CLINICAL AND VACCINE IMMUNOLOGY, May 2009, p. 646–652 Vol. 16, No. 5
1556-6811/09/$08.00+0 doi:10.1128/CVI.00407-08

Comparison of the Levels of Immunogenicity and Safety of Zostavax in Adults 50 to 59 Years Old and in Adults 60 Years Old or Older[▽]

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Received 7 November 2008/Returned for modification 22 December 2008/Accepted 25 February 2009

Zostavax has been shown to be efficacious in the prevention of herpes zoster and generally well tolerated in clinical trials among subjects 60 years old or older. This prespecified combined analysis from two studies compares the levels of immunogenicity and safety of Zostavax in subjects 50 to 59 years old versus those in subjects ≥60 years old. Varicella-zoster virus (VZV) antibody (Ab) titers were measured by glycoprotein enzyme-linked immunosorbent assay at baseline and 4 weeks postvaccination. Noninferiority was evaluated by estimated geometric mean severalfold rise (GMFR) ratio (50 to 59 years old/≥60 years old) and two-sided 95% confidence interval (CI). Success was defined by a lower bound (LB) of the 95% CI of the GMFR ratio of >0.67. Acceptability of postvaccination VZV Ab was defined by an LB of the 95% CI of the GMFR of >1.4. Safety data were recorded for 28 days postvaccination by standardized vaccination report card. The estimated GMFRs from baseline to 4 weeks postvaccination were 2.6 (95% CI, 2.4, 2.9) in subjects 50 to 59 years old and 2.3 (95% CI, 2.1, 2.4) in subjects ≥60 years old. The estimated GMFR ratio (50 to 59 years old/≥60 years old) was 1.13 (95% CI, 1.02, 1.25). No serious Zostavax-related adverse experiences were reported. After a dose of Zostavax, the GMFR of the VZV Ab response in subjects 50 to 59 years old was noninferior to that in subjects ≥60 years old. The VZV Ab response was acceptable in both age groups. Zostavax was generally well tolerated in both age groups.

Herpes zoster (HZ), also known as shingles, is a manifestation of reactivation of varicella-zoster virus (VZV), which, as a primary infection, is responsible for chickenpox (varicella). The incidence and severity of HZ increase with age (14, 26, 28). In the United States, Canada, and Europe, the overall annual incidence of HZ is consistently estimated to be 3 to 4 per 1,000 population (1, 7, 8, 11, 15, 18, 22). The annual risk of developing HZ increases markedly around 50 years of age and rises sharply afterwards, up to 1% per year among those over 75 years of age. The lifetime risk of HZ is estimated to range from 10% to 30% in the general population, with estimates closer to 30% in recent studies (2, 4, 5, 8, 14, 15), and is as high as 50% in individuals reaching 85 years of age (14, 26, 32).

Zostavax (live zoster vaccine), a vaccine for the prevention of HZ (shingles) in individuals ≥60 years of age, has been recently licensed in the United States (3, 13, 30) and was subsequently licensed by the European Union for the prevention of HZ and HZ-related postherpetic neuralgia (PHN) in individuals ≥50 years of age (9). As demonstrated by the Shingles Prevention Study (SPS), Zostavax has been shown to reduce the incidence of HZ and PHN in adults ≥60 years of age and to lessen acute and chronic pain associated with HZ, presumably through boosting of VZV-specific immune responses (19, 24). The SPS demonstrated that the VZV antibody (Ab) response correlated with vaccine effect in preventing HZ (19).

Two recent studies of Zostavax enrolled subjects ≥50 years of age. Protocol 010 (formulation bridging study) demonstrated that the refrigerator-stable formulation of Zostavax elicits a VZV Ab response that is noninferior to that of the frozen formulation of Zostavax (10). The study enrolled and vaccinated a total of 367 subjects; approximately half of them (n = 182) received refrigerated-formulation Zostavax, and the other half (n = 185) received frozen-formulation Zostavax. Among the 367 subjects vaccinated, 135 were 50 to 59 years of age, and 232 were ≥60 years of age. Protocol 011 (concomitant use with influenza virus vaccine) demonstrated that Zostavax administered concomitantly with inactivated influenza virus vaccine elicits a VZV Ab response that is noninferior to that when the two vaccines are administered separately (16). The study enrolled and vaccinated a total of 762 subjects; approximately half of them (n = 382) received Zostavax and influenza virus vaccine concomitantly on day 1, whereas the other half (n = 380) received influenza virus vaccine and Zostavax 28 days apart. Frozen-formulation Zostavax was administered in this study. Among the 762 subjects vaccinated, 259 were 50 to 59 years of age, and 503 were ≥60 years of age.

The purpose of this article is to present integrated analyses of the VZV Ab responses to Zostavax among subjects 50 to 59 years of age in comparison with the responses in subjects ≥60 years of age using combined immunogenicity data from protocol 010 and protocol 011. The safety evaluation of the combined data in the two age groups will also be discussed.

(Data from the manuscript were presented at the National Foundation for Infectious Diseases 10th Annual Conference on Vaccine Research, Baltimore, MD, 2007, and at Vaccine Congress 2007, Amsterdam, The Netherlands, 2007.)

MATERIALS AND METHODS

Study design. Patients included in the present analysis were from two multicenter clinical studies completed between 2005 and 2006, both of which were randomized, double-blind (blinded to subject, investigator, and sponsor), controlled clinical trials of Zostavax (live zoster vaccine). The methods and results for each of these studies

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▽ Published ahead of print on 4 March 2009.

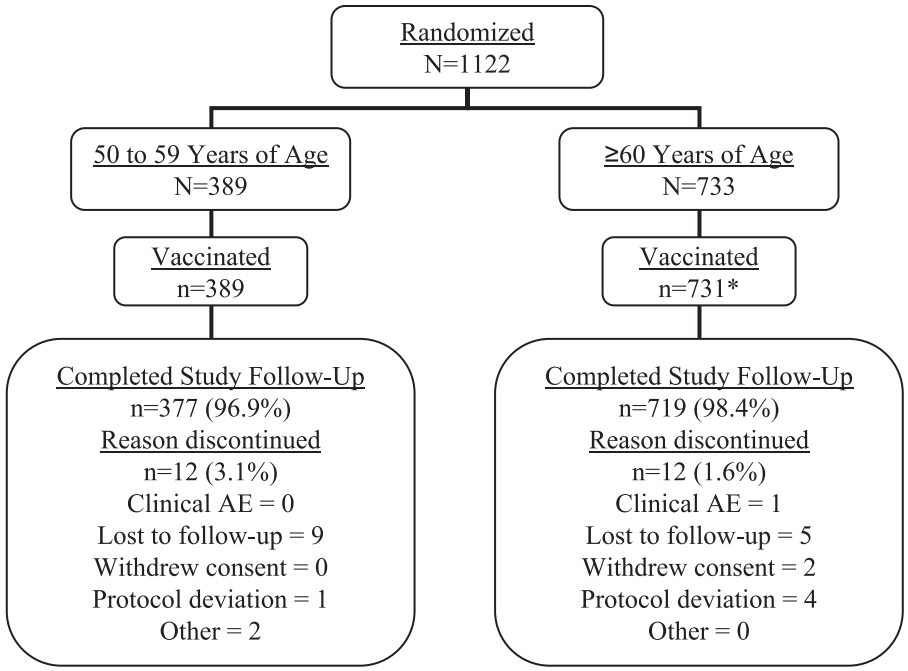

FIG. 1. Subject accounting.

were described previously (10, 16). Healthy, varicella history-positive, HZ history-negative men and women ≥50 years of age were eligible for enrollment. Subjects provided written informed consent before they were enrolled.

Randomization was stratified by age group (50 to 59 years and ≥60 years). Subjects were monitored for injection-site and systemic clinical adverse experiences (AEs), varicella or varicella-like rash, HZ or HZ-like rash, and exposure to varicella/HZ for 28 days after each injection. VZV Ab titers from blood samples collected prevaccination and 4 weeks postvaccination were determined by glycoprotein enzyme-linked immunosorbent assay (gpELISA), a validated assay that measures immunoglobulin G antibody responses to VZV glycoproteins (12, 19, 24).

The primary hypotheses were that (i) the geometric mean severalfold rise (GMFR) in VZV Ab responses from prevaccination to 4 weeks postvaccination of Zostavax among subjects 50 to 59 years of age is noninferior (defined by the lower bound [LB] of the 95% confidence interval [CI] of the GMFR ratio [50 to 59 years old/≥60 years old] being >0.67) to that among subjects ≥60 years of age, and (ii) the GMFR in VZV Ab responses from prevaccination to 4 weeks postvaccination of Zostavax is acceptable (defined by the LB of the 95% CI of the GMFR being >1.4) among subjects 50 to 59 years of age and among subjects ≥60 years of age. Safety information within 28 days postvaccination among both age groups was summarized.

Vaccine description. Zostavax and placebo (for protocol 011 only) were supplied to the study centers in 0.7-ml, single-dose vials and stored at −15°C or colder. Zostavax and placebo were reconstituted with sterile diluent immediately prior to administration. Subjects received a single 0.65-ml subcutaneous injection. The potencies of Zostavax used in both studies (protocol 010, ~50,000 PFU/dose; protocol 011, ~58,000 PFU/dose) were similar to Zostavax potencies studied in the SPS (10, 16, 24).

Endpoints. The primary immunogenicity endpoints were (i) the geometric mean titer (GMT) of VZV Ab at 4 weeks postvaccination by gpELISA and (ii) the GMFR of VZV Ab from prevaccination to 4 weeks postvaccination.

The primary safety endpoints were (i) vaccine-related serious AEs during the 28-day follow-up period after each injection by vaccination group; (ii) vaccination report card (VRC)-prompted injection-site AEs through 5 days following vaccination; (iii) VRC-prompted rashes, varicella, and HZ during the 28-day follow-up period after vaccination; and (iv) any systemic AEs during the 28-day follow-up period after vaccination.

Statistical analyses. Noninferiority and acceptability hypotheses were tested in the per-protocol population. Noninferiority was evaluated by estimating the GMFR ratio (50 to 59 years old/≥60 years old) and its two-sided 95% CI, after adjusting for prevaccination titers using an analysis of covariance (ANCOVA) model. Noninferiority was defined by the LB of the 95% CI of the GMFR ratio being >0.67 (i.e., <1.5-fold decrease in GMFR). Acceptability of the postvaccination VZV Ab was defined by the LB of the 95% CI of the GMFR being >1.4

TABLE 1. Demographics

Characteristic	Value for group	
	50–59 yr of age (n = 389)	≥60 yr of age (n = 731)
No. (%) of subjects under protocol:		
010		
Refrigerated formulation	66 (17.0)	116 (15.9)
Frozen formulation	69 (17.7)	116 (15.9)
011		
Concomitant vaccination	129 (33.2)	253 (34.6)
Sequential vaccination	125 (32.1)	246 (33.7)
No. (%) of subjects of gender:		
Male	163 (41.9)	334 (45.7)
Female	226 (58.1)	397 (54.3)
Age (yr)		
Mean (SD)	54.6 (2.8)	68.1 (6.2)
Median	54	67
Range[a]	47–59	60–97
No. (%) of patients of race:		
Caucasian	245 (63.0)	591 (71.0)
African American	91 (23.4)	147 (20.1)
Hispanic	43 (11.1)	41 (5.6)
Asian	3 (0.8)	18 (2.5)
Other[b]	7 (1.8)	6 (0.8)

[a] One subject was 47 years old and was included in the group comprised of subjects 50 to 59 years of age.
[b] Native American, Indian, African, Asiatic, or multiracial.

TABLE 2. VZV gpELISA Ab responses

Protocol	Endpoint	50–59 yr of age (n = 389)			≥60 years of age (n = 731)		
		No. of subjects	GMT (gpELISA U)	95% CI	No. of subject	GMT (gpELISA U)	95% CI
010	GMT prevaccination	133	238.5	196.0, 290.3	231	314.6	269.9, 366.6
	GMT week 4	128	747.3	601.3, 928.6	226	797.5	686.6, 926.4
	GMFR	126	3.2	2.6, 3.9	225	2.5	2.2, 2.9
011	GMT prevaccination	252	269.0	235.1, 307.7	494	255.0	229.7, 283.1
	GMT week 4	244	630.2	558.4, 711.1	483	543.1	496.3, 594.4
	GMFR	242	2.4	2.1, 2.7	478	2.1	2.0, 2.3
Combined	GMT prevaccination	385	258.0	231.4, 288.3	725	272.7	250.1, 297.3
	GMT week 4	372	668.2	599.4, 745.0	709	613.9	567.4, 644.2
	GMFR	368	2.6	2.4, 2.9	703	2.3	2.1, 2.4

(the lower bound of the 95% CI of the GMFR from prevaccination to 6 weeks postvaccination for the vaccine lots used in the SPS). For safety, risk differences and associated 95% CIs were determined.

RESULTS

Participant accounting and demographics. Figure 1 presents an accounting, by age group, of the number of subjects who were randomized to a study-specific vaccination group, who were vaccinated, and who completed or discontinued the study. A total of 1,122 subjects were randomized, with 1,120 subjects being vaccinated (367 in protocol 010 and 753 in protocol 011, as presented in Table 1). Overall, 1,096 of the 1,120 subjects (97.9%) completed the respective studies, and 24 subjects (2.1%) discontinued (Fig. 1); the reasons for discontinuation were generally comparable between the two age groups. However, the rate of discontinuation due to loss to follow-up was numerically higher among subjects in the younger age group. The two age groups were generally balanced with respect to gender, vaccination group assignment, and race.

Immunogenicity. In each study and in the two studies combined, the VZV Ab GMT increased substantially from prevaccination to week 4 postvaccination in both age groups (Table 2). The overall GMTs for the combined studies at day 1 and week 4 postvaccination were generally comparable between the two age groups (50 to 59 years of age and ≥60 years of age). The GMFRs from prevaccination to week 4 postvaccination were also generally comparable between the two age groups although numerically slightly higher in the age group of 50 to 59 years, an observation which was consistent across the two studies.

After adjusting for prevaccination titers, the estimated GMFR ratio (50 to 59 years of age/≥60 years of age) of the VZV Ab response between the age groups, based on an ANCOVA model, was 1.13 (95% CI, 1.02 to 1.25), demonstrating that the VZV Ab response induced by Zostavax in subjects 50 to 59 years of age was noninferior to that in subjects ≥60 years of age. In addition, as the LB of the 95% CI of the GMFR ratio was >1.0, the GMFR at week 4 postvaccination was slightly higher (reached statistical significance) in subjects 50 to 59 years of age.

To further quantify the effect of age, study, vaccination group, and prevaccination titer on the rise postvaccination, an ANCOVA model with a natural-log-transformed rise at week 4 postvaccination as a response variable and vaccination group, age group, protocol, and log-transformed prevaccination titers as the covariates was utilized (Table 3). The age group with 50- to 59-year-old subjects showed a significantly (marginally) higher VZV Ab response at week 4 postvaccination than did the ≥60-year-old age group (1.13; 95% CI, 1.02 to 1.25). The level of prevaccination VZV Ab titers had a statistically significant (P value of <0.001) effect on the VZV Ab response at week 4 postvaccination. The vaccination group assignment within each study did not have a statistically significant effect on the rise at week 4 postvaccination after adjusting for the prevaccination titer.

A test for the age-group-by-study interaction was conducted for the GMFR from prevaccination to week 4 postvaccination.

TABLE 3. Integrated statistical analysis of the effect of age group, study, vaccination group, and prevaccination titer on rise in titers from prevaccination to week 4 postvaccination based on data combined from protocol 010 and protocol 011 (per-protocol population)

Parameter	Estimated regression coefficient (95% CI)	Fold difference (95% CI)[a]
Age group (50–59 yr vs ≥60 yr)	0.119 (0.016, 0.222)	1.13 (1.02, 1.25)
Study (protocol 010 vs protocol 011)	0.276 (0.130, 0.422)	1.32 (1.14, 1.53)
Vaccination group (Zostavax with PGSU vs Zoxtavax with PGS)[c]	−0.131 (−0.302, 0.039)	0.88 (0.74, 1.04)
Vaccination group (concomitant vs nonconcomitant)	−0.068 (−0.187, 0.051)	0.93 (0.83, 1.05)
One-unit increase in log-transformed prevaccination titers	−0.419 (−0.461, −0.377)	0.66 (0.63, 0.69)[b]

[a] Computed using an ANCOVA model in which the natural-log-transformed week 4 titer is the response variable and vaccination group, age, and natural-log-transformed prevaccination titers are the covariates.
[b] $P < 0.001$.
[c] PGSU, phosphate-gelatin-sucrose-urea; PGS, phosphate-gelatin-sucrose.

TABLE 4. Clinical AE summary (days 1 to 28 following any vaccination) by age group

Parameter[a]	50–59 yr of age (n = 389)		≥60 yr of age (n = 731)	
	No. of subjects	% of subjects	No. of subjects	% of subjects
Total	389		731	
Subjects with follow-up	382	98.2	730	99.9
Subjects with one or more AE	231	60.5	323	44.2
Injection-site AEs	193	50.5	250	34.2
Systemic AEs	96	25.1	139	19.0
Subjects with vaccine-related AEs[b]	199	52.1	256	35.1
Injection-site AEs[b]	193	50.5	249	34.1
Systemic AEs[b]	22	5.8	21	2.9
Subjects with serious AEs	1	0.3	5	0.7
Serious vaccine-related AEs	0	0.0	0	0.0
Death	0	0.0	0	0.0
Subjects who discontinued due to 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] Determined by the investigator to be possibly, probably, or definitely related to the vaccine.

The interaction was not statistically significant (P value of 0.867) at the 10% level, which indicates that the VZV Ab responses at week 4 postvaccination in the two age groups were consistent across the two studies (protocol 010 and protocol 011).

The estimated GMFR of the VZV Ab titers from prevaccination to week 4 postvaccination was 2.6 (95% CI, 2.4 to 2.9) in subjects 50 to 59 years of age and 2.3 (95% CI, 2.1 to 2.4) in subjects ≥60 years of age. Since each of the LBs of the 95% CI was >1.4, and the one-sided P value for testing the acceptability hypothesis (GMFR of >1.4) was <0.025, the criteria for acceptability of the VZV Ab responses induced by Zostavax in both age groups were met.

AEs. Table 4 presents an integrated summary of the number and percentage of subjects with clinical AEs reported within 28 days postvaccination, by age group, for subjects vaccinated with Zostavax in the combined protocols. Safety follow-up was obtained for 1,112 of the 1,120 vaccinated subjects. In protocol 010, all vaccinated subjects with safety follow-up were included in the safety summaries and analyses. In protocol 011, only subjects with safety follow-up during the 28-day period following the administration of Zostavax were included. The safety evaluation following the administration of placebo and/or influenza virus vaccine was not included in the following summaries and analyses, except for those subjects who reported systemic clinical AEs following the concomitant administration of influenza virus vaccine and Zostavax.

As shown in Table 4, 60.5% of subjects 50 to 59 years of age reported one or more clinical AEs, whereas 44.2% of subjects ≥60 years of age reported one or more clinical AEs. In subjects 50 to 59 years of age, approximately 25.1% of subjects reported systemic clinical AEs, but only 5.8% of subjects reported vaccine-related systemic clinical AEs. In subjects ≥60 years of age, 19.0% of the subjects reported systemic clinical AEs, but only 2.9% of the subjects reported vaccine-related systemic clinical AEs. The majority of the AEs were considered by the subject to be mild or moderate in both age groups.

The most commonly reported systemic clinical AEs in subjects 50 to 59 years of age were headache (4.5%), upper respiratory tract infection (URI) (2.9%), and back pain (2.1%). Among these most commonly reported systemic clinical AEs, headaches were deemed to be vaccine related in 1.0% of subjects. The most commonly reported systemic clinical AE in subjects ≥60 years of age was URI (2.1%), with 0.3% reporting URIs that were deemed to be vaccine related. Overall, the number and percentage of subjects reporting any systemic clinical AEs were greater in the younger age group than in the older age group.

One (0.3%) out of 382 subjects with safety follow-up in the group comprised of subjects 50 to 59 years of age and 5 (0.7%) out of 730 subjects with safety follow-up in the group comprised of subjects ≥60 years of age reported serious clinical AEs (Table 5). No serious clinical AEs related to Zostavax were reported in either of the two studies. Furthermore, no deaths occurred during either study.

Table 6 presents a summary of the number and percentage of all subjects who reported injection-site AEs within 5 days following vaccination with Zostavax for the combined clinical studies. Only AEs reported at the injection site for Zostavax are included, and all are considered to be related to Zostavax vaccination.

The most frequently reported injection-site AEs (≥10% in

TABLE 5. List of serious AEs during 28 days postvaccination by age group

Group and age of subject (yr)	Vaccine given	AE	Day of onset	Vaccine relationship
50–59				
54	Flu vaccine and Zostavax	Convulsion	22	Probably not
≥60				
62	Zostavax	Upper limb fracture	23	Definitely not
70	Flu vaccine and Zostavax	Basal cell carcinoma	11	Definitely not
71	Flu vaccine and Zostavax	Congestive heart failure	18	Definitely not
72	Zostavax	Gastroenteritis	7	Definitely not
74	Flu vaccine and Zostavax	Multiple AEs[a]	6	Probably not

[a] Acute pulmonary edema, aortic valve stenosis, arrhythmia, congestive heart failure, chronic obstructive pulmonary disease, myocardial infarction, pneumonia, and respiratory failure.

TABLE 6. Summary of VRC-prompted injection-site AEs on days 1 to 5 following any vaccination[b]

Parameter	50–59 yr of age (n = 389)		≥60 yr of age (n = 731)		Estimated risk difference (%) (95% CI)
	No. of subjects	Estimated risk (%)	No. of subjects	Estimated risk (%)	
Subjects with follow-up	382		729		
Subjects without follow-up	7		2		
Subjects with ≥1 injection-site AE	193	50.4	248	34.0	
Injection-site erythema[a]	155	40.4	187	25.6	14.8 (9.0, 20.7)
Injection-site pain[a]	160	41.7	179	24.6	17.1 (11.3, 23.0)
Injection-site pruritus	27	7.0	26	3.6	3.4 (0.7, 6.6)
Injection-site awelling[a]	131	34.0	136	18.7	15.3 (9.8, 20.9)
Injection-site warmth	8	2.1	2	0.3	1.8 (0.6, 3.8)

[a] These items were prompted for on the VRC. *P* values are provided only for these events.
[b] The same subject may appear in different categories but was counted only once in each category.

either age group) were erythema, pain, and swelling, all of which were prompted for on the VRC. These AEs were reported by a higher proportion of subjects 50 to 59 years of age than subjects ≥60 years of age.

Table 7 provides a list of the PCR assay results for those subjects who reported and were diagnosed by the investigator as having developed a varicella-like rash, HZ, or HZ-like rash following any vaccination, regardless of the rash location, by age group. One varicella-like rash, from a 58-year-old female 2 days following vaccination, was positive for herpes simplex virus (type undetermined). There was no statistically significant difference between the two age groups; however, only two of the seven rash cases had specimens available for PCR.

DISCUSSION

This combined analysis demonstrates that the immunogenicity (as measured by gpELISA) and safety profile of Zostavax administered to subjects 50 to 59 years of age are generally similar to those of Zostavax administered to subjects ≥60 years of age.

In the SPS, the immune response to vaccination measured by gpELISA at 6 weeks postvaccination was shown to correlate with protection against HZ (22, 31), and the boost in VZV-specific Ab observed after vaccination is thought to be an indirect reflection of the activation and increase of VZV-specific memory T cells (19). Therefore, the gpELISA response can be used as an indirect tool to assess the VZV-specific cellular immune response when measured 2 to 6 weeks postvaccination (16, 17, 23, 31). Consequently, the measurement of VZV-specific Ab responses by gpELISA was used in the two studies included in this analysis to compare the VZV-specific immune response induced by Zostavax.

The results obtained in the present integrated analysis indicate that the GMFR of VZV Ab titer from prevaccination to 4 weeks postvaccination induced by Zostavax in subjects 50 to 59 years of age is noninferior to that in subjects ≥60 years of age. Although no cellular immune assay was used in this analysis to assess the effect of vaccination, the observed increase in the VZV Ab response was comparable to that seen in the immunological substudy of the SPS (19, 23, 31). Subjects 50 to 59 years of age demonstrated a slightly larger rise in VZV Ab titers from baseline to week 4 postvaccination than did subjects ≥60 years of age.

Zostavax is generally well tolerated in subjects 50 to 59 years of age and in subjects ≥60 years of age, consistent with data from previously reported Zostavax clinical trials (6, 17, 20, 23, 24, 29, 31). Although the proportions of subjects who reported nonserious clinical AEs were generally higher in the group comprised of subjects 50 to 59 years of age than in the group comprised of subjects ≥60 years of age, most were mild or moderate in intensity. This age-related finding was seen not only following the administration of Zostavax but also following the administration of influenza virus vaccine and placebo in protocol 011 (16).

TABLE 7. Subjects with varicella or varicella-like rash or HZ or HZ-like rash by age group[a]

Age group and protocol	Gender	Age (yr)	Rash diagnosis	Onset (days) postvaccination	Total duration (days)	Max no. of lesions	Intensity	Laboratory confirmation
50–59 yr of age								
010	F	50	Varicella-like rash	6	8	3	NA	No sample
011	F	58	Varicella-like rash	2	11	3	Moderate	Positive for HSV
≥60 yr of age								
011	F	64	Herpes zoster	11	26	50	Moderate	QNS
011	F	66	Varicella-like rash	14	11	1	Mild	No sample
011	F	71	Zoster-like rash	8	25	6	Moderate	No sample
011	F	72	Varicella-like rash	2	6	4	Mild	No sample
011	F	82	Zoster-like rash	27	NA	10	Moderate	Negative

[a] M, male; F, female; NA, not available (not reported); QNS, insufficient sample; HSV, herpes simplex virus (type not determined); negative, positive for beta-globin but negative for VZV-WT, VZV-O, and HSV DNA.

Because of the demographic structure of the population in industrialized countries (i.e., "baby boomers"), 50- to 59-year-olds represent a very large cohort: ~37 million people in the United States, ~61 million in the countries of the European Union, ~4 million in Canada, and ~3 million in Australia/New Zealand (http://www.census.gov/ipc/www/idb/tables.html#region). Overall, ~60 to 70% of all HZ cases occur in people ≥50 years of age: ~20% in the 50- to 59-year-old cohort and ~45% in people ≥60 years of age (1, 8, 14, 15).

Although the duration of protection conferred by Zostavax is unknown at this point, experience with pneumococcal vaccine suggests that among older adults, both magnitude and durability of protection improve with successively younger populations (27). Additionally, even though no direct efficacy data are available for Zostavax in persons 50 to 59 years of age, data from the SPS showed that vaccine efficacy on HZ rash was higher in younger subjects (64% in subjects 60 to 69 years of age) than in older subjects (38% in subjects ≥70 years of age) (19, 24). Together with the data presented here, this finding suggests that the vaccine efficacy on HZ rash in the 50- to 59-year-old cohort would be at least 64%. Using 2005 population data, zoster vaccination beginning at 50 years of age could translate over 10 years into an additional number of HZ cases prevented of ~1.3 million in the United States, ~2.2 million in the European Union, ~145,000 in Canada, and ~105,000 in Australia/New Zealand.

Thus, routine vaccination beginning at 50 years of age could increase the number of HZ cases that could be prevented each year by at least 50% compared with vaccinating only people ≥60 years of age. Preventing these cases would also prevent the corresponding burden of HZ complications including PHN. In addition to the medical impact, vaccinating younger individuals could prevent work productivity loss, since the majority of individuals 50 to 59 years of age are employed (e.g., ~70% in the United States) (21, 25).

The natural immunity conferred by an HZ episode may not last any longer than that conferred by vaccination, and there may be no advantage in deferring vaccination until after 60 years of age compared with starting vaccination after 50 years of age. Therefore, not protecting younger people against a first HZ episode between 50 and 59 years of age would constitute a clear clinical and public health disadvantage of a delayed vaccination strategy. Overall, the risk-benefit of vaccinating this younger cohort is expected to be as good as that in the older age groups.

In summary, after a dose of Zostavax, the GMFR of VZV Ab from baseline to 4 weeks postvaccination in subjects 50 to 59 years of age is noninferior to that in subjects ≥60 years of age. The VZV Ab response is acceptable in both age groups. Zostavax is generally well tolerated in both age groups. Zoster vaccination of individuals 50 to 59 years of age could have an important clinical and public health impact.

ACKNOWLEDGMENTS

We thank all the subjects who participated in this study; the Zostavax Protocol 010 Study Group (R. Cain, H. Fields, L. Gilderman, M. Goldberg, W. Larson, J. Lawless, A. Mercado, T. Nolan, W. Miser, L. Padget, M. Pescasio, E. Sheldon, L. Sher, and B. Wieskopf); the Zostavax Protocol 011 Study Group (P. Bristol, E. Cheng, D. Claassen, M. Cooperman, C. Fisher, L. Harris, P. Harvey, S. Hull, K. Hrdina, R. Ifle, B. Kerzner, C. Klein, S. Leotta, R. Mills, A. Murray, E. Padilla, H. Samer, E. Sobel, H. Stamps, and M. Tomlinson), Merck & Co., Inc. Functional Teams, including the Clinical Research Specialist Organization, Worldwide Clinical Data Management Operations, Clinical Research Operations, and the Serology Laboratory; and R. Rutledge for her invaluable assistance and knowledge of the Zostavax clinical program. All authors were involved in study concept and design, analysis and interpretation of data, and preparation of the manuscript.

Funding for this research was provided by Merck & Co., Inc., which reviewed and approved the manuscript. All authors work for Merck Research Laboratories, North Wales, PA, and may hold stock and/or stock options in the company.

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