REVIEW OF 103552/5079
REVIEWER: Philip R. Krause, M.D.
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STUDY SUMMARIES

I. Brief study summaries

Protocol 025 was initiated prior to licensure of Varivax, and included 10-year followup of children aged 12 months to 12 years of age, immunized with one or two doses of vaccine. In protocol 025, the two vaccine doses were administered at a 3 month interval. This was an open, randomized, multicenter study, including 2216 subjects (1102 in the two-dose group) with a mean age of 4.0 years. Its initial goal was to assess immunogenicity, so no provision was initially made to assess efficacy. However, breakthrough varicella incidence was quantified, allowing comparisons between 1 and 2 dose regimens, as well as with historical rates of varicella. In addition, breakthrough rates after household exposures were compared with historical rates of household exposure transmission. Other endpoints were immunogenicity and safety.

Protocol 007 studied the safety and immunogenicity of providing a second dose of varicella vaccine, 3-6 years after an initial dose. This was an open, randomized, multicenter study, initially of just one dose of vaccine. After 3-6 years, a subset of 422 subjects (mean age: 3.7 years at 1st immunization; 417 of whom were 1-12 years of age at the time of initial vaccination, the remainder were 13-17) received a second dose of vaccine from the 1991 consistency lots (all >1350 pfu/dose). Immunogenicity and safety were major endpoints of the study. In addition, breakthrough rates were passively followed for 10 years. Some of these children (265) received initial doses below 1350 pfu.

Protocol 014 (Proquad) was a double blind, multicenter randomized study that evaluated a second dose of Varivax given concomitantly with a second dose of MMR-II at 4-6 years of age (N=195), as a control group for administration of MMRV at this age. Mean age at dose 2: 4.3 years. Endpoints were safety (42 day follow-up) and immunogenicity.

Some children in these studies with negative VZV serology were offered additional vaccinations. They were treated in the analyses as though they were vaccine failures, assuming that these individuals would have contracted varicella at the rate of unimmunized individuals.

Table 2.7.3-ped2dose: 10

VARIVAX™ Protocol 025
Summary of Subject Characteristics

	VARIVAX™ One-Dose Regimen (N=1114) n (%)	VARIVAX™ Two-Dose Regimen† (N=1102) n (%)	Total (N=2216) n (%)
Age at the Initial Vaccination:			
Mean (years):	3.8	4.1	4.0
Median (years):	3.0	3.0	3.0
Number of Children in Given Age Range			
12 to 15 months†	69 (6.2)	65 (5.9)	134 (6.0)
16 to 23 months	167 (15.0)	143 (13.0)	310 (14.0)
2 to 4 years	522 (46.9)	492 (44.6)	1014 (45.8)
5 to 12 years	356 (32.0)	402 (36.5)	758 (34.2)
Range (Years):			
Male (years)‡	1 to 12	1 to 12	1 to 12
Female (years)	1 to 12	1 to 12	1 to 12
Gender			
Male	594 (53.3)	548 (49.7)	1142 (51.5)
Female	520 (46.7)	554 (50.3)	1074 (48.5)
Race			
Black	36 (3.2)	35 (3.2)	71 (3.2)
Caucasian	976 (87.6)	985 (89.4)	1961 (88.5)
Other	102 (9.2)	82 (7.4)	184 (8.3)

† Two Doses of varicella vaccine given 3 months apart.
‡ Includes Case Number 03508, who was an 11-month-old male vaccinated in the 2-dose regimen group.
VZV = Varicella-zoster virus.
N = Number of subjects vaccinated in the given regimen.
n = Number of subjects in each category.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.

[Ref. 5.3.5.4; R2]

II. Total Database

The total number of children aged 1-12 receiving a second dose of Varivax in these studies was 1102+417+195=1714.

III. Ages studied

The mean ages at time of the second dose were: Protocol 025: 4 years (1102 subjects); Protocol 007: about 9 years (417 subjects); Procol 014: 4.3 years (195 subjects). Subject demographics are summarized in tables 2.7.3.ped2dose: 10, 11 and 12. From these tables, it may be seen that the studies included 113 children aged 12-15 months, and 208 children aged 16-24 months at the time of vaccination for a total of 321 children in the 1-2 year age group at time of initial vaccination. This age group is among the most important, because this age group corresponds with likely first vaccinations for most U.S. children. An further analysis of children in the 1-2 year age group at the time of second vaccination is presented under "Benefit" in section III.C.

Table 2.7.3-ped2dose: 12

ProQuad™ Protocol 014
Summary of Subject Characteristics in
M-M-R™II + VARIVAX™ Vaccination Group

	M-M-R™II + VARIVAX™ N=195 n (%)
Gender	
Male	118 (60.5)
Female	77 (39.5)
Age (Years)	
Mean	4.3
SD	0.5
Median	4.0
Range	4 to 6
Male	4 to 6
Female	4 to 5
Race	
African American	25 (12.8)
Asian/Pacific	3 (1.5)
Caucasian	153 (78.5)
Hispanic	7 (3.6)
Other	7 (3.6)
Primary Vaccination History Status	
Concomitant	126 (64.6)
Nonconcomitant	69 (35.4)

Concomitant = Subjects received their primary M-M-R™II and VARIVAX™ on the same day.
Nonconcomitant = Subjects received their primary M-M-R™II and VARIVAX™ on different days.
N = Total Number subjects vaccinated.
SD = Standard deviation.
[Ref. 5.3.5.1; P014]

Table 2.7.3-ped2dose: 11

VARIVAX™ Protocol 007 (Amendment 007)
Subject Characteristics—Subjects 12 Months to 12 Years of Age (at Dose 1)
Who Received 2 Doses of Varicella Vaccine 4 to 6 Years Apart

	Varicella Vaccine 4 to 6 Years After Initial Vaccination With 1987 Production Lots (N=417) n (%)
Age at the Initial Vaccination	
Mean (years)	3.7
Median (years)	3.0
Number of Children in Given Age Range	
12 to 15 months	48 (11.5)
16 to 23 months	65 (15.6)
2 to 4 years	151 (36.2)
5 to 12 years	153 (36.7)
Range (Years)	
Male (years)	1 to 12
Female (years)	1 to 12
Gender	
Male	235 (56.4)
Female	182 (43.6)
Race	
Caucasian	417 (100.0)

N = Number of subjects who received both injections 4 to 6 years apart.
n = Number of subjects in each category.
[Ref. 5.3.5.4; R3]

IV. Dose intervals studied

Protocol 025: 3 months between doses (1102 subjects)
Protocol 007: 4-6 years between doses (417 subjects)
Protocol 014: ~ 3 years between doses, assuming most initial vaccinations at 12-18 months (195 subjects)

V. Duration of studies

Protocol 025: 10 years
Protocol 007: 10 years
Protocol 014: short term (6 week immunogenicity & safety endpoints)

BENEFIT

I. Public health and individual benefit of better VZV vaccine responses

Overall, better VZV vaccine responses (if achievable) would plausibly be associated with improved public health, both on the individual and population level. Boosting of VZV vaccine responses could potentially reduce concerns about duration of vaccine efficacy. These concerns are important because, if immunity were insufficient in adults, they might be susceptible to more severe disease, and if immunity were insufficient in women who subsequently become pregnant, their children might be more susceptible to congenital varicella syndrome. In addition, studies of outbreaks suggest that individuals with weak anti-VZV responses may be at greater risk of further transmitting the virus. Reduction in transmissibility or incidence of breakthrough disease would reduce exposure likelihood for the unvaccinated, including those in whom vaccine is contraindicated.

II. Evidence of improved efficacy

A. Efficacy endpoint

A laboratory-confirmed case of varicella was diagnosed if a varicella-like illness was reported and a antibody titer was consistent with a case (either 4-fold increase between acute and convalescent with one titer >=200 U/ml or both acute and convalescent titers >= 200 U/ml) observed, at least 42 days after vaccination. Laboratory findings were considered suggestive if there was a 4-fold rise and at least one titer was 50-199 U/ml. Cases in which serum was missing or insufficient are included as cases in the summary of subjects with breakthrough varicella. Cases meeting none of these three criteria (i.e., laboratory confirmed not to be varicella) were considered not to be varicella-- otherwise, all cases were counted (Vol 5 of 9, p. 15).

Based on the originally submitted material, these criteria could theoretically have led to a slightly increased chance of failure to identify varicella in the 2-dose group. Because the 2-dose group is likely to have higher antibody titers, there might be individuals in this group who have high acute titers (but less than 200), but because their titer is high, a reduced chance of experiencing a 4-fold titer increase in response to a true breakthrough event. Examination of the data from the study suggested that this may have occurred, as there were no cases serologically confirmed not to be varicella in the one-dose group (Table 3, Vol. 5, p. 24), but there were 7 such cases in the two-dose group (Table 4, Vol. 5, p. 25). To address this issue, a supplementary analysis was performed and submitted on 3/3/2005, confirming that even if these cases of varicella that were excluded on serological grounds are included in the analysis, the results of the studies do not change.

B. Efficacy & Control groups

Efficacy was examined by comparing breakthrough rates with expected wild-type infection rates in unvaccinated individuals, based on historical data. Use of this

technique to arrive at a clear efficacy estimate is difficult, because wild-type exposure rates may depend on a variety of factors, including age, day care and school exposure, relative vaccination rate of exposure cohort, etc.

For the long-term breakthrough studies, background exposure rates were assumed to be 14.1%/year, based on age-matched data from the Kentucky study of Finger, et al.. For household exposures, they were assumed to be 87%/exposure, based on the study of Ross. Based on these assumptions, the aggregate efficacy of vaccine in protocol 025 is shown in table 2.7.3-ped2dose:3. Estimated efficacy for the single dose regimen was 94.3%, and for the two-dose regimen was 98.3%. While it is possible that the assumed exposure rates overestimated actual exposures, and that vaccine efficacy was not actually this high, the 2-dose regimen clearly provided a statistically significant advantage in efficacy as compared with the single dose regimen.

Table 2.7.3-ped2dose: 3

Estimated Vaccine Efficacy for Children Who Received 1 or 2 Doses (Given 3 Months Apart) of Varicella Vaccine (Active Follow-Up) (VARIVAX™ Protocol 025)

	VARIVAX™ 1-Dose Regimen (N=1114)	VARIVAX™ 2-Dose Regimen (N=1102)	p-Value
Number of subjects at start of long-term follow-up	1103	1017	
Total person-years over 10 years of follow-up	8025.81	7499.54	
Observed average annual incidence rate of varicella postvaccination (95% CI)	0.8% (0.6%, 1.0%)	0.2% (0.1%, 0.4%)	
Age-adjusted expected annual varicella incidence rate based on unvaccinated susceptibles	14.2%	13.9%	
Estimated vaccine efficacy (95% CI)	94.3% (92.8%, 95.6%)	98.3% (97.3%, 99.0%)	<0.001

N = Number of subjects vaccinated.
CI = Confidence interval.

[Ref. 5.3.5.4; R1]

C. Duration of efficacy

Duration of vaccine efficacy was evaluated both by examining breakthrough rates over time, both in general and in response to household exposures

Tables 2.7.3-ped2dose:1 and 2 show breakthrough rates over the ten year follow-up period, both with one and with two doses. Cumulative breakthrough rates were dramatically lower over time in the 2-dose than in the single-dose group. Of note, in the 2-dose group, no cases of varicella were observed between years 7-10 (although 2 were re-vaccinated). In contrast, there were 14 cases in the single-dose group in this time frame (also with 2 revaccinations). Thus, the significantly improved protection afforded by 2 doses appears to last at least 7-10 years based on these breakthrough

Table 2.7.3-ped2dose: 1

Life-Table Estimates of Event Rates Based on Person-Years in Subjects Enrolled in the 1-Dose Regimen Group (Active Follow-Up)
Number Vaccinated = 1114
(VARIVAX™ Protocol 025)

Time Interval Postdose 1	Number at Risk at Interval Start	Number Censored[f] During Interval	Number Reported Varicella Cases (Median of Max. Total Lesions[i]) During Interval	Number Revaccinated During Interval	Number With Event[g] During Interval	Person-Years at Risk	Annual Event[g] Rate[h] During Interval	Cumulative Event Rate	95% Confidence Interval on Cumulative Event Rate
1st Year (Days 43 to 364)	1103.0	0.0	2 (17.0)	4	2.2	972.1	0.2%	0.2%	(0.0%, 0.5%)
2nd Year (Days 365 to 729)	1100.8	128.4	11 (29.5)	0	11.3	1025.5	1.1%	1.3%	(0.6%, 2.0%)
3rd Year (Days 730 to 1094)	961.1	86.3	6 (14.0)	0	6.3	880.1	0.7%	2.0%	(1.2%, 2.9%)
4th Year (Days 1095 to 1459)	868.6	9.0	19 (19.0)	0	19.2	853.2	2.3%	4.2%	(3.0%, 5.5%)
5th Year (Days 1460 to 1824)	840.3	56.2	10 (37.0)	1	10.3	811.8	1.3%	5.4%	(4.0%, 6.9%)
6th Year (Days 1825 to 2189)	773.8	24.1	2 (12.5)	0	2.3	756.0	0.3%	5.7%	(4.2%, 7.2%)
7th Year (Days 2190 to 2555)	747.5	34.1	4 (25.5)	1	4.3	720.8	0.6%	6.3%	(4.7%, 7.9%)
8th Year (Days 2556 to 2920)	709.1	48.2	3 (50.0)	0	3.3	688.0	0.5%	6.7%	(5.1%, 8.4%)
9th Year (Days 2921 to 3285)	657.6	17.1	2 (39.0)	0	2.2	647.2	0.3%	7.1%	(5.4%, 8.7%)
10th Year (Days 3286 to 4015)	638.3	635.0	3 (23.5)	1	3.3	671.1	0.5%	7.5%	(5.5%, 9.5%)

[f] The cutoff date is 21-Mar-2003.
[g] One subject (Case 4301 in Study Site 1076) in Year 2, 1 subject (Case 2002 in Study Site 1082) in Year 3, and 2 subjects (Case 1330 in Study Site 1078; Case 2373 in Study Site 1085) in Year 5 had no data for number of lesions.
[h] Event is defined as an actual case of varicella or an expected case of varicella for revaccinated children by assuming that they would develop varicella at a rate of 9.1% per year after revaccination.
[i] Event rate = Number with events/person-year at risk.
Notes:
1. Fifteen (15) cases reported ≤42 days postvaccination were excluded from summary.
2. Two (2) children were excluded from summary due to developing herpes zoster during follow up.
3. Last follow-up date for varicella postvaccination is 16-Mar-2003.
4. The day range of the last time interval of follow-up was extended to include subjects whose last contacts with the study occurred after 10 years since their initial vaccination.

[Ref. 5.3.5.4; R1]

Table 2.7.3-ped2dose: 2

Life-Table Estimates of Event Rates Based on Person-Years in Subjects Enrolled in the 2-Dose Regimen Group (Active Follow-Up)
Number Vaccinated = 1102
Two Doses Given 3 Months Apart

Time Interval Postdose 2	Number at Risk at Interval Start	Number Censored[f] During Interval	Number Reported Varicella Cases (Median of Max. Total Lesions) During Interval	Number Revaccinated During Interval	Number With Event[g] During Interval	Person-Years at Risk	Annual Event[g] Rate[h] During Interval	Cumulative Event Rate	95% Confidence Interval on Cumulative Event Rate
1st Year (Days 43 to 364)	1017.0	7.0	0 (N/A)	0	0.0	896.2	0.0%	0.0%	(0.0%, 0.0%)
2nd Year (Days 365 to 729)	1010.0	173.1	3 (20.0)	1	3.1	940.1	0.3%	0.3%	(0.0%, 0.7%)
3rd Year (Days 730 to 1094)	833.8	11.0	2 (51.5)	0	2.1	827.9	0.3%	0.6%	(0.1%, 1.1%)
4th Year (Days 1095 to 1459)	820.7	13.0	3 (17.0)	0	3.1	813.4	0.4%	1.0%	(0.3%, 1.6%)
5th Year (Days 1460 to 1824)	804.6	49.0	6 (16.0)	0	6.1	782.9	0.8%	1.7%	(0.8%, 2.6%)
6th Year (Days 1825 to 2189)	749.5	23.0	3 (20.0)	0	3.0	739.9	0.4%	2.1%	(1.1%, 3.1%)
7th Year (Days 2190 to 2555)	723.5	20.0	0 (N/A)	0	0.0	707.8	0.0%	2.1%	(1.1%, 3.1%)
8th Year (Days 2556 to 2920)	703.4	63.1	0 (N/A)	1	0.1	663.0	0.0%	2.1%	(1.1%, 3.1%)
9th Year (Days 2921 to 3285)	640.3	29.1	0 (N/A)	1	0.1	627.7	0.0%	2.2%	(1.2%, 3.2%)
10th Year (Days 3286 to 4015)	611.1	611.0	0 (N/A)	0	0.1	500.5	0.0%	2.2%	(1.2%, 3.2%)

[f] The cutoff date is 21-Mar-2003.
[g] Event is defined as an actual case of varicella or an expected case of varicella for revaccinated children by assuming that they would develop varicella at a rate of 9.1% per year after revaccination.
[h] Event rate = Number with events/person-year at risk.
N/A = Not applicable.
Notes:
1. Two (2) cases reported ≤42 days postvaccination were excluded from summary.
2. Last follow-up date for varicella postvaccination is 16-Mar-2003.
3. The day range of the last time interval of follow-up was extended to include subjects whose last contacts with the study occurred after 10 years since their initial vaccination.

[Ref. 5.3.5.4; R1]

Table 2.7.3-ped2dose: 4

Annual Report of Household Exposure to Varicella Following a 1-Dose Regimen of Varicella Vaccine (Active Follow-Up)
Number Vaccinated = 1114
(VARIVAX™ Protocol 025)

Time Interval Postdose 1	Number of Subjects With Household Exposure	Number of Cases After Household Exposure	Observed Varicella Rate After Household Exposure	Median Number of Lesions in Varicella Cases
1st Year (Days 28 to 364)	15	0	0.0%	N/A
2nd Year (Days 365 to 729)	9	1	11.1%	10
3rd year (Days 730 to 1094)	14	0	0.0%	N/A
4th Year (Days 1095 to 1459)	25	5	20.0%	10
5th Year (Days 1460 to 1824)	6	2	33.3%	34
6th Year (Days 1825 to 2189)	10	0	0.0%	N/A
7th Year (Days 2190 to 2554)	10	0	0.0%	N/A
8th Year (Days 2555 to 2919)	6	0	0.0%	N/A
9th Year (Days 2920 to 3284)	0	0	0.0%	N/A
10th Year (Days 3285 to 3649)	0	0	0.0%	N/A
Combined	95	8	8.4%	14

N/A = Not applicable.

[Ref. 5.3.5.4; R1]

data.

Table 2.7.3-ped2dose: 5

Annual Report of Household Exposure to Varicella Following a 2-Dose Regimen of Varicella Vaccine
(Active Follow-Up)
Number Vaccinated = 1102
(VARIVAX™ Protocol 025)
Two Doses Given 3 Months Apart

Time Interval Postdose 1	Number of Subjects With Household Exposure	Number of Cases After Household Exposure	Observed Varicella Rate After Household Exposure	Median Number of Lesions in Varicella Cases
1st Year (Days 28 to 364)	16	0	0.0%	N/A
2nd Year (Days 365 to 729)	15	0	0.0%	N/A
3rd year (Days 730 to 1094)	32	2	6.3%	52
4th Year (Days 1095 to 1459)	7	0	0.0%	N/A
5th Year (Days 1460 to 1824)	5	1	20.0%	2
6th Year (Days 1825 to 2189)	6	0	0.0%	N/A
7th Year (Days 2190 to 2554)	12	0	0.0%	N/A
8th Year (Days 2555 to 2919)	3	0	0.0%	N/A
9th Year (Days 2920 to 3284)	9	0	0.0%	N/A
10th Year (Days 3285 to 3649)	0	0	0.0%	N/A
Combined	96	3	3.1%	3

N/A = Not applicable.
[Ref. 5.3.5.4; R1]

In addition, the median number of lesions in those cases of breakthrough varicella that did occur did not substantially increase over time, either in the single or the two-dose groups, and certainly was no higher in the two-dose group.

Efficacy also was estimated after household exposures. While household exposures are rarer than community exposures, the high rate of transmission after a household exposure (around 90% in most series, and estimated at 87% by Ross) affords another opportunity to estimate vaccine efficacy under more stringent conditions.

Household exposure results are shown in tables 2.7.3-ped2dose:4 and 5. The total number of household exposures was comparable between the 1 and 2-dose groups. Although the number of cases was small, there appeared to be better efficacy in the 2-dose than the single dose group. Based on the historical transmission rate of 87%, this translates to a vaccine efficacy after household exposure of 90.3% [81.7-95.7%] for the single dose, and 96.4% [89.8-99.3%] for the two-dose regimen. Again, it appears that the two-dose regimen is more efficacious than the single-dose regimen. There were not a sufficient number of household exposures to determine whether this efficacy declined over time or to show a statistically significant difference, however.

In protocol 007, a total of 2 cases of breakthrough varicella were reported over the 10-year follow-up period (Vol. 1 of 1, p. 14). Because this follow-up was passive, there may have been additional cases, especially considering that all of these individuals were in their teens or even twenties by the end of the study. However, this low number of reports is consistent with vaccine efficacy over this observation period.

III. Evidence of improved immunogenicity

A. GMTs and proportion with titer above 5 U/ml

If 2 doses of vaccine are truly better than one, one would expect to see improved immune responses. For varicella vaccines, a gpELISA titer above 5 is considered to correlate with statistically significant protection. Thus, the proportion of individuals with titers above 5 is of substantial interest. In addition, the geometric mean titers, as a measure of general vaccine immunogenicity, are of interest. Of less interest is the seroconversion rate, as previous analyses have not shown clinical correlations simply with seroconversion (and in fact, low level seroconversion wasn't necessarily better than non-conversion in preventing breakthrough disease).

Protocol	025	007	014
# enrolled in 2-dose arm	1102	417	195
# with serology available after dose 2	769	356	171
% with serology available	70%	85%	88%

Interpretation of the serological data should also consider the fact that serology wasn't available on some of the subjects. The reasons for missing data were independent of titer level, so this missing data does not significantly interfere with interpretation of the study results.

Table 2.7.3-ped2dose: 13

Comparison of Immunogenicity Results per Dose Across VARIVAX™ Protocols 025 and 007, and ProQuad™ Protocol 014

Varicella Vaccine Timing of Doses (Clinical Study)	Dose 1				Dose 2			
	6 Weeks Postdose 1		Predose 2		6 Weeks Postdose 2		3 Months Postdose 2	
	Percentage * of Subjects With Titer ≥5 gpELISA Units/mL	GMT	Percentage of Subjects With Titer ≥5 gpELISA Units/mL	GMT	Percentage of Subjects With Titer ≥5 gpELISA Units/mL	GMT	Percentage of Subjects With Titer ≥5 gpELISA Units/mL	GMTs
0 & 3 months (VARIVAX™ Protocol 025)	87.3% (743/851)	12.8	N/A	N/A	99.5% (765/769)	141.5	N/A	N/A
0 & 4 to 6 years (VARIVAX™ Protocol 007)	86.5% (321/371)	16.5	84.7% (305/360)	26.8	100% (67/67)†	212.3†	99.7% (355/356)	126.1
4 to 6 years of age (ProQuad™ Protocol 014‡)	N/A	N/A	88.9%§ (152/171)	24.6§	99.4% (170/171)	209.3	N/A	N/A

† Not per-protocol planned visits.
‡ The second dose was administered concomitantly with M-M-R™II during the study in children 4 to 6 years of age, after a primary dose of VARIVAX™ and M-M-R™II previously administered in routine clinical practice.
§ Predose 2 time point is presented instead of 6 weeks Postdose 1, for which data were generally not available.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
GMT = Geometric mean titer.
N/A = Not applicable.

[Ref. 5.3.5.4; R2], [Ref. 5.3.5.4; R3], [Ref. 5.3.5.1; P014]

Table 2.7.3-ped2dose: 7

Summary of VZV Antibody Responses at 6 Weeks Postdose 1 and 6 Weeks Postdose 2 in Initially VZV-Seronegative Children (Per-Protocol Analysis) VARIVAX™ Protocol 025 (Two Doses Given 3 Months Apart)

Endpoint	VARIVAX™ 1-Dose Regimen (N=1114)			VARIVAX™ 2-Dose Regimen (N=1102)					
	Week 6 Postdose 1			Week 6 Postdose 1			Week 6 Postdose 2		
	n	Observed Response	(95% CI)	n	Observed Response	(95% CI)	n	Observed Response	(95% CI)
% ≥5 gpELISA units/mL	892	84.9% (757/892)	(82.3%, 87.2%)	851	87.3% (743/851)	(84.9%, 89.5%)	769	99.5% (765/769)	(98.7%, 99.9%)
SCR	892	98.9% (882/892)	(97.9%, 99.5%)	851	99.5% (847/851)	(98.8%, 99.9%)	769	99.9% (768/769)	(99.3%, 100%)
GMT (gpELISA units/mL)	892	12.0	(11.2, 12.8)	851	12.8	(11.9, 13.7)	769	141.5	(132.3, 151.3)

gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
VZV = Varicella-zoster virus.
N = Number of subjects vaccinated in the given regimen.
n = Number of subjects contributing to the analysis.
GMT = Geometric mean titer.
SCR = Seroconversion rate.
CI = Confidence interval.

[Ref. 5.3.5.4; R2]

Table 2.7.3-ped2dose:13 summarizes the 6-week immunogenicity results across the studies. In these three studies, regardless of interval between

doses or age of vaccinee, the two dose regimen led to GMTs between 141.5 and 212.3, substantially higher than that after a single dose or prior to the second dose in the same individuals. At 6 weeks post dose 2, >99% of vaccinees had titers above 5 U/ml. At 3 months post-dose 2, titers may have begun to wane (in protocol 007), but >99% were still above 5 U/ml and the 6 week sample was smaller, possibly biasing the result.

Table 2.7.3-ped2dose:7 shows the result from protocol 025 in more detail, also including the single dose group. The result in the single dose group was comparable to that after the first dose in the two-dose group.

Table 2.7.3-ped2dose:8 shows the result from protocol 007 in more detail. Examination of the confidence intervals makes the significance of the differences between the one and two dose regimens clearer.

Table 2.7.3-ped2dose: 8

Summary of VZV Antibody Responses at 6 Weeks Postdose 1, Immediately Predose 2, 7 to 10 Days Postdose 2, 6 Weeks Postdose 2, and 3 Months Postdose 2 in Initially VZV-Seronegative Subjects—Subjects 12 Months to 12 Years of Age (at Dose 1) Who Received 2 Doses of Varicella Vaccine 4 to 6 Years Apart (Amendment 07 of VARIVAX™ Protocol 007)

	Dose 1 (N=417)		Dose 2 (N=417)		
Endpoint	Postdose 1 Week 6 n=371	Immediately Predose 2 n=360	Postdose 2 Days 7 to 10 n=306	Postdose 2 Week 6† n=67	Postdose 2 Month 3 n=356
% ≥5 gpELISA units/mL (s/n) (95% CI)	86.5% (321/371) (82.6%, 89.8%)	84.7% (305/360) (80.6%, 88.3%)	99.7% (305/306) (98.2%, 100%)	100% (67/67) (94.6%, 100%)	99.7% (355/356) (98.4%, 100%)
SCR (s/n) (95% CI)	100% (371/371) (99.0%, 100%)	98.6% (355/360) (96.8%, 99.5%)	100% (306/306) (98.8%, 100%)	100% (67/67) (94.6%, 100%)	100% (356/356) (99.0%, 100%)
GMT (gpELISA units/mL) (95% CI)	16.5 (14.5, 18.7)	26.8 (22.2, 32.5)	149.8 (130.4, 172.2)	212.3 (162.8, 276.9)	126.1 (111.9, 142.0)

† The 6 weeks Postdose 2 time point was not preplanned in the protocol of the study.
Dose 1 was manufactured as part of the 1987 Production Lots. Dose 2 was manufactured as part of the 1991 Production Lots (9-6-6-6 Process).
N = Number of subjects who received both injections 4 to 6 years apart.
n = Number of subjects contributing to the analysis.
s = number of responding subjects.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
VZV = Varicella-zoster virus.
GMT = Geometric mean titer.
SCR = Seroconversion rate.
CI = Confidence interval.
[Ref. 5.3.5.4; R3]

Table 2.7.3-ped2dose: 9

Summary of Antibody Responses to VZV at Prevaccination and Postvaccination in Subjects Who Had Previously Received M-M-R™II and VARIVAX™ (ProQuad™ Protocol 014)

		M-M-R™II + VARIVAX™ (N=195)	
Time Point	Parameter	n	Observed Response (95% CI)
Prevaccination	GMT (gpELISA units/mL)	171	24.6 (19.1, 31.8)
	% ≥5 gpELISA units/mL	171	88.9% (83.2%, 93.2%)
6 weeks postvaccination	GMT (gpELISA units/mL)	171	209.3 (171.2, 255.9)
	% ≥5 gpELISA units/mL	171	99.4% (96.8%, 100%)

Percentages were calculated as the number of subjects who met the criterion divided by the number of subjects contributing to the per-protocol analysis.
N = Number of subjects in vaccinated in study group 3.
N = Number of subjects contributing to the per-protocol analysis.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
GMT = Geometric mean titer.
CI = Confidence interval.
[Ref. 5.3.5.1; P014]

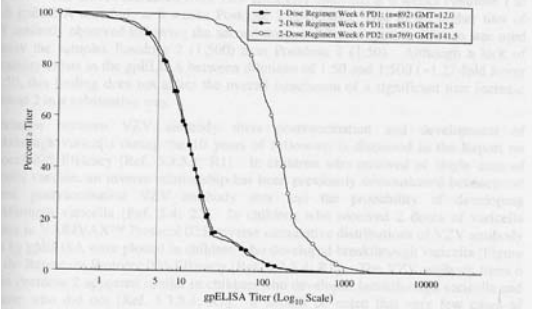
Table 2.7.3-ped2dose:9 shows the result from MMRV protocol 014 in more detail. Again, the confidence intervals show significant improvements in immunogenicity with two doses as compared with one.

The effect on immunogenicity of a second dose also may be seen graphically by examining the reverse cumulative distributions of antibody titers. In each study (see

figures 2.7.3-ped2dose:1, 2, and 3) the second dose caused a significant shift in antibody titer distribution.

Figure 2.7.3-ped2dose: 1

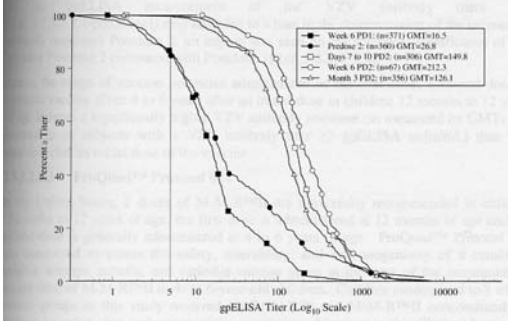
Reverse Cumulative Distribution of VZV Antibody Titers
at 6 Weeks Postdose 1 and 6 Weeks Postdose 2 by Vaccination Regimen of
Varicella Vaccine in Initially Seronegative Subjects
(VARIVAX™ Protocol 025)
Two Doses Given 3 Months Apart



n = Number of subjects who contributed to the summary and the corresponding GMT.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
GMT = Geometric mean titer (in gpELISA units/mL).
PD = Postdose.
[Ref. 5.3.5.4; R2]

Figure 2.7.3-ped2dose: 2

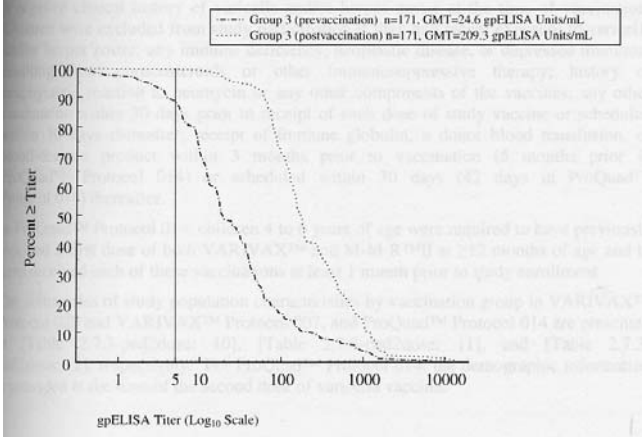
Reverse Cumulative Distribution of VZV Antibody Titers at 6 Weeks
Postdose 1, Immediately Predose 2, and at 7 to 10 Days, 6 Weeks, and 3 Months
Postdose 2 in Initially VZV-Seronegative Subjects—Subjects 12 Months to 12 Years of
Age (at Dose 1) Who Received 2 Doses of Varicella Vaccine 4 to 6 Years Apart
(Amendment 07 of VARIVAX™ Protocol 007)



Dose 1 was manufactured as part of the 1987 Production Lots. Dose 2 was manufactured as part of the 1991 Production Lots (VARIVAX™ by the 9-6-6-6 Process).
n = Number of subjects who contributed to the summary and the corresponding GMT.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
GMT = Geometric mean titer (in gpELISA units/mL).
PD = Postdose.
VZV = Varicella-zoster virus.
[Ref. 5.3.5.4; R3]

Figure 2.7.3-ped2dose: 3

Reverse Cumulative Distribution of VZV Antibody Titers
at Prevaccination and Postvaccination in Subjects Who Received Concomitant
Administration of VARIVAX™ and M-M-R™II
and Had Previously Received M-M-R™II and VARIVAX™
(Per-Protocol Population)
ProQuad™ Protocol 014

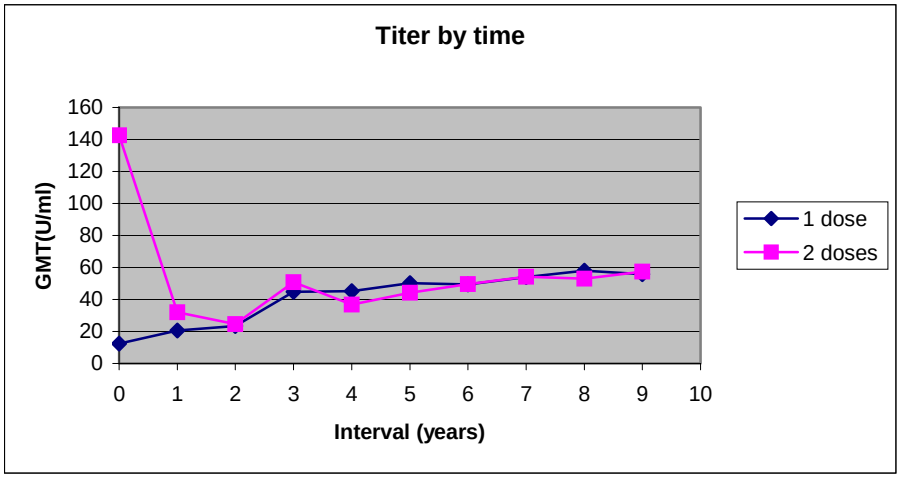


n = Number of subjects who contributed to the summary and the corresponding GMT.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
GMT = Geometric mean titer (in gpELISA units/mL).
[Ref. 5.3.5.1; P014]

B. Duration of immunogenicity

The duration of immunogenicity was examined both in study 025 and 007. Antibody responses were measured on an annual basis after immunization for about 10 years.

In protocol 025, see Table 7 (Vol. 6, pp. 38-39) subjects who received a single dose gradually experienced a rise in antibody titers from a GMT of 12.5 U/ml 6 weeks after immunization, to 50.3 5 years after immunization. Until year 10, antibody titers stayed at approximately this level (range: 49.4-58.0). Subjects who received two doses (at a 3 month interval) started with titers (GMT) at 142.6 at 6 weeks after immunization. By year 2, titers were lower, at 32.0, and by year 3 were 24.6. Thereafter, titers followed a pattern similar to that of the single dose of vaccine, with titers stabilizing around 50 U/ml. These results are graphed immediately below.



Thus, in protocol 025, the advantage with respect to antibody response of two doses appeared to mostly vanish within 2 years of immunization. This may (in part) be due to (non-inoculation based) boosting of both single and 2-dose populations, which probably accounted for the increase in titer of GMTs in both populations after year 2. This boosting could have been a result either of exogenous VZV exposures, or of internal boosting due to reactivation of vaccine strain (as previously hypothesized).

In protocol 007 (see table 2.7.3-ped2dose:15), subjects who received a single dose gradually experienced a rise in antibody titers over 4 years of follow-up, from 16.5 6 weeks after immunization and 12.8 one year after immunization, to a GMT of about 30 U/ml. Subjects who received two doses of vaccine started with higher titers, around 120 U/ml. Within one year, this titer dropped to 59.1, and the titer stayed at approximately this level (range: 44.7-73.3) over the entire 10 year follow-up period.