



Infectious Disease Practice

Long-term immunogenicity and safety of RZV primary vaccination and revaccination in kidney transplant recipients



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SUMMARY

Objectives: Immunogenicity and safety of recombinant zoster vaccine (RZV) were evaluated in the long-term and after revaccination in kidney transplant (KT) recipients on daily chronic immunosuppressive treatment.

Methods: This phase 3b, single-arm, multicenter trial, evaluated KT recipients for varicella zoster virus (VZV) glycoprotein E (gE)-specific humoral and cell-mediated immune (CMI) responses and safety ~4–8 years post-primary RZV series (two doses) given at ≥18 years of age; and after revaccination (two doses, one month apart), ~6–8 years post-primary RZV series. Solicited and unsolicited adverse events (AEs) were recorded for seven and 30 days after each revaccination dose. Serious AEs (SAEs), including biopsy-proven allograft rejection and potential immune-mediated diseases, were recorded throughout the study.

Results: 68 participants were enrolled and 47 revaccinated. Persistent humoral and CMI responses remained ≥2.4-fold and ≥6.1-fold above pre-vaccination levels. One revaccination dose provided robust

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humoral (22.3-fold) and CMI (276.2-fold) above pre-vaccination responses. No vaccine-related SAEs were observed.

Conclusions: This study demonstrates sustained immunogenicity against VZV gE for up to ≥ 8 years, functional immune memory with a robust anamnestic response at 6–8 years, and an acceptable safety profile after revaccination, reinforcing RZV's value for herpes zoster prevention in adult KT recipients on daily immunosuppression.

Clinical trial registration: NCT04176939

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Introduction

The availability of the adjuvanted recombinant zoster vaccine (RZV, *Shingrix*, GSK) was an important development for the prevention of herpes zoster (HZ) in at-risk immunocompromised (IC) individuals. The persistence of immune responses following primary vaccination and durable immune memory contribute important evidence toward understanding long-term RZV-mediated protection against HZ.

HZ is a disease characterized by a painful vesicular rash, typically confined to a single dermatome.¹ The risk of HZ increases due to factors that weaken the immune system or affect immune function, such as age and immunocompromising conditions or therapies.^{2,3} Moreover, IC populations face higher risks of severe HZ and complications such as postherpetic neuralgia or disseminated disease,⁴ emphasizing the importance for HZ prevention within these at-risk populations. RZV is currently the only vaccine option for people with severe immunosuppression, as live-attenuated vaccines are contraindicated.⁵

RZV, a subunit vaccine consisting of varicella zoster virus (VZV) glycoprotein E (gE) and the AS01_B Adjuvant System, was initially approved by the United States (US) Food and Drug Administration and the European Medicines Agency for the prevention of HZ in people ≥ 50 years of age (YOA).^{6,7} The indication was extended to individuals ≥ 18 YOA who are or will be at increased risk of HZ due to immunodeficiency or immunosuppression caused by known disease or therapy in the US and individuals ≥ 18 YOA who are at increased risk of HZ in the European Union.^{6,7} RZV is widely approved globally, including additional countries across Asia and Latin America.⁸

RZV was studied in adult (≥ 18 YOA) IC individuals, including those with HIV, solid tumors, hematologic malignancies, autologous stem cell transplants, and kidney transplant (KT), and was found to be both efficacious and immunogenic.^{9–13} During a median follow-up of 21 months, RZV efficacy against HZ was 68.2% in individuals who underwent autologous hematopoietic stem cell transplantation (auHSCT)¹² and a post-hoc analysis with a median follow-up of 11.1 months, showed that RZV efficacy against HZ was 87.2% in individuals with hematologic malignancies.^{11,12} Humoral and cell-mediated immune (CMI) responses remained above pre-vaccination baseline levels until at least 12 months after the last dose in all clinical trials^{9,10,12,13} and until at least 24 months in individuals who underwent auHSCT.^{9–13} While vaccination in general is more challenging in IC individuals because of biological and treatment-related factors,^{14–16} these findings demonstrate that vaccination with RZV can still elicit robust immune responses and provide efficacy in those at increased risk. A pooled safety analysis of studies showed that RZV has a clinically acceptable safety profile in IC populations that, along with vaccine efficacy and immunogenicity results, supports a favorable benefit-risk profile of RZV vaccination in IC populations who are at an increased risk of HZ.¹⁷

To evaluate the durability of immune response and long-term safety in an IC/immunosuppressed population, KT recipients were selected as representatives of patients who are immunocompromised secondary to the sustained use of immunosuppressive medications required to prevent transplant

rejection. These data are informative and may be reassuring for RZV use in other IC cohorts; however, they should not be construed as definitive evidence for all IC patient groups or other solid organ transplant-type recipients.

Participants for this study were enrolled based on their participation in the RZV arm of the parent study, a phase 3 randomized clinical trial evaluating immunogenicity and safety of RZV in adult KT recipients on daily chronic immunosuppressive treatment (CIST).¹³ In the parent study, participants received two doses of RZV or placebo (N=132 each) 4–18 months after KT. RZV was immunogenic with an acceptable safety profile through at least 12 months post-primary vaccination series.¹³

Objectives of the present extension study were to assess the safety and persistence of immune responses to RZV approximately 4–8 years after primary vaccination, as well as to assess the immunogenicity and safety of revaccination with two RZV doses given 1–2 months apart, 6–8 years after primary vaccination, in KT recipients taking daily CIST.

Materials and methods

Study design and population

This phase 3b, open-label, single-arm, long-term follow-up (LTFU) study with revaccination phase (ClinicalTrials.gov: NCT04176939) was conducted at 15 sites in seven countries (Spain, Canada, South Korea, Belgium, Finland, Panama, and Taiwan) between December 2019 and August 2024. The parent study concluded with a final follow-up visit at 12 months post-dose 2 of the primary vaccination series, as originally designed.¹³ Participants in this extension study were enrolled following a minimum of two years after the completion of the parent study.

KT recipients were eligible for the LTFU phase if they had received two RZV doses 1–2 months apart in the parent study (NCT02058589),¹³ without receiving any HZ vaccination after the parent study completion. This extension study evaluated RZV-specific immune responses and safety through 6–8 years post-primary vaccination series (Fig. 1). Due to timing differences between the last visit in the parent study and the first visit in this extension study, each annual visit in the extension study corresponded to an overlapping range of approximately two years after the completion of the primary vaccination series (also referred to as years post-dose 2 [YPD2]): Visit 1 (~4–6 YPD2), Visit 2 (~5–7 YPD2), and Visit 3 (~6–8 YPD2) (Fig. 1). For clarity and clinical context, study data are presented in terms of YPD2 rather than by study visit timing. Each year is defined as a one-year range, e.g., 4YPD2 represents data collected from 3.5 to less than 4.5 YPD2.

Participants who were ineligible for or opted out of revaccination remained under evaluation for immunogenicity and safety following primary vaccination until the study's conclusion. While these data are included in figures and tables, they are excluded from the study's conclusions due to the limited sample size.

KT recipients were eligible for the revaccination phase of this study if they had a functional allograft, were on maintenance CIST—including mycophenolate compounds, calcineurin inhibitors,

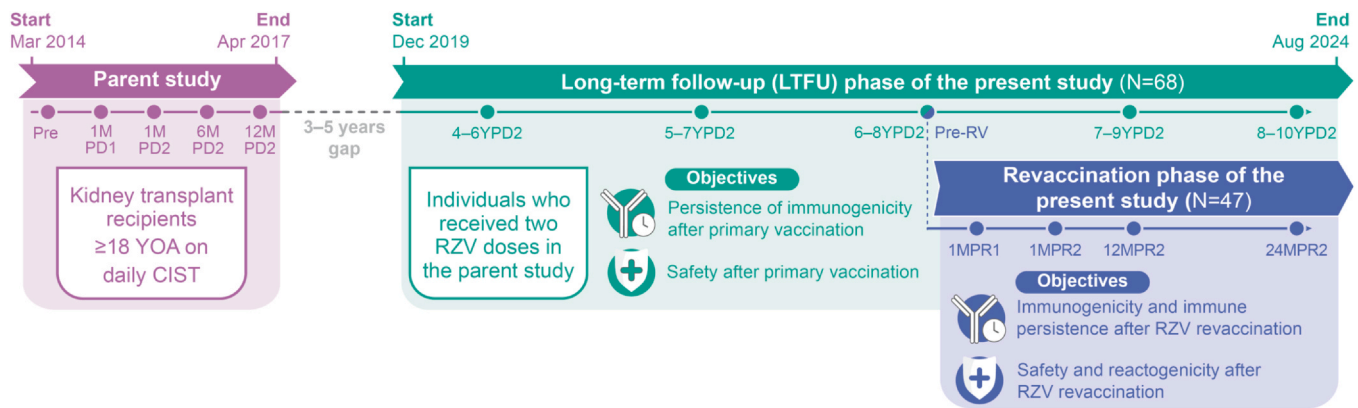


Fig. 1. Study design. The initial RZV dose of the two-dose revaccination series was administered at 6–8YPD2/Pre-RV, approximately two years after the enrollment in the LTFU phase. CIST, chronic immunosuppressive treatment; MPD1 or 2, months post-dose 1 or 2; MPR1 or 2, months post-revaccination dose 1 or 2; N, number of participants; Pre, pre-vaccination; Pre-RV, pre-revaccination; RZV, recombinant zoster vaccine; YPD2, years post-dose 2; YOA, years of age.

mammalian target of rapamycin (mTOR) inhibitors, or corticosteroids—for at least 30 days prior to the first revaccination and had no episodes of allograft rejection within the 90 days preceding the first revaccination. Participants with a confirmed history of HZ within the year prior to revaccination were excluded. The revaccination phase timepoints are referred to as PRE-RV (day of revaccination dose 1), 1MPR1 (one month post-revaccination dose 1; day of revaccination dose 2), 1MPR2 (one month post-revaccination dose 2), 12MPR2 (12 months post-revaccination dose 2), and 24MPR2 (24 months post-revaccination dose 2). The initial dose of the two-dose revaccination series was administered during Visit 3 (6–8YPD2/PRE-RV), approximately two years after the enrollment in the LTFU phase.

Full eligibility criteria and study procedures followed during the COVID-19 pandemic are available in the [Supplementary Methods](#).

Interventions

Two doses (0.5 mL/dose) of RZV were administered one month apart by intramuscular injection into the deltoid muscle. Each dose of RZV contained 50 µg of recombinant VZV gE antigen and the GSK proprietary AS01_B Adjuvant System (containing 50 µg of 3-*O*-desacyl-4'-monophosphoryl lipid A, 50 µg of *Quillaja saponaria* Molina, fraction 21 [QS21, licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation], and liposome). Laboratory testing personnel were blinded to treatment allocation, with codes used to link each participant and study to their respective samples. These codes did not indicate the treatment assigned to participants.

Ethics

The study was conducted according to consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guidelines, and applicable laws and regulations. The protocol and its amendment were approved by the relevant ethics committees and can be accessed at <https://www.gsk-studyregister.com/en/trial-details/?id=212340>. Written informed consent was provided by all participants before any study-specific procedures were performed.

Objectives

During the LTFU phase, the primary objective was to assess the persistence of humoral immunity, while secondary objectives

included evaluating the persistence of CMI responses and safety, in terms of vaccine-related serious adverse events ([S]AEs), HZ episodes, AEs of special interest, and allograft dysfunction.

In the revaccination phase, the primary objective was to evaluate humoral immune responses following each RZV revaccination dose. Secondary objectives included: 1) assessing CMI responses after each RZV revaccination dose, 2) persistence of humoral and CMI responses following the second RZV revaccination dose, and 3) assessing reactogenicity and safety after each RZV revaccination dose (i.e., solicited administration-site and systemic AEs, unsolicited AEs, SAEs, AEs of special interest, HZ episodes, allograft dysfunction). The study objectives and endpoints are detailed in the [Supplementary Methods](#).

Case definitions

Suspected HZ was defined as the presence of a new rash characteristic of HZ (i.e., unilateral and dermatomal distribution accompanied by pain [broadly defined to include allodynia, pruritus, or other sensations]), or a vesicular rash suggestive of VZV infection regardless of the dermatomal distribution and without an alternative diagnosis. For participants with suspected HZ, swabs from three distinct lesions were collected for polymerase chain reaction (PCR) testing. Confirmation of HZ cases followed an established algorithm incorporating PCR analysis and adjudication by the HZ ascertainment committee, as previously described.^{18,19}

Immunogenicity assessments

Blood samples to assess humoral immunity in the LTFU phase were collected annually: at enrollment, and at 12- and 24-months post-enrollment representing approximately 4–8 years post-primary vaccination series for all participants combined. Those not re-vaccinated continued in the LTFU phase for two additional years.

The pre-revaccination blood sample (6–8 years post-primary vaccination) served as both the final LTFU time point, and the baseline pre-revaccination (PRE-RV) data point for revaccinated participants. For revaccinated participants, additional blood samples were collected at 1MPR1, 1MPR2, 12MPR2, and 24MPR2.

For CMI analyses, blood samples were collected from a subset of participants (CMI subcohort; allocation details provided in the [Supplementary Methods](#)) at the same timepoints.

Anti-gE antibody concentrations were measured by anti-gE enzyme-linked immunosorbent assay (ELISA) with a technical cut-off of assay quantification of 97 milli-international units per mL (mIU/mL). Frequencies of gE-specific CD4[2+] T-cells (cluster-of-differentiation-4-positive [CD4⁺] T-cells expressing at least two of the four

assessed activation markers: interferon- γ [IFN- γ], interleukin 2 [IL-2], tumor necrosis factor- α [TNF- α], and CD40 ligand [CD40L]) were measured per one million CD4⁺ T-cells, as described previously.²⁰

Reactogenicity and safety assessments

Diary cards were provided to all participants to record solicited administration-site (pain, redness, and swelling), and systemic (fatigue, fever, gastrointestinal symptoms [nausea, vomiting, diarrhea, and/or abdominal pain], headache, myalgia, and shivering) AEs during the first seven days after each revaccination dose, and unsolicited AEs during the 30 days after each revaccination dose. Solicited and unsolicited AE intensity was graded from 1 (mild) to 3 (severe). Solicited symptoms reported beyond the seven-day solicitation period were subsequently classified as unsolicited AEs. SAEs and potential immune-mediated diseases (pIMDs) were recorded from the first revaccination dose to 12MPR2. AEs and SAEs leading to withdrawal from the study (which may include fatal SAEs, biopsy-proven allograft rejections, and pIMDs), SAEs related to study vaccination, biopsy-proven allograft rejections, intercurrent medical conditions (i.e., clinical events which occurred during the study with the potential to alter or confound the interpretation of the immunologic assessments, including HZ), and pregnancies were collected during the entire study period. Allograft function was assessed based on serum/plasma creatinine values obtained during regular clinical follow-up for allograft management, and sampling times were not specifically scheduled in the protocol. Allograft dysfunction was defined as a ≥ 1.2 -fold rise in serum/plasma creatinine versus baseline. Baseline was defined as the average of ≥ 2 creatinine measures within two months before an allograft rejection event or HZ case, extending to 3–4 months if needed; and the average of ≥ 3 measures within three months before revaccination, extending to 4–5 months if needed. An absence of clinically obtained creatinine measurements in the baseline window precluded assessment of dysfunction in some individuals and limited overall allograft dysfunction evaluation. In the event of suspected HZ, the HZ clinical course was documented using an HZ-specific diary and the Zoster Brief Pain Inventory questionnaire. Potential causal relationship to vaccination was assessed by the investigator for all but solicited administration-site AEs which were automatically classified as related to vaccination.

Statistical methods

The sample size was based on the number of participants from the parent study¹³ expected to participate in the current study, with a maximum of 86 individuals. All statistical analyses for immunogenicity and safety endpoints were descriptive. Samples that could potentially confound interpretation of results were eliminated from analysis of immunogenicity, as predefined in the Protocol and the Statistical Analysis Plan.

The enrolled set included participants from the parent study (NCT02058589) who completed the primary vaccination series, met eligibility criteria, and provided informed consent. Safety during the LTFU phase was assessed in this set. The per-protocol set (PPS) for persistence of immune responses included participants with at least one annual immunogenicity measure in the first two years before revaccination and no important protocol deviations leading to exclusion; for those not revaccinated, samples collected through the end of the study were also included.

For the revaccination phase, the exposed set for safety included all participants who received at least one RZV dose in the current study. The PPS for immunogenicity included those with one or two revaccination doses, post-dose immunogenicity measures, and no important protocol deviations leading to exclusion.

Geometric mean concentrations (GMCs) of anti-gE antibodies, mean geometric increases (MGIs), anti-gE antibody seropositivity rates, and vaccine response rates were calculated with 95% confidence intervals (CIs). MGI is defined as the geometric mean of the within-subject ratios of the post-vaccination to pre-vaccination anti-gE antibody concentrations.

The vaccine response rate was defined as the percentage of participants with post-vaccination anti-gE antibody concentrations 1) ≥ 4 -fold above anti-gE antibody concentrations pre-vaccination for participants who were seropositive at baseline, or 2) ≥ 4 -fold above the ELISA assay cut-off of 97 mIU/mL for participants who were seronegative at baseline.

Median fold increase (with interquartile range) of anti-gE antibody concentrations was calculated. Mean (with standard deviation [SD]) and median (with interquartile range) frequency of gE-specific CD4[2+] T-cells were calculated. Immunogenicity tables and figures include data from present study participants collected during the parent study, starting from pre-primary vaccination series, to provide a comprehensive representation of immune responses from pre-primary vaccination through the end of the present study.

Numbers and percentages of participants with AEs, SAEs, pIMDs, biopsy-proven allograft rejections, suspected or confirmed HZ cases, and confirmed HZ cases reported in this study were tabulated with exact 95% CIs.

All analyses were performed with SAS version 3.5.

Results

Study participants

Out of 68 participants enrolled in the study, 49 (72.1%) participants completed the study, including 43 revaccinated and six non-revaccinated participants. Nineteen (27.9%) participants withdrew before the end of the study. The most common reasons for withdrawal were AEs requiring expedited reporting (seven [10.3%] participants, six in the LTFU phase and one after revaccination), all of which were unrelated fatal SAEs, and consent withdrawal not due to an AE/SAE (five [7.4%] participants) (Fig. 2). Eleven participants withdrew before or at Visit 3 (Month 24, PRE-RV) and four participants did not attend Visit 3 onward and were also considered withdrawn. Among the remaining 53 participants, 47 received at least one revaccination dose, and 46 received both revaccination doses.

The mean age $\pm$ SD of participants was 58.5 ± 12.3 years at enrollment into the extension study (60.7 ± 10.2 years at first revaccination). Forty-six (67.6%) participants in the extension study were male (Table 1). Demographic characteristics of the revaccinated participants were similar (Table 1).

Persistence of humoral immunity after the primary vaccination series

Median fold increase of anti-gE antibodies ranged from 2.4 to 3.8 over pre-vaccination through LTFU. The GMCs were 1313.3 (95% CI: 993.7–1735.6) mIU/mL at pre-vaccination and 3017.1 (1417.0–6423.8) to 3977.6 (2714.2–5829.0) mIU/mL at 4–8 years post-primary vaccination series (Fig. 3A, Table 2). A scatterplot of the anti-gE antibody concentrations over time is presented in Fig. 4A. MGIs consistently indicated higher responses compared to pre-vaccination, ranging from 2.65 (95% CI: 1.78–3.96) to 3.29 (1.86–5.82) at 4–8 years post-primary vaccination series with seropositivity rates of $\geq 94.1\%$ (95% CI: 71.3–99.9) at all timepoints (Table 2).

Data by study Day 1, Month 12, and Month 24 are presented in Supplementary Table 1.

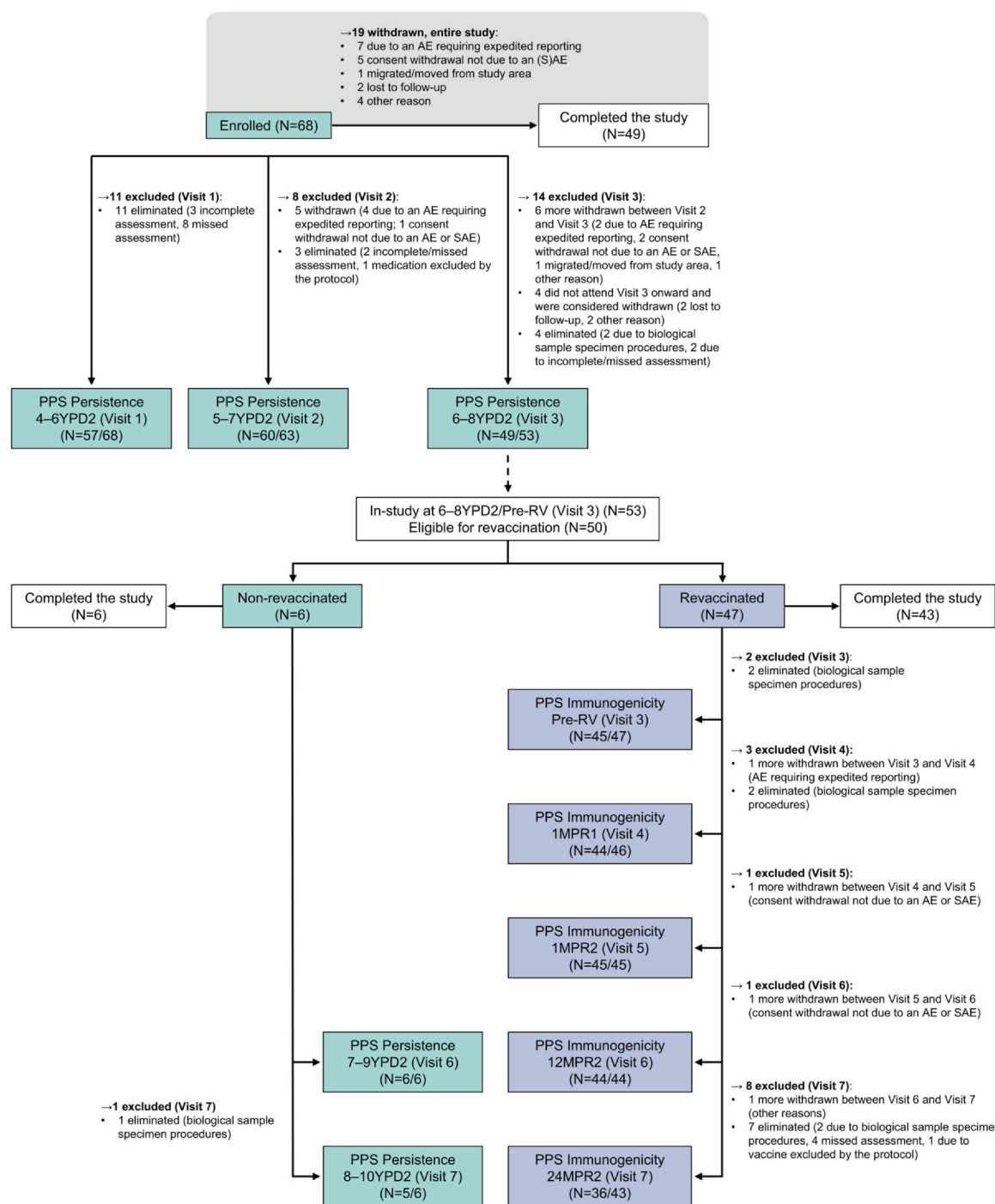


Fig. 2. Participant flow. The PPS at each study visit included all available and eligible participants remaining in the study at that timepoint. The number of participants excluded from the PPS at a given visit may differ across visits and does not represent a cumulative count throughout study end. The number of participants (N=#/#) is reported as participants included in the PPS at a given Visit/participants in-study at a given Visit. Withdrawals include participants who withdrew at or prior to the visit presented and eliminations include participants who were excluded only for the visit presented. MPR1 or 2, months post-revaccination dose 1 or 2; N, number of participants (included in the PPS/present at a given Visit); PPS, per-protocol set; Pre-RV, pre-revaccination; (S)AE, (serious) adverse event; Y, years post-dose 2.

Persistence of CMI responses after the primary vaccination series

Median frequency of gE-specific CD4[2+] T-cells ranged from 178.9 to 827.8 at 4–8 years post-primary vaccination series compared to 31.0 at pre-vaccination (Fig. 3B, Table 3). A scatterplot of the frequency of gE-specific CD4[2+] T-cells over time is presented in Fig. 4B. Durable median fold increase of the frequency of gE-specific CD4[2+] T-cells ranged from 6.1 to 124.3 over pre-vaccination

(Table 3). Data by study Day 1, Month 12, and Month 24 are presented in Supplementary Table 1.

Safety after the primary vaccination series

None of the participants experienced biopsy-proven allograft rejection episodes during the gap between the parent and current study. Three (4.4%) participants had suspected HZ episodes during this period.

Table 1
Demographic characteristics (enrolled set and exposed set).

Characteristic	Enrolled participants (N=68)	Revaccinated participants (N=47)
Mean (SD) age, y	58.5 (12.3)	60.7 (10.2)
Age category, n (%)		
18–49 y	14 (20.6)	*
≥50 y	54 (79.4)	41 (87.2)
Sex, n (%)		
Male	46 (67.6)	29 (61.7)
Female	22 (32.4)	18 (38.3)
Race, n (%)		
White	46 (67.6)	32 (68.1)
Asian	14 (20.6)	*
Black or African American	*	*
Other	*	*
Maintenance immunosuppressive therapy, n (%)		
All 3 classes (CIS+CS+MMF)	46 (67.6) ^a	31 (66.0) ^b
Any 2 classes	21 (30.9) ^a	15 (31.9) ^b

CIS, calcineurin inhibitor or sirolimus or other mTOR inhibitor; CS, corticosteroids; MMF, mycophenolate mofetil/compound; n (%), number of participants in a given category; N, number of participants; SD, standard deviation; y, years.

* Cells with values < 11 are not reported for confidentiality reasons.

^a At the time of primary vaccination.

^b At the time of first revaccination.

During the LTFU phase, two (2.9%) participants experienced biopsy-proven allograft rejection episodes: one acute antibody-mediated and one acute T-cell-mediated. Both events occurred more than 64 months post-primary vaccination series and were assessed as unrelated to RZV vaccination. Both participants recovered with treatment, and kidney function was preserved. Additionally, three (4.4%) participants developed PCR-confirmed HZ during the LTFU phase. Allograft dysfunction associated with either allograft rejection or HZ episodes, as defined in the protocol, was not observed or could not be assessed.

No participants experienced any related SAEs. Six participants died due to SAEs, which were assessed as unrelated to primary vaccination. All deaths occurred more than 46 months after the primary vaccination series.

Immunogenicity after revaccination

The GMCs of anti-gE antibodies increased substantially after revaccination, demonstrating a robust anamnestic immune response at 1MPR1 (one month after the first revaccination dose) (Fig. 3A, Table 2). Pre-revaccination, GMC was 2828.5 mIU/mL (95% CI: 1886.6–4240.5) or a median of 2.2-fold above the pre-vaccination level, while at 1MPR1, it rose to 27655.5 mIU/mL (95% CI: 17882.7–42769.1) or 22.3-fold above the pre-vaccination and 8.2-

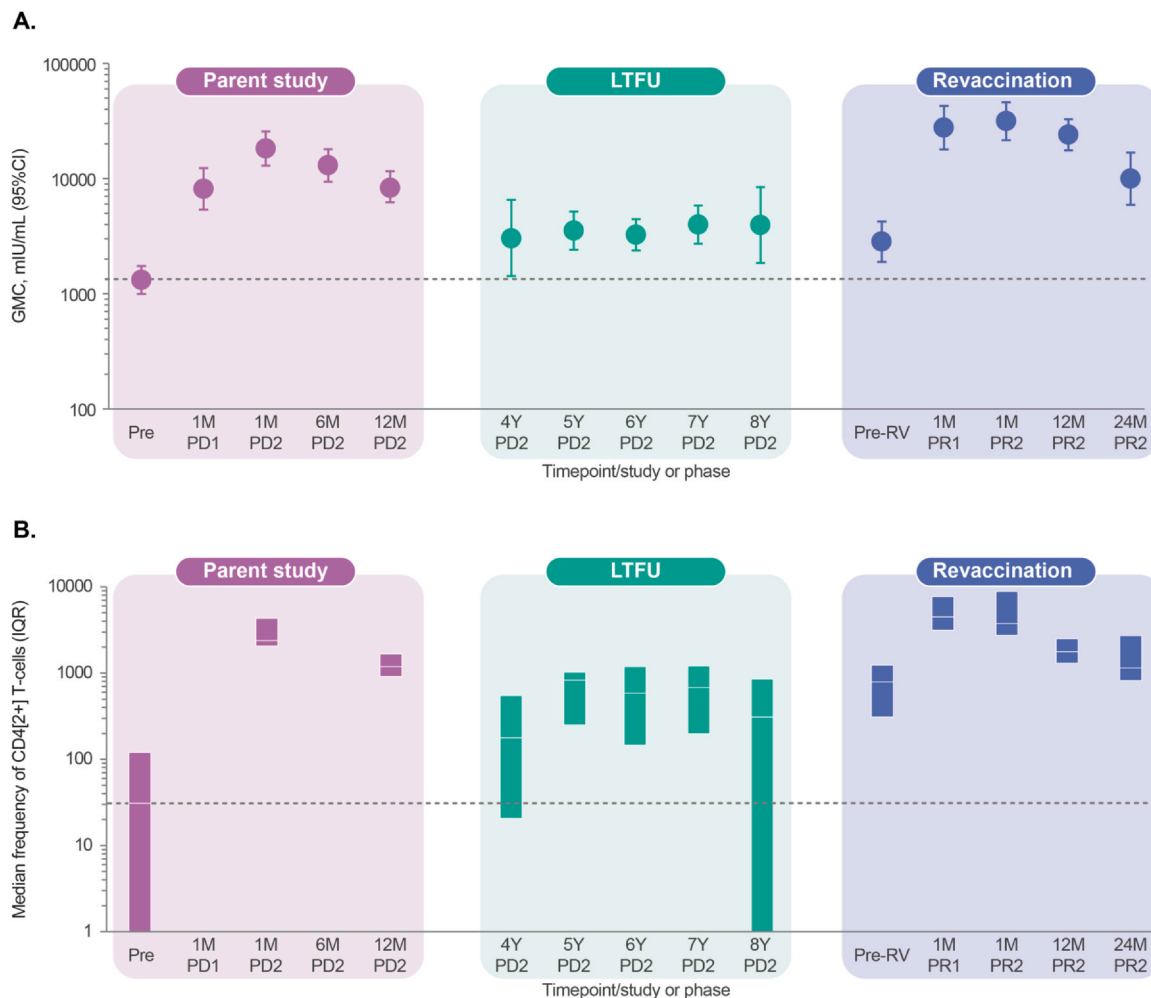


Fig. 3. Evolution of anti-gE antibody concentrations (A) and gE-specific CD4[2+] T-cell frequencies (B) after primary vaccination (per-protocol set for analysis of persistence) and after revaccination (per-protocol set for immunogenicity after revaccination). CD4[2+] T-cells, cluster-of-differentiation-4-positive (CD4⁺) T-cells expressing at least 2 of the 4 assessed activation markers (interferon- γ [IFN- γ], interleukin 2 [IL-2], tumor necrosis factor- α [TNF- α], and CD40 ligand [CD40L]); CI, confidence interval; gE, glycoprotein E; GMC, geometric mean concentration; IU, international units; IQR, interquartile range; LTFU, long-term follow-up; MPD1 or 2, months post-dose 1 or 2; MPR1 or 2, months post-revaccination dose 1 or 2; Pre-RV, pre-revaccination; Pre, pre-vaccination; YPD2, years post-dose 2.

Table 2

Seropositivity rates, GMCs, MGIs, and median fold increase of anti-gE antibody concentrations after primary vaccination (per-protocol set for analysis of persistence), after revaccination compared to pre-vaccination and after revaccination compared to pre-revaccination (per-protocol set for immunogenicity after revaccination).

Time points	N	Seropositivity*, % (95% CI)	GMC, mIU/mL (95% CI)	MGI (95% CI)	Median (IQR) fold increase
Primary vaccination					
Pre-vaccination	68	95.6 (87.6–99.1)	1313.3 (993.7–1735.6)	-	-
1MPD1	68	97.1 (89.8–99.6)	8138.8 (5369.0–12337.6)	6.20 (4.38–8.76)	5.8 (1.6–15.2)
1MPD2	68	98.5 (92.1–100)	18207.4 (12928.3–25642.1)	13.86 (9.91–19.40)	13.8 (5.5–36.9)
6MPD2	68	98.5 (92.1–100)	13007.1 (9411.3–17976.8)	9.90 (7.20–13.62)	10.7 (3.9–22.9)
12MPD2	68	98.5 (92.1–100)	8309.8 (6100.0–11320.0)	6.33 (4.69–8.53)	6.5 (2.5–15.6)
4YPD2	17	94.1 (71.3–99.9)	3017.1 (1417.0–6423.8)	2.92 (1.30–6.56)	2.4 (1.0–3.7)
5YPD2	37	97.3 (85.8–99.9)	3527.3 (2407.2–5168.4)	2.65 (1.78–3.96)	2.4 (1.1–4.4)
6YPD2	59	98.3 (90.9–100)	3247.3 (2376.7–4436.9)	2.71 (1.88–3.90)	2.6 (1.1–6.7)
7YPD2	40	100 (91.2–100)	3977.6 (2714.2–5829.0)	2.82 (1.95–4.08)	2.7 (1.3–7.6)
8YPD2	17	100 (80.5–100)	3949.4 (1849.1–8435.3)	3.29 (1.86–5.82)	3.8 (1.9–8.3)
9YPD2	4	100 (39.8–100)	8186.1 (1494.7–44834.3)	4.90 (1.59–15.11)	5.4 (2.7–9.0)
10YPD2	2	100 (15.8–100)	13690.7 (7466.9–25102.0)	4.37 (0.00–8131.38)	5.2 (2.4–7.9)
Revaccination vs pre-vaccination					
Pre-revaccination	45	97.8 (88.2–99.9)	2828.5 (1886.6–4240.5)	2.32 (1.50–3.59)	2.2 (1.1–4.2)
1MPR1	44	100 (92.0–100)	27655.5 (17882.7–42769.1)	22.36 (13.66–36.61)	22.3 (8.0–80.6)
1MPR2	44	100 (92.0–100)	31517.0 (21581.1–46027.3)	25.23 (16.23–39.24)	23.1 (10.3–58.5)
12MPR2	44	100 (92.0–100)	23989.4 (17539.6–32811.0)	20.26 (13.81–29.70)	21.3 (8.6–33.5)
24MPR2	36	100 (90.3–100)	9985.8 (5917.8–16850.0)	8.67 (4.71–15.98)	11.9 (4.3–18.6)
Revaccination vs pre-revaccination					
1MPR1	44	100 (92.0–100)	27655.5 (17882.7–42769.1)	9.67 (6.37–14.67)	8.2 (3.8–19.8)
1MPR2	44	100 (92.0–100)	31517.0 (21581.1–46027.3)	10.55 (7.21–15.44)	10.6 (4.4–20.9)
12MPR2	44	100 (92.0–100)	23989.4 (17539.6–32811.0)	8.47 (6.21–11.56)	8.1 (4.4–11.2)
24MPR2	36	100 (90.3–100)	9985.8 (5917.8–16850.0)	3.35 (1.92–5.83)	3.5 (2.1–6.4)

Notes: Data from participants included in the present study going back to pre-primary vaccination in the parent study were included to provide a complete picture of responses from pre-primary vaccination up to the end of the present study.

MGI is defined as the geometric mean of the within-subject ratios of the post-vaccination to pre-vaccination anti-gE antibody concentrations.

X years post-dose 2 represents a range. For example, four years post-dose 2 is from 3.5 up to less than 4.5 years post-vaccination dose 2.

%, percentage of participants with a response; CI, confidence interval; gE, glycoprotein E; GMC, geometric mean concentration; IQR, interquartile range; IU, international units; M, month; MGI, mean geometric increase; MPD1 or 2, months post-dose 1 or 2; MPR1 or 2, months post-revaccination dose 1 or 2; N, number of participants with available results; Y, year; YPD2, years post-dose 2.

* Percentage of participants with value above the assay cut-off (97mIU/mL).

fold above the pre-revaccination level. The second revaccination dose stimulated minimal further elevation to a GMC of 31517.0 mIU/mL (95% CI: 21581.1–46027.3) at 1MPR2, corresponding to a 23.1-fold increase compared to pre-vaccination and 10.6-fold increase compared to pre-revaccination. Responses persisted through 12MPR2, at 21.3-fold increase versus pre-vaccination with GMC of 23989.4 mIU/mL (95% CI: 17539.6–32811.0) and remained over pre-revaccination up to at least 24MPR2 (at 11.9-fold over pre-vaccination) with a GMC of 9985.8 mIU/mL (95% CI: 5917.8–16850.0) (Fig. 3A, Table 2). All post-revaccination responses remained above pre-vaccination levels up to at least 24 months after the second revaccination dose, with MGIs ranging from 25.23 (95% CI: 16.23–39.24) through 20.26 (13.81–29.70) to 8.67 (4.71–15.98) at 1-, 12- and 24MPR2, respectively (Table 2). Post-revaccination responses at 1MPR1 and 1MPR2 increased above pre-revaccination levels and subsequently declined over time, while remaining above both pre-vaccination and pre-revaccination levels through at least 24 months after the second revaccination dose (Table 2). Seropositivity was 100% for all participants at all post-revaccination timepoints (Table 2).

For revaccinated participants, the vaccine response rate for anti-gE antibody concentrations was 88.6% (95% CI: 75.4–96.2) at 1MPR1, as compared to 78.3% (63.6–89.1) at one month post-primary vaccination series. Vaccine response rates for anti-gE antibody concentrations post-revaccination relative to pre-revaccination levels are shown in Supplementary Table 2.

CMI responses showed a similar pattern as humoral immune responses where the median frequency of gE-specific CD4[2+] T-cells was 793.5 at pre-revaccination and increased to 4476.2 at 1MPR1, followed by a slight decline to 3747.3 at 1MPR2. Responses remained above pre-revaccination levels through at least 24 months after the second revaccination dose, with median frequencies of 1777.4 at 12MPR2 and 1144.9 at 24MPR2 (Fig. 3B, Table 3).

Reactogenicity and safety after revaccination

Within seven days after revaccination, 42 (91.3%) participants experienced at least one solicited AE, with 11 (23.9%) participants experiencing at least one grade 3 solicited AE. The most frequently reported solicited administration-site AE was pain (40 [87.0%] participants) and the most frequently reported solicited systemic AE was fatigue (31 [67.4%] participants) (Fig. 5). Solicited AEs occurred in 41 (89.1%) and 37 (82.2%) of participants within seven days post-revaccination with dose 1 and dose 2, respectively. Administration-site AEs occurred in 38 (82.6%) of participants revaccinated with dose 1 and 32 (71.1%) of those revaccinated with dose 2, respectively. Systemic AEs occurred in 34 (73.9%) of participants revaccinated with dose 1 and in 29 (64.4%) of those revaccinated with dose 2, respectively. For all solicited administration-site AEs, the overall per-dose median duration was three days. For all solicited systemic AEs, the median duration per-dose was two days, except for fever, which was one day.

Within 30 days after revaccination, 12 (25.5%) participants experienced at least one unsolicited AE, with three (6.4%) participants experiencing a grade 3 unsolicited AE. Two (4.3%) participants experienced at least one related unsolicited AE (one participant experienced fatigue, myalgia, and headache, the other participant experienced administration-site pruritus), with one (2.1%) participant experiencing a grade 3 related unsolicited AE (i.e., fatigue).

Ten (21.3%) participants experienced at least one SAE from the first revaccination dose until the study end, and none of these events were assessed as causally related to revaccination. The most commonly reported SAE was COVID-19 (four [8.5%] participants). There were no suspected or confirmed HZ cases in the two years post-revaccination.

From the first revaccination dose until study end, one (2.1%) participant died. A female participant, 85–90 YOA, with a history of

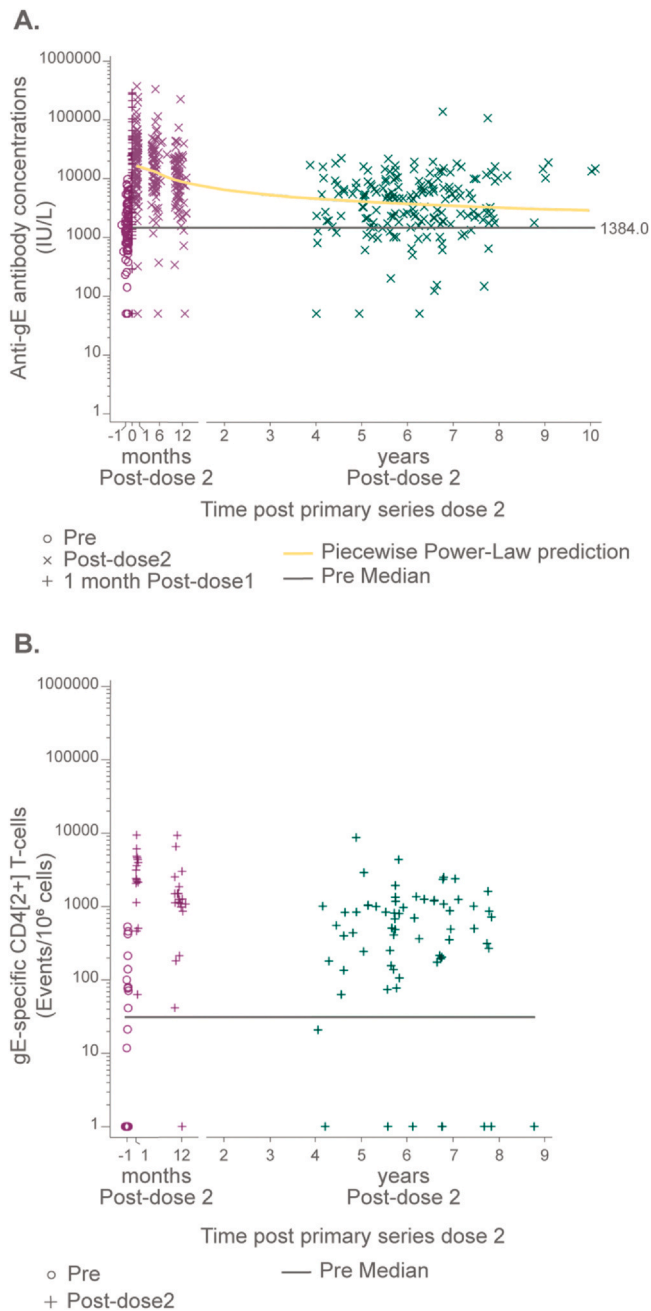


Fig. 4. Anti-gE antibody concentrations after primary vaccination (per-protocol set for analysis of persistence) (A) and frequency of gE-specific CD4[2+] T-cells after primary vaccination (per-protocol set for analysis of persistence) (B). CD4[2+] T-cells, cluster-of-differentiation-4-positive (CD4⁺) T-cells expressing at least 2 of the 4 assessed activation markers (interferon- γ [IFN- γ], interleukin 2 [IL-2], tumor necrosis factor- α [TNF- α], and CD40 ligand [CD40L]); gE, glycoprotein E; IU, international units; Pre, pre-vaccination.

renal transplant on maintenance immunosuppression, insulin treated diabetes, difficult to control hypertension and underlying cardiovascular disease received first revaccination dose of RZV. Fifteen days post-revaccination, the participant was diagnosed with a hypertensive intracerebral hemorrhage. On presentation, blood pressure was markedly elevated, and imaging was consistent with cerebral hemorrhage. Despite intensive supportive measures, the hemorrhage progressed with rising intracranial pressure and respiratory compromise. The participant died two days after event onset. The investigator assessed the fatal SAE as not related to the study vaccine.

Four revaccinated participants had post-revaccination serum/plasma creatinine increases ≥ 1.2 -fold but < 1.5 -fold versus the pre-revaccination baseline. There was one (2.1%) unrelated biopsy-proven allograft rejection episode, approximately one year after revaccination, related to non-adherence to immunosuppressive treatment. Allograft dysfunction associated with allograft rejection, as defined in the protocol, could not be assessed. This participant recovered with treatment and kidney function was preserved.

One participant (2.1%) experienced a pIMD (gout) between the first revaccination until 1MPR2. Gout occurred after the first revaccination dose, was assessed as not causally related to revaccination, and did not recur after the second revaccination dose.

Discussion

Previously published results from the primary RZV vaccination series in KT recipients ≥ 18 YOA on daily CIST demonstrated that RZV was immunogenic, with humoral and CMI responses persisting through at least 12 months after the primary RZV vaccination series with an acceptable safety profile. Of note, overall occurrences of renal function changes and rejection episodes were similar between RZV and placebo groups.¹³

The results of the present follow-up study demonstrate that RZV-induced immune responses are maintained long-term, through at least eight years, in adult KT recipients on CIST. Persistent immune responses, with humoral levels remaining at least 2.4-fold and CMI levels at least 6.1-fold above pre-vaccination levels annually over several years, demonstrate a relatively stable plateau of immune persistence. This pattern of response is consistent with long-term immunogenicity of RZV in immunocompetent adults ≥ 50 YOA at the time of primary vaccination.^{21–23} Additionally, long-term safety and preserved allograft function were also demonstrated in this study.

Studies have consistently shown that inactivated and/or adjuvanted vaccines do not increase the risk of allograft rejection or dysfunction in transplant recipients despite some earlier concerns.^{14,15} Results of the parent and present study support these conclusions in that RZV vaccination does not appear to increase the risk for rejection of the transplanted kidney. Two participants experienced a biopsy-proven allograft rejection episode during the LTFU phase between five and six years post-primary vaccination series; neither were considered related to RZV. The study did not observe any calculable kidney dysfunction (defined as a ≥ 1.2 -fold increase in serum creatinine levels) in association with either allograft rejection or an HZ episode, though assessment was not possible in several cases. In addition, no related SAEs nor causally related deaths were observed during the LTFU phase.

The durable humoral and CMI responses, along with the favorable safety profile, continue to support the positive benefit-risk profile of RZV administration for the prevention of HZ in KT recipients. These findings may assist healthcare professionals in making informed decisions regarding HZ prevention strategies for this population and other IC populations, in alignment with current recommendations.

The revaccination phase results demonstrated that a single revaccination dose elicited robust humoral (22.3-fold increase) and CMI (276.2-fold increase) responses over pre-vaccination levels, exceeding the peak immune responses observed at one month post-primary vaccination series. Also, compared to pre-revaccination levels, the anti-gE antibody GMCs and the median CD4[2+] T-cell frequencies increased approximately eight-fold (humoral) and six-fold (CMI) after the first revaccination dose, with a minimal benefit from the second revaccination dose, indicating robust anamnestic responses following a single revaccination dose. These results are aligned with previously observed patterns in immunocompetent adults ≥ 50 YOA^{21,22} and confirm that repeating the two-dose vaccination series is unnecessary to restore strong immunogenicity. These

Table 3

Frequency of gE-specific CD4[2+] T-cells (per 10⁶ CD4⁺ T-cells) after primary vaccination (per-protocol set for analysis of persistence), after revaccination compared to pre-vaccination and compared to pre-revaccination (per-protocol set for immunogenicity after revaccination).

Time point	N	Mean (SD)	Median (IQR)	N _{MFI}	Median (IQR) fold increase
Primary vaccination					
Pre-vaccination	20	107.72 (165.09)	31.0 (1.0–119.6)		-
1MPD2	17	3112.43 (2320.98)	2379.2 (2055.6–4307.0)	16	59.5 (23.9–479.3)
12MPD2	20	1832.76 (2235.74)	1186.2 (914.8–1669.0)	19	21.0 (10.6–211.4)
4YPD2	5	349.02 (423.10)	178.9 (20.7–548.6)		-
5YPD2	14	1327.50 (2225.01)	827.8 (250.1–1021.1)	8	124.3 (5.7–888.5)
6YPD2	24	790.05 (916.66)	586.1 (146.4–1187.5)	14	9.4 (2.8–155.5)
7YPD2	16	901.91 (845.35)	680.2 (197.6–1207.7)	13	6.1 (2.2–172.0)
8YPD2	7	534.01 (570.28)	309.9 (1.0–853.2)	6	38.8 (1.6–266.0)
9YPD2	1	1.00	1.0 (1.0–1.0)		-
Revaccination vs pre-vaccination					
Pre-revaccination	23	1215.13 (1765.57)	793.5 (309.9–1235.8)	16	42.5 (2.9–526.7)
1MPR1	20	6350.65 (6464.84)	4476.2 (3136.7–7704.6)	15	276.2 (23.4–780.1)
1MPR2	18	5157.27 (3635.37)	3747.3 (2758.1–8906.2)	13	406.9 (53.6–1921.0)
12MPR2	20	2358.74 (1764.36)	1777.4 (1297.7–2505.4)	14	143.9 (12.8–929.7)
24MPR2	16	1844.06 (1736.74)	1144.9 (818.1–2724.1)	11	15.2 (2.0–741.5)
Revaccination vs pre-revaccination					
1MPR1	20	6350.65 (6464.84)	4476.2 (3136.7–7704.6)	20	5.7 (3.3–10.1)
1MPR2	18	5157.27 (3635.37)	3747.3 (2758.1–8906.2)	18	5.5 (3.8–11.1)
12MPR2	20	2358.74 (1764.36)	1777.4 (1297.7–2505.4)	20	2.4 (1.7–4.3)
24MPR2	16	1844.06 (1736.74)	1144.9 (818.1–2724.1)	16	1.7 (1.0–2.5)

Note: Data from participants included in the present study going back to pre-primary vaccination in the parent study were included to provide a complete picture of responses from pre-primary vaccination up to the end of the present study.

CD4[2+] T-cells, CD4-positive (CD4⁺) T-cells expressing at least 2 of the 4 assessed activation markers (interferon- γ [IFN- γ], interleukin 2 [IL-2], tumor necrosis factor- α [TNF- α], and CD40 ligand [CD40L]); gE, glycoprotein E; IQR, interquartile range; M, month; MPD2, months post-dose 2; MPR1 or 2, months post-revaccination dose 1 or 2; N and N_{MFI}, number of participants with available results for analyses of cell frequencies and median fold increase in frequencies; SD, standard deviation; Y, year; YPD2, years post-dose 2.

data support the presence of immune memory, which not only triggers a strong anamnestic response but may also demonstrate the capacity to respond to potential viral reactivation.

The RZV safety profile in revaccinated KT recipients was consistent with the RZV safety profile in this population after primary vaccination.¹³ To date, there is insufficient clinical evidence to indicate a need for future dosing. Additional long-term effectiveness data are recommended to assess the duration of protection against HZ post-primary vaccination to further optimize outcomes for these populations at high risk of HZ.

The results presented here should be interpreted considering the study strengths and limitations. The main study strength is the collection of long-term immunogenicity and safety data for up to at least eight years after RZV vaccination in an IC population, in this case KT recipients, all of whom require daily immunosuppression. This population allowed the study of RZV immunogenicity and safety in chronically immunosuppressed individuals and may also serve as a useful reference for other or broader IC populations. The

demographic features of this study's population (sex, race, and immunosuppressive therapy distribution) are similar to those previously reported for KT recipients. Specifically, 67.6% of participants in this study were male and 67.6% identified as White, reflecting demographic patterns observed in transplant registries and studies from the US and Canada, which have reported that approximately 60% of KT recipients were male and the majority were White.^{24–26} The distribution of immunosuppressive regimens, with 67.6% on triple immunosuppression (calcineurin inhibitors or mTOR inhibitors, corticosteroids, and mycophenolate compounds) and 30.9% on two-class therapy, also aligns with evidence indicating that these combinations are commonly used among transplant recipients.²⁵ An additional study strength is that the overall safety of the KT recipients was closely monitored.

On the other hand, caution should be exercised when interpreting the results due to the limited sample size, the unavailability of a concurrent control group, and the descriptive nature of the statistical analyses. The protocol definition of allograft dysfunction

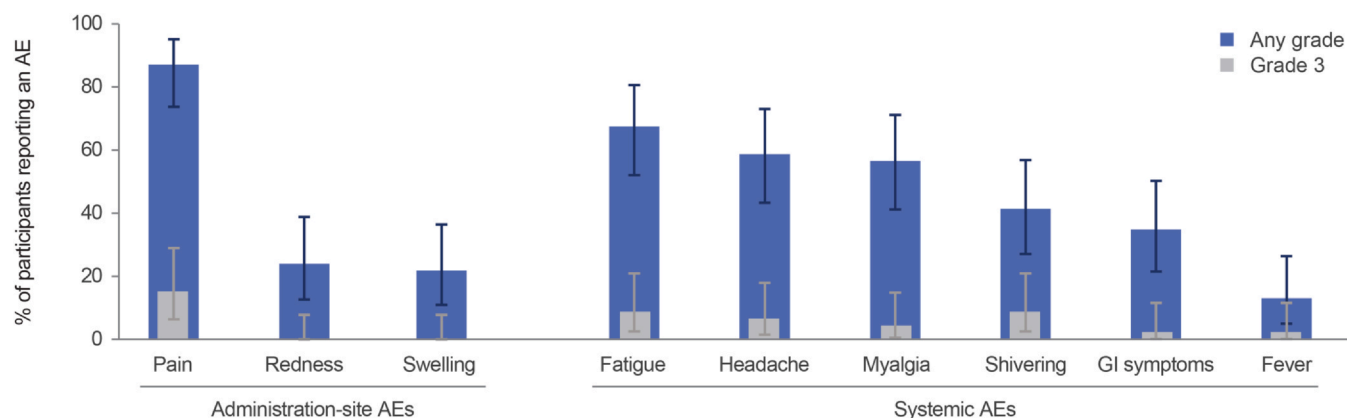


Fig. 5. Frequency of solicited adverse events following revaccination (exposed set). Error bars indicate 95% confidence intervals. Grade 3 intensity was defined as > 100 mm in diameter for injection-site redness and swelling, and as preventing normal daily activity for all other solicited events. GI symptoms included nausea, vomiting, diarrhea and/or abdominal pain. AE, adverse event; GI, gastrointestinal.

was narrow, and the available data within that definition were insufficient to produce a baseline, making the assessment of allograft dysfunction not calculable for some cases.

In conclusion, RZV induced durable immune responses in KT recipients receiving chronic immunosuppressive therapy. Humoral and CMI responses induced by the two-dose primary RZV series persisted above pre-vaccination levels for up to eight years post-primary vaccination series, the last assessment in this LTFU. In this population, a single additional RZV dose given 6–8 years after primary vaccination elicited strong vaccine-specific anamnestic immune responses. No long-term vaccine-related safety concerns were identified; the post-revaccination safety profile was similar to that observed after primary vaccination, and no vaccine-related allograft rejections occurred.

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CRediT authorship contribution statement

MMH and PEV contributed to the conceptualization of the study. ASF, TR, RP, JBP, FO, DK, and Y-JC performed the data acquisition. MMH, PEV, AK, MT, FA, and AM-O conducted the data analysis. All authors contributed to data interpretation. All authors had full access to the analyses, revised the manuscript, and granted their final approval of the paper before submission.

Data availability

GSK makes available anonymized individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to www.clinicalstudydatarequest.com. To access data for other types of GSK sponsored research, for study documents without patient-level data and for clinical studies not listed, please submit an inquiry via the website.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Melinda M. Hutton, Manyee Tsang, Fatine Atig, and Agnes Mwakingwe-Omari are GSK employees. Peter E. Vink and Adrienne Kuxhausen were employees of GSK at the time of the study conduct. Melinda M. Hutton, Peter E. Vink, Manyee Tsang, Fatine Atig, and Agnes Mwakingwe-Omari hold financial equities in GSK. Rafael Pérez declares honoraria for lectures from Astra Zeneca. Ana Sanchez Fructuoso, Tom Robberechts, and Jae Berm Park have nothing to declare. Fernanda Ortiz declares consulting fees from Viafor Pharma and Medaffcon, and honoraria for lecture from Takeda. Deepali Kumar declares consulting fees from GSK, Takeda, Merck, Pfizer, CSL Behring, and Allovir. Deepali Kumar further declares payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing, or educational events from Viracor Eurofins. Deepali Kumar declares that her institution received grants or contracts from GSK and Moderna. Yang-Jen Chiang declares support from GSK for the current study. The authors declare no other financial or non-financial relationships or activities.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.jinf.2026.106758](https://doi.org/10.1016/j.jinf.2026.106758).

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