

FDA Statistical Review and Evaluation

Document for the Vaccines and Related Biological Products
Advisory Committee
(VRBPAC)

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ZOSTAVAX™: Zoster vaccine live (Oka/Merck)

Indication: Prevention of herpes zoster (shingles), prevention of postherpetic neuralgia (PHN), and reduction of acute and chronic zoster-associated pain for individuals 50 years of age or older.

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Introduction

In the application for licensure of ZOSTAVAX™, Merck submitted information from 6 randomized studies and one open-label study in which a total of ~ 20,000 subjects received zoster vaccine live (Oka/Merck). Merck also submitted information from a ProQuad™ study and a VARIVAX™ study. Protocol 004 is the pivotal phase III clinical trial for this application. This statistical briefing document covers protocol 004.

Protocol 004

This was a multi-center (22 sites), double-blind, placebo-controlled, randomized study to evaluate the efficacy, immunogenicity, and safety of administration of zoster virus vaccine. A total of ~38,500 varicella history-positive and HZ history-negative subjects 60 years of age or older were randomized (1:1 ratio, stratified by site and age group: 60 to 69 years and ≥70 years) to receive a single dose of zoster virus vaccine or placebo.

Initial (release) potency of the vaccine ranged from 44,000 PFU/mL to 114,184 PFU/mL. Approximately 96% of the vaccinees received heat-aged vaccine with release doses ranging from 44,000 PFU/mL to 79,200 PFU/mL.

Merck's analyses

Efficacy

The **primary endpoint** for this study is the Herpes Zoster Burden Of Illness (HZ BOI) during the 6 months (Day 0 to 182) following HZ rash onset. The HZ BOI is a severity-by-duration measure defined by the HZ incidence, severity, and duration of HZ-associated pain and discomfort. HZ BOI (in a subject) is defined as “the area under the worst pain and discomfort response (rated on a 0 to 10 scale) versus time curve during the 6-month period following HZ rash onset in an individual subject who develops HZ.” For an evaluable HZ case (Merck stated “The results of the Clinical Evaluation Committee review were combined with the results of the Central PCR Laboratory, as well as virus culture” to determine the evaluable case), computation of HZ BOI score is as above. Subjects who did not develop HZ were assigned an HZ BOI score of zero. Then Merck defines VE_{BOI} (vaccine efficacy based on BOI) as $VE_{BOI} = 1 - R_{BOI}$ where R_{BOI} is the ratio of mean HZ BOI (stratified by age) of the vaccine relative to the placebo group (see Appendix for details of the calculation of VE_{BOI}).

The original **secondary endpoint** is the incidence of PHN.

For regulatory submission purposes, Merck proposed to treat these two endpoints as co-primary and to define success of the study as showing efficacy in at least one of the two

endpoints. An adjustment for multiple hypothesis testing to control the overall type I error rate at the two-sided 0.05 level was implemented.

The two **primary hypotheses** are

“Zoster vaccine will reduce ‘Burden of Illness’ (BOI) associated with herpes zoster (HZ)”;

“Zoster vaccine will reduce the incidence of postherpetic neuralgia (PHN).”

The success criteria are “ VE_{BOI} (vaccine efficacy based on BOI) $> 47\%$ and lower bound of the 95% CI $> 25\%$,” and “ VE_{PHN} (vaccine efficacy based on PHN incidence) $> 62\%$ and lower bound of the 95% CI $> 25\%$,” respectively.

Merck concludes that

“Compared with placebo, the zoster vaccine reduced the BOI related to HZ pain. The estimated VE_{BOI} was 61.1% with 95% CI of (51.1%, 69.1%)”;

“Compared with placebo, the zoster vaccine reduced the incidence of PHN. The estimated VE_{PHN} was 66.5% with 95% CI of (47.5%, 79.2%).”

The three additional **secondary hypotheses, originally designated as tertiary hypotheses** are

“Zoster vaccine will reduce the incidence of HZ”;

“Zoster vaccine will reduce the duration of HZ pain”;

“Zoster vaccine will reduce ADLI (Activity of Daily Living Interference).”

The success criteria are “The lower bound of the 95% CI of VE_{HZ} (vaccine efficacy based on HZ incidence) $> 25\%$,” and “p-value based on the stratified log-rank test < 0.05 to compare the duration of HZ pain between the two groups,” and “The lower bound of the 95% CI of $VE_{ADLI:HZ}$ (vaccine efficacy based on substantial ADLI beyond that of VE_{HZ}) $> 0\%$.”

Merck concludes that

“Compared with placebo, the zoster vaccine reduced the incidence of HZ. The estimated VE_{HZ} was 51.3% with 95% CI of (44.2%, 57.6%)”;

“Compared with placebo, the zoster vaccine reduced the duration of clinically significant pain associated with HZ. The median durations in vaccine and placebo groups are 20 days vs. 22 days respectively, and p-value = 0.04”;

“The lower bound of the 95% CI of $VE_{ADLI:HZ}$ = -9.4%.”

Immunogenicity

The Cell Mediated Immunity (CMI) substudy consists of a randomly selected subgroup of subjects (N=1,395) from those who were enrolled at the San Diego and Denver sites. Blood samples were collected from participants in this substudy. There is no formal statistical hypothesis associated with immunogenicity. Merck reported that at 6 weeks postvaccination, VZV IFN- γ ELISPOT counts were significantly higher in the zoster vaccine group than in the placebo group [2.2-fold difference with 95% CI of (1.9, 2.5)].

Safety

Merck reported that “Four vaccine-related serious adverse experiences occurred within 42 days postvaccination (2 in each group), among the entire study population.” Polymyalgia and asthma occurred in the zoster vaccine group, and anaphylaxis and polymyalgia rheumatica occurred in the placebo group.

Merck’s Overall Conclusion

Merck concluded “In subjects 60 years of age or older who received 1 dose of zoster vaccine or placebo, (compared to placebo) the zoster vaccine significantly reduced the burden of illness related to HZ pain, the incidence of PHN, the incidence of HZ, and the median duration of clinically significant pain associated with HZ. Zoster vaccine did not reduce the risk of having substantial ADLI. The zoster vaccine was generally well tolerated.”

Reviewer’s Comments

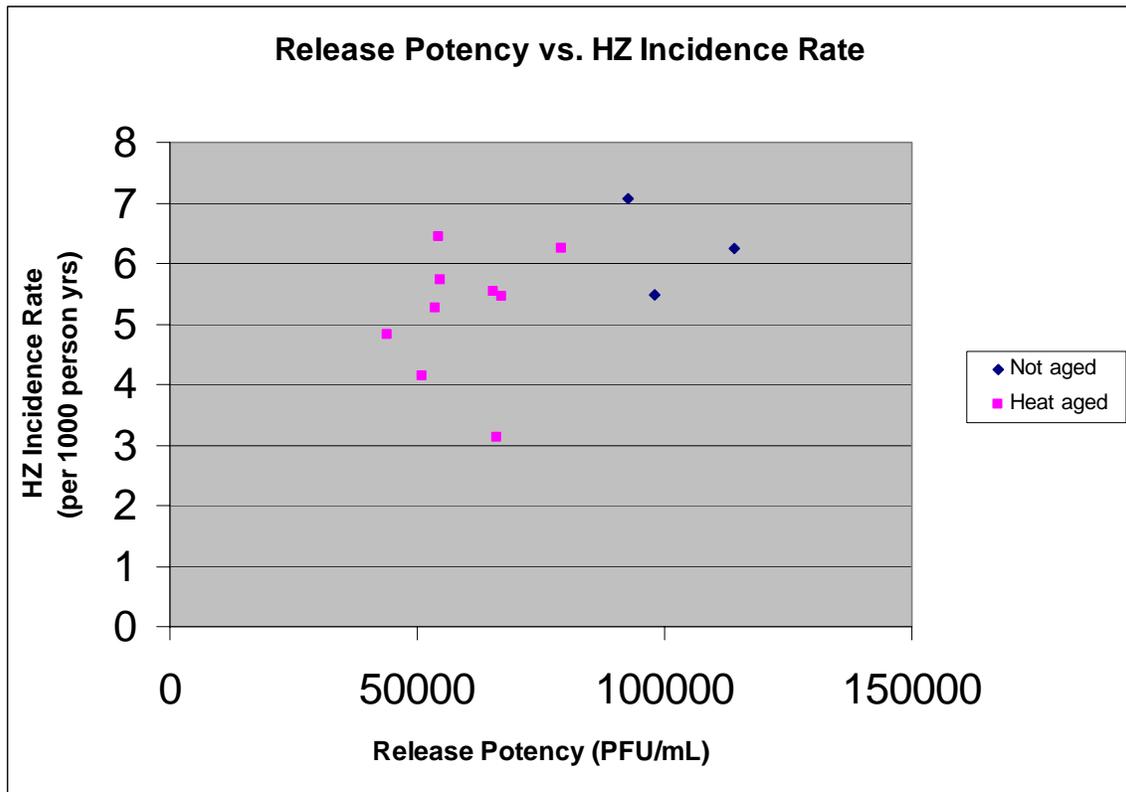
1. As shown in the following Table 1, the vaccinees are very heterogeneous with respect to release potency of the vaccine, ageing process of the vaccine (not aged vs. heat-aged), and the duration of follow-up time. The reviewer does not find any clear association between the release potency of the vaccine and the HZ incidence among vaccinees (see Figure 1). As Merck stated, “No dose response was observed in vaccine efficacy against HZ and PHN across the potencies used in the trial.” It is unclear, however, whether release potency of 100,000 PFU/mL (for example) without ageing is comparable to the release potency of 100,000 PFU/mL after heat-ageing.

Table 1. Incidence of Evaluable HZ Cases by Clinical Lot (MITT* population)

PLACEBO (N=19247)					Zoster Vaccine (N=19254)					
# Subjects	# HZ Cases	Total Follow-up Time (yrs)	Incidence Rate (per 1000 person yrs)	Average Follow-up Time (days)	LOT # Release Potency (PFU/mL)	# Subjects	# HZ Cases	Total Follow-up Time (yrs)	Incidence Rate (per 1000 person yrs)	Average Follow-up Time (days)
19247	642	57736	11.120	1096	1535W-E046 Not aged 97,821	278	6	1097	5.469	1441
					1536W-E047 Not aged 114,184	278	7	1119	6.256	1470
					1537W-E048 Not aged 92,581	279	8	1133	7.061	1483
					1553W-E462 Heat aged 66,000	326	4	1277	3.132	1430
					1554W-E463 Heat aged 79,200	326	8	1282	6.240	1436
					1555W-E464 Heat aged 65,400	326	7	1266	5.529	1418
					1562W-E471 Heat aged 54,600	2906	56	9764	5.735	1227
					1563W-E472 Heat aged 54,300	2903	63	9766	6.451	1229
					1564W-E473 Heat aged 67,000	2901	53	9745	5.439	1227
					1588W-G479 Heat aged 44,000	2912	35	7271	4.814	912
					1589W-G480 Heat aged 53,700	2908	38	7238	5.250	909
1590W-G481 Heat aged 51,100	2911	30	7247	4.140	909					
19247	642	57736	11.120	1096		19254	315	58203	5.412	1104

*The modified intent-to-treat (MITT) population included all subjects randomized in the study who were followed for at least 30 days postvaccination and did not develop an evaluable case of HZ within the first 30 days postvaccination.

Figure 1.



2. It is not clear from the submission whether subjects were randomly assigned to vaccine lots, and if so, how.
3. The HZ BOI (Burden of Illness) is a composite endpoint that incorporates the HZ incidence, severity, and duration of HZ-associated pain. Each subject's BOI is determined by an HZ pain curve based on IZIQ (Initial Zoster Impact Questionnaire) and ZBPI (Zoster Brief Pain Inventory) over a 182-day period. While the reviewer agrees that Merck's method of deriving BOI from the area under the HZ pain curve could be one of several useful measures to quantify the disease burden associated with HZ, the reviewer also perceives that the BOI index could be misleading. For example, let's suppose that 2,000 subjects are randomized either to zoster vaccine or placebo. Two years after the study starts, there are 10 HZ cases in the vaccine group and 20 in the placebo group. If a subject with HZ in the placebo group says his/her worst pain score is 3 (out of ten) on IZIQ and all ZBPI questionnaires, then his/her BOI is $3 \times 182(\text{days}) = 546$. Let's assume all twenty HZ cases have the same BOI. On the other hand, if a subject with HZ in the vaccine group says his/her worst pain score is 2 (out of ten) on the IZIQ and all ZBPI questionnaires, then his/her BOI is $2 \times 30(\text{days}) = 60$ (pain score under 3 does not contribute to BOI after 30 days from rash onset). Let's assume all ten HZ cases have the same BOI. Then $VE_{BOI} = 1 -$

$[(10 \times 60) / (20 \times 546)] = 94.5\%$. In this case, the vaccine reduces the incidence rate of HZ by half (vaccine efficacy based on HZ incidence is 50%). However, using the composite endpoint combining HZ incidence and severity, the BOI vaccine efficacy is 94.5.

4. As is shown in Table 2 below, at any time point (from Day 0 to Week 26), the difference in medians of worst pain scores (based on the ZBPI questionnaire) between the two groups does not exceed 1, except at Day 0 (difference in medians is 2). The mean difference does not exceed 0.4 at any time point except at Day 0 (mean difference is 1.4).

Table 2. Comparison of Worst Pain Scores on ZBPI (MITT population) among HZ cases

Time after HZ rash onset	Placebo (642 HZ cases)			Zoster vaccine (315 HZ cases)		
	# of HZ cases who took ZBPI	Mean worst pain	Median worst pain	# of HZ cases who took ZBPI	Mean worst pain	Median worst pain
Day 0 (HZ rash onset)	58	5.03	5	28	3.64	3
Day 1	158	4.25	4	72	4.06	3.5
Day 2	242	4.16	4	114	4.28	4
Day 3	239	4.51	4	122	4.63	4
Day 4	219	4.24	4	98	4.48	5
Day 5	175	3.95	4	94	3.97	4
Day 6	211	3.86	3	84	3.93	3
Day 7	189	3.85	3	84	4.04	4
Day 8	168	3.43	3	65	3.84	4
Day 9	163	3.79	3	92	3.37	3
Day 10	201	3.66	3	87	3.83	3
Week 2 (Day 12 ~ Day 16)	581	3.18	3	278	3.09	2
Week 3 (Day 19 ~ Day 23)	497	2.56	2	236	2.15	1
Week 4 (Day 26 ~ Day 30)	509	2.02	1	248	1.85	0
Week 5 (Day 33 ~ Day 37)	503	1.50	0	227	1.41	0
Week 6 (Day 40 ~ Day 44)	466	1.21	0	216	1.13	0
Week 7 (Day 47 ~ Day 51)	489	1.14	0	219	0.92	0
Week 8 (Day 54 ~ Day 58)	481	1.05	0	229	0.74	0
Week 10 (Day 68 ~ Day 72)	449	0.85	0	226	0.56	0
Week 12 (Day 82 ~ Day 86)	440	0.77	0	214	0.56	0
Week 16 (Day 110 ~ Day 114)	416	0.59	0	197	0.32	0
Week 20 (Day 138 ~ Day 142)	389	0.49	0	190	0.29	0
Week 24 (Day 166 ~ Day 170)	390	0.42	0	167	0.17	0
Week 26 (Day 180 ~ Day 184)	361	0.38	0	144	0.17	0

5. It appears that efficacy of the vaccine with respect to BOI *beyond* the efficacy on the HZ incidence is minimal (see the reviewer’s *exploratory* comparison of median HZ BOI among HZ cases in the following Table 3). However, it is clear that efficacy regarding HZ incidence met the pre-specified success criterion, assuming surveillance and ascertainment of the HZ cases were appropriate.

Table 3. Comparison of BOI between Vaccine and Placebo Groups

	Zoster vaccine	Placebo	
# subjects	19254	19247	
# HZ cases	315	642	
Total follow-up time (yrs)	58203	57736	
mean follow-up per subject (yrs)	3.02	3.00	
<hr/>			
HZ incidence rate Per 1000 person-yrs	5.41	11.12	VE _{HZ} = 51.3% (44.3%, 57.4%)
HZ incidence rate (crude rate)	1.64%	3.34%	VE _{HZ} = 51.0% (44.0%, 57.1%)
<hr/>			
Sum of HZ BOI	46341	114057	
mean HZ BOI per HZ case	147.1	177.7	
median HZ BOI among HZ cases	82.50	87.75	p-value (Wilcoxon) = 0.25
mean HZ BOI per subject	2.41	5.93	VE _{BOI} = 61.1% (51.1%, 69.1%)

6. It also appears that efficacy of the vaccine on PHN *beyond* the efficacy of the vaccine on the HZ incidence is minimal (see the reviewer’s *exploratory* comparison of percent of PHN among HZ cases in the following Table 4).

Table 4. Comparison of PHN Incidence between Vaccine and Placebo Groups

	Zoster vaccine	Placebo	
# subjects	19254	19247	
# HZ cases	315	642	
Total follow-up time (yrs)	58203	57736	
mean follow-up per subjects (yrs)	3.02	3.00	
# PHN cases	27	80	
percent of PHN among HZ cases	8.57%	12.5%	p-value (Fisher) = 0.08
PHN incidence rate per1000 person-yrs	0.464	1.384	VE _{PHN} = 66.5% (48.4%, 78.3%)

7. Efficacy of the vaccine on the duration of clinically significant pain *beyond* the efficacy of the vaccine on the HZ incidence appears to be minimal even though it is statistically significant after age adjustment (see Table 5 below for an *exploratory* analysis by the reviewer).

Table 5. Comparison of Duration of Clinically Significant Pain between the Vaccine and Placebo Groups

	Zoster vaccine	Placebo	
# subjects	19254	19247	
# HZ cases	315	642	
Median duration of clinically significant pain (days)	19	22	p-value (log-rank) =0.10
p-value based on the protocol-specified stratified (by age) log-rank test = 0.04			

8. The BOI index is a composite measure that consists of three components (HZ incidence, severity, and duration of pain). Thus, PHN (a severe case of HZ) incidence is an element of the BOI (thus not independent of the BOI). Likewise, HZ incidence and duration of pain are elements of BOI (not independent of the BOI). Considering this lack of independence in the metrics used to evaluate efficacy, the appropriateness of separate claims of efficacy in reducing HZ BOI and in reducing the incidence of HZ (or the incidence of PHN or the duration of pain) may warrant consideration.

Appendix

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3. Analyses of Vaccine Efficacy With Respect to the HZ BOI Measure

The efficacy analysis with respect to the HZ BOI will be analyzed using the fixed-number-of-events approach for the BOI methodology developed by Chang, Guess, and Heyse [1]. The analysis will be stratified by age group (60 to 69, ≥70 years of age) using total followup times for HZ case surveillance in each age group as weights. The HZ BOI for the vaccine and placebo recipients for each age group can be estimated by:

$$T_{V_k} = \frac{I}{M_{V_k}} \sum_{i=1}^{n_{V_k}} S_{V_{ki}} \quad T_{P_k} = \frac{I}{M_{P_k}} \sum_{i=1}^{n_{P_k}} S_{P_{ki}}, \quad (7.1)$$

where:

k is an index for age group (k=1 for age group 60 to 69 years; k=2 for age group 70+ years)

T_{P_k} is the observed HZ BOI Score for the placebo group in age group k

T_{V_k} is the observed HZ BOI Score for the vaccine group in age group k

M_{P_k} is the number of subjects randomized to the placebo group in age group k

M_{V_k} is the number of subjects randomized to the vaccine group in age group k

$S_{P_{ki}}$ is the HZ severity of illness score determined by the pain AUC for subject i in the placebo group in age group k

$S_{V_{ki}}$ is the HZ severity of illness score determined by the pain AUC for subject i in the vaccine group in age group k

n_{P_k} is the number of cases of HZ in the placebo group in age group k

n_{V_k} is the number of cases of HZ in the vaccine group in age group k

According to the Protocol, the calculation of HZ BOI Scores will account for differences in follow-up time for HZ case surveillance between the vaccine and placebo groups. Let F_V and F_P be the total HZ follow-up time for the vaccine and placebo groups, respectively, with two age groups combined. As a general guidance, if the difference in HZ follow-up time between the vaccine

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and placebo groups is greater than 0.5% of the total HZ follow-up time (i.e., $|F_V - F_P| > 0.005 * (F_V + F_P)$), then the sample sizes M_{V_k} and M_{P_k} for calculating the HZ BOI for each age group in (7.1) will be replaced by the HZ follow-up time F_{V_k} and F_{P_k} , respectively.

Note that the vaccine efficacy (VE_{BOI}) is defined as

$$VE_{BOI} = 1 - R_{BOI} \quad (7.2)$$

where $R_{BOI} = BOI_V / BOI_P$ is the ratio of HZ BOI between the vaccine and placebo groups. To estimate R_{BOI} stratifying by age group (60 to 69, ≥ 70 years of age), let $\hat{R}_{BOI,k} = T_{V_k} / T_{P_k}$ be the ratio of the observed BOIs between the vaccine and placebo groups for age group k. Then, the log-transformed ratio of HZ BOI between the vaccine and placebo groups, $\log(R_{BOI})$, can be estimated as the weighted average of the age-specific log-transformed ratios of HZ BOI between the vaccine and placebo groups:

$$\log(\hat{R}_{BOI}) = \sum_{k=1}^2 W_k \log(\hat{R}_{BOI,k}) \quad (7.3)$$

where $W_k = (F_{V_k} + F_{P_k}) / \sum_{j=1}^2 (F_{V_j} + F_{P_j})$ is the weight assigned to age group k that is proportional to the total follow-up time for HZ case surveillance in age group k. Then the point estimate for the vaccine efficacy can be calculated by:

$$\hat{VE}_{BOI} = 1 - \exp(\log(\hat{R}_{BOI})) \quad (7.4)$$

Per Protocol, the CI for VE_{BOI} will be obtained by first constructing a CI for $\log(R_{BOI})$, say (D_L, D_U) , based on $\log(\hat{R}_{BOI})$ using the Delta method (first order Taylor series approximation). Then the CI for R_{BOI} is $(\exp[D_L], \exp[D_U])$, and the corresponding CI for VE_{BOI} can be calculated as $(1 - \exp[D_U], 1 - \exp[D_L])$.

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Simulations have been conducted to compare the error coverage rates and power performance of the CI obtained using this log-delta method with those of the CI obtained using the simple delta method on \hat{R}_{BOI} (without taking the log-transformation) and of the CI obtained using the Fieller's theorem. The simulation results suggest that the log-delta CI controls the error rate (particularly the left-tail error rate, which corresponds to the type I error rate of interest in the primary efficacy analysis) better than the other two methods.

The following formula gives the details of calculating the CI for $\log(\hat{R}_{BOI})$ under the fixed-number-of-event design. Based on the Delta method, the variance (V_D) of $\log(\hat{R}_{BOI})$ is:

$$V_D = \sum_{k=1}^2 W_k^2 Var(\log(\hat{R}_{BOI,k})) \quad (7.5)$$

where

$$\begin{aligned} Var(\log(\hat{R}_{BOI,k})) &= Var(T_{V_k})/T_{V_k}^2 + Var(T_{P_k})/T_{P_k}^2 - 2Cov(T_{P_k}, T_{V_k})/(T_{P_k}T_{V_k}) \\ Var(T_{P_k}) &= (n_k p_{P_k} \sigma_{P_k}^2 + n p_{P_k} p_{V_k} \mu_{P_k}^2) / M_{P_k}^2 \\ Var(T_{V_k}) &= (n_k p_{V_k} \sigma_{V_k}^2 + n_k p_{P_k} p_{V_k} \mu_{V_k}^2) / M_{V_k}^2 \\ Cov(T_{P_k}, T_{V_k}) &= -n_k p_{P_k} p_{V_k} \mu_{P_k} \mu_{V_k} / (M_{P_k} M_{V_k}) \end{aligned} \quad (7.6)$$

and consistent estimates of μ_{P_k} , μ_{V_k} , p_{P_k} , p_{V_k} , $\sigma_{P_k}^2$, and $\sigma_{V_k}^2$ are obtained by:

$$\begin{aligned} \hat{\mu}_{P_k} &= \frac{1}{n_{P_k}} \sum_{i=1}^{n_{P_k}} S_{P_{ki}}, \quad \hat{\mu}_{V_k} = \frac{1}{n_{V_k}} \sum_{i=1}^{n_{V_k}} S_{V_{ki}} \\ \hat{p}_{P_k} &= \frac{n_{P_k}}{n_{P_k} + n_{V_k}}, \quad \hat{p}_{V_k} = 1 - \hat{p}_{P_k} \\ \hat{\sigma}_{P_k}^2 &= \frac{1}{n_{P_k} - 1} \sum_{i=1}^{n_{P_k}} (S_{P_{ki}} - \hat{\mu}_{P_k})^2, \quad \hat{\sigma}_{V_k}^2 = \frac{1}{n_{V_k} - 1} \sum_{i=1}^{n_{V_k}} (S_{V_{ki}} - \hat{\mu}_{V_k})^2 \end{aligned}$$

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As a result, a consistent estimate of V_D , denoted by \hat{V}_D , is obtained by substituting these consistent estimates in formula (7.5) and (7.6). Based on the large sample theory, the $(1-\alpha)100\%$ CI for the log-transformed relative BOI $\log(\hat{R}_{BOI})$ is:

$$(D_L, D_U) = (\log(\hat{R}_{BOI}) - Z_{\alpha/2} \sqrt{\hat{V}_D}, \log(\hat{R}_{BOI}) + Z_{\alpha/2} \sqrt{\hat{V}_D}) \quad (7.7)$$

where $Z_{\alpha/2}$ is the upper $\alpha/2$ percentile of the standard normal distribution.

In addition, the log-transformed HZ BOI Score for each treatment group, T_V and T_P , can be calculated as:

$$\log(T_V) = \sum_{k=1}^2 W_k \log(T_{V_k})$$

$$\log(T_P) = \sum_{k=1}^2 W_k \log(T_{P_k})$$

where W_k is the same as in formula (7.3). The associated 95% CI for the HZ BOI Score will be provided by treatment group and age group based on the normal approximation.

4. Test for Treatment-by-Age-Group Interaction With Respect to the HZ BOI

In parallel to the stratified analysis of VE_{BOI} , a test of treatment by age group interaction will be explored. The following test statistic can be used to test for the interaction:

$$Z_{int} = \log(\hat{R}_{BOI,1}) - \log(\hat{R}_{BOI,2}) \quad (7.8)$$

The variance of Z_{int} is $V_Z = \sum_{k=1}^2 Var(\log(\hat{R}_{BOI,k}))$. A consistent estimate of V_Z ,

denoted by \hat{V}_Z , can also be obtained as in formula (7.5). Hence the p-value for the treatment by age group interaction is: