Protocol Title: Clinical Study of the Safety of Quadrivalent Live Attenuated Influenza Vaccine (LAIV4) in Children with Asthma of Varying Levels of Severity

Statistical Analysis Plan Date: March 2, 2020

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Centers for Disease Control and Prevention

Clinical Immunization Safety Assessment (CISA) Project

Clinical Study of the Safety of Quadrivalent Live Attenuated Influenza Vaccine (LAIV4) in Children with Asthma of Varying Levels of Severity

Short Title: Safety after IIV4 versus LAIV4 in Young Asthma Children

Statistical Analysis Plan

Version 1.0

March 2, 2020

1 INTRODUCTION

This document describes the statistical procedures that will be utilized for the CISA protocol Safety of quadrivalent live attenuated influenza vaccine (LAIV4 vs. IIV4) in children with asthma of varying levels of severity. This statistical analysis plan (SAP) describes the methods of statistical analysis. The initial draft SAP (Version 0.1) was written prior to any data being analyzed in order to avoid bias. Any subsequent changes that occur to the study protocol warranting changes to the analysis procedures will be documented in the SAP. Table 1 below will be used for tracking changes to the SAP (both draft versions (0.X) and the final version (X.0). The day of vaccination is Day 1.

Table 1. Statistical Analysis Plan Versions

Version	Date of Approval	Major Changes from Prior Version
0.2	NA	NA
0.3	Oct. 30, 2019	NA
0.4	Jan. 06, 2020	NA
0.5	Jan. 29, 2020	NA
0.9	Feb. 05, 2020	NA
1.0	Mar. 02, 2020	Final SAP

2 PROTOCOL OBJECTIVES

2.1 Primary

PO 1: To compare proportions of participants with asthma exacerbations during the 42 days (until day 43) after quadrivalent live attenuated influenza vaccine (LAIV4) versus quadrivalent inactivated influenza vaccine (IIV4) in children with asthma aged 5-17 years.

The hypothesis for this primary objective is that the proportion of participants with asthma exacerbation(s) after LAIV4 is non-inferior to the proportion of participants with asthma exacerbation(s) after IIV4 (proportion is NOT higher in the LAIV4 group vs. the IIV4 group).

2.2 Secondary

SO 1: To compare the proportion of participants with asthma exacerbations during the 14 days after receipt of LAIV4 or IIV4.

SO 2: To compare the proportion of participants with asthma symptoms and unscheduled albuterol use during the 14 days after receipt of LAIV4 or IIV4.

SO 3: To compare the proportion of participants that experience a clinically significant decrease in Peak Expiratory Flow Rate (PEFR) from baseline during the 14 days after receipt of LAIV4 or IIV4.

2.3 Exploratory

EO 1: To compare the proportions of participants with asthma exacerbations during the 14 and 42 days after receipt of LAIV4 or IIV4, by asthma severity group (Appendix 1).

EO 2: To compare the proportion of participants with asthma symptoms and unscheduled albuterol use during the 14 days after receipt of LAIV4 or IIV4, by asthma severity group.

EO 3: To compare the proportion of participants who experience a clinically significant decrease in PEFR from baseline during the 14 days after receipt of LAIV4 or IIV4, by asthma severity group.

EO 4: To describe and compare changes in Peak Expiratory Flow Rate (PEFR) from baseline (pre-vaccination) PEFR after vaccination over time during the 14 days after receipt of LAIV4 or IIV4, by asthma severity group.

EO 5: To compare change in Childhood Asthma Control Test (c-ACT) score (participants aged 5-11 years) or Asthma Control Test (ACT) score (participants aged 12-17 years) from baseline through 42 days after LAIV4 or IIV4, by asthma severity group

EO 6: To compare asthma symptom days using Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) from baseline during the 14 days after vaccination by asthma severity group.

EO 7: To compare rates of medical utilization for asthma-related symptoms during the 14 and 42 days after LAIV4 or IIV4, by asthma severity group.

EO 8: To describe and compare systemic reactogenicity events during the 14 days after receipt of LAIV4 or IIV4, by asthma severity group.

EO 9: To describe and compare serious adverse events after LAIV4 vs. IIV4 during the 42 days after vaccination and assess relatedness to vaccine.

EO 10: To describe and compare asthma symptoms and control among participants with and without a history of allergic rhinitis or hay fever, used as a proxy for allergic versus non-allergic asthma.

3 STUDY OUTCOME MEASURES

3.1 Primary

POM 1.1: Proportion of participants with asthma exacerbations after LAIV4 vs. IIV4 during the 42 days after LAIV4 vs. IIV4 (Day 1 through Day 43)

Note: Asthma exacerbation is defined as: any acute episode of progressively worsening shortness of breath (dyspnea), cough, wheezing, chest tightness, and/or respiratory distress during the 42 days after influenza vaccination for which the patient seeks unscheduled medical attention (e.g., healthcare provider office or Emergency Department visit or hospitalization) or receives a new prescription for systemic corticosteroids.

3.2   Secondary

SOM 1.1: Proportion of participants with asthma exacerbations during the 14 days after LAIV4 vs. IIV4

Note: For the purposes of this outcome measure, the above definition of asthma exacerbation (section 3.1) is modified to include the time period of 14 days after receipt of influenza vaccine (LAIV4 or IIV4)

SOM 2.1: Proportion of participants with asthma symptoms of cough during the 14 days after LAIV4 vs. IIV4

SOM 2.2: Proportion of participants with asthma symptoms of wheezing during the 14 days after LAIV4 vs. IIV4

SOM 2.3: Proportion of participants with asthma symptoms of tightness in chest during the 14 days after LAIV4 vs. IIV4

SOM 2.4: Proportion of participants with asthma symptoms of nighttime awakening during the 14 days after LAIV4 vs. IIV4

SOM 2.5: Proportion of participants with unscheduled albuterol use to treat asthma symptoms during the 14 days after LAIV4 vs. IIV4

SOM 3.1: Proportion of participants who experience a clinically significant decrease in peak flow measurement from baseline during the 14 days after LAIV4 vs. IIV4
Note: A clinically significant decrease in peak flow is defined as: a decrease of ≥20% in PEFR from baseline PEFR.

3.3   Exploratory

EOM 1.1: Proportion of participants with asthma exacerbations by asthma severity group (Mild vs. Moderate-Severe) during the 14 days after receipt of LAIV4 or IIV4

EOM 1.2: Proportion of participants with asthma exacerbations by asthma severity group (Mild vs. Moderate-Severe) during the 42 days after receipt of LAIV4 or IIV4

EOM 2.1: Proportion of participants with asthma symptoms of cough by asthma severity group (Mild vs. Moderate-Severe) during the 14 days after receipt of LAIV4 or IIV4

EOM 2.2: Proportion of participants with asthma symptoms of wheezing by asthma severity group (Mild vs. Moderate-Severe) during the 14 days after receipt of LAIV4 or IIV4

EOM 2.3: Proportion of participants with asthma symptoms of tightness in chest by asthma severity group (Mild vs. Moderate-Severe) during the 14 days after receipt of LAIV4 or IIV4

EOM 2.4: Proportion of participants with asthma symptoms of nighttime awakening by asthma severity group (Mild vs. Moderate-Severe) during the 14 days after receipt of LAIV4 or IIV4

EOM 2.5: Proportion of participants with unscheduled albuterol use to treat asthma symptoms by asthma severity group (Mild vs. Moderate-Severe) during the 14 days after receipt of LAIV4 or IIV4

EOM 3.1: Proportion of participants that experience a clinically significant decrease in Peak Flow measurement during the 14 days after vaccination with LAIV4 or IIV4, by asthma severity group (Mild vs. Moderate-Severe)

Note: A clinically significant decrease in peak flow is defined as a decrease of ≥ 20% in PEFR from baseline PEFR.

EOM 4.1: Numerical changes in Peak Flow when compared to baseline during the 14 days after LAIV4 vs IIV4, by asthma severity group (Mild vs. Moderate-Severe)

EOM 4.2: Description of changes in Peak Flow when compared to baseline during the 14 days after LAIV4 vs IIV4, by asthma severity group (Mild vs. Moderate-Severe)

EOM 5.1 Changes in Childhood Asthma Control Test (cACT) scores (participants aged 5-11 years) or Asthma Control Test (ACT) scores (participants aged 12-17 years) from baseline during the 42 days after LAIV4 or IIV4, by asthma severity group (Mild vs. Moderate-Severe)

EOM 6.1: Maximum number of asthma symptom days using Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) from baseline during the 14 days after vaccination with LAIV4 or IIV4, by asthma severity group (Mild vs. Moderate-Severe)

EOM 7.1: Rates of medical utilization for asthma-related symptoms during the 14 days after LAIV or IIV4 by asthma severity group (Mild vs. Moderate-Severe)

EOM 7.2: Rates of medical utilization for asthma-related symptoms during the 42 days after LAIV or IIV4 by asthma severity group (Mild vs. Moderate-Severe)

EOM 8.1: Description and comparison of systemic reactogenicity events during the 14 days after LAIV or IIV4 by asthma severity group (Mild vs. Moderate-Severe)
  a. *Proportions of systemic reactogenicity events during the 14 days after LAIV or IIV4 by asthma severity group*

EOM 9.1: Description and comparison of serious adverse events during the 42 days after IIV4 or LAIV4 and performance of a relatedness assessment
  a. *Proportions of serious adverse events during the 42 days after IIV4 or LAIV4 and performance of a relatedness assessment*

EOM 10.1: Description and comparison of asthma symptoms and asthma control (PROSE, and c-ACT/ACT scores) among participants with and without a history of allergic rhinitis or hay fever, as a proxy for allergic versus non-allergic asthma during the 42 days after IIV4 or LAIV4

    a. *Proportions of asthma symptoms and asthma control (PROSE, and c-ACT/ACT scores) among participants with and without a history of allergic rhinitis or hay fever, as a proxy for allergic versus non-allergic asthma during the 42 days after IIV4 or LAIV4*

4 STUDY DESIGN

4.1 Study Description

This study is a prospective, randomized open-label clinical trial that will be conducted during the 2018-2019 and 2019-2020 influenza seasons. During the 2018-2020 seasons, approximately 300 children aged 5-17 years with a physician diagnosis of persistent asthma will be enrolled at Vanderbilt University Medical Center (Lead site), Cincinnati Children's Hospital Medical Center (contributing site), and Duke University Medical Center (contributing site). In the first season (2018-2019), only children aged 5-11 were eligible; in the second season (2019-2020), the age group was expanded to include children aged 5-17 years. Vanderbilt will enroll about 100 participants, Cincinnati will enroll about 110 participants, and Duke will enroll about 90 participants during these two seasons. In 2018-2019 season, there were 53 children aged 5-11 years enrolled, therefore in 2019-2020 season, we strive to enroll 94, 65, and 88 children at Vanderbilt University Medical Center, Cincinnati Children's Hospital Medical Center, and Duke University Medical Center, respectively. Children will be followed for up to 42 days following vaccination. Eligible children will be randomized 1:1 to receive either a single intranasal dose of licensed quadrivalent LAIV (LAIV4) or an intramuscular injection of quadrivalent IIV4 (IIV4), stratifying by asthma severity (mild vs. moderate/severe) and age group (5-11, 12-17 years old) at Visit 1. Day 1 is the day of vaccination.

Parents will record the occurrence of fever, solicited adverse events, medical care utilization, and daily symptom assessment on the memory aid along with peak flow measurements. In addition, parents will be contacted through phone call(s), email(s), and/or text messages(s) at visits 2-6 (See Protocol "Figure 1. Participant Flow Chart" and "Table 1: Schedule of Events".

4.2 Sample Size and Power

This study aims to enroll approximately 300 participants (approximately 100 from Vanderbilt, approximately 110 from Cincinnati, and approximately 90 from Duke). We assume that the proportion of participants with asthma exacerbation(s) in 42 days after vaccination is 12% after LAIV4 and IIV4 [1]. We also assume that ~10% of the children may drop out, yielding a total sample of at least 270 (135 LAIV4 and 135 IIV4).

Our research hypothesis is that the proportion of participants with asthma exacerbation(s) in the LAIV4 (experimental group) will not be higher than in the IIV4 group (control group). The power estimate is shown below, given delta of 10% and one-sided alpha is set at 5% level.

Proportion of participants with asthma exacerbation(s) in control IIV4 group (pc)	Proportion of participants asthma exacerbation(s) in LAIV4 experimental group (pe)	Estimated power to reject H0: pe – pc>=10%

| 12% | 12% | 81.1% |

The null hypothesis is that the proportion of participants with asthma exacerbation(s) in the LAIV4 group will be inferior (higher) than the proportion in the IIV4 group. The null hypothesis will be rejected (and delta margin noninferiority claimed) when the upper bound of the 95% one-sided confidence interval for the pe minus pc is less than 10%. IBM SPSS SamplePower software version 3.0.1 was used for the power calculation which was not adjusted for stratifying by site.

4.3 Randomization
Participants will be randomized (1:1) to receive either a single intranasal dose of licensed quadrivalent LAIV4 or an intramuscular injection of quadrivalent inactivated influenza vaccine (IIV4), stratifying by asthma severity (mild vs. moderate/severe) in both influenza seasons and age group (5-11 and 12-17 years old) in the second influenza season (2019-20). The permuted block randomizations will be done separately for each site (i.e., Vanderbilt University Medical Center, Duke University Medical Center and Cincinnati Children's Hospital Medical Center), with varying block size of either 4 or 6. Each site may have more than one clinic to recruit participants, and proportions of participants with mild or moderate/severe asthma can vary by clinics. Randomization will be accomplished using the REDCap System, hosted at Vanderbilt. Since this is a web-based system, it is easily accessible to the other collaborating sites as well. This study will be open label and study staff and subjects will not be blinded to treatment arm assignments.

5 PARAMETERS OF ANALYSIS

5.1 Data Collection and Storage
Data will be handled according to the study manual of procedures (MOP) and entered by study personnel onto REDCap database.

5.2 Analytic Issues
There are three sites participating in the study (Vanderbilt, Cincinnati, Duke) and analysis of the primary objective of the non-inferiority hypothesis will be tested and stratified by site to account for site variation. The first secondary objective will be stratified by site as well, though the rest of the secondary and exploratory objectives will not be stratified by site. There will be one primary objective and first secondary objective evaluated on a one-sided alpha at 0.05 level and assessed based on overlapping two-sided 90% binomial confidence upper boundaries. All other analyses are two-sided and alpha at 0.05 level. There will be no adjustments to the alpha level for all secondary and exploratory analyses except the first secondary objective.

6 ANALYSIS POPULATIONS

6.1 Intent-to-Treat (ITT) Population:
The ITT Population includes any participant that was enrolled, randomized into the study, and received a study vaccine at Visit 1.

6.2 Per Protocol Population for 43 Days:
The Per Protocol Population for 43 days (PP43) is a subset of the ITT Population. This is defined as all participants who were randomized, vaccinated, completed study procedures

through day 43, had no protocol deviations that are likely to affect the objectives, and did not receive a second dose of influenza vaccine before day 43.

6.3   Per Protocol Population for 15 Days:
The Per Protocol Population for 15 days (PP15) is a subset of the ITT Population. This is defined as all participants who were randomized, vaccinated, completed study procedures through day 15, had no protocol deviations that are likely to affect the objectives, and did not receive a second dose of influenza vaccine before day 15.

The Per Protocol Population for 43 days is the primary analysis population for the Primary Objective. Statistical analyses for the Primary Objective will be performed for the ITT population and the Per Protocol for 43 days, or the ITT Population only if no participants are excluded from the Per Protocol Population. The Per Protocol population for 15 days is the primary analysis population for the Secondary Objectives. Statistical analyses for the Secondary Objectives will be performed for the ITT population and Per Protocol population for 15 days, or the ITT Population only if no participants are excluded from the Per Protocol Population. The list of protocol deviations that meet criteria for exclusion from analysis is provided in Appendix 2.

In the ITT population, participants will be analyzed according to randomization assignment, rather than treatment group. If applicable, sensitivity analyses on primary and secondary objectives will be done on datasets defined by treatment group. For example, if a participant was assigned to LAIV4 and inadvertently received IIV4 that participant would be reassigned to the IIV4 treatment group in the sensitivity analyses.

7   BASELINE DATA AND FLOW CHART

7.1   Presentation of Baseline Data
The following baseline data will be presented, including data by site, asthma severity levels (mild and moderate-severe), history of allergic rhinitis or hay fever, and vaccination group: age, age-group (5-11 and 12-17 years), gender, ethnicity, race, receipt of influenza vaccine in the past 12 months, influenza season vaccinated (2018-19 and 2019-20), influenza dose received (1 or 2), and BMI.

7.2   Flow Chart
The number of enrolled participants will be presented in a flow chart by site, asthma severity levels, and vaccination group. The number of visits completed and missed will be presented along with the completeness of memory aid. A CONSORT diagram will be presented.

8   ANALYSIS OF STUDY OBJECTIVES
Descriptive analyses will be summarized for continuous variables with mean, standard deviation, median, and interquartile range. Categorical variables will be summarized with frequencies and percentages. Explanatory figures will be generated to evaluate the data distribution. Comparisons of demographic characteristics between LAIV4 and IIV4 groups will be conducted using Pearson Chi-square and Wilcoxon tests appropriately.

All analyses will be performed using R 3.6.2 (r-project.org), SAS version 9.4, or STATA version 16, or updated software from these programs.

8.1 Primary Objective

The primary objective (PO 1) of the study is to compare proportions of participants with asthma exacerbation(s) during the 42 days after LAIV4 versus IIV4 in children with asthma aged 5-17 years.

The hypothesis for this primary objective is that the proportion of participants with asthma exacerbation(s) after LAIV4 is non-inferior to the proportion of participants with asthma exacerbation(s) after IIV4 (the proportion of participants with asthma exacerbation(s) after vaccination is not higher in the LAIV4 group vs. the IIV4 group). Asthma exacerbations will be assessed from day 1 through day 43. This information is captured on the memory aid forms and recorded in the REDCap database. *Any unscheduled medical attention (e.g., healthcare provider office, emergency department visit, hospitalization) due to any acute episode of progressively worsening shortness of breath/ dyspnea, cough, wheezing, chest tightness, and/or respiratory distress OR received a new prescription for systemic corticosteroids after LAIV4 vs. IIV4 during the 42 days post-vaccination will be counted as asthma exacerbations yes (1) and asthma exacerbations no (0) otherwise, for this analysis.*

This objective will be assessed using a one-sided non-inferiority test with the alpha level set at 0.05 and non-inferiority margin of 10%. The null hypothesis is LAIV4 is inferior to IIV4 in regard to the proportion of subjects having asthma exacerbations during the 42 days post-vaccination (i.e., LAIV4 will have a higher proportion of asthma exacerbations compared to IIV4).

$$H_o: LAIV4 - IIV4 \geq 0.1\ (10\%)$$

The alternative hypothesis is LAIV4 is non-inferior to IIV4 in regard to the proportion of subjects having asthma exacerbations during the 42 days post-vaccination.

$$H_a: LAIV4 - IIV4 < 0.1\ (10\%)$$

The proportions will be compared between LAIV4 versus IIV4 using a Cochran-Mantel-Haenszel method in a stratified analysis by site to control for three sites at the one-sided alpha 0.05 level. The upper bound of 95% one-sided confidence interval for the proportion difference between two vaccine groups will be used to make this assessment and we will reject Ho if it's less than 10%.

The proportion difference and corresponding 95% confidence interval for asthma exacerbations with or without adjusting for site will also be calculated. We may perform comparisons between LAIV4 versus IIV4 adjusting for asthma severity groups (Mild vs. Moderate-Severe) or adjusting for both site and asthma severity groups (Mild vs. Moderate-Severe) if possible.

8.2 Secondary Objectives

There are three secondary objectives for this study.

   a) The first secondary objective (SO 1) is to compare the proportion of participants with asthma exacerbations during the 14 days after receipt of LAIV4 or IIV4.

The analysis is similar to primary objective 1 using a one-sided non-inferiority test with the alpha level set at 0.05 and non-inferiority margin of 10% though asthma exacerbation proportions during the 14 days post-vaccination is the outcome.

Asthma exacerbations will be assessed from day 1 through day 15. This information is captured on the memory aid forms and recorded in the REDCap database. Definition of asthma exacerbation: *Any unscheduled medical attention (e.g., healthcare provider office, emergency department visit, hospitalization) due to any acute episode of progressively worsening shortness of breath/ dyspnea, cough, wheezing, chest tightness, and/or respiratory distress OR received a new prescription for systemic corticosteroids after LAIV4 vs. IIV4 during the 14 days post-vaccination will be counted as asthma exacerbations yes (1) and asthma exacerbations no (0) otherwise, for this analysis.*

SO 1 secondary objective will use one-sided (alpha=0.05) non-inferiority test.

b) The second secondary objective (SO 2) is to compare the proportion of participants with asthma symptoms and unscheduled albuterol use during the 14 days after receipt of LAIV4 or IIV4.

Proportions of subjects with each asthma symptom (yes or no) along with unscheduled albuterol use to treat asthma symptoms (yes or no) will be compared between two treatment groups using Chi-square tests. Proportions and difference of proportions between two treatment groups will be reported along with their 95% CIs.

The information regarding each symptom of cough, wheeze, tightness in chest, nighttime awakening and unscheduled albuterol use to treat asthma symptoms during Days 1-15 will be captured at home on the Memory Aid documents and solicited by study staff during phone calls or other communication methods. Data will be entered by study staff into the REDCap database.

SO 2 secondary objective will use the two-side (alpha=0.05) superiority test

c) The third secondary objective (SO 3) is to compare the proportion of participants who experience a clinically significant decrease in Peak Expiratory Flow Rate (PEFR) from baseline during the 14 days after receipt of LAIV4 or IIV4.

Proportions of subjects with a clinically significant ($\geq$20%) decrease after vaccination in PEFR from baseline (yes or no) will be compared between two treatment groups using a Chi-square test. A postvaccination decrease of ($\geq$20%) for each participant will be categorized as Yes if it occurred on one or more days during the 14 days after vaccination. Proportions and difference of proportions by two treatment groups will be reported along with their 95%CIs.

Study staff will document baseline (pre-vaccination) highest of 3 PEFRs on Day 1. Daily highest of 3 PEFR values during Days 1-15 will be documented on the Memory Aid; study staff will enter the highest daily PEFR value into the REDCap database.

SO 3 secondary objective will use the two-side (alpha=0.05) superiority test

No adjustments will be made to the alpha level (two-sided alpha=0.05) for SO2, SO3 secondary objective analyses.

8.3 Exploratory Objectives
There are ten exploratory objectives for this study.

a) The first exploratory objective (EO 1) is to compare proportion of participants with asthma exacerbations by asthma severity group (Mild vs. Moderate-Severe) during the 14 days or 42 days after receipt of LAIV4 or IIV4

Two Mantel-Haenszel Chi-square tests will be used to compare the proportions of asthma exacerbations by treatment and asthma severity groups at 14 and 42 days after receipt of LAIV4 or IIV4, respectively.

b) The second exploratory objective (EO 2) is to compare the proportion of participants with asthma symptoms and unscheduled albuterol use by asthma severity group (Mild vs. Moderate-Severe) during the 14 days after receipt of LAIV4 or IIV4

Five Mantel-Haenszel Chi-square tests will be used to compare the proportions of each of four asthma symptoms and unscheduled albuterol use by treatment and asthma severity groups.

c) The third exploratory objective (EO 3) is to compare the proportion of participants that experience a clinically significant decrease in PEFR from baseline during the 14 days after receipt of LAIV4 or IIV4, by asthma severity group (Mild vs. Moderate-Severe).

The Mantel-Haenszel Chi-square test will be used to compare the proportions of a clinically significant decrease (≥20%) in PEFR from baseline by treatment and asthma severity groups.

d) The fourth exploratory objective (EO 4) is describe and compare changes in Peak Expiratory Flow Rate (PEFR) to baseline during the 14 days after receipt of LAIV4 or IIV4, by asthma severity group (Mild vs. Moderate-Severe).

The numerical changes of PEFR from the baseline during the 14 days post vaccination will be graphed and compared by asthma severity group using either t-test or Wilcoxon rank-sum test. Comparisons of mean or median of maximal change from baseline will also be performed between the two treatment groups using either t-test or Wilcoxon rank-sum test and 95%CIs of such differences will be presented.

e) The fifth exploratory objective (EO 5) is to compare change in Childhood Asthma Control Test (c-ACT) scores (participants aged 5-11 years) or Asthma Control Test (ACT) scores (participants aged 12-17 years) from baseline during the 42 days after LAIV4 or IIV4, by asthma severity group (Mild vs. Moderate-Severe).

The numerical changes of c-ACT and ACT from the baseline during the 14 days post-vaccination will be graphed and compared by asthma severity group using either t-test or Wilcoxon rank-sum test. We may categorize c-ACT and ACT into

well-controlled, poorly controlled, and very poorly controlled groups and run Mantel-Haenszel Chi-square test by treatment and asthma severity groups.

f) The sixth exploratory objective (EO 6) is to compare asthma symptom days using Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations (PROSE) from baseline during the 14 days after vaccination by asthma severity group (Mild vs. Moderate-Severe).

The numerical changes of PROSE from the baseline during the 14 days post-vaccination will be graphed and compared by asthma severity group using either t-test or Wilcoxon rank-sum test.

g) The seventh exploratory objective (EO 7) is to compare rates of medical utilization for asthma-related symptoms during the 14 and 42 days after LAIV4 or IIV4, by asthma severity group.

Two Mantel-Haenszel Chi-square tests will be used to compare rates of medical utilization for asthma-related symptoms by treatment and asthma severity groups at 14 and 42 days after receipt of LAIV4 or IIV4, respectively.

h) The eighth exploratory objective (EO 8) is to describe and compare reactogenicity events during the 14 days after receipt of LAIV4 or IIV4, by asthma severity group. Reactogenicity will be assessed by grading on a 0-3 scale, with 0 being used for no events, grade 1 (mild), grade 2 (moderate), and grade 3 (severe).

Reactogenicity is assessed by:
1. Runny nose/nasal congestion
2. Sore throat
3. Chills
4. Earache/ear pain
5. Headache
6. Muscle aches/sore muscles
7. Bone/joint pain
8. Decreased activity/lethargy/fatigue
9. Rash/hives
10. Stomach pain
11. Nausea/vomiting

These events will be graded based on the following scale

1. Grade 0: Symptom did not occur
2. Grade 1: Noticed a change but does not interfere with things done on a normal day
3. Grade 2: Interferes with activity but did not require a doctor's office visit or missed day of school/daycare
4. Grade 3: Prevents daily activity and/or required a doctor's office visit and/or missed day of school/daycare

Fever will be assessed by the following grading scale

1. Grade 0: <100.4 ˚F
2. Grade 1: 100.4 – 100.9 ˚F
3. Grade 2: 101 – 102.1 ˚F
4. Grade 3: >102.1 ˚F

For each reactogenicity reaction, summary statistics will be performed such as frequencies and percentages for categorical variables and mean/standard deviation or median/interquartile range for continuous variables. Results will be presented as none, mild, moderate and/or severe reactions. There will be statistical comparisons among moderate/severe reactogenicity reactions by treatment groups and asthma severity groups (Mild vs. Moderate-Severe) using Mantel-Haenszel tests.

i)   The ninth exploratory objective (EO 9) is to describe and compare serious adverse events during the 42 days after LAIV4 or IIV4 and assess relatedness to vaccine

For each serious adverse event and assessing relatedness, summary statistics will be performed such as frequencies and percentages for categorical variables and mean/standard deviation or median/interquartile range for continuous variables. The Mantel-Haenszel test will be used for comparisons of proportions of having at least one SAE by treatment groups and asthma severity levels. Listing of the serious adverse events by study LAIV4 or IIV4 groups will also be presented.

j)   The tenth exploratory objective (EO 10) is to describe and compare asthma symptoms and asthma control (PROSE, and c-ACT/ACT scores) among participants with and without a history of allergic rhinitis or hay fever, as a proxy for allergic versus non-allergic asthma.

For each asthma symptom and control, summary statistics will be performed such as frequencies and percentages for categorical variables and mean/standard deviation or median/interquartile range for continuous variables. The Mantel-Haenszel test will be used for comparisons of proportions of having at least one symptom by treatment groups and allergic asthma status (history of allergy rhinitis or hay fever vs. no history of these conditions).

No adjustments will be made to the alpha level (two-sided alpha=0.05) for these exploratory objective analyses.

9   PROTOCOL DEVIATIONS
See Appendix 2

10 SENSITIVITY ANALYSES
If applicable, sensitivity analyses on primary and secondary objectives will be done on datasets defined by treatment group. If applicable, sensitivity analyses on primary and secondary objectives will be done on datasets defined by treatment group. For example, if a participant was assigned to LAIV4 and inadvertently received IIV4 that participant would be reassigned to the IIV4 treatment group in the sensitivity analyses.

11 REFERENCES

1.   Fleming, D.M., et al., *Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma.* Pediatr Infect Dis J, 2006. **25**(10): p. 860-9.

Appendix 1

Table 1: Asthma severity categories and prescription long-acting controller medications*
for children with persistent asthma, aged 5-17 years

Classification of Asthma Severity		
Treatment of Persistent Asthma		
Mild Persistent	Moderate Persistent	Severe Persistent
Low-dose ICS OR Montelukast OR Cromolyn sodium	Low-dose ICS + Montelukast OR Low-dose ICS + LABA OR Medium-dose ICS	Medium-dose ICS + Montelukast or LABA OR Any High-dose ICS OR Omalizumab/Xolair OR Mepolizumab/Nucala OR Chronic systemic steroids

Abbreviations: LABA: long-acting beta-agonist; ICS: inhaled corticosteroids

Controller medications include inhaled corticosteroids, oral corticosteroids, leukotriene receptor antagonists, long-acting beta agonists, and biologics.

Appendix 2: Protocol Deviations that Result in Exclusion from PP15 and PP43 Populations

The following major deviations from the protocol will result in exclusion from the PP15 and PP43 populations.

1. Subjects who do not meet all eligibility criteria at the time of visit 1 will be excluded from the PP15 and PP43 populations.
2. Subjects in whom asthma severity was not assessed according to Appendix Table 1, will be excluded from analysis.
   a. Note: Subjects in whom asthma severity was assessed according to Appendix 1, but in whom corrected severity is available, will be assigned to the correct severity group for analysis.
3. Subjects who receive an investigational product at any time during the study period will be excluded
   a. Note: If receipt of investigational product occurs after Day 15, the subject will remain eligible for analysis in the PP15 population.
4. Subjects who receive a licensed, non-study vaccine will be excluded
   a. Note: If receipt of non-study vaccine occurs after Day 15, the subject will remain eligible for analysis in the PP15 population.
5. Subject who were assigned to a vaccine group but received the wrong product (e.g., subject assigned to LAIV4 group and received IIV4)