Table 2.7.3-ped2dose: 15

Observed VZV Antibody Persistence Rates Postvaccination Along With Geometric Mean Titer (GMT) and Percent of Subjects With a VZV Antibody Titer ≥5 gpELISA Units/mL in Initially VZV-Seronegative Subjects (Predose 1) Who Were Seropositive Postvaccination†—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)

Time Interval	n	Observed VZV Seropositivity Rate During Interval	GMT (gpELISA Units/mL)	95% CI on GMT	Percent With VZV Antibody Titer ≥5 gpELISA Units/mL During Interval	95% CI on Percent With VZV Antibody Titer ≥5 gpELISA Units/mL
Week 6 PD 1	371	100% (371/371)	16.5	(14.5, 18.7)	86.5% (321/371)	(82.6%, 89.8%)
Year 1 PD 1	348	99.7% (347/348)	12.8	(11.1, 14.9)	77.6% (270/348)	(72.8%, 81.9%)
Year 2 PD 1	221	99.5% (220/221)	11.7	(9.6, 14.2)	72.9% (161/221)	(66.5%, 78.6%)
Year 3 PD 1	136	100% (136/136)	17.2	(12.7, 23.2)	78.7% (107/136)	(70.8%, 85.2%)
Year 4 PD 1	138	100% (138/138)	30.3	(21.6, 42.6)	81.9% (113/138)	(74.4%, 87.9%)
Month 3 PD 2	356	100% (356/356)	126.1	(111.9, 142.0)	99.7% (355/356)	(98.4%, 100%)
Year 1 PD 2	116	100% (116/116)	59.1	(47.2, 74.1)	100% (116/116)	(96.9%, 100%)
Year 2 PD 2	207	100% (207/207)	73.3	(61.6, 87.2)	99.5% (206/207)	(97.3%, 100%)
Year 3 PD 2	168	100% (168/168)	67.2	(55.5, 81.4)	99.4% (167/168)	(96.7%, 100%)
Year 4 PD 2	170	100% (170/170)	54.5	(44.6, 66.5)	97.6% (166/170)	(94.1%, 99.4%)
Year 5 PD 2	149	99.3% (148/149)	54.0	(43.9, 66.3)	98.0% (146/149)	(94.2%, 99.6%)
Year 6 PD 2	152	100% (152/152)	63.0	(51.7, 76.7)	98.7% (150/152)	(95.3%, 99.8%)
Year 7 PD 2	130	100% (130/130)	58.4	(45.1, 75.8)	96.9% (126/130)	(92.3%, 99.2%)
Year 8 PD 2	77	100% (77/77)	44.7	(32.7, 61.2)	96.1% (74/77)	(89.0%, 99.2%)
Year 9 PD 2	98	100% (98/98)	54.1	(40.6, 72.1)	98.0% (96/98)	(92.8%, 99.8%)

† Subjects contributed to Postdose 1 persistence if they were initially (Predose 1) seronegative and seropositive at 6 weeks Postdose 1 (Days 27 to 84). Subjects contributed to Postdose 2 persistence if they were initially (Predose 1) seronegative and seropositive within 3 months Postdose 2 (Days 5 to 130). A subject was considered as serostatus positive if the optical density (OD) for the subject's last available serology sample in the indicated time interval was ≥0.11.
n = Number of initially seronegative subjects who were seropositive based on the Week 6 Postdose 1 time point (Days 27 to 84) for Postdose 1 persistence or within 3 months (Days 5 to 130) for Postdose 2 persistence and had an antibody persistence blood sampling at the specific time point.
VZV = Varicella-zoster virus.
gpELISA = Glycoprotein enzyme-linked immunosorbent assay.
GMT = Geometric mean titer.
CI = Confidence interval.
PD = Postdose.

[Ref. 5.3.5.4; R3]

The reasons for the differences between protocols 007 and 025 aren't clear. In protocol 007, a longer term difference in GMTs between one and two doses was observed, while in protocol 025, a longer-term immunogenicity difference was not observed. Perhaps the shorter follow-up in the single dose group of protocol 007 prevented identification of boosting to levels (at least by year 5 or later) comparable to those observed with the 2 dose group. In addition, protocol 007, which was initiated earlier, might have been subject to larger amounts of wild-type varicella exposure that might have further boosted the 2-dose group to higher levels even in the 1-2 year time frame after immunization. Alternatively, it could be that an interval larger than 3 months between doses is optimal.

We requested comment from the sponsor on the optimal interval between doses. The sponsor reasonably pointed out that 1) the second dose reduces the reported incidence of breakthrough varicella (i.e., improves efficacy as compared with one dose), even with the shorter interval between doses, and that 2) that improved efficacy between ages 2 and 5 is an important age for that improved efficacy (because this is a time of great likelihood of exposure), if the goal is to reduce incidence of breakthrough varicella.

C. Immunogenicty by age at immunization.

To assure that the response to the second dose of vaccine did not vary depending on the timing of the first dose, we asked the sponsor to provide efficacy, immunogenicity, and safety subgroup analyses of 12-15, and 16-24 month old (at the time of the first vaccine dose) vaccine recipients. Some of the published studies of varicella school outbreaks

from CDC suggested increased susceptibility to varicella among children vaccinated at earlier ages, when maternal antibodies could be present.

In this analysis, the estimated vaccine efficacy (calculated as before, by comparing breakthrough rates with expected wild-type infection rates in the unimmunized) was as follows:

Age at 1st vaccination	Estimated efficacy (1 dose)	Estimated efficacy (2 doses)
12-15 months	91.8% (82.1-97.0%)	93.5% (83.3-98.2%)
16-24 months	90.0% (84.3-94.0%)	98.1% (94.4-99.6%)

For children who received their first vaccine dose at 12-15 months, the efficacy of the second dose of varicella is unclear based on this study, as the confidence intervals for efficacy of one and two dose regimens overlap (in part due to the small sample size). The efficacy point estimate for 2 doses in the 12-15 month old group does exceed that for one dose in either the 12-15 month old or the 16-24 month old group. The confidence intervals on the efficacy of the second dose also overlap between 12-15 month old and 16-24 month old groups.

Robust responses to the second dose of vaccine are more obvious when the immunogenicity of the second dose is examined. Based on immunogenicity, the time of initial vaccination did not influence response to the second dose. These data are abstracted from tables 9-10 of the responses to our questions, received 3/3/05 and 3/15/05.

	DOSE 1 (pre-dose 2)		DOSE 2	
Age @ dose 1	% gpELISA≥5	GMT	% gpELISA≥5	GMT
12-15 months				
Study 025	90%	17.2	97.8%	156.6
Study 007	82.9% (88.9%)	13.8 (25.4)	100%	131.0 (d. 7)
16-24 months				
Study 025	96.0%	15.4	100%	184.1
Study 007	84.1% (70.0%)	14.8 (17.3)	100%	334.5 (d. 42)

Tables 11 and 12 of that same submission do not identify any concerning effect of the timing of initial vaccination on safety parameters, including injection site reactions, systemic clinical complaints, or varicella like rashes (either at or not at the injection site). A modest increased number of injection site complaints in the 16-24 month old group after dose 2 was balanced by a modest decrease in the number of complaints in this group after dose 1, as compared with the 12-15 month old group. Tables 13 and 14 show no effect on the timing of initial vaccination on incidence of fever.

In conclusion, the data are insufficient to make a statistical comparison of efficacy of the second dose in the 12-15 month old age group relative to that of the 16-24 month group. However, they do demonstrate immunogenicity in this group, which is very likely to be associated with efficacy.

IV. Conclusion regarding benefit

Overall, there is very significant indication of better short term immune responses when 2 doses are given instead of 1. This translates to improved breakthrough frequencies and efficacy in protecting against household exposure. The duration of effect appears to be at least 7-10 years, based on the breakthrough studies, although the immunogenicity study from protocol 025 does not show dramatically improved immune responses beyond 2 years.

A second dose of varicella vaccine thus has long-term benefit in preventing breakthrough varicella.

RISK

I. Safety

A. Adequacy of safety database

As noted, the total database for a second dose of varicella is 1714 children. The following table describes the database for safe administration of a second dose of a varicella vaccine in the second year of life. This is considered to be an important age for immunization, because of perceived greater vulnerability of children in this age group to adverse events after immunizations.

Study	**Second dose VARIVAX**	**MMRV as second dose**
MMRV protocol 009		303
MMRV Protocol 011		1025
Protocol 025 (this supplement)	208	

Thus, the total database of 12-23 month olds that includes a second dose of VARIVAX given at 90 days after the first dose is 208 children, and if those who received MMRV at a second dose are included, the total database is 1536 children. Children who received MMRV actually had a much higher dose of varicella component than those who had VARIVAX, and thus, this is a stringent test of vaccine safety.

In the context of other information about two doses of varicella vaccine, the data provided from study 025 in this file, plus the data in the MMRV file provide sufficient assurance that the live attenuated varicella vaccine is safe when given as a second dose in 12-23 month olds.

B. Injection site complaints and rashes

Table 2.7.4:3 summarizes adverse experience reports in protocol 025. Rates of systemic clinical complaints were lower on the second dose than the first, suggesting that the first dose may be responsible for such complaints in at least about 85%-65% = 20% of vaccinees. Injection site complaints were somewhat higher after the second dose than the first dose, but not at a clinically significant level (25.7 vs. 23.%). Injection site varicella like rashes were much less common after the second dose than the first dose, as were non-injection site varicella-like rashes.

In the immediate (0-4 day) post-vaccination period of study 025, injection site complaints (erythema and swelling) were present at a higher level after dose 2 than after dose 1 (see Table 2.7.4:9).

Table 2.7.4: 3

Overall Summary of Clinical Safety Data by Vaccination Regimen and Dose—
Days 0 to 42 Postvaccination
(VARIVAX™ Protocol 025)
Two Doses Given 3 Months Apart

Clinical Complaint	VARIVAX™ 1-Dose Regimen (N=1114) n (%)	VARIVAX™ 2-Dose Regimen Dose 1 (N=1102) n (%)	VARIVAX™ 2-Dose Regimen Dose 2 (N=1022) n (%)
Subjects with no follow-up	3	14	8
Subjects with follow-up	1098	1081	981
Subjects with missing CRFs	13	7	33
Injection-site complaints	259 (23.6)	278 (25.7)	253 (25.8)
Systemic clinical complaints	961 (87.5)	928 (85.8)	650 (66.3)
Varicella-like rash, injection site	42 (3.8)	40 (3.7)	16 (1.6)
Varicella-like rash, noninjection site	39 (3.6)	37 (3.4)	12 (1.2)

Percentages are calculated based on the number of subjects with follow-up after each dose within the indicated vaccination regimen.
Injection-site complaints includes varicella-like rash at the injection site.
N = Number of subjects who received the indicated injection.
n = Number of subjects in each category.
CRF = Case report form.

[Ref. 5.3.5.4; R2]

As seen in table 2.7.4:5, in study 007, the rate of injection site complaints was also higher after dose 2 than dose 1 (45.3% vs. 19.0%). Rates of systemic clinical complaints and varicella-like rashes were considerably lower after dose 2 than dose 1. It is possible that the higher rates of injection site complaints were partly related to the greater relative ages of the children who received the second dose, which was 4-6 years after the first dose, and thus at an age where children might have been more likely to articulate injection site complaints. The rates of injection site complaints (erythema, soreness, pruritus, and swelling) after dose 2 in study 007 was higher than that observed in protocol 025 (45% vs 25%), although comparable to study 014 (40.4% at the varicella site, Table 2.7.4:7, Vol. 1, p. 22), in which the children were at ages most comparable to those in protocol 007 at the time of the second dose.

Table 2.7.4: 9

Comparison of Injection-Site Complaint Incidence Rates Between Dose 1 and Dose 2
Within the 2-Dose Regimen Group
(Incidence ≥1% in One or More Groups)
Days 0 to 4 Postvaccination
(VARIVAX™ Protocol 025)
Two Doses Given 3 Months Apart

Clinical Complaint	n	VARIVAX™ 2-Dose Regimen Dose 1 (N=1102) % (s/n)	Dose 2 (N=1022) % (s/n)	Risk Difference (Dose 2 - Dose 1) Percentage Point (95% CI)†	p-Value‡
Injection-Site Complaints	**974**	**21.7% (211/974)**	**25.4% (247/974)**	**3.7 (0.4,7.0)**	**0.030**
Erythema	974	5.2% (51/974)	15.2% (148/974)	10.0 (7.5,12.6)	<0.001
Soreness	974	18.4% (179/974)	16.4% (160/974)	-2.0 (-4.8,0.9)	0.178
Swelling	974	2.5% (24/974)	10.6% (103/974)	8.1 (6.2,10.2)	<0.001

† Two-sided 95% CI for the difference between 2 rates is based on the method of Tango T., Stat Med 1998; 17: 891-908.

‡ p-Value is computed using the McNemar's test for the null hypothesis of no difference in incidence rates between the 2 injections within the 2-dose regimen group.

N = Number of subjects who received the indicated injection.
n = Number of subjects with follow-up data for the indicated category following both Dose 1 and Dose 2.
s = Number of subjects in each category.
CI = Confidence interval.

[Ref. 5.3.5.4; R2]

Those who reported injection site reactions consistently reported an increased rate of systemic clinical complaints (for example, 80.6% vs 61.3% in protocol 025) in the studies, but not of fevers, serious AEs, or varicella-like rashes. These systemic complaints spanned a variety of AEs, but none that were serious or appear to be likely to be associated with any syndrome that could be associated with the second vaccination. For example (in protocol 025), 51.4% of those with injection site complaints reported upper respiratory infections, while only 37.8 of those without injection site complaints did. There is no plausible relationship between 2nd dose injection site complaints and upper respiratory infections. Every "systemic complaint" for which there was more than a single report occurred at a higher rate among those who had an injection site complaint than among those who did not, including fatigue, cough, irritability/nervousness, physician visit, diarrhea, headache, loss of appetite, vomiting, etc.

Table 2.7.4: 5

Overall Summary of Clinical Safety Data by Vaccination Dose—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 Protocol 007) (Days 0 to 42 Postvaccination)

Clinical Complaint	Dose 1 (N=417) n (%)	Dose 2 (N=417) n (%)
Subjects with no follow-up	1	9
Subjects with follow-up	416	406
Subjects with missing CRFs	0	2
Injection-site complaints	79 (19.0)	184 (45.3)
Systemic clinical complaints	346 (83.2)	253 (62.3)
Varicella-like rash, injection site	17 (4.1)	6 (1.5)
Varicella-like rash, noninjection site	27 (6.5)	2 (0.5)

Percentages are calculated based on the number of subjects with follow-up after each dose.
Injection-site complaints includes varicella-like rash at the injection site.
Dose 1 was manufactured as part of the 1987 Production Lots. Dose 2 was manufactured as part of the 1991 Production Lots [redacted]
N = Number of subjects who received both injections 4 to 6 years apart.
n = Number of subjects in each category.
CRF = Case report form.
[Ref. 5.3.5.4; R3]

It seems likely that there is a reporting bias here—those who are reporting an objective finding such as an injection site reaction are more likely to also complain about other things, while those with vaguer or non-specific complaints would be less likely to report them on their own without an injection site reaction to induce a complaint. Thus, the increased report of systemic complaints among those with injection site

Table 2.7.4: 7

ProQuad™ Protocol 014
Clinical Adverse Experience Summary
for Subjects Who Received M-M-R™II and VARIVAX™
(Days 1 to 43 Postvaccination)

Adverse Experience	M-M-R™II + VARIVAX™ N=195 n	(%)
Subjects with no follow-up	2	
Subjects with follow-up	193	
Injection-site complaints at the VARIVAX™ injection site	78	(40.4)
Injection-site complaints at the M-M-R™II injection site	76	(39.4)
Systemic clinical complaints	114	(59.1)
Varicella-like rash, injection site	0	(0.0)
Varicella-like rash, noninjection site	0	(0.0)

Percentages are calculated based on the number of subjects with follow-up after any visit.
[Ref. 5.3.5.1; P014]

complaints is not concerning, or indicative of a specific vaccine AE syndrome involving systemic complaints.

C. Fever

VZV vaccine, as a live attenuated vaccine, may cause fever in recipients. The expectation is that the immune response associated with the first dose would blunt spread of the infection and thus also febrile responses in a second dose.

Table 2.7.4: 13

Number (%) of Subjects With Elevated Temperature by Vaccination Regimen and Dose
(Days 0 to 42 Postvaccination)
VARIVAX™ Protocol 025
(Two Doses Given 3 Months Apart)

Temperature	VARIVAX™ 1-Dose Regimen (N=1114)	VARIVAX™ 2-Dose Regimen	
		Dose 1 (N=1102)	Dose 2 (N=1022)
	n (%)	n (%)	n (%)
Subjects with no follow-up	5	18	14
Subjects with follow-up	1096	1077	975
Subjects with missing CRFs	13	7	33
Maximum Temperature (Oral Equivalent)			
<102.0 °F (<38.9 °C) or normal	925 (84.4)	923 (85.7)	873 (89.5)
≥102.0 °F (≥38.9 °C) or abnormal	171 (15.6)	154 (14.3)	102 (10.5)

Percentages are calculated based on the number of subjects with follow-up after each dose within the indicated vaccination regimen.
All temperatures were converted to oral equivalent by adding 1.0°F to axillary temperatures or subtracting 1.0°F from rectal temperatures; otic temperatures were treated as oral temperatures.
In the 1-dose regimen, 4 subjects reported temperature as abnormal without numerical readings.
In the 2-dose regimen, 5 subjects following the receipt of Dose 1 and 1 subject following the receipt of Dose 2 reported temperatures as abnormal without numerical readings.
N = Number of subjects who received the indicated injection.
n = Number of subjects in each category.
CRF = Case report form.
[Ref. 5.3.5.4; R2]

Table 2.7.4: 14

Comparison of Rates of Elevated Temperature Between Dose 1 and Dose 2
Within the 2-Dose Regimen Group (Days 0 to 42 Postvaccination)
VARIVAX™ Protocol 025
(Two Doses Given 3 Months Apart)

Maximum Temperature (Oral Equivalent)	VARIVAX™ 2-Dose Regimen				
	n	Dose 1 (N=1102)	Dose 2 (N=1022)	Risk Difference (Dose 2 – Dose 1) Percentage Point (95% CI)†	p-Value‡
		% (s/n)	% (sn/)		
≥102.0 °F (≥38.9°C) or abnormal	969	14.0 (136/969)	10.4 (101/969)	-3.6 (-6.3,-1.0)	0.007

† Two-sided 95% CI for the difference between 2 rates is based on the method by Tango T., Stat Med 1998; 17: 891-908.
‡ p-Value is computed using the McNemar's test for the null hypothesis of no difference in incidence rates between the 2 injections within the 2-dose regimen group.
N = number of subjects who received the indicated injection.
n = Number of subjects with follow-up data for the indicated category following both Dose 1 and Dose 2.
s = Number of subjects in each category.
CI = Confidence interval.
[Ref. 5.3.5.4; R2]

Table 2.7.4:13 shows the proportion of subjects who had elevated temperatures after each dose in study 025. The proportion with no or low-grade fevers (less than 102ºF) within 42 days of vaccination was comparable between one dose, and either dose of the two-dose regimen, at 84.4%, 85.7%, and 89.5%, respectively. The proportion with temperatures above 102ºF was 15.6% and 14.3% after one dose, but only 10.5% after two doses. Because these children were observed for 42 days, it is likely that some of these fevers were unrelated to vaccine. However, these data suggest that at least about 5% of recipients had fever due to Varivax after the first dose.

Table 2.7.4:14 provides similar insight into the rate of fever after one vs. two doses in protocol 025. The slightly different numbers are due to the inclusion in table 14 only of individuals for whom follow-up data are available after both doses. In this case, at least 3.6% (1.0-6.3%) of fevers after the first dose could clearly be attributable to vaccine. It isn't clear how many fevers after the second dose are attributable to vaccine, but the amount clearly is less by this amount, which was statistically significant at a p value of 0.007.

Table 2.7.4: 15

Number (%) of Subjects With Elevated Temperature by Vaccination Dose—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 Protocol 007) Days 0 to 42 Postvaccination

Temperature	Dose 1 (N=417) n (%)		Dose 2 (N=417) n (%)	
Subjects with no follow-up	1		10	
Subjects with follow-up	416		405	
Subjects with missing CRFs	0		2	
Maximum temperature (oral equivalent):				
<102.0 °F (<38.9 °C) or normal	362	(87.0)	379	(93.6)
≥102.0 °F (≥38.9 °C) or abnormal	54	(13.0)	26	(6.4)

Percentages are calculated based on the number of subjects with follow-up after each dose.
All temperatures have been converted to oral equivalent by adding 1.0°F to axillary temperatures or subtracting 1.0°F from rectal temperatures. Otic temperatures were treated as oral temperatures.
Two (2) subjects following the receipt of Dose 1 and 1 subject following the receipt of Dose 2 reported temperatures as abnormal without numerical readings.
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 in each category.
CRF = Case report form.

[Ref. 5.3.5.4; R3]

Fever incidence also was examined in protocols 007 and 014. In protocol 007 (Table 2.7.4:15), 13% had a temperature above 102ºF after dose 1, while only 6.4% had a temperature above 102ºF after dose 2. In protocol 014, 9.4% reported a fever above 102ºF after the second dose.

Thus, in all 3 studies, the incidence of fever was lower after dose 2 than dose 1, as would be expected.

Additional information was requested and provided to address whether the second dose of varicella vaccine caused low-grade fevers. Although in and of themselves, low grade fevers would not be of high concern, if they were also associated with other events, this could have been a signal that might

Table 2.7.4: 15

Number (%) of Subjects With Elevated Temperature by Vaccination Dose—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 Protocol 007) Days 0 to 42 Postvaccination

Temperature	Dose 1 (N=417) n (%)		Dose 2 (N=417) n (%)	
Subjects with no follow-up	1		10	
Subjects with follow-up	416		405	
Subjects with missing CRFs	0		2	
Maximum temperature (oral equivalent):				
<102.0 °F (<38.9 °C) or normal	362	(87.0)	379	(93.6)
≥102.0 °F (≥38.9 °C) or abnormal	54	(13.0)	26	(6.4)

Percentages are calculated based on the number of subjects with follow-up after each dose.
All temperatures have been converted to oral equivalent by adding 1.0°F to axillary temperatures or subtracting 1.0°F from rectal temperatures. Otic temperatures were treated as oral temperatures.
Two (2) subjects following the receipt of Dose 1 and 1 subject following the receipt of Dose 2 reported temperatures as abnormal without numerical readings.
Dose 1 was manufactured as part of the 1987 Production Lots. Dose 2 was manufactured as part of the 1991 Production Lots [redacted]
N = Number of subjects who received both injections 4 to 6 years apart.
n = Number of subjects in each category.
CRF = Case report form.

have suggested other potential AEs that could be vaccine associated, that would be reasonable to look out for with the second dose of vaccine. The 0-4 day period after vaccination is important because this is the time frame in which immediate reactogenicity to vaccine components would be most apparent. In the provided data (3/3/2005), it is clear that in each of the studies where a comparison is possible, the incidence of low-grade fevers and in the 0-4 day post-vaccination period was reduced after the second dose of vaccine, as compared with the first dose of vaccine. Thus, the provided data adequately address this question.

D. Serious AEs

Serious adverse events also were examined in each of the three studies. In study 025, there was a case of impetigo 19 days after immunization. While bacterial superinfection of skin lesions is a plausible mechanism by which impetigo could occur, there isn't any reason to believe this would be more likely after a second, rather than a first dose of vaccine. In fact, with a lower incidence of VZV-like rashes, this seems to be less likely with second as opposed to first doses of vaccine.

Table 2.7.4: 18

Listing of Subjects With Serious Clinical Adverse Experiences in VARIVAX™ Protocol 025

Allocation Number	WAES Number	Gender	Age at Entry into Study	Relative Day of Onset Postdose	Adverse Experience	Vaccine Relationship	Outcome
2210	92090655	F	22 M	19	Impetigo	Unknown[1]	Recovered
				223	Rocky mountain spotted fever	Probably not	Recovered
2259	92080378	M	3 Y	44	Upper respiratory tract infection	Not related	Recovered
				46	Asthma	Not related	Recovered
2381	92080145	F	2 Y	17	Accidental exposure	Not related	Recovered

[1] It is not known if the impetigo was thought to be vaccine related or not.
WAES = Worldwide Adverse Experience System.
[Ref. 5.3.6; R5]

In protocol 007, there was a case of sore throat, rhinorrhea, lymphadenopathy and fever reported 20 days after a dose (see Table 2.7.4:19). This is consistent with a non-specific viral syndrome, and seems unlikely to be vaccine-related.

Table 2.7.4: 19

Listing of Subjects With Serious Clinical Adverse Experiences in VARIVAX™ Protocol 007

Allocation Number	WAES Number	Gender	Age at Entry into Study	Relative Day of Onset Postdose	Adverse Experience	Vaccine Relationship	Outcome
96	93050925	M	11 Y	20	Lymphadenopathy	Probably not	Recovered
				20	Pharyngolaryngeal pain	Probably not	Recovered
				20	Rhinorrhea	Probably not	Recovered
				20	Pyrexia	Probably not	Recovered
576	97062146	F	9 Y	3114	Alcohol poisoning	Not Related	Recovered

WAES = Worldwide Adverse Experience System.
[Ref. 5.3.6; R5]

No serious AEs were reported in protocol 014 (Vol. 1 of 1, p. 41).

All other serious clinical adverse experiences were judged to be "not related" to vaccination, and I concur with this assessment. Thus, serious AEs appear not to be an

issue that would influence a determination regarding the safety of a second dose of varicella vaccine.

II. Evaluation of theoretical concerns about a second dose of varicella vaccine.

A. Excipients

One potential theoretical concern with giving a second dose of vaccine is that there might be increased reactogenicity, because the first dose could prime a subsequent response to cellular materials or other excipients. Because of the relatively low efficiency of VZV growth, each dose of vaccine contains significant quantities of cellular materials, making this a potentially greater likelihood for this vaccine than for others.

Although there was a higher number of injection site reactions after the second dose as compared with the first, this difference was fairly small and the severity of the reactions was not increased. Thus, it seems unlikely that responses to non-vaccine antigens are an issue with a second dose of varicella vaccine.

B. Anaphylaxis

There have been reports of anaphylaxis, mostly attributed to gelatin in vaccine. It appears that anaphylaxis may occur more frequently in children previously exposed to gelatin. Thus, the question arises whether the parenteral exposure to gelatin from the first dose of vaccine could increase the likelihood of an anaphylactic response upon the second dose in a small minority of children. No cases of anaphylaxis were observed in the clinical trials or in WAES reports after a second dose of vaccine. Thus, this remains a theoretical concern, with no data to support this concern in the context of a second dose of vaccine.

C. Effect on zoster risk

If vaccine virus were to establish latency and potentially reactivate, providing double the dose of vaccine could theoretically double the zoster risk (by doubling the exposure to vaccine strain). Because the zoster risk from Oka vaccine strains is believed to be lower than that from wild-type strains, this additional risk probably is not significant. In addition, the improved immune response associated with a second dose could mitigate any potential zoster cases (and the lower incidence of varicella-like rashes suggests that complications associated with live virus replication occur at a lower rate with the second dose than with the first). In the 10-year follow-up of protocol 025, the zoster incidence in children who had one dose was 2/1114, and in children who had two doses was 0/1102.

D. Concomitant administration issues.

A single dose of varicella vaccine has been studied as a concomitant vaccination with many other childhood vaccines, although concomitant administration with inactivated poliovirus vaccines have not been studied (there was no interaction with oral poliovirus

vaccine). The vaccine most likely to be given concomitantly with varicella vaccine in the context of a second dose is MMR. Responses to the second dose in conjunction with MMR were studied in protocol 014 (although without a control group), achieving responses similar to those in protocols 007 and 025.

Thus, I do not believe that concomitant administration issues should influence a decision to approve this supplement.

III. Conclusion regarding risk

Overall, the VZV replication-related risks associated with a second dose of varicella vaccine appear to be lower than those associated with the first dose, with some increase in the incidence of injection site complaints. A second dose of vaccine was generally well-tolerated and based on the provided studies, seems unlikely to lead to serious adverse consequences. Other data on vaccine safety, including that from single-dose studies, and that from the already licensed 2-dose schedule in adolescents and adults, provides additional reassurance.

REVIEW OF LABEL CHANGES

The proposed label changes (in the unnumbered volume) are reasonable and accurately recapitulate the results of the studies presented in this application.

FINAL RECOMMENDATION

I recommend approval of this supplement.