



## STATISTICAL REVIEW AND EVALUATION BLA (MID-CYCLE)

**BLA/Supplement Number:** 125430/0

**Product Name:** VariZIG®

**Indication(s):** VariZIG, Varicella Zoster Immune Globulin (Human), is indicated for post-exposure prophylaxis of varicella in high risk individuals.

**Applicant:** CANGEN

**Date(s):** June 28 , 2012

**Review Priority:** Priority

**Statistical Branch:** Therapeutic Evaluation Branch

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## **1. EXECUTIVE SUMMARY**

VariZIG, Varicella Zoster Immune Globulin (Human), is indicated for post-exposure prophylaxis of varicella in high risk individuals. The efficacy and safety of VariZIG in post-exposure prophylaxis of high risk individuals exposed to VZV (Varicella Zoster Virus) is supported by data collected from two clinical trials VZ-006 and VZ-009. Study VZ-009 is currently ongoing. Data collected up to September 1, 2011 are included in all analyses.

### **1.1 Conclusions and Recommendations**

VariZIG was shown to be well-tolerated and with an efficacy profile comparable to that of licensed VZIG<sup>TM</sup>, in preventing or modifying the course of varicella infection in pregnant women without immunity to VZV. The final results of Phase III clinical trial VZ-009 are currently unavailable.

### **1.2 Brief Overview of Clinical Studies**

The VZ-006 study was a randomized, comparative study examining efficacy of VariZIG and VZIG<sup>TM</sup> in a single population at high risk of varicella complications, non-immune pregnant women exposed to VZV. The study included three arms, VariZIG administered intramuscularly (IM), VariZIG administered intravenously (IV) and VZIG<sup>TM</sup> IM. Due to both IM and IV routes of administration, the study was not blinded. VZ-006 was designed to compare the efficacy and safety of VariZIG IM or IV to previously licensed VZIG IM.

The VZ-009 study is an open-label expanded access treatment study designed to provide investigational VariZIG on as-required-basis to individuals in the USA at high risk of varicella complications. VZ-009 was initiated to meet an unmet need when the previous varicella zoster immune globulin, VZIG<sup>TM</sup> became unavailable. The study design, selection of study population and follow-up period are based on the recommendations of the advisory committee on immunization practices (ACIP) for the prevention of varicella published by the CDC.

### **1.3 Major Statistical Issues and Findings**

The frequency of varicella among patients treated with VariZIG was 29% (5 of 17) by the IM route and 29% (6 of 21) by the IV route compared to 42% (8 of 19) for patients treated with IM commercial VZIG<sup>TM</sup>; the differences between the investigational groups and commercial group were not statistically significant (p-value = 0.643). When averaged across all patients, the mean weighted CIS scores were slightly lower for the VariZIG IM group (1.35) and VariZIG IV group (0.90) compared to commercial IM VZIG (1.42). Response to the medications was similar between the strata; 35% (12 of 34) of patients contracted varicella in the first stratum (exposure to VZV of 1-4 days) and 30% (7 of 23) of patients contracted varicella in the second stratum (exposure to VZV 5-14 days). This difference was not statistically significant. The data suggest however, that those patients who received treatment within 1-4 days of exposure will have milder symptoms compared to those who were exposed 5-14 days prior to treatment, which may translate in better clinical outcome. Signs and symptoms as well as the “pox box” results (percentages of lesions that were maculopapular,

vesicular, crusted or healed) for patients who contracted varicella demonstrated a general improvement in symptoms by the time of the Closeout visit in all three treatment groups.

## 2. INTRODUCTION

### 2.1 Overview

The following Phase 3 studies were conducted:

**Table 1-1 Clinical Studies Designed to Demonstrate Efficacy of VariZIG**

Study ID	Study Design	Dosage, route of administration and duration	Study Subjects Included in Efficacy Analyses
VZ-006	Phase 3, multi-centre, randomized, active controlled study in at-risk pregnant women exposed to varicella virus.	Single dose of VZIG at 125 IU/10 kg IM, up to a maximum dose of 625 IU or VariZIG at 125 IU/ 10 kg IM or 125 IU/ 10 kg IV, up to a maximum dose of 625 IU.	Pregnant women (n = 57): VZIG IM (n=19) VariZIG IM (n=17) VariZIG IV (n=21)
VZ-009 <sup>2</sup>	Phase 3, open-label, multi-centre expanded access protocol in at-risk patients exposed to individuals with VZV infections.	Single dose of VariZIG at 125 IU/10 kg body weight IM, to a maximum dose of 625 IU	Healthy, non-immune adults (n=2) Immunocompromised adult and pediatric patients (n=147) Infants <sup>1</sup> (n=78) Pregnant women (n=70)

<sup>1</sup> Infant population also includes newborns and pre-term infants.

<sup>2</sup> Study VZ-009 is currently ongoing. Data collected up to September 1, 2011 is included in all analyses.

### Efficacy evaluation VZ-006

The clinical study VZ-006 examined the safety and efficacy of the IM VariZIG and IV VariZIG compared to a commercial preparation of IM VZIG. The study population recruited into this clinical trial was composed of pregnant women without immunity to VZV. No clinically significant differences were found in the assessments conducted on patients randomized to receive IM VariZIG, IV VariZIG, or commercial VZIG. Administration of VariZIG as a single IM or IV dose of 625 international units did not identify any new or untoward risk beyond that previously identified through the use of human immune globulin preparations. The efficacy of VariZIG and licensed VZIG was evaluated through comparison of the number of patients contracting varicella, and the CIS for each treatment group and stratum. The CIS was used as a quantitative measure for constitutional illness (chickenpox) and the comparison did not show significant differences between the test articles (VariZIG and licensed VZIG), between treatment arms (IM and IV route) or between strata (length of exposure to VZV: 1-4 days or 5-14 days). In summary, VariZIG was shown to be well-tolerated and with an efficacy profile comparable to that of licensed VZIG, in preventing or modifying the course of varicella infection in pregnant women without immunity to VZV.

### Safety evaluation VZ-006

Overall the adverse events observed in subjects treated with IM VariZIG and commercial IM VZIG were similar both in terms of incidence and severity. All related adverse events were consistent with those expected after IM administration of a human immune globulin preparation. A total of four serious adverse events were reported during study VZ-006. These include 3 reports of abortion (2 spontaneous abortions and 1 therapeutic abortion) and one report of asthma exacerbation. None of these serious events were considered related to the study drug. No deaths were reported during the period under review in this clinical trial.

#### **Efficacy evaluation VZ-009**

The VZ-009 study objectives are to outline the handling and use of VariZIG which is distributed by FFF Enterprises under the expanded access protocol, as well as to collect safety and efficacy data for VariZIG in subjects exposed to varicella zoster virus (VZV) and at high risk for developing complications. This is an ongoing open-label expanded access study. VariZIG is released on an individual case basis after subject eligibility for the study is confirmed and the investigator requests product by completing a VariZIG Release Form. There is no formal sample size planned, as VariZIG is being distributed to prevent or reduce the serious complications of varicella in subjects at high risk. The interim report includes the data available up to September 1, 2011.

#### **Safety evaluation VZ-009**

The safety of VariZIG was evaluated based on assessments of related adverse events, laboratory results (if available), and concomitant medications at each study visit. Overall, VariZIG was well tolerated in VZ-009 study subjects.

#### **Overall conclusions**

VariZIG was shown to be well-tolerated and with an efficacy profile comparable to that of licensed VZIG, in preventing or modifying the course of varicella infection in pregnant women without immunity to VZV. This conclusion is based on VZ-006 study and the interim data of VZ-009 study.

## **2.2 Data Sources**

This is an electronic submission.

Clinical data are located in Module 2 (Files summary-of-clinical-efficacy and summary-of-clinical-safety)

Efficacy data from the study VZ-009 will be included with the final study report.

## **3. STATISTICAL EVALUATION**

VZ-006 is a randomized, active controlled clinical trial comparing IV VariZIG, IM VariZIG, and IM licensed VZIG. Pregnant women without immunity to VZV (confirmed by a -----(b)(4)-----) and who had close contact with individuals infected with varicella were stratified on the basis of time from first exposure (1-4 days and 5-14 days) and randomized to receive 125 IU per 10 kg body weight to a maximum dose of 625 IU of licensed VZIG or VariZIG. Sixty pregnant women were enrolled and received study drug; 57 are included in the per-protocol analysis of efficacy. All 60

patients are included in the safety analyses. Duration of treatment: VariZIG (IM or IV) and VZIG (IM) were administered at Day 0 (Baseline) as a single infusion. Subjects were subsequently followed for safety and efficacy up to 42 days from the Baseline assessment.

### **3.1 Evaluation of Efficacy**

#### **Criteria for evaluation**

- Time of development of symptoms of varicella, if it occurred.
- Constitutional Illness Score (CIS).
- The number of lesions in the “pox box” (percentages of lesions that were maculopapular, vesicular, crusted or healed), and CIS at other post-Baseline evaluation times.

#### **Analysis Sets**

#### **Handling of Missing Data**

No imputation was used

#### **Patient Disposition, Demographic and Baseline Characteristics**

##### **Demographic characteristics**

There were two studies conducted to examine efficacy of VariZIG at the intended dose (125 IU/10 kg, up to a maximum of 625 IU) and route of administration (IM) in high risk populations; study VZ-006 and study VZ-009.

One of the treatment groups in study VZ-006 examined efficacy of VariZIG IM in non-immune pregnant women (n=17) exposed to VZV. The mean age of pregnant women in the VariZIG IM treatment group from study VZ-006 was 29.2 (SD  $\pm$ 5.95) years, with a range of 20 to 41 years. The majority of pregnant women in this study arm were Caucasian (76.5%), while the remaining subjects (23.5%) declared themselves as “Other”.

Study VZ-009 examined the efficacy of VariZIG IM in the prevention and reduction of varicella and varicella-related complications in several subject populations; the subjects were categorized into multiple high risk populations including: immunocompromised adult and pediatric (n=147) patients, infants (n=78), pregnant women (n=70) and healthy non-immune adults (n=2). Table 3-1 presents available demographic data for each high risk population in the interim report for study VZ-009.

**Table 3-1 Summary of Demographics in Subject Populations included in VZ-009 Efficacy Analysis**

Demography variable	Healthy non-immune adults (n=2)	Immunocompromised patients (n=147)		Infants <sup>2</sup> (n=78)	Pregnant women (n=70)
		Adults (n=15)	Pediatric <sup>1</sup> (n=132)		
Age (years, days for infants)					
Mean ± SD	29.7 ± 16.3	42.8 ± 16.1	7.1 ± 4.5	41.6 ± 73.7	29.3 ± 6.4
Range	18 – 41	18 – 71	0 – 17	0 – 381	16 – 43
Sex (n, %)					
Female	2 (100%)	9 (60.0%)	70 (53.0%)	34 (43.6%)	70 (100%)
Male	0 (0%)	6 (40.0%)	62 (47.0%)	44 (56.4%)	0 (0%)
Race (n, %)					
Caucasian	2 (100%)	8 (53.3%)	84 (63.6%)	40 (51.3%)	42 (60.0%)
Black or African American	0 (0%)	2 (13.3%)	13 (9.8%)	10 (12.8%)	2 (2.9%)
Asian	0 (0%)	1 (6.7%)	1 (0.8%)	4 (5.1%)	4 (5.7%)
Hispanic or Latino	0 (0%)	3 (20.0%)	28 (21.2%)	20 (25.6%)	15 (21.4%)
American Indian or Alaska Native	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Subject Declined to Provide	0 (0%)	0 (0%)	2 (1.5%)	3 (3.8%)	0 (0%)
Missing or Unknown	0 (0%)	1 (6.7%)	3 (2.3%)	1 (1.3%)	7 (10.0%)

<sup>1</sup> Immunocompromised pediatric patient category includes newborns, pre-term infants, infants and toddlers, children and adolescents.

<sup>2</sup> Infant subject category is for all infants including newborns and pre-term infants.

The mean ages of pregnant women in the VariZIG IM treatment group from study VZ-006 and pregnant women from study VZ-009 is similar (29.2 vs. 29.3 years, respectively). The majority of pregnant women from study VZ-006 were Caucasian (76.5%), which was similar to pregnant women in study VZ-009 (60.0% Caucasian); however, other races of pregnant women were represented in study VZ-009.

### The primary efficacy variable

Incidence of varicella

### Efficacy assessments and results

The historical incidence of Varicella in untreated high risk populations is given in Table 1-2 below.

**Table 1-2 Historical Incidence of Varicella in Untreated High Risk Populations:**

	Adults	Pregnant Women	Immunocompromised/ Immunodeficient	Newborns, Pre-term Infants
Incidence of varicella	70%	70%	88%	50%
Pneumonia (%)	14%	14%	19%	18%
Mortality (%)	1%	Unknown	7%	30%

In general, continuous household exposure to varicella or disseminated herpes zoster results in the highest risk of contracting VZV, with an estimated attack rate of 85% (range: 65-100%). In high risk populations incidence of varicella has been reported to range from 50% to 88%. In immunocompromised individuals, incidence of varicella has been reported to be approximately 88%. Mortality in childhood cancer patients with varicella has been reported to be 7%, with pneumonia observed in 19%. The onset of

varicella in pregnant women from 5 days prior to 2 days later delivery results in clinical varicella in over 50% of infants with severe varicella in 17-30% of newborn infants. Neonatal death has been reported to occur in up to 30% of this population. The incidence of varicella in non-immune pregnant women and adults ranges has been reported to be between 70-89%, with the incidence of pneumonia ranging between 14-50% of cases.

The incidence of varicella reported in pregnant women treated with VariZIG IM from study VZ-006 was 29% (5/17), and the overall incidence for all treatment groups, VariZIG (IM or IV) or VZIG (IM), was 33% (19/57). When compared to the historical reference rate, VariZIG was effective in preventing varicella in pregnant women in both studies (study VZ-009). An analysis comparing the efficacy data from study VZ-006 and study VZ-009 was not performed. There were no subgroup efficacy analyses performed.

Overall, the study VZ-009 shows that VariZIG significantly reduced the incidence of varicella ( $p<0.0001$ ) when compared to population specific historical untreated controls Table 5-2).

The primary efficacy analysis planned was based on the final clinical review of varicella captured in the case report form at the last study visit. The incidence of clinical varicella in pregnant women treated with VariZIG was 5.7% in VA-009. The primary efficacy analysis planned was based on the final clinical review of varicella captured in the case report form at the last study visit. To account for efficacy data captured elsewhere in the case report forms, a robustness analysis was also performed. The incidence of clinical varicella in the robustness population was 6.8% in the VZ-009 study. The efficacy data from study VZ-006 (pregnant women) and VZ-009 (high risk groups) clinical trials is summarized in Tables 2-1 and 5-2.

**Table 2-1 Comparison of Incidence of Varicella in Subjects treated with VariZIG and Historical Incidence of Varicella in Untreated Individuals**

<b>High Risk Population</b>	<b>Historical Incidence of Varicella in Untreated Individuals</b>	<b>n<sup>1</sup></b>	<b>Incidence of Varicella in VariZIG-treated Subjects</b>	<b>95% Confidence Interval</b>	<b>P-value<sup>2</sup></b>
Pregnant Women	70%	70	5.7% (n=4)	(1.6% - 14.0%)	<.0001*
Immunocompromised patients	88%	153	5.2% (n=8)	(2.3% - 10.0%)	<.0001*
Infants including newborns, pre-term infants	50%	78	12.8% (n=10)	(6.3% - 22.3%)	<.0001*



**Table 5-2 Results of Efficacy Studies for VariZIG**

Study ID	Treatment Arm	No. Enrolled/Completed <sup>1</sup>	Primary Endpoint Incidence of Varicella	Statistical Test/P value
VZ-006	VZIG, IM	19/19	42%	Two-sided Chi-square test/p=0.05 p=0.643
	VariZIG, IM	19/17	29%	
	VariZIG, IV	22/21	29%	
VZ-009	VariZIG, IM	372/297 <sup>2</sup>	Historical untreated rate/post-VariZIG treatment rate	Two-sided exact binomial test/ $\alpha = 0.05$
		Pregnant women 80/70	70% / 5.7%	p<0.0001
		Immunocompromised patients 174/147	88% / 5.2%	p<0.0001
		Newborns and pre-term infants 113/78	50% / 12.8%	p<0.0001
		Non-immune adults 5/2	N/A <sup>3</sup>	N/A <sup>3</sup>

<sup>1</sup> Number of subjects enrolled in study/number of subjects included in efficacy analysis population.

<sup>2</sup> From the start of the study until September 1, 2011, data for 372 subjects were returned to Cangene; 297 subjects had adequate efficacy information returned to Cangene.

<sup>3</sup> Incidence of varicella was not calculated for this high risk population since the minimum size of 30 subjects required for efficacy analysis was not achieved as of September 1, 2011. However, out of the two subjects in this high risk population, one subject developed varicella.

## Statistical Methodologies in Study VZ-006

All tests were two-sided and the probability of type I error was set at 0.05. Of principal interest were two comparisons, IV VariZIG versus IM commercial VZIG and IM VariZIG versus commercial VZIG IM. These pairwise comparisons were undertaken only if the omnibus test for three treatments proved significant. To evaluate the efficacy data from patients in the three treatment groups, nominal data were analyzed using the chi-square test. For variables which were ordinal, the Kruskal-Wallis test was used. The data for continuous variables were fitted to an ANOVA model including treatment, strata and the two-way interaction terms. Differences in incidence rates between the three groups were tested using the Chi-square test.

## Results and Conclusions

The efficacy of VariZIG and licensed VZIG was evaluated through comparison of the patients at the time of development of symptoms of varicella, if it occurred, the CIS for each treatment group, the number of lesions in the pox box and percentage that were maculopapular, vesicular, crusted or healed. The frequency of varicella among patients treated with VariZIG was 29% (5 of 17) by the IM route and 29% (6 of 21) by the IV route compared to 42% (8 of 19) for patients treated with IM commercial VZIG; the differences between the investigational groups and commercial group were not statistically significant (p-value = 0.643). When averaged across all patients, the mean weighted CIS scores were slightly lower for the VariZIG IM group (1.35) and VariZIG IV group (0.90) compared to commercial IM VZIG (1.42). Response to the medications was similar between the strata; 35% (12 of 34) of patients contracted varicella in the first stratum (exposure to VZV of 1-4 days) and 30% (7 of 23) of patients contracted varicella in the second stratum (exposure to VZV 5-14 days). This difference was not statistically significant. The data suggest however, that those patients who received treatment within 1-4 days of exposure will have

milder symptoms compared to those who were exposed 5-14 days prior to treatment, which may translate in better clinical outcome. Signs and symptoms as well as the “pox box” results for patients who contracted varicella demonstrated a general improvement in symptoms by the time of the Closeout visit in all three treatment groups.

### **Efficacy conclusions**

The present clinical study examined the safety and efficacy of the IM VariZIG and IV VariZIG compared to a commercial preparation of IM VZIG. The study population recruited into this clinical trial was composed of pregnant women without immunity to VZV. No clinically significant differences were found in the assessments conducted on patients randomized to receive IM VariZIG, IV VariZIG, or commercial VZIG. Administration of VariZIG as a single IM or IV dose of 625 IU did not identify any new or untoward risk beyond that previously identified through the use of human immune globulin preparations. The efficacy of VariZIG and licensed VZIG was evaluated through comparison of the number of patients contracting varicella, and the CIS for each treatment group and stratum. The CIS was used as a quantitative measure for constitutional illness (chickenpox) and the comparison did not show significant differences between the test articles (VariZIG and licensed VZIG), between treatment arms (IM and IV route) or between strata (length of exposure to VZV - 1-4 days or 5-14 days). In summary, VariZIG was shown to be well-tolerated and with an efficacy profile comparable to that of licensed VZIG, in preventing or modifying the course of varicella infection in pregnant women without immunity to VZV.

### **3.2 Evaluation of Safety**

**VZ-006 Study:** A total of 92 adverse events were reported by 31 of the 41 subjects (76%) treated with either IM or IV VariZIG. The majority of adverse events were mild in intensity (79%) and 24 events (26%) were assessed by the investigator as related to the administration of VariZIG. The most frequent adverse events overall were pruritus (12%), headache (10%), injection site pain (9%), and nausea (9%). Eighty-two adverse events were reported by 31 of the 38 subjects (82%) who received IM administration of VariZIG or commercial VZIG, and 51 events were reported by 16 of the 22 subjects (73%) who received IV administration of VariZIG. The most frequent event in subjects who received IM administration of VariZIG or commercial VZIG was pain at the injection site (17 events in 17 patients). In those receiving IV administration of VariZIG, the most frequent event was pruritus (8 events in 2 patients). Overall the adverse events observed in subjects treated with IM VariZIG and IM VZIG were similar both in terms of incidence and severity. All related adverse events were consistent with those expected after IM administration of a human immune globulin preparation. A total of four serious adverse events were reported during study VZ-006. These include 3 reports of abortion (2 spontaneous abortions and 1 therapeutic abortion) and one report of asthma exacerbation. None of these serious events were considered related to the study drug. No deaths were reported during the period under review in this clinical trial.

**VZ-009 Study:** Overall, VariZIG was well tolerated in VZ-009 study subjects. The most common adverse events (AEs) were pyrexia (4%) and neutropenia (3%, due to a large number of immunocompromised patients included in the safety population). Out of the 337 subjects included in the overall safety analysis, 96 subjects (11.6%) reported 353 AEs; 20 subjects (5.9%) reported 53 AEs considered as related to VariZIG; most of the

related AEs were isolated cases including headache, nausea, chills, fatigue, flushing, injection site reactions, arthralgia and rash, all reported at a frequency of < 1%. The majority of these related AEs are expected adverse drug reactions for immune globulin products, such as VariZIG. There were also isolated cases of serum sickness, nasopharyngitis, varicella, abnormal laboratory results, arthritis and insomnia (< 1%) which were related to VariZIG. Some of these events could have also been related to the subject's underlying conditions. There were 46 SAE cases with 84 SAE terms reported for 41 subjects, including six deaths (none were related to VariZIG). Out of the reported 84 SAEs, there were six SAEs considered as related to VariZIG. The most significant VariZIG-related SAE was an isolated case of serum sickness. The development of the other five VariZIG-related SAEs could have been due to patients' underlying conditions.

### 3.3 Gender, Race, Age and Other Special/Subgroup Populations

The study population recruited into vz-006 clinical trial was composed of pregnant women. The mean age of pregnant women in the VariZIG IM treatment group from study VZ-006 was 29.2 (SD  $\pm 5.95$ ) years, with a range of 20 to 41 years. The majority of pregnant women in this study arm were Caucasian (76.5%), while the remaining subjects (23.5%) declared themselves as "Other". The study population of vz-009 is given in the following table:

**Table 3-1 Summary of Demographics in Subject Populations included in VZ-009 Efficacy Analysis**

Demography variable	Healthy non-immune adults (n=2)	Immunocompromised patients (n=147)		Infants <sup>2</sup> (n=78)	Pregnant women (n=70)
		Adults (n=15)	Pediatric <sup>1</sup> (n=132)		
Age (years, days for infants)					
Mean $\pm$ SD	29.7 $\pm$ 16.3	42.8 $\pm$ 16.1	7.1 $\pm$ 4.5	41.6 $\pm$ 73.7	29.3 $\pm$ 6.4
Range	18 – 41	18 – 71	0 – 17	0 – 381	16 – 43
Sex (n, %)					
Female	2 (100%)	9 (60.0%)	70 (53.0%)	34 (43.6%)	70 (100%)
Male	0 (0%)	6 (40.0%)	62 (47.0%)	44 (56.4%)	0 (0%)
Race (n, %)					
Caucasian	2 (100%)	8 (53.3%)	84 (63.6%)	40 (51.3%)	42 (60.0%)
Black or African American	0 (0%)	2 (13.3%)	13 (9.8%)	10 (12.8%)	2 (2.9%)
Asian	0 (0%)	1 (6.7%)	1 (0.8%)	4 (5.1%)	4 (5.7%)
Hispanic or Latino	0 (0%)	3 (20.0%)	28 (21.2%)	20 (25.6%)	15 (21.4%)
American Indian or Alaska Native	0 (0%)	0 (0%)	1 (0.8%)	0 (0%)	0 (0%)
Native Hawaiian or Other Pacific Islander	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Subject Declined to Provide	0 (0%)	0 (0%)	2 (1.5%)	3 (3.8%)	0 (0%)
Missing or Unknown	0 (0%)	1 (6.7%)	3 (2.3%)	1 (1.3%)	7 (10.0%)

<sup>1</sup> Immunocompromised pediatric patient category includes newborns, pre-term infants, infants and toddlers, children and adolescents.

<sup>2</sup> Infant subject category is for all infants including newborns and pre-term infants.

## **4. SUMMARY AND CONCLUSIONS**

### **4.1 Statistical Issues and Collective Evidence**

Based on the sponsor's statistical analysis (see section 1.3 Major Statistical Issues and Findings), the original goal of the study was to show superiority of VariZIG over VZIG. The results of the studies did not support this hypothesis. Since there was no statistically significant difference in performance of the products, the sponsor claims noninferiority. To claim noninferiority, a correct statistical hypothesis of noninferiority should be formulated and an appropriate statistical analysis should be done.

I verified the statistical estimates of confidence intervals in table 2-1.

### **4.2 Conclusions and Recommendations**

VariZIG was shown to be well-tolerated and with an efficacy profile comparable to that of licensed VZIG, in preventing or modifying the course of varicella infection in pregnant women without immunity to VZV. The final results of Phase III clinical trial VZ-009 are currently unavailable. The study results regarding the frequency of varicella and CIS scores are reported as "no statistically significant" based on non-significant p-values. Such statistically insignificant results do not automatically lead to the no-difference (equivalent) conclusion among the treatment groups under consideration. I recommend the sponsor to report the confidence intervals of the treatment differences and defer to the clinical reviewer to comment on the study results with respect to the clinical significance.

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