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

(ClinicalTrials.gov ID: NCT05007041)

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Disclaimer

- The findings and conclusions in this presentation are those of the presenter and do not necessarily represent the official position of the Centers for Disease Control and Prevention
- Mention of a product or company name is for identification purposes only and does not constitute endorsement by CDC
- This study was supported by the CDC Clinical Immunization Safety Assessment (CISA) Project

Study Team

- **Duke University**
  - Principal Investigator: Kenneth Schmader, MD
  - Investigators: Emmanuel B. Walter, MD, MPH, Wes Rountree, MPH, Marek S. Poniewierski MD, MS
- **CDC**
  - Principal Investigator: Karen Broder, MD
  - Investigators: Michael McNeil, MD, MPH, Oidda Museru MSN, MPH
- **John Hopkins University (JHU)**
  - Principal Investigator: Kawsar Talaat, MD

Rationale

- Novel (nonaluminum) adjuvants are powerful immune stimulants employed in vaccine platforms to improve immunogenicity and efficacy. In recent years, the FDA licensed several vaccines with novel adjuvants
- Vaccines with novel adjuvants are more reactogenic than vaccines without adjuvants.
- Clinicians may opt to administer these vaccines simultaneously.
- Data are needed on the safety of the simultaneous administration of vaccines with novel adjuvants
- For older adults seeking to prevent herpes zoster and influenza, data are needed on the safety of simultaneous administration of recombinant zoster vaccine (RZV; Shingrix) and quadrivalent adjuvanted inactivated influenza vaccine (aIIV4; Fluad Quadrivalent)

Study Design and Population

- Type:
  - Prospective, randomized, observer blinded clinical trial
  - Blinded except for vaccine administrator
- Population:
  - Immunocompetent, cognitively intact, community-dwelling persons, aged ≥65 years
  - Not received the seasons flu vaccine or RZV
  - Subjects enrolled at Duke University Medical Center (Lead Site) and Johns Hopkins University (Contributing Site) during the 2021-2022 and 2022-2023 flu seasons
- Intervention:
  - Randomized 1:1 to receive either <RZV and aIIV4> or <RZV and HD-IIV4*>
- Study visit schedule (summary):
  - Day 1: receive RZV dose 1 and influenza vaccine simultaneously
  - Day 60:receive RZV dose 2
  - Day 103:complete study
  - Safety outcomes collected throughout study; blood collected for influenza immunogenicity assessment (lab analysis not completed)

*quadrivalent high-dose inactivated influenza vaccine (Fluzone High-dose Quadrivalent)

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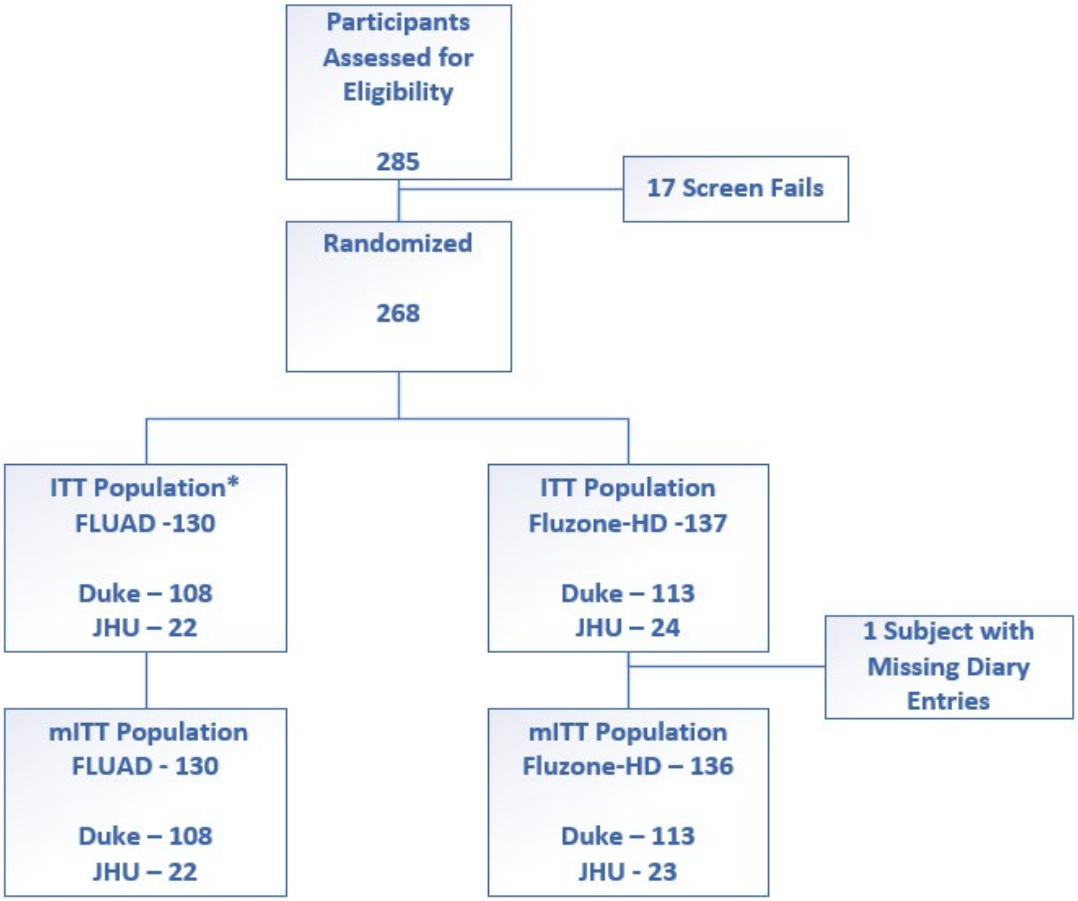
Analysis Populations

Intention-to-Treat (ITT) Population: defined as all subjects who are randomized and vaccinated (received at least one study vaccine).

Modified Intention-to-Treat (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.

Consort Diagram



*Incorrect age group randomization. Subject was terminated because they had already been randomized. This subject was then re-randomized using the correct age group and provided a new Subject ID.

Demographic Summary

Characteristic	Fluzone-HD (n=137)	FLUAD (n=130)	Total (N= 267)
Gender			
Male	68 (49.6%)	69 (53.1%)	137 (51.3%)
Female	69 (50.4%)	61 (46.9%)	130 (48.7%)
Race			
White Only	124 (90.5%)	123 (94.6%)	247 (92.5%)
Black Only	12 (8.8%)	7 (5.4%)	19 (7.12%)
Other	1 (0.7%)	0 (0.0%)	1 (0.37%)
Ethnicity			
Hispanic or Latino	1 (0.7%)	2 (1.5%)	3 (1.12%)
Non-Hispanic or Latino	134 (97.8%)	128 (98.5%)	262 (98.1%)
Unknown	2 (1.5%)	0 (0.0%)	2 (0.75%)
Age			
65-69	48 (35%)	44 (33.8%)	92 (34.5%)
70 or more	89 (65%)	86 (66.2%)	175 (65.5%)

Primary Objective

PO1: 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 versus RZV and HD-IIV4 group.

Hypothesis: The proportion of participants with at least one severe (Grade 3) solicited reactogenicity event will be noninferior (not higher) in the RZV and aIIV4 group compared with the RZV and HD-IIV4 group.

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Primary Outcome: mITT Population

Outcome: Proportion of participants with at least one severe (Grade 3) solicited local or systemic reactogenicity event on days 1-8 after RZV dose 1 in each study group

	1+ Grade 3 Event							
	No		Yes		Noninferiority Test 10% Margin			
Group	N	%	N	%	Diff	Lower CI	Upper CI	p-value
FLUAD	115	88.46	15	11.54	.	.	.	.
Fluzone-HD	119	87.50	17	12.50	-0.0096	-0.0894	0.0710	0.0037

***Met noninferiority objective with a 10% noninferiority margin, the upper bound is less than 10%. The confidence interval contains 0, so there is no claim of superiority.**

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Secondary Objectives

- **SO1:** 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 dose 1 and HD-IIV4 group (non-inferiority analysis)

- **SO2:** 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 dose 1 and HD-IIV4 group (non-inferiority analysis)

- **SO3:** 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 (95% confidence interval (CI) comparison)

Secondary Outcome SO1:mITT Population

SO1: 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

	1+ Grade 3 Event							
	No		Yes		Noninferiority Test 10% Margin			
Group	N	%	N	%	Diff	Lower CI	Upper CI	p-value
FLUAD	122	93.85	8	6.15	.	.	.	.
Fluzone-HD	130	95.59	6	4.41	0.0174	-0.0404	0.0777	0.0031

***Met noninferiority objective with a 10% noninferiority margin, the upper bound is less than 10%. The confidence interval contains 0, so there is no claim of superiority.**

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Secondary Outcome SO2:mITT Population

SO2: 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

	1+ Grade 3 Event							
	No		Yes		Noninferiority Test 10% Margin			
Group	N	%	N	%	Diff	Lower CI	Upper CI	p-value
FLUAD	123	94.62	7	5.38	.	.	.	.
Fluzone-HD	123	90.44	13	9.56	-0.0417	-0.1090	0.0247	<.0001

***Met noninferiority objective with a 10% noninferiority margin, the upper bound is less than 10%. The confidence interval contains 0, so there is no claim of superiority**

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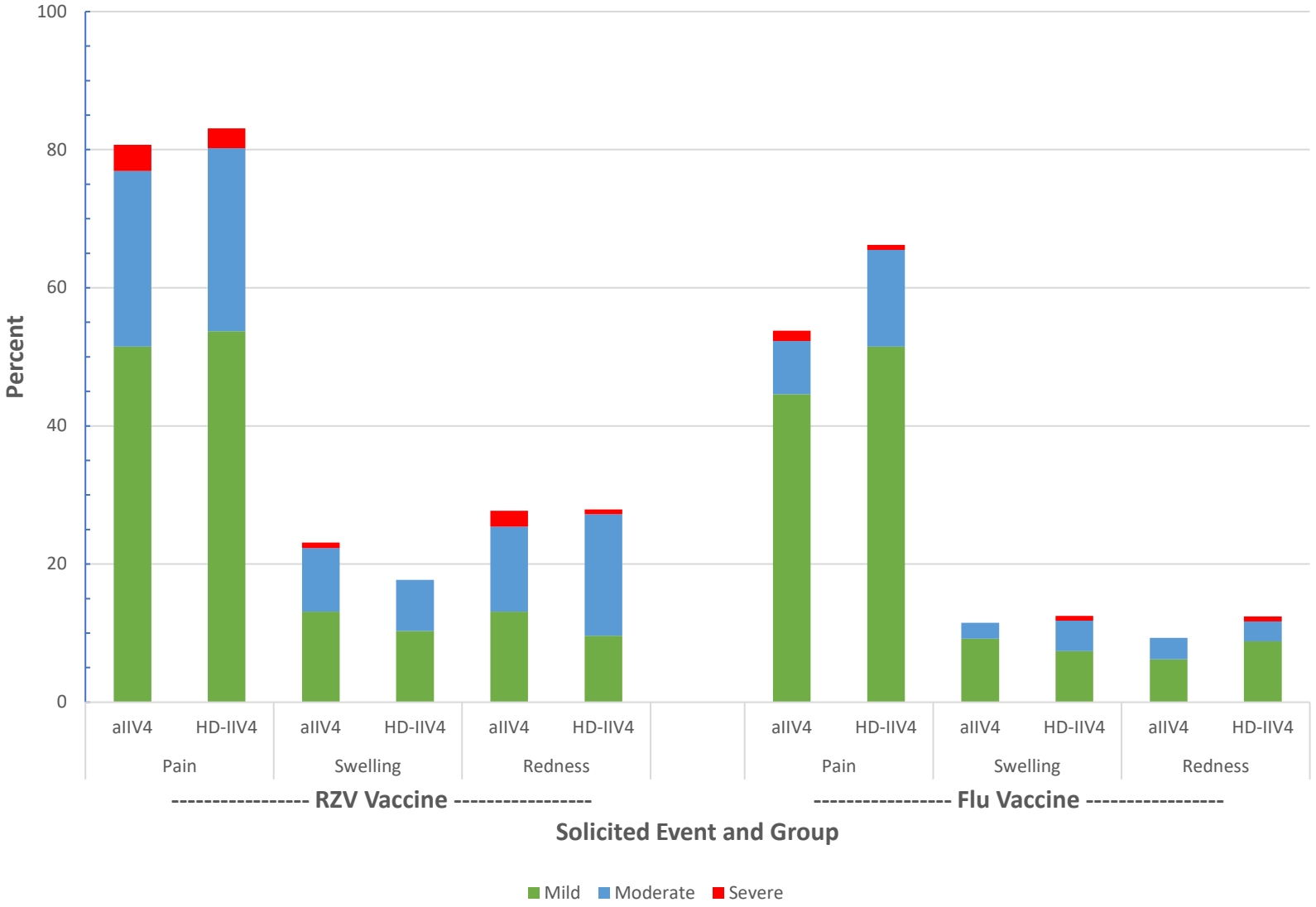
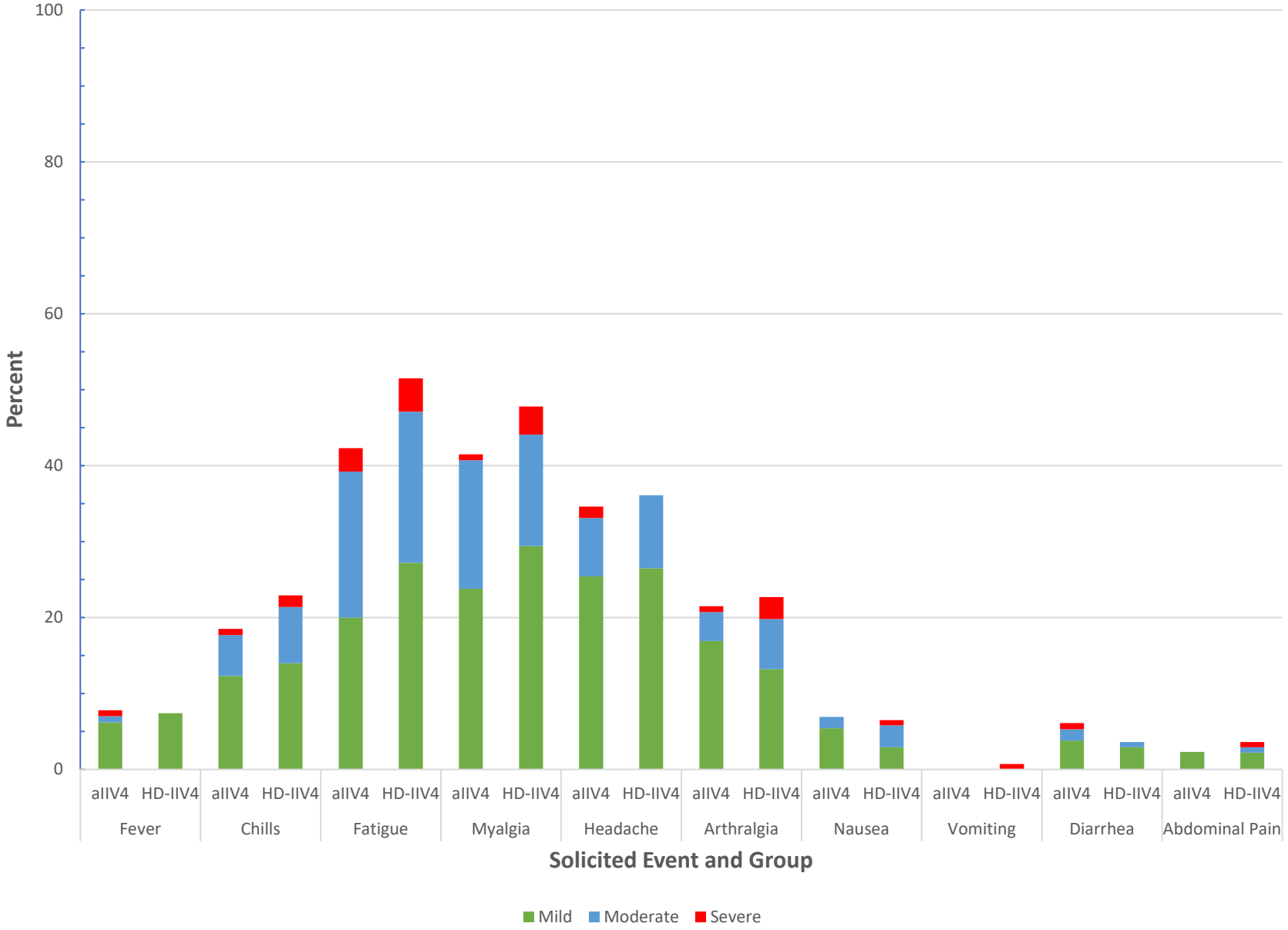
Local Reactions: RZV Dose 1 and Influenza Vaccines



No significant differences in proportion of moderate/severe local reactogenicity events between aIIV4 and HD-IIV4 groups

Systemic Reactions: RZV Dose 1 and Influenza Vaccines



No significant differences in proportion of moderate/severe systemic reactogenicity events between aIIV4 and HD-IIV4 groups

Secondary Outcome SO3: ITT Population

Subjects with at Least One Serious Adverse Event (SAE) Within 43 Days

SO3: Proportion of participants with at least one serious adverse event or adverse event of clinical interest after RZV dose 1 within 43 days.

- 6 Subjects reported at least one SAE within 43 Days

	At Least One Serious Adverse Event Within 43 Days					
	No		Yes		Percent Yes	FLUAD-Fluzone-HD 95% CI of the Difference
Group	N	%	N	%	95% CI	95% CI
FLUAD	129	99.23	1	0.77	(0.02, 4.21)	
Fluzone-HD	132	96.35	5	3.65	(1.20, 8.31)	-2.88 (-6.36, 0.60)

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ITT Population
All Subjects with at Least One Serious Adverse Event through Entire Study Period

- 9 subjects reported at least one SAE during study period

	At Least One Serious Adverse Event					
	No		Yes		Percent Yes	FLUAD-Fluzone-HD 95% CI of the Difference
Group	N	%	N	%	95% CI	95% CI
FLUAD	126	96.92	4	3.08	(0.84, 7.69)	
Fluzone-HD	132	96.35	5	3.65	(1.20, 8.31)	-0.57 (-4.89, 3.75)

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Summary of SAEs within 43 days of RZV dose 1 and influenza vaccination*

Group	Age group years	Relatedness	Clinical description
aIIV4	≥70	Not related	**Pacemaker due to arrhythmia**
HD-IIV4	65-69	Not related	**Numbness, Cerebrovascular accident (CVA)**
HD-IIV4	≥70	Not related	**Acute hyperkalemia**
HD-IIV4	≥70	Not related	**Shortness of breath**
HD-IIV4	≥70	Not related	**Acute pulmonary embolism and acute deep vein thrombosis**
HD-IIV4	65-69	Possibly related	**Left partial cranial nerve III palsy**

*All participants with SAE required hospitalization or had prolongation of hospitalization; no deaths

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Summary of SAEs >43 days of RZV dose 1 and influenza vaccination *

Group	Age group years	Relatedness	Clinical description
aIIV4	≥70	Not related	**Heptocellular carcinoma**
aIIV4	≥70	Not related	**Revision of right shoulder rotator cuff surgery**
aIIV4	65-69	Not related	**Chronic obstructive pulmonary diseases (COPD) exacerbation**

*All participants with SAE required hospitalization or had prolongation of hospitalization; no deaths

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Safety Assessments: Adverse Events

- Pre-specified Adverse Events of Special Interest (AESI)
  - Syncope during the post-vaccination monitoring period in clinic: none
  - Anaphylaxis in the first 24 hours after immunization: none
  - New-onset immune-mediated disease during 42 days after vaccination: one case of partial cranial nerve III palsy (also considered an SAE): patient was in the HD-IIV4 group

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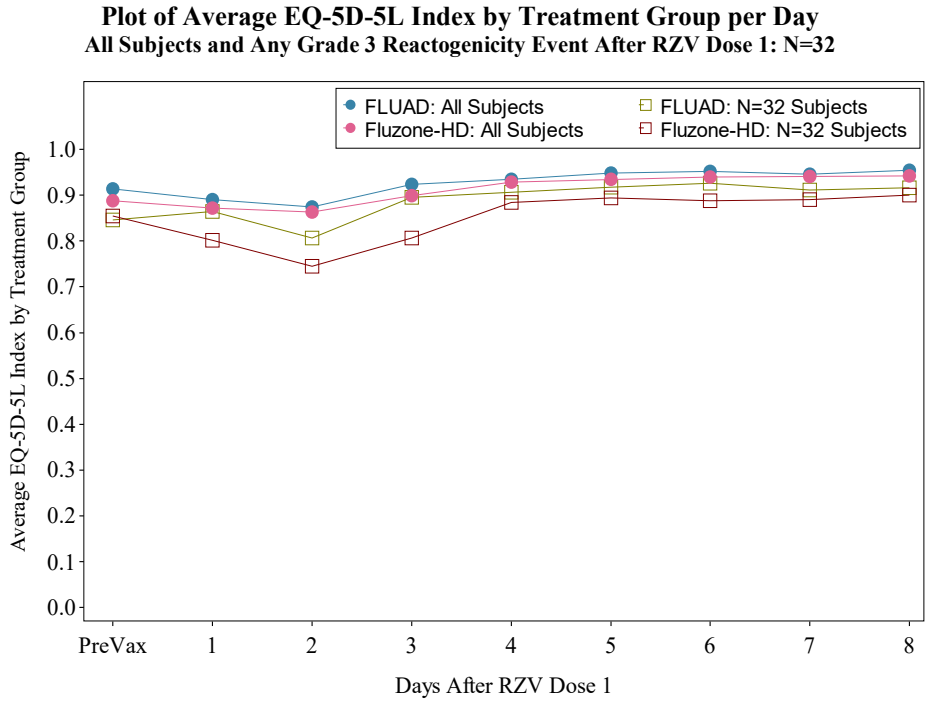
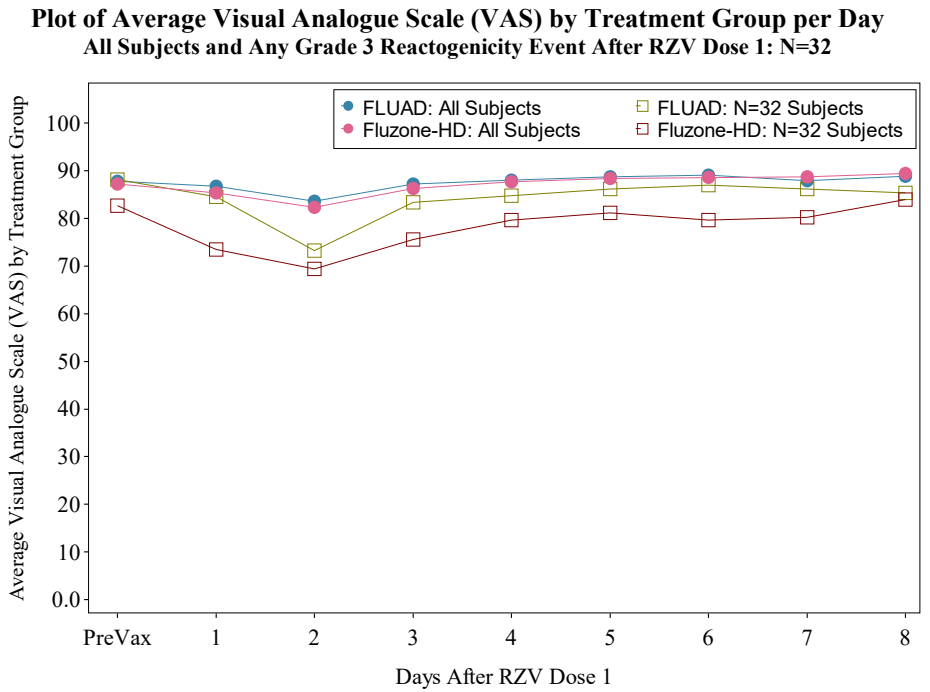
Exploratory Objective

- Objective: To describe and compare changes in health-related quality of life after RZV dose 1 and aIIV4 with RZV dose 1 and HD-IIV4





Limitations

- Enrollment limited by COVID-19 pandemic; enrolled ~70% of target
- Study population mostly white, non-Hispanic
- Study too small to detect rare adverse events

Conclusion

- The proportion of participants with at least one severe local or systemic reaction was not higher after RZV dose 1 and aIIV4 (11.5%) compared to RZV dose 1 and HD-IIV4 (12.5%)
- The frequency of moderate-severe local and systemic reactogenicity events were similar when RZV dose 1 was administered with aIIV4 or HD-IIV4
- Few participants had serious adverse events during the study after RZV dose 1 was administered with aIIV4 (3.1%) or HD-IIV4 (3.7%); the clinical conditions were those expected in a population of older adults
- From a safety standpoint, this study supports simultaneous administration of RZV and aIIV4 as an acceptable option for vaccine delivery in older adults

Extra Slides

Serious Adverse Event Definition

- An SAE is defined as an adverse event that results in one of the following:
  - Death
  - Is life threatening
  - Hospitalization or prolongation of existing hospitalization
  - Persistent or significant disability/incapacity
  - Important medical events that may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this (SAE) definition

Injection Site Reactions Grading

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

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Systemic Reactions Grading

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
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

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EQ-5D-5L and VAS

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY
- I have no problems walking ❑
- I have slight problems walking ❑
- I have moderate problems walking ❑
- I have severe problems walking ❑
- I am unable to walk ❑

SELF-CARE
- I have no problems washing or dressing myself ❑
- I have slight problems washing or dressing myself ❑
- I have moderate problems washing or dressing myself ❑
- I have severe problems washing or dressing myself ❑
- I am unable to wash or dress myself ❑

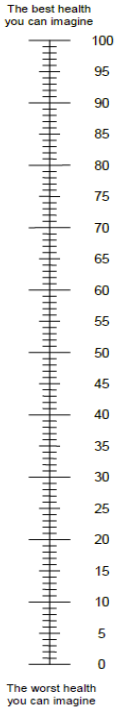
USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*
- I have no problems doing my usual activities ❑
- I have slight problems doing my usual activities ❑
- I have moderate problems doing my usual activities ❑
- I have severe problems doing my usual activities ❑
- I am unable to do my usual activities ❑

PAIN / DISCOMFORT
- I have no pain or discomfort ❑
- I have slight pain or discomfort ❑
- I have moderate pain or discomfort ❑
- I have severe pain or discomfort ❑
- I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION
- I am not anxious or depressed ❑
- I am slightly anxious or depressed ❑
- I am moderately anxious or depressed ❑
- I am severely anxious or depressed ❑
- I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Subject Inclusion Criteria

- Male or female age ≥ 65 years
- Intention of receiving IIV and RZV based on ACIP-CDC guidelines
- Able to speak English
- Willing to provide written informed consent
- Living in the community
- Intention of being available for entire study period and complete all relevant study procedures, including follow-up phone calls and clinic visits.
- If HIV positive, HIV should be clinically stable

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Subject Exclusion Criteria

- IIV or recombinant influenza vaccine (RIV) receipt during the respective 2021-2022 or 2022-2023 influenza season prior to study enrollment
- Prior receipt of recombinant zoster vaccine (Shingrix)
- For non-COVID-19 Vaccines:
  - Receipt of any inactivated vaccine within 2 weeks prior to enrollment in this study
  - Receipt of any live vaccine within 4 weeks prior to enrollment in this study
  - Planning receipt of any non-COVID-19 vaccine during the entire period
- For COVID-19 Vaccines:
  - Receipt of COVID-19 vaccine within 2 weeks prior to enrollment in this study. For those who have initiated a COVID-19 vaccine series, enrollment is not allowed until 2 weeks after the final dose of a COVID-19 vaccine is completed.
  - Planning receipt of a COVID-19 vaccine within 2 weeks after administration of study influenza and first dose recombinant zoster study vaccines.
- Have acute illness or exacerbation of chronic illness within 72 hours of study vaccination
- Hospitalization within the last 30 days for any reason
- History of febrile illness (> 100.0°F or 37.8°C) within the past 24 hours prior to IIV administration
- Has immunosuppression as a result of an underlying illness or treatment, or use of chemotherapy or radiation therapy within the preceding 12 months
- Has an active neoplastic disease (excluding non-melanoma skin cancer or prostate cancer that is stable in the absence of therapy) *Participants with a history of malignancy may be included if, after previous treatment by surgical excision, chemotherapy or radiation therapy, the participant has been observed for a period that in the investigator's estimation provides a reasonable assurance of sustained cure
- A history of autoimmune disease, that requires immunosuppressive agents or any other chronic medical condition considered clinically significant by the investigator

Subject Exclusion Criteria

- Use of chronic oral or intravenous administration (≥14 days) of immunosuppressive doses of steroids, i.e., prednisone >10 mg per day, immunosuppressants or other immune-modifying drugs within 30 days of starting this study. (Use of topical, nasal, or inhaled steroids is permitted)
- Thrombocytopenia, bleeding disorder, or anticoagulant use contraindicating intramuscular injection (a daily aspirin may be acceptable)
- Contraindication to IIV receipt including history of severe allergic reaction after a previous dose of any influenza vaccine; or to a vaccine component, including egg protein
- Contraindication to RZV including history of a severe allergic reaction to any component of the RZV vaccine (including saponin or polysorbate 80) or to dose 2 of RZV
- History of Guillain-Barré syndrome
- History of Hepatitis C or active Hepatitis B
- Receipt of blood or blood-derived products (including immunoglobulin) within 6 months prior to study vaccination
- Dementia, any cognitive condition, or substance abuse that could interfere with study compliance
- Anyone who is already enrolled or plans to enroll in another clinical trial with an investigational product within 28 days of vaccine receipt. Co-enrollment in observational or behavioral intervention studies are allowed at any time while enrollment in a clinical trial involving an investigational product (other than vaccine) may occur after 28 days following vaccine receipt
- Any condition which, in the opinion of the investigators, may pose a health risk to the subject or interfere with the evaluation of the study objectives
- Anyone who is a relative of any research study personnel
- Anyone who is an employee of any research study personnel