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Immunogenicity and safety of the adjuvanted recombinant zoster vaccine co-administered with the 23-valent pneumococcal polysaccharide vaccine in adults ≥50 years of age: A randomized trial

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ABSTRACT

Background: This study evaluated immunogenicity and safety of the adjuvanted recombinant zoster vaccine (RZV) when the first dose was co-administered with the 23-valent pneumococcal polysaccharide vaccine (PPSV23) in adults aged ≥50 years.
Methods: In this open label, multi-center study (NCT02045836), participants were randomized 1:1 to receive either the first dose of RZV and PPSV23, co-administered at Day 0 and the second dose of RZV at Month 2 (Co-Ad group), or PPSV23 at Day 0, the first dose of RZV at Month 2 and second dose of RZV at Month 4 (Control group). Co-primary objectives were the RZV vaccine response rate (VRR) in the Co-Ad group and the non-inferiority of the antibody responses to RZV and PPSV23 in the Co-Ad group compared to the Control group. Reactogenicity and safety were also assessed.
Results: 865 participants were vaccinated (Co-Ad: 432, Control: 433). VRRs to RZV were >98% in both groups. Humoral immune responses to co-administration of RZV and PPSV23 were non-inferior to sequential administration. All three co-primary immunogenicity objectives were met. Solicited local symptoms after the first RZV dose were reported by similar percentages of participants in both groups. Solicited general symptoms were more frequently reported when the first dose of RZV and PPSV23 were co-administered. No differences were apparent between groups after the second RZV dose.
Conclusions: No immunologic interference was observed between RZV and PPSV23 when co-administered in adults ≥50 years. No safety concerns were raised.

Abbreviations: VZV, varicella-zoster virus; HZ, herpes zoster; PHN, postherpetic neuralgia; CDC, United States Centers for Disease Control and Prevention; YOA, years of age; ZVL, zoster vaccine live; RZV, adjuvanted recombinant zoster vaccine; PPSV23, 23-valent pneumococcal polysaccharide vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; IDP, invasive pneumococcal disease; gE, glycoprotein E; M, month; GMC, geometric mean concentration; GMT, geometric mean titer; ELISA, enzyme-linked immunosorbent assay; MOPA, multiplex opsonophagocytic assay; VRR, vaccine response rate; (S)AE, (serious) adverse event; pIMD, potential immune-mediated disease; CI, confidence interval; LL/UL, lower/upper limit; TVC, total vaccinate cohort; ATP, according-to-protocol.

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1. Introduction

Reactivation of latent varicella-zoster virus (VZV) leads to herpes zoster (HZ) which typically manifests as a painful vesicular dermatomal rash [1–3]. The most common complication of HZ is postherpetic neuralgia (PHN), chronic pain that can last for months or even years after the zoster rash has resolved [4,5]. The risk and incidence of HZ increases significantly with age likely due to an age-dependent decline in VZV-specific cellular immunity [6–9]. The risk is highest in adults ≥50 years of age (YOA), in whom 60% of all HZ cases occur [10]. Immunocompromised individuals are also at higher risk of developing HZ, regardless of age [6].

Vaccination is known to reduce the risk of developing HZ [7]. A live-attenuated VZV vaccine (Zostavax, ZVL) was found to reduce incidence of HZ by 69.8% and 51.3% in adults 50–59 and ≥60 YOA, respectively, and incidence of PHN by 66.5% in adults ≥60 YOA [11,12]. Currently, in the United States (US), ZVL is approved for use in immunocompetent adults ≥50 YOA and recommended for those ≥60 YOA [13].

A recombinant vaccine, containing the VZV glycoprotein E (gE) and the $AS01_B$ Adjuvant System (Shingrix, RZV), elicits strong anti-gE cellular and humoral immune responses that persist above pre-vaccination levels for at least 9 years [14]. RZV showed 97.2% overall efficacy for the prevention of HZ in adults aged ≥50 YOA [15]. High efficacy against the incidence of HZ (91.3%) and PHN (88.8%) was also observed in individuals ≥70 YOA [16]. RZV is approved for use in immunocompetent adults ≥50 YOA in Canada and the US [17,18].

Similar to HZ, the risk of pneumococcal pneumonia and invasive pneumococcal disease (IPD) is higher in adults ≥50 YOA. The 23-valent pneumococcal polysaccharide vaccine (Pneumovax 23, PPSV23) is approved for use in adults ≥50 YOA, including populations at increased risk for pneumococcal disease [19]. At the time this study was designed, PPSV23 was recommended by the US Centers for Disease Control and Prevention (CDC) for the prevention of IPD in adults ≥65 YOA and in adults ≥19 YOA at increased risk for pneumococcal disease [20,21]. It was also recommended for populations at high risk for pneumococcal disease, including elderly, in Australia, Japan and most European countries [22–24]. In the US, the 13-valent pneumococcal conjugate vaccine (Prevnar 13/Prevenar 13, PCV13) has been recommended in addition to PPSV23 for adults ≥65 YOA as of September 2014 [25] and for all persons aged ≥19 YOA at increased risk for pneumococcal disease as of October 2012 [26].

In 2015, less than one third of the elderly population in the US was vaccinated against HZ and less than two thirds against pneumococcal infection [27]. As co-administration may help overcoming programmatic barriers of vaccination in adults ≥50 YOA, this study evaluated the immunogenicity and safety of both vaccines when the first dose of RZV was co-administered with PPSV23 compared to a sequential administration.

2. Material and methods

2.1. Study design

This was a phase III, open-label, randomized and controlled multi-center study conducted at 9 study centers – US (3), Canada (3) and Estonia (3) – between March 2014 and June 2016. Participants were randomized (1:1) using a central randomization system on internet (SBIR, GSK) to one of the two parallel study arms. Participants in the Co-Ad group received the first dose of RZV and PPSV23, co-administered at Day 0 (D0), in different arms and the second dose of RZV at Month 2 (M2), while participants in the Control group received PPSV23 at D0, first dose of RZV at M2 and second dose of RZV at M4.

The study protocol was reviewed and approved by Independent Ethics Committees. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study is registered on ClinicalTrials.gov (NCT02045836).

Co-primary objectives of the study were to evaluate the vaccine response rate (VRR) to RZV 1 month post-second dose of the vaccine in the Co-Ad group; to demonstrate the non-inferiority of the anti-gE geometric mean concentrations (GMCs) following the second RZV dose in the Co-Ad vs Control group; and to demonstrate the non-inferiority of PPSV23 immunogenicity in the Co-Ad vs Control group for 12 selected serotypes included in PPSV23 (1, 3, 4, 5, 6B, 7F, 9 V, 14, 18C, 19A, 19F and 23F), by comparing opsonophagocytic activity geometric mean titers (GMTs). Of note, these 12 serotypes are common to currently approved pneumococcal vaccines PPSV23 and PCV13 in the countries where the study was conducted. The evaluation of the safety and reactogenicity of RZV and PPSV23 when co-administered or administered sequentially was a secondary objective.

2.2. Study participants

Adults ≥50 YOA at the time of first vaccination were eligible for inclusion. Written informed consent was provided by all participants before study start. Adults were excluded from participation if they had previously received any pneumococcal, VZV or HZ vaccine, had a history of HZ, were administered or planning to use any investigational or non-registered product or vaccine or non-study vaccine from 30 days prior to inclusion in the study through 30 days after the second dose of RZV, had a documented pneumococcal infection within 5 years, had received immunosuppressants or other immune-modifying drugs for more than 14 consecutive days within 6 months or had received long-acting immune-modifying drugs 6 months before first study vaccination. Adults with cerebrospinal fluid leaks, cochlear implants, chronic renal failure, nephrotic syndrome and functional or anatomic asplenia, were also excluded from participation in the study.

2.3. Study vaccines

The RZV (Shingrix, GSK1437173A, GSK) contained 50 μg of VZV gE and the $AS01_B$ Adjuvant System containing 50 μg MPL (3-*O*-desacyl-4′-monophosphoryl lipid A; produced by GSK), 50 μg QS-21 (*Quillaja saponaria* Molina, fraction 21; licensed by GSK from Antigenics LLC, a wholly owned subsidiary of Agenus Inc., a Delaware, USA corporation) and liposome per 0.5 mL of reconstituted vaccine. The PPSV23 (Pneumovax 23, Merck Sharp & Dohme Corp.) contained 25 μg of capsular polysaccharide from each of 23 pneumococcal serotypes and 0.25% phenol as preservative per 0.5 mL monodose syringe. The 23 serotypes are: 1, 2, 3, 4, 5, 6B, 7F, 8, 9 N, 9 V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F.

2.4. Outcomes and assessments

2.4.1. Assessment of immunogenicity

Humoral immune responses to the vaccines were assessed from blood samples collected from the Co-Ad group at D0 (pre-vaccination for both vaccines), M1 (1 month post-vaccination for PPSV23), and M3 (1 month post-second dose of RZV); and from samples collected from the Control group at D0 (pre-vaccination for PPSV23), M1 (1 month post-vaccination for PPSV23), M2 (pre-vaccination for RZV), and M5 (1 month post-second dose of RZV).