Centers for Disease Control and Prevention

Clinical Immunization Safety Assessment (CISA) Project

NCT05007041

Safety of Simultaneous Vaccination with Zoster Vaccine Recombinant (RZV) and Quadrivalent Adjuvanted Inactivated Influenza Vaccine (aIIV4)

Short Title: Simultaneous RZV and aIIV4 Vaccination

Statistical Analysis Plan

Version 2.0

May 7, 2024

1 INTRODUCTION

This document describes the statistical procedures that will be utilized for the CISA protocol Safety of Simultaneous Vaccination with Zoster Vaccine Recombinant (RZV) and Quadrivalent Adjuvanted Inactivated Influenza Vaccine (aIIV4) that was approved on September 7, 2022. This statistical analysis plan (SAP) describes the methods of statistical analysis. The initial draft SAP (Version 0.1) was developed 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 (both draft versions (0.X) and the final version (X.0). Table 1 below will be used for tracking of changes to the SAP. In this study of 400 adults age ≥65 years, participants aged 65 to 69 years will be randomized (1:1) to receive either simultaneous RZV and aIIV4 or RZV and HD-IIV4 using a permuted block randomization scheme stratified by Lead and Contributing Site. A separate permuted block, stratified by site will be allocated for subjects who are age 70 years and older.

Table 1. Statistical Analysis Plan Versions

Version	Date of Approval	Major Changes from Prior Version
0.1	TBD	NA
0.2	TBD	Section 3.3 – Exploratory objective # 7: Specified sample collection dates Section 8.1. – Primary Objective: Corrected age range
0.3	TBD	Added Under Study Objective Outcomes (SO1, SO2, EO1, EO2, EO3, EO5, and EO6): *This information will also be presented by age-group for the subset of subjects aged 65-69 versus those subjects aged 70 years or older. No formal statistical hypothesis testing (i.e., no p-values) will be performed, only the confidence boundary of the difference will be presented.* Added minor edits Added EQ-5D & EQ VAS Post-vaccination score description
1.0	11/27/2022	Minor edits provided by the CDC
2.0	5/7/2024	Corrected minor typo in description of EO4 in Section 8.3 Corrected minor typo in description of SO1 in Section 3.2

2 PROTOCOL OBJECTIVES

2.1 Primary

1. To compare the proportion of participants with at least one severe (Grade 3) solicited local or systemic reactogenicity event after RZV dose 1 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group.
    - Hypothesis: The proportion of participants with at least one severe (Grade 3) solicited reactogenicity event after RZV dose 1 will be noninferior (not higher) in the RZV and aIIV4 group compared with the RZV and HD-IIV4 group.

2.2 Secondary

1. To compare the proportion of participants with at least one severe (Grade 3) solicited local reactogenicity event after RZV dose 1 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group.
2. To compare the proportion of participants with at least one severe (Grade 3) solicited systemic reactogenicity event after RZV dose 1 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group.
3. To compare the proportion of participants with at least one serious adverse event or adverse event of clinical interest after RZV dose 1 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group through Day 43 and describe these events.

2.3 Exploratory

1. To compare the proportion of participants with at least one severe (Grade 3) solicited local or systemic reactogenicity event after RZV dose 2 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group.
2. To compare the proportion of participants with at least one severe (Grade 3) solicited local reactogenicity event after RZV dose 2 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group.
3. To compare the proportion of participants with at least one severe (Grade 3) solicited systemic reactogenicity event after RZV dose 2 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group.
4. To compare the proportion of participants with at least one serious adverse event or adverse event of clinical interest after RZV dose 2 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group and describe these events through the entire study period.
5. To compare the proportion of participants with moderate-to-severe (Grade 2-3) solicited local or systemic reactogenicity event after RZV dose 1 in the RZV and aIIV4 group vs. RZV dose 1 and HD-IIV4 group.
6. To compare the proportion of participants with moderate-to-severe (Grade 2-3) solicited local or systemic reactogenicity event after RZV dose 2 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group.
7. To compare serum hemagglutination inhibition (HAI) antibody titers after RZV dose 1 and HD-IIV4 with RZV dose 1 and aIIv4 for each of the four influenza vaccine strains contained in the respective vaccine for that season in the full study population and by age.
8. To describe and compare changes in health-related quality of life after RZV dose 1 and aIIV4 with RZV dose 1 and HD-IIV4 in the full study population and by age group.

3 STUDY ENDPOINTS/OUTCOME MEASURES

3.1 Primary

1. Proportion of subjects reporting at least one severe (grade 3) solicited local or systemic reactogenicity event on days 1-8 after RZV dose 1 in each study group.

3.2 Secondary

1. Proportion of participants with at least one severe (grade 3) solicited local reactogenicity event on days 1-8 after RZV dose 1 in each study group.
2. Proportion of participants with at least one severe (grade 3) solicited systemic reactogenicity event on days 1-8 after RZV dose 1 in each study group.
3. Proportion of participants with at least one serious adverse event or adverse event of clinical interest after RZV dose 1 and clinical description of these events in each study group through Day 43.

3.3 Exploratory

1. Proportion of participants with at least one severe (grade 3) solicited local or systemic reactogenicity event on days 1-8 after RZV dose 2 in each study group.
2. Proportion of participants with at least one severe (grade 3) solicited local reactogenicity event on days 1-8 after RZV dose 2 in each study group.
3. Proportion of participants with at least one severe (grade 3) solicited systemic reactogenicity event on days 1-8 after RZV dose 2 in each study group.
4. Proportion of participants with serious adverse events and adverse events of clinical interest after RZV dose 2 and clinical description of these events in each study group through the entire study period.
5. Proportion of participants with at least one moderate-to-severe (Grade 2-3) solicited local or systemic reactogenicity event on days 1-8 after RZV dose 1 in each study group.
6. Proportion of participants with at least one moderate-to-severe (Grade 2-3) solicited local or systemic reactogenicity event on days 1-8 after RZV dose 2 in each study group.
7. HAI titers by vaccination group and age group:
    a. The proportion of subjects achieving seroconversion at day 29 (an HAI titer $\geq$ 1:40 at day 29 if the baseline titer is < 1:10 or a minimum four-fold rise in HAI titer if the baseline titer is $\geq$ 1:10) for each influenza strain in the respective season's vaccine.
    b. Proportion of subjects with a seroprotective HAI titer (≥ 1:40) pre- and post-immunization at day 29 for each IIV antigen in the respective season's vaccine.
    c. The geometric mean HAI titer (GMT) at baseline (Day 1) and Day 29 for each IIV antigen in the respective season's vaccine.
    d. The geometric mean fold rise (GMFR) in HAI titer at Day 29 for each IIV antigen in the respective season's vaccine.
8. Change in scores on the EuroQOL 5 dimensions-5 level (EQ-5D-5L) and EuroQOL visual analogue scale (EQ VAS) pre-vaccination and post-vaccination will be compared between the vaccination groups and age groups.

4 STUDY DESIGN

4.1 Main Study Description

This study is a prospective, randomized, blinded clinical trial to assess the safety of simultaneous RZV and aIIV4 versus simultaneous RZV and HD-IIV4 in 400 adults age ≥65 years. Older adults who have not received RZV (Shingrix vaccine) or IIV during the 2021-2022 and 2022-2023 influenza seasons will be enrolled; participants enrolling in the 2022-2023 influenza season may have received influenza vaccine in the prior season. Detailed health and demographic data will be collected from study participants at baseline prior to influenza vaccine receipt. With Day 1 serving as the day of vaccination, participants will be followed through Day 8 (total 8 days) for symptoms of reactogenicity. Vaccinations will be performed by unblinded study staff with all follow-up assessments being conducted by blinded staff. Study subjects will be blinded throughout the study. Participants will be followed through Day 43 after each dose of RZV for adverse events and adverse events of clinical interest, including

health care utilization, and through the entire period of enrollment for serious adverse events and immune-mediated conditions (see Appendix A).

4.2 Laboratory

4.2.1 Influenza Hemagglutination Inhibition Assay

Participants will have blood draws on Day 1 (before vaccination) and Day 29 to be stored for serum hemagglutination inhibition (HAI) antibody titers. HAI antibody titers will be compared between groups receiving aIIV4 or IIV4-HD for each of the four influenza vaccine strains contained in the respective vaccines for that season.

4.3 Sample Size and Power

Safety: Based on information from the pre-licensure trials for RZV, we assume that 14% of adults ≥65 years will have at least one severe solicited local or systemic reactogenicity event after RZV dose 1. We have selected a clinically meaningful noninferiority margin of 10%. Statistical calculations, without consideration for study drop-out, show that with a one-side alpha level of 0.025, we would need 380 total subjects (190 subjects in each group across all study sites) to have at least 80% power to be able to demonstrate that the proportion of adults ≥65 years with at least one severe solicited local or systemic reactogenicity event after RZV dose 1 is noninferior after RZV and allV4 versus RZV and HD-IIV4. Assuming a 5% drop out rate, we plan to recruit and randomize 400 total subjects.

4.4 Randomization

Participants aged 65 to 69 years will be randomized (1:1) to receive either simultaneous RZV and aIIV4 or RZV and HD-IIV4 using a permuted block randomization scheme stratified by Lead (Duke University) and Contributing Site (Johns Hopkins University). A separate permuted block will be allocated for subjects who are age 70 years and older. The project statistician will generate permuted block randomization schemes, which will be uploaded to REDCap (see below). The randomization schedule will not be available to the study staff, so the next randomization allocation will not be known before randomization occurs. Following confirmation of study eligibility criteria during Visit 1, participant randomization will be through REDCap with treatment allocation recorded on the case report form (CRF).
In the event that REDCap is unavailable, manual randomization will occur through the use of envelopes. The project statistician will prepare 20 envelopes per participant age group per site (total of 40 per site) that will use the same randomization strategy as the primary scheme embedded in REDCap. When an unblinded team member is informed of the participant's age group, he/she will pull the next envelope in order. In order to capture the allocation per subject, a separate form in REDCap will be used by the unblinded personnel to add the assignment. A log will need to be kept at the site capturing these instances.

5 PARAMETERS OF ANALYSIS

5.1 Data Collection and Storage

The novel Vanderbilt-designed resource developed specifically for online collection of research information, the Research Electronic Data Capture (REDCap) platform (https://projectredcap.org/), will be used to design study forms, including the case report forms, adverse event forms, and short customized questionnaires to collect information from study subjects. REDCap provides: 1) a streamlined process for rapidly building a database; 2) an intuitive interface for collecting data, with data validation and audit trail; 3) automated export procedures for seamless data downloads to common statistical packages; 4) branching logic, file uploading, and calculated fields; and 5) a quick and easy protocol set-

up. This system will be used by Duke for data management. All electronic linkages will fulfill regulations for protection of human subjects and requirements to minimize the risk of breach of confidentiality.

All study-related documents containing protected health information, e.g., enrollment logs, case report forms, diaries completed by study participants, will be maintained in secure research offices at Duke and Johns Hopkins University, which are accessible to research staff only.

The study team will utilize a secure, encrypted, file transfer method for sharing study documents and data with the CDC. No personal identifiers will be included in any shared documents or datasets.

5.2 Analytic Issues

There are two sites participating in the study and analysis of the primary objective will be stratified by site (Duke University and Johns Hopkins University) to account for this unit of randomization. All objectives will be stratified by site when applicable. The alpha will be set at a one-sided 0.025 level for noninferiority testing and at the alpha 0.05 level otherwise. There will be no adjustments to the alpha level for multiple comparisons. Should an interim safety analysis be required, the alpha level will be adjusted to assure the overall type I error is maintained at the one-sided alpha 0.025 level for the primary outcome of non-inferiority.

6 ANALYSIS POPULATIONS

6.1 Intention-to-Treat (ITT) Population:

For Secondary Objective 3 and Exploratory Objectives 4 and 8, the primary analysis population will be the ITT Population; defined as all subjects who are randomized and vaccinated (received at least one study vaccine).

6.2 Modified Intention-to-Treat (mITT) Population:

For Primary Objective 1, Secondary Objectives 1 and 2, and Exploratory Objectives 1, 2, 3, 5 and 6 the primary analysis population will be the mITT Population; defined as all subjects who are randomized, vaccinated (received at least one study vaccine), and provide at least one day of complete data on the symptom diary.

6.3 Immunogenicity Population

For Exploratory Objective 7 (immunogenicity analyses) the primary analysis population will be the Immunogenicity Population defined as subjects who received study vaccines, provide baseline and Visit 4 blood draws of acceptable volume and quality within the protocol-defined time frame with no protocol violations affecting immunogenicity.

Protocol Violations for Exclusion from Immunogenicity Populations:

1. Did not receive both RZV Dose 1 and influenza vaccine.
2. No pre- and/or post-vaccination blood draw.
3. Vaccine administered outside of the vaccination window (±1-2 weeks).
4. Receipt of any other vaccine between the pre- and post-vaccination blood draws.
5. New immunosuppression disorders between the pre- and post-vaccination blood draws or receipt of immunosuppressive medication between the pre- and post-vaccination blood draws.
6. Subject who was inadvertently enrolled and randomized to the study, though they were later learned to have had met criteria for study exclusion that would have affected immunogenicity.

7 BASELINE DATA AND FLOW CHART

7.1 Presentation of Baseline Data

The following baseline information will be presented by treatment group: age, sex at birth ethnicity, race, employment status, highest education level, and if the participant lives alone. Summary statistics (e.g., mean, standard deviation, interquartile range) will be presented for continuous variables. Categorical variables will be described with frequencies and percentages. Other common conditions will be presented as a part of the manuscript's Table 1 and will be further broken down by site.

Common Conditions for Table 1.

A. Cardiac and Pulmonary Conditions Affected by Influenza in Older Adults
    a. Hypertension
    b. Coronary Artery Disease
    c. Congestive Heart Failure
    d. Atrial Fibrillation
    e. Valvular Heart Disease
    f. COPD
    g. Asthma

B. Common Conditions in Older Adults Reported in Clinical Trials
    a. Hyperlipidemia
    b. Diabetes mellitus
    c. Hypothyroidism
    d. Osteoarthritis
    e. Hearing Loss
    f. Depression
    g. Gastroesophageal Reflux Disease
    h. End Stage Renal Disease

C. Statin Use

7.2 Flow Chart

The number of enrolled participants will be presented in a flow chart by treatment group along with a breakdown of the two analysis populations.

8 ANALYSIS OF STUDY OBJECTIVES

8.1 Primary Objective

1. To compare the proportion of older adults with at least one severe (Grade 3) solicited local or systemic reactogenicity event after RZV dose 1 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group
    - Hypothesis: The proportion of participants with at least one severe (Grade 3) solicited reactogenicity event after RZV dose 1 will be noninferior (not higher) in the RZV and aIIV4 group compared with the RZV and HD-IIV4 group

This objective will be assessed in the mITT Population using a one-sided site-stratified noninferiority test with the alpha level set at 0.025 and noninferiority margin of 10%. The null hypothesis is simultaneous vaccination with RZV and allV4 is inferior (i.e., RZV and allV4 will have a higher proportion) to RZV and HD-IIV4 with regard to the proportion of adults with at least one severe (Grade 3) solicited local or systemic reactogenicity event on days 1-8 after RZV dose 1.

Ho: RZV and allV4 - RZV and HD-IIV4 ≥ 0.10 (10%)

The alternative hypothesis is RZV and allV4 is noninferior to RZV and HD-IIV4 with regard to the proportion of adults with at least one severe (Grade 3) solicited local or systemic reactogenicity event after RZV dose 1.

Ha: RZV and allV4 - RZV and HD-IIV4 < 0.10 (10%)

The upper bound of a site-stratified Newcombe binomial confidence interval with Cochran-Mantel-Haenszel (CMH) weighting of the difference will be used to make this assessment.

This information is captured on the symptom diary CRF in the REDCap database. The grading criteria for injection site pain is provided in Tables 1 and 2.

Table 1. Injection-site Reactogenicity

Symptom	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Pain	Any pain neither interfering with nor preventing normal every day activities.	Painful when limb is moved and interferes with every day activities.	Significant pain at rest. Prevents normal every day activities.
Induration/ Swelling	≥ 20 mm to ≤ 50 mm diameter	> 50 mm to ≤ 100 mm diameter	> 100 mm diameter
Erythema (Redness)	≥ 20 mm to ≤ 50 mm diameter	> 50 mm to ≤ 100 mm diameter	> 100 mm diameter

Table 2. Systemic Reactogenicity

Systemic	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)
Fever (°C)	≥ 37.5 - < 38.4° C ≥ 100.0 - < 101.1° F	≥ 38.4 - < 39° C ≥ 101.1 - < 102.2° F	≥ 39° C ≥ 102.2° F

Table 1. Injection-site Reactogenicity

Fatigue/ Malaise	Fatigue that is easily tolerated	Fatigue that interferes with normal activity	Fatigue that prevents normal activity
Myalgia	Myalgia that is easily tolerated	Myalgia that interferes with normal activity	Myalgia that prevents normal activity
Arthralgia	Arthralgia that is easily tolerated	Arthralgia that interferes with normal activity	Arthralgia that prevents normal activity
Headache	Headache that is easily tolerated	Headache that interferes with normal activity	Headache that prevents normal activity
Gastrointestinal symptoms (nausea, vomiting, diarrhea, and/or abdominal pain)	Gastrointestinal symptoms that are easily tolerated	Gastrointestinal symptoms that interfere with normal activity	Gastrointestinal symptoms that prevent normal activity
Chills/Shivering	Shivering that is easily tolerated	Shivering that interferes with normal activity	Shivering that prevents normal activity

This information will also be presented by age-group for the subset of subjects aged 65-69 versus those subjects aged 70 years or older. No formal statistical hypothesis testing (i.e., no p-values) will be performed, only the confidence boundary of the difference will be presented.

8.2 Secondary Objectives

1. To compare the proportion of participants with at least one severe (Grade 3) solicited local reactogenicity event on days 1-8 after RZV dose 1 in the RZV and aIIV4 group vs. RZV dose 1 and HD-IIV4 group.

   The proportions of participants with at least one severe (Grade 3) solicited local reactogenicity event on days 1-8 after RZV dose 1 in the mITT Population will be compared between vaccine groups using the same statistical methodology as for Primary Objective 1. A one-sided site-stratified noninferiority test to determine if RZV dose 1 and allV4 is noninferior to RZV dose 1 and HD-IIV4 with the alpha level set at 0.025 and a 10% noninferiority margin.

   This information will also be presented by age-group for the subset of subjects aged 65-69 versus those subjects aged 70 years or older. No formal statistical hypothesis testing (i.e., no p-values) will be performed, only the confidence boundary of the difference will be presented.

2. To compare the proportion of participants with at least one severe (Grade 3) solicited systemic reactogenicity event on days 1-8 after RZV dose 1 in the RZV and aIIV4 group vs. RZV dose 1 and HD-IIV4 group.

   The proportions of participants with at least one severe (Grade 3) solicited systemic reactogenicity event on days 1-8 after RZV dose 1 in the mITT Population will be compared between vaccine groups using the same statistical methodology as for Primary Objective 1. A one-sided site-stratified noninferiority test to determine if RZV dose 1 and

allV4 is noninferior to RZV dose 1 and HD-IIV4 with the alpha level set at 0.025 and a 10% noninferiority margin.

This information will also be presented by age-group for the subset of subjects aged 65-69 versus those subjects aged 70 years or older. No formal statistical hypothesis testing (i.e., no p-values) will be performed, only the confidence boundary of the difference will be presented.

3. To compare the proportion of participants with at least one serious adverse event or adverse event of clinical interest after RZV dose 1 in the RZV and aIIV4 group vs. RZV dose 1 and HD-IIV4 group through Day 43 and describe these events.

   The proportion and 95% exact binomial confidence interval, as well as the difference between vaccine groups and a 95% confidence interval of the difference in proportions, in the ITT Population of serious adverse events and events of clinical interest through Day 43 will be presented by site, vaccine group, and relatedness. Listings of the serious adverse events will also be presented. Adverse events of clinical interest include syncope during post-vaccination monitoring in clinic, anaphylaxis in the first 24 hours after immunization, and new onset immune-mediated disease as defined in Appendix A.

8.3 Exploratory Objectives

1. To compare the proportion of participants with at least one severe (Grade 3) solicited local or systemic reactogenicity event on days 1-8 after RZV dose 2 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group.

   The proportions of participants with at least one severe (Grade 3) solicited local or systemic reactogenicity event on days 1-8 after RZV dose 2 in the mITT Population will be compared between vaccine groups using the same statistical methodology as for Primary Objective 1. A one-sided site-stratified noninferiority test to determine if RZV dose 2 and allV4 is noninferior to RZV dose 2 and HD-IIV4 with the alpha level set at 0.025 and a 10% noninferiority margin.

   This information will also be presented by age-group for the subset of subjects aged 65-69 versus those subjects aged 70 years or older. No formal statistical hypothesis testing (i.e., no p-values) will be performed, only the confidence boundary of the difference will be presented.

2. To compare the proportion of participants with at least one severe (Grade 3) solicited local reactogenicity event on days 1-8 after RZV dose 2 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group.

   The proportions of participants with at least one severe (Grade 3) solicited local reactogenicity event on days 1-8 after RZV dose 2 in the mITT Population will be compared between vaccine groups using the same statistical methodology as for Primary Objective 1. A one-sided site-stratified noninferiority test to determine if RZV dose 2 and allV4 is noninferior to RZV dose 2 and HD-IIV4 with the alpha level set at 0.025 and a 10% noninferiority margin.

This information will also be presented by age-group for the subset of subjects aged 65-69 versus those subjects aged 70 years or older. No formal statistical hypothesis testing (i.e., no p-values) will be performed, only the confidence boundary of the difference will be presented.

3. To compare the proportion of participants with at least one severe (Grade 3) solicited systemic reactogenicity event on days 1-8 after RZV dose 2 in the RZV and aIIV4 group vs. RZV and HD-IIV4 group.

   The proportions of participants with at least one severe (Grade 3) solicited systemic reactogenicity event on days 1-8 after RZV dose 2 in the mITT Population will be compared between vaccine groups using the same statistical methodology as for Primary Objective 1. A one-sided site-stratified noninferiority test to determine if RZV dose 2 and aIIV4 is noninferior to RZV dose 2 and HD-IIV4 with the alpha level set at 0.025 and a 10% noninferiority margin.

   This information will also be presented by age-group for the subset of subjects aged 65-69 versus those subjects aged 70 years or older. No formal statistical hypothesis testing (i.e., no p-values) will be performed, only the confidence boundary of the difference will be presented.

4. To compare the proportion of participants with at least one serious adverse event or adverse event of clinical interest after RZV dose 2 in the RZV and aIIV4 group vs. RZV dose 2 and HD-IIV4 group and describe these events through the entire study period.

   The proportion and 95% exact binomial confidence interval in the ITT Population of serious adverse events and events of clinical interest through the entire study period will be presented by site, vaccine group, and relatedness. Listings of the serious adverse events will also be presented. Non-overlapping confidence boundaries will be an indication of a statistical difference between the vaccine groups.

5. To compare the proportion of participants with moderate-to-severe (Grade 2-3) solicited local or systemic reactogenicity event on days 1-8 after RZV dose 1 in the RZV and aIIV4 group vs. RZV dose 1 and HD-IIV4 group.

   The proportions of participants with at least one moderate-to-severe (Grade 2-3) solicited local or systemic reactogenicity event on days 1-8 after RZV dose 1 in the mITT Population will be compared between vaccine groups using the same statistical methodology as for Primary Objective 1. A one-sided site-stratified noninferiority test to determine if RZV dose 1 and aIIV4 is noninferior to RZV dose 1 and HD-IIV4 with the alpha level set at 0.025 and a 10% noninferiority margin.

   This information will also be presented by age-group for the subset of subjects aged 65-69 versus those subjects aged 70 years or older. No formal statistical hypothesis testing (i.e., no p-values) will be performed, only the confidence boundary of the difference will be presented.

6. To compare the proportion of participants with moderate-to-severe (Grade 2-3) solicited local or systemic reactogenicity event on days 1-8 after RZV dose 2 in the RZV and aIIV4 group vs. RZV dose 2 and HD-IIV4 group.

The proportions of participants with at least one moderate-to-severe (Grade 2-3) solicited local or systemic reactogenicity event on days 1-8 after RZV dose 2 in the mITT Population will be compared between vaccine groups using the same statistical methodology as for Primary Objective 1. A one-sided site-stratified noninferiority test to determine if RZV dose 2 and aIIV4 is noninferior to RZV dose 2 and HD-IIV4 with the alpha level set at 0.025 and a 10% noninferiority margin.

This information will also be presented by age-group for the subset of subjects aged 65-69 versus those subjects aged 70 years or older. No formal statistical hypothesis testing (i.e., no p-values) will be performed, only the confidence boundary of the difference will be presented.

7. To compare serum hemagglutination inhibition (HAI) antibody titers after RZV dose 1 and HD-IIV4 with RZV dose 1 and aIIV4 for each of the four influenza vaccine strains contained in the respective vaccine for that season in the full study population and by age.

   The proportion of subjects achieving seroconversion at day 29 (an HAI titer > 1:40 at day 29 if the baseline titer is < 1:10 or a minimum four-fold rise in HAI titer if the baseline titer is > 1:10) for each influenza strain in the respective season's vaccine in each vaccine group will be presented along with the difference between vaccine groups and a 95% confidence interval of the difference in proportions.

   The proportion of subjects with a seroprotective HAI titer (≥ 1:40) pre- and post-immunization at day 29 for each IIV antigen in the respective season's vaccine in each vaccine group will be presented along with a 95% confidence interval, as well as the difference between vaccine groups and a 95% confidence interval of the difference in proportions.

   The geometric mean HAI titer (GMT) at Day 1 and Day 29 for each IIV antigen in the respective season's vaccine in each vaccine group will be presented along with a 95% confidence interval, as well as the difference between vaccine groups (on the log10 scale) and a 95% confidence interval of the difference in GMTs for each vaccine group (on the log10 scale).

   The geometric mean fold rise (GMFR) in HAI titer at Day 29 for each IIV antigen in the respective season's vaccine in each vaccine group will be presented along with a 95% confidence interval.

   This information will also be prepared by age-group (65-69 years and ≥70 years).

8. To describe and compare changes in health-related quality of life after RZV dose 1 and aIIV4 with RZV dose 1 and HD-IIV4 in the full study population and by age-group (administered on study Day 60).

EQ-5D and EQ VAS Scale

The EQ-5D is a standardized, generic measure of health status that provides information on health-related quality of life and activities of daily living relevant to older adults: mobility, self-care, usual activities, pain/discomfort and anxiety/depression (http://www.euroqol.org/)

(23). In addition, the instrument contains the EQ Visual Analogue Scale (EQ-VAS) which measures the respondent's self-rated health.

The EQ-5D-5L is the new version of the EQ-5D that increases the levels of severity from three to five to significantly increase reliability and sensitivity while maintaining feasibility and reducing ceiling effects. The descriptive system comprises 5 dimensions of mobility, self-care, usual activities, pain/discomfort, anxiety/depression. For each of these dimensions, there are 5 response levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking in the box against the most appropriate statement in each of the 5 dimensions. This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state from 11111 as best health and 55555 as worst health. These numbers are converted to a Utility Index that ranges from -0.109 (worst health) to 1.000 (best health) for US specific values. The minimum clinically important difference ranges from 0.05 to 0.1 depending on health conditions being studied. The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' (100) and 'the worst health you can imagine' (0). The respondent marks an 'X' on the scale number to indicate how their health is 'today.' The minimum clinically important difference on the VAS is 8.

The EQ VAS has a range of 0 (worst health) to 100 (best health).

Post-vaccination EQ-5D and EQ VAS index values will be calculated by the lowest/worst index value scores from baseline. The changes from baseline for the index values will be assessed within vaccine group using a linear regression model adjusting for site since these will follow a normal distribution. The VAS minimum clinically important difference is 8, so categorical comparisons (less than 8 points, within 8 points, greater than 8 points) will be made using a Mantel-Haenszel statistic in a stratified analysis by site. The Mann-Whitney U test (Wilcoxon rank-sum test) will be used to compare the difference scores from baseline between the two vaccine groups for the index values and VAS.

The statistical tests described above will also be performed by age-group (65-69 years and ≥70 years). This testing will be considered exploratory with an alpha level of 0.05 with no alpha adjustment.

9 REFERENCES

Xin Yan & Xiao Gang Su (2010) Stratified Wilson and Newcombe Confidence Intervals for Multiple Binomial Proportions, Statistics in Biopharmaceutical Research, 2:3, 329-335, DOI: 10.1198/sbr.2009.0049

Appendix A: Immune-Mediated Conditions

Gastrointestinal disorders	**Liver disorders**
• Celiac disease • Crohn's disease • Ulcerative colitis • Ulcerative proctitis	• Autoimmune cholangitis • Autoimmune hepatitis • Primary biliary cirrhosis • Primary sclerosing cholangitis
Musculoskeletal disorders	**Neuroinflammatory disorders**
• Antisynthetase syndrome • Dermatomyositis • Mixed connective tissue disorder • Polymyalgia rheumatic • Polymyositis • Psoriatic arthropathy • Relapsing polychondritis • Rheumatoid arthritis • Scleroderma, including diffuse systemic form and CREST syndrome • Spondyloarthritis, including ankylosing spondylitis, reactive arthritis (Reiter's Syndrome) and undifferentiated spondyloarthritis • Systemic lupus erythematosus • Systemic sclerosis	• Acute disseminated encephalomyelitis, including site specific variants (e.g., non-infectious encephalitis, encephalomyelitis, myelitis, myeloradiculomyelitis) • Cranial nerve disorders, including paralyses/paresis (e.g., Bell's palsy) • Guillain-Barré syndrome, including Miller Fisher syndrome and other variants • Immune-mediated peripheral neuropathies and plexopathies, including chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy and polyneuropathies associated with monoclonal gammopathy • Multiple sclerosis • Narcolepsy • Optic neuritis • Transverse myelitis • Myasthenia gravis, including Eaton-Lambert syndrome
Metabolic diseases	**Skin disorders**
• Addison's disease • Autoimmune thyroiditis (including Hashimoto thyroiditis) • Diabetes mellitus type I • Grave's or Basedow's disease	• Alopecia areata • Autoimmune bullous skin diseases, including pemphigus, pemphigoid and dermatitis herpetiformis • Cutaneous lupus erythematosus • Erythema nodosum • Erythema multiforme • Morphea • Lichen planus • Psoriasis • Sweet's syndrome • Vitiligo
Vasculitides	**Others**
• Large vessels vasculitis including: giant cell arteritis such as Takayasu's arteritis and temporal arteritis • Medium sized and/or small vessels vasculitis including: polyarteritis nodosa, Kawasaki's disease, microscopic polyangiitis, Wegener's granulomatosis, Churg–Strauss syndrome	• Antiphospholipid syndrome • Autoimmune hemolytic anemia • Autoimmune glomerulonephritis (including IgA nephropathy, glomerulonephritis rapidly progressive, membranous glomerulonephritis, membranoproliferative glomerulonephritis, and mesangioproliferative glomerulonephritis) • Autoimmune myocarditis/cardiomyopathy

(allergic granulomatous angiitis), Buerger's disease thromboangiitis obliterans, necrotizing vasculitis and anti-neutrophil cytoplasmic antibody (ANCA) positive vasculitis (type unspecified), Henoch-Schonlein purpura, Behcet's syndrome, leukocytoclastic vasculitis	• Autoimmune thrombocytopenia • Goodpasture syndrome • Idiopathic pulmonary fibrosis • Pernicious anemia • Raynaud's phenomenon • Sarcoidosis • Sjögren's syndrome • Stevens-Johnson syndrome • Uveitis