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Immunogenicity and safety of zoster vaccine live administered with quadrivalent influenza virus vaccine

Myron J. Levin [a], Ulrike K. Buchwald [b,*], Julie Gardner [b], Jason Martin [b], Jon E. Stek [b], Elizabeth Brown [b], Zoran Popmihajlov [b]

[a] University of Colorado Anschutz Medical Campus, Aurora, CO, USA
[b] Merck & Co., Inc., Kenilworth, NJ, USA

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ABSTRACT

Objectives: Randomized, blinded, placebo-controlled trial to evaluate the safety and immunogenicity of ZOSTAVAX™ (ZV) administered concomitantly with quadrivalent inactivated influenza vaccine (IIV4) in adults ≥ 50 years of age (NCT02519855).
Methods: Overall, 440 participants were randomized into the Concomitant Group (CG) and 442 into the Sequential Group (SG). The CG received ZV and IIV4 at separate injection sites on Day 1 and matching placebo at Week 4. The SG received placebo and IIV4 (2015–2016 influenza season) at separate injection sites on Day 1 and ZV at Week 4.
Immunogenicity endpoints: Varicella-zoster virus (VZV) antibody geometric mean titer (GMT) and geometric mean fold-rise (GMFR) from baseline to 4 weeks postvaccination, measured by glycoprotein enzyme-linked immunosorbent assay (gpELISA) and adjusted for age and prevaccination titer. Influenza strain-specific GMT at baseline and 4 weeks postvaccination was measured by hemagglutination inhibition (HAI) assay.
Safety endpoints: Injection-site and systemic adverse experiences (AEs) within 28 days following any vaccination and serious AEs throughout the study.
Results: The adjusted VZV antibody GMT ratio (CG/SG) was 0.87 (95%CI: 0.80, 0.95), meeting the prespecified noninferiority criterion. The VZV antibody GMFR in the CG was 1.9 (95%CI: 1.76, 2.05), meeting the acceptability criterion. Influenza antibody GMT ratios for A/H1N1, A/H3N2, B/Yamagata and B/Victoria were 1.02 (95%CI: 0.88, 1.18), 1.10 (95%CI: 0.94, 1.29), 1.00 (95%CI: 0.88, 1.14), and 0.99 (95%CI: 0.87, 1.13), respectively. The frequency of vaccine-related injection-site and systemic AEs was comparable between groups. No vaccine-related serious AE was observed.
Conclusion: The concomitant administration of ZV and IIV4 to adults ≥ 50 years of age induced VZV-specific and influenza-specific antibody responses that were comparable to those following administration of either vaccine alone, and was generally well tolerated.

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1. Introduction

Herpes zoster (HZ) is an often painful, vesicular dermatomal rash resulting from reactivation of varicella-zoster virus (VZV) that has remained latent in sensory ganglia after primary VZV infection [1]. The frequency and severity of HZ and its most common debilitating complication, postherpetic neuralgia (PHN), increase with age due to waning VZV-specific cell-mediated immunity (CMI) associated with immunosenesence and with disease- or therapy-induced immunocompromising conditions [2]. Zoster vaccine (ZV; ZOSTAVAX®; Merck & Co., Inc., Kenilworth, NJ), is a one-dose, live attenuated VZV vaccine, that is the licensed intervention for prevention of HZ in people ≥50 years of age in the United States (US) [3,4]. ZV enhances VZV-specific immunity and thereby reduces the incidence of HZ, PHN, and the burden of illness due to HZ [5–9]. The vaccine is also approved in many countries outside of the US for prevention of HZ and HZ-related complications in people ≥50 years of age [10].

Routine annual influenza vaccination is recommended by the Advisory Committee on Immunization Practices (ACIP) for all individuals ≥6 months of age [11]. Influenza attributable morbidity and mortality is highest in older adults and individuals with

* Corresponding author at: Merck & Co., Inc., 2000 Galloping Hill Rd., UG-D3009 Kenilworth, NJ 19454, USA.
E-mail address: ulrike.buchwald@merck.com (U.K. Buchwald).

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co-morbidities, emphasizing the importance of adequate vaccination coverage in these risk groups [12–14]. Trivalent inactivated influenza vaccine (IIV3) includes antigens from influenza A/H1N1 and A/H3N2 and one of the two influenza B lineages. However, both influenza B lineages (B/Yamagata and B/Victoria) have contributed to recent seasonal epidemics, resulting in insufficient protection by IIV3 during some annual epidemics [15,16]. For this reason the inclusion of antigens of two strains from each of the influenza B lineages in inactivated quadrivalent influenza vaccines (IIV4) offers more reliable protection [15].

The immunogenicity and safety of the concomitant administration of ZV with IIV3 in adults ≥50 years of age was previously demonstrated [17]. The current study (NCT02519855; V211-062) was conducted in subjects ≥50 years of age to assess the immunogenicity and safety of concomitant administration of ZV and IIV4.

Immunization with any influenza vaccine in adults ≥50 years of age has been moderately successful, achieving an annual coverage of >60% in the United States [18]. In contrast, only 22% of 60–64 year olds and 34% of older adults have received ZV. Thus, concomitant administration of ZV with IIV4 will be an efficient means to increase immunization rates against HZ [18].

2. Methods

2.1. Study design and population

This Phase III randomized, placebo-controlled, blinded (subject, investigator, sponsor) clinical trial evaluated the immunogenicity, safety, and tolerability of one dose of ZV administered concomitantly with IIV4 at 38 centers in the United States between September 2015 and January 2016. The ethical review committee of each site approved the protocol, which was conducted in conformance with applicable requirements.

Men and women ≥50 years of age with a history of varicella or residence in a VZV-endemic country for ≥30 years were eligible for the study. Subjects were excluded if they had a history of: hypersensitivity to vaccine components; HZ or prior receipt of any varicella or zoster vaccine; receipt of an influenza vaccine for the 2015–2016 influenza season; or other conditions that could influence the immunogenicity and safety assessments of either vaccines (see Supplementary information for full inclusion/exclusion criteria).

Approximately 870 subjects were to be assigned via a central randomization procedure in a 1:1 ratio to either the Concomitant Group (CG) or the Sequential Group (SG). Randomization was stratified by age (50–59 years, 60–69 years, and ≥70 years of age). Subjects in the CG received ZV (blinded) in the right arm and IIV4 (open-label) in the left arm on Day 1 and placebo (blinded) in the right arm at Week 4. Subjects in the SG were received placebo (blinded) in the right arm and IIV4 (open-label) in the left arm on Day 1 and ZV (blinded) in the right arm at Week 4. Study visits were scheduled at Day 1, Week 4 and Week 8.

2.2. Study objectives and hypotheses

The primary study objectives and hypotheses were to determine whether the concomitant administration of ZV and IIV4 at 4 weeks postvaccination induces: (1) VZV antibody responses that are noninferior to those of ZV administered alone; (2) acceptable VZV antibody responses; and (3) strain-specific influenza antibody responses that are noninferior to those of IIV4 administered alone. Criteria for non-inferiority and acceptability of antibody responses were pre-specified and based on model-adjusted analyses.

Secondary objectives were to assess the safety and tolerability of ZV and to compare the strain-specific influenza seroconversion rates in the two vaccination groups when administered concomitantly with IIV4. No formal safety hypothesis was tested.

2.3. Vaccine description

The lyophilized ZV and placebo were supplied in ~0.65-mL single-dose vials and stored at 2-to-8 °C. The ZV and matching placebo were reconstituted with sterile diluent immediately prior to administration, and were indistinguishable from each other. IIV4 for the 2015–2016 influenza season was obtained from a commercial source and provided to the study sites as open-label inventory (Fluzone® Quadrivalent vaccine; Sanofi Pasteur, Swiftwater, PA, USA) [19].

2.4. Immunogenicity measurements and endpoints

Serologic testing for VZV-specific antibodies was performed on all sera at baseline on the day of ZV administration (CG: Day 1; SG: Week 4) and postvaccination at 4 weeks after ZV administration (CG: Week 4; SG: Week 8). The VZV-specific antibody response was assessed using a validated gpELISA (Covance Laboratories, West Trenton, NJ) [20]. The primary immunogenicity endpoint for VZV response was the geometric mean titer (GMT) by gpELISA at 4 weeks postvaccination and the geometric mean fold-rise (GMFR) of VZV antibody from baseline to 4 weeks postvaccination.

The strain specific influenza antibody responses were assessed at Day 1 as baseline titer and at Week 4 as postvaccination titer in both vaccination groups. Antibody responses were assessed using the validated HAI assay (FOCUS Laboratories, Valencia, CA) [21].

2.5. Safety measurements and endpoints

All vaccinated subjects were followed for injection-site and systemic adverse experiences (AEs) for 28 days after using an electronic vaccination report card (eVRC). The subjects completed the eVRC daily after each injection, recording injection-site and systemic AEs, temperatures (if they felt febrile), and any concomitant vaccines or medications. Injection-site reactions (erythema, swelling, pain) were solicited for 5 days after each vaccination as maximum size (inches) of erythema or swelling and maximum intensity of pain or tenderness (none, mild, moderate, severe). All injection-site AEs were considered vaccine-related.

2.6. Statistical methods

2.6.1. Immunogenicity

The immunogenicity analyses were performed on the Per-Protocol population, which included subjects who received all vaccinations within prespecified visit windows and did not have any protocol violations that could affect the immunogenicity assessments. The noninferiority tests regarding the GMTs of antibodies to VZV and to each of the influenza strains were based on a constrained longitudinal data analysis with a special model structure that adjusts for age and prevaccination VZV and influenza titer, respectively [22]. Data from subjects who had evaluable antibody titers at only one time point (baseline or postvaccination) were used in this longitudinal model. Success of the noninferiority hypothesis test depended on the lower bound of the two-sided 95% CI of the GMT ratio (CG/SG) being greater than 0.67. The acceptability hypothesis of the VZV antibody GMFR was evaluated with a similar longitudinal data analysis model that only included data from the CG. The statistical criterion for an acceptable GMFR corresponded to the lower bound of the 2-sided 95% CI on GMFR of the VZV antibody titer in the CG being >1.4. This GMFR value is based on comparisons of fold-rise of gpELISA titer in subjects who did develop and those who did not develop HZ in the pivotal ZV efficacy trial and has been used previously in the ZV clinical program [17,23].

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