CLINICAL AND VACCINE IMMUNOLOGY, Feb. 2008, p. 314–319 Vol. 15, No. 2
1556-6811/08/$08.00+0 doi:10.1128/CVI.00310-07

A Double-Blind, Randomized, Controlled, Multicenter Safety and Immunogenicity Study of a Refrigerator-Stable Formulation of Zostavax▽

Larry I. Gilderman,[1] James F. Lawless,[2] Thomas M. Nolen,[3] Tina Sterling,[4] Ruth Z. Rutledge,[4] Doreen A. Fernsler,[4] Neal Azrolan,[5] Santosh C. Sutradhar,[6] William W. Wang,[4] Ivan S. F. Chan,[6] Katia Schlienger,[4] Florian Schödel,[4] and Jeffrey L. Silber,[4]*
for the Zostavax Protocol 010 Study Group

University Clinical Research, Pembroke Pines, Florida[1]; FFM Clinical Research, Camillus, New York[2]; Tomac, Inc., Columbiana, Alabama[3]; Infectious Disease/Vaccine Clinical Research, Merck & Co., Inc., West Point, Pennsylvania[4]; Medical Communications, Merck & Co., Inc., West Point, Pennsylvania[5]; and Clinical Biostatistics, Merck & Co., Inc., West Point, Pennsylvania[6]

Received 27 July 2007/Returned for modification 11 September 2007/Accepted 21 November 2007

The vaccine Zostavax has been shown to prevent herpes zoster (HZ) and postherpetic neuralgia and is recommended for individuals ≥60 years of age. This study compared the safety and the immunogenicity of a refrigerator-stable formulation (Zostavax refrigerated) with those of the current formulation (Zostavax frozen) in subjects ≥50 years of age. Subjects with a negative history for HZ were randomized 1:1 to receive one dose of either formulation. Enrollment was stratified 1:2 by age (50 to 59 years and ≥60 years). Safety was evaluated for 28 days postvaccination. Varicella-zoster virus (VZV) antibody responses were measured by a glycoprotein enzyme-linked immunosorbent assay (gpELISA). The primary endpoints were the VZV antibody geometric mean titer (GMT; day 28), the VZV antibody geometric mean rise (GMR; days 1 to 28), and the incidence of vaccine-related serious adverse experiences (AEs) over 28 days. The refrigerated (n = 182) and frozen (n = 185) formulations induced similar GMTs (727.4 and 834.4 gpELISA units/ml, respectively); the estimated GMT ratio (refrigerated formulation/frozen formulation) was 0.87 (95% confidence interval, 0.71 to 1.07). The GMRs were 2.6- and 2.9-fold, respectively. No vaccine-related serious AEs were reported in either group, and the safety profiles of the formulations were generally similar. The frequencies of injection-site AEs during follow-up were 35.6% and 46.4% in the refrigerated and the frozen formulation groups, respectively, and were generally mild. The frequencies of systemic AEs were similar in the two groups, and those of vaccine-related AEs were ~6% in both groups. The refrigerator-stable formulation of Zostavax has an acceptable safety profile and is as immunogenic as the frozen formulation; thus, the vaccine may be used in clinical settings where freezer availability is limited.

Herpes zoster (HZ), also known as shingles, is an often serious condition associated with the reactivation of varicella-zoster virus (VZV) in individuals who have been exposed to the virus earlier in life (11, 12). After the initial infection, which manifests clinically as chickenpox, VZV can become latent and reside in the dorsal or cranial nerve ganglia. The reactivation of VZV as HZ is usually characterized by a unilateral, dermatomally distributed cutaneous rash.

The incidence of HZ in the general population has been estimated to be between 0.3 and 0.4% annually in the United States, Canada, and Europe (6, 9, 22, 37). The risk of developing HZ increases dramatically upon reaching 50 years of age, and this risk subsequently increases to a rate that approximates 1% per year by the age of 75 years (30, 31, 38). The long-lasting pain associated with HZ, termed postherpetic neuralgia (PHN), is the most common complication and cause of morbidity from HZ in immunocompetent patients (12, 17, 29, 36). Worldwide, the lifetime risk of developing HZ has recently been estimated to be close to 30% in the general population and can be as high as 50% in individuals who reach the age of 85 years (9, 13, 18). Characterized by persistent pain following the healing and subsequent disappearance of the HZ rash, the frequency and severity of PHN increase with age and may occur in as many as 25 to 50% of patients with HZ over the age of 50 years (30, 31, 32, 33).

The use of antiviral agents has been shown to reduce the severity and duration of acute HZ symptoms, as well as the duration of PHN, but only if they are administered within the first 72 h after the onset of the rash; however, these agents provide only minimal protection against the development of the debilitating PHN, which can persist for months or even years (10, 14, 16, 34).

The vaccine Zostavax was developed for the prevention of HZ and its complications, especially HZ-associated pain and PHN. Zostavax has been shown to decrease the frequency of HZ and PHN in adults (19, 23, 27). In addition, vaccination with Zostavax has been associated with a reduction of the acute and chronic pain associated with HZ, via a mechanism that probably involves boosting of the VZV-specific immune response (19, 28). Zostavax was licensed for use in the United States, European Union, and Australia in 2006. Recently, the Advisory Committee on Immunization Practices of the U.S.

* Corresponding author. Mailing address: Merck Research Laboratories, P.O. Box 1000, UG3CD-28, North Wales, PA 19454-1099. Phone: (267) 305-7963. Fax: (267) 305-7769. E-mail: jeffrey_silber@merck.com.
▽ Published ahead of print on 12 December 2007.

Centers for Disease Control and Prevention recommended Zostavax for universal vaccination of older adults in the United States (3).

The currently marketed formulation of Zostavax (Zostavax frozen), manufactured with a phosphate-gelatin-sucrose (PGS) stabilizer, allows the distribution of the formulation only where storage and cold-chain (freezer) temperatures can be maintained (2, 3, 8, 24). The development of a refrigerator-stable formulation would therefore allow the use of Zostavax in expanded clinical settings. The purpose of this study was to support the development of a refrigerator-stable formulation of Zostavax with a confirmatory clinical trial with VZV antibody-seropositive adults ≥50 years of age.

MATERIALS AND METHODS

Vaccine description. Zostavax (zoster vaccine live; Oka/Merck) is a single-dose, sterile, lyophilized, preservative-free, live attenuated virus vaccine (23, 27) manufactured by Merck & Co., Inc., West Point, PA. This study compared two Zostavax formulations: a refrigerator-stable formulation with phosphate-gelatin-sucrose-urea (PGSU) stabilizer and a frozen formulation with PGS stabilizer. The formulations were visually indistinct, supplied in identical glass vials, and shipped to the study sites frozen on dry ice. To maintain study blinding and generally equivalent potencies between the formulations throughout the duration of the study, both formulations were stored at −15°C (+5°F) or colder until they were reconstituted. Immediately preceding administration, both vaccines were reconstituted with 0.7 ml of sterile diluent. Each subject received a single ~0.65-ml subcutaneous injection of either the refrigerated (PGSU) or the frozen (PGS) formulation, each at a potency of approximately 50,000 PFU/dose. Consistent with the intended storage and use of the PGSU- and PGS-containing formulations, the study vaccines are referred to henceforth as the Zostavax refrigerated and Zostavax frozen formulations, respectively.

Study design. This was a randomized, controlled, double-blind (with in-house blinding), multicenter study conducted in the United States to evaluate the safety, tolerability, and immunogenicity of the Zostavax refrigerated formulation performed between July and October 2005. Varicella history-positive adults were randomized in a 1:1 ratio to receive either the Zostavax refrigerated or the Zostavax frozen formulation. Enrollment was stratified in a 1:2 ratio by age (50 to 59 years and ≥60 years) in order to acquire safety and immunogenicity data with a broader age group of subjects. Vaccinations were administered on day 1. All subjects were monitored for exposure to varicella or HZ or the development of any varicella/varicella-like or HZ/HZ-like rashes, as well as any other adverse experiences (AEs). Injection-site reactions, rashes, and other AEs were recorded by each subject by the use of a vaccination report card (VRC) for 28 days postvaccination.

Blood samples were obtained from all subjects immediately before vaccination and at day 28 postvaccination and were assessed for VZV antibody titer by a glycoprotein enzyme-linked immunosorbent assay (gpELISA) (25, 35). The gpELISA is a validated, well-characterized assay that has successfully been used to compare formulations and to demonstrate lot consistency in pediatric varicella vaccine trials (4, 21, 25). In a substudy of the pivotal Shingles Prevention Study, the immune response elicited by a dose of Zostavax was evaluated by using the gpELISA and two cellular immunity assays (the gamma interferon enzyme-linked immunospot assay and responder cell frequency) (19, 23). The statistical analyses of the immunogenicity data in the substudy demonstrated that the results obtained by all three assays correlated with vaccine-induced protection against HZ; but the immune response measured by gpELISA, in terms of the postvaccination geometric mean titer (GMT) and the geometric mean rise (GMR) in the VZV antibody titer from the baseline to the period postvaccination, correlated best with protection against HZ (23). Therefore, this assay was chosen as the optimal tool for immunologic bridging within and between clinical studies of Zostavax, including a comparison of the VZV-specific immune responses to the two vaccine formulations evaluated in this clinical study.

Study population. Immunocompetent subjects 50 years of age and older with a history of varicella or residence in a country where VZV infection is endemic were eligible for the study. Subjects were excluded if they had a clinical history of hypersensitivity or anaphylactic reactions to gelatin or neomycin, used any form of nontopical antiviral therapy, had received a live vaccine within 4 weeks prior to the study dose or an inactivated vaccine within 1 week prior to the study dose, or another vaccination was planned before the subject was due to complete the study. Study exclusions also included a history of HZ, pregnancy, or breast-feeding; the plan to conceive within the duration of the study; known or suspected immune dysfunction; and alcohol or other substance abuse that might interfere with the evaluation required by the study.

Safety surveillance. The primary safety parameter of interest in the study was the frequency of vaccine-related serious AEs. All subjects were monitored for 28 days after vaccination for general safety and tolerability. During this period, subjects used a VRC to record AEs, such as fever, injection-site reactions, and systemic AEs. Each subject was asked to report immediately to the study site any varicella/varicella-like or HZ/HZ-like rashes and any serious AEs. The relationship between each AE and the study vaccination was assessed by the study investigator.

Immunogenicity measurements. The two coprimary hypotheses were that (i) the GMT of VZV antibodies at 28 days postvaccination in subjects who received the Zostavax refrigerated formulation would be noninferior to that in subjects who received the Zostavax frozen formulation and that (ii) the Zostavax refrigerated formulation would induce an acceptable rise in the VZV antibody titers from prevaccination to 28 days postvaccination. The coprimary endpoints were the GMTs of VZV antibodies in both vaccination groups at 28 days postvaccination and the GMR in VZV antibody titers from the baseline to the period postvaccination among the recipients of the Zostavax refrigerated formulation. The gpELISA methodology for measuring VZV antibody has been described elsewhere (25, 35).

Statistical methods. The primary and secondary immunogenicity analyses were based on the per protocol population. With 162 evaluable subjects (as planned) in each vaccination group and an estimated standard deviation of 1.1 for the natural log of the VZV gpELISA antibody titer, the overall power to claim that the study was a success with respect to the two primary immunogenicity hypotheses was 91.2% (91.3% · 99.9%), assuming the independence of the two primary hypothesis tests. The first coprimary hypothesis was tested by estimating the GMT ratio (GMT of the Zostavax refrigerated formulation/GMT of the Zostavax frozen formulation) and its 95% confidence interval (CI) by using a longitudinal regression model with adjustment for the prevaccination antibody titer, age, and study center. The statistical criterion for success on the noninferiority hypothesis corresponded to a value for the lower bound of the two-sided 95% CI on the GMT ratio (GMT of the Zostavax refrigerated formulation/GMT of the Zostavax frozen formulation) of >0.67. The second coprimary hypothesis was tested by estimating the GMR in the Zostavax refrigerated group from prevaccination to day 28 postvaccination. The statistical criterion for success on the acceptability hypothesis corresponded to a value for the lower bound of the two-sided 95% CI on the GMR of >1.2-fold. The point estimate and its 95% CI were calculated by use of a *t* distribution. The secondary immunogenicity hypothesis was tested by estimating the GMR in the Zostavax frozen formulation group from prevaccination to day 28 postvaccination.

RESULTS

Subject characteristics and accounting. A total of 368 subjects were enrolled and randomized in the study, and 367 subjects were vaccinated; the data for 1 subject, who withdrew consent prior to the day 1 blood draw and who was not vaccinated, are not included in any of the following data analyses. Five additional subjects were screened but not randomized.

Table 1 provides details of the subject demographics across the two vaccination groups. The Zostavax refrigerated and Zostavax frozen groups were similar with regard to gender (female subjects represented 53% and 57% of the enrollment in the two groups, respectively) and mean age (63.4 and 63.2 years, respectively). In addition, the distributions of the subjects according to age (50 to 59, 60 to 69, and ≥70 years of age) and race were similar between the two groups.

Figure 1 illustrates an accounting of all subjects vaccinated in the study. A subject was considered to have completed the study if the subject received the study vaccine, completed the scheduled blood draws, and returned a completed VRC at the day 29 postvaccination visit. By the use of these criteria, 361 of the 368 subjects (98.1%) were considered to have completed the study. Among the seven subjects who discontinued the study, no safety

TABLE 1. Subject population demographics

Characteristic	No. (%) of subjects	
	Refrigerated formulation group (n = 182)	Frozen formulation group (n = 185)
Gender		
Male	85 (46.7)	79 (42.7)
Female	97 (53.3)	106 (57.3)
Age (yr)[a]		
50 to 59	66 (36.3)	69 (37.3)
60 to 69	69 (37.9)	71 (38.4)
≥70	47 (25.8)	45 (24.3)
Race		
Caucasian	124 (68.1)	126 (68.1)
Hispanic	30 (16.5)	34 (18.4)
African American	19 (10.4)	15 (8.1)
Asian/Pacific Islander	6 (3.3)	6 (3.2)
Other[b]	3 (0.8)	4 (0.1)

[a] For the refrigerated formulation group, the mean age ± standard deviation was 63.4 ± 9.2 years (median age, 62 years; age range, 50 to 88 years). For the frozen formulation group, the mean age ± standard deviation was 63.2 ± 8.4 years (median age, 63 years; age range, 50 to 85 years).
[b] Native American, Indian, African, or multiracial.

follow-up was obtained for two subjects in each vaccination group. These subjects were excluded from all safety analyses. Two additional subjects withdrew their consent after vaccination. The numbers and percentages of subjects who discontinued the study and the reasons for discontinuation were generally similar between the two vaccination groups.

Safety and tolerability. Table 2 provides a summary of the numbers and the percentages of clinical AEs reported from day 1 to day 28 postvaccination. One serious AE was reported in the study: a case of gastroenteritis in the Zostavax refrigerated group, which was determined by the investigator to be definitely not related to the study vaccine. In general, clinical AEs were reported at a lower rate by the recipients of the Zostavax refrigerated formulation than by the recipients of the Zostavax frozen formulation. The majority of both injection-site AEs and systemic AEs were rated by the subjects as mild in intensity. The most frequently reported injection-site AEs (≥10% in both vaccination groups) were erythema, pain, and swelling, all of which were reported at lower frequencies by subjects who received the Zostavax refrigerated formulation. The incidences of systemic clinical AEs were similar in both vaccination groups, with ~6% determined to be vaccine related in either vaccination group. One non-injection-site varicella-like rash with three lesions was reported by one subject in the Zostavax refrigerated group. No subject discontinued the study due to an AE.

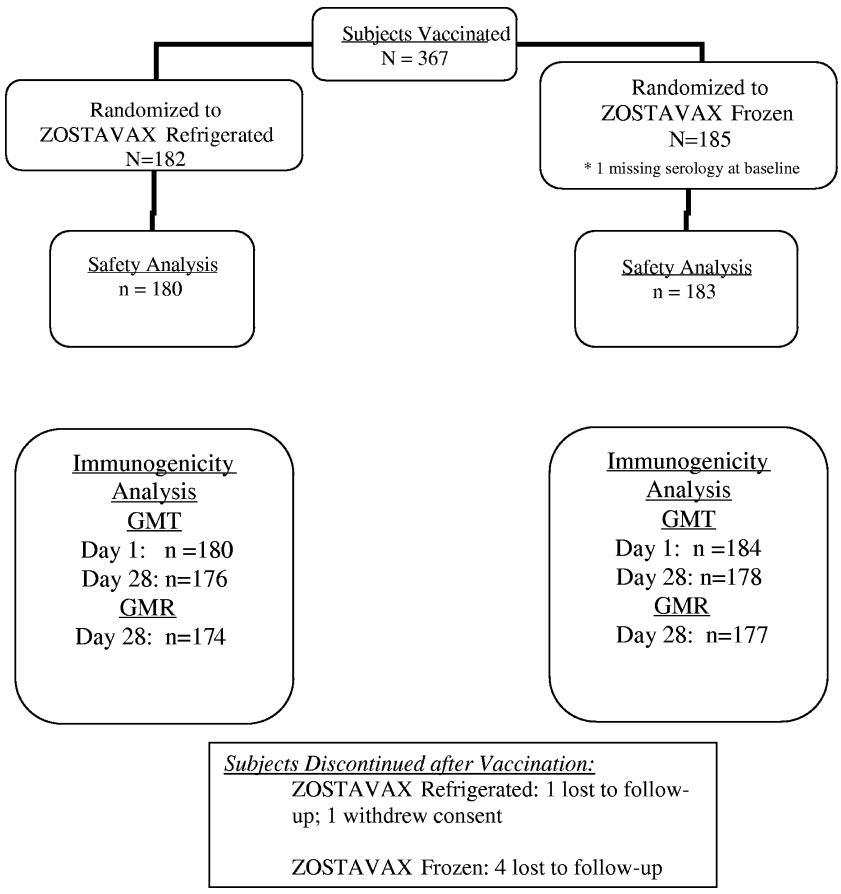

FIG. 1. Subject accounting.

TABLE 2. AEs following one dose of either the Zostavax frozen or the Zostavax refrigerated formulation, day 1 to day 28 postvaccination

Group	No. (%) of subjects[a]	
	Refrigerated group (n = 182)	Frozen group (n = 185)
All subjects	182	185
Subjects with follow-up	180 (98.9)	183 (98.9)
Subjects with one or more AEs	82 (45.6)	101 (55.2)
Injection-site AEs[b,c]	64 (35.6)	85 (46.4)
Systemic AEs	34 (18.9)	39 (21.3)
Subjects with vaccine-related AEs[c]	68 (37.8)	87 (47.5)
Injection-site AEs[c]	64 (35.6)	85 (46.4)
Systemic AEs[c]	10 (5.6)	11 (6.0)
Subjects with serious AEs	1 (0.6)	0 (0.0)
Vaccine-related serious AEs	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)
Subjects who discontinued due to any AE	0 (0.0)	0 (0.0)
Subjects who discontinued due to a vaccine-related AE	0 (0.0)	0 (0.0)

[a] The same subject may appear in different categories but is counted only once in each category.
[b] All injection-site AEs were considered vaccine related.
[c] Determined by the investigator to be possibly, probably, or definitely related to the vaccine.

Immunogenicity. Table 3 presents the VZV antibody response for each age stratum and for the two strata combined, by vaccination group. For both age strata, the GMT increased substantially from prevaccination to day 28 postvaccination in both the Zostavax refrigerated and the Zostavax frozen formulation vaccination groups (GMRs, 2.6- and 2.9-fold for the two formulations, respectively, for the age groups combined). A statistical analysis for the comparison of the VZV antibody titers in both vaccination groups at day 28 postvaccination is as follows. By use of the GMT as the endpoint, the estimated GMTs for the Zostavax refrigerated group (n = 182) and the Zostavax frozen group (n = 185) were 727 and 834, respectively. The estimated GMT ratio (Zostavax refrigerated formulation/Zostavax frozen formulation) was 0.87 (95% CI, 0.71 to 1.07; P = 0.005), which meets the prespecified criterion that the VZV antibody response induced by the Zostavax refrigerated formulation is similar to that observed with the Zostavax frozen formulation. The estimated responses, GMT ratios, 95% CIs, and one-sided P value for the testing of noninferiority (GMT ratio [refrigerated formulation/frozen formulation], >0.67) were computed on the basis of a longitudinal regression model adjusted for prevaccination VZV antibody titers, age (years), and study center. The P value for the testing of the treatment-by-age-stratum interaction was 0.496. The P value for the testing of the treatment-by-center interaction was 0.656. A lower bound of the 95% CI on the difference (GMT ratio) that excludes a 1.5-fold decrease implies that the difference is statistically significantly less than the prespecified clinically relevant decrease of 1.5-fold and allows a conclusion of similarity (noninferiority). The P value for the testing of noninferiority (≤0.025) also supports this conclusion.

The results of the acceptability analysis performed on the basis of the VZV antibody responses in the Zostavax refrigerated and the Zostavax frozen vaccination groups at day 28 postvaccination are as follows. By use of the GMR as the endpoint, the estimated GMRs of the VZV antibody response for the Zostavax refrigerated group (n = 174) and the Zostavax frozen group (n = 177) were 2.6-fold (95% CI, 2.2- to 3.0-fold; $P < 0.001$) and 2.9-fold (95% CI, 2.4- to 3.4-fold; $P < 0.001$), respectively. The one-sided P value for the testing of the acceptability for GMR (>1.2-fold) was computed on the basis of the t test. The 95% CIs were also computed on the basis of the t distribution. Since the lower bound of the 95% CI was >1.2 in each case and the one-sided P value for the testing of the acceptability hypothesis (GMR, >1.2-fold) was <0.025 for both vaccination groups, the VZV antibody responses induced by both Zostavax formulations were found to be acceptable.

Figure 2 shows the reverse cumulative distribution of the VZV-specific antibody titer at day 1 and day 28 for each vaccination group. The data presented in Fig. 2 are consistent with the results of the noninferiority analysis described above, indicating that the Zostavax refrigerated formulation induced a response in VZV antibodies at 28 days postvaccination similar to that of the Zostavax frozen formulation.

TABLE 3. VZV-specific antibody titer by age stratum and vaccination group (per protocol population)

Age group (yr)	Time point	Refrigerated formulation group (n = 182)				Frozen formulation group (n = 185)			
		No. of subjects	Geometric mean endpoint titer[a] (95% CI)	Median (range) geometric mean endpoint titer	Geometric mean fold rise from day 1 (95% CI)	No. of subjects	Geometric mean endpoint titer (95% CI)	Median (range) geometric mean endpoint titer	Geometric mean fold rise from day 1 (95% CI)
50–59	Day 1	65	244 (179, 331)	214 (21, 8,606)		68	234 (181, 302)	216 (26, 2,166)	
	Wk 4	62	731 (542, 987)	779 (43, 21,284)		66	763 (553, 1,051)	976 (44, 25,748)	
	Wk 4	61			3.1 (2.3, 4.2)	65			3.3 (2.5, 4.3)
≥60	Day 1	115	302 (242, 377)	252 (24, 19,371)		116	328 (264, 406)	268 (35, 28,546)	
	Wk 4	114	710 (580, 870)	773 (68, 38,606)		112	897 (719, 1,121)	988 (82, 36,807)	
	Wk 4	113			2.3 (1.9, 2.8)	112			2.7 (2.2, 3.3)
Combined	Day 1	180	279 (234, 334)	244 (21, 19,371)		184	289 (245, 341)	256 (26, 28,546)	
	Wk 4	176	717 (607, 848)	773 (43, 38,606)		178	845 (704, 1,014)	979 (44, 36,807)	
	Wk 4	174			2.6 (2.2, 3.0)	177			2.9 (2.4, 3.4)

[a] The endpoint titers are expressed as gpELISA units/ml.

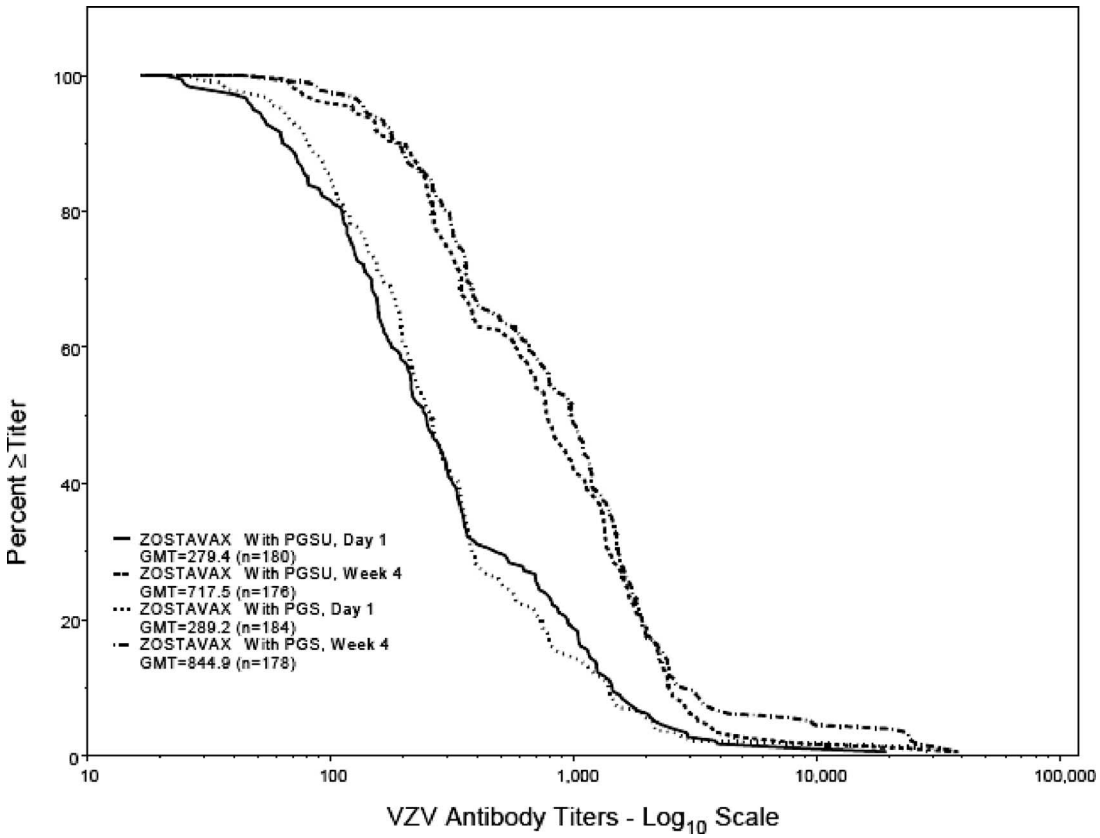

FIG. 2. Reverse cumulative distribution of VZV-specific antibody titers at prevaccination and 4 weeks postvaccination by vaccination group.

DISCUSSION

A zoster vaccine has been developed and licensed for the prevention of HZ and its complications, especially HZ-associated pain and PHN (11, 12, 23). However, the initial zoster vaccine formulation, manufactured with the PGS stabilizer (the Zostavax frozen formulation) and stored at −15°C, allows the distribution of the formulation only where freezer storage can be maintained (2, 3, 4, 24). The development of a refrigerator-stable formulation of the vaccine would enable the use of Zostavax in expanded clinical settings. Therefore, this study evaluated a refrigerator-stable formulation of Zostavax (which uses the PGSU stabilizer) in VZV antibody-seropositive adults.

Two other Oka/Merck varicella vaccines, Varivax and ProQuad, were also initially developed with the PGS stabilizer and were subsequently evaluated in similarly designed bridging studies and compared with the refrigerator-stable, PGSU formulations (1, 21). The bridging studies for these pediatric vaccines confirmed that the safety and immunogenicity profiles of the PGS- and PGSU-based formulations were comparable. The refrigerator-stable formulations of Varivax and ProQuad have subsequently been licensed in more than 26 countries (5, 7, 26). All three vaccines are formulated to deliver a particular minimum potency at expiry, according to the package circular (in the case of Zostavax, the minimum is 19,400 PFU per dose).

The safety hypothesis for the current study was whether the safety and tolerability of the Zostavax refrigerated and Zostavax frozen formulations were similar. Overall, injection-site AEs were reported by a lower proportion of subjects who received the Zostavax refrigerated formulation than by those who received the Zostavax frozen formulation, and as a consequence, the overall rate of vaccine-related AEs was lower in the Zostavax refrigerated vaccination group than in the Zostavax frozen vaccination group. No differences in the reported frequencies of vaccine-related systemic AEs were observed between the two formulations. Therefore, the safety and tolerability of the Zostavax refrigerated formulation appear to be similar to those observed for the Zostavax frozen formulation.

The GMTs of the VZV-specific antibody responses induced by these two vaccine formulations were found to be similar in adults 50 to 59 years of age, as well as in those ≥60 years of age, when they were measured by the gpELISA at 28 days postvaccination. Interestingly, in this study, the GMT at the baseline for the cohort of subjects 50 to 59 years of age was numerically lower than that seen for the cohort of subjects ≥60 years of age. The baseline titers were generally similar between these age groups in another study that evaluated the use of Zostavax concomitantly with influenza vaccine (15) and also between subjects 60 to 69 and ≥70 years of age in the pivotal efficacy study (20). The age-based trend seen in the current study appears to be attributable to the lower baseline titers in younger Hispanic subjects, a trend which was not observed in black or white subjects (data not shown). The antibody re-

sponses in both age strata were robust for each formulation and were comparable to those observed in other studies of the frozen formulation. In addition, this study found that the antibody responses to both the Zostavax refrigerated and the Zostavax frozen formulations were acceptable, based on a prespecified criterion for success. Together, these data indicate that the immunogenicities of the Zostavax refrigerator-stable and frozen formulations are similar. On the basis of the results from this study and the study of the concomitant use of Zostavax with the influenza vaccine (15), Zostavax is now licensed for use starting at 50 years of age in Australia, Switzerland, and the European Union.

Thus, the use of a PGSU-stabilized formulation has no detrimental effect on the safety or immunogenicity profile of Zostavax. The availability of a refrigerator-stable formulation of Zostavax will allow the use of this important vaccine in expanded clinical settings where freezer availability is limited.

ACKNOWLEDGMENTS

Other than those authors who are employees of Merck & Co., Inc. (as indicated in the affiliations), L.I.G., J.F.L., and T.M.N. have been investigators for the sponsor. Employees may hold stock and/or stock options in the company.

We thank all the subjects who participated in this study and the Merck gpELISA laboratory.

The members of the Zostavax Protocol 010 Study Group are H. J. Fields, W. E. Larsen, A. L. Mercado, L. G. Padget, M. D. Pescasio, E. A. Sheldon, L. D. Sher, B. D. Wieskopf, M. A. Goldberg, W. F. Miser, and R. Cain.

REFERENCES

1. **Bernstein, H. H., K. Eves, K. Campbell, S. B. Black, J. D. Twiggs, K. S. Reisinger, R. M. Conti, C. E. Flodmark, L. Rombo, S. Klopfer, F. Schödel, J. Hartzel, B. J. Kuter, and the Refrigerator-Stable Formulation Study Group for ProQuad.** 2007. Comparison of the safety and immunogenicity of a refrigerator-stable versus a frozen formulation of ProQuad (measles, mumps, rubella, and varicella virus vaccine live). Pediatrics **119:**e1299–e1305.
2. **Brockelsby, G.** 2005. Vaccine and drug storage. Dermatol. Nurs. **17:**373–374.
3. **Centers for Disease Control and Prevention.** 2007. Recommended adult immunization schedule—United States, October 2007–September 2008. http://www.cdc.gov/vaccines/recs/schedules/adult-schedule.htm. MMWR Morb. Mortal. Wkly. Rep. **56**:Q1–Q4.
4. **Cunningham, A. L.** 2006. Zoster vaccine live (Oka/Merck). Drugs Aging **23:**532.
5. **Diaz, C., P. Dentico, R. Gonzalez, R. G. Mendez, S. Cinquetti, J. L. Barben, A. Harmon, I. Chalikonda, J. G. Smith, J. E. Stek, A. Robertson, M. J. Caulfield, L. R. Biasio, J. L. Silber, C. Y. Chan, R. Vessey, J. Sadoff, I. F. S. Chan, H. Matthews, W. Wang, K. Schlienger, F. P. Schödel, and the Protocol 049 Study Group.** 2006. Safety, tolerability, and immunogenicity of a two-dose regimen of high-titer varicella vaccine in subjects ≥13 years of age. Vaccine **24:**6875–6885.
6. **Fairley, C. K., and E. Miller.** 1996. Varicella-Zoster virus epidemiology—a changing scene? J. Infect. Dis. **174:**S314–S319.
7. **Farrington, E. A.** 1995. Varicella zoster vaccine (Varivax). Pediatr. Nurs. **21:**358–361.
8. **Fernando, M.** 2004. An analysis of clinical risks in vaccine transportation. Br. J. Commun. Nurs. **9:**411–415.
9. **Garnett, G. P., and B. T. Grenfell.** 1992. The epidemiology of varicella-zoster virus infections—the influence of varicella on the prevalence of herpes-zoster. Epidemiol. Infect. **108:**513–528.
10. **Geffray, L.** 1998. Prevention of varicella-zoster-virus infections. Med. Mal. Infect. **28:**746–756.
11. **Gnann, J. W., and R. J. Whitley.** 2002. Herpes zoster. N. Engl. J. Med. **347:**340–346.
12. **Hope-Simpson, R. E.** 1975. Postherpetic neuralgia. J. R. Coll. Gen. Pract. **157:**571–575.
13. **Jung, B. F., R. W. Johnson, D.R. Griffin, and R. H. Dworkin.** 2004. Risk factors for postherpetic neuralgia in patients with herpes zoster. Neurology **62:**1545–1551.
14. **Kato, Y., I. Homma, and K. Ichiyanagi.** 1995. Postherpetic neuralgia. Clin. J. Pain **11:**336–338.
15. **Kerzner, B., A. V. Murray, E. Cheng, R. Ifle, P. R. Harvey, M. Tomlinson, J. L. Barben, K. Rarrick, J. E. Stek, M. O. Chung, F. P. Schödel, W. W. Wang, J. Xu, I. S. F. Chan, J. L. Silber, and K. Schlienger.** 2007. Safety and immunogenicity profile of the concomitant administration of Zostavax and inactivated influenza vaccine in adults aged 50 and older. J. Am. Geriatr. Soc. **55:**1499–1507.
16. **Klenerman, P., T. E. Peto, G. A. Luzzi, and B. E. Juel-Jensen.** 1989. Antiviral treatment and postherpetic neuralgia. Br. Med. J. **298:**832–836.
17. **Kost, R. G., and S. E. Straus.** 1996. Postherpetic neuralgia—pathogenesis, treatment, and prevention. N. Engl. J. Med. **335:**32–42.
18. **Kost, R. G., and S. E. Straus.** 1997. Postherpetic neuralgia—predicting and preventing risk. Arch. Intern. Med. **157:**1166–1167.
19. **Levin, M. J., M. Murray, H. A. Rotbart, G. O. Zerbe, C. J. White, and A. R. Hayward.** 1992. Immune-response of elderly individuals to a live attenuated varicella vaccine. J. Infect. Dis. **166:**253–259.
20. **Levin, M. J., M. N. Oxman, J. H. Zhang, G. R. Johnson, H. Stanley, A. R. Hayward, et al.** VZV-specific immune responses in elderly recipients of a herpes zoster vaccine. J. Infect. Dis., in press.
21. **Mendez, R., F. Henderson, K. Reisinger, E. Malacaman, A. Harmon, M. Waters, C. D. Meechan, I. S. F. Chan, W. W. Wang, C. Y. Chan, S. J. R. Vessey, J. L. Silber, F. Schödel, et al.** 2004. Immunogenicity and safety of process upgrade varicella vaccine (PUVV) with new stabilizer as compared to PUVV with current stabilizer when administered concomitantly with M-M-RII in healthy children, abstr. 303. 22nd Annu. Meet. Eur. Soc. Paediatr. Infect. Dis.
22. **Mullooly, J. P., K. Riedlinger, C. Chun, S. Weinmann, and H. Houston.** 2005. Incidence of herpes zoster, 1997-2002. Epidemiol. Infect. **133:**245–253.
23. **Oxman, M. N., M. J. Levin, G. R. Johnson, K. E. Schmader, S.E. Straus, L. D. Gelb, R. D. Arbeit, M. S. Simberkoff, A. A. Gershon, L. E. Davis, A. Weinberg, K. D. Boardman, H. M. Williams, J. H. Zhang, P. N. Peduzzi, C. E. Beisel, V. A. Morrison, J. C. Guatelli, P. A. Brooks, C. A. Kauffman, C. T. Pachucki, K. M. Neuzil, R. F. Betts, P. F. Wright, M. R. Griffin, P. Brunell, N. E. Soto, A. R. Marques, S. K. Keay, R. P. Goodman, D. J. Cotton, J. W. Gnann, Jr., J. Loutit, M. Holodniy, W. A. Keitel, G. E. Crawford, S. S. Yeh, Z. Lobo, J. F. Toney, R. N. Greenberg, P. M. Keller, R. Harbecke, A. R. Hayward, M. R. Irwin, T. C. Kyriakides, C. Y. Chan, I. S. F. Chan, W. W. Wang, P. W. Annunziato, and J. L. Silber for the Shingles Prevention Study Group.** 2005. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N. Engl. J. Med. **352:**2271–2284.
24. **Petrovic, V., Z. Seguljev, and B. Gajin.** 2005. Maintaining the cold chain for vaccines. Med. Pregl. **58:**333–341.
25. **Provost, P. J., D. L. Krah, B. J. Kuter, D. H. Morton, T. L. Schofield, E. H. Wasmuth, C. J. White, W. J. Miller, and R. W. Ellis.** 1991. Antibody-assays suitable for assessing immune-responses to live varicella vaccine. Vaccine **9:**111–116.
26. **Reisinger, K. S., M. L. H. Brown, J. Xu, B. J. Sullivan, G. S. Marshall, B. Nauert, D. O. Matson, P. E. Silas, F. Schödel, J. O. Gress, B. J. Kuter, and the Protocol 014 Study Group for ProQuad.** 2006. A combination measles, mumps, rubella, and varicella vaccine (ProQuad) given to 4- to 6-year-old healthy children vaccinated previously with M-M-RII and Varivax. Pediatrics **117:**265–272.
27. **Robinson, D. M., and C. M. Perry.** 2006. Zoster vaccine live (Oka/Merck). Drugs Aging **23:**525–531.
28. **Saibara, T., T. Maeda, S. Onishi, and Y. Yamamoto.** 1993. Depressed immune functions in the early phase of varicella-zoster virus reactivation. J. Med. Virol. **39:**242–245.
29. **Schmader, K.** 1998. Postherpetic neuralgia in immunocompetent elderly people. Vaccine **18:**1768–1770.
30. **Schmader, K.** 1999. Herpes zoster in the elderly: issues related to geriatrics. Clin. Infect. Dis. **28:**736–739.
31. **Schmader, K.** 2001. Herpes zoster in older adults. Clin. Infect. Dis. **32:**1481–1486.
32. **Tenser, R. B.** 2001. Herpes zoster infection and postherpetic neuralgia. Curr. Neurol. Neurosci. Rep. **1:**526–532.
33. **Tyring, S. K.** 1992. Natural history of varicella zoster virus. Semin. Dermatol. **11:**211–217.
34. **Tyring, S. K.** 1996. Early treatment of herpes zoster. Hosp. Pract. (Minneapolis) **31:**137–144.
35. **Wasmuth, E. H., and W. J. Miller.** 1990. Sensitive enzyme-linked-immunosorbent-assay for antibody to varicella-zoster virus using purified Vzv glycoprotein antigen. J. Med. Virol. **32:**189–193.
36. **Watson, C. P.** 1999. Postherpetic neuralgia. Contrib. Microbiol. **3:**128–140.
37. **Wharton, M.** 1996. The epidemiology of varicella-zoster virus infections. Infect. Dis. Clin. N. Am. **10:**571–578.
38. **Whitley, R. J., and J. W. Gnann.** 1999. Herpes zoster: focus on treatment in older adults. Antivir. Res. **44:**145–154.