

- At least 2 years after the last marketing authorization for the investigational product has been approved or the Sponsor has discontinued its research with the investigational product, or
- At least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the Sponsor.

At the end of such period, the investigator must notify the Sponsor in writing of her/his intent to move and/or destroy any study material. Approval from the Sponsor must be granted prior to any action being taken.

13.5.2 Sample Retention

All samples will be retained according to applicable SOPs and regulations. Blood samples may be stored and used for further analysis related to this research.

13.6 Changes to the Protocol

This protocol cannot be altered or changed except through a formal protocol amendment, which requires the written approval of the Sponsor. The protocol amendment must be signed by the investigator and approved by the IRB before it may be implemented. Protocol amendments will be filed with the appropriate regulatory agency(ies) having jurisdiction over the conduct of the study.

13.7 Use of Information and Publication

All information concerning AVTX-002, Sponsor operations, patent applications, formulas, manufacturing processes, basic scientific data, and formulation information supplied by of the Sponsor or designee to the investigator and not previously published, is considered confidential and remains the sole property of the Sponsor. Case report forms also remain the property of the Sponsor. The investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by the Sponsor in connection with the continued development of AVTX-002 and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

The information generated by this study is the property of the Sponsor. Publication or other public presentation of AVTX-002 data resulting from this study requires prior review and written approval of the Sponsor. Abstracts, manuscripts, and presentation materials should be provided to the Sponsor for review at least 30 days prior to the relevant submission deadline.

It is agreed that the results of the study will not be submitted for presentation, abstract, poster exhibition or publication by the investigator until of the Sponsor has reviewed and commented on such a presentation or manuscript for publication.

14 PUBLIC POSTING OF STUDY INFORMATION

The Sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigator information (e.g., site name, investigator name, site location, site contact information).

15 ETHICAL AND LEGAL CONSIDERATIONS

15.1 Declaration of Helsinki and Good Clinical Practice

This study will be conducted in compliance with the protocol, the April 1996 ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the 1996 Version of the Declaration of Helsinki, and the applicable regulations of the country(ies) in which the study is conducted.

15.2 Subject Information and Informed Consent

It is the responsibility of the investigator to ensure that written informed consent is obtained from the subjects before any activity or procedure is undertaken that is not part of routine care including baseline assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject is requested to sign and date the subject informed consent or a certified translation, if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, included but not limited to: the objectives, potential benefits and risks, inconveniences, and the subject's rights and responsibilities. A signed copy of the informed consent and assent documentation (if applicable [such as a complete set of subject information sheets and fully executed signature pages]) must be given to the subject. This document may require translation into local language. Signed consent/assent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the Sponsor with a copy of the consent and assent (as applicable) form which was reviewed by the IRB/EC, and which received favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the Sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national requirements) prior to the study start that another party (such as the Sponsor or coordinating principal investigator) is responsible for this action. If the IRB/EC requires modification of the sample subject information and consent document provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

15.3 Institutional Review Board or Ethics Committees

A properly constituted, valid IRB/EC according to local laws and regulations must review and approve the protocol, the investigator's informed consent and assent (as applicable) document, and related subject information and any other study materials requiring review (such as recruitment information) before the start of the study.

Until written approval by the IRB has been received by the investigator, no subject may undergo any study procedure solely for determining eligibility for this study. Investigational product will

not be released until the Sponsor, or its designee has received written IRB/EC approval.

Prior to implementing changes in the study, the Sponsor and the IRB/EC must approve and provide documentation of favorable opinion/approval of any revisions to informed consent documents and amendments to the protocol unless there is a subject safety issue.

Depending on location (outside European Union [EU] or inside EU) the IRB/EC will be apprised of the progress of the study and of any changes made to the protocol at least yearly. This may be done by the investigator (outside EU and in some cases, inside EU) or the Sponsor (in some cases inside EU). These updates include information on any serious or significant AEs.

Upon study completion, the investigator will provide the IRB/EC with final report/summary as required.

15.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after where the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the Sponsor. The following information is collected: any significant payments from Sponsor or subsidiaries such as grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consulting or honoraria; any proprietary interest in investigational product; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 (b) (1998).

15.5 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the Sponsor/CRO.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to participate in a study, the Sponsor and/or its representatives reviews their medical records and data collected as part of the study. These records and data may be reviewed by others including the monitor/auditor from the Sponsor or its representatives, national or local authorities, or the IRB/EC which gave the approval for the study, third parties with whom the Sponsor may develop, register, or market the investigational product. The Sponsor and its representatives will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, the initials and date of birth may also be collected and used to assist the Sponsor to verify the accuracy of data.

The results of the studies, containing the subjects' unique identifying number, relevant medical records and possibly initials and dates of birth, will be recorded. They may be transferred to and used in other countries which may not afford the same level of protection that applies within the countries where the study is conducted. The purpose of such transfer would include supporting

regulatory submissions, to conduct new data analyses to publish or present the study results or to answer questions asked by regulatory or health authorities.

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INVESTIGATOR'S AGREEMENT

PROTOCOL NUMBER:	AVTX-002-NEA-201
PROTOCOL 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
FINAL PROTOCOL:	17 Oct 2022

I have read this protocol and agree to conduct this clinical trial as outlined herein. I will ensure that all subinvestigators and other study staff members have read and understand all aspects of this protocol. I agree to cooperate fully with Avalo Therapeutics, Inc., and designee during the study. I will adhere to all FDA, ICH, and other applicable regulations and guidelines regarding clinical trials on an investigational product during and after study completion.

Principal Investigator:

Printed Name: _____

Signature:

Date: _____