Statistical Analysis Plan

An investigator-initiated, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the safety, tolerability, and efficacy of an alternative injection site and associated adjustments to dosing and treatment regimen for allergen immunotherapy with a commercially-available, FDA-approved allergenic extract for the immunotherapy treatment of allergic rhinitis and conjunctivitis due to pollen from the conifer Mountain Cedar.

Study number: TASC-ILIT-MC-2018

TX-SMILE: TeXan Allergy & Sinus Center Mountain Cedar Intra-Lymphatic ImmunothErapy Study

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ABBREVIATIONS:

AE	Adverse Event
CRF	Case Report Form
ITT	Intent-to-Treat
SAP	Statistical Analysis Plan
ICH	International Conference on Harmonization
PP	Per Protocol
ILIT	Intralymphatic Immunotherapy
FDA	Food & Drug Administration
PBO	Placebo
TLF	Tables, listings, and figures
TCS	Total combined score
DSS	Daily symptom score
DMS	Daily medication score
TSS	Total safety score

Statistical Analysis Plan

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for the TX-SMILE study, number TASC-ILIT-MC-2018, an investigator-initiated, multi-center, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the safety, tolerability, and efficacy of an alternative injection site and associated adjustments to dosing and treatment regimen for allergen immunotherapy with a commercially-available, FDA-approved allergenic extract for the immunotherapy treatment of allergic rhinitis and conjunctivitis due to pollen from the conifer Mountain Cedar.

This investigation is a phase 2 proof-of-concept study to evaluate an alternative injection site location (inguinal lymph node versus subcutaneous injection into the upper aspect of the arm) with an associated reduction in the extract dose and number of injections required for treatment of seasonal allergic rhinitis and conjunctivitis due to the conifer Mountain Cedar using an FDA-approved, commercially available product, Mountain Cedar pollen allergenic extract (ALK-Abelló, Inc., Port Washington, NY 11050; US Government License No. 1256).

The structure and content of this SAP is intended to provide sufficient detail to meet the requirements identified by the Food and Drug Administration (FDA) and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): E9 Guidance on Statistical Principles in Clinical Trials. All work planned and reported for this SAP will follow accepted guidelines and standards, as published by the American Statistical Association.

The following documents were reviewed as the basis for preparation of this SAP;

- Clinical Study Protocol TASC-ILIT-MC-2018
- Case Report Form (CRF) for TASC-ILIT-MC-2018
- ICH E9 Guidance on Statistical Principles for Clinical Trials
- ICH E6 Structure and Content of Clinical Study Reports
- ICMJE Recommendations for Manuscript Preparation
- CONSORT Statement and Checklist for Reporting Clinical Trial Results

The reader of this SAP is encouraged to read the clinical study protocol for additional details on the conduct and operations of the study. Discrepancies between definitions

or explanations between the SAP and protocol will be described. For analytic purposes, definitions in the SAP will prevail.

2. STUDY OBJECTIVE(S), TREATMENTS, AND ENDPOINT(S)

2.1 Study Objective(s)

The TX-Smiles study protocol defined six objectives for the clinical trial, which are as follows:

1. To evaluate the systemic safety of ILIT for Mountain Cedar pollinosis relative to intranodal injections of placebo control based on the proportion of subjects receiving allergenic extract versus the proportion of subjects receiving placebo:
    1.1. experiencing anaphylaxis, or
    1.2. treated with epinephrine, or
    1.3. Experiencing any other treatment-emergent, serious adverse event (SAE) within 60 minutes of the procedure.

2. To evaluate the safety profile of ILIT versus placebo using a standardized scoring system for systemic AEs of interest (AEIs) up to 60 minutes post-procedure

3. To evaluate the efficacy of ILIT relative to placebo during the 2018-2019 Texas Mountain Cedar allergy season as assessed by the daily total combined score (TCS), a composite of the Daily Symptoms Score (DSS) and Daily Medication Score (DMS).

4. To evaluate the tolerability of ILIT using a patient-reported outcome measure

5. To assess the patients' self-reported satisfaction with treatment at the end-of-study.

6. To assess the induction of tolerance to the causative allergen using allergen-specific serum IgE testing

2.2 Treatment Comparisons

2.2.1 Treatment Abbreviations for Data Display

This study included two groups into which patients were randomly allocated in a 1:1 ratio. The active, intralymphatic immunotherapy group, which received a series of three (3) injections of 0.1 mL of the allergenic extract of Mountain Cedar Pollen (ALK-Abelló, Inc., Port Washington, NY 11050; US Government License No. 1256). This group will be denoted as "ILIT" in tables, listings and figures/graphs. ILIT is an abbreviation for "Intralymphatic Immunotherapy".

The control group in this study was treated with a series of three (3) injections of 0.1 mL of diluent as placebo control, which was sterile saline solution containing 0.4% phenol as a preservative (ALK-Abelló, Inc., Port Washington, NY). This group will be denoted as "PBO" in tables, listings and figures/graphs. PBO is an abbreviation for "placebo."

2.3 Study Endpoints

The endpoints defined for this study are as follows:

Primary Efficacy Endpoint:

1. Average daily TCS during the 2018-2019 Mountain Cedar pollen season

Secondary Efficacy Endpoints:

1. Proportion of days during pollen season for which active patients experience a lower TCS than placebo patients
2. Patient reported pain or discomfort immediately after and 30 minutes post ILIT procedure
3. Patient-reported treatment satisfaction at the end of the study
4. Reduction in skin reactivity assessed using allergenic-specific serum IgE testing from pre-treatment to post-treatment (the end-of-study visit)

Exploratory Endpoints:

1. Use of rescue inhalers by patients with stable asthma

Safety Endpoints:

1. Proportion of subjects experiencing a serious, treatment-emergent AE up to 60 minutes after an intranodal injection procedure
2. Proportion of subjects experiencing systemic reactions to ILIT relative to placebo and severity of reactions relative to placebo as assessed by the Total Safety Score (TSS)
3. Proportion of subjects reporting local injection site reactions relative to placebo and severity of local reactions relative to placebo, as assessed by the TSS

4. STUDY DESIGN

TASC-ILIT-MC-2018 is a randomized, double-blind, parallel-group, placebo-controlled study.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Significance Level and Power

To determine sample size, the following were assumed:

- Tests will be two-sided and performed at the $\alpha = 0.05$ significance threshold
- Study participants will complete the diary assessments (DSS, DMS) to yield a daily TCS on at least 50% of the possible days during the allergy season
- The difference between the average daily TCS for the placebo group and the ILIT group will 8.0 with an assumption that the standard deviation of the average daily TCS is 9.0 across both groups
- The randomization will be 1:1
- Using a priori samples size for multiple linear regression with an effect size 0.50 (f^2) for the active treatment group
- The screen failure rate is estimated to be approximately 12%

- A total of 26 screened patients will be required to enroll a total of 23 subjects into this two-treatment parallel-design study (up to 16 per group), the probability is 80% that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is a 0.50 effect size under multiple linear regression with two predictors (Soper, D.S. (2018). A-priori Sample Size Calculator for Multiple Regression [Software]. Available from http://www.danielsoper.com/statcalc).

5.2. Definition of Clinical Relevance

The total symptom score (TCS) is the primary efficacy endpoint and a composite of the DSS and DMS for the peak allergy season, following the method of Blaiss and colleagues (Blaiss et al., 2010). This approach is consistent with EAAAI (Pfaar et al., 2014), FDA (Guideline Allergic Rhinitis: Developing Drug Products for Treatment Guidance for Industry, Draft Guidance Feb 2016), and WAO recommendations for use of an integrated efficacy assessment of both symptoms and medication usage. The advantages and disadvantages of the total combined score approach are outlined in Pfaar et al 2014, the EAAAI position paper on the development of allergy treatments. This tool integrates well characterized and validated symptoms measures of rhinoconjunctivitis on a 0-3 point scale where 0 = no symptoms; 1 = mild symptoms (sign/symptom clearly present, but minimal awareness; easily tolerated); 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable); and, 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping). By integrating this with measures of rescue

medication use, the combined burden of symptoms and treatment are calculated. Previous studies have reported differences in the TCS in the range of 1 to 8 units. A difference of 1 on the TCS corresponds to reducing a single mild symptom to absent, while a difference of 6 corresponds to not needing a daily anti-histamine or the complete reduction of two symptoms from severe to not present. A large pivotal study by Blaiss et al., formed the basis for approval of oral grass pollen immunotherapy based on a 1.5 point difference on the TCS between active and placebo groups at a significance level of $p = 0.001$.

6. ANALYSIS POPULATIONS

The populations as defined below were used in study summaries and analyses.

Intent-to-Treat (ITT) Analysis Dataset: will include all consented participants and be used for subject listings and demographics tables.

Modified Intention-to-Treat (MITT) Analysis Dataset: will include all consented participants who received at least one (1) study intervention (intralymphatic injection) and completed at least one (1) complete daily e-diary assessment and be used for production of efficacy tables, subject listings, and demographics tables.

Safety Analysis Dataset: will include all participants who took received at least one (1) dose of study intervention (intralymphatic injection) regardless of whether they provided any diary data and will be used for safety tables and tolerability tables.

Per-Protocol (PP) Analysis Dataset: will include the subset of participants in the MITT data set who received three study treatment injections and completed at least one e-diary responses during the allergy season (defined below), and had no other major protocol violations, and will be used for production of supplementary efficacy tables and analyses.

Additional exploratory datasets for sub-populations and post hoc analysis will include the adjusted per protocol dataset (aPP-IgE) for baseline serum IgE, which is the PP datset subset of patients with baseline levels of mountain cedar-specific serum IgE greater than 0.3 (definitively positive) and the aPP subset for controlled asthma (aPP-A), if there are sufficient numbers of patients with confirmed, controlled asthma at baseline.

The mountain cedar pollen season will be defined from the first date of a mountain cedar pollen count greater than or equal to 100 ppm thru the date with a pollen

count greater than or equal to 100 ppm followed by five consecutive days with a pollen count below 100 ppm during the Winter 2018-2019 mountain cedar pollen season in Central Texas.

6. CONSIDERATIONS FOR DATA ANALYSIS

6.1 Programming Environment

Data analysis will be conducted in R Studio version 1.1.456 and Python 3.7 using Spyder 3.3.3. Both systems will be run inside Anaconda Navigator.

6.2 Multicenter Studies

Although originally planned as a multicenter study to accommodate the possibility that pollen counts would vary significantly between areas, all patients were enrolled from the Austin, Texas area at the Austin, Texas site, site 001. Because this was a single-center study, no by site analysis will be conducted.

6.3 Strata and Covariates

The primary efficacy analyses on the daily symptom and medication scores (DSS, DMS) and Total Combined score will be examined in relation to the baseline Mountain Cedar-specific serum IgE level as an explanatory covariate using either a linear mixed model or stratified into low and high baseline serum IgE immunoreactive groups.

6.4 Subgroups

There are two potential subgroups of interest. The first subgroup of interest is subjects with controlled asthma identified in their baseline medical history. The second subgroup of interest is patients with other allergies identified in their baseline medical history. In both cases, it is anticipated that there will be few subjects enrolled and thus statistical tests will not be performed on subgroups due to small number of expected subjects. However, if there are sufficient numbers patients enrolled in the study across both treatment arms, subgroups will be examined for exploratory analysis.

Subgroup analyses for efficacy and safety may be conducted for dichotomized sub-groups based on sex (M/F) and age (18-65 years versus / >65 years). Sub-

group analysis will be exploratory. Identification of additional co-variates and use of additional co-variates in regression models will be considered exploratory.

6.6 Significance level

For prespecified analysis, a significance level of $p < 0.05$ will be used. However, as an exploratory, proof-of-concept study, p-values will be reported for parametric and non-parametric tests.

6.7 Multiplicity

There is a single primary endpoint, with a single primary hypothesis test, so no adjustment for multiplicity is needed for the primary endpoint.

To adjust for multiplicity among the secondary endpoints, a fixed testing order will be used. The secondary endpoints will be tested in the pre-specified order, if the primary endpoint is found to statistically significant. Testing will proceed to the next endpoint if the preceding endpoint is found to be statistically significant at the 5% (two-sided) level. The moment an endpoint is found not to be significant at the 5% (two-sided) level, all remaining endpoints will be considered exploratory, instead of confirmatory. No adjustment for multiplicity will be made for the exploratory endpoints.

The Holm-Bonferroni correction will be used for pre-specified multiple comparisons due to correlation between endpoints based on the TCS.

7. DATA HANDLING METHODS

7.1 Missing Data

No imputations for missing days of diary.

7.2 Premature Discontinuation

Not applicable.

7.3 Visit Windows

Visit windows and checks are based on the following table:

Screening Visit	Treatment Visit 1[c]	Treatment Visit 2	Treatment Visit 3	Patient Diary	End-of-Study Visit 4
Day -21 to Day 1	Day 1	Day 28 +/-3	Day 56 +/-6	Approx. Dec 2018 to March 2019	March – April 2019

7.4 Data Derivations

The following derivations will be made to produce analysis datasets.

1) Age at enrollment = Date of Enrollment – Date of birth
2) Total Combined Score: see below
3) Cumulative Safety Score: See below

Total Combined Score (TCS) is the sum of the daily symptom scores (DSS) and daily medication scores (DMS) for rhinoconjunctivitis. TCS will be calculated for each patient on each day that a diary result is available.

Daily Symptom Score (DSS) is derived from the patient diary according to the following rubric.

	no symptoms = 0	mild symptoms = 1	moderate symptoms = 2	severe symptoms = 3
1. runny nose				
2. stuffy nose				
3. sneezing				
4. itchy nose				
5. gritty/itchy eyes				
6. watery eyes				

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Total DSS = Sum of individual symptoms scores.

Daily Medication Score (DMS) is derived from the patient diary according to the following rubric.

	No	Yes	
Did you use an oral antihistamine (Zyrtec) today?			If yes, score = 6
Dis you use antihistamine eye drops (olopatadine) today?			If yes, score = 6
Did you use a nasal corticosteroid (Flonase) today?			If yes, score = 8

Total DMS = Sum of scores for medical use reported on each day.

Thus, for each patient on each day during the allergy season is TCS = DSS + DMS. Since all patients were instructed to take a daily oral anti-histamine, the expected lower-bound for the TCS is a score of 6.

Total Safety Score – Each patient will receive a calculated Safety Score at each Treatment Visit (1, 2, and 3) based on the key below. A cumulative Safety Score for each patient will be calculated from the sum of the Safety Score at each visit. The Total Safety Score for a treatment group will be the sum of the cumulate Safety Score for each patient in the assigned group (ILIT or PBO).

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Subject ID:
Injection # (write in 1, 2, or 3):

RECORDING INSTRUCTIONS: Mark/code the box(es) indicating reactions experienced by this subject following injection (D = definitely related to study, P = probably related to study, N = not related to study)

ILIT protocol defined grading scale for severity# of adverse events			
	Mild	Moderate	Severe
LOCAL REACTIONS			
Lymph node swelling			
Itch			
Redness			
Other*			
SYSTEMIC REACTIONS			
Rhinorrhea			
Sneezing			
Dyspnea			
Cough			
Wheeze			
Pruritus			
Rash			
Angioedema			
Nausea			
Vomiting			
Diarrhea			
Headache			
Other*			

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Safety Scoring Key	
Reaction	Point value
None	0
Local - if any marks in white boxes	1
Systemic mild (WAO Grade 1/2) - if any marks in green boxes	2
Systemic moderate (WAO Grade 3) - if any marks in yellow boxes	3
Systemic severe (WAO Grade 4) - if any marks in red boxes	4

Severity will be determined by study staff. Local reactions will be divided into: 1) mild: events require minimal or no treatment and do not interfere with the patient's daily activities; 2) moderate: events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning; 3) severe: events interrupt a patient's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating. Systemic reaction severity will be based on the World Allergy Organization grading for systemic allergic reactions (mild = grades 1/2, moderate = grade 3, severe = grade 4/5).

*Will be specified if unexpected, unlisted reaction occurs.

7. STUDY POPULATION

Subject disposition information for the total analysis dataset will be generated. Descriptive statistics will be generated in summary tables comparing the active treatment and placebo groups across demography, baseline MQT results, comorbid allergic asthma, duration of Mountain Cedar pollen allergy, number of baseline concomitant medications for the ITT, MITT, PP, and Safety datasets. Nominal variables will be described by number and percentages of patients in each category. Quantitative variables will be described using means, standard deviations and percentiles, as appropriate. Number and percentage of missing values will be tabulated and reported, as appropriate.

7.1. Subject Disposition

Subject disposition from screening, enrollment, treatment, thru to drop-out or completion will be presented in tabular format. Subject enrollment start and end dates will be reported by site.

8.2 Protocol Violations

A listing of protocol deviations/violations will be produced.

8.3 Demographic Characteristics

Demographic variables (e.g., sex, age, ethnic origin, and race) will be summarized by descriptive statistics (count and percentage only) using tabular format.

8.4 Medical History

Patients with other allergies by group and with controlled asthma by group will be summarized in tabular format. Clinically significant medical history will be reported by group and organ system.

8.5 Physical Exam

Clinically significant findings on physical exams before and after completion of the study will be reported in tabular format by organ system.

8.6 Treatment Compliance

Listing of patients by treatment visit with dates and windows will be produced.

9. EFFICACY ANALYSIS

9.1 Primary Efficacy Analysis

Objective: To evaluate the efficacy of ILIT relative to placebo during the 2018-2019 Texas Mountain Cedar allergy season as assessed by the daily total combined score (TCS), a composite of the Daily Symptoms Score (DSS) and Daily Medication Score (DMS).

Endpoint: Average daily TCS during the 2018-2019 Mountain Cedar pollen season

Population: The per protocol dataset, which includes participants who received three study treatment injections and completed at least 50% of expected electronic diary responses during the allergy season, with no major protocol violations.

Analysis Period: The analysis period will be peak mountain cedar pollen season in the local area, defined as the period when the first cedar pollen count was above 100 ppm to the last date pollen was above 100 ppm followed by more than five (5) consecutive days with a count below 100 ppm.

Statistical Testing Method and Considerations: The TCS is a repeated measure, but statistical comparisons were between group average TCS scores during peak season. Between group comparisons will be made using either ANOVA, a parametric test, if the underlying data distribution supports use of parametric testing, otherwise the comparison will be made using a non-parametric test, the Kruskal-Wallis test, based on rank order.

9.2 Secondary Efficacy Analyses

Objective: To evaluate the proportion of days during pollen season for which active patients experience a lower TCS than placebo patients.

Endpoint: The percentage of days during peak pollen season for which the group average TCS score was lower in the immunotherapy group versus placebo control.

Population: The per protocol dataset.

Analysis Period: The analysis period will be peak mountain cedar pollen season in the local area, defined as the period when the first cedar pollen count was above 100 ppm to the last date pollen was above 100 ppm followed by more than five (5) consecutive days with a count below 100 ppm.

Statistical Testing Method and Considerations: The Clopper-Pearson binomial exact test of difference of proportions will be used for this comparison using the Holm-Bonferroni correction for multiple tests due to correlation between endpoints based on the same underlying TCS data.

9.3 Exploratory Analyses

Exploratory analyses, including sensitivity analyses for baseline covariates will not be subject to correction for multiple testing.

1. Objective: To evaluate patient reported pain or discomfort immediately after and 30 minutes post ILIT procedure

   Endpoint: Average pain score reported on the NRS-11 immediately after and 30-minutes after ILIT procedure.

   Population: The per protocol dataset.

   Analysis Period: The NRS-11 was administered immediately and 30-minutes after each injection during the treatment period.

   Statistical Testing Method and Considerations: Average score at both time periods will be pooled by group across treatment visits. Between group comparisons will be made using the Mann-Whitney test.

2. Objective: To assess patient-reported treatment satisfaction at the end of the study

   Endpoints: The patient-reported treatment satisfaction at the end of the study, a binary, yes-no question from the Patient Experience Questionnaire, a

validated rating scale and the Patient Global Impression – Improvement, a seven-Likert rating scale ranging from “Very much better” to “Very much worse”.

Population: Per protocol dataset

Statistical Testing Method and Considerations: For the PEQ, a dichotomous variable, between group testing will be performed using a paired-samples t-test. For the PGI-I, between group comparisons will be performed using the Wilcoxon rank sum test.

3. Objective: To assess changes in mountain cedar allergen-specific serum IgE testing from pre-treatment to post-treatment (the end-of-study visit).

   Endpoint: Changes in laboratory-reported mountain-cedar specific serum IgE levels between screening and post-treatment.

   Population: Per protocol dataset

   Statistical Testing Method and Considerations: As a continuous positive variable, changes in serum IgE will be analyzed using Welch’s 2-sample t-test.

4. Objective: Use of rescue inhalers by patients with stable asthma

   Endpoint: Counts of rescue inhaler uses by group.

   Population: Per protocol dataset.

   Statistical Testing Method and Considerations: Enrollment was not stratified on the presence of stable asthma. In the event that sufficient numbers of asthmatic patients are included in both study groups, then the count of inhaler events are will be examined. Formal hypothesis testing is not anticipated due to the low expected sample size and lack of stratification.

9.3 Other Efficacy Analyses

Efficacy analysis will be repeated on the subset of the PP dataset that was positive for allergic asthma at baseline. In addition, this subset will be assessed for differences in frequency of rescue inhaler use. Safety assessments may be repeated as exploratory using allergic asthma as a baseline co-variate. The use of immunologic response on end-of-study serum IgE testing may be used for exploratory correlative analysis of primary and secondary efficacy outcomes measured by the TCS. Additional predictors in the efficacy analysis multiple regression model will be assessed, including baseline allergen-specific serum IgE levels.

9.3.1 Laboratory Evaluations

To assess the induction of tolerance to the causative allergen using allergen-specific serum IgE testing changes (reduction) in mountain-cedar specific serum IgE reactivity will be assessed from pre-treatment to post-treatment (the end-of-study visit) as noted above in section 9.2. This is the only planned laboratory analysis.

10. SAFETY ANALYSIS

Safety analyses will compare treatment groups using appropriate methods according to their nominal or quantitative nature and will include descriptive statistics rather than formal hypothesis testing for noninferiority due to the small overall sample size. The study included a formal stopping rule in the event two systemic allergic reactions were detected.

The total safety score (TSS) and proportion of subjects with any treatment-emergent SAE, as defined in the composite safety endpoint, will be assessed using the Mann-Whitney test. Data will be presented in the form of descriptive statistics and appropriate tables and graphs with a conclusion on whether the significance level allowed the null hypothesis for each test to be rejected.

Safety Objective: To evaluate the safety profile of ILIT versus placebo using a standardized scoring system, the Total Safety Score worksheet, for AEs of interest (AEIs) up to 60 minutes post-procedure.

Safety Endpoints:

- Proportion of subjects experiencing a serious, treatment-emergent AE up to 60 minutes after an intranodal injection procedure
- Proportion of subjects experiencing systemic reactions to ILIT relative to placebo and severity of reactions relative to placebo as assessed by the Total Safety Score (TSS)
- Proportion of subjects reporting local injection site reactions relative to placebo and severity of local reactions relative to placebo, as assessed by the TSS

Additional safety tables and listings will include summaries of all patients experiencing anaphylaxis or treated with epinephrine, by group and a table of TSS reactions by severity by group.

Safety Population:

Safety analysis will include all participants who received at least one dose of study intervention regardless of whether they provided any diary data.

Calculation cumulative safety score (sum of TSS) across all patients by group will be performed in accordance with the scoring instruction described in section 7.4

10.2 Adverse Events

Spontaneously reported adverse events collected in the CRF will be summarized by counts and proportions according to body system classification and by group in tabular or narrative format.

10.5 Vital Signs

Vital signs were analyzed during the study as part of study monitoring using range checks and were reported as AEs in accordance with the criteria defined in the study protocol. Additional analysis of vital signs will not be performed.

10.6 Physical Examinations

Changes to physical examination finds from screening to end-of-study will be reported in a listing.