

Final Clinical Review Memo

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Application Type	Biologics License Application
STN	125430
CBER Received Date	29-Jun-2012
PDUFA Goal Date	29-Dec-2012
Division / Office	DH / OBRR
Priority Review	Yes
Reviewer Name(s)	Charles Maplethorpe, M.D., Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Cangene Corporation
Established Name	Varicella Zoster Immune Globulin (Human)
(Proposed) Trade Name	VariZig <sup>®</sup>
Pharmacologic Class	Hyperimmune Globulin (Human)
Formulation(s), including Adjuvants, etc	Intramuscular formulation
Dosage Form(s) and Route(s) of Administration	Lyophilized, diluent supplied Intramuscular administration
Dosing Regimen	Dosing of VariZIG is based on body weight. Administer a single dose of VariZIG
Indication(s) and Intended Population(s)	VariZIG is a Varicella Zoster Immune Globulin (Human) indicated for post-exposure prophylaxis in high risk individuals. High risk groups include:

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	<ul style="list-style-type: none"><li>• immunocompromised children and adults,</li><li>• newborns of mothers with varicella shortly before or after delivery,</li><li>• premature infants,</li><li>• infants less than one year of age,</li><li>• adults without evidence of immunity,</li><li>• pregnant women.</li></ul> <p>VariZIG administration is intended to reduce the severity of varicella.</p>
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## 1 EXECUTIVE SUMMARY

Cangene Corporation has submitted BLA STN125430 for their Varicella Immune Globulin (Human) (VariZIG<sup>®</sup>) product. The sought indication from the submitted package insert is as follows:

Varizig is a Varicella Zoster Immune Globulin (Human) indicated for post-exposure prophylaxis in high risk individuals.

High risk groups include:

- immunocompromised children and adults,
- newborns of mothers with varicella shortly before or after delivery,
- premature infants,
- infants less than one year of age,
- adults without evidence of immunity,
- pregnant women.

Varizig administration is intended to prevent or reduce the severity of varicella.

The **Pediatric Research Equity Act (PREA)** does not apply because the product has Orphan Designation.

STN125430/0 has been granted **Priority Review**, with an Action Due date of December 29, 2012.

### Product Description

Varizig<sup>®</sup> is manufactured from pooled plasma collected from individuals who have high serum titers reactive against varicella virus in a varicella ---b(4)----- . The manufacturing process includes solvent-detergent virus inactivation and nanofiltration steps that have been validated for viral removal/inactivation. The product is supplied as a lyophilized powder with a -b(4)-- diluent for reconstitution. Varizig is available in a single-use vial of 125 IU. Varizig is accompanied by a vial of 8.5 mL of Sterile Diluent used for reconstitution. Each vial of Varizig is reconstituted with 1.25 mL of sterile diluent.

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Table of Clinical Studies

Cangene conducted the following clinical studies to support licensure:

Study	Purpose of Study
VZ-001	<ul style="list-style-type: none"><li>to assess safety of VariZIG.</li></ul> N = 10
VZ-003	<ul style="list-style-type: none"><li>to provide evidence of effectiveness of intravenous (IV) VariZIG in the reduction of post-herpetic neuralgia.</li><li>safety of VariZIG.</li></ul>
VZ-006	<ul style="list-style-type: none"><li>to establish safety and effectiveness of VariZIG in preventing or ameliorating maternal infections with varicella zoster virus</li><li>to compare safety and efficacy of IV and intramuscular (IM) routes of administration of VariZIG</li></ul>
VZ-008	<ul style="list-style-type: none"><li>to establish comparative bioavailability (bioequivalence) of VariZIG and VZIG, following IM administration</li><li>to demonstrate safety of VariZIG compared to VZIG.</li></ul> N = 35
VZ-009	<ul style="list-style-type: none"><li>to provide VariZIG to high risk individuals in the USA and to collect safety and efficacy data for VariZIG.</li></ul> Ongoing; N = 372 cases reported to Cangene by September 1, 2011.

Regulatory Background

- IND 7201 was submitted by Cangene on Jun 26, 1997. The sponsor stated the purpose was to add a U.S. study site to an ongoing Canadian phase 3 study that used VariZIG to treat pregnant women exposed to varicella virus and who were known to be at risk for contracting chickenpox.
- IND 7201 was placed on clinical hold in a July 24, 1997 teleconference. The [November 13, 1997, clinical hold letter](#) contains the following items:
  - questions about the appropriateness of the primary endpoint, the Constitutional Illness Score (CIS) at day 7; a question about the protocol not using varicella infection rate as the primary endpoint,
  - questions about the justification of the sample size, given the absence of phase 2 data that could inform the phase 3 study design,
  - a concern whether the enrollment of subjects who had been exposed to varicella virus more than 96 hours prior to dosing is justified,

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- a concern about lack of validation of anti-VZ test kits that would be used to control the manufacture of the product and to evaluate clinical outcomes, and
- a concern about lack of blinding in the study, and incompleteness of the statistical analysis plan.
- November 1, 2000, Cangene requested inactivation of IND 7201 and conducted the clinical studies in Canada.
- In 2005, Cangene held discussions with FDA and reactivated IND 7201.
  - Among the points discussed was the path to licensure. Cangene sought advice on pursuing licensure by showing pharmacokinetic comparability to the licensed product VZIG, manufactured by Massachusetts Public Health Biological Laboratories (MPHBL).
- MPHBL decided to discontinue manufacturing VZIG in 2006, for business reasons. Therefore, a Blood Products Advisory Committee (BPAC) meeting was held on July 21, 2005, to discuss the following questions:
  1. Please discuss what laboratory and clinical data would be sufficient to demonstrate efficacy of a new anti-varicella antibody preparation, for prophylaxis of severe varicella infection. In particular, please comment on
    - a. Which target populations would be most informative to study
    - b. What surrogate markers would be appropriate for assessment of efficacy
    - c. Other considerations for clinical trials
  2. Please comment on whether the available scientific data support use of IGIV or acyclovir as a substitute for VZIG for prophylaxis of severe VZV infection in any clinical settings
- A transcript of the July, 2005, BPAC meeting, with inserted slides, is contained in [Appendix 2](#).
  - BPAC discussed the difficulties in designing a licensure trial for varicella immune globulin (given the rarity of the population at risk after varicella vaccination has become standard), the lack of information on appropriate surrogates for clinical benefit, and the lack of appropriate contemporaneous control groups to permit valid data analysis.
  - There was no resolution of the path-to-licensure problem.
- STN 125430 for VariZIG was submitted on June 29, 2012, and under priority review has an action due date of December 29, 2012.
  - An information request containing clinical items was issued on October 4, 2012. The responses are contained in [Appendix 7](#).

Clinical studies submitted to support licensure

The main clinical studies submitted to support licensure are the following:

1. [VZ-006](#), a 3-arm randomized, open-label, active controlled [intramuscular VZIG 125 IU/10 kg (maximum dose 625 IU), Massachusetts Public Health Biologic Laboratories (MPHBL)] study in non-immune pregnant women exposed to varicella virus within 1-4 days of enrollment (stratum 1) or 5-14 days (stratum 2), with investigational study arms of

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- a. intramuscular VariZIG 125 IU/10 kg (maximum dose 625 IU), or
  - b. intravenous VariZIG 125 IU/10 kg (maximum dose 625 IU),.
2. [VZ-009](#), an open-label expanded access study using VariZIG 125 IU/10 kg (maximum dose 625 IU), with a dose adjustment schedule for infants), to treat “high risk” subjects exposed to varicella virus up to 10 days prior to enrollment. These high risk groups included the following:
  - a. Immunocompromised pediatric patients.
  - b. Immunocompromised adult patients.
  - c. Full term infants (including infants < 1 year of age).
  - d. Pre-term infants.
  - e. Pregnant women
  - f. Newborns whose mothers had VZV infection shortly before delivery (<5 days).
  - g. Newborns whose mothers had VZV infection shortly after delivery (<2 days).
  - h. Healthy non-immune adults.

**Clinical Study Results**

**VZ-006 -- Varicella-exposed, serologically confirmed varicella-naïve pregnant women.**

Sixty (60) women enrolled, and 3 were excluded from the efficacy analysis due to inappropriate enrollment (subjects -----b(6)--- were immune at baseline; -b(6)----- had active varicella infection at enrollment).

There were two enrollment strata based on the time from exposure to treatment, as follows:

1. Stratum 1: 1-4 days from exposure
2. Stratum 2: 5-14 days from exposure

The proposed primary endpoint for study VZ-006 was never uniquely specified, and was changed by the sponsor over time, as follows:

1. 1997 (IND 7201): [Constitutional Illness Score \(CIS\)](#) at day 7 after treatment initiation
2. [2005 meeting](#): CIS at time of clinical varicella (rash)
3. STN125430 (and in places in IND 7201): rate of varicella infection determined clinically (rash, symptoms; but not by serological confirmation)

**Applicant's Per Protocol Efficacy Analysis: Subjects with Clinical Varicella**

Study Arm	No. Enrolled	No. with Varicella Infection (%)
VZIG i.m.	19	8 (42%)
VariZIG i.m	17	5 (29%)
VariZIG i.v.	21	6 (29%)

These outcome differences between study arms are claimed by the applicant to be not statistically significant (p = 0.643).

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The applicant compares these outcomes to a theoretical historical control rate of 70%, and claims the 95% confidence interval for the 29% attack rate for VariZIG i.m. excludes the theoretical historical control rate of 70%.

The applicant proposes this historical control rate based on an observed varicella attack rate of 87% in a household (sibling) contact study [Ross A.H. *et al.*, *NEJM* 267(8):369-376 (1962)]. The applicant apparently arbitrarily diminishes the reported 87% attack rate in the Ross study to a proposed theoretical historical control attack rate of 70% for study VZ-006, recognizing that some varicella exposures in VZ-006 are likely to be less intense than those in the Ross study.

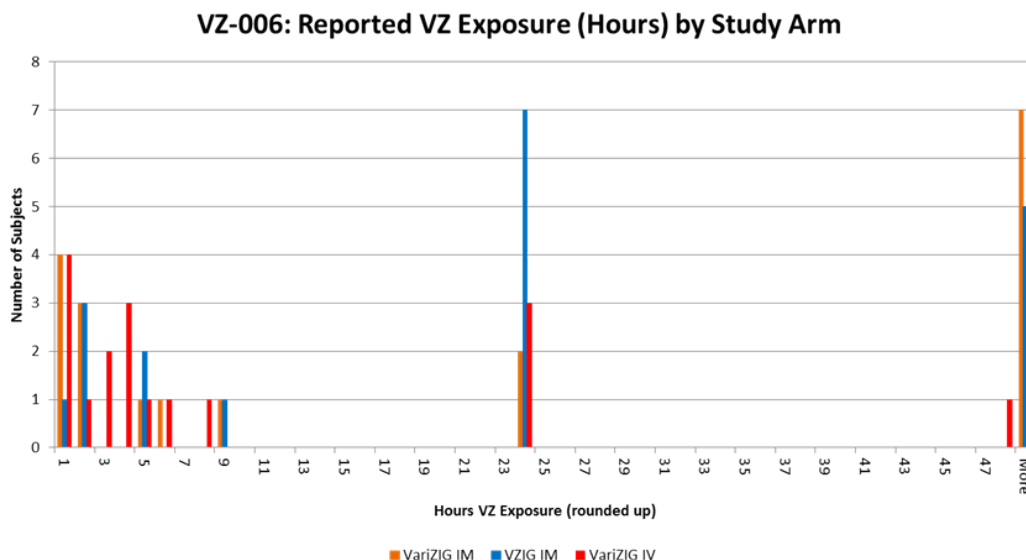
There has been no prospective agreement with FDA on the theoretical historical control attack rate of 70% for study VZ-006.

FDA Analysis of the Incidence of Clinical Varicella in VZ-006

Protocol VZ-006 did not precisely define ‘clinical varicella’; however, it is apparent from the applicant’s analyses that ‘clinical varicella’ is to be interpreted as the observation of typical varicella pock lesions after exposure to persons experiencing chickenpox or zoster. By this definition, the applicant includes subjects as having ‘clinical varicella’ even if the Constitutional Illness Score is zero at every time point.

Although a follow-up anti-VZ antibody measurement was made at day 42, the results of this test did not influence the determination of ‘clinical varicella’; therefore, subjects with subclinical varicella were not considered in the applicant’s analysis.

FDA reviewed the reported varicella exposure times and derived the following frequency histogram after rounding times up to the nearest hour:



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It is apparent that the distribution of varicella exposure times for VZ-006 differs markedly from the expected distribution for a household contact study, such as the Ross study, where all exposure times are expected to be at least 24 hours.

Therefore, outcomes were analyzed by the extent of varicella exposure being less than or more than 24 hours. The following chart shows the results:

Number of Subjects with Clinical Varicella by Strata and Exposure Time

	VariZIG IM		VZIG IM		VariZIG IV	
Stratum	< 24 hours	>24 hours	< 24 hours	>24 hours	< 24 hours	>24 hours
1-4 days	1/8	3*/3*	0/3	5/8	0/7 <sup>†</sup>	3/5
Subject IDs of infected	--b(6)---	---b(6)----- ---		--b(6)----- --		---b(6)-----
5-14 days	0/2	1/5	0/4	3/4	0/7	3/3
Subject IDs of infected		--b(6)---		--b(6)-----		--b(6)----- --

\* -b(6)--- is excluded from the analysis because she had clinical varicella at baseline

<sup>†</sup> -b(6)---, in the non-infected VariZIG IV stratum 1 group, does not have a submitted VZ exposure time; therefore, for this analysis --b(6)----- is included in the denominator of the less than 24 hours exposure group.

It is clear that the low attack rate for subjects in the < 24 hours exposure group (1 case of clinical varicella in 30 subjects) implies that most of the subjects in this group did not have exposures intense enough to justify inclusion with the > 24 hours exposure group (18 cases of clinical varicella in 29 subjects).

Therefore, if the analysis considers only subjects with varicella exposure times more than 24 hours, and if the data for the two VariZIG arms are combined, the following numbers, rates, and 95% confidence intervals are obtained:

	No. Infected/No. Subjects	Attack Rate	95% Confidence Interval
VariZIG	10/16	63%	(35.4%--84.8%)
VZIG	8/12	67%	(35% -- 90%)

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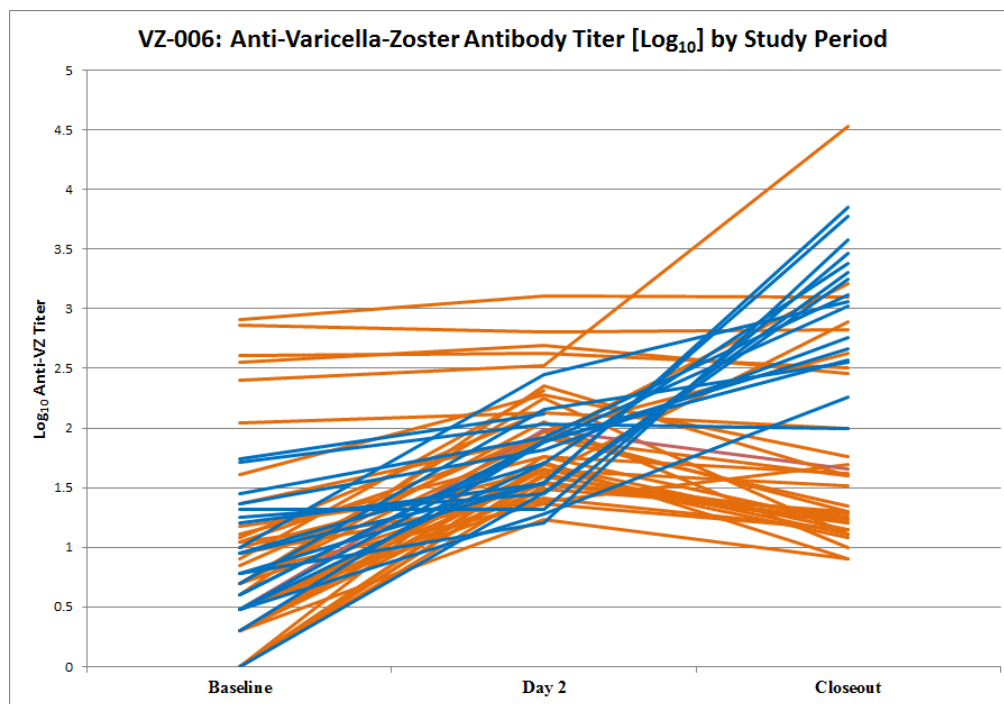
With the above analysis, the 95% confidence interval no longer excludes the theoretical historical control attack rate of 70%.

**Therefore, these data cannot be used to support a claim for prevention of varicella for either VariZIG or for VZIG.**

FDA Analysis of the Anti-Varicella-Zoster Antibody Results and the Potential for Missed Subclinical Infections and Missed Baseline Seropositives

Protocol VZ-006 collected serum samples at baseline, day 2 after dosing, and at day 42 (closeout). Samples were tested using a VZ -----b(4)----- The results of the -----b(4)----- were not used in the determination of clinical varicella outcomes (which was based solely on the observation of varicella pocks). Therefore, it is possible that subjects with subclinical varicella infections may have been missed.

The following chart shows the results for the -----b(4)----- measurements of individual subjects for the 3 study periods: Baseline, Day 2, and Closeout (which was approximately on day 42). The results are color-coded, blue denoting subjects judged to have clinical varicella outcomes, and orange denoting subjects judged not to have clinical varicella outcomes. The plotted data are the  $\text{Log}_{10}$  of the anti-VZV titer as, measured in the -----b(4)-----



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In the group judged not to have clinical varicella (orange lines), there are 4 subjects who have a 100-fold increase in their anti-VZV titer at Closeout compared to Baseline. These subjects are the following: -b(6)- VariZIG IV; -b(6)- VZIG IM; -b(6)- VariZIG IV; and -b(6)----- VZIG IM. (See [6.1.12.6](#) for the individual anti-VZ antibody titers.)

These 4 subjects may have had subclinical VZ infections.

In addition, the 6 highest baseline anti-VZV titers all occur in the group judged not to have had varicella; however, only the subject with the highest baseline value, -b(6)-, was judged to have been inappropriately enrolled into VZ-006, and was excluded from the analysis for this reason.

The applicant states (Dec. 7, 2012) that the -b(4)---- results were not specified in protocol VZ-006 to play a role in outcome analysis, and that the -b(4)----- has a high degree of variability in its results.

The anti-VZ antibody results further call into question the appropriateness of a prevention claim, because subclinical infections may have been missed by not considering these data. Note that some VZ virus infection rates following exposure reported in the literature have included both clinical evidence of infection in terms of physical signs and symptoms of chickenpox, as well as the finding of a 4-fold rise in antibody titer to VZ virus [Zaia J.A. et al., J. Inf. Dis. 147:737-743 (1983)].

Applicant's Analysis of the Constitutional Illness Score (CIS) in VZ-006

The original protocol VZ-006 stated that the primary endpoint was the CIS at day 7 after treatment. The CIS methodology was based on a study of the use of acyclovir to treat varicella patients [Wallace, et al. *Ann Int Med* 117:358-363 (1992)]. FDA requested justification for the day 7 endpoint in the context of the VZ-006 study design; however, this endpoint was never accepted by FDA as being adequately justified (see [Appendix 1](#), Chronology of Regulatory Events).

The VZ-006 study results showed that the day 7 CIS was zero for every subject, except subject -b(6)---- who was excluded from the analysis because the subject had varicella at study entry.

The applicant changed the time point for evaluation of the CIS to the time of clinical varicella (time of rash onset).

The [Constitutional Illness Score \(CIS\)](#) for subjects contracting varicella gave the following results:

**Applicant's Post Hoc Analysis of CIS Scores at the Time of Clinical Varicella**

Characteristic	Value	Treatment			Total (n=57)
		IM VZIG (n=19)	IM NP-001 (n=17)	IV NP-001 (n=21)	

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Characteristic	Value	Treatment			Total (n=57)
		IM VZIG (n=19)	IM NP-001 (n=17)	IV NP-001 (n=21)	
CIS Score	CIS 0 <sup>1</sup>	13 <sup>2</sup>	13 <sup>3</sup>	16 <sup>4</sup>	42
	CIS 1	0	0	2	2
	CIS 2	0	0	0	0
	CIS 3	1	0	1	2
	CIS 4	3	0	0	3
	CIS 5	0	1	0	1
	CIS 6	2	3	0	5
	CIS 7	0	0	2	2
Mean Weighted CIS Score		1.42	1.35	0.90	
Contracted Varicella <sup>5</sup>	No	11 (58%)	12 (71%)	15 (71%)	38 (67%)
	Yes	8 (42%)	5 (29%)	6 (29%)	19 (33%) <sup>6</sup>

1. Patients who did not develop clinical varicella were assigned a score of 0.

2. Patients –b(6)----- developed varicella and had a CIS score of 0.

3. Patient –b(6)---- developed varicella and had a CIS of 0.

4. Patient –b(6)----- developed varicella and had a CIS of 0.

5. Omnibus comparison between groups for overall incidence of varicella, p=0.040. No significant differences noted for any pairwise group comparison.

6. Between group comparison for positive varicella, p=0.643.

Source: Original BLA 125430/0; Clinical Study Report for study VZ-006 Vol 5.3.5.1, p.23

The applicant states the “comparison did not show significant differences between the test articles ( NP-001 and licensed VZIG) or between strata (length of exposure to VZV - 1-4 days or 5-14 days).” [Original BLA 125430/0; Clinical Study Report for study VZ-006 Vol 5.3.5.1, p.49]

This reviewer agrees with the applicant’s conclusion that significant differences are not seen between study arms or strata.

The applicant claims a demonstration of efficacy for amelioration of varicella symptoms, as measured by the CIS, by stating as follows (page 36 of the VZ-006 clinical report);

The mean weighted CIS at the time of varicella of 1.42 ( IM VZIG), 1.35 (NP-001 IM), and 0.90 (NP-001 IV) are significantly lower than the expected CIS of 2.8 in this group (Wallace 1992).

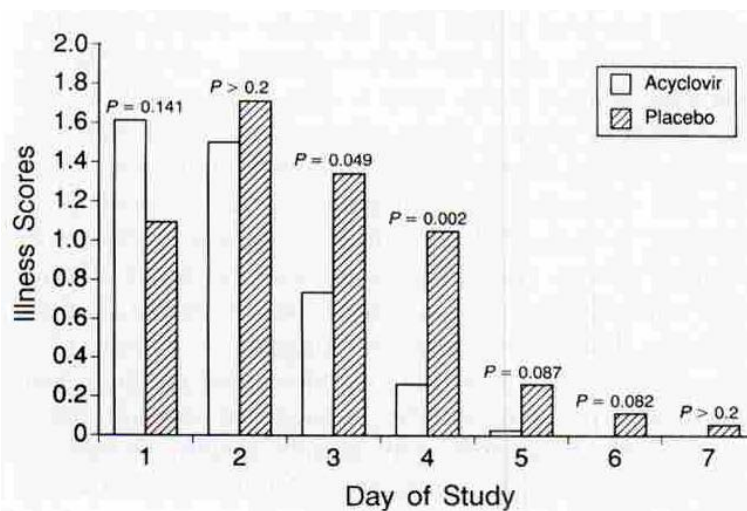
Regarding the derivation of the expected CIS of 2.8 in a historical control, the applicant states the following (page 12 of the VZ-006 clinical report):

Wallace et al. (1992) provided data to estimate the CIS standard deviation for patients one day after [acyclovir or placebo] treatment for a VZV infection; the mean CIS was 1.35

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and the pooled CIS standard deviation was 2.04. It is assumed that 70% of exposed patients will develop VZV infections and that the mean CIS will be 4 at Day 7 for patients developing infections and 0 otherwise; then the overall mean would be 2.8 and the standard deviation would range between 2.0 and 2.6. With 20 patients per treatment group, the sample size is adequate to detect a treatment group difference ranging from 1.8 to 2.4 with 80% power for a two-sided hypothesis test of the equality of the means with 5% Type I error.

The 1992 Wallace study, from which the CIS is adapted, was a study of the use of acyclovir to treat young adults who demonstrated varicella lesions within 24 hours prior to study entry. The following figure shows the CIS results of the Wallace study (*Ann Int Med* 117(5):358-362 (1992):



**Figure 2. Daily constitutional illness scores of patients treated within 24 hours.**

It can be seen that the applicant's claim that the mean of CIS at day 1 was 1.35 appears to be supported by the above figure. However, it is not clear how the applicant derives the assumption that "the mean CIS will be 4 at Day 7 for patients developing infections." FDA has not accepted the plan for analysis of the CIS.

Therefore, there is inadequate support from study VZ-006 for a claim that VariZIG lessens varicella symptoms based on the submitted data.

### Study VZ-006 Safety.

There were no deaths. There were 4 serious adverse events (worsening asthma – NP001 i.m. study arm; spontaneous abortion – 2 subjects – 1 in VZIG arm, 1 in NP001 im. Arm; therapeutic abortion).

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Tables of adverse events for study VZ-006 are given in [Appendix 3](#) (non-serious adverse events (NSAEs)) and [Appendix 4](#) (serious adverse events (SAEs)).

**VZ-009 – Expanded Access for High Risk Subjects.**

Study VZ-009 evaluated the incidence of varicella infection as the primary endpoint. Outcomes were compared to historical control rates.

This approach was not agreed upon with CBER.

The following table gives these results:

**Applicant's Table 11-6 Comparison of Incidence of Varicella in Subjects Treated with VariZIG and Historical Incidence of Varicella in Untreated Individuals**

High Risk Population	Historical Incidence of Varicella in Untreated Individuals	n <sup>1</sup>	Incidence of Varicella in VariZIG-treated Subjects	95% Confidence Interval	P-value <sup>2</sup>
Pregnant Women	70%	70	5.7% (n=4)	(1.6% - 14.0%) <sup>3</sup>	<.0001*
Immunocompromised patients	88%	153	5.2% (n=8)	(2.3% - 10.0%)	<.0001*
Infants including newborns, pre-term infants and infants <1 year	50%	78	12.8% (n=10)	(6.3% - 22.3%)	<.0001*

<sup>1</sup> n = number of VariZIG doses for post-exposure prophylaxis of varicella.

<sup>2</sup> One sample two-sided exact binomial test.

<sup>3</sup> Gray shading has been added to this cell by the reviewer to emphasize this result that appears to be substantially different than the outcomes reported for the maternal exposure study VZ-006. The reasons for this difference are not known.

\* Statistically significant ( $\alpha=0.05$ ).

Source: Original BLA 125430/0; Clinical Study Report for study VZ-009 Vol 5.3.5.1, p.48 of 306

FDA comment on the evaluation of efficacy in study VZ-009

Study VZ-009 was incompletely monitored and reported (see [Appendix 7](#)). Therefore, no statistical analysis comparing outcomes of VZ-009 to other outcome rates is meaningful.

**Study VZ-009 Safety.**

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Tables of adverse events for study VZ-009 are given in [Appendix 5](#) (non-serious adverse events) and [Appendix 6](#) (serious adverse events).

There were [6 serious adverse events due to coagulopathy](#) in Expanded Access study VZ-009.

Adverse event reporting was not uniform across study sites for study VZ-009. For example, on June 22, 2006, there was a varicella exposure incident in the NICU at Wesley Medical Center in Wichita, KS. Thirteen (13) premature infants were treated with VariZIG i.m., with adverse events (including 2 deaths) as shown in the following table:

**All received VariZIG 125 Units in 1.2 mL i.m.**

SUBJID	NSAE	SAE	Day after last dose
--b(6)----- --			
--b(6)----- --	Dermatitis Diaper		4
	Haematochezia		5
--b(6)----- --			
--b(6)----- --			
--b(6)----- --			
--b(6)----- --			
--b(6)----- --	Metabolic Acidosis		2
	Hypoalbuminaemia		6
--b(6)----- --	Hypothermia		5
	Sepsis		5
--b(6)----- --	Haematochezia		3
		Death [Bronchopulmonary Dysplasia]	6
--b(6)----- --		Intraventricular Haemorrhage	1
		Disseminated Intravascular Coagulation	2
		Convulsion	2
		Pulmonary	2

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SUBJID	NSAE	SAE	Day after last dose
		Haemorrhage	
		Death	3
--b(6)----- --	Sepsis		4
	Metabolic Acidosis		15
	Skin Disorder "Skin Breakdown"		21
--b(6)----- --		Staphylococcal Sepsis	3
		Coagulopathy	6
		Thrombocytopenia	6
	Convulsion		6
	Hypotension		8
	Pneumonia		9
	Metabolic Acidosis		9
	Adrenal Insufficiency		13
	Dermatitis Diaper		14
	Hydronephrosis		22
	Bronchopulmonary Dysplasia		25
	Staphylococcal Sepsis		25
	Pneumonia		28
	Necrotising Enterocolitis Neonatal		36
--b(6)----- --			

In contrast to this, a similar exposure to 9 premature infants at Winthrop University Hospital in Mineola, NY [VM-00510 to VM-00518] resulted in no adverse events being reported.

The above concerns about the monitoring and reporting of safety in VZ-009 were communicated to the applicant on October 4, 2012, and the applicant's response (see [Appendix 7](#)) states that VZ-009 was intended to address a shortage of varicella immune globulin products for high-risk

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patients, and that the incompleteness of the study databases was known and expected. The applicant stated that efforts to update the safety database for VZ-009 will continue.

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**Conclusions and Considerations.**

1. The results of VZ-006 support a claim of safety in varicella non-immune pregnant women exposed to varicella virus.
2. The results of VZ-006 do not support a claim for the prevention of varicella infection in varicella non-immune pregnant women exposed to varicella virus.
3. The results of VZ-006 do not support a claim for mitigation of the varicella disease process (as measured by reduction in the Constitutional Illness Score) in varicella non-immune pregnant women exposed to varicella virus.
4. Comparisons of VZ-006 safety and efficacy outcomes for VariZIG to VZIG outcomes were under-powered to detect differences. There was no pre-specified non-inferiority margin in the plan for analysis.
5. A conclusion of efficacy cannot be based on the VZ-006 study results, although these data can be supportive of other study data.
6. VZ-009, the expanded access study, was not designed to provide safety or efficacy data for product licensure, and the data for VZ-009 do not contribute to a substantial demonstration of safety or efficacy.
7. Post-exposure prophylaxis of high-risk varicella-naïve patients with immune globulin products containing antibodies against Varicella-Zoster Virus has become standard practice since the licensure of VZIG in 1981. A 1987 published review of all cases of varicella at St. Jude's Children's Hospital from March 1962 through 1986 [*Pediatrics* 80(4):465-475 (1987)] allowed a comparison of outcomes between the pre-VZIG era and the five-year period when VZIG was available. The authors state that in untreated immunocompromised children contracting varicella (N = 127), pneumonitis developed in 28% of cases; however, in a comparable group of children who received VZIG prophylaxis (N = 45), pneumonitis occurred in only 11% of cases. It is not possible to compare the rates of adverse events, such as pneumonitis, in study VZ-009 to rates reported in this paper because monitoring for adverse events in study VZ-009 was incomplete (see [Appendix 7](#)). In addition, the concomitant use of antivirals, such as acyclovir, would confound any such attempted comparison.
8. A pharmacokinetic comparison study VZ-008 of VariZIG and VZIG conducted in normal volunteers gave results that can be interpreted to demonstrate acceptably comparable outcomes (see review of Iftekhar Mahmood, Ph.D.).

**Recommendation.**

I recommend that VariZIG be licensed based on the results of the pharmacokinetics study VZ-008 that showed pharmacokinetic outcomes reasonably comparable to those of the licensed product VZIG can be achieved through appropriate dosing of VariZIG. Studies VZ-006 and VZ-009 can be considered supportive for safety, and they showed similar trends for efficacy

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outcomes for VariZIG and VZIG, although hypotheses based on pre-specified margins were not tested.

**Letter-ready final comments for the applicant:** [Post Marketing Commitment]

1. Please submit a final study report for a non-clinical study that examines whether and to what extent ----b(4)-----  
-----  
-----  
-----  
----- Please commit to a time frame for submission of the final report.
2. Please commit to a time frame for submitting the final study report for the --b(4)-----  
-----

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## 2. Clinical and Regulatory Background

Varicella Immune Globulin (VZIG)( Massachusetts Public Health Biologic Laboratories) was licensed in 1978. It is not available due to voluntary license withdrawal due to cessation of business activities. The following statements are excerpted from the year 2000 version of the VZIG package insert:

### **CLINICAL PHARMACOLOGY:**

- This product contains IgG class varicella-zoster antibodies representative of the contributions of the large number of normal persons who donated plasma to the pool from which the product was derived.
- Upon absorption into the circulation, the antibodies persist for one month or longer.
- The precise concentration of varicella-zoster antibodies that must be achieved or maintained in order to attenuate Varicella is not known.
- In the clinical studies demonstrating its efficacy, VZIG was given within 96 hours of chickenpox exposure (4,5).
  - When administered as described below, the product has been shown to significantly reduce mortality and morbidity from varicella among immunodeficient children.
  - Lack of treatment of such patients has been associated with
    - a mortality of 7%,
    - a pneumonia rate of 25%,
    - an encephalitis rate of 5%, and
    - widespread pox (more than 100 pox) in 87% (6,7).
- Clinical studies have shown that Varicella-Zoster Immune Globulin (Human) was able to significantly modify
  - the expected severity of chickenpox, and that
  - the observed frequencies of
    - death (1%),
    - pneumonia (6%),
    - encephalitis (0%), and
    - widespread pox (27%)
  - were less than one quarter of those observed in the past when hyperimmune globulin was not given (4).
- Although controlled clinical studies of VZIG efficacy in susceptible neonates, infants and healthy adults have not been done to date,
  - it is expected that VZIG will also attenuate VZV infection in these groups (8).

### **Pregnant Women.**

- Pregnant women may be at higher risk of complications of chickenpox than healthy adults (18).

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- They should be evaluated the same way as other adults.
- There is no evidence that administration of VZIG to a susceptible, pregnant woman will prevent
  - viremia,
  - fetal infection or
  - congenital varicella syndrome.
- Therefore the primary indication for VZIG in pregnant women is to prevent complications of varicella in a susceptible adult patient rather than to prevent intrauterine infection.
- Pregnant women should be evaluated for type of exposure and history of previous infection as described for healthy adults.

## 2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

See [Appendix 1](#) for a Chronology of Regulatory Events.

## 2.6 Other Relevant Background Information

IND 7201 was placed on clinical hold on July 24, 1997, for issues stated in a November 13, 1997 clinical hold letter, which are as follows:

1. The submitted protocol [VZ-006] is not designed to support licensure for use of this product to treat pregnant women who are exposed to Varicella/Zoster virus (VZV).

The primary endpoint, the Constitutional Illness Score (CIS) at day 7 is problematic because it apparently has subjective components which may confound an unblinded study, and because its evaluation at day 7 may not be appropriate for subjects who enroll immediately after VZV exposure (days 1-4).

We recommend that VZV infection rate be used as a primary endpoint for this trial, with infant infection/complication rate as an important secondary endpoint. Please comment.

2. The sample size may be inadequately justified due to erroneous assumptions about VZV transmission rates in the exposed patient population. Please submit or cross-reference clinical data which support the following assumptions upon which the proposed clinical study is based:
  - a. the assumption that 70% of the exposed subjects will become infected with varicella virus as evidenced by the primary endpoint measurement of the trial, and
  - b. the assumption that administration of VZIG can have an effect on disease outcome if given more than 96 hours after exposure to varicella.

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These assumptions affect the eligibility criteria, the determination of the subgroup in which the primary endpoint is evaluated for efficacy, and the calculation of sample size.

We note that a study by Enders (1994) reported much lower viral transmission rates after exposure to varicella.

3. Has the anti-VZ test kit that will be used to retrospectively exclude enrolled subjects based upon prior immunity to Varicella/Zoster been validated? If so, please submit or cross-reference the validation. If not, we recommend that the protocol be amended to specify that the analysis for efficacy will be on an intent-to-treat basis without retrospective eligibility exclusions for prior viral exposure. Please comment.
4. We recommend that the protocol exclude subjects who have a clinically diagnosed immunodeficiency, those who are immunosuppressed, or who have a defined level of thrombocytopenia.

The following comments concern clinical trial design and the statistical analysis plan:

5. We recommend that the protocol be amended to include blinding and other procedures to reduce bias. Please amend the protocol to specify the blinding procedures, including those for the outcome evaluators.
6. Please amend the Data Analysis Plan to clearly specify the subgroup in which the primary endpoint will be evaluated for efficacy.
7. We note that the data analysis plan does not allow for the evaluation of the stated objective of comparing the intravenous and intramuscular administration routes. Please comment.
8. For the purpose of an intent-to-treat analysis, what outcomes will be assigned to off-study subjects? We recommend that they be considered as treatment failures. Please comment.

### **3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES**

#### **3.1 Submission Quality and Completeness**

The Expanded Access Study VZ-009 was incompletely monitored, and not all data from completed subjects has been submitted. As a result, conclusions on safety and efficacy for study VZ-009 are difficult to derive from the database.

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#### 4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

##### 4.1 Chemistry, Manufacturing, and Controls

##### RELEASE SPECIFICATION

The batch release specification for VariZIG is shown in Table 1. Tests are performed at Cangene Corporation 155 Innovation Drive facility (Winnipeg, Manitoba, Canada) except where noted.

**Table 1 Release Specifications for VariZIG**

<b>Reference No.</b>		<b>7.4000</b>	
<b>Approval Date:</b>		<b>2012-01-15</b>	
<b>Test Parameter</b>	<b>Method Type</b>	<b>Method No.</b>	<b>Acceptance Criteria</b>
<b>Identity</b>			
--b(4)----- -----	--b(4)-----	--b(4)---	--b(4)----- -----
<b>Purity</b>			
--b(4)-----	--b(4)----- -----	--b(4)---	--b(4)---
<b>Impurities – Product Related</b>			
--b(4)-----	--b(4)----- -----	--b(4)---	--b(4)---
--b(4)-----	--b(4)----- -----	--b(4)---	--b(4)---
Immunoglobulin A	---b(4)-----	--b(4)---	≤40 µg/mL
--b(4)-----	---b(4)-----	--b(4)---	--b(4)----- ----- ----- -----
--b(4)-----	---b(4)-----	--b(4)---	--b(4)----- ----- ----- -----
--b(4)-----	---b(4)-----	--b(4)---	--b(4)----- ----- ----- -----
--b(4)----- -----	---b(4)-----	--b(4)---	--b(4)-----
<b>Impurities – Process Related</b>			
--b(4)----- -----	--b(4)----- -----	--b(4)---	--b(4)---
Bacterial Endotoxins	--b(4)---	--b(4)---	--b(4)---
TnBP --b(4)---	--b(4)---	--b(4)---	--b(4)---

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<b>Reference No.</b>		<b>7.4000</b>	
<b>Approval Date:</b>		<b>2012-01-15</b>	
<b>Test Parameter</b>	<b>Method Type</b>	<b>Method No.</b>	<b>Acceptance Criteria</b>
Triton X-100	--b(4)---	--b(4)---	--b(4)---
--b(4)---	--b(4)---	--b(4)---	--b(4)---
<b>Potency</b>			
--b(4)---	--b(4)---	--b(4)---	--b(4)---125 IU/vial
--b(4)---	--b(4)---	--b(4)---	--b(4)---
<b>Quantity</b>			
Total Protein	--b(4)---	--b(4)---	<250 mg/vial
<b>General Tests</b>			
pH	--b(4)---	--b(4)---	--b(4)---
pH (1%)	--b(4)---	--b(4)---	--b(4)---
General Safety Test <sup>b</sup>	--b(4)---	--b(4)---	Meets 21 CFR 610.11 requirements
Bulk Material Sterility <sup>a</sup>	--b(4)---	--b(4)---	Meets 21 CFR 610.12 requirements
Final Container Sterility	--b(4)---	--b(4)---	Meets 21 CFR 610.12 requirements
Polysorbate 80	--b(4)---	--b(4)---	--b(4)---
Glycine	--b(4)---	--b(4)---	--b(4)---
Chloride	--b(4)---	--b(4)---	--b(4)---
Reconstitution time	Visual	--b(4)---	<10 minutes

a The -----b(4)----- and --b(4)--- Material Sterility are performed on VariZIG DS but the results are reported with the final product.

b The General Safety Test is performed by --b(4)----- in compliance with --b(4)----- requirements.

Source: Original BLA 125430/0; Specifications Vol 3.2.P..5.1

## Potency

Potency units are assigned using a ---b(4)----- that detects antibodies directed against varicella-derived glycoproteins. The assay is conducted as follows:

- -----b(4)-----
- ---b(4)-----
- --b(4)-----
- ---b(4)-----

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- --b(4)--- -----  
-----  
-----

--b(4)-- -----

--b(4)-- -----  
-----

[ b(4) ]

--b(4)--- -----

--b(4)-- -----  
-----

**Lack of information on levels of anti-Protein S antibodies in product**

It is important to note that the submission does not measure the levels of anti-Protein S antibodies that have been reported to be present after varicella infection [*Journal of Pediatric Hematology/Oncology* (24)5:413-416 (2002)].

**4.4.1 Mechanism of Action**

VZ infection is controlled mainly through cell-mediated immunity. Anti-VZ antibodies may play a role in decreasing the extent of viral spread during periods of viremia, however this has not yet been confirmed in animal models or by clinical data.

**4.4.3 Human Pharmacokinetics (PK)**

See clinical pharmacology review memo of Iftekhar Mahmood, Ph.D. OBRR/DH.

**5. Sources of Clinical Data and Other Information Considered in the Review**

**5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review**

Protocols were submitted to IND 7201.

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5.3 Table of Studies/Clinical Trials

Type of Study	Study ID	Location of Study Report	Objective(s) of the Study	Study Design and type of Control	Test Product(s); Dosage Regimen; Route of Administration	No. of Subjects (N, total; n, treatment group)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	VZ-001	5.3.5.2	Primary: to assess safety of VariZIG.	Single center, Phase 1, open-label, no control	VariZIG; 625 IU; IM 50 IU/kg; IV	N = 10 n = 5	Healthy	Single dose	Complete; Full
Safety/Efficacy	VZ-003	5.3.5.4	Primary: to provide evidence of effectiveness of IV VariZIG in the reduction of post-herpetic neuralgia.	Single center, Phase 2, double-blind, randomized study, placebo control	VariZIG; 10 IU/kg; IV 50 IU/kg; IV Saline (placebo); 0.5 mL/kg; IV	N = 24 n = 6 n = 10 n = 8	Post-herpetic neuralgia patients	Single dose	Prematurely terminated; Abbreviated
Safety/Efficacy	VZ-006	5.3.5.1	Primary: to establish safety and effectiveness of VariZIG in preventing or ameliorating maternal infections with varicella zoster virus. <del>Secondary: to compare</del>	Multi-center, Phase 3, randomized, active control	VariZIG; 125 IU/10 kg, up to a maximum of 625 IU; IM 125 IU/10 kg, up to a maximum of 625 IU; IV VZIG; 125 IU/10 kg; IM	N = 60 n = 19 n = 22 n = 19	Pregnant women	Single dose	Complete; Full

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<b>Type of Study</b>	<b>Study ID</b>	<b>Location of Study Report</b>	<b>Objective(s) of the Study</b>	<b>Study Design and type of Control</b>	<b>Test Product(s); Dosage Regimen; Route of Administration</b>	<b>No. of Subjects (N, total; n, treatment group)</b>	<b>Healthy Subjects or Diagnosis of Patients</b>	<b>Duration of Treatment</b>	<b>Study Status; Type of Report</b>
BE	VZ-008	<b>5.3.1.2</b>	Primary: to establish comparative bioavailability (bioequivalence) of VariZIG and VZIG, following IM administration.	Single center, Phase 1, double-blind, randomized, parallel arm study	VariZIG; 12.5 IU/kg; IM VZIG; 12.5 IU/kg; IM	N = 35 n = 18  n = 17	Healthy	Single dose	Complete; Full
Safety/Efficacy	VZ-009	<b>5.3.5.1</b>	Primary: to provide VariZIG to high risk individuals in the USA and to collect safety and efficacy data for VariZIG.	Multi-center, Phase 3, open-label, expanded access protocol, historical efficacy control	VariZIG; 125 IU/10kg, up to a maximum dose of 625 IU; IM	N = 372 1	High risk individuals 2	Single dose 3	Ongoing; Interim

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## 5.4 Consultations

### 5.4.1 Advisory Committee Meeting

The July 21, 2005, Blood Products Advisory Committee meeting discussed potential paths to licensure for Varicella Immune Globulin products. See [Appendix 2](#) for the transcript.

### 5.4.2 External Consults/Collaborations

CBER/OBRR reviewers have consulted Philip Krause, M.D., OVRP, at various times since the original submission of IND 7201 in 1997 for advice on clinical and biological issues related to varicella-zoster infection (see [Appendix 1](#) Chronology of Regulatory Events).

## 5.5 Literature Reviewed

The “Wallace Algorithm” for the “CIS Score” that is used as the primary endpoint for study VZ-006 is taken from a study of the use of acyclovir to treat varicella infection in patients with verified infections [*Ann Intern Med* 117:358-363 (1992)].

In that study, 206 active duty Navy and Marine Corps patients (San Diego) who presented with verified varicella infection were randomized to acyclovir 800 mg p.o. 5X daily for 7 days, or to placebo. Enrollment was stratified by time since disease onset:

- < 24 hrs, or
- 25-72 hrs.

Subjects were monitored daily, for 7 days, for the following:

- Lesion counts [25cm x 25cm “pox box” on chest], calculating percent of lesions in the following categories:
  - maculopapular
  - vesicular
  - crusted
  - healed
- Symptom scores [Constitutional Illness Score (CIS)] obtained by daily summing of the severity scores for the following outcomes:
  - anorexia
  - lethargy
  - fever

[These complaints were graded as “none” – 0 points, “mild” – 1 point, “moderate” – 2 points, “severe” – 3 points; for fever: <37.8 °C – 0 points, 37.8 to 38.3 °C – 1 point, 38.4 to 39.4 °C – 2 points, >39.4 °C – 3 points]
- Temperature
- Lab tests to monitor disease course
  - White blood cell count
  - Hematocrit
  - Platelet count

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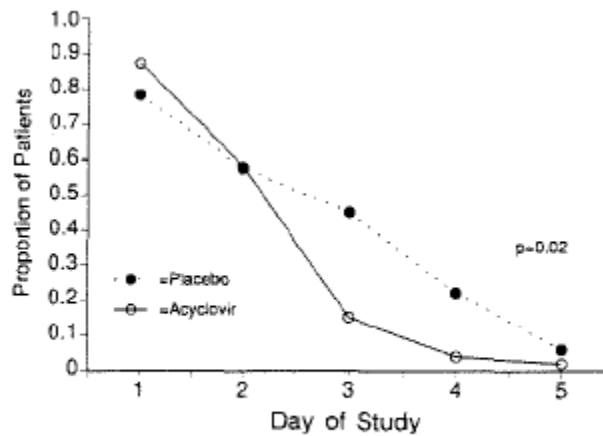
- Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase, blood urea nitrogen, and serum creatinine.

The following results were reported:

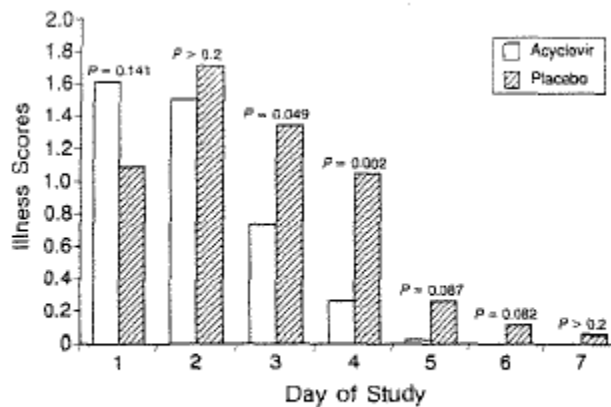
**Table 2. Cutaneous Effects of Varicella**

Variable	Early Group ( $\leq 24$ Hours)			Late Group (25 to 72 Hours)		
	Acyclovir ( $n = 38$ )	Placebo ( $n = 38$ )	<i>P</i> Value	Acyclovir ( $n = 36$ )	Placebo ( $n = 36$ )	<i>P</i> Value
Time to maximum number of skin lesions, <i>d</i>	1.5	2.1	0.002	1.3	1.2	$> 0.2$
Time of new lesion formation, <i>d</i>	2.7	3.3	0.03	3.0	2.3	0.03
Time to onset of cutaneous healing, <i>d</i>	2.6	3.3	$< 0.001$	2.4	2.3	$> 0.2$
Time to 100% crusting, <i>d</i>	5.6	7.4	0.001	7.0	6.8	$> 0.2$
Maximum number of lesions, <i>n</i> *	268	500	0.04	233	158	0.03

\* Wilcoxon rank-sum test. All other comparisons by log-rank test with median values from Kaplan-Meier product-limit plots.



**Figure 1. Proportion of patients with fever in the early treatment group, acyclovir compared with placebo.**



**Figure 2. Daily constitutional illness scores of patients treated within 24 hours.**

The authors made the following conclusions:

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- Early therapy with oral acyclovir decreases the time to cutaneous healing of adult varicella, decreases the duration of fever, and lessens symptoms.
- Initiation of therapy after the first day of illness is of no value in uncomplicated cases of adult varicella.
- The low frequency of serious complications of varicella (pneumonia, encephalitis, or death) precluded any evaluation of the possible effect of acyclovir on these outcomes.

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

Study VZ-006

“Randomized Trial of Varicella Zoster Immune Globulin (NP-001) to Prevent or Modify the Course of Varicella Zoster Virus Infection in Pregnant Women”

The study was conducted in Canada. The study was initiated before the sponsor filed IND 7201, which was placed on clinical hold for trial design issues. The sponsor inactivated IND 7201, continuing the study in Canada, and later re-activated the IND and occasionally sought advice from FDA on manufacturing and trial design issues.

### 6.1.1 Objectives (Primary, Secondary, etc)

- To compare safety and efficacy of intravenous and intramuscular routes of administration of VZIG.

### 6.1.2 Design Overview

Randomized, actively controlled (VZIG), comparing i.v. NP-001, i.m. NP-001, and licensed i.m. VZIG in prevention or amelioration of the sequelae of maternal varicella infection during pregnancy

The study was not blinded.

### 6.1.3 Population

#### Inclusion Criteria

1. Pregnant women without immunity to varicella zoster virus confirmed by a latex agglutination test.
2. Women who have had close contact with individuals infected with varicella.
3. Informed consent.
4. Knowledge of time and length of varicella exposure.
5. Willingness to fulfill requirements for participation in clinical study.

#### Exclusion Criteria

1. More than 14 days of known exposure to varicella.
2. History of hypersensitivity to blood products.
3. Disease with a potential risk of transmission *via* blood or plasma.

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4. Viral hepatitis at any time or in the absence of a history of hepatitis; exposure in the past 6 months to viral hepatitis.
5. History of malignancy.
6. Known immunity to VZV.
7. Vaccination to VZV.
8. Shingles.
9. Active acne that would interfere with assessments.
10. Infections other than varicella that would interfere with study assessments.
11. History of, or suspected, substance abuse.
12. Use of any investigational drug within the prior 3 months.
13. An opinion of the Investigator that it would be unwise to enroll the patient.

#### 6.1.4 Study Treatments or Agents Mandated by the Protocol

**NP-001** is an investigational sterile, freeze-dried gamma globulin fraction containing antibodies present in people at high levels after infection with the virus causing chickenpox (varicella). NP-001 is suitable for administration by IM or IV injection. Lot #0411502 and lot #0405601 were used.

**Licensed VZIG** was produced by the Massachusetts Public Health Biologic Laboratories and was licensed for sale by the US FDA in 1980 (but it is no longer available). This is a sterile, freeze-dried gamma globulin fraction containing antibodies present at high levels after infection with the virus causing chickenpox and it is suitable for IM injection only. The following lot numbers were used: MVZIG-56VI, MVZIG-58, MVZIG-59RF, MVZIG-62, and MVZIG-57.

Pregnant women without immunity to varicella zoster virus confirmed by latex agglutination test were stratified on the basis of time from first exposure (1-4 days or 5-14 days) and randomized to receive 125 units per 10 kg body weight to a maximum dose of 625 units of VZIG as

- a) licensed VZIG,
  - b) IM NP-001 or
  - c) IV NP-001
- Study drug was administered within 4 hours of reconstitution.
  - Subjects randomized to the IV arm of therapy had reconstituted NP-001 (625 units) infused into a suitable vein.
  - Subjects randomized to the IM NP-001 arm of therapy had reconstituted NP-001 given as a single or divided dosage of up to 625 units into a suitable muscle.
  - Subjects randomized to the Commercial VZIG arm of therapy had product administered IM as directed by package labelling. VZIG was administered only under the direct supervision of the investigator or a qualified subinvestigator previously identified to the Sponsor.
  - The date and time of administration of drug were recorded by the investigator or the subinvestigator for each study patient in this trial.
  - NP-001 was not to be used other than as specified in the protocol.

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### 6.1.6 Sites and Centers

	Investigator
Sick Children's Hospital, Toronto (Site Code: HSCTOR)	Dr. Gideon Koren
B.C. Women's Health Centre, Vancouver (Site Code: BCWHCV)	Dr. Deborah Money
CHILDREN'S HOSPITAL OF WESTERN Ontario, London (Site Code: CHWOLO)	Dr. Michael Rieder
Health Sciences Centre, Winnipeg (Site Code: HSCWPG)	Dr. Fred Aoki
Hopital Ste. Justine, Montreal (Site Code: HSJMON)	Dr. Marc Boucher

### 6.1.7 Surveillance/Monitoring

Study-eligible women were given a baseline assessment that included medical history, physical exam, and laboratory testing. After study drug administration, subjects returned to the study site for physical exam and varicella antibody test. Subjects returned for testing on days 7, 14 and 28, and whenever signs or symptoms of varicella infection were noted. A “close-out assessment” was done at 6 weeks after dosing. The following table shows these events:

**Schedule of Events**

	Screening	Baseline	Day 2	At time of Varicella Development <sup>2</sup>	Day 7 <sup>1</sup>	Day 14 <sup>1</sup>	Day 28 <sup>1</sup>	Close-out
Admission Criteria	X							
Informed Consent		X						
Medical History		X						
Maternal Anti-VZV Antibodies - Serological Screen	X							
Maternal Anti-VZV Antibodies-Titre		X	X					X

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Determination								
Physical Exam		X	X	X	X	X	X	X
Vital Signs		X	X	X	X			X
Hematology		X		X	X			X
Clinical Chemistry		X		X	X			X
Urinalysis		X		X	X			X
Adverse Events			X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X		X
Dosage Records		X						

Hematology Tests to include: RBC counts; hemoglobin, hematocrit; WBC counts and differential, platelet counts, reticulocytes.

Clinical Chemistry tests to include: albumin and total protein, alkaline phosphatase, ALT, total bilirubin, direct bilirubin, Creatinine. BUN.

Urinalysis to include: appearance and color, specific gravity, protein, glucose, pH, occult blood, microscopic examination.

Physical Exam to include signs, symptoms and severity of varicella infection of mother.

<sup>1</sup> Day 7, day 14, and day 28 assessments will be performed within one day of the scheduled time for these assays (eg. 27- 29 days for the 4 week assessment)

<sup>2</sup> If necessary.

## 6.1.8 Endpoints and Criteria for Study Success

### Primary Endpoint.

The primary endpoint changed from the original submission of IND 7201, which used the constitutional illness score (CIS), to later times during product development, which used number of infected subjects as the primary endpoint. The submission mentions both endpoints in different places in the submission.

The Wallace algorithm [*Ann Intern Med* 117:358-363 (1992)] for [constitutional illness scores \(CIS\)](#) at day 7 was the primary study endpoint in the original submission of IND 7201.

### Efficacy Variable(s)

The following efficacy variables were to be compared across study arms:

- the number of 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,
- stratum, and
- CIS at other post-Baseline evaluation times.

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## 6.1.9 Statistical Considerations & Statistical Analysis Plan

### Statistical and Analytical Plans

- Statistical analysis was done by –b(4)-----  
-----
- For determining the differences in incidence rates, the primary statistical test for between group comparisons was the Chi-square test.
- A survival-type analysis was undertaken to determine whether the time to clinical varicella differed among the three treatment groups. All tests are two sided.

### Determination of Sample Size

- Wallace et al.(1992) provided data to estimate the CIS standard deviation for patients one day after treatment for a VZV infection; the mean CIS was 1.35 and the pooled CIS standard deviation was 2.04.
- It is assumed that 70% of exposed patients will develop VZV infections and that the mean CIS will be 4 at Day 7 for patients developing infections and 0 otherwise; then the overall mean would be 2.8 and the standard deviation would range between 2.0 and 2.6.
- With 20 patients per treatment group, the sample size is adequate to detect a treatment group difference ranging from 1.8 to 2.4 with 80% power for a two-sided hypothesis test of the equality of the means with 5% Type I error.

## 6.1.10 Study Population and Disposition

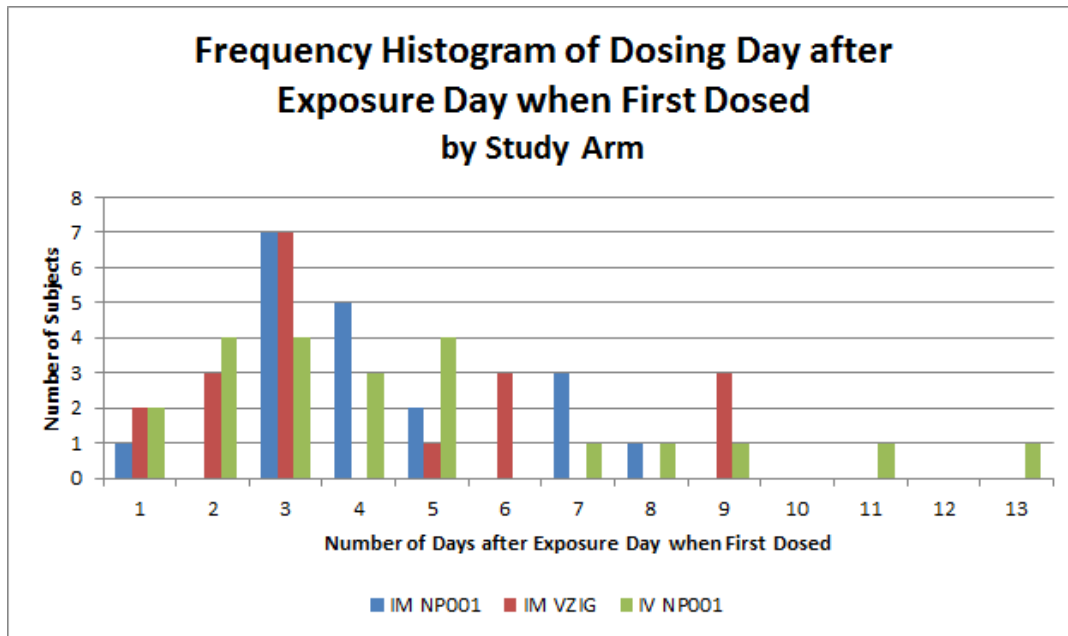
Sixty (60) pregnant women without immunity to varicella zoster virus confirmed by a latex agglutination test were stratified based on time from first exposure (1-4 days or 5-14 days), and randomized to treatment.

**Number of Subjects per Treatment Group**

<b>No. of Subjects in Group</b>	<b>Treatment</b>
19 (32%)	received a single IM administration of NP-001 at 625 units
22 (37%)	received a single IV infusion of NP-001 at 625 units
19 (32%)	received an IM administration of licensed VZIG (active control) at 625 units
<b>60 Total</b>	

The following frequency histogram shows the time from reported VZV exposure to the time of the first dose of varicella immune globulin, by study arm:

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- All of the patients enrolled were included in the intent-to-treat analysis of efficacy and in the analysis of safety;
- of these, 57 were included in the per-protocol analysis of efficacy.

Of 60 subjects treated with study medication, 10 subjects (17%) did not complete the study. The reasons for not completing the study are given by the sponsor as follows:

- Subject –b(6)-, did not come to the closeout visit of the study due to lack of transportation. She delivered her baby soon after.
- Subject –b(6)-----, had a therapeutic abortion and did not return for the follow-up visits.
- Subject –b(6)-----, failed to return for follow-up visits, telephone calls were unsuccessful in convincing the subject to complete study participation.
- Subject –b(6)-, found it difficult to return for assessments, because she was near delivery, so she voluntarily withdrew from the study.
- Subject –b(6)-, was on bed rest and could not come for the closeout visit.
- Subject –b(6)-----, had a spontaneous abortion and did not return for the follow-up visits.
- Subject –b(6)-----, delivered her baby during the study, and did not return for the follow-up visits.
- Subject –b(6)-----, stated that she was busy looking after her children and therefore could not come for the closeout visit.
- Subject –b(6)-, had a spontaneous abortion and did not return for follow-up visits.
- Subject –b(6)-, was withdrawn from study: did not meet entry criteria.

Three subjects were enrolled and treated, and then were found to not have met the eligibility criteria. The sponsor states, “the following three subjects should not have been enrolled in the study and were excluded from the analysis of efficacy. They were however, included in the intent-to-treat assessment of safety.”

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- Subject –b(6)-tested negative with the latex agglutination (LA) at the baseline assessment. During physical examination, four vesicles, one macule, and one crusted macule was observed. The subject was enrolled in the study and received study drug. The subject developed chickenpox rash the following day (Day-2 assessment).
- Subject –b(6)---was not tested for chickenpox antibodies with the LA test at the time of enrollment. The subject received study drug and was sent home. The following day, when the laboratory performed LA screening it was positive and the Investigator withdrew the subject from the study.
- For Subject –b(6)-----, the results of antibody screening from the laboratory was verbally reported as "non-reactive." The subject was enrolled in the trial, and received study drug. Upon receipt of the hard copy of the laboratory report, however, it was noted that the result was "reactive."

### 6.1.10.1 Populations Enrolled/Analyzed

#### 6.1.10.1.1 Demographics

**Patient Characteristics by Treatment**

Characteristic	Value	Treatment			Total (n=57)	P- Value <sup>2</sup>
		IM VZIG (n=19)	IM NP-001 (n=17)	IV NP-001 (n=21)		
Age (years)	Mean ± SD Range	28.68±4.0 19-35	29.18±6.0 20-41	31.48±5.6 23-46	30.03±5.5 19-46	0.210
Height (cm)	Mean ± SD Range	162.32±6.9 152-178	165.53±7.4 155-178	161.57±7.7 147-178	162.77±7.4 147-178	0.235
Weight (kg)	Mean ± SD Range	68.24±16.0 47-109	67.54±8.4 53-85	66.98± 15.3 43-104	67.22±13.4 43-109	0.959
Type of Contact	Direct with lesions	0 (0%)	2 (12%)	0 (0%)	2 (4%)	0.440
	Household	15 (79%)	9 (53%)	15 (71 %)	39 (68%)	
	Workplace	1 (5%)	2 (12%)	2 (10%)	5 (9%)	
	Daycare	1 (5%)	2 <sup>1</sup> (12%)	0 (0%)	3 (5%)	
	Other	2 (10%)	2 (12%)	4 (19%)	8 (14%)	
Days Since Contact	0	1 (5%)	1 (6%)	0 (0%)	2 (3%)	0.645
	1-4	10 (53%)	11 (65%)	13 (62%)	34 (60%)	
	5-8	4 (21%)	5 (29%)	6 (29%)	15 (26%)	
	9-14	3 (16%)	0 (0%)	2 (9%)	5 (9%)	
	Not recorded	1 (5%)	0 (0%)	0 (0%)	1 (2%)	
Duration of	< 3 hrs	3 (16%)	6 (35%)	5 (24%)	14 (25%)	0.244

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Characteristic	Value	Treatment			Total (n=57)	P- Value <sup>2</sup>
		IM VZIG (n=19)	IM NP-001 (n=17)	IV NP-001 (n=21)		
Exposure	3-12 hrs	2 (10%)	3 (18%)	7 (33%)	12 (21%)	
	> 12 hrs	13 (68%)	8 (47%)	8 (38%)	29 (51%)	
	Not recorded	1 (5%)	0 (0%)	1 (5%)	2 (4%)	
Age Group	< 20	1 (5%)	0 (0%)	0 (0%)	1 (2%)	0.780
	21-29	9 (47%)	7 (41%)	7 (33%)	23 (40%)	
	31-39	9 (47%)	9 (53%)	13 (62%)	31 (54%)	
	> 41	0 (0%)	1 (6%)	1 (5%)	2 (4%)	
Ethnicity	Caucasian	12 (63%)	14 (82%)	16 (76%)	42 (74%)	0.799
	Black	1 (5%)	0 (0%)	0 (0%)	1 (2%)	
	Hispanic	0 (0%)	0 (0%)	1 (5%)	1 (2%)	
	Asian	2 (10%)	0 (0%)	1 (5%)	3 (5%)	
	Other	4 (21%)	3 (18%)	3 (14%)	10 (18%)	
Gestation Week	0-12 wks	6 (32%)	6 (35%)	9 (43%)	21 (18%)	0.847
	13-24 wks	6 (32%)	6 (35%)	5 (24%)	7 (30%)	
	>24	7 (37%)	5 (29%)	7 (33%)	19 (33%)	
Strata	1-4 days	11 (58%)	11 (65%)	12 (57%)	34 (60%)	--
	5-14 days	8 (42%)	6 (35%)	9 (43%)	23 (40%)	

<sup>1</sup>One patient also had household contact.

<sup>2</sup>Omnibus test among the three groups.

Adapted from: Original BLA 125430/0; Clinical Study Report for study VZ-006 Vol 5.3.5.1, p.20

### 6.1.10.1.3 Subject Disposition

Sixty (60) women enrolled, and 3 were excluded from the efficacy analysis due to inappropriate enrollment (subjects –b(6)----- were immune at baseline; -b(6)---- had active varicella infection at enrollment).

### 6.1.11.1 Analyses of Primary Endpoint(s)

#### Signs and Symptoms in Patients who Contracted Varicella (n=19)

### 6.1.11 Efficacy Analyses

ID	Strata & Drug	Visit	Days from Randomization	Pruritus	Anorexia	Lethargy	Temperature
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ID	Strata & Drug	Visit	Days from Randomization	Pruritus	Anorexia	Lethargy	Temperature
--b(6)----- --	1 IM NP-001	Day 14 (97.10.29) Clinical Varicella Day 28 Closeout	14 15 42 30	None Moderate Mild None	Mild Moderate None None	Mild Moderate None None	<37.8 <37.8 <37.8 <37.8
-b(6)-----	1 IM NP-001	Clinical Varicella (97.05.24) Day 28	18 28 40	Severe	Mild None	Moderate None	<37.8 <37.8
--b(6)--	1 IM COMM VZIG	Day 14	14	Moderate	Mild	Mild	<37.8
--b(6)-----	1 IM COMM VZIG	Day 14 (97.06.16) Day 28 Closeout	14 29 43	Mild None None	Mild None None	Mild None None	<37.8 <37.8 <37.8
--b(6)-----	1 IV NP-001	Day 28 (97.08.01) Closeout	28 46	None None	None None	None None	<37.8 <37.8
--b(6)-----	1 IV NP-001	Day 14 (97. 10.14) Day 28 Closeout	13 27	Mild None None	Severe None None	Severe None None	<37.8 <37.8
--b(6)-----	1 IM NP-001	Day 14 (98.01.28) Day 28 Closeout	14 28 42	None None None	None None None	None None None	<37.8 <37.8 <37.8
--b(6)--	1 IV NP-001	Clinical Varicella	12	None	None	Mild	<37.8
-b(6)-----	1 IM COMM VZIG	Clinical Varicella Day 28	21 27	Severe None	None None	Mild None	<37.8 <37.8
--b(6)-----	1 IM NP-001	Day 14 Day 28	16 28	None None	Mild None	Severe None	37.8 to 38. <37.8
-b(6)--	1 IM COMM VZIG	Clinical Varicella	12	None	None	None	<37.8
--b(6)-----	1 IM COMM VZIG	Clinical Varicella Day 28 Closeout	15 27 42	None Mild None	Moderate None None	Mild None None	>39.4 <37.8 <37.8
-b(6)---	1 IM NP-001	Day 2 Day 7 Day 14	2 7 14	Mild Mild None	Mild None None	Mild Mild None	<37.8 <37.8 <37.8

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ID	Strata & Drug	Visit	Days from Randomization	Pruritus	Anorexia	Lethargy	Temperature
--b(6)-----	2 IM COMM VZIG	Clinical Varicella (97.02.09) Day 28 Closeout	18 29 42	Moderate None None	Moderate None None	Moderate None None	<37.8 <37.8 <37.8
-b(6)--	2 IV NP-001	Clinical Varicella (97.11.17)	12	Severe	Moderate	Moderate	<37.8
--b(6)-----	2 IM COMM VZIG	Day 14 (97.12.26) Day 28 Closeout	20 31 41	None None None	None None None	None None None	<37.8 <37.8 <37.8
--b(6)-----	2 IV NP-001	Clinical Varicella Day 14 Closeout	11 17 41	Mild None None	None None None	Mild None None	37.8 to 38. <37.8 <37.8
--b(6)-----	2 IM COMM VZIG	Day 14 Day 28 Closeout	14 24 41	Severe Severe Mild	Mild Severe None	None Severe None	<37.8 38.4 to 39. <37.8
--b(6)-----	2 IV NP-001	Day 14 Day 28 Closeout	14 28 49	Mild None None	None None None	None None None	<37.8 <37.8 <37.8
-b(6)--	2 IM NP-001	Clinical Varicella	18	Mild	Moderate	Moderate	37.8 to 38.

<sup>1</sup>Subject --b(6)--- had clinical varicella at baseline and therefore should not have been enrolled in the study.

Source: Original BLA 125430/0; Clinical Study Report for study VZ-006 Vol 5.3.5.1, p.32

The gray background denotes subjects ----b(6)----- who are reported to have experienced clinical varicella, although all CIS scores were zero; these subjects did have pocks that were clinically judged to be varicella.

**Distribution of Symptoms Among all Patients (n=57)**

		IMVZIG (n=19)	IM NP001 (N=17)	IV NP001 (n=21)	p-Value
Pruritus:	None	14	14	17	0.732
	Mild	1	1	3	
	Moderate	2	1	0	
	Severe	2	1	1	
Anorexia:	None	14	13	19	0.468
	Mild	3	2	0	
	Moderate	2	2	1	
	Severe	0	0	1	

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		<b>IMVZIG (n=19)</b>	<b>IM NP001 (N=17)</b>	<b>IV NP001 (n=21)</b>	<b>p-Value</b>
Lethargy:	None	14	13	17	0.884
	Mild	4	0	2	
	Moderate	1	3	1	
	Severe	0	1	1	
Temperature:	<37.8°	18	15	21	0.639
	37.8 to 38.3°	0	2	1	
	>39.4°	1	0	0	

Source: Original BLA 125430/0; Clinical Study Report for study VZ-006 Vol 5.3.5.1, p.22

**Analysis of CIS Scores at the Time of Clinical Varicella**

Characteristic	Value	Treatment			Total (n=57)
		<b>IM VZIG (n=19)</b>	<b>IM NP-001 (n=17)</b>	<b>IV NP-001 (n=21)</b>	
CIS Score	CIS 0 <sup>1</sup>	13 <sup>2</sup>	13 <sup>3</sup>	16 <sup>4</sup>	42
	CIS 1	0	0	2	2
	CIS 2	0	0	0	0
	CIS 3	1	0	1	2
	CIS 4	3	0	0	3
	CIS 5	0	1	0	1
	CIS 6	2	3	0	5
	CIS 7	0	0	2	2
Mean Weighted CIS Score		1.42	1.35	0.90	
Contracted Varicella <sup>5</sup>	No	11 (58%)	12 (71%)	15 (71%)	38 (67%)
	Yes	8 (42%)	5 (29%)	6 (29%)	19 (33%) <sup>6</sup>

1. Patients who did not develop clinical varicella were assigned a score of 0.

2. Patients –b(6)----- developed varicella and had a CIS score of 0.

3. Patient –b(6)---- developed varicella and had a CIS of 0.

4. Patient –b(6)---- developed varicella and had a CIS of 0.

5. Omnibus comparison between groups for overall incidence of varicella, p=0.040. No significant differences noted for any pairwise group comparison.

6. Between group comparison for positive varicella, p=0.643.

Source: Original BLA 125430/0; Clinical Study Report for study VZ-006 Vol 5.3.5.1, p.23

**CIS Scores for Subjects with Clinical Varicella; mean (range)**

		Treatment					
		<b>IM VZIG (n=8)</b>		<b>IM NP-001 (n=5)</b>		<b>IV NP-001 (n=6)</b>	
	Strata	N		N		N	
Days of Clinical	1 (1-4 days)	5	3.4 (0-6)	4	4.3 (0-6)	3	2.7 (0-7)

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		Treatment					
		IM VZIG (n=8)		IM NP-001 (n=5)		IV NP-001 (n=6)	
Varicella							
	2 (5-14 days)	3	3.3 (0-6)	1	6	3	3.7 (1-7)

The following table shows the CIS for individual subjects at the various study periods:

	Stratum	Subject ID	Screening	Baseline	Day 2	Day 7	Day 14	Day 28	Closeout	At Time of Varicella Development
VariZIG IM	Days 1 - 4	-b(6)--	0	0	0	0	2	0	0	4
		-b(6)--	0	0	0	0	0	0	0	
		-b(6)--	0	0	0	0	0	0	0	3
		-b(6)--	0	0	0	0	0	0	0	
		-b(6)--	0	0	0	0		0	0	
		-b(6)--	0	0	0	0	0	0	0	0
		-b(6)--	0	0	0	0	0	0	0	
		-b(6)--	0	0	0	0	0			4
		-b(6)--	0	0	0	0	0			
		-b(6)--	2	2	2	1	0		0	
	Days 5 - 14	-b(6)--	0	0	0	0	0	0	0	
		-b(6)--	0	0	0	0	0		0	
		-b(6)--	0	0		0				
		-b(6)--	0	0						
		-b(6)--		0	0	0	0			
		-b(6)--	0	0	0	0	0	0	0	5
VZIG IM	Days 1 - 4	-b(6)--	0	0	0	0	0	0	0	
		-b(6)--	0	0	0	0	0	0	0	
		-b(6)--	0	0	0	0	2			2
		-b(6)--	0	0	0	0	2	0	0	2
		-b(6)--	0	0	0					
		-b(6)--	0	0	0	0		0	0	
		-b(6)--	0	0	0	0	0	0	0	
		-b(6)--				0	0	0		1
		-b(6)--								0
		-b(6)--	0	0	0	0	0	0	0	6
	Days 5 - 14	-b(6)--	0	0	0	0	0	0	0	4
		-b(6)--	0	0	0	0			0	
		-b(6)--	0	0	0	0			0	
		-b(6)--		0	0	0	0	0	0	
		-b(6)--					1	8	0	1
		-b(6)--	0	0	0	0	0		0	
		-b(6)--	0	0	0	0	0	0	0	

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At Time of Varicella Development	Closeout	Day 28	Day 14	Day 7	Day 2	Baseline	Screening	Subject ID	Stratum	
	0	0	0	0	0	0	0	-b(6)--		
	0	0	0	0	0	0	0	-b(6)--		
	0	0	0	0	0	0	0	-b(6)--		
	0	0	0	0	0	0	0	-b(6)--		
	0	0	0		0	0	0	-b(6)--		
6	0	0	6	0	0	0	0	-b(6)--		
	0			0	0	0	0	-b(6)--		
	0	0	0	0	0	0		-b(6)--		
1								-b(6)--		
	0		0	0	0	0		-b(6)--		
				0	0	0		-b(6)--		
	0	0	0	0	0	0	0	-b(6)--		
	0	0	0	0	0	0	0	-b(6)--		
4					0	0	0	-b(6)--		
2	0		0					-b(6)--		
		0						-b(6)--		
	0	0	0	0	0	0	0	-b(6)--		
	0	0	0	0	0	0	0	-b(6)--		
	0	0	0	0	0	0	0	-b(6)--		
	0	0	0	0	0	0	0	-b(6)--		

6.1.12 Safety Analyses

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6.1.12.2 Overview of Adverse Events

IM and IV NP-001 Adverse Events

	IM COMM VZIG Number of Subjects= 19				IM NP-001 Number of Subjects= 19				IV NP-001 Number of Subjects= 22			
	Events		Subjects Reporting Event		Events		Subjects Reporting Event		Events		Subjects Reporting Event	
Preferred Term	All	Related	All	Related	All	Related	All	Related	All	Related	All	Related
<b>Adverse Events</b>	40	14	16	11	38	12	15	10	42	6	16	3
<b>Body as a Whole</b>	22	12	14	11	21	12	13	10	14	1	9	1
Asthenia	0	0	0	0	1	1	1	1	2	0	2	0
Chills	0	0	0	0	2	0	2	0	0	0	0	0
Fever	2	0	2	0	2	0	1	0	2	0	2	0
Flu Syndrome	0	0	0	0	2	0	2	0	0	0	0	0
Headache	4	2	2	2	4	3	4	3	4	0	2	0
Infection	1	0	1	0	3	0	3	0	2	0	2	0
Injection Site Reaction	1	1	1	1	0	0	0	0	2	1	2	1
Malaise	1	0	1	0	0	0	0	0	0	0	0	0
Neck Rigid	1	0	1	0	0	0	0	0	0	0	0	0
Pain	3	0	2	0	0	0	0	0	0	0	0	0
Pain Abdomen	0	0	0	0	0	0	0	0	1	0	1	0
Pain Back	0	0	0	0	0	0	0	0	1	0	1	0
Pain Chest	0	0	0	0	1	0	1	0	0	0	0	0
Pain Injection Site	9	9	9	9	8	8	8	8	0	0	0	0
<b>Cardiovascular System</b>	0	0	0	0	1	0	1	0	1	0	1	0

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	IM COMM VZIG Number of Subjects= 19				IM NP-001 Number of Subjects= 19				IV NP-001 Number of Subjects= 22			
	Events		Subjects Reporting Event		Events		Subjects Reporting Event		Events		Subjects Reporting Event	
Preferred Term	All	Related	All	Related	All	Related	All	Related	All	Related	All	Related
Cardiovascular Disease	0	0	0	0	0	0	0	0	1	0	1	0
Migraine	0	0	0	0	1	0	1	0	0	0	0	0
<b>Digestive System</b>	4	1	3	1	2	0	2	0	10	1	8	1
Anorexia	0	0	0	0	0	0	0	0	2	0	2	0
Diarrhea	0	0	0	0	0	0	0	0	1	0	1	0
Gastrointestinal Disease	0	0	0	0	0	0	0	0	1	0	1	0
Nausea	3	1	3	1	2	0	2	0	4	1	4	1
Vomit	1	0	1	0	0	0	0	0	2	0	2	0
<b>Hemic and Lymphatic System</b>	1	0	1	0	0	0	0	0	1	1	1	1
Ecchymosis	0	0	0	0	0	0	0	0	1	1	1	1
Lymphadenopathy	1	0	1	0	0	0	0	0	0	0	0	0
<b>Metabolic and Nutritional Disease</b>	2	0	2	0	1	0	1	0	2	0	2	0
Edema	0	0	0	0	1	0	1	0	0	0	0	0
Edema Peripheral	1	0	1	0	0	0	0	0	0	0	0	0
Phosphatase Alkaline Increase	0	0	0	0	0	0	0	0	1	0	1	0
Weight	1	0	1	0	0	0	0	0	1	0	1	0

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	IM COMM VZIG Number of Subjects= 19				IM NP-001 Number of Subjects= 19				IV NP-001 Number of Subjects= 22			
	Events		Subjects Reporting Event		Events		Subjects Reporting Event		Events		Subjects Reporting Event	
Preferred Term	All	Related	All	Related	All	Related	All	Related	All	Related	All	Related
Decrease												
<b>Musculoskeletal System</b>	0	0	0	0	0	0	0	0	1	1	1	1
Myalgia	0	0	0	0	0	0	0	0	1	1	1	1
<b>Nervous System</b>	2	1	2	1	1	0	1	0	5	1	4	1
Dizziness	2	1	2	1	0	0	0	0	0	0	0	0
Hypertonia	0	0	0	0	0	0	0	0	1	0	1	0
Insomnia	0	0	0	0	1	0	1	0	1	0	1	0
Somnolence	0	0	0	0	0	0	0	0	2	0	2	0
Vasodilat	0	0	0	0	0	0	0	0	1	1	1	1
<b>Respiratory System</b>	3	0	2	0	6	0	5	0	1	0	1	0
Asthma	1	0	1	0	2	0	2	0	0	0	0	0
Cough Increase	1	0	1	0	2	0	2	0	0	0	0	0
Epistaxis	0	0	0	0	1	0	1	0	0	0	0	0
Pharyngitis	1	0	1	0	1	0	1	0	1	0	1	0
<b>Skin and Appendages</b>	3	0	2	0	4	0	4	0	3	1	3	1
Acne	1	0	1	0	0	0	0	0	0	0	0	0
Pruritus	0	0	0	0	2	0	2	0	1	1	1	1
Rash	0	0	0	0	2	0	2	0	1	1	1	1
Rash Maculopapular	1	0	1	0	0	0	0	0	0	0	0	0
Rash Vesiculobullous	1	0	1	0	0	0	0	0	0	0	0	0

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	IM COMM VZIG Number of Subjects= 19				IM NP-001 Number of Subjects= 19				IV NP-001 Number of Subjects= 22			
	Events		Subjects Reporting Event		Events		Subjects Reporting Event		Events		Subjects Reporting Event	
Preferred Term	All	Related	All	Related	All	Related	All	Related	All	Related	All	Related
Special Senses	1	0	1	0	1	0	1	0	1	0	1	0
Corneal Lesion	1	0	1	0	0	0	0	0	0	0	0	0
Otitis Media	0	0	0	0	1	0	1	0	0	0	0	0
Taste Perversion	0	0	0	0	0	0	0	0	1	0	1	0
Urogenital System	2	0	2	0	1	0	1	0	3	0	3	0
Abortion	2	0	2	0	0	0	0	0	1	0	1	0
Hemorrhage Vaginal	0	0	0	0	0	0	0	0	2	0	2	0
Infection Urinary Tract	0	0	0	0	1	0	1	0	0	0	0	0

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### 6.1.12.3 Deaths

There were no deaths.

### 6.1.12.4 Nonfatal Serious Adverse Events

See [Appendix 4](#).

### 6.1.12.5 Adverse Events of Special Interest (AESI)

There were no cases of varicella pneumonitis.

### 6.1.12.6 Clinical Test Results

Anti-VZ antibody titers were measure at baseline, day 2, and at 'closeout' (approximately day 42). These data were not used to classify outcomes (see Executive Summary). The following table gives the Log<sub>10</sub> anti-VZ titers measured in the –b(4)-----

			Log <sub>10</sub> –b(4)----- Titer by Period			
Clinical Varicella?	Study Arm	Subject ID	Baseline	Day 2	Closeout	> 100 X Baseline at Closeout
No	IM VZIG	--b(6)--	0	1.612784	2.889302	1
No	IM VZIG	--b(6)--	2.401401	2.522444	4.524889	1
No	IV NP001	--b(6)--	1.041393	1.908485	3.209783	1
No	IV NP001	--b(6)--	0	1.973128	2.622214	1
No	IM NP001	--b(6)--	2.041393	2.130334	1.995635	0
No	IM NP001	--b(6)--	1.361728	1.919078	1.60206	0
No	IM NP001	--b(6)--	0.30103	1.643453		0
No	IM NP001	--b(6)--	0.30103	1.544068	1.278754	0
No	IM NP001	--b(6)--	0.954243	1.414973		0
No	IM NP001	--b(6)--	1.041393	1.380211	1.69897	0
No	IM	--b(6)--	0.778151	1.361728	1.146128	0

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			Log <sub>10</sub> –b(4)----- Titer by Period			
Clinical Varicella?	Study Arm	Subject ID	Baseline	Day 2	Closeout	> 100 X Baseline at Closeout
	NP001					
No	IM NP001	--b(6)--	1.176091	1.531479	1.230449	0
No	IM NP001	--b(6)--	0.477121	1.414973	1.146128	0
No	IM NP001	--b(6)--	0.477121	1.477121		0
No	IM NP001	--b(6)--	0.477121	1.591065	1.255273	0
No	IM NP001	--b(6)--	0.69897	1.544068	1.20412	0
No	IM VZIG	--b(6)--	2.857332	2.802089	2.821514	0
No	IM VZIG	--b(6)--	1.113943	1.755875	1.623249	0
No	IM VZIG	--b(6)--	0	1.518514		0
No	IM VZIG	--b(6)--	0	1.623249	1.079181	0
No	IM VZIG	--b(6)--	0	1.69897	1.146128	0
No	IM VZIG	--b(6)--	1	1.643453	1.518514	0
No	IM VZIG	--b(6)--	0.30103	1.230449	0.90309	0
No	IM VZIG	--b(6)--	0.477121	1.491362	1.30103	0
No	IM VZIG	--b(6)--	2.609594	2.624282	2.507856	0
No	IV NP001	--b(6)--	0.30103	1.763428	1.20412	0
No	IV NP001	--b(6)--	0.69897	2.252853	1.113943	0
No	IV NP001	--b(6)--	1.079181	2.133539		0
No	IV NP001	--b(6)--	0.845098	1.968483	1.30103	0
No	IV NP001	--b(6)--	0	1.716003	0.90309	0

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			Log <sub>10</sub> –b(4)----- Titer by Period			
Clinical Varicella?	Study Arm	Subject ID	Baseline	Day 2	Closeout	> 100 X Baseline at Closeout
No	IV NP001	--b(6)--	1.612784	2.274158	1.763428	0
No	IV NP001	--b(6)--	0.477121	1.982271	1.653213	0
No	IV NP001	--b(6)--	0.477121	1.653213	1.113943	0
No	IV NP001	--b(6)--	0.69897	2.053078	1	0
No	IV NP001	--b(6)--	0.69897	1.919078	1.342423	0
No	IV NP001	--b(6)--	0.90309	2.311754		0
No	IV NP001	--b(6)--	0.60206	2.357935	1.60206	0
No	IV NP001	--b(6)--	2.55145	2.691081	2.453318	0
No	IV NP001	--b(6)--	2.912753	3.107888	3.100715	0
Yes	IM NP001	--b(6)--	0.778151	1.20412	3.576457	1
Yes	IM NP001	--b(6)--	1.20412	1.531479	3.852236	1
Yes	IM VZIG	--b(6)--	0	1.462398	3.301247	1
Yes	IM VZIG	--b(6)--	1.322219	1.322219	3.468347	1
Yes	IM VZIG	--b(6)--	0.477121	1.70757	3.375298	1
Yes	IM VZIG	--b(6)--	0.778151	1.544068	3.779669	1
Yes	IV NP001	--b(6)--	0.30103	1.880814	3.017868	1
Yes	IV NP001	--b(6)--	0.477121	1.880814	2.666518	1
Yes	IV NP001	--b(6)--	1	2.444045	3.055378	1
Yes	IM NP001	--b(6)--	1.361728	1.819544	2.755112	0
Yes	IM	--b(6)--	0.954243	1.531479		0

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			Log <sub>10</sub> -b(4)----- Titer by Period			
Clinical Varicella?	Study Arm	Subject ID	Baseline	Day 2	Closeout	> 100 X Baseline at Closeout
	NP001					
Yes	IM NP001	--b(6)--	0.477121	1.278754	2.255273	0
Yes	IM NP001	--b(6)--	1.447158	1.919078	3.116608	0
Yes	IM VZIG	--b(6)--	0.954243	1.70757		0
Yes	IM VZIG	--b(6)--	0.60206	1.892095	2.568202	0
Yes	IM VZIG	--b(6)--	1.740363	2.120574		0
Yes	IM VZIG	--b(6)--	1.255273	1.447158	3.24403	0
Yes	IV NP001	--b(6)--	0.69897	2.152288	2.555094	0
Yes	IV NP001	--b(6)--	1.716003	2.037426	1.995635	0
Yes	IV NP001	--b(6)--	0.60206	1.886491		0

#### 6.1.12.7 Dropouts and/or Discontinuations

Three subjects were excluded from the efficacy analysis because of inappropriate enrollment (subjects ---b(6)----- were immune at baseline; -b(6)-- had active varicella infection at enrollment).

## 6.2 Trial #2 Study VZ-009

“Safety and Efficacy of Varicella Zoster Immune Globulin (Human) (VariZIG™) in Patients At-Risk of Varicella Infection”

### Objectives (Primary, Secondary, etc)

- to outline the handling and use of VariZIG which is distributed by FFF Enterprises under the Expanded Access IND
- to collect safety and efficacy data for VariZIG

### 6.2.2 Design Overview

Study VZ-009 was an open-label Expanded Access Protocol to provide VariZIG to high risk subjects following exposure to VZV in the USA. The study was conducted by the U.S. distributor of the product, FFF Enterprises, Inc.

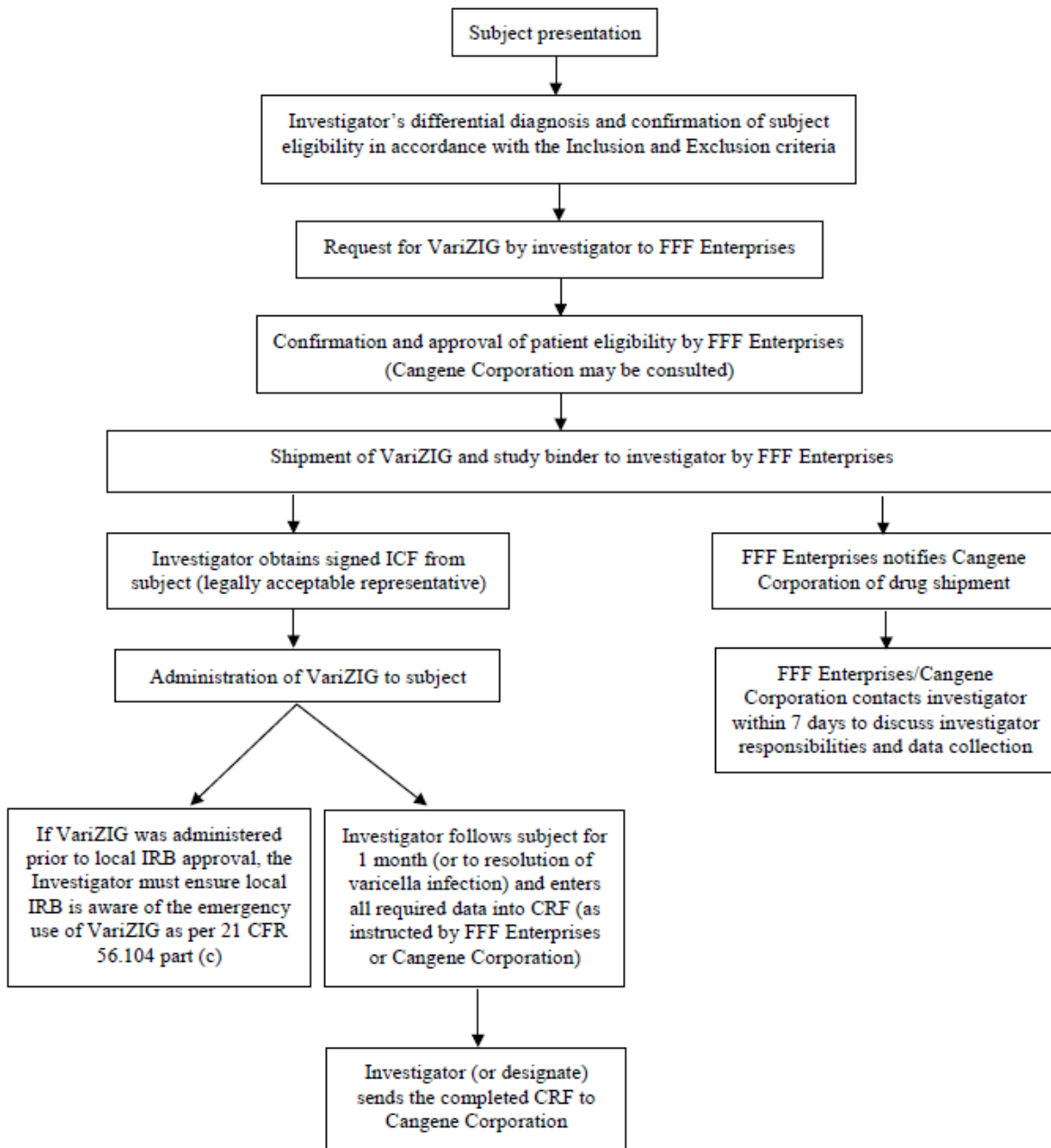
There were four visits prescribed in the protocol, as follows:

- Baseline visit (visit 1)
  - collection of eligibility data,
  - medical history,
  - varicella exposure history,
  - informed consent,
  - hematology and blood chemistry parameters (if available),
  - VariZIG administration and
  - adverse event monitoring.
- Two observational visits
  - Visit 2 conducted between Day 1-4 and
  - Visit 3, between Day 7-20, collect data on safety and efficacy.
- Visit 4 between Day 28-42, include the overall clinical review of varicella infection and completion of adverse event and safety data.
- Follow-up with for 4 weeks (or to resolution of varicella infection) and completion of the CRF was encouraged.

The following schema shows the study design:

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Figure 1: Schematic Diagram of VariZIG Release and Data Collection



### 6.2.3 Population

1. Signed and dated ICF.
2. Cangene Corporation (or designate) VariZIG release requirement.
3. Any of the following high risk subjects exposed to VZV ideally within the previous 96 hours but **within the previous 10 days maximum** (protocol version 4.0):

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- a. Immunocompromised pediatric patients.
- b. Immunocompromised adult patients.
- c. Full term infants (including infants < 1 year of age).
- d. Pre-term infants.
- e. Pregnant women
- f. Newborns whose mothers had VZV infection shortly before delivery (<5 days).
- g. Newborns whose mothers had VZV infection shortly after delivery (<2 days).
- h. Healthy non-immune adults.

**Exclusion Criteria**

1. Subjects with known immunity to VZV [i.e. previous varicella infections or varicella vaccination (received 2 doses of the varicella vaccine)].
2. Hypersensitivity to blood or blood products, including IV or IM human immunoglobulin preparations.
3. Hypersensitivity to any component of VariZIG, its diluent or any packaging component.
4. History of selective IgA deficiency.
5. Evidence of VZV infection (chicken pox or shingles) at study entry.
6. Subjects that were severely thrombocytopenic (platelets < 50 x 10<sup>9</sup>/L).

**6.2.4 Study Treatments or Agents Mandated by the Protocol**

Weight of Subject		Dose		Volume to Administer* (mL)
Kg	lb	Units	Number of vials	
≤10.0	≤22.0	125	1	1.2
10.1-20.0	22.1-44.0	250	2	2.4
20.1-30.0	44.1-66.0	375	3	3.6
30.1-40.0	66.1-88.0	500	4	4.8
>40.0	>88.0	625	5	6.0

\* Volume of VariZIG to be administered to the subject after reconstitution.

- The maximum dose was 625 units for subjects with weight > 40 kg.
- The original protocol recommended a dose of 62.5 units (0.6 ml) for infants under 5 kg body weight; however this dose was increased to 125 units (1.2 ml) after consultations by the sponsor with CDC (Atlanta).
- There were no restrictions on the use of prior or concomitant therapy.

**6.2.5 Directions for Use**

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Most subjects received VariZIG by the intramuscular route of administration, as per protocol, with a few subjects receiving it by the intravenous route of administration.

### 6.2.6 Sites and Centers

Nationwide expanded access

### 6.2.7 Surveillance/Monitoring

	Visit 1	Visit 2	Visit 3	Visit r
	Day 0/Baseline	Day 1 to Day 4	Day 7 to Day 20 (or approximate day of varicella rash development)	Day 28 to Day 42 (closeout) or Early Termination
Admission Criteria	X			
Signed Informed Consent	X			
Medical History	X			
History of Varicella Exposure	X			
Hematology <sup>2</sup>	X	X	X	X
Blood Chemistry <sup>2</sup>	X	X	X	X
VariZIG Dosing <sup>3</sup>	X			
Adverse Events	X <sup>4</sup>	X	X	X
Concomitant Medications	X <sup>5</sup>	X	X	X
Evaluation of Varicella Lesion(s)		X	X	X

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	<b>Visit 1</b>	<b>Visit 2</b>	<b>Visit 3</b>	<b>Visit r</b>
	<b>Day 0/Baseline</b>	<b>Day 1 to Day 4</b>	<b>Day 7 to Day 20 (or approximate day of varicella rash development)</b>	<b>Day 28 to Day 42 (closeout) or Early Termination</b>
Overall Clinical Review of Varicella Infection				X

<sup>1</sup>If appropriate; <sup>2</sup>If available; <sup>3</sup>Re-dosing of VariZIG may occur on Days other than Day 0, if clinically justified;

<sup>4</sup>Post dosing; <sup>5</sup>Record all transfusions and prescription, non-prescription and herbal medications.

Source: Original BLA 125430/0; Clinical Study Report for study VZ-00 Vol 5.3.5.1.2, p.18

**Clinical Assessments Conducted During VZ-009 Study**

<b>Assessment</b>	<b>Visit 1 (Baseline)</b>	<b>Visit 2 (D1 – D4)</b>	<b>Visit 3 (D7 – D20)</b>	<b>Visit 4 (D28 – D42)</b>
Adverse events		√	√	√
Blood chemistry tests*: Total bilirubin, AST, ALT, alkaline phosphatase, lactate dehydrogenase, creatinine, BUN	√	√	√	√
Hematology tests*: Hemoglobin, hematocrit, WBC count and differential, RBC count and platelet count	√	√	√	√
Evaluation of varicella lesions - type, number, size, location of the body and percent of body area affected		√	√	√
Assessment for incidence of pneumonia, encephalitis, pox count > 100				√

\* If available; D: Day post VariZIG administration.

Source: Original BLA 125430/0; Clinical Study Report for study VZ-00 Vol 5.3.5.1.2, p.27

## 6.2.8 Endpoints and Criteria for Study Success

Efficacy assessments were based on evaluation of the following:

- incidence of varicella (chickenpox),
- mortality,

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- pneumonia,
- encephalitis and
- complications due to VZV infection

## 6.2.9 Statistical Considerations & Statistical Analysis Plan

Protocol VZ-009 planned to analyze the incidence of clinical varicella as a primary endpoint, as well as secondary endpoint of mortality due to VZ infection, varicella pneumonia, varicella encephalitis, number of subjects with pox count > 100, and other complications of varicella in high-risk subjects.

Study VZ-009 was incompletely monitored and reported (see [Appendix 7](#)). Therefore, no statistical analysis comparing outcomes of VZ-009 to other outcome rates is possible.

## 6.2.10 Study Population and Disposition

### 6.2.10.1.1 Demographics

**Table 11-4 Summary of Study Population Demographics Based on Safety Population<sup>1</sup>**

Demography Variable		Overall <sup>3</sup> (n=372)
Age <sup>2</sup> (years)	n	372
	Mean (SD)	12.2 (14.65)
	Median	6.1
	Range	0.0 - 75.8
Gender [n (%)]	Female	224 (60.2)
	Male	148 (39.8)

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Demography Variable		Overall <sup>3</sup> (n=372)
Race [n (%)]	White	204 (54.8)
	Black or African American	38 (10.2)
	Asian	19 (5.1)
	Hispanic or Latino	79 (21.2)
	American Indian or Alaska Native	2 (0.5)
	Native Hawaiian or Other Pacific Islander	1 (0.3)
	Subject Declined to Provide	7 (1.9)
	Not Reported	22 (5.9)
Weight (kg)	n	372
	Mean (SD)	34.3 (33.99)
	Median	20.0
	Range	0.5 – 145.0

<sup>1</sup> If demographic information was missing on the CRF, available data provided on the DRF was used.

<sup>2</sup> Age is calculated from the date of VariZIG administration, if available. If not available, age is calculated from the date of Informed Consent or the date of drug request.

<sup>3</sup> Total number of subjects in the safety population. Only the demographic information for initial dose is included in the summary for subjects who received more than 1 dose of VariZIG.

## 6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 10-1 Composition of Safety and Efficacy Populations in VZ-009 Study

Type of high risk subject (Abbreviation)	Safety Population No. of Subjects <sup>1</sup> (No. of VariZIG doses) Total = 372 (379)	Efficacy Population No. of Subjects (No. of VariZIG doses) Total = 297 (303)
Healthy non-immune adults (HA)	5 (5)	2 (2)
Pregnant women (PW)	80 (81)	70 (70)
Immunocompromised adults (IC-Ad)	22 (22)	15 (15)
Immunocompromised pediatric	152 (158)	132 (138)
Full term newborns, age: 0-27 days	37 (37)	29 (29)
Pre-term infants (Pt)	69 (69)	43 (43)
Infants, age: 28 days – 1 year (If)	7 (7)	6 (6)

<sup>1</sup> There were 337 subjects for whom AE page was submitted to Cangene.

<sup>2</sup> Immunocompromised pediatric subjects consisted of adolescents, IC-AI (age: 12 – 18 years), children, IC-Ch (age: 2 – 11 years), toddlers, IC-To (age: 1 – 2 years), infants, IC-If (age: 28 days – 1 year), full term newborns, IC-Nb (age: 0 – 27 days) and pre-term infants, IC-Pt.

Source: Original BLA 125430/0; Clinical Study Report for study VZ-009 Vol 5.3.5.1.2, p.39 of 306

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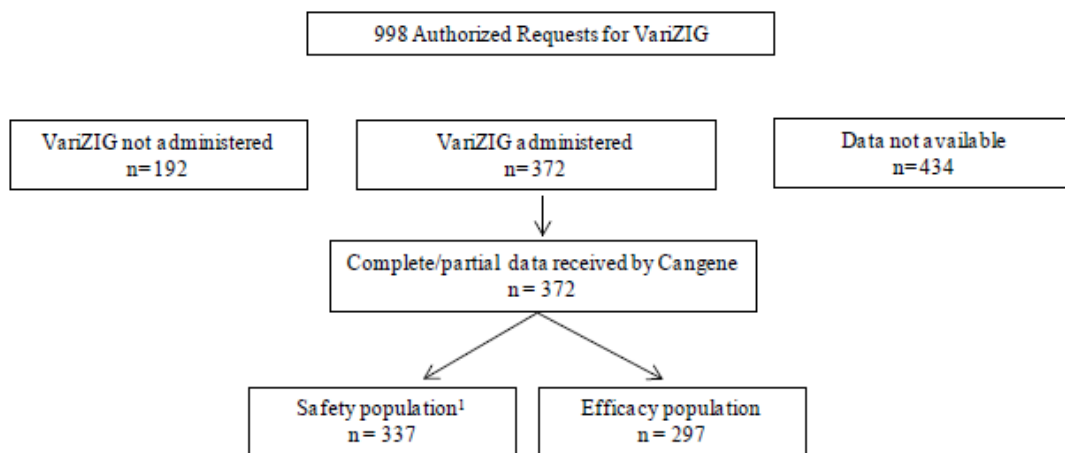
### 6.2.10.1.3 Subject Disposition

From the VZ-009 study report (page 38):

To obtain VariZIG, the investigator (or delegate) was required to complete a DRF to determine subject eligibility for VZ-009. For eligible subjects, a subject identification number (ID) was assigned and VariZIG was released by FFF Enterprises. The completed DRFs with subject ID were submitted to Cangene for database entry. From the start of the study (March 7, 2006) to the data collection cut-off (September 01, 2011), there were 998 authorized requests for VariZIG administration. Of the 998 authorized requests, 192 individuals did not receive the drug, as confirmed by site personnel. This report includes the 372 individuals for whom data was received and VariZIG was administered (Section 9.7.1.1).

Post-dosing subject data was not received for the remaining 434 subjects. Of the 372 subjects in this report, a total of 337 subjects with sufficient information on incidence of adverse events are included in the safety analysis population. This population includes four subjects (VM-00215, VM-00216, VM-00301 and VM-00779) for whom CRF data was extracted from submitted SAE forms. A total of 303 subjects had sufficient efficacy data to allow inclusion into the primary efficacy analysis population. A summary of subject disposition is provided in Figure 2.

**Figure 2 Disposition of Subjects in Study VZ-009 up to September 1, 2011**



n = number of subjects.

<sup>1</sup> Safety data received by Cangene include information derived from CRFs and SAE forms.

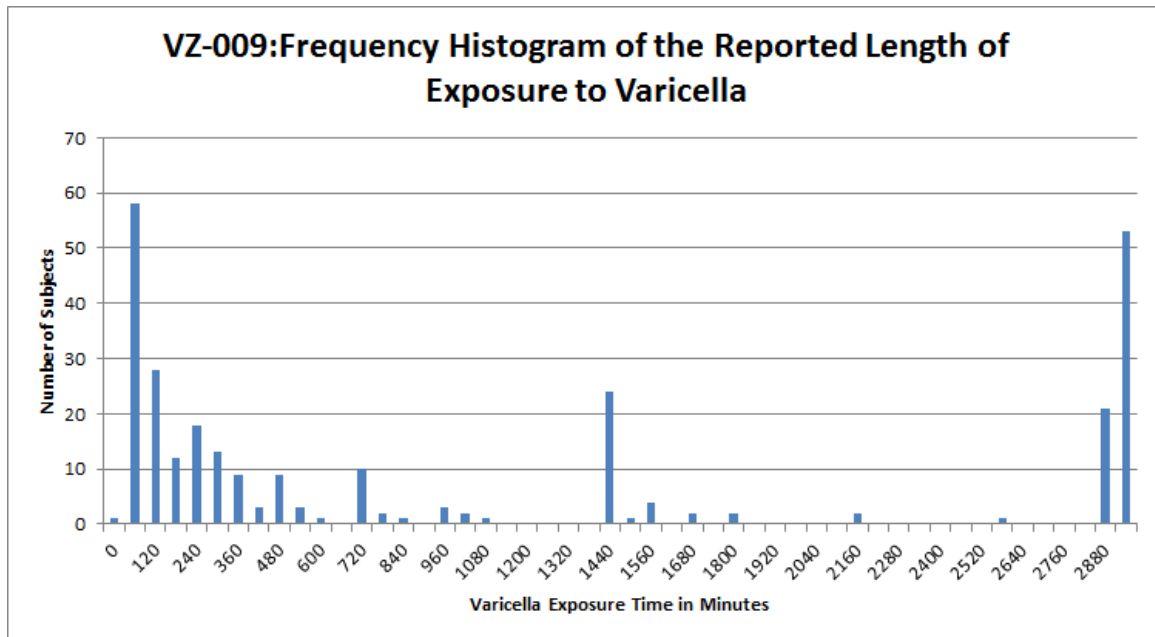
Source: Original BLA 125430/0; Clinical Study Report for study VZ-009 Vol 5.3.5.1.2, p.38 of 306

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### 6.2.11 Efficacy Analyses

The duration of varicella contact is not reported for 77 of 361 subjects listed in database VARHIST, which gives the history of exposure to varicella.

For the 284 subjects with reported varicella exposure times, the following chart shows the distribution of exposure times (in minutes):



It can be seen that reported exposure times can be classified into three groups:

Varicella Exposure Time	Number of Subjects
Less than 24 hours	174
24-48 hours	36
More than 48 hours	53

It can be seen from the above table that 173/283 (61%) of subjects for whom varicella exposure time data were reported had exposures less than 24 hours.

Of the 78 subjects for whom the duration of varicella contact was not reported, 5 subjects (6%) developed varicella, and infection information is not reported for 6 subjects (8%).

Of the 283 subjects for whom varicella exposure times are available, 18 subjects developed varicella, and infection information is not reported for 24 subjects.

### 6.2.12.2 Overview of Adverse Events

See [Appendix 5](#) for non-serious adverse events and [Appendix 6](#) for serious adverse events.

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In those appendices, subjects with pink background had adverse events in the following list that possibly could have occurred because of thrombotic or coagulopathic events: “Cardiac Arrest”, “Deep Vein Thrombosis”, “Disseminated Intravascular Coagulation”, “Exacerbation of Thrombocytopenia”, “Increased PTT”, “Intracranial Hemorrhage”, “Intraventricular Hemorrhage”, “Necrotizing Enterocolitis”, “Petechiae – Chest, Platelets”, “Pulmonary Hemorrhage”, “Thrombocytopenia”, “Unresponsive”.

In those appendices, subjects with red backgrounds are the subjects listed in section [6.2.12.4](#) “Nonfatal Serious Adverse Events” who had thrombotic or coagulopathic adverse events.

**6.2.12.3 Deaths**

Subject ID (Subject Population <sub>1</sub> )	Cause of death	SAE Case #
VM-00039 (IC-AI)	Intracranial hemorrhage	VZ009-00001
VM-00088 (Pt)	Bronchopulmonary dysplasia	VZ009-00008
VM-00089 (Pt)	Intraventricular hemorrhage	VZ009-00004
VM-00779 (IC-Nb)	Cardiac failure congestive	US-144894
VM-00903 (IC-Ad)	Respiratory failure	US-145151
VM-00914 (IC-Ch)	Neoplasm Malignant	US-145137

Source: Original BLA 125430/0; Clinical Study Report for study VZ-009 Vol 5.3.5.1.2, p.61

**Table 14-28 Narratives of Deaths Reported in VZ-009 Study**

Subject ID (Subject Population)	Narrative
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Subject ID (Subject Population)	Narrative
VM-00039 (IC-AI)	<p>Encephalitis Herpes, Status Epilepticus, Coma, Acute Graft-Versus-Host Disease, Cardiac Arrest, Blood Pressure Fluctuation, Renal Insufficiency, Hemorrhage Intracranial, Case VZ009-00001</p> <p>A 13 year-old female subject (immunocompromised adolescent) had prolonged exposure in hospital to another patient with primary varicella on April 24, 2006. She received one dose of VariZIG (625 IU) on April 28, 2006.</p> <p>The subject had a medical history of osteogenic sarcoma of the skull at age 9 months requiring high- dose radiation which was complicated with brain necrosis requiring surgical debridement and resulted in left sided weakness. In 2005, she developed acute lymphoblastic leukemia. Since January 2006 she started to present self-limited seizures. In April 2006 she had a bone marrow transplant.</p> <p>On the night of May 2, 2006, she had a self-limited focal seizure. At noon, May 3, 2006 she had a left sided seizure that progressed into a generalized tonic/clonic seizure. She was transferred to PICU. Over the next 24 hours she became increasingly unresponsive and was intubated. On May 9, 2006</p> <p>HHV6 encephalitis was identified by PCR testing; the same day she was also diagnosed with severe graft-versus-host disease (GVHD).</p> <p>While in the hospital, the subject developed cardiac arrest on May 19, 2006. She remained pancytopenic after her bone marrow transplantation. Due to the co-morbidities and treatment with nephrotoxic agents, her hospital stay was complicated with renal insufficiency which required dialysis. She became hypertensive. A CT scan revealed a large intracranial hemorrhage. On this basis the family withdrew medical support. The subject died on --b(6)-----</p> <p>Her physician reported that all of these events resulted from her bone marrow transplant complicated by HHV6 encephalitis and severe GVHD. None of them were thought to be related to VariZIG.</p>
VM-00088 (Pt)	<p>Bronchopulmonary Dysplasia, Case VZ009-00008</p> <p>A one month old female preterm infant (23 weeks gestation, 0.403 kg at birth) received 125 IU (1.2mL) IM dose of VariZIG on June 22, 2006 after she was exposed to varicella virus while in hospital June 19, 2006. The patient's comorbid conditions were respiratory distress, hypotension and neonatal anemia due to extreme prematurity. At the time of study enrollment the infant was on 100% oxygen and high frequency ventilation.</p> <p>The patient continued to deteriorate with complications such as cholestatic jaundice, thrombocytopenia, hydrocephalus and suspected sepsis. The parents decided to remove the ventilator support which resulted in death. The cause of death on the death certificate was severe bronchopulmonary dysplasia (BPD).</p> <p>The investigator indicated that there was no relationship to either the varicella exposure or VariZIG administration.</p>

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Subject ID (Subject Population)	Narrative
VM-00089 (Pt)	<p>Intraventricular Haemorrhage, Pulmonary Haemorrhage, Convulsion, Disseminated Intravascular Coagulation, Case VZ009-00004</p> <p>A premature male infant (24 weeks, 6 days of gestation) born on --b(6)-----was exposed to varicella zoster on June 19, 2006. He received one dose of 125 U (1.2 mL) of VariZIG IM on June 22, 2006.</p> <p>Due to the prematurity, he had bronchopulmonary dysplasia complicated with isolated bowel perforation and worsening thrombocytopenia. On June 22, 2006 a cerebral sonogram revealed grade 2 hemorrhage (platelets had decreased to 21,000/<math>\mu</math>L). Repeat ultrasound revealed grade 4 intraventricular hemorrhage. Thrombocytopenia was a baseline condition, which worsened contributing to disseminated intravascular coagulation (DIC). Mechanical support was withdrawn and patient died on --b(6)-----</p> <p>The cause of death was extreme prematurity and intracranial hemorrhage, not related to VariZIG.</p>
VM-00779 (Nb)	<p>Cardiac Failure Congestive, Case US-144894</p> <p>A male newborn subject at 38 weeks gestation born on --b(6)-----was diagnosed with hypoplastic left heart syndrome in uterus. After he was exposed to varicella he received 125 IU of VariZIG IM on October 11, 2009.</p> <p>On September 30, 2009 he underwent Norwood-Type Stage I reconstruction surgery (right ventricle to pulmonary artery conduit insertion with Sano shunt modification and atrial septectomy). On October 1, 2009 he required extracorporeal membrane oxygenation (ECMO) due to low cardiac output syndrome and junctional ectopic tachycardia. On October 4, 2009 the ECMO was removed.</p> <p>The following day, he became hypotense and required cardiopulmonary resuscitation. He was found to have significant intraventricular hemorrhage. The same day, he underwent urgent reconstruction of right common carotid artery and ligation of right internal jugular vein. On October 13, 2009 he had mediastinal exploration operation and chest closure.</p> <p>Despite medical and surgical support the subject developed irrevocable uncompensated cardiac failure and died on --b(6)-----</p> <p>According to the investigator the subject did not die as a result of receiving VariZIG, the infant was born with a cyanotic heart defect and was not expected to live.</p>

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Subject ID (Subject Population)	Narrative
VM-00903 (IC-Ad)	<p>Respiratory Failure, Case US-145151</p> <p>A 29 year-old female subject with a history of HIV/AIDS diagnosed in February 2010 and related complications with CNS toxoplasmosis and previous treatment for Kaposi sarcoma, received 625 IU of VariZIG IM on August 28, 2010 after exposure to varicella virus.</p> <p>On August 24, 2010 she was admitted to hospital for dyspnea, cough, fever, diffuse myalgias, neck pain and headache. A spinal tap done on admission showed CSF (cerebral spinal fluid) positive for varicella zoster and she was diagnosed with possible disseminated varicella the next day. On the second hospital day, the subject became hypotensive and her respiratory status declined rapidly requiring PEEP (positive end-expiratory pressure).</p> <p>By August 27, 2010 it was thought that the subject had become septic; although multiple blood cultures had no growth except one culture obtained on September 4, 2010 [positive for VRE (vancomycin resistant enterococci)].</p> <p>On --b(6)-----the subject died of respiratory failure secondary to severe acute respiratory distress syndrome (ARDS) or pulmonary Kaposi, unrelated to the administration of the VariZIG. The investigator stated that the subject was severely immunosuppressed and critically ill. They first thought she had disseminated varicella; however, the subject did not develop varicella. Varicella virus was not isolated in respiratory viral cultures or CSF viral culture; it was detected only by PCR (polymerase chain reaction) in the CSF sample on the day of admission. If it was varicella pneumonia, the virus should have been detected in the BAL (broncho-alveolar lavage) too. The investigator also stated that if the subject had disseminated varicella, she already had it on admission. The subject had very severe respiratory disease of unknown etiology (ARDS) or Kaposi sarcoma.</p>
VM-00914 (IC-Ch)	<p>Neoplasm Malignant, Case US-145137</p> <p>A 6 year-old male subject with a history of relapsed stage IV MYCN – non-amplified neuroblastoma since April 6, 2010 was exposed to varicella virus and received 375 IU of VariZIG IM on October 6, 2010.</p> <p>On --b(6)-----after VariZIG administration) the subject died due to progression of the neuroblastoma; the immediate cause of death was respiratory failure. No autopsy was performed. The principal investigator assessed the event as unrelated to VariZIG.</p>

\* The subject was classified as a healthy non-immune adult on the CRF by the investigator; however, the subject had Hodgkin lymphoma relapse soon before administration of VariZIG.

#### 6.2.12.4 Nonfatal Serious Adverse Events

**Table 14-29 Narratives for other Serious and Certain other Significant Adverse Events Reported in VZ-009 Study**

Subject ID (Subject Population)	Narrative

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Subject ID (Subject Population)	Narrative
VM-00011 (Nb)	<p>Pneumonia Bacterial, Case VZ009-00002</p> <p>A male newborn, born --b(6)-----to a mother with varicella lesions 5 days before delivery, received 62.5 IU of VariZIG. Within the same day, the newborn developed pneumonia (bacterial suspected).</p> <p>A chest x-ray and significant laboratory tests results including C-reactive protein, WBC, lymphocytes, provided the diagnosis of pneumonia. The patient was treated with cefotaxime for 10 days. Acyclovir was also added. Cerebral spinal fluid was negative for varicella zoster by PCR, ruling out pneumonia related to varicella. The event resolved completely with no residual effects and the infant was discharged from the hospital on April 11, 2006.</p>
VM-00031 (IC-Ch)	<p>Neutropenia, Case VZ009-00031</p> <p>A 5 year-old female subject with a known history of Acute Lymphoblastic Leukemia was exposed to varicella on April 3, 2006 by another playmate at school that developed varicella lesions on April 4, 2006. The subject was administered a total dose of 250 IU of VariZIG IM on April 6, 2006.</p> <p>On May 17, 2006, during the Day 42 visit (close out), the investigator reported neutropenia based on the blood test results; WBC was 0.6 K/mm<sup>3</sup>, neutrophils at 26%. Prior, on Day 13 (April 19, 2006) WBC count was 2.2 K/mm<sup>3</sup>.</p> <p>Neutropenia was ongoing at the end of the study. No corrective treatment was reported. The investigator considered the event of neutropenia conditional and unrelated to VariZIG and due to chemotherapy and assessed the seriousness as medically</p>
VM-00039 (IC-Al)	<p>Encephalitis Herpes, Status Epilepticus, Coma, Acute Graft-Versus-Host Disease, Cardiac Arrest, Blood Pressure Fluctuation, Renal Insufficiency, Hemorrhage Intercranial, Case VZ009-00001</p> <p>See narrative in <a href="#">Table 14-28</a>.</p>
VM-00065 (IC-Ch)	<p>Febrile Neutropenia , Case VZ009-00005</p> <p>A 5 year-old female subject (immunocompromised child) received 250 IU of VariZIG IM on June 2, 2006, post exposure to varicella. The subject had a history of Wilm's tumor stage III and had recently received chemotherapy treatment with cyclophosphamide and etoposide from June 6 to 12, 2006.</p> <p>On June 23, 2006, she was admitted to the hospital with diagnosis of febrile neutropenia. She presented in the emergency room with increased temperature (38.6°C), vomiting and lethargy. Her skin appeared pale with bruises over her legs and arms; WBC count of 0.1 K/mm<sup>3</sup>.</p> <p>The course in the hospital was eventful, she was treated with Filgrastim; the events completely resolved on June 25, 2006, and the patient was discharged from the hospital on that day.</p> <p>The investigator considered the event to be severe and unrelated to VariZIG.</p>

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Subject ID (Subject Population)	Narrative
VM-00066 (IC-Ch)	<p>Cystitis Haemorrhagic, Staphylococcal Bacteraemia, Case VZ009-00003</p> <p>An 8 year-old female subject (immunocompromised child) with history of meduloblastoma since November 2005 and chemotherapy with cisplatin and etoposide, was administered one dose of 375 IU of VariZIG IM on June 2, 2006 post varicella exposure.</p> <p>On June 15, 2006, the subject developed fever and the next day, she presented hematuria and was admitted to the hospital with diagnosis of haemorrhagic cystitis. She empirically started antibiotic therapy with ceftriaxone (changed to cefotaxime) and Mesna. On June 18, 2006 the events resolved and was discharged on June 20, 2006.</p> <p>On June 26, 2006, she developed fever of 38°C with chills and decreased oral intake and the patient was re-admitted for hemorrhagic cystitis to rule out bacteremia. This time the blood cultures were positive for <i>Staphylococcus aureus</i>. By June 30, 2006 infection resolved and the patient was discharged home to finish antibiotic therapy. The investigator considered that neither the hemorrhagic cystitis nor the infection was related to VariZIG.</p>
VM-00088 (Pt)	<p>Bronchopulmonary Dysplasia, Case VZ009-00008</p> <p>See narrative in <a href="#">Table 14-28</a>.</p>
VM-00089 (Pt)	<p>Intraventricular Haemorrhage, Pulmonary Haemorrhage, Convulsion, Disseminated Intravascular Coagulation, Case VZ009-0004</p> <p>See narrative in <a href="#">Table 14-28</a>.</p>
VM-00091 (Pt)	<p>Staphylococcal Sepsis, Coagulopathy, Thrombocytopenia, Case US-144813</p> <p>A premature female infant (24 weeks of gestation with weight of 0.561 kg) born on --b(6)-----was exposed to chicken pox on <b>June 19, 2006</b>; she received 125 IU of VariZIG IM on June 22, 2006. Fetal and maternal complications included placental abruption, maternal insulin dependent diabetes and fetal hydrocephaly. Apgar scores were 1, 2 and 3 at one, three and five minutes respectively.</p> <p>The baseline conditions included bronchopulmonary dysplasia, patent ductus arteriosus, hypoperfusion, superior vena cava syndrome, metabolic acidosis, hydronephrosis, and anemia of prematurity.</p> <p>On June 25, 2006 the patient developed sepsis due to <i>Staphylococcus epidermidis</i> infection. Platelet count on June 28, 2006 was <math>119 \times 10^9/L</math>; PT 1.5 sec (normal range: 0.8-1.2 sec), PTT 56 sec (normal range: 23-36 sec), fibrinogen 111 mg/dL (normal range: 160-440 mg/dL). The patient was diagnosed with thrombocytopenia which was subsequently considered to have escalated to the diagnosis of coagulopathy treated with cryoprecipitate, platelets and red blood cells. The case was complicated by seizures, adrenal insufficiency, hypotension, necrotizing enterocolitis. The subject received treatment including antibiotic therapy and blood and platelets transfusions. The events were resolved on September 21, 2006.</p> <p>The investigator considered the events to be severe and unrelated to VariZIG.</p>

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Subject ID (Subject Population)	Narrative
VM-00135 (IC-Ch)	<p>Chills, Pyrexia, Tinea Versicolour, Rash Vesicular, Case VZ009-00006</p> <p>A 3 year-old male subject (immunocompromised child) with a history of Wiskott Aldrich Syndrome and bone marrow transplant, was exposed to varicella from his cousin on July 5, 2006 and received 250 IU (2.6mL) of VariZIG IM on July 11, 2006.</p> <p>On July 28, 2006 he developed vomiting and diarrhea. On August 1, 2006, he presented to the clinic with chills/rigors and a vesicular lesion on the abdomen. The lesion was dime sized vesiculo-erythematous base rash diagnosed as tinea versicolor. He also developed circular erythematous rash on the forehead also diagnosed as ringworm treated with Clotrimizole and resolved on August 14, 2006. Chickenpox was ruled out. He was discharged on August 3, 2006 with all symptoms resolved.</p> <p>The investigator indicated that the event was moderate and unrelated to VariZIG.</p>
VM-00166 (IC-To)	<p>Bacteraemia, Case VZ009-00023</p> <p>A 14 month old female subject (immunocompromised toddler) diagnosed with retinoblastoma on April 28, 2006 was exposed to chicken pox on September 6, 2006 at daycare. On September 8, 2006, the subject received a 125 IU dose of VariZIG IM.</p> <p>On September 26, 2006 (19 days after VariZIG administration), the subject was admitted for bacteremia, fever and line infection. On admission, she had fever of 38.4°C and 39.3°C the following day. She remained afebrile for the rest of the hospital stay. On examination there was a brownish discharge at catheter site. Blood cultures grew <i>Pseudomonas aeruginosa</i> and at the catheter site grew methicillin-resistant <i>Staphylococcus aureus</i>. She received treatment with gentamycin, ceftazidime and Timentin. The infection was resolved on September 30, 2006 and the subject discharged home.</p> <p>The investigator considered bacteremia as unrelated to VariZIG.</p>
VM-00168 (IC-To)	<p>Streptococcal Bacteraemia, Case VZ009-00009</p> <p>A 21 month old female subject (immunocompromised toddler) born on December 06, 2004 was diagnosed in February 2006 with Juvenile myelomonocytic leukemia, had a bone marrow transplant (July 2006) and GVHD (August 2006). The subject received 150 IU dose of VariZIG IV on September 13, 2006 after exposure to varicella September 10, 2006 in hospital.</p> <p>On September 26, 2006, the patient was seen in the emergency department for a breath holding spell; as precaution blood cultures drawn from the central line grew <i>Streptococcus mitis/oralis</i>. On September 28, 2006 she was admitted to the hospital for an infection. She was treated with Vancomycin IV; the infection was resolved with no residual effects and she was discharged from the hospital on October 9, 2006.</p> <p>The investigator confirmed that VariZIG was given IV in error (no events were associated). The infection was moderate and unrelated to VariZIG.</p>

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Subject ID (Subject Population)	Narrative
VM-00215 (IC-AI)	<p>Deep Vein Thrombosis, Case VZ009-00010</p> <p>A 16 year-old female subject (immunocompromised adolescent) recently diagnosed with osteosarcoma of the right knee in September 2006. She received 625 IU of VariZIG IM on December 1, 2006 after exposure to varicella in hospital the previous day.</p> <p>On December 31, 2006, the subject was brought to the emergency room for swelling of arm/chest to investigate DVT or line infection (Broviac) and was admitted to the hospital. Blood cultures showed no isolated organisms. A CT scan on January 1, 2007 revealed clot and filling deficit in the left arm. The catheter was removed and treatment with Lovenox for DVT was initiated and prophylactic antibiotic therapy with ceftriaxone. The patient remained in hospital to have a peripherally inserted central catheter (PICC) line placed and resumed her chemotherapy regimen. She was discharged on January 11, 2007.</p> <p>The investigator indicated that the DVT was moderate, due to the catheter and unrelated to VariZIG.</p>
VM-00216 (IC-Ch)	<p>Dehydration, Gastroenteritis, Thrombocytopenia, Mucosal Inflammation, Vasculitis, Enterococcal Infection, Case VZ009-00011</p> <p>A 6 year-old female subject (immunocompromised child) with history of medulloblastoma under chemotherapy received 250 IU of VariZIG IM on December 1, 2006 after exposure to varicella in hospital the previous day.</p> <p>On December 11, 2006, the subject was admitted to the hospital with gastroenteritis (vomiting and diarrhea); in addition, she developed mucositis, thrombocytopenia with petechiae due to chemotherapy. While in the hospital she developed vancomycin-resistant <i>Enterococcus faecium</i> (VRE) sepsis associated with the Broviac catheter, which had to be removed and replaced on January 15, 2007. She also developed methotrexate induced vasculitis with erythema and edema of the palms and soles.</p> <p>By January 16, 2007 the events resolved and the subject was discharged home.</p> <p>The investigator considered the events moderate and unrelated to VariZIG. He also indicated that the VRE sepsis was due to a vascular catheter related infection. Thrombocytopenia and mucositis were due to the chemotherapy.</p>
VM-00217 (Nb)	<p>Varicella, Case VZ009-00012</p> <p>A 9 day-old female infant, born on -----(b)(6)-----, to a mother with varicella lesions 5 days before delivery. received 125 IU of VariZIG IM on December 6, 2006. By December 14, 2006 the subject developed varicella lesions and was hospitalized for disseminated varicella.</p> <p>At the ER, the subject presented with pustular lesions and oral yeast infection. She was treated with acyclovir and IV fluids. She was discharged on December 31, 2006. The adverse event was completely resolved on January 5, 2007.</p> <p>The diagnosis was confirmed as varicella infection unrelated to VariZIG but rather related to congenital exposure.</p>

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Subject ID (Subject Population)	Narrative
VM-00238 (IC-AI)	<p>Varicella, Pyrexia, Neutropenia, Hypotension, Case VZ009-00013</p> <p>A 13 year-old female subject (immunocompromised adolescent) with a recent history of Stage IVa Hodgkin's Lymphoma since December 2006 received 625 IU of VariZIG IM on January 18, 2007 after her sister developed varicella 2 days before.</p> <p>The subject had just completed her third cycle of chemotherapy treatment on February 6, 2007. On February 10, 2007, she was hospitalized for fever and neutropenia. She had fever (39.3°C) for a day, left peri-orbital headache and complaining of dizziness and weakness. She also presented multiple erythematous papules about 1mm, non-vesicular, with some scabbing from scratching on back, scalp, arms and legs; negative induration consistent with varicella.</p> <p>The following day, she became hypotensive; she was infused with platelets, RBCs and IV fluids;</p> <p>hydrocortisone, Acyclovir and antibiotics were added due to septic shock concerns. Blood and urine cultures were negative.</p> <p>By February 16, 2007, all events resolved, the patient was stable, afebrile, with no new complaints and discharged home on 10 days of oral Acyclovir.</p> <p>The investigator considered that the neutropenia was severe, unrelated to VariZIG and due to chemotherapy. Hospitalization was primarily for neutropenia. He also indicated that subject had prolonged household exposure to varicella that may have longer than 96 hours.</p>
VM-00283 (IC-AI)	<p>Varicella, Case VZ009-00014</p> <p>A 17 year-old male subject (immunocompromised adolescent) with a history of Evans syndrome, common variable immunodeficiency disease, irritable bowel, growth deficiency, diabetes and ITP received 625 IU of VariZIG IM on March 22, 2007 after varicella exposure from a sibling.</p> <p>On April 9, 2007, he developed non-productive cough, no fever, and no rash or pruritus was noted. One papular, non-vesicular lesion was noted on the right side of his chest. By April 12, 2007, there were 25 distinct papuloerythematous lesions, 3-4 vesicular. The cough had improved. The chest was clear and negative for upper respiratory infection. The rash was non-pruritic and not painful. Acyclovir 400 mg PO TID was prescribed as an outpatient.</p> <p>On April 16, 2007 varicella was confirmed. He had maculopapular rash with vesicles (about 100) in different stages, some crusted. By April 26, 2007 the rash had resolved, no vesicular lesions, 3 scattered crusted lesions remained.</p> <p>The subject was not hospitalized but the investigator reported the case as a medically significant SAE. The investigator considered the varicella infection was mild and unrelated to VariZIG. He thought that the subject had prolonged exposure in the household to a sibling that may have been longer than 96 hours and he did not consider it lack of effect.</p>

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Subject ID (Subject Population)	Narrative
VM-00301 (IC-Ad)	<p>Abdominal Pain, Arthralgia, Decreased Appetite, Fatigue, Pyrexia, Asthenia, Case VZ009-00017</p> <p>A 37 year-old female subject (immunocompromised adult) with a history of lupus erythematosus, biliary stent for an unknown reason and chronic abdominal pain received 625 IU of VariZIG IM on April 23, 2007 after she was exposed to varicella in the household to her daughter with varicella lesions on April 19, 2007.</p> <p>On May 3, 2007, the subject developed fever (temperature to 101°F), acute on chronic abdominal pain, weakness, arthralgia, and decreased appetite. On May 4, 2007, the subject was managing her activities of daily living (ADLs) with some help from her family. The attending physician considered the events to be disabling.</p> <p>Laboratory work-up revealed liver enzymes were elevated (in the past she had similar issues associated with the biliary stent). <b>Lupus flare was ruled out.</b> The subject had been maintained on chronic narcotics for the pain. As of June 11, 2007, she was still on treatment. Since then, she was lost to follow-up. <b>She did not develop varicella; IgG antibodies were positive for anti-VZV (May 4, 2007) and IgM results (May 8, 2007) were negative.</b></p> <p>The events were considered significantly disabling/incapacitating, severe and unrelated to VariZIG.</p>
VM-00304 (Pt)	<p>Convulsion, Case VZ009-00021</p> <p>A 7 month-old male subject (preterm infant) diagnosed with Lissencephaly was exposed to on April 29, 2007 to a nurse who later developed zoster lesions. On May 2, 2007, the subject received a dose of 125 IU of VariZIG IM.</p> <p>The subject was having 3-4 seizures/day prior to VariZIG. The convulsions were controlled with Phenobarbital, Dilantin and Klonopin. One week after VariZIG administration, the frequency of seizures increased to 20 to 40 per day, lasting from 1 - 2.5 minutes each. This frequency continued for approximately three more weeks and then the convulsions progressively decreased to one a day. Anticonvulsive therapy had to be adjusted. The event resolved on May 28, 2007.</p> <p>The investigator considered the increased frequency of seizures moderate, disabling and possibly related to VariZIG; although seizures are common occurrence in patients with Lissencephaly.</p>
VM-00310 (IC-Ch)	<p>Varicella, Case VZ009-00016</p> <p>A 3 year-old female subject (immunocompromised child) with a history of a heart transplant at 4 month of age and subsequently immunosuppressed received 250 IU of VariZIG IM on May 9, 2007 after she was exposed to herpes zoster from her father.</p> <p>The patient was admitted to the hospital on May 22, 2007 for concerns with active varicella. She was treated with acyclovir and by May 28, 2007 the infection resolved and she was discharged home.</p> <p>The investigator considered the varicella infection was moderate and unrelated to VariZIG. He also did not consider this event to be a lack of effect; he rather believed that VariZIG at least decreased the eventual number of lesions.</p>

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<b>Subject ID (Subject Population)</b>	<b>Narrative</b>
VM-00326 (IC-Ch)	<p>Catheter Site Haemorrhage, Coagulopathy, Case VZ009-00015</p> <p>A 10 year-old male subject (immunocompromised child) with a history of liver transplant for biliary atresia and chronic diarrhea received 500 IU of VariZIG IM on May 23, 2007 after he was exposed to varicella while in the hospital..</p> <p>On May 27, 2007 the dressing at the peripherally inserted central catheter (PICC) site started to bleed. New dressing was applied but quickly became blood saturated as well. The third pressure dressing was successful. The patient's prothrombin time (PT) and partial thromboplastin time (PTT) were both prolonged beyond the level of detection. Repeat PT/PTT was the same. It was considered to be coagulopathy of undetermined origin. However, the coagulopathy resolved spontaneously without intervention and the subject was released from the hospital on May 29, 2007 (hospitalization extended for two days due to this event).</p> <p>The investigator indicated that the coagulopathy was transient of unknown etiology but suspected to be iatrogenic because a heparin flush and the rapid resolution. He also considered the event unrelated to VariZIG.</p>
VM-00334 (IC-Ch)	<p>Pyrexia, Sinusitis Bacterial, Case VZ009-00022</p> <p>A 7 year-old female subject (immunocompromised child) diagnosed on May 20, 2005 with Acute Lymphoblastic Leukemia treated with chemotherapy was exposed to chickenpox June 1, 2007. On June 5, 2007, the subject received 250 IU of VariZIG IM.</p> <p>On July 6, 2007 (32 days after VariZIG administration); the subject had a history of 3-4 days of headache, running nose, cough and poor appetite. Temperature was 38.4°C. She was referred to the hospital and admitted the same day with diagnosis of fever with neutropenia and bacterial sinusitis. Lab from June 9, 2007 revealed WBC count 1.7 K/mm<sup>3</sup> and positive PCR for EBV. A head CT scan revealed chronic sinusitis. She was treated with ceftazidime and clindamycin. No treatment given for neutropenia and mononucleosis (not serious). On July 9, 2007 the subject was discharged from the hospital. The events were resolved on June 17, 2007.</p> <p>The investigator indicated that the fever, neutropenia and the sinusitis were not related to VariZIG. Neutropenia was the result of 2 years of chemotherapy.</p>
VM-00347-1 (IC-Al)	<p>Pneumonia, Case VZ009-00025</p> <p>A 14 year-old, male subject, with medical history of cystic fibrosis and recent bilateral lung transplant was exposed to his mother's shingles on June 24, 2007. He received 625 IU of VariZIG IV on June 26, 2007.</p> <p>On July 28, 2007, the subject was hospitalized with diagnosis of pneumonia after he developed fever, productive cough, decreased energy, increased respiratory rate, dyspnea on exertion, and left lower lobe infiltrate.</p> <p>During the hospitalization, the subject had a bracheoalveolar lavage performed. Treatment was started on IV Timentin, Tobramycin, and Colisthemethate. Cultures were negative for bacteria, fungus, acid fast bacilli (AFB) and viruses. PCP stain was negative and a biopsy showed no rejection. The pneumonia resolved on August 1, 2007 and he was discharged from hospital that day.</p> <p>The pneumonia was considered by the investigator to be severe and unrelated to VariZIG. The IV administration of VariZIG was uneventful.</p>

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Subject ID (Subject Population)	Narrative
VM-00347-1 (IC-AI)	<p>Pneumonia, Case VZ009-00027</p> <p>A 14 year-old, male subject with medical history of cystic fibrosis and recent bilateral lung transplant was exposed to shingles on June 24, 2007. He received 625 IU of VariZIG IV on June 26, 2007.</p> <p>The subject had previous hospitalization due to pneumonia on July 28, 2007 (Case VZ009-00025).</p> <p>On August 30, 2007, the subject was admitted to hospital for pneumonia due to a positive MRSA and other penicillium species. On September 4, 2007 cultures grew abundant MRSA and pseudomonas. On October 17, 2007 bronchial alveolar lavage showed <i>Aspergillus flavus</i>. Antibiotic therapy and antifungal treatment was also given. He was discharged on October 19, 2007.</p> <p>The investigator considered the bacterial and fungal pneumonia severe and unrelated to VariZIG.</p>
VM-00347-2 (IC-AI)	<p>Pneumonia, Case VZ009-00026</p> <p>A 14 year-old male subject with a medical history of cystic fibrosis and recent bilateral lung transplant was exposed to his mother's shingles (twice) on June 26, 2007 and October 5, 2007. He received the first dose of 625 IU of VariZIG IV on June 26, 2007. The subject received a second dose of 625 IU of VariZIG IV on October 5, 2007.</p> <p>The subject had two previous admissions to the hospital for pneumonia; July 28, 2007 (Case VZ009-00025) and on August 30, 2007 to October 19, 2007 (Case VZ009-00027).</p> <p>On October 31, 2007 he was hospitalized with symptoms of fever, upper respiratory infection (URI) symptoms, and dyspnea and diagnosed with pneumonia. A bronchoscopy on October 31, 2007 showed thick mucoid secretions; a culture grew &gt;100,000 colonies of <i>Pseudomonas aeruginosa</i>. Pneumonia was treated with Meropenem, Tobramycin, and Ceftazidime. On November 7, 2007 the patient developed diarrhea due to <i>Clostridium difficile</i> infection (not serious) and was treated with Flagyl. Both events resolved at the time of discharge from the hospital on November 15, 2007.</p> <p>The investigator considered pneumonia to be severe and unrelated to VariZIG; <i>Clostridium difficile</i> infection (diarrhea) was not serious and not related. The IV administration was uneventful.</p>

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<b>Subject ID (Subject Population)</b>	<b>Narrative</b>
VM-00348 (IC-Ch)	<p>Pancytopenia, Pseudomonas Infection, Pyrexia, Neutropenia, Case VZ009-00018</p> <p>A 9 year-old female subject (immunocompromised child) currently being treated for pre B cell acute lymphoblastic leukemia (ALL) diagnosed in December 2006. She had a household exposure to varicella (June 22, 2007) and was administered 500 IU of VariZIG IM on June 25, 2007.</p> <p>Subject has a past medical history of vincristine sulfate (VCR) toxicity with leg weakness and bilateral foot drop, steroid-induced hyperglycemia, bilateral renal calculi, neutropenia and recent hospitalization (before VariZIG treatment) for an uncontrollable pain and dehydration on April 8, 2007). During that hospitalization, the subject had her third dose of chemotherapy with vincristine/doxorubicin. She received packed red blood cells (PRBCs) and platelets transfusions as necessary throughout her hospitalization. She had slow recovery and was still neutropenic when discharged on June 27, 2007.</p> <p>On June 28, 2007, while at home, she became febrile and was re-admitted with fever (38.5°C), mucositis and neutropenia. In the hospital, blood cultures drawn, grew pseudomonas. She was placed on ceftazidime and ciprofloxacin. She had significant pain during this hospitalization and required increasing doses of analgesics. Meanwhile the blood glucose increased &gt;500 mg/dL controlled with insulin.</p> <p>On July 7, 2007, the subject was discharged home with improved condition.</p> <p>The investigator indicated that the events were severe and unrelated to VariZIG, rather due to chemotherapy.</p>
VM-00361 (PW)	<p>Premature Separation of Placenta, Case VZ009-00019</p> <p>A 24 year-old pregnant female subject at 36 weeks 5 days of pregnancy was exposed to chicken pox on July 12, 2007. On July 15, 2007, the subject received a 625 IU dose of VariZIG IM.</p> <p>On July 28, 2007 (13 days after VariZIG administration), the subject developed acute abdominal pain associated with vaginal bleeding and admitted with diagnosis of premature separation of placenta that required caesarean section. She delivered a healthy female neonate. While in the hospital, she developed back pain and sinus infection and allergies (all not serious). She was discharged on July 31, 2007.</p> <p>The investigator considered the placental abruption not related to VariZIG.</p>
VM-00374 (IC-AI)	<p>Neutropenia, Case VZ009-00024</p> <p>A 16 year-old male subject diagnosed with HIV and a history of recurrent neutropenia, and non-compliance with medication, was exposed to chickenpox on July 25, 2007 in a residential facility where he was under care for direct observed therapy (DOT) for HIV medication noncompliance. On July 27, 2007, the subject received a 625 IU dose of VariZIG IM.</p> <p>One month prior to VariZIG administration the subject's absolute neutrophil count (ANC) was 468 cells/μL; by June 25, 2007 the ANC was 374 cells/μL. On July 27, 2007 diagnosis of neutropenia was made. Ten days post VariZIG injection, the ANC was 520 cells/μL. The neutropenia resolved by October 1, 2007.</p> <p>The investigator considered neutropenia to be mild and not related to VariZIG.</p>

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Subject ID (Subject Population)	Narrative
	He believed the neutropenia was caused by the antiretroviral therapy.
VM-00380 (PW)	<p>Congenital Anomaly, Case VZ009-00020</p> <p>A 39 year-old pregnant female subject with 17 weeks 1 day of pregnancy was exposed to chicken pox on August 1, 2007. On August 5, 2007, the subject received 625 IU of VariZIG IM.</p> <p>The subject had a consult with an obstetrician (high risk specialist) on August 20, 2007, to discuss ultrasound results showing fetal anomalies (consistent with Holoprosencephaly). On August 23, 2007 (19 days after VariZIG administration), the subject was admitted to the hospital for dilatation and evacuation. The procedure failed; the following day, she was taken to the operation room for a hysterotomy. The subject tolerated the procedure well, the course in the hospital was uneventful and she was discharged from the hospital on August 27, 2007.</p> <p>The pathology revealed a male fetus with no internal anomalies identified. The chromosome analysis revealed normal karyotype female (46 XX) (possibly representing maternal karyotype).</p> <p>The Investigator assessed the event of congenital anomaly as not related to VariZIG.</p>
VM-00471 (Nb)	<p>Varicella, Case VZ009-00028</p> <p>Full term newborn female subject born --b(6)-----was exposed to varicella from a mother who developed Varicella one days after to birth. She received 125 IU of VariZIG IM on January 10, 2008. On January 20, 2008 the subject was admitted to the hospital for neonatal varicella and started on Acyclovir. She developed approximately 150 poxes covering the entire body. Blood cultures and urine cultures taken at admission were negative. An MRI of the brain showed small hemorrhage that was consistent with birth trauma and was considered normal for her age. She was maintained in the hospital to finish the treatment; she was discharged home on January 30, 2008.</p> <p>The blood spinal tap was positive for Varicella on spinal fluid. A ----b(4)----- was negative for varicella IgG ten days post VariZIG dosing.</p> <p>The investigator considered this case to be a lack of efficacy for VariZIG due to the number of pox, complications and undetected antibody level. Cangene verified that the stability of the lot number 0040511 demonstrated potency of (b)(4) 125 IU in specification.. It was possible that – b(4)----- test result was a false negative, that the antibody was consumed due to a large VZV exposure or there was a dosing administration error.</p>

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Subject ID (Subject Population)	Narrative
VM-00567 (IC-Ch)	<p>Febrile Neutropenia, Case US-144807</p> <p>A 6 year-old, male patient recently diagnosed with Acute Lymphoblastic Leukemia since April 2008 was exposed to chickenpox on June 6, 2008. On June 9, 2008, the patient received a dose of 375 IU of VariZIG IM.</p> <p>The subject received chemotherapy (methotrexate and vincristine) on June 25, 2008. On June 26, 2008 (17 days after VariZIG administration), he was admitted to the hospital for neutropenic fever, with temperature of 102°F and fatigue.</p> <p>At time of admission absolute neutrophil count (ANC) was 300 cells/<math>\mu</math>L, by the 3<sup>rd</sup> day the ANC dropped to 0 cells/<math>\mu</math>L. He also had poor appetite with associated complaints of nausea and emesis and continued to have fever and chills. The blood cultures were negative.</p> <p>Physical examination was negative for any changes and his blood chemistries were monitored, he did have a slight elevation of his liver enzymes with AST of 89 U/L and ALT of 117 U/L. All other results were within acceptable range.</p> <p>By July 3, 2008, he had been afebrile for more than 48 hours; the ANC count recovered to 2.2 cells/<math>\mu</math>L, WBC of 4.85 K/mm<sup>3</sup>, Haemoglobin of 11.1 K/mm<sup>3</sup> and platelets 562K/mm<sup>3</sup>. The same day he was discharged from the hospital in stable condition.</p> <p>The investigator assessed the event of febrile neutropenia to be severe and unrelated to VariZIG.</p>
VM-00567 (IC-Ch)	<p>Anaphylactic Reaction, Case US-144808</p> <p>A 6 year-old, male subject with a history of Pre-B Acute Lymphoblastic Leukemia since April 2008 was exposed to chickenpox on June 6, 2008. On June 9, 2008, he received a dose of 375 IU of VariZIG IM.</p> <p>On June 18, 2008 (9 days after VariZIG administration), the boy received chemotherapy with PEG, vincristine and methotrexate. About four hours after, the child was admitted to the hospital with an allergic reaction. He had developed itchy eyes, diffuse rash, swollen throat, difficulty breathing, gagging and emesis. He was given 70 mg of Solumedrol and 30 mg of Benadryl. The subject improved slowly over the next two days. Claritin and hydroxyzine were also used to improve the patient's rash, swelling and itchiness.</p> <p>By June 20, 2008 the allergic reaction resolved and the subject was discharged from the hospital in good condition. Final diagnosis was anaphylaxis due to PEG-asparaginase.</p> <p>The investigator assessed the event of anaphylactic reaction as severe and unrelated to VariZIG.</p>

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Subject ID (Subject Population)	Narrative
VM-00684-1 (IC-Ch)	<p>Folliculitis, Case VZ009-00030</p> <p>An 8 year-old male with a known history of Acute Lymphoblastic Leukemia diagnosed on September 17, 2007 and undergoing maintenance chemotherapy since March 21, 2008 received 625 IU of VariZIG IM on March 25, 2008. The subject was exposed to varicella from another boy with varicella on March 21, 2008.</p> <p>On March 31, 2008 the subject developed pruritus on his arms and neck and a blotchy rash on his face along with decreased appetite, nausea and mild stomach ache; by the evening, there were numerous bumps and vesicles on arms, neck and face. The next day, he was admitted to the hospital for probable varicella infection.</p> <p>The Varicella Zoster Virus PCR was negative on April 1, 2008 but he was treated empirically with Acyclovir. The event was re-evaluated by pediatricians and concluded that the rash was consistent with folliculitis. The subject was discharged from the hospital on April 3, 2008.</p> <p>The study investigator confirmed that the rash was mild, due to folliculitis and not related to VariZIG.</p>
VM-00684-3 (IC-Ch)	<p>Varicella, Case VZ009-00032</p> <p>The subject is a 9 year-old male with history of Acute Lymphoblastic Leukemia (ALL) since September 2007. He had received two previous doses of VariZIG for exposure to varicella on March 25, 2008 and May 23, 2008. On January 25, 2009, he had the exposure to a contact with varicella at school. On January 26, 2009, the subject received a dose of 625 IU of VariZIG IM.</p> <p>On February 11, 2009 (17 days after VariZIG administration), the subject developed small papular skin lesions, fever, back pain, and headache and was admitted to the hospital for varicella infection. During the hospitalization, the lesions became vesicular and scattered over the face, trunk and feet. He was febrile until February 13, 2009. The following day, the lesions started to dry and had multiple scabbing. He was treated with Acyclovir and Famciclovir. He was discharged home on February 15, 2009. The event was completely resolved by February 17, 2009. A culture sample confirmed varicella zoster virus.</p> <p>The investigator assessed varicella as moderate infection and not related to VariZIG. She considered that VariZIG may have caused milder course of infection because this patient was immunocompromised.</p>

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Subject ID (Subject Population)	Narrative
VM-00690 (Nb)	<p>Varicella, Case VZ009-00034</p> <p>A 2 day-old female infant with weight of 2.66 kg was born at 38 weeks by spontaneous vaginal delivery. She was exposed to varicella from her mother who developed chicken pox after delivery. The baby received 125 IU of VariZIG IM on January 30, 2009.</p> <p>On February 9, 2009, the infant developed two lesions on her face. The next day the lesions spread to her stomach, back, legs and arms and a few more lesions on her face for an approximate of 100 poxes. The infant was reported otherwise well without fever or other skin lesions; she was acting normally and eating well but admitted to the hospital for varicella treatment. She received Acyclovir until February 16, 2009 when she was discharged. Varicella infection was considered resolved.</p> <p>The investigator assessed the event to be mild and considered unrelated to VariZIG.</p>
VM-00693 (IC-Ad)	<p>Pancreatitis, Case VZ009-00035</p> <p>An 18 year-old female with history of SLE, lupus nephritis, pancreatitis, pancreatic pseudocysts, insulin dependent diabetes and bone infarction at the epicondyle of right femur received 625 IU of VariZIG IM on February 11, 2009 after exposure to varicella from a hospital employee during previous hospitalization.</p> <p>On March 18, 2009 she was just discharged from the hospital after rituximab treatment. The next day (37 days after VariZIG administration), she was admitted to the hospital with suspicion of recurrent pancreatitis.</p> <p>On admission, she had moderated intermittent LUQ pain with radiation to her back. She also had four episodes of non-bloody yellowish-green vomiting during the morning and she was complaining of decreased appetite. Relevant laboratory revealed ESR and CRP elevated; amylase and lipase were mildly elevated.</p> <p>The subject continued to improve. Pancreatic enzymes eventually normalized. An abdominal ultrasound showed improvement of the pancreatic pseudocysts and no evidence of pancreatitis or gallstones. On April 20, 2009, the event of pancreatitis was considered resolved and the patient was discharged from the hospital with medications. The investigator assessed the final diagnosis of pancreatitis as severe and unrelated to VariZIG.</p>
VM-00694 (Nb)	<p>Varicella, Case US 144841</p> <p>A 7 day-old newborn male was exposed to varicella in uterus; her mother developed varicella three days after the delivery. On --b(6)----- (five days after birth), he received a dose of 125 IU of VariZIG IM.</p> <p>On February 25, 2009 in the morning, body rash was noticed, no fever and was feeding well. He was taken to the hospital and admitted on the same day for risk of complications from active chicken pox infection and treated with Acyclovir. The dermatological examination showed 59 poxes mostly papular, vesicular with 2 early pustules distributed along the face, trunk and extremities. The PCR diagnostic test detected varicella zoster virus.</p> <p>On February 28, 2009, the subject was discharged with scabbed lesions. Meanwhile during the hospitalization, the neonate developed transient low absolute neutrophil count (ANC) of 0.5 cells/<math>\mu</math>L (normal range: 1.0 - 9.5 cells/<math>\mu</math>L).</p> <p>On March 2, 2009, the subject was a normal acting baby, eating well, no fever, skin seen with scabbed chickenpox. The ANC was normal (2.1 cells/<math>\mu</math>L).</p> <p>The investigator assessed the event of varicella infection to be mild and not related to VariZIG. She considered neutropenia secondary to varicella.</p>

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Subject ID (Subject Population)	Narrative
VM-00704 (IC-AI)	<p>Nausea, Vomiting, Case US-144809</p> <p>A 17 year old female patient with a medical history of Lupus, GERD and Lupus nephropathy received 625 IU of VariZIG IM on March 26, 2009 after she was recently exposed to varicella. Since February 2009, the subject has been taking the following medications: Cellcept 500 mg PO q12 hrs; Prednisone 10 mg PO, QD and Lasix 20 mg PO QD for Lupus; Prilosec 20 mg PO QD for GERD and Calcium 600U PO QD as supplement.</p> <p>On March 30, 2009 the patient experienced nausea and vomiting and went to the emergency department of the hospital. The subject was treated with Phenergan intravenously and was discharged on the same day. The subject said that nausea persisted from March 30, 2009 until 06-April 6, 2009.</p> <p>The investigator assessed the events of nausea and vomiting related to VariZIG and considered to be of moderate intensity and medically significant; however, most of the events associated with VariZIG occur almost immediately post infusion. The patient's concomitant diseases and the medications may have caused or contributed to the development of the events.</p>
VM-00706 (Nb)	<p>Varicella, Case US-145312</p> <p>Subject VM-00706 is a 3 day old newborn Hispanic male born --b(6)-----to a mother with varicella lesions two days prior to delivery.</p> <p>Varicella exposure and treatment: The subject was exposed to varicella from his mother who developed lesions March 28, 2009. The mother was noted to have fever hours after delivery on March 30, 2009. The subject (4.69 kg) received 125 IU VariZIG IM in 0.5 mL on April 2, 2009.</p> <p>Clinical course of varicella: The subject developed varicella on April 13, 2009, 11 days after treatment. On April 15, 2009, 23 papular and vesicular lesions (0.2 to 0.4 cm in size) were noted, two on the face, 3 – 4 on the feet and several on the trunk, affecting 20% of the body area. The subject was admitted to hospital on April 15, 2009 for neonatal chickenpox and treated for 5 days (SAE case US 145312). Varicella had resolved at the last assessment on May 1, 2009. The subject was assessed as 'Ok' with only 2 crusted lesions remained on the right foot when evaluated at a WBC (Well Baby Clinic). No complications of varicella were noted on clinical review in the CRF.</p>

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<b>Subject ID (Subject Population)</b>	<b>Narrative</b>
VM-00754 (HA)*	<p>Neutropenia, Nausea, Vomiting, Case US-144896</p> <p>An 18 year-old female subject diagnosed with Hodgkin lymphoma in 2008 and relapse in 2009, was exposed to chickenpox. She received 625 IU of VariZIG IM on August 18, 2009.</p> <p>On August 26, 2009 the patient was admitted to the hospital for chemotherapy for relapsed Hodgkin lymphoma; absolute neutrophil count (ANC) was 3290 cells/<math>\mu</math>L.</p> <p>The subject had a history of difficulty tolerating chemotherapy because nausea and vomiting. To diminish her symptoms, she received multiple anti-emetics along with visualization exercises. By August 28, 2009 the nausea and vomiting was grade 3 toxicity as per NCIC (National Cancer Institute Criteria).</p> <p>In addition, she developed neutropenia (unknown results) which resolved September 4, 2009.</p> <p>She was discharged on September 3, 2009 in good condition to continue with anti-emetics. The nausea and vomiting were resolved on September 13, 2009.</p> <p>The investigator considered the neutropenia, nausea and vomiting severe and unrelated to VariZIG.</p>
VM-00779 (IC-Nb)	<p>Cardiac Failure Congestive, Case US-144894</p> <p>See narrative in Table 14-28.</p>
VM-00903 (IC-Ad)	<p>Respiratory Failure, Case US-145151</p> <p>See narrative in Table 14-28.</p>
VM-00914 (IC-Ch)	<p>Neoplasm Malignant, Case US-145137</p> <p>See narrative in Table 14-28.</p>
VM-00982 (Pt)	<p>Cytomegalovirus Infection, Case US-145246</p> <p>A premature (unknown age of gestation) female baby subject with weight of 1.16 kg presented at birth bronchopulmonary dysplasia, patent ductus arteriosus, anemia and osteopenia of prematurity was exposed to varicella on May 20, 2011 from the nurse caring for her 2 months after birth. She received</p> <p>14 units (0.14 mL) of VariZIG IM on May 24, 2011.</p> <p>On May 31, 2011 she acquired a cytomegalovirus infection (urine CMV positive); platelets count was</p> <p>54 K/mm<sup>3</sup> which progressively increased without requiring transfusion; by June 5, 2011 was 199 K/mm<sup>3</sup>. The CMV was treated with oral Valganciclovir for 6 weeks.</p> <p>The investigator considered the thrombocytopenia to be mild and CMV to be moderate; both unrelated to VariZIG. He considered that the thrombocytopenia was due to the CMV and the CMV was most likely acquired from maternal breast milk.</p> <p>The subject was administered a reduced dose which was calculated by the investigator based on the AAP Red Book due to the subject's weight of about 1.1 kg and not by the recommended dose as per product label.</p>

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Subject ID (Subject Population)	Narrative
VM-00995 (IC-AI)	<p>Serum Sickness, Case US-145211</p> <p>A 14 year-old female subject with a medical history of T-cell ALL (acute lymphoblastic leukemia) in consolidation was exposed to varicella; she received 625 IU of VariZIG IM on June 11, 2011.</p> <p>Starting on June 16, 2011, the patient had pain in her left wrist which progressively worsened with swelling; also, pain in her right elbow and both hips and felt extreme fatigue with hematocrit of 20%. The next day, she was admitted to hospital for possible polyarthritis and fever. A wrist X-ray showed minimal soft tissue thickening and wrist needle aspirate yielded negative cultures. She received prophylactic treatment with vancomycin. It was thought to be infectious or reactive arthritis.</p> <p>On June 18, 2011, she had a fever of 39°C. She also developed a mild non serious hypersensitivity due to vancomycin and resolved 2 days later. A chest x-ray showed new medial retrocardiac opacity/infiltrate, not well-seen on lateral view, possibly representing atelectasis, infection or <i>Mycoplasma pneumonia</i>. She had a positive Mycoplasma IgM antibody but <i>Mycoplasma pneumonia</i> by immunofluorescence antibody was negative. She did not have any evidence of prior strep infection, given the negative Streptozyme and negative antistreptolysin O titer.</p> <p>By June 22, 2011, the symptoms resolved and was discharged from the hospital. She did require 1 packed red blood cell infusion on the day prior to discharge.</p> <p>The final diagnosis was serum sickness which was the cause of the symptoms; the investigator considered the event to be severe and related to VariZIG. The retro-cardiac infiltration was unrelated to VariZIG.</p>
VM-00997 (IC-Ch)	<p>Bacteraemia, Case US-145230</p> <p>A 3 year old male subject with metastatic suprarenal and bone marrow neuroblastoma since February 4, 2011 and under chemotherapy was exposed to varicella on June 7, 2011 and received 250 IU of VariZIG IM on June 11, 2011.</p> <p>On June 15, 2011, he underwent resection of primary tumor and received the 6<sup>th</sup> course of Vincristine, doxorubicin and cyclophosphamide postoperatively. His chemotherapy has been complicated by severe nausea and vomiting after cisplatin and etoposide. He was discharged from the hospital on July 2, 2011.</p> <p>He had done well until July 7, 2011 when he developed fever, neutropenia, abdominal pain, and distention and increased vomiting and admitted to the hospital. Blood cultures and samples from the catheter line were positive for coagulase-negative Staphylococcus and <i>Streptococcus anginosus</i> treated with Ceftazidime and Clindamycin. His laboratory studies on admission were remarkable for a hematocrit of 17.4%, platelet count of 13 K/mm<sup>3</sup> total white counts &lt; 200/mm<sup>3</sup>, with the ANC of 0 cells/μL. He was also treated with total parenteral nutrition (TPN), blood and platelets transfusions.</p> <p>All the events resolved and the subject was discharged home on July 15, 2011.</p> <p>The investigator considered infection and neutropenia to be severe and unrelated to VariZIG, rather related to the patient's underlying neuroblastoma and concurrent chemotherapy.</p>

\* The subject was classified as a healthy non-immune adult on the CRF by the investigator; however, the subject had Hodgkin lymphoma relapse soon before administration of VariZIG.  
Source: Original BLA 125430/0; Clinical Study Report for study VZ-009 Vol 5.3.5.1, p.303 of 306

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6.2.12.5 Adverse Events of Special Interest (AESI)

Thrombotic/Coagulopathic Adverse Events

Source of SAE	Narrative
EIND 13013, Cangene ID 001	<p><b>Intracranial Hemorrhage</b>, Case EAP_00001</p> <p>A 21 month-old female diagnosed with adenosine deaminase deficiency (ADA) leading to severe combined immunodeficiency (SCID).</p> <p>On April 18 and 19, 2006 the patient was vaccinated for mumps, measles, rubella (MMR) and varicella.</p> <p>The patient had attenuated virus infections of measles, mumps, rubella but varicella became disseminated. She received 125 IU of VariZIG<sup>®</sup> IV on April 25, 2006 and another 125 IU dose IV on May 16, 2006.</p> <p>On May 6, 2006, she developed hypoxia. A scope of her lungs indicated no inflammation of the mucosa. Initial assessment of all organs did not reveal any findings, but she late developed renal insufficiency. She received 3 lymphocyte transfusions from a patient recovering from varicella. On May 17, 2006, the patient developed nosocomial adenovirus infection causing respiratory insufficiency which ultimately led to the use of extracorporeal membrane oxygenation (ECMO). On --b(6)-----, she developed catastrophic intracranial hemorrhage unrelated to her infections, which resulted in her death. The autopsy confirmed a large left hemispheric intracerebral hemorrhage with uncal and cerebellar tonsillar herniation.</p> <p>The attending physician considered the events to be severe and unrelated to VariZIG<sup>®</sup>.</p>

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Source of SAE	Narrative
VZ-009 study, subject VM-00039	<p>Encephalitis Herpes, Status Epilepticus, Coma, Acute Graft-Versus-Host Disease, Cardiac Arrest, Blood Pressure Fluctuation, Renal Insufficiency, <b>Hemorrhage Intracranial</b>, Case VZ009-00001</p> <p>A 13 year-old female subject (immunocompromised adolescent) had prolonged exposure in hospital to another patient with primary varicella on April 24, 2006. She received one dose of VariZIG (625 IU) on April 28, 2006.</p> <p>The subject had a medical history of osteogenic sarcoma of the skull at age 9 months requiring high-dose radiation which was complicated with brain necrosis requiring surgical debridement and resulted in left sided weakness. In 2005, she developed acute lymphoblastic leukemia. Since January 2006 she started to present self-limited seizures. In April 2006 she had a bone marrow transplant.</p> <p>On the night of May 2, 2006, she had a self-limited focal seizure. At noon, May 3, 2006 she had a left sided seizure that progressed into a generalized tonic/clonic seizure. She was transferred to PICU. Over the next 24 hours she became increasingly unresponsive and was intubated. On May 9, 2006 HHV6 encephalitis was identified by PCR testing; the same day she was also diagnosed with severe graft-versus-host disease (GVHD).</p> <p>While in the hospital, the subject developed cardiac arrest on May 19, 2006. She remained pancytopenic after her bone marrow transplantation. Due to the co-morbidities and treatment with nephrotoxic agents, her hospital stay was complicated with renal insufficiency which required dialysis. She became hypertensive. A CT scan revealed a large intracranial hemorrhage. On this basis the family withdrew medical support. The subject died on --b(6)-----</p> <p>Her physician reported that all of these events resulted from her bone marrow transplant complicated by HHV6 encephalitis and severe GVHD. None of them were thought to be related to VariZIG.</p>
VZ-009 study, subject VM-00089	<p><b>Intraventricular Haemorrhage, Pulmonary Haemorrhage, Convulsion, Disseminated Intravascular Coagulation</b>, Case VZ009-00004</p> <p>A premature male infant (24 weeks, 6 days of gestation) born on --b(6)-----was exposed to varicella zoster on <b>June 19, 2006</b>. He received one dose of 125 U (1.2 mL) of VariZIG IM on June 22, 2006.</p> <p>Due to the prematurity, he had bronchopulmonary dysplasia complicated with isolated bowel perforation and worsening thrombocytopenia. On June 22, 2006 a cerebral sonogram revealed grade 2 hemorrhage (platelets had decreased to 21,000/<math>\mu</math>L). Repeat ultrasound revealed grade 4 intraventricular hemorrhage. Thrombocytopenia was a baseline condition, which worsened contributing to disseminated intravascular coagulation (DIC). Mechanical support was withdrawn and patient died on --b(6)-----</p> <p>-----</p> <p>The cause of death was extreme prematurity and intracranial hemorrhage, not related to VariZIG.</p>

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Source of SAE	Narrative
VZ-009 study, subject, VM-00091	<p>Staphylococcal Sepsis, <b>Coagulopathy</b>, Thrombocytopenia, Case US-144813</p> <p>A premature female infant (24 weeks of gestation with weight of 0.561 kg) born on --b(6)----- was exposed to chicken pox on June 19, 2006; she received 125 IU of VariZIG IM on June 22, 2006.</p> <p>Fetal and maternal complications included placental abruption, maternal insulin dependent diabetes and fetal hydrocephaly. Apgar scores were 1, 2 and 3 at one, three and five minutes respectively.</p> <p>The baseline conditions included bronchopulmonary dysplasia, patent ductus arteriosus, hypoperfusion, superior vena cava syndrome, metabolic acidosis, hydronephrosis, and anemia of prematurity.</p> <p>On June 25, 2006 the patient developed sepsis due to <i>Staphylococcus epidermidis</i> infection. Platelet count on June 28, 2006 was <math>119 \times 10^9/L</math>; PT 1.5 sec (normal range: 0.8-1.2 sec), PTT 56 sec (normal range: 23-36 sec), fibrinogen 111 mg/dL (normal range: 160-440 mg/dL). The patient was diagnosed with thrombocytopenia which was subsequently considered to have escalated to the diagnosis of coagulopathy treated with cryoprecipitate, platelets and red blood cells. The case was complicated by seizures, adrenal insufficiency, hypotension, necrotizing enterocolitis. The subject received treatment including antibiotic therapy and blood and platelets transfusions. The events were resolved on September 21, 2006. The investigator considered the events to be severe and unrelated to VariZIG.</p>
VZ-009 study, subject VM-00215	<p><b>Deep Vein Thrombosis</b>, Case VZ009-00010</p> <p>A 16 year-old female subject (immunocompromised adolescent) recently diagnosed with osteosarcoma of the right knee in September 2006. She received 625 IU of VariZIG IM on December 1, 2006 after exposure to varicella in hospital the previous day.</p> <p>On December 31, 2006, the subject was brought to the emergency room for swelling of arm/chest to investigate deep vein thrombosis (DVT) or line infection (Broviac) and was admitted to the hospital. Blood cultures showed no isolated organisms. A CT scan on January 1, 2007 revealed clot and filling deficit in the left arm. The catheter was removed and treatment with Lovenox for DVT was initiated and prophylactic antibiotic therapy with ceftriaxone. The patient remained in hospital to have a peripherally inserted central catheter (PICC) line placed and resumed her chemotherapy regimen. She was discharged on January 11, 2007.</p> <p>The investigator indicated that the DVT was moderate, due to the catheter and unrelated to VariZIG.</p>

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Source of SAE	Narrative
VZ-009 study, subject VM-00326	<p><b>Catheter Site Haemorrhage, Coagulopathy.</b> Case VZ009-00015</p> <p>A 10 year-old male subject (immunocompromised child) with a history of liver transplant for biliary atresia and chronic diarrhea received 500 IU of VariZIG IM on May 23, 2007 after he was exposed to varicella while in the hospital.</p> <p>On May 27, 2007 the dressing at the peripherally inserted central catheter (PICC) site started to bleed. New dressing was applied but quickly became blood saturated as well. The third pressure dressing was successful. The patient's prothrombin time (PT) and partial thromboplastin time (PTT) were both prolonged beyond the level of detection.</p> <p>Repeat PT/PTT was the same. It was considered to be coagulopathy of undetermined origin. However, the coagulopathy resolved spontaneously without intervention and the subject was released from the hospital on May 29, 2007 (hospitalization extended for two days due to this event).</p> <p>The investigator indicated that the coagulopathy was transient of unknown etiology but suspected to be iatrogenic because a heparin flush and the rapid resolution. He also considered the event unrelated to VariZIG.</p>

### 11.1 Risk-Benefit Considerations

The medical literature indicates that immunocompromised individuals as well as pregnant women are at increased risk of experiencing complications of varicella infection, such as pneumonia, encephalitis, and death. We are unaware of any adequate and well-controlled studies having been conducted to prove the efficacy of any varicella immune globulin biologic product in these high-risk groups, either in reducing the incidence of infection upon exposure or in reducing morbidity among those infected and manifesting clinical chickenpox. Epidemiologic data comparing the incidence of complications of varicella before and after the availability of varicella immune globulin (but before the advent of acyclovir therapy), are suggestive of efficacy for the licensed product VZIG. Any such efficacy of VZIG is expected to be shared by VariZIG, based on the pharmacokinetic results from study VZ-008 (See clinical pharmacology review memo). The adverse event profile of VariZIG in the submitted trials appears roughly comparable to the previously licensed product, VZIG. No new safety signals for VZIG or for VariZIG have been identified from review of the submitted data.

VarZIG is made from high-titer anti-VZ antibody donated blood. Therefore, it will contain antibodies from persons recently-infected with VZV and persons recovering from recent shingles.

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After the original submission of IND 7201 (VariZIG) in 1997, there have appeared a series of papers claiming that anti-Protein S autoantibodies can arise after varicella infection, and that these autoantibodies might play a role in the serious adverse event post-varicella purpura fulminans. In the original submission of STN 125430, the applicant did not address the possibility that VariZIG may contain antibodies against human Protein S. During review, FDA issued an information request on this concern ([Appendix 7](#)); the applicant replied that anti-Protein S antibodies can be assumed not to present in clinically-relevant levels because the blood donors are required to be healthy.

## 11.2 Risk-Benefit Summary and Assessment

The risk-benefit is acceptable for licensure.

## 11.4 Recommendations on Regulatory Actions

I recommend licensure. VariZIG can be licensed based on the comparability of its pharmacokinetic parameters to those of the licensed product VZIG, with supportive safety data from studies VZ-006 and VZ-009.

## 11.5 Labeling Review and Recommendations

Labeling review has been ongoing, with ongoing discussions with the applicant. I have no additional recommendation for labeling.

## 11.6 Recommendations on Postmarketing Actions

1. I recommend that the submit a final study report for a non-clinical study that examines whether and to what extent ----b(4)-----  
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2. ---b(4)--- -----  
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APPENDIX 1. CHRONOLOGY OF REGULATORY EVENTS

Chronology of Regulatory Events

24-Jun-1997	IND 7201 submitted
24-Jul-1997	IND 7201 HOLD telecon
13-Nov-1997	<p>IND 7201 Clinical Hold letter issued; hold items:</p> <ul style="list-style-type: none"><li>• Stated VZV infection rate should be primary endpoint, with infant medical status as important secondary endpoint<ul style="list-style-type: none"><li>◦ Stated lack of sufficient information on Constitutional Illness Score (CIS) for it to be used as the primary endpoint</li></ul></li><li>• Stated sample size inadequately justified due to:<ul style="list-style-type: none"><li>◦ Lack of justification of the historical control rate for infection (70%)</li><li>◦ Lack of justification for effect of VZIG if given more than 96 hours after VZ contact</li></ul></li><li>• Requested validation for the anti-VZ test kit that would be used to exclude subjects from the analysis group</li><li>• Requested exclusion of pregnant subjects having additional high-risks beyond seronegativity to VZ</li><li>• Requested blinding procedures be used</li><li>• Requested clarification on the primary endpoint and analysis group</li><li>• Requested the analysis plan that will be used to compare the IV and IM routes of administration of VariZIG</li><li>• Requested details for handling off-study subjects in the analysis plan</li></ul>
10-Dec 1999	<p>Pre-BLA meeting From the minutes:</p> <ul style="list-style-type: none"><li>• FDA suggested Cangene Corporation use “intent-to-treat” as the primary analysis and not exclude any data. Both ITT and per-protocol analyses will be presented.</li><li>• FDA told the sponsor that they must share responsibility with the clinical investigator for the assessment of the safety of the trial and it was appropriate to second-guess the clinical investigator and provide both the sponsor’s assessment of relatedness of AEs to product administration as well as the investigator’s assessments whenever the two differ.</li><li>• FDA stated that Cangene Corporation changed the protocol without FDA notification. The protocol initially submitted to the FDA was based on safety. However the studies performed were analyzed for equivalence between test product given IM, test product given IV and licensed comparator given IV. The protocol for study VZ006 was never amended to reflect the actual equivalence-type statistical analysis performed, and no minimum standard of equivalence (“delta”) was incorporated into the protocol or discussed with FDA before the study was completed and results analyzed. The fact that no criteria to evaluate equivalence or non-inferiority were set up <i>a priori</i> makes FDA’s task of reviewing the trial more difficult.</li><li>• FDA suggested that it was not uncommon to see a sponsor come in with a claim for an original formulation then establish equivalence against another version of the product.</li><li>• FDA recommended that Cangene Corporation put together a Pharmacokinetic study and submit it for review to assure acceptability prior to performing their</li></ul>

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	<p><b>studies.</b> Submission of a BLA should be delayed until the data from an acceptable PK study are available</p> <ul style="list-style-type: none"> <li>• FDA informed Cangene Corporation that it was mandatory to include PK studies, all adverse events and raw data in the application..</li> <li>• FDA acknowledged the sponsor's initiative in conducting the studies on VZV IG for the indication being sought. Based on what was presented, the manufacturer needed to find a way of presenting the data in a way that would persuade the FDA that the product worked was safe and satisfied everyone's concerns.</li> </ul>
2000	Discussions with FDA on a—b(4)----- formulation
01-Nov-2000	Telecon: Cangene stated trials will not continue under IND 7201 and inactivation will be requested
26-Sep-2001	FDA issued inactivation letter for IND 7201
15-Sep-2005	<p>Internal meeting;</p> <ul style="list-style-type: none"> <li>• “It was recommended that Phil Krause in OVRP be contacted to provide information as to the extent that the assay has been validated. It is necessary to determine to what extent the binding assay correlates with protection.”;</li> <li>• “FDA is willing to consider this BLA under accelerated approval using surrogate markers. Cangene would need to present an acceptable PK study and if acceptable, would be required to submit a phase IV study to evaluate safety. ”</li> </ul>
20-Sep-2005	<p>External meeting: Regarding VZ-006 (pregnancy exposure):</p> <ul style="list-style-type: none"> <li>• Majority were secondary exposures, not primary exposures</li> <li>• Infection rate was a post hoc analysis</li> <li>• FDA questioned adequacy of sample size to claim noninferiority for endpoints such as pneumonia, encephalitis, and death, which had zero frequency</li> <li>• Comparison to historical control infection rate of 70% was post hoc and not adequately justified</li> <li>• FDA said secondary exposures may not have been real exposures, and the lower infection rate in the later strata (5-24 days since exposure) remains unexplained; Cangene agreed there had not been an analysis of the duration and type of exposure between strata</li> <li>• There was uncertainty about the timepoint for the CIS scores (Cangene thought they were at the time of varicella onset, whereas the protocol stated they were to be at day 7)</li> <li>• There was discussion about incomplete data for PK (days 0, 2, and 42)</li> <li>• FDA comments on adequacy of data for BLA filing: <ul style="list-style-type: none"> <li>○ Safety data is limited to 67 adults; the product has not been distributed in Canada despite licensure there</li> <li>○ No pediatric data; FDA advised collection of infant and pre-term data on dosing safety, perhaps from other VZ Ig products</li> <li>○ No clinical data on viral safety testing</li> </ul> </li> <li>• FDA recommendations on path to licensure: <ul style="list-style-type: none"> <li>○ FDA referred to the 1999 preBLA meeting at which FDA recommended a PK study comparing VariZIG™ by IM and routes against VZIG by IM route, and said this is the path of choice; design details were discussed</li> <li>○ FDA said a phase 4 study would be required under accelerated approval if clinical benefit could not be inferred from the surrogate PK data</li> </ul> </li> <li>• FDA rejected Cangene's proposal to submit a treatment protocol under 21 CFR</li> </ul>

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	<p>312.34; however, FDA did entertain the submission of an expanded access protocol with cost recovery</p> <ul style="list-style-type: none"> <li>FDA had additional comments: <ul style="list-style-type: none"> <li>Adequate dosing for IM and IV routes have not been established for equivalency to VZIG IM dosing</li> <li>A concern was expressed about the applicability of normal volunteer PK dosing to appropriate dosing in pregnant women</li> <li>A concern was expressed about lack of justification of using CIS score as the primary endpoint; FDA noted other analyses for infection rate and historical control comparisons were post hoc</li> <li>FDA said the sample size was inadequate for making claims about rates of important secondary endpoints (pneumonia, encephalitis, and death)</li> <li>FDA expressed a concern about the adequacy of the antibody data based on limited timepoints, and lack of information on the coefficient of variation for the assay</li> </ul> </li> </ul>
22-Dec-2005	<p>Telecon:</p> <ul style="list-style-type: none"> <li>FDA said protocols VZ-008 (PK) and VZ-009 (expanded access) may proceed</li> <li>FDA rejected Cangene's argument that the PK of the VariZIG™ IV route could be extrapolated to be superior, and therefore more effective, than the PK of the VZIG IM route of administration</li> <li>"FDA informed Cangene that unless they study IV administration, their product would not be licensed for IV administration"</li> <li>FDA made comments on VZ-009 (expanded access) among which were: <ul style="list-style-type: none"> <li>-b(4)-----</li> <li>FDA said the comparison of 16 subjects to a historical control is not justified, either for the sample size or for the historical control</li> <li>FDA said antibody data is needed from VZ-009, even though normal control PK data is available</li> <li>FDA discussed the different types of phase 4 studies that may be required, depending on the path to licensure</li> </ul> </li> </ul>
17-Jan-2006	FDA letter with comments on protocols VZ-008 and VZ-009, and noting the request to re-activate IND 7201
27-Feb-2006	Telecon reminding Cangene not to refer to VZ-009 as a treatment protocol, stating the -b(4)--- should be deleted from the VZ-009 protocol
17-Mar-2006	FDA letter approving Cost Recovery for VZ-009
23-Mar-2006	Telecon clarifying items for calculation of Cost Recovery
29-Mar-2006	FDA letter re-activating IND 7201
04-May-2006	FDA letter responding to Cangene's questions about IRB "qualification" of investigators
07-Sep-2006	<p>FDA letter with comments on VZ-008, among which are:</p> <ul style="list-style-type: none"> <li>Request to include data from female subjects</li> <li>Request (repeated from Jan 16, 2006, letter) for validation of potency and plasma anti-VZ assays</li> <li>Request for discrepancies in assaying potency of VZIG, with implications for VZ-008 PK study</li> <li>"Regarding your use of AUC to Day 28 for comparability, this is not generally recognized as acceptable, as it represents approximately one half-life. The general</li> </ul>

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	rule is that the AUC to use for 'bioequivalence' should represent $\geq 80\%$ of the AUC extrapolated to infinity. As you will be measuring antibody levels to Day 84, it should be possible to use $AUC_{0-84}$ for comparability.”
07-Sep-2007	Telecon discussing cost recovery item justification
27-Sep-2007	Telecon discussing cost recovery item justification
12-Oct-2006	FDA letter granting Cost Recovery
08-Nov-2006	FDA letter discussing IRB issues
12-Jan-2007	Telecon requesting CVs for investigators
06-Mar-2007	Telecon requesting CVs for investigators
04-May-2007	Telecon asking Cangene to continue using VZIG as a control in VZ-008 and to measure its potency, with adjustments for any decrease in potency
06-Jun-2007	FDA letter urging Cangene not to discontinue the VZIG arm in VZ-008
06-Nov-2007	FDA letter: <ul style="list-style-type: none"> <li>• Advises against unblinding VZ-008</li> <li>• Urges continuation of VZIG arm</li> <li>• Requests variability data for –b(4)– for testing samples</li> </ul>
13-Dec-2007	Telecon asking Cangene to continue using VZIG as a control in VZ-008 and to measure its potency, with adjustments for any decrease in potency (as before)
20-Mar-2008	Telecon discussing required tracking of blood product information and submission requirements
10-Jul-2009	Fax of FDA responses to meeting request questions: <ol style="list-style-type: none"> <li>1. “Does the agency agree with the modified licensure pathway put forward by Cangene?” → No</li> <li>2. “If the agency does not agree with the proposed pathway, would the agency agree to discussing the proposed licensure at a Blood Products Advisory Committee (BPAC) meeting to determine whether clinicians consider the data package appropriate for clinical use?” → (refer to answer to question 3)</li> <li>3. “If the agency does not agree to the modified licensure pathway or the proposal to discuss with the BPAC, what additional data would the agency expect to see in order to submit a BLA?” → “Pharmacokinetic modeling and simulation studies to define a VariZIG dose that would be bioequivalent to VZIG is acceptable. The sponsor, however, should first discuss their modeling and simulation method with the agency. Once a dose of VariZIG which is presumed to be bioequivalent to VZIG is found, then a PK study of VariZIG should be conducted in healthy subjects (n = 17 or 18) and you compare these PK parameters with the PK data of VZIG obtained so far in your development program.”</li> </ol>
14-Jul-2009	Telecon cancelling meeting and noting PK requirements stated in July 10, 2009, telecon
01-Oct-2010	Telecon (refers to Sep 30, 2010, internal discussion); Cangene was asked to submit: <ul style="list-style-type: none"> <li>• Unblinded data from VZ-008</li> <li>• A prospective plan for analyzing the data from VZ-008, including modeling simulation</li> <li>• Request to analyze data by actual potency of each vial administered</li> </ul>
19-Nov-2010	Telecon for emergency IND
01-Feb-2011	Telecon responding to Cangene’s questions in Oct 26, 2010, submission:

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	<ol style="list-style-type: none"> <li>1. “Does the agency agree in principle with the general modeling and simulation (M &amp; S) approach proposed by Cangene (pages 3 and 4 of the package submitted to the FDA on October 25, 2010)?” → Yes</li> <li>2. “Cangene is proposing to identify a VariZIG dose that will be non-inferior (in terms of Cmax and AUC) to a VZIG dose, which is consistent with Cangene’s previous M&amp;S work on the VIGIV licensure program. As the principal clinical concern is inadequate antibody levels, non-inferiority will ensure that patients received as much, if not greater, anti-VZV levels with VariZIG compared to the prior VZIG product. Will the FDA accept PK non-inferiority rather than bioequivalence?” → “Please apply the 90% confidence interval in your analysis. Although the Agency would accept non-inferiority, both the upper and lower bounds of the confidence interval will be reviewed for decision making. Please also provide details of your methodology for determining non-inferiority”</li> <li>3. “Cangene only plans to make –b(4)- with the –b(4)----- incorporation into the program prior to BLA submission. Will the Agency accept the BLA with a –b(4)--conformance lot released with the –b(4)----- potency test? Also, since release and stability data collection for the –b(4)---- assay will be limited at time of BLA filing, Cangene is planning to revisit acceptance criteria for –b(4)----- testing as more data become available. Does the Agency agree to this approach?” → “FDA will accept a –b(4)---- conformance lot released with your ---b(4)----- potency test, as long as your –b(4)--- correlates well with ---b(4)----- test. Thus, we do not object to your re-evaluation of acceptance criteria for –b(4)----- as more data become available.”</li> </ol>
23-Feb-2011	<p>Cangene submits IND 7201 amendment 45 requesting extension of post-exposure treatment up to 10 days</p> <ul style="list-style-type: none"> <li>• Refers to study results from VZ-006</li> <li>• Refers to Enders &amp; Miller 2000 (included in STN125430 refs.)</li> <li>• Refers to Miller et al 1993 (included in STN125430 refs.)</li> <li>• Refers to EMA Core SPC for human Varicella immunoglobulin for intramuscular use. (CPMP/BPWG/3726/02). July 27, 2005</li> </ul>
02-Mar-2011	Telecon for emergency IND for 4 neonates more than 96 hours after VZ exposure
14-Apr-2011	<p>Telecon to discuss IND 7201 amend 45 requesting extension of post-exposure time to 10 days:</p> <ol style="list-style-type: none"> <li>1. “VZ-006 - Cangene has given rates for "contracted varicella" and also states that subjects treated earlier had milder symptoms. “ <ol style="list-style-type: none"> <li>a. “Please define ‘contracted varicella’,</li> <li>b. please give rates for VariZIG and VZIG separately instead of having combined them,</li> <li>c. please provide data to support ‘milder symptoms’. “</li> </ol> </li> <li>2. “Historical data - Please provide the references (2 and 3) - the current description is unclear with your terms of subclinical infection, infection rate, expected infection, etc. “</li> </ol>
06-May-2011	<p>Telecon to discuss ---b(4)---- (cross ref.: IND 7201 amend 16 Dec 15, 2006)</p> <ol style="list-style-type: none"> <li>1. “Does FDA have an in house assay that could be used to comparatively test the potencies of VariZIG and the lot of VZIG Cangene is planning to use for VZ 008?”</li> </ol> <p><b>FDA response:</b> The FDA does not have a validated in-house assay for potency.</p>

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	<p>2. “For the pivotal comparative pharmacokinetic study, VZ-008, Cangene is proposing to dose by label claim potency, and then potency correct the serum anti-VZV levels based on actual measured content. Cangene will utilize the same assay format for serum sample analysis as well as measured content assessment. The rationale for proceeding in this manner is to (a) maintain the blind of the study and (b) an appropriate assay has not been identified and the only remaining VZIG product will expire March 12, 2007. As such, Cangene is planning to proceed with the study as currently approved. Does FDA have any concerns with the study proceeding in this manner?”</p> <p><b>FDA Response:</b> The linearity of the –b(4)--- over several fold dilutions must be confirmed. Cangene agreed to validate the –b(4)----- to cover the larger range needed for the test samples.</p> <p>3. “Based on the discrepant results between the b(4)assays methods, Cangene is evaluating the possibility of –b(4)----- method, as has been suggested by the FDA previously. In order to determine the feasibility of this –b(4)--, Cangene will need to validate the –b(4)--- as per current standards. If the assay can be appropriately validated, does FDA have any concerns with VariZIG being manufactured using this approach?”</p> <p><b>FDA Response:</b> The FDA supports our use of the –b(4)---- as long as the assay is appropriately validated. The correlations between –b(4)-----assay and ---b(4)-----has been well established.</p> <p>4. “If the FDA agrees with Cangene’s proposed strategy in question #3, the product that is to be used in study VZ-008 (and previous clinical studies) will not be fully representative of the product to be marketed. In order to address this, Cangene is proposing to potency correct the VZ-008 anti-VZV serum levels based on the -b(4)--- results. This would allow for an “apples-to-apples” comparison based on b(4)--- antibody results, which would demonstrate that a Cangene manufactured product is bioequivalent to the currently licensed VZIG. Does FDA agree that the data generated with the current product in study VZ-008 would be appropriate for licensing a subsequent product that has potency defined by the –b(4)----</p> <p><b>FDA response:</b> The –b(4)---- can be used for licensure but a full validation of the clinical assay (with a broad range) will be needed. The correlation between the -b(4)----- and the other methods (above) has been well established.</p>
12-Dec-2012	<p>Fax responding to Cangene’s pre-BLA meeting questions  <b>Clinical, Chemistry, Manufacturing and Controls (CMC),</b></p> <p><u><b>Sponsor Question CMC 1:</b></u>  -----b(4)-----  -----  -----  -----  -----</p>

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	<p>---b(4)--- ----- ----- -----</p> <p><b><u>FDA Response to Question CMC 1:</u></b> We are agreeable to accepting b(4) conformance lot to support licensure of VariZIG. We may opt to schedule an inspection during conformance lot manufacture and would like to coordinate timing with Cangene. Please indicate whether there were any major manufacturing process changes anticipated for the conformance lot that would differentiate it from clinical lots.</p> <p><b><u>Sponsor Question CMC 2:</u></b> <i>Cangene has established shelf-life dating based on stability studies with the lyophilized product employing the Varicella–Zoster Virus (VZV) –b(4)----- assay for potency determinations. Cangene intends to employ this dating on future lots of VariZIG. Cangene is proposing to –b(4)----- ----- to ensure that the label claim of b(4)125 IU/vial is achieved at release and b(4) IU/vial at the end of shelf-life.</i></p> <p><i>Does the Agency agree with this approach and is the proposed shelf-life specification acceptable?</i></p> <p><b><u>FDA Response to Question CMC 2:</u></b> Determination of the shelf life will be based on data provided in the BLA; we cannot comment without reviewing the data. However, if VariZIG potency appears to be maintained at b(4) 125 IU/vial (rather than b(4) IU/vial) over this dating period with sufficient confidence intervals, the 30-month specification is likely to be acceptable. As Cangene is aware, dating period adjustments are possible post-licensure as data becomes available. In the BLA submission, please provide data on potency of the clinical lots used, and the time frame of use, for each trial supporting licensure. Please expand upon reasons for delay in implementing the –b(4)---, and problems, if any, with validation. Please also submit where available –b(4)-- and –b(4)----- results for testing VZIG (MPH) material.</p> <p><b><u>Sponsor Question CMC 3:</u></b> <i>The potency of all lyophilized lots of VariZIG manufactured to date has been determined based on the Varicella–Zoster Virus (VZV) –b(4)----- assay. Due to limited results with the –b(4)-----, Cangene is intending to continue using the Varicella–Zoster Virus (VZV) –b(4)----- assay as the potency assay for product release and stability. Therefore, Cangene will continue manufacturing lots with the current label claim of b(4)125 IU/vial determined with the Varicella–Zoster Virus (VZV) –b(4)----- assay and filling the product to a maximum of 250 mg of protein per vial. Testing of product potency by the –b(4)----- assay will be performed in parallel and the results reported ‘for information only’ until sufficient data is available to establish a potency specification for this assay.</i></p> <p><i>Can the Agency confirm that this approach is acceptable to support BLA filing?</i></p>
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	<p><b><u>FDA Response to Question CMC 3:</u></b> This approach is acceptable to support BLA filing; we note that –b(4)----- values have been lower than –b(4)---- values. The final –b(4)----- potency specification should depend upon linkage of both assays to results obtained using –b(4)--- and if possible, the historical –b(4)----- potency standard.</p> <p><b><u>Sponsor Question CMC 4:</u></b> <i>As the bioavailability of the –b(4)----- has been previously demonstrated for the licensed products, Cangene does not intend on conducting any additional clinical studies to support -----(b)(4)----- for the VariZIG product.</i></p> <p><i>Does the Agency concur that no clinical studies will be required when Cangene is filing its PAS for the -----b(4)-----</i></p> <p><b><u>FDA Response to Question CMC 4:</u></b> We concur with the PAS approach for the formulation change. Please confirm that you will cross-reference safety and PK data for HepaGam B and WinRho SDF when administered intramuscular.</p> <p><b><u>Additional Comments for Questions CMC 4:</u></b></p> <ol style="list-style-type: none"><li>Please provide thrombin generation test results for your current IND lot of VariZIG and for the conformance lot (when available) to the BLA, with a summary risk assessment [for thrombotic events] for VariZIG.</li><li>Will Cangene be able to validate a –b(4)----- step in the manufacturing in time for conformance lot production?</li><li>Please note, we will also request samples of the conformance lot for –b(4)--- testing during the BLA submission.</li></ol> <p><b>Clinical</b></p> <p><b><u>Sponsor Question Clinical 1:</u></b> <i>In order to meet the efficacy requirements for BLA approval, Cangene proposes to submit clinical efficacy data from two open label, historically controlled studies VZ-006 (see Appendix IV) and VZ-009 (see Appendix VI), which demonstrate VariZIG's efficacy compared to the previously licensed VZIG (MPHBL) and untreated, literature based controls.</i></p> <p><i>Does the Agency agree that the clinical data from these two studies will be sufficient to demonstrate VariZIG's efficacy in the proposed at-risk patient populations?</i></p> <p><b><u>FDA Response to Question Clinical 1:</u></b> FDA cannot comment on sufficiency of data without full review. Based on the pre-BLA package, we agree with the historical control approach, and use of studies VZ-006 and VZ-009 to support efficacy. We understand the limitations on patient numbers in your PK study comparing VariZIG to VZIG; however, to</p>
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	<p>the extent that you can model the comparison, this may also provide support for licensure.</p> <p><b><u>Sponsor Question Clinical 2:</u></b> <i>Cangene proposes to submit comparative PK data from studies VZ-006 (using an Varicella–Zoster Virus (VZV) –b(4)-----; see Appendix IV) and VZ-008 (using –b(4)---; see Appendix V) in order to demonstrate comparable PK, as opposed to bioequivalence, between VariZIG and the previously marketed VZIG.</i></p> <p><i>Will the agency accept the comparable PK data, in conjunction with the efficacy data, as adequate information to demonstrate VariZIG will be expected to have a similar clinical efficacy profile as the VZIG product? If so, does the agency agree with the proposed indication and patient populations, which are consistent with the previously marketed product package insert?</i></p> <p><b><u>FDA Response to Question Clinical 2:</u></b> The PK comparability and the clinical information will both be important to support licensure. If this combined information is sufficient, we are likely to agree that the VZIG proposed indications and patient populations are reasonable to include in the package insert.</p> <p><b><u>Sponsor Question Clinical 3:</u></b> <i>In the BLA, Cangene will submit safety data from four controlled clinical studies (see Appendices II to V) and the expanded access program VZ-009 (see Appendix VI) that cover more than 400 subjects administered VariZIG.</i></p> <p><i>Does the agency agree that this safety dataset will be adequate to support VariZIG licensure for intramuscular administration to the proposed populations?</i></p> <p><b><u>FDA Response to Question Clinical 3:</u></b> Yes.</p> <p><b><u>Sponsor Question Clinical 4:</u></b> <i>Assuming that FDA is willing to accept the BLA submission for VariZIG with the clinical and product development information as presented, Cangene plans to continue the VZ-009 expanded access program only until BLA approval.</i></p> <p><i>Does the Agency agree that neither VZ-009 nor any other clinical trial will be requested as a post licensure commitment given the extensive clinical history with this class of product?</i></p> <p><b><u>FDA Response to Question Clinical 4:</u></b> We cannot make any statement regarding post-licensure requirements before the review of the submission.</p> <p><b><u>ADDITIONAL FDA COMMENTS:</u></b> Please include your pharmacovigilance plan in your BLA submission, including any plans you may have for any post-marketing safety studies as well as any planned expanded (e.g., 15 or 30 day reports not routinely required by 21 CFR</p>
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	<p>600.80) adverse event reporting. A guidance document for pharmacovigilance planning may be found at:  <a href="http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129423.pdf">http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm129423.pdf</a>.</p> <p>In addition the following guidance documents may be useful references:</p> <p>1. <a href="http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf">http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf</a>  2. <a href="http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm092257.pdf">http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm092257.pdf</a></p>
15-Dec-2012	FDA Meeting to discuss preparation for BLA submission
18-Jan-2012	<p>FDA letter containing FDA minutes of Dec 15, 2011 meeting</p> <p>FDA provided their proposed responses to Cangene's questions on December 12, 2011. After reviewing the proposed responses, the sponsor notified FDA on December 14, 2011 of their decision to limit the meeting to discuss only question number's CMC 2, 3, and 4 and Clinical 1 and 4. During the meeting Cangene indicated they no longer intended to discuss question Clinical 4.</p> <p><b><u>Discussion:</u></b></p> <p>The next batch of Varicella Zoster Immune Globulin (Human) will be manufactured, using the same manufacturing processes used for previous lots, the week of January 30, 2012. Cangene is unable to delay (until submission of the biologics license application, expected to be April 2012) manufacture of this lot because it would affect contractual agreements with Health Canada.</p> <p>After this lot is manufactured, there will be no plasma remaining for another lot of Varicella Zoster Immune Globulin (Human). In May or June 2012, Cangene will be manufacturing freeze- dried WinRho a with a fill size comparable to Varicella Zoster Immune Globulin (Human).</p> <p><b>Clinical, Chemistry, Manufacturing and Controls (CMC):</b></p> <p><b><u>Sponsor Question CMC 2:</u></b></p> <p><i>Cangene has established shelf-life dating based on stability studies with the lyophilized product employing the Varicella-Zoster Virus (VZV) –b(4)----- assay for potency determinations. Cangene intends to employ this dating on future lots of VariZIG. Cangene is proposing –b(4)----- to ensure that the label claim of b(4)125 IU/vial is achieved at release and –b(4)-- IU/vial at the end of shelf-life.</i></p> <p><i>Does the Agency agree with this approach and is the proposed shelf-life specification acceptable?</i></p> <p><b><u>FDA Response to Question CMC 2:</u></b></p> <p>Determination of the shelf life will be based on data provided in the BLA; we cannot comment without reviewing the data. However, if VariZIG potency appears to be maintained at b(4) 125 IU/vial (rather than –b(4)----) over this dating period with sufficient confidence intervals, the 30-month specification</p>

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	<p>is likely to be acceptable. As Cangene is aware, dating period adjustments are possible post-licensure as data becomes available. In the BLA submission, please provide data on potency of the clinical lots used, and the time frame of use, for each trial supporting licensure. Please expand upon reasons for delay in implementing the –b(4)–, and problems, if any, with validation. Please also submit where available –b(4)– and –b(4)– results for testing VZIG (MPH) material.</p> <p><b><u>Sponsor Question CMC 3:</u></b> <i>The potency of all lyophilized lots of VariZIG manufactured to date has been determined based on the Varicella–Zoster Virus (VZV) –b(4)– assay. Due to limited results with the –b(4)– assay Cangene is intending to continue using the Varicella–Zoster Virus (VZV) –b(4)– assay as the potency assay for product release and stability. Therefore, Cangene will continue manufacturing lots with the current label claim of b(4)125 IU/vial determined with the Varicella–Zoster Virus (VZV) –b(4)– assay and filling the product to a maximum of 250 mg of protein per vial. Testing of product potency by the –b(4)– assay will be performed in parallel and the results reported ‘for information only’ until sufficient data is available to establish a potency specification for this assay.</i></p> <p><i>Can the Agency confirm that this approach is acceptable to support BLA filing?</i></p> <p><b><u>FDA Response to Question CMC 3:</u></b> This approach is acceptable to support BLA filing; we note that –b(4)– values have been lower than –b(4)– values. The final –b(4)– potency specification should depend upon linkage of both assays to results obtained using MPH VZIG and if possible, the historical MPH VZIG potency standard.</p> <p><b><u>Additional discussion:</u></b> FDA agreed previously to accept a correlating study with the functional assay. FDA will review the information before determining the correlation between the –b(4)– FDA will need assurance that the potency of the product will not change. FDA prefers to see a linkage of the –b(4)– assays to the –b(4)– to the VZIG [Massachusetts Public Health (MPH) product] to the Massachusetts’s standard. Cangene did not obtain MPH VZIG potency standard. Cangene compared their potency data to data presented at the Blood Product Advisory Committee meeting.</p> <p>The correlation data, public data, MPH potency standard, and MPH VZIG data will be reviewed by FDA for adequacy. Cangene will determine potency of VariZIG based on the potency results for this –b(4)– lot. Any change in potency specification will be submitted in a Prior Approval Supplement, post-approval of the application.</p> <p><b><u>Sponsor Question CMC 4:</u></b></p>
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**Appendix 2. July 21, 2005, Blood Products Advisory Committee transcript – Discussion of Licensure Criteria for Varicella Immune Globulin**

	<p><i>As the bioavailability of the ----b(4)----- has been previously demonstrated for the licensed products, Cangene does not intend on conducting any additional clinical studies to support ----- b(4)----- for the VariZIG product.</i></p> <p><i>Does the Agency concur that no clinical studies will be required when Cangene is filing its PAS for -----b(4)--- formulation?</i></p> <p><b><u>EDA Response to Question CMC 4:</u></b> We concur with the PAS approach for the formulation change. Please confirm that you will cross-reference safety and PK data for HepaGam B and WinRho SDF when administered intramuscular.</p> <p><b><u>Additional Comments for Questions CMC 4:</u></b></p> <ol style="list-style-type: none"><li>Please provide --b(4)----- test results for your current IND lot of VariZIG and for the conformance lot (when available) to the BLA, with a summary risk assessment [for thrombotic events] for VariZIG.</li><li>Will Cangene be able to validate a --b(4)----- in the manufacturing in time for conformance lot production?</li><li>Please note, we will also request samples of the conformance lot for b(4)--- testing during the BLA submission.</li></ol> <p><b><u>Additional discussion:</u></b> The BLA will be filed with product made in the freeze-dried method. Methods for reducing the --b(4)----- level are still being evaluated. Cangene plans to submit a Type C meeting request to discuss manufacturing method to reduce the --b(4)----- levels. Currently, lots of VariZIG have not been tested for --b(4)----- levels. Cangene will submit in the BLA a commitment to add a --b(4)----- . With the BLA, Cangene will submit samples of the conformance lot.</p> <p><b><u>Clinical:</u></b></p> <p><b><u>Sponsor Question Clinical 1:</u></b> <i>In order to meet the efficacy requirements for BLA approval, Cangene proposes to submit clinical efficacy data from two open label, historically controlled studies VZ-006 (see Appendix IV) and VZ-009 (see Appendix VI), which demonstrate VariZIG's efficacy compared to the previously licensed VZIG (MPHBL) and untreated, literature based controls.</i></p> <p><i>Does the Agency agree that the clinical data from these two studies will be sufficient to demonstrate VariZIG's efficacy in the proposed at-risk patient populations?</i></p> <p><b><u>EDA Response to Question Clinical 1:</u></b></p>
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## Appendix 2. July 21, 2005, Blood Products Advisory Committee transcript – Discussion of Licensure Criteria for Varicella Immune Globulin

	<p>FDA cannot comment on sufficiency of data without full review. Based on the pre-BLA package, we agree with the historical control approach, and use of studies VZ-006 and VZ-009 to support efficacy. We understand the limitations on patient numbers in your PK study comparing VariZIG to VZIG; however, to the extent that you can model the comparison, this may also provide support for licensure.</p> <p><b>Additional discussion:</b></p> <p>Cangene plans to submit a post hoc analysis. They will perform and additional post hoc analysis on study VZ-008 for pK and how they would have looked if all sites had performed a pK on all enrollees. FDA considers this approach reasonable, but there is concern that the data will not be susceptible to modeling.</p> <p><b>General Discussion:</b></p> <ul style="list-style-type: none"> <li>• This product/indication has been granted Orphan Designation.</li> <li>• Cangene has already communicated to CDC that they intend to proceed with submission of a BLA.</li> </ul>
02-Feb-2012	Telecon to clarify items in the Dec 15,2011, meeting minutes
29-Jun-2012	STN 125430 for Varicella Immune Globulin submitted by Cangene
09-Jul-2012	FDA information request for STN 125430
08-Aug-2012	FDA information request for STN 125430
15-Aug-2012	FDA information request for STN 125430
02-Oct-2012	FDA information request for STN 125430
04-Oct-2012	FDA information request for STN 125430
09-Oct-2012	FDA information request for STN 125430
02-Nov-2012	FDA information request for STN 125430
08-Nov-2012	FDA information request for STN 125430

**Appendix 2. July 21, 2005, Blood Products Advisory Committee transcript – Discussion  
of Licensure Criteria for Varicella Immune Globulin**

**APPENDIX 2. JULY 21, 2005, BLOOD PRODUCTS ADVISORY COMMITTEE TRANSCRIPT –  
DISCUSSION OF LICENSURE CRITERIA FOR VARICELLA IMMUNE  
GLOBULIN**

**FOOD AND DRUG ADMINISTRATION**

**CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

This transcript has not been edited or corrected, but appears as received from the commercial transcribing service. Accordingly the Food and Drug Administration makes no representation as to its accuracy.

**83rd Meeting of:**

**THE BLOOD PRODUCTS**

**ADVISORY COMMITTEE**

July 21, 2005

Gaithersburg Holiday Inn  
1 Montgomery Village Avenue  
Gaithersburg, Maryland

Reported By:

## **Appendix 2. July 21, 2005, Blood Products Advisory Committee transcript – Discussion of Licensure Criteria for Varicella Immune Globulin**

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- FDA Perspective and Questions for the Committee
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**KARL-GOSTA LJUNGSTROM, MD, PhD**, Associate Professor of Surgery at Karolinska Institutet, Senior Vascular Surgeon, Department of Surgery, Danderyd, Sweden

**MONA MARIN, MD**, Medical Epidemiologist, National Immunization Program, CDC, Atlanta, Georgia

At this time, if I could, I would just like to introduce the two new temporary voting members. They are, on the right-hand side of the room -- that is the audience's right -- we have Dr. Philip LaRussa. He is professor of clinical pediatrics, Columbia Presbyterian Hospital, New York, New York.

On the other side of the room we have Dr. Jane Seward. She is chief of viral vaccine preventable diseases, disease branch, National Immunization Program, CDC. Thank you for joining us. Dr. Allen, I turn it over to you.

DR. ALLEN: Thank you. Topic two, the first topic for this afternoon, is the scientific basis for the review of varicella zoster immunoglobulin.

As we will learn very quickly, there is going to be a change in the production of this, and the committee is asked to recommend alternatives for the FDA and other government agencies. We will start with a background presentation by Dr. Dorothy Scott of the Food and Drug Administration. Dr. Scott.

**Agenda Item: Scientific Basis for review of Varicella Zoster Immune Globulin. Background.**

## Scientific Basis for Review of Varicella Zoster Immune Globulin Products

Blood Products Advisory Committee

July 21, 2005

Dorothy Scott, M.D.

OBRR/CBER

DR. SCOTT: Good morning. I will try, best as I can, to lay out the issues for you. What we are asking you to discuss is the scientific basis for review of a new varicella zoster immunoglobulin product.

### Varicella Zoster Immune Globulin (VZIG)

- Licensed in 1981
- Intramuscular preparation sourced from selected high anti-VZV plasma units
- Indications – Prevention/Modification of severe varicella disease in:
  - Immune compromised children and adults
  - Premature infants
  - Infants < 1 year age
  - Selected non-immune pregnant women and healthy adults
- Should be administered within 96 hours of varicella exposure

First, I want to give you some background on the current product. VZIG, as it is called -- it is an IM product -- was licensed in 1981 by FDA.

It is an intramuscular preparation source from selected high anti-varicella antibody plasma units. In other words, all plasma units are tested that come in, and the ones that meet a certain titer cut off are used for this. So, it is a specific immune globulin.

[Type text]

The indications in the package insert are for prevention or modification of severe varicella disease in susceptible people, that is, people who have not had varicella before, in general.

These include immune compromise children and adults, premature infants, selected infants less than one year of age, and selected non-immune pregnant women and healthy adults. You will be hearing about these in more detail. It should be administered within 96 hours of varicella exposure.

## VZIG Licensure 1981

- Study subjects: immune compromised children with household exposure to varicella
- Trial design: randomized, double-blind
- Comparators:
  - Historical controls (Feldman et al, Pediatrics 56: 388-97, 1975)
  - Zoster Immune Globulin (unlicensed IG prepared from plasma of donors convalescing from shingles)

How did we go about licensing VIG in 1981? That was a long time ago, but there was a clinical study. The study subjects are immune compromised children with household exposure to varicella. Many of these were cancer patients.

The trial design was random access, double blind study, but there were two comparators. Obviously, you couldn't blind the historical controls but, compared to the new VZIG product, were historical controls from a paper by Feldman et al, which was essentially the natural history of varicella infection in immune compromised children.

The other comparator was zoster immunoglobulin. This is an interesting product. It was an unlicensed immunoglobulin, although it was under study, and it was prepared from plasma of people that were convalescing from shingles. So, these would be adults who had been re-infected or have self-reinfected, if you will, with varicella.

Now, the problem with that is that it was very difficult to get people who were convalescing from shingles in sufficient quantities to get as much plasma to make as much product as was needed. That is why it is called ZIG. It was not pursued.

## VZIG Pivotal Trial for Licensure<sup>1</sup>

	VZIG	ZIG	Historical controls <sup>2</sup>
Pox count > 100	12/81 (15%)	13/83 (16%)	87%
Pneumonia	3/81 (4%)	3/83 (4%)	25%
Hepatitis	0	0	10%
Encephalitis	0	0	5%
Death	0	0	7%

<sup>1</sup> Zaia et al, JID 147: 737-43, 1983.

<sup>2</sup> Feldman et al, Pediatrics 56:388-97, 1975

These are the results of that first study, which was considered the pivotal trial for licensure. I will just orient you to this slide.

What we are looking at is readouts or end points that signify severe varicella disease. These include pox count greater than 100, pneumonia, hepatitis, encephalitis and, of course, death. These are the comparators. The ZIG product, the zoster immune globulin, and the historical controls.

What you can see is that, if you compare VZIG to ZIG, you get a very similar rate of pox count greater than 100, in the 15 to 16 percent range, of pneumonia around four percent, no hepatitis, encephalitis, and no death.

Now, subsequent to this, there was another study that compared different doses of VZIG and, in your package insert, I believe that those numbers actually have the data from that second study as well.

So, these will be slightly different but the point is, really, in comparison to the natural history of this disease in immune compromised children, you have quite a great difference in terms of substantially less severe disease, pox count, and organ system involvement and, very important, fatalities.

## VZIG Supply

- Sole manufacturer – Massachusetts Public Health Biological Laboratories (MPHBL)
- MPHBL plasma fractionation facility scheduled to close
- VZIG Supply (MPHBL report)
- Are there alternative, effective therapies to prevent severe VZV disease?
- What scientific evidence is needed to support licensure of another VZIG product?

So, what brings us to you today? Well, the sole U.S. manufacturer of this product is Massachusetts Public Health Biological Laboratories.

Their fractionation facility is scheduled to close. Dr. Ambrosino will be talking to you about the current supplies of VZIG and when we anticipate we might run out of that, and you will have an update in more detail about the supply.

The questions they are asking are, whether there are alternative effective therapies to prevent severe varicella disease. In other words, do we need VZIG.

The other question that we would like the committee to discuss is what scientific evidence would be needed to support licensure of a new product.

## Possible alternatives to VZIG – no controlled trials

- Antiviral medications, e.g. acyclovir
- IGIV



[Type text]

differences in titers, considering this is a serial two-fold dilution. It wasn't assessed more precisely than that.

So, what does this mean? This means that if you take any immune globulin off the shelf that is not a titered product, you don't know if you are going to be giving your patients something like this, or something like this.

The other thing that we don't learn from this is whether or not there are any differences in antibody affinity among these products or antibody function compared with VZIG.

## VZIG/VZIGIV Licensure

- Possible target population(s) for study – exposed, non-immune subjects
  - Immune compromised children/adults
  - Pregnancy (for prevention of severe infections in the mother and/or neonatal infection)
  - Non-immune otherwise healthy individuals
- Which population(s) would be most informative/useful to study?
- Are surrogate markers useful predictors efficacy?

So, now on to the licensure questions or, rather, what information would be needed to support licensure. There are many possible target populations for study.

Naturally, these will be exposed, presumably non-immune subjects, the kinds of people who would receive VZIG now.

For example, immune compromised children or adults or both, pregnant women for prevention of severe infections in the mother, but also neonates. I should have made that a separate line, for prevention of severe infections in children, or neonatal infections. Premature infants would be included, or non-immune, otherwise healthy individuals but, of course, the rate of severe varicella here is not very high.

So, our question to you will be, among other things, what populations would be the most informative or important to study, and I think you will get a lot of that information from Dr. LaRussa's talk to help you think about it.

## Why surrogate markers? One Potential option for licensure via Accelerated Approval (21 CFR 601.40-46)

- Approval may be granted on the basis of **adequate and well controlled clinical trials establishing that the product has an effect on surrogate endpoint that is reasonably likely**, based on epidemiologic, therapeutic, pathophysiologic, or other evidence **to predict clinical benefit**, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.
- Note: as a condition, the applicant must study the product further to verify its clinical benefit post-licensure)

Another question is whether surrogate markers can be useful predictors of efficacy. Well, where does that question come from?

Well, there are a couple of potential paths for licensure and, right now, FDA doesn't particularly favor one over the other, but one mechanism of licensure is based on surrogate markers.

This is defined in the CFR where you can have an approval based on adequate and well controlled clinical trials, showing that the product has an effect on a surrogate end point that is reasonably likely to predict clinical benefit.

An example of a surrogate marker study, for example, would be a pharmacokinetic study or comparison of one product to another, with a kind of measurement or output, a PK measurement of antibody titers, or antibody function.

So, that is what I am talking about in this situation when I say a surrogate marker study. It would still be a clinical study. You might not have to have the immune compromised populations but, again, that is something I think we would like to hear from the committee on.

## Possible Surrogate Markers for VZIG Efficacy (PK study)

- Serum anti-VZV antibody tests:
  - Solid-phase assays – ELISA, FAMA, IFA, complement fixation, etc.
  - gpELISA: correlates with protection in vaccine studies
    - Levels needed for protection in immune compromised patients unknown
  - In vitro neutralization
  - Animal models

Potential surrogate markers would include serum antiviral antibody tests, and there are a number of these, which I have listed here, and Dr. LaRussa will mention as well.

They have varying ease and varying specificities. The GP ELISA, in particular, I mention because that is correlated with protection in vaccine studies, but the levels needed for protection in immune compromised patients are really unknown because, of course, the vaccine studies were on healthy subjects.

In vitro neutralization tests are also possible. These are typical plaque assay types of tests. Animal models are very difficult, because humans are the only natural host of this infection. Great apes can also be infected.

The animal models that have been described either involve normal cell cultures or ganglion cultures, and SCID human mice with human skin, as well as human systems.

These don't seem particularly practical to use as an assay in a case like this, where you would have multiple samples.

## Questions to the Committee

1. Please discuss what laboratory and clinical data would be sufficient to demonstrate efficacy of a new anti-varicella antibody preparation, for prophylaxis of severe varicella infection. In particular, please comment on
  - a. Which target populations would be most informative to study
  - b. What surrogate markers would be appropriate for assessment of efficacy
  - c. Other considerations for clinical trials
2. Please comment on whether the available scientific data support use of IGIV or acyclovir as a substitute for VZIG for prophylaxis of severe VZV infection in any clinical settings

So, these are the questions we are asking you to think about. Please discuss what laboratory and clinical data would be sufficient to demonstrate efficacy of a new preparation of VZIG for prophylaxis of severe varicella infection.

In particular, we would like to have comments on which target populations are most informative, what surrogate markers would be appropriate for assessment of efficacy, and other considerations that you would have that you think are important for a clinical trial.

We would also like you to comment on whether the available scientific data support the use of IGIV or acyclovir as a substitute for VZIG for prophylaxis of severe varicella infection in any clinical setting.

## Speakers

1. Donna Ambrosino, M.D., and Catherine Hay, Ph.D., MPHBL. VZIG manufacture, potency testing, and current supply status.
2. Philip LaRussa, M.D., Professor of Clinical Pediatrics, Columbia University. Severe Varicella Zoster disease, correlates of protection, and post-exposure prophylaxis options.
3. Mona Marin, M.D., NIP/CDC. ACIP and Red Book recommendations for post-exposure prophylaxis of severe varicella zoster infections

[Type text]

We are very fortunate to have some excellent speakers who have worked with VZIG and with varicella for a number of years, in some cases.

First, we will hear from Massachusetts Public Health Biological Laboratories. Dr. Donna Ambrosino will discuss the supply situation and the discontinuation of manufacturing. Katherine Hay will discuss some aspects of manufacture that are important to know about for the sake of a new product.

Dr. LaRussa will tell us about severe varicella zoster disease, the correlates of protection, or rather, what is known about that, and post-exposure prophylaxis options.

Mona Marin from CDC will tell us about the ACIP (*Advisory Committee on Immunization Practices*) and red book recommendations for post-exposure prophylaxis. Thank you very much, and I will take any questions.

DR. ALLEN; Dr. Lew?

DR. LEW: On the table that you showed us, actually the graph, you compared the levels by the GP ELISA titer in the different IVIGs. I am assuming you did this recently?

With time, as everyone gets immunized, all the children, and they grow up and they are the ones doing the donation, it may change.

DR. SCOTT: That is right, and in fact, based on the age of donors, we might expect that a lot of these people would not have been immunized and this reflects more the natural infection. That is absolutely the case.

I think the point that you are also making is that if we take you can take an IVIG off the shelf, or if we even say a certain product usually has high titers, that this could become a moving target one way or the other.

DR. SEWARD: I just want to comment that these tests were all done this year. They were all done earlier this year.

DR. SCOTT: Thanks to Scott Schmid, who works a lot on these viruses at CDC. We are very grateful to him for accepting the samples and running them.

DR. ALLEN: Other clarification questions for Dr. Scott? Okay, we will certainly have a chance to discuss that more fully at a later point. Thank you very much.

Why don't we, at this point, move on to the presentations by Dr. Ambrosino and Dr. Hay. Welcome, and tell us about VZIG manufacture, potency, testing, and the current supply status, please.

**Agenda Item: VZIG Manufacture, Potency Testing and Current Supply Status.**

# **Varicella Zoster Immune Globulin (VZIG)**

**Donna M. Ambrosino, M.D.**

Director and Professor  
Massachusetts Biologic Laboratories  
University of Massachusetts Medical School

**Catherine A. Hay, Ph.D.**

Senior Director of Regulatory Affairs  
Massachusetts Biologic Laboratories  
University of Massachusetts Medical School

DR. HAY: Good afternoon. I am Catherine Hay and, as Dr. Scott mentioned, we have been invited here to talk about the manufacturing process and the supply issues.

## **Overview**

- Plasma Screening Assay
- Manufacturing Process
- Potency Assay
- Supply Issues (Dr. Ambrosino)

I will be discussing the plasma screening assay, the manufacturing process, and the potency assay, and then I will hand over to Dr. Ambrosino, who will address the supply issues.

## **Plasma Screening**

- Units screened by Complement Fixation Assay (positive at 1:50 dilution)
- Both pheresis and recovered plasma used

As Dr. Scott mentioned, before any plasma is accepted for use in manufacturing, it is screened for the presence of antibodies to varicella zoster virus.

## **Complement Fixation Assay**

- In-house assay
- “A Guide to the Performance of the Standard Diagnostic Complement Fixation Method and Adaptation to Micro Test.” US DHHS, PHS, CDC, February 1981

The assay that we use is a complement fixation assay and, for units to be accepted for further manufacturing use, they have to be positive at the one to 50 dilution. We are currently approved to use both recovered plasma and plasma obtained from apheresis.

The complement fixation assay is the standard -- it is an in-house assay, and it is the standard assay based on the CDC's method that is described in the reference given on this slide.

## VZV Antibody Screening

	01/2003 - 12/2003	01/2004- 10/2004
Plasma Samples screened for VZV antibodies	69851	37783
# Positive Samples	4205	2407
% Positives	6.0	6.4
Liters Pooled	1267	751

This slide just shows some recent data from our screenings of the last two years. The plasma is supplied by the American Red Cross, New England region, and these figures represent initial screens of random plasma samples.

You can see that, for both 2003 and 2004, the percentage of positives has remained fairly constant at around six percent.

## Manufacturing Process

- Cold ethanol precipitation (Cohn-Oncley)
- Solvent/detergent viral inactivation step
- Final liquid formulation
  - 10-18% IgG
  - pH 6.4-7.2
  - 0.3 M Glycine

On to the manufacturing process. Briefly, we use the Cohn-Oncley method, the cold ethanol precipitation process.

This is followed by a solvent detergent viral inactivation step. The product is then formulated to content 10 to 18 percent IgG at a pH of 6.4 to 7.2 and 0.3 mole of glycine.

[Type text]



This next slide is a very simplified manufacturing process flow diagram. You can trace the progress through the fractions from the plasma pool to the fraction three supernatant.

At this point, there is an ultra-filtration step which concentrates the product to seven percent IgG before it is subjected to the solvent detergent viral inactivation step using Trion butyl phosphate and Triton X-100.

After the TNBP and Triton have been removed by chromatography, there is a further concentration by ultra-filtration, and then the product is formulated, sterile filtered, and filled.

## Potency Assay (since 1984)

- Virgo Immunofluorescence Assay
  - Kit manufactured by Hemagen
    - slide test: antibody-antigen complex formed; fluorescein-labelled anti-human antibody added; apple-green fluorescence in presence of antibody-antigen complex
  - Positive and negative controls from kit
  - In-house standard (qualified for use by comparison to previous standard)
  - 2-fold dilutions (1:1024 – 1: 32768)
  - Endpoint is highest dilution showing positive reaction

Before we release the product for distribution, we perform 11 assays on the final filled products, but the one that I want to address today is the potency assay.

[Type text]

We originally used the FAMA assay to perform this assay but, since 1984, we have changed to the Virgo Immunofluorescence assay.

We use a kit that is manufactured by Hemagen, and basically it is a slide test. The first step, you form your antibody antigen complex. You then add a fluorescein labeled anti-human antibody and, if there is a positive reaction, you get an apple green fluorescence.

We get positive and negative controls from the kit and the in-house standards is one of our previous lots of VZIG, and they are qualified for use by comparison to the previous standard.

We make two-fold dilutions of the test samples and the standards and run them in the assay, and the end point is the highest dilution showing a positive reaction. That is the apple green fluorescence.

## Potency Assay

### Acceptance criteria:

- In-house standard titer: 8192  
(allowed range: 4096 – 16384)
- Final vial specification:  
potency ratio:  $\geq 0.8 \times$  in-house standard

In order for the assay to be acceptable, both the positive and negative controls have to meet pre-defined acceptance criteria, and our in-house standard titer has to be 8192 plus or minus one two-fold dilution.

For the final product to meet the potency specification, it has to be at least 80 percent of the in-house standard.

## Potency Data

Lot number	Titer (geometric mean)	Potency Ratio
MVZIG-62	4871	1.0
MVZIG-64	8192	1.0
MVZIG-65	8192	1.0
MVZIG-68	8192	1.2
MVZIG-70	8192	1.0
MVZIG-71	8192	1.0
MVZIG-73RF2	8192	1.0
MVZIG-76	8192	1.2
MVZIG-77	9742	1.2

I just wanted to show you some potency data from some lots of VZIG that were manufactured from 1997 onwards. You can see that the titer of the lots remains fairly reproducible and constant throughout this time period.

That was my very brief overview of the manufacturing process, and now I will turn you over to Dr. Ambrosino to discuss the supply issues.

DR. AMBROSINO: One comment about the technical questions. We were hoping to keep that simple, but we do have a technical expert, Dr. Stan Cruz, who is the senior director of manufacturing and development, is here with us, and he and I could answer additional questions you might have. There are many, many steps to the fractionation.

Dot was kind enough also to allow us -- I only have six slides in four minutes -- to tell you why we stopped manufacturing VZIG, and I thought that was important for the committee to know.

## Massachusetts Biologic Laboratories University of Massachusetts Medical School

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- ONLY **non-profit** FDA-licensed **vaccine** and **biologic** manufacturer in the US.
- Td vaccine for US
- Develop new monoclonal antibodies
- Blood Products

The biological laboratories is the only non-profit FDA licensed manufacturer of both vaccines and biologics in the United States. It is a rather unique organization.

We have three product streams, essentially Td vaccine, which we make 20 percent of the United States need, we develop new monoclonal antibodies, and our third product line with blood products.

### Massachusetts Biologic Laboratories 1894 - 2005

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1894



2007



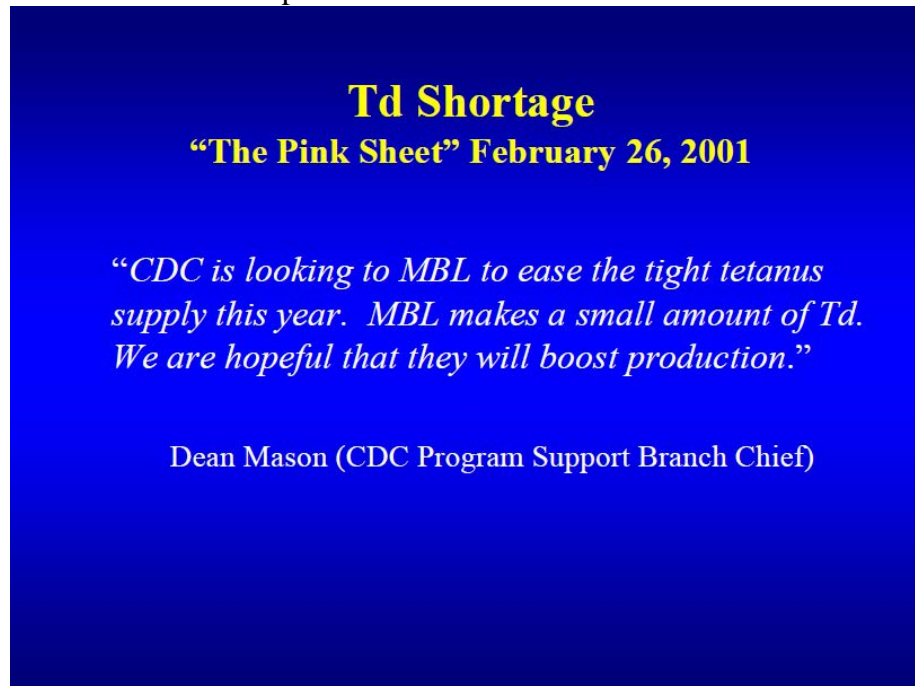
2005

[Type text]

Now, we have a long past history, as you can see by these pictures, showing my office which, I must tell you, is pictured in that first picture, unchanged at the top of the hill there.

It was very clear to us some years ago that we needed a new manufacturing facility to continue to manufacture products. As you can see in the lower picture, our newer facility will open in the next year or so.

When we designed all that, we had to make some choices of how could we continue to manufacture the three product lines we had.



We decided we had already made a commitment for tetanus vaccine. There was a shortage that you all remember in 2001, and we had promised the Centers for Disease Control that we would continue to manufacture Td and, frankly, ramp up from one to nine million units of vaccine for the country. We thought TD vaccine was something we needed to preserve.

## Entering the New Field of Monoclonal Antibody (MAB) Development

- **Orphan Products**  
(a.k.a. too small for big pharmaceutical companies)
- **Urgent public health need**



We also made monoclonal antibodies with these two missions in mind, orphan products, also known as too small for big pharma, and urgent public health need.

We have three or four of these products in clinical studies and manufacturing that we feel are crucial and, thus, we are committed to this new technology, monoclonal antibodies.

## MBL Blood Products

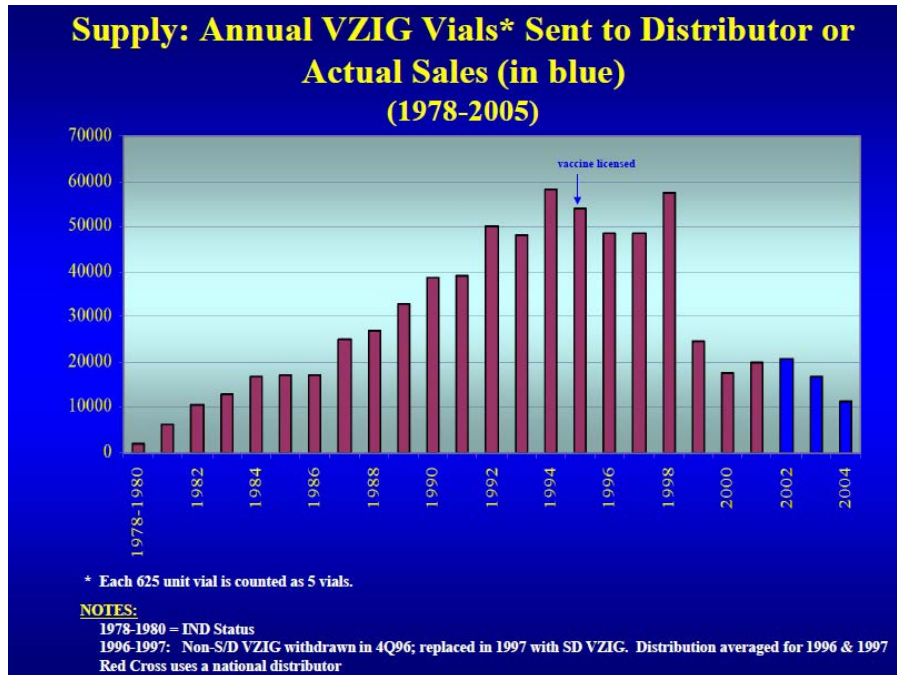
1. **Albumin** [Human]
2. **RespiGam®** (Respiratory Syncytial Virus Immune Globulin Intravenous [Human])
3. **VIG** (Vaccinia Immune Globulin Intravenous [Human])
4. **CytoGam®** (Cytomegalovirus Immune Globulin Intravenous [Human])
5. **BabyBIG** (Botulism Immune Globulin Intravenous [Human])
6. **VZIG** (Varicella Zoster Immune Globulin [Human])
7. **ISG** (Immune Globulin [Human] for IM Use Only)

Then the final list, therefore, raw blood products, which we list here for you. Today we are only talking about VZIG.

We didn't take this choice lightly. This was a thoughtful, very intense with world experts joining us to make the final decision of what it would mean if we closed down fractionation.

[Type text]

After all of that, the group and, at the end, me, decided that it was the wisest thing to do to stop making blood products at the biological laboratories. We are only 150 people. Now we have grown to 300.



Given that, where are we with VZIG? I am showing in this graph here the distribution of VZIG by units. These are pediatric units. You divide by five to know how many adult doses you would need.

Bottom line, as you can see, since the development of the product by us all the way through the licensure, the need was going up.

As vaccine got licensed and chicken pox dropped dramatically in this country -- what a wonderful success story -- the number of immunocompromised people being exposed and, therefore, needing VZIG, dropped like a stone as well.

We are delighted, and the blue bars there show the last three years of actual sales. That data is the strongest and definitive.

As you can see, in the last year we dropped yet a half again, 20,000 the previous year, 10,000 units this last calendar year.

Ten thousand units means, divide by five, 2,000 adults were all that requested VZIG in the United States and Canada.

I have to tell you that is requested. We don't really know if those were used. Sometimes hospitals just buy this from our distributors and then it outdates. So, we don't really know how much is used, but no more than 2,000 adults last year were treated.

## Current Supply

- We estimate that supply will last until January 2006 (although may be a few months longer)
- No pediatric dose vials available

So, what is our current supply? I can give you very complicated numbers, but I have to tell you that what we do is, we are making a conservative estimate here.

We say, well, what if we sell exactly what was sold last year, assuming that is, in fact, an over-estimate, given that the disease continues to drop.

If we take that estimate of exactly what we sold last year, the supply that we have in hand will last at least through January. In fact, probably a few months longer than that, but we wanted to be conservative.

The pediatric doses, there used to be pediatric doses as well as adult. For the last six months, there have only been adult doses available. Therefore, the 600-something units, vials, are what is available, and this estimates through January are taking that into account.

In those very brief comments, I wanted to add that I also would be glad to answer questions after you hear from Dr. Marin and Dr. LaRussa. This was a very challenging decision for the biologic laboratories.

I am charged with making the decisions of what products we are making will matter the most and, thus, when we have to make difficult choices, at the end of the day, make the difficult choices, but we will be glad to tell you why we don't think we need VZIG any longer, but would obviously defer to the other speakers first. Thank you.

DR. ALLEN: Clarification questions for Dr. Hay and Dr. Ambrosino? I have got two quick questions. You showed -- Dr. Hay, you showed a slide that had the antibody screening, and only six percent were positive for antibody.

I assume that you continued just to get the recovered plasma from the Red Cross, rather than trying to identify specific donors and asking them to come back as source plasma donors.

DR. AMBROSINO: It is a complicated question. The answer is in between that. In fact, it is Red Cross that decides this.

I tried to get numbers, frankly, of has that percentage changed over the 20 years. We don't have accurate numbers because we can't, from the records, determine how many were known positives before that came back.

[Type text]

So, all I can tell you that that last number, that it is six percent, and it is a mixture, but we think it is around six percent of random donors.

DR. ALLEN: Okay, and the second question in the manufacturing process, your final liquid formulation is 10 to 18 percent IgG. I assume that that is adjusted to give you the titer that you want. Is that correct?

DR. AMBROSINO: No. The specs, the product is manufactured first into the final concentration. That is what is allowed, 10 to 18 percent. Actually, it is almost always 16 percent.

Then, once you have made the product at 16 percent, you then test the titer and the titer, as you saw, is always around the 8,000. You don't formulate to the titer, you formulate to the specs, that you want around 16 percent IgG for injection.

DR. ALLEN: Thank you.

DR. LA RUSSA: I just want to make a comment, in case anybody is left with the impression that only six percent of the adult population has lasting immunity to varicella.

The beauty of using complement fixation is that it is not a terribly sensitive test. So, you are actually screening for high titer units.

DR. ALLEN: Thank you for that clarification.

DR. KATZ: That is kind of my question because I am not familiar with the comp fixed titers. Approximately, what is one to 50 in a FAMA? Do we know?

DR. AMBROSINO: Similar, I think would be the fair assessment, similar, and it depends on how you run your FAMA. I think, to answer your question appropriately, similar. Dr. LaRussa, I think, will go over some results there that will specifically address that a little better in terms of when you give product to patients and measure in different ways, what do you see.

DR. LAAL: Are you making murine monoclonal antibodies or human monoclonal antibodies?

DR. AMBROSINO: The question is what kind of monoclonal antibodies. We are making only human monoclonal antibodies to SARS, C-difficile, as well as rabies at the moment.

DR. LAAL: So, you have not considered making human monoclonal antibodies to this?

DR. AMBROSINO: I think it is a very good question. We did consider it, and our judgment, frankly, is that it is not a wise path. We really feel that IVIG used in the right way will, in fact, substitute and is a good alternative. I only said that because I was asked the question.

DR. EPSTEIN: Can you comment on the correlation between the comp fixed titer and the GP ELISA titer?

DR. AMBROSINO: Not well. I can tell you -- Dorothy, maybe you can tell me if I remember correctly -- the range in titers there, for the VZIG, and I don't have that up here, were done as GP ELISA for that product.

I can tell you that product had an 8,000 or so titer by our test, the kit, essentially. I think if you look at that then -- Dorothy, do you remember what the VZIG was on that graph -- 9,000? So, close.

DR. ALLEN: Other questions for clarification? They will be here later in the discussion. So, we can certainly come back to you for a resource. Thank you very much.

[Type text]

The next presentation will be by Dr. Philip LaRussa, severe varicella zoster disease, correlates of protection and post-exposure prophylaxis options. It will be a 45-minute presentation.

**Agenda Item: Severe Varicella Zoster Disease, Correlates of Protection and Post-Exposure Prophylaxis Options.**

## **Varicella-Zoster Virus: Clinical Manifestations & Options for Post-exposure Prophylaxis**

Philip LaRussa, M.D.  
Columbia University  
July 21, 2005

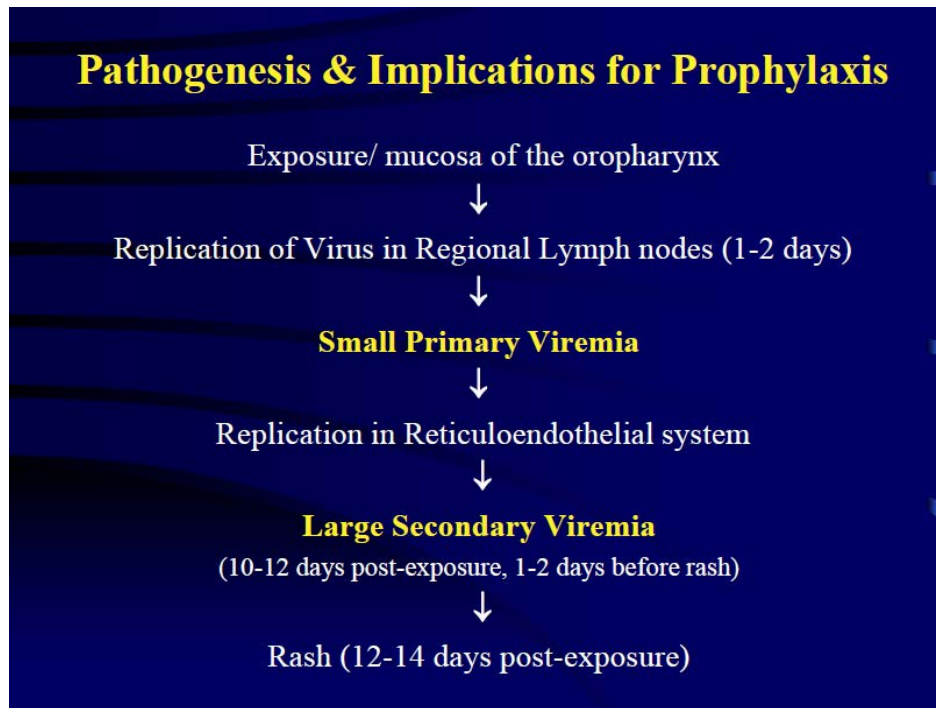
### **Topics for Discussion**

- Clinical Manifestations of Severe Varicella
- Epidemiology of Varicella in the Vaccine Era
- Correlates of Protection against Varicella
- Options for Post-exposure Prophylaxis

DR. LA RUSSA: My job today is to remind you all what varicella used to be like before we had an effective vaccine, to tell you a little bit about what the vaccine has done to the epidemiology of disease, tell you what little we know about correlates of protection, and then discuss some of the options for post-exposure prophylaxis.

[Type text]

At the end of the presentation I added a bunch of slides to sort of fill out some details on some of the options, because we won't have time to go over every study that was ever done.



I think it is probably worthwhile spending a minute talking about the pathogenesis of varicella, because it makes it a little easier to understand why some preparations work at some points and not at other points.

What we think is going on is that you come in contact with the virus probably mostly through the mucosa of the oral pharynx.

Then pretty quickly we know that virus gets into the lymphocytes and the regional lymph nodes, and there is a short period of replication there, probably a day or two.

Then there is a small primary viremia that spreads the virus and, for lack of a better term, to anywhere where there is a reticular endothelial system, probably tissue monocytes and macrophages.

The virus then lays dormant there for a while and just prior, probably 24 to 48 hours, before the individual develops rash, there is really a large secondary viremia which we think spreads the virus to the skin, and then you develop the rash.

So, you really have two opportunities for post-exposure prophylaxis. One is to effect this small primary viremia in the beginning, and the second is to effect this larger, secondary viremia much later on.

I will give you the punch line now, is that we think VZIG probably works at this point, because once you give it beyond this point, it doesn't seem to have a whole lot of effect.

We think the antivirals probably work at this point. It is kind of interesting. You will see that, although they don't do a whole lot to decrease the frequency of infection in individuals who are exposed, they do quite a good job in preventing severe disease, and probably what they are doing is limiting this secondary viremia.



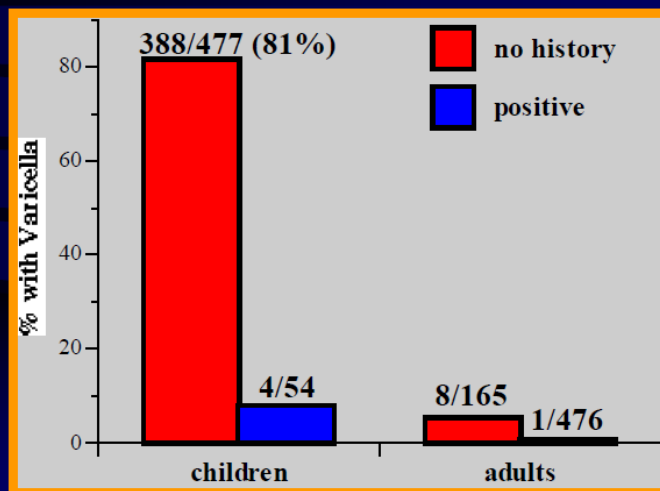
So, this is a typical case of varicella in the normal kid. This was actually my son, and he developed over 300 lesions. The average is about 300 in the normal kid.

You can get new crops of lesions for up to a week afterwards. Usually then the lesions crust over and the crust eventually falls off.

It can be quite an annoyance to the child, and also to the parents who have to take care of that sort of cranky individual.

The other thing I should say is that there is quite a variation in the range of disease, from kids that have five lesion and absolutely no constitutional symptoms to kids with much more severe disease, that I will show you in a minute.

## Varicella is highly contagious after household exposure



Ross, 1962

[Type text]

I wanted to show you this. This is from Ave Ross' study in 1962, just so we cement the idea that varicella is highly contagious.

In his study, 81 percent of the children who had a household contact with a negative history came down with disease.



Zoster is the reactivation of latent virus as you get older and your immune system stops working as well as it should.

You get a reactivation in the dermatomal distribution that represents reactivation from the dorsal root ganglia.

As you all probably know, there has been some very exciting news about the effect of a high titer varicella vaccine in limiting reactivation of virus, and hopefully we will be doing more of this in the future.

## **Varicella in Healthy Children: How Serious Can It Be?**

- **Severe Complications**
  - Cerebellar Ataxia, Encephalitis
  - Arthritis, Hepatitis
  - Hemorrhagic Varicella
  - Invasive Group A Streptococcal Infections
- **Pre-Vaccine era:**
  - Hospitalizations:  $\geq 10,000$  per year
  - Deaths: 50 - 100 per year

[Type text]

So, what about healthy kids? How severe can disease be? In the pre-vaccine era, the severe complications were things like cerebellar ataxia, which occurred in about one in 4,000 kids who developed varicella.

Encephalitis developed in about one out of 50,000 kids with varicella. All the ataxias pretty much got better, although sometimes it would take months for that to happen. Many of the kids with encephalitis were left with permanent damage.

Hemorrhagic varicella occasionally occurred in a healthy child, but a more pressing problem was invasive group A strep infections and, at one time, it was estimated that about 13 percent of invasive group A strep infections occurred within a month after varicella.

These are the old figures from the old pre-vaccine era, 10,000 to 15,000 hospitalizations per year, 50 to 100 deaths per year, and about half of these in healthy adults.

### **Severe Varicella in a Healthy 9 Year Old Female**



This is a healthy child. I took care of this kid. We worked this kid up for probably six months afterwards to figure out what immunodeficiency she had that caused such severe varicella.

Eventually her mother got disgusted with us and took her away, and she essentially was the other end of the bell curve in terms of lesions.

## Who is at Higher Risk for Serious Disease?

- **Immunocompromised Patients**
  - **Leukemia, Lymphoma:**
    - 60 children with cancer on Chemotherapy/Pre-Antiviral Era (Feldman, 1975):
      - 19 (32%) severe disease, 4 (7%) fatal
    - 288 children with cancer/antiviral Era (Feldman, 1987):
      - 150 Received VZIG: attack rate = 5% ?? w/50% ↓ in pneumonia
      - 127 untreated: 7% mortality; 28% pneumonitis (25% mortality)
      - 18 treated with ACV: no pneumonitis
  - **Bone Marrow, Heart, Kidney Transplants**
  - **HIV**
  - **Immunosuppressive Therapy**
- **Children with Asthma**
  - **Low dose steroids?**

Immunocompromised individuals have different problems, and I want to go over a couple of these studies, not so much to tell you what you already know, but when you start to look back at the old literature, which a lot of the recommendations for VZIG are made, you get to start to see the holes and gaps in knowledge.

So, Sandy Feldman did a study where he looked at kids with cancer. Most of these were leukemic kids. This was in the pre-chemotherapy era. About a third had severe disease, and about seven percent, altogether, died. Again, pretty small numbers.

He went back again and looked in the post-chemotherapy era, and showed that treatment, at least with acyclovir, the frequency of severe disease decreased.

There is a common bias that is buried in the back of this paper where he says something like, even with the availability of high titered anti-varicella immunoglobulin preparation, the incidence of varicella in the immunocompromised children has not changed much over time, although the incidence of severe varicella with pneumonia decreased.

I think that is something we need to remember when we start to think about replacing VZIG, is that this is not a product that always prevented varicella. What we relied on it for was preventing severe disease, and I think you need to keep that in mind when you start designing new products.

I have the HIV infected kids down here on the list. In fact, those kids now do pretty well. Our problems with them was more chronic disease than severe and fatal disease, and now that they are all on highly active anti-retroviral therapy, they actually do very well.

I just mention that when their CD4 counts are over 25 percent, and they are susceptible to varicella, we actually vaccinate them.

## Who is at Higher Risk for Serious Disease?

- **Neonates:**
  - 30% mortality with maternal varicella within 5 days before delivery
- **Normal Adults:**
  - Pregnant women
  - Smokers
  - Health Care Workers
  - Parents

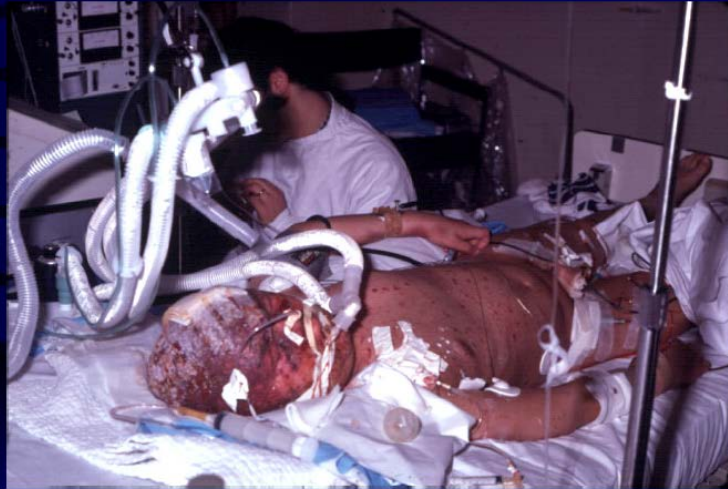
Neonates are also a problem, and older studies describe 30 percent mortality in the period of time when the mother had varicella four or five days prior to delivery and, in some studies, two days after.

We think why it is that period that is a problem, in essence, at that point in time, the fetus gets a large intravenous load of virus, but the mother has not made an antibody response yet.

If, in fact, you look at infants whose moms had varicella, let's say seven, ten or 14 days prior to delivery, in essence, those babies get virus and antibody at the same time. They still develop varicella, but they don't develop severe or fatal disease.

Normal adults also get more severe varicella. There was one study where the mean number of lesions in adults was about 400 compared to about 300 in children, and I will show you some cases.

### **Child with Leukemia and Severe Varicella**



This is a child at our institution who had varicella and leukemia, and you can see he obviously wasn't doing very well. These are hemorrhagic lesions here.

I only show you this is because, if you are thinking in the back of your minds that we can get away with using antivirals for treatment, and that we don't need to prophylax, what I will tell you is that varicella goes so quickly in the immunocompromised patients that you often don't have time to treat or, if you do treat, your treatment is ineffective.

### **Fatal Varicella in a Child with Juvenile Rheumatoid Arthritis Receiving High Dose Steroid Therapy**



I just want to make the point that prophylaxis is a very important thing. This is a child with juvenile rheumatoid arthritis who is on a bucket of steroids, came in with varicella in the early afternoon, and was dead by that evening.

## Varicella in Healthy Adults, Deaths

- **23 year old parent**
  - Pneumonia (day 4), IV acyclovir (day 5)
  - Hemorrhagic rash, D.I.C. (day 13), death (day15)
- **25 year old parent**
  - Pneumonia (day 3), encephalitis (day 4), IV acyclovir
  - Death (day 18)
- **32 year old, Crohn's Disease, prednisone 40 mg/day, 4 weeks**
  - Varicella diagnosed on day 3 of rash, no antiviral therapy
  - Hemorrhagic rash, D.I.C., death (day 4)

Healthy adults, again, I just want to make a point. If you look at what their problems are, hemorrhagic varicella, pneumonia, they are all getting their varicella from children or family members who are children. Hopefully, there will be less of this in time, but just remember that even young adults are relatively immunocompromised to herpes viruses compared to young children.

## Severe Varicella in a Healthy Adult



This is the adult. This is actually an old slide of Dr. Gershon's from Bellview. This is an adult with severe varicella. Here is his x-ray, and you can see the classic bilateral interstitial pneumonitis.

## **Risks During Pregnancy**

- Maternal risk probably highest in 3rd trimester:
  - Reports of fatal pneumonia
- Many susceptible adults come from tropical countries

What about pregnancy? I think when you talk about prevalence, you have to remember not to forget the mothers. What happens is that obviously they are adults, and they will be at risk for severe varicella because they are adults.

You also have to remember that there are studies showing that there is a progressive increase in specific immunodeficiency toward herpes viruses as you go from first to second to third trimester.

So, pregnant women may be even more at risk for severe varicella than age matched non-pregnant women. Then the other thing I want to mention here is, if you think this problem is going to get to be less important as time goes on, just remember that a lot of our varicella susceptible women come from tropical countries, and there the incidence of varicella is much lower. So, we have a higher pool of susceptible women coming in from those regions.

## **Congenital Varicella**



This is a typical case of congenital varicella. The usual story here is the mother develops chicken pox during the first or early second trimester.

This has rarely happened when the mother develops zoster, but almost all these reports are with maternal varicella, atrophy and hypoplasia of the limb. This child had visceral disease and obviously did not do well.

## **Fatal Neonatal Varicella**



This is varicella around term. So, this is when the mom develops varicella in that risk period I talked to you, five days before, two days after, and you can see that this child developed fatal hemorrhagic varicella.

## Zoster in a 3 month old



Finally, the last thing that you need to remember is that children who are exposed to varicella in utero, that is their first contact with the virus.

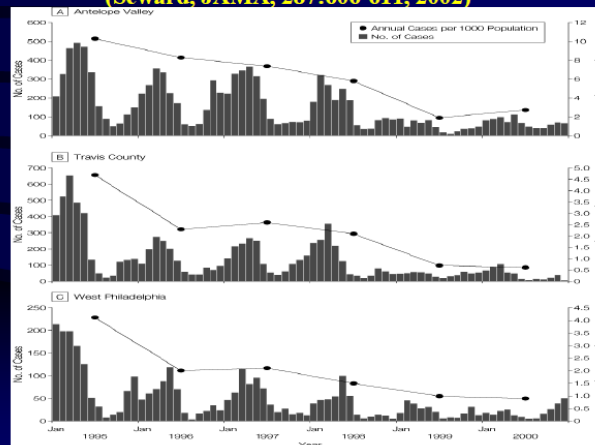
It has been estimated that up to 18 percent of those children who were actually infected in utero will go on to develop zoster during the first year of life.

## How Has Varicella Vaccine Changed the Epidemiology of Varicella

So, one slide to show you what varicella with vaccine has done to the epidemiology, these are Jane Seward's slides. There are more updated slides.

[Type text]

### Varicella Disease After Introduction of Varicella Vaccine in the United States, 1995 - 2000 (Seward, JAMA, 287:606-611, 2002)



The important point here is the downward trends. What I think I need to remind you of is this vaccine has been extraordinarily successful, despite what you may read in the paper or elsewhere.

I think this program is being tweaked to make it even more successful, but my hope is that we are going to see less and less varicella as time goes on.

I can tell you, in northern Manhattan, where I practice, it is now rare that I get called about children with varicella. So, it really does work, even in inner city populations.

### Correlates of Protection

Now, it comes to the less satisfying part, where we talk about correlates of protection. I am going to try to give you examples here that point out some themes.

# Correlates of Protection

- Ross, NEJM, 1962: 452 secondary contacts: More ISG less varicella
- Gershon, et. al., J Clinical Microbiology, 1978:
  - Immunocompromised children immunized within 3 days of exposure with either Zoster Immune Globulin (ZIG) or Immune Serum Globulin (ISG)

<u>Preparation</u>	<u>FAMA&gt;2 @48 hrs; GMT</u>		<u>Varicella</u>
<u>ZIG (0.15 ml/kg)</u>			
1:1024	22/22 (4 - 32)	11.7	10/22, all mild
1:512	15/18 (<2 - 16)	5.2	<2: 2/3, severe >2: 7/15, mild
<u>ISG (1:128)</u>			
0.6 ml/kg	7/7 (4 - 16)	7.3	0/7
1.2 ml/kg	13/13 (4 - 16)	9.4	3/13, all mild

So, the first attempt was by Ave Ross in the 1960s, and basically what he did was, he looked at secondary contacts of individuals who had varicella.

He did this by history. If you were history negative, then you were assumed to be susceptible. If you were history positive, you were assumed to be immune.

Using that kind of definition puts a little bit of noise in the system that you wouldn't have if you had looked at serologic titers.

Be that as it may, he showed that you could use immune serum globulin to sort of temper the severity of varicella, but it didn't do a whole lot to prevent varicella.

What he did show was that the more immune serum globulin you used, the more likely you were to have milder disease.

Gershon, in the 1970s, compared zoster immune globulin and immune serum globulin. What they did was, they looked at two preps of zoster immune globulin.

You can see that the titers here were about 5:512 to 1:1024. These are within one tube of each other. So, they are pretty similar.

Compare that to immune serum globulin that had a titer of 1:128. I think these were done -- this is 1978. It was probably done by complement fixation. I am sorry; it was FAMA.

Basically, why I show you this is that this is the first attempt to try to figure out what is going on in the patient.

With this dose of ZIG, all of the exposed individuals seroconverted, although there was quite a range. This is the geometric mean titer here.

About half of them came down with disease, but all of them had mild disease. With this preparation, almost all of them converted, but some of them didn't. The geometric mean titer was lower.

Here is the first attempt to look at what happened in the patient. In the few did that did not have a seroconversion, two of three of them came down with severe disease, where all the ones that did have a seroconversion, all of them had mild disease, and the attack rate was about 50 percent.

[Type text]

They then compared that to immune serum globulin, one titer, but two different doses. Basically, what they found here is that everybody converted. The geometric mean titers were a bit lower than here, and there was some varicella, but all of it mild.

Her conclusion from this was that, if you were very careful about the lots of immune serum globulin that you used, you probably could get away with using some of it.

## Correlates of Protection

- Orenstein, et. al., J Pediatrics, 1981:
  - High risk recipients of ZIG who had a 4 fold-rise in CF antibody titer at 48 hours compared to pre-ZIG titers were less likely to develop varicella than those who did not show a 4-fold rise:
    - 22.4% (n=49) vs. 44.7% (n=85)
    - 45 of the 48 4-fold rises were from <2 to 4
  - Recipients of higher titer ZIG(1:2,560-5,120) were more likely to have a 4 fold-rise in CF antibody titer than those receiving Low titer ZIG (1:1280)
  - Complications were more frequent in recipients of low-titered ZIG
- Zaia, et. al., JID, 1983:
  - Antibody titers 48 hours post-VZIG/ZIG did not correlate with infection rate or severity of disease

Now, Walter Orenstein, in 1981, took this a little bit further. Basically, what he showed was that, if you looked at recipients of zoster immune globulin who had a four-fold rise in CF titers at 48 hours, compared to those that didn't, the ones that had the four-fold rise were less likely to develop varicella than those that did not show it. So, 22 percent versus 44 percent.

What he said in the paper was that 45 of the 48 of the four-fold rises were from less than two to four. What is interesting about that is that there is this background of people with positive CF titers that still come down with disease.

We tend to think about complement fixation as a relatively insensitive test, and I am not bothered by someone who is comp fixed negative and positive by a more sensitive assay, but it was a surprise for me to go back and see that the specificity of comp fix was not that great, at least at these titers.

Walter also showed that, if you got high titered ZIG, you were more likely to have a four-fold rise in titer, and that complications were more complicated in recipients of low titered ZIG.

So, again, this is evidence that the more varicella specific antibody you give, and the higher the titer the patient ends up with, the more likely you are to impact the severity of disease.

It is interesting that John Zaia, in a 1983 study, could not find a correlation with infection rate and titers at 48 hours post-administration. Some of that may have been due to small numbers.

## Correlates of Protection

- Healthy Individuals
  - Susceptible:
    - FAMA  $< 2$
  - Immune:
    - Adults with a history of varicella:
      - FAMA  $> 4$  or a positive VZV skin test
    - Children in Vaccine trials: 6 week post-immunization gpELISA  $> 5$  units
    - How do we separate out the role of the cell-mediated immune response ?

So, what do we know about the correlates of protection? Well, we can say pretty convincingly that if you have a FAMA titer less than two, that you are going to be susceptible and likely to come down with disease.

The problem is, what do you say about people who have positive titers, whether they are positive FAMAs, positive GP ELISAs or positive other tests?

The confusion here is that most of the data we have here actually comes from either vaccine trials or people that had wild type disease earlier in life.

The problem here is that you are trying to focus in on antibodies, which are obviously important for this question of prophylaxis, but you can't separate out what the effect of the cell mediated immune response is.

We know that is important. We first noticed that many years ago when people noticed that children with A gammaglobulinemia and hypogammaglobulinemia did perfectly fine when they developed varicella because they had an intact cell mediated immune system.

### Immunity to Varicella in Vaccinated Leukemic Children Attack Rate at Household Exposure (n=39)

<u>Ab/CMI</u>	<u>Varicella/ Exposed</u>	<u>Attack Rate(%)</u>
+/+	3/ 27	10
+/-	2/ 6	33
-/+	0/ 3	0
-/-	3/3	100

Gershon, et. al. Infectious Disease Clinics of North America, 1996

A second piece of evidence -- this is, again, from Ann Gershon's vaccine studies in the leukemic kids -- again, very, very small numbers, but she looked at leukemic vaccinees who had either different combinations of positive antibody in CMI, varicella specific CMI, at the time of exposure and found that, if you had neither, you didn't do well as far as the attack rate.

If you had both, you did do pretty well, but you could get away with antibody and still not come down with disease most of the time and, if you had CMI, that was also good.

Again, I don't want to make too much of this because the numbers are so small, but the bottom line is, everything we look at in terms of vaccine data is really sort of clouded by the cell mediated immune response.

### Options for Post-Exposure Prophylaxis in At-Risk Individuals

- IGIV
- Vaccine
- Antivirals
- VZIG
- (ISG or therapeutic antivirals)

[Type text]

So, what are the options? Let me just say first here that neither of these -- I put these here just to be complete. Neither of these, I think, should be considered as an option for the reasons that I have talked about before.

**IGIV**

- **Advantages:**
  - Some data to support its use
  - Currently has good anti-varicella titers
    - Will need 300 - 400mg/kg (3 - 8ml/ kg)
  - Usually in ample supply
- **Disadvantages:**
  - Cost and difficulty of administration:
    - Intravenous line needed
    - 2 - 4 hours for administration
    - Volume of administration in Newborns?
  - Not titered for VZV antibodies
  - Waning Anti-varicella titers in the post-vaccine era?

So, what about intravenous gammaglobulin? There are some advantages. There is some data to support its use, and I will show you some of that in a minute.

Currently, it has good anti-varicella antibody titers, and if we figure out what the appropriate dose is on a per milligram of IgG dose, we probably can do a pretty good job with IVIG, and we will probably need something in this range.

We can argue about whether this is 200 to 400, and I put the volumes here, so you can start to think about what that would mean to small children.

It is usually in ample supply, although that is not always the case. Last year we did have shortages of IVIG, and did have to come up with a hierarchy of who was going to get it and who would not.

There are problems on the other end, and when I mean the other end, the people who are going to use the IVIG and the patients who have to get it.

Cost and difficulty of administration, you need to put an intravenous line in to give it, you can't give it quickly, you have to run it in slowly.

You may at least want to think about the volume of administration in newborns, if you are going to give eight mls per kilo to a three kilo kid, that is 24 ccs. That is a decent volume of fluid, not something that is a huge problem, but we should think about it.

As was talked about before, it is not titered for VZV antibodies. So, it will be a moving target as time goes on.

Not only as time goes on, but from lot to lot, and this is obviously going to happen as antibody titers go down over time.

## IGIV Prophylaxis in High Risk Children

- **Shu-Huey, et. al., *Pediatr Hematol and Oncology*, 1992:**
  - 5 VZV susceptible leukemic children
  - IGIV (200mg/kg) within 3 days of a household exposure
  - No varicella developed in any of the five (7 exposures)
- **Kavaliotis et. al., *Med and Pediatr Oncol*, 1998:**
  - 52 pediatric oncology patients (79 exposures)
  - Prophylaxis within 6-24 hours after exposure
    - 11 VZIG – 0 infected
    - 30 IGIV – 3 infected
    - 38 VZIG+IGIV – 3 infected
  - Varicella was mild, recovered after ACV (IV 7 days + PO 7 days)
  - Only 11% of patients developed varicella
- **Ferdman (i.e. *Feldman*), et. al., *PID*, 2000:**
  - 3 patients who developed varicella despite IGIV therapy (7, 11, 30 days before exposure)
  - Varicella was mild (IGIV, CD4 count, acyclovir therapy)
  - IGIV-treated individuals with profound T cell deficiency or dysfunction may not respond as well and VZIG prophylaxis should be considered

This was one paper in the literature from 1984, and these were oncology patients who were susceptible, but they had not been exposed. Again, very small numbers, given either VZIG or two different quantities of intravenous gammaglobulin.

The findings were that the antibody titers were good for four to six weeks after IVIG, and were equivalent to the titers measured at three to four weeks after VZIG. So, what that means is you got to the right level and you actually kept it there for a longer period of time.

The maximum antibody titers were similar in all three groups, but they were achieved more quickly with IVIG. So, there is some potential advantage there.

I will just quickly go through a couple of these studies in high risk individuals. Again, very, very small numbers, five kids here, given IVIG at 200 milligrams per kilo within three days, no varicella after seven exposures, 52 pages with 79 exposures, prophylaxed within six to 24 hours, and they did relatively well. Although there was some infection, the varicella was mild.

I just wanted to point this out. This is another approach that some people have used, is to give VZIG at the time of exposure and give IVIG later on.

Some people have also given VZIG and then, in the second half of the incubation period, also given an antiviral to try to cover all bases.

When you look at your presentation, just correct your spelling. This is Ferdman, not Feldman, as I put in the handout.

This is just one of those cautionary tales of three patients who developed varicella. They were getting, I think, monthly IVIG and they had received their last dose seven and 11 and 30 days before exposure. All of them were mild.

It just reminds you that you do need an intact immune system to have a good response to varicella, and that you shouldn't expect that these preparations are actually going to prevent varicella.

## Vaccine for Post-exposure Prophylaxis

- **Advantages:**

- Data in healthy individuals
  - < 13 years of age at  $\leq 36$  hours post-exposure:
    - 0/42 vaccinated vs. 1/1 unvaccinated developed varicella
- Long-lasting protection
- Easy to administer

- **Disadvantages:**

- Not appropriate for immunocompromised hosts, Pregnant women or Newborns
- Efficacy of one dose for post-exposure prophylaxis in Healthy Adults?

I put vaccine here just for the sake of completeness, but also because healthy adults are in your high risk groups, and we may at least want to think about doing some studies where we potentially could use vaccine in healthy adults.

There is some data in the paper that Barbara Watson and Jane Seward wrote. They looked at kids 13 years of age or less, and gave vaccine at less than 36 hours post-exposure.

This was done, I think, on the basis of history -- right, Jane, not serology -- and none of the 42 vaccinated kids came down with varicella as opposed to one of the unvaccinated kids. I did not include an effectiveness analysis up there because of those numbers.

The advantage here is that you are giving long-lasting protection. So, it is not temporary, like you would have with an immune globulin preparation, and it is easy to use.

The disadvantage, it is not appropriate for immunocompromised patients, pregnant women or newborn, and we really don't know what the efficacy would be with one dose in adults.

That is something we should look at, but remember, we need two doses of vaccines in adults and adolescents over the age of 13 to get a good immune response. So, I don't know what one dose would do, but I think it is something we should look at.

## Antivirals for Prophylaxis

- **Advantages**
  - Some data in healthy children
  - Available (Acyclovir, Famciclovir, Valacyclovir)
  - **Effective after the window for use of VZIG has passed**
- **Disadvantages:**
  - Limited data in immunocompromised patients
  - Class C drugs in pregnancy
  - Use as P.O. prophylaxis in newborns?
  - Most of the data is with Acyclovir
    - Poor adsorption of P.O. Acyclovir
  - No liquid formulations of Famciclovir or Valacyclovir
    - Limits use in young children & infants
  - Multiple day regimen/ compliance will effect efficacy

What about antivirals? Well, there is some data in healthy children, and I will show you some of that. There are good antiherpes antivirals available, and the major advantage of this is that, if you have missed the window where you can give an immune globulin preparation, you can still come back and give an antiviral for prophylaxis.

The disadvantages are that there is really limited data in immunocompromised patients. They are class C drugs in pregnancy.

I would be very hesitant to use them by the oral route in the newborns, not knowing whether they would be absorbed, although there is one study that did do that.

Most of the data is with acyclovir, absorption of p.o. acyclovir runs about 18 percent at best. When we used p.o. acyclovir for treatment of varicella in immunocompromised patients, we used a dose that was four or five times the recommended dose, so that we would get the appropriate levels, and that level of drug causes a decent amount of GI upset.

So, you might say, well, we have Famciclovir and Valacyclovir that have p.o absorptions of about 70 percent. The problem is, there are no liquid formulations of those. So, you would limit its use in young children and infants.

Finally, and sort of a contrast with what you have with immune globulin preparations, where you give it and you know the person has gotten it, here you are relying on the person to take this drug for a multiple day period and, I think outside of the study setting, you might get lower efficacy than you have seen in some of the studies.

## Oral ACV During The Incubation Period (1)

- Suga, et. al., Arch Dis Child, 1993:

	<u>ACV post-household exposure</u>		
	<u>0-3 days</u>	<u>6-10 days</u>	<u>No ACV</u>
Participants	13	14	19
Infection rate:	85%	79%	100%
Clinical attack rate:	91%	27%	100%
Severity:		milder	

Now, the studies that were originally done in Japan were actually not done to test its usefulness as a prophylactic agent.

They were actually done to test the hypothesis that there were two viremias during varicella, and that the second one is most important.

So, the original study looked at this by giving acyclovir in the first three days, six to 10 days after exposure, and no acyclovir.

Where you can see that the infection rates were not a whole lot different, the clinical attack rate was much lower with the six to 10-day period, which would roughly correspond to when the second viremia is, and clinical disease was described as milder. So, we think that is where the antivirals are having their effect.

## VZIG

- **Advantages:**

- Benefits and Limitations are well understood
- Long-standing experience
- Utility in those who can not be vaccinated or when antivirals are not appropriate
- Small volume for newborns

- **Disadvantages:**

- Cost of continuing production/ new source
- Limited period of protection
- May be more expensive to make in the vaccine era

So, what about VZIG? Its advantages are that its benefits and its limitations are well understood, and we have a lot of experience with this.

It is useful in those that can't be vaccinated, or when antivirals are not appropriate, and it has a small volume. The disadvantages are why we are here today, so I won't dwell on those.

So, then what I did was, I went back to the high risk groups and I said, if I had my choice, what would be my first choice, what would be my second choice and what would be my third choice. I have to tell you, this is purely my personal opinion, it is not the result of any expert panel review.

## What Are Our Options for Prophylaxis in VZV-Susceptible High Risk, Exposed Patients?

- Immunocompromised Patients
  - Leukemia, Lymphoma, Transplants, Immunosuppressive Therapy, HIV :
    - **VZIG**, or IGIV? or Antiviral ??

For the immunocompromised patients, I would still like to use VZIG. I think we could probably get away with IVIG at the appropriate dose, and I think antivirals might work, although my guess is, I would want to see studies to see if they did work, or I would want to see studies where these were used in combinations, one of these plus an anti-viral.

## What Are Our Options in VZV-Susceptible High Risk, Exposed patients?

- Neonates:
  - **VZIG**, or IGIV? or Antiviral ??
- Normal Adults:
  - Pregnant women:
    - **VZIG**, or IGIV? or Antiviral ??
  - Other Adults:
    - **VZIG** or IGIV? or Antiviral ?? or Vaccine ??

Neonates, I think VZIG is the core choice. Again, we could probably do with IVIG if we had to. I really don't know about antivirals.

Pregnant women, again, probably VZIG, and we probably could get away with IVIG. Other adults, the same. In fact, we might want to think about vaccine studies at this point. I would not recommend that we try that as a substitute without studies.

## Summary

- There probably is still a need for VZIG
- IGIV is probably equivalent to VZIG in the appropriate dose
- Antivirals may be useful, especially if the window for VZIG/ IGIV is missed, but should be tested in populations other than healthy children
- Vaccine will be of limited utility as a substitute for VZIG

In summary, I think there probably still is a need for VZIG. I think IGIV is probably equivalent in the appropriate dose, although we will have to do those studies.

Antivirals may be useful, especially in the post-VZIG window, and I think vaccine will be of limited utility as a substitute. Thank you.

DR. ALLEN: Excellent. Thank you for a very nice overview. Clarification questions for Dr. LaRussa?

DR. SEWARD: I have a comment on the -- can you go back to the slides on IGIV, the study with the largest number?

I mean, you know, these studies of post-exposure use of any product are as good as the exposure data are strong.

Household exposure data, you really do expect eight or nine out of 10 exposures to result in disease. The numbers here, the second study with 52, is hospital exposures, and there is no control group.

## IGIV Prophylaxis in High Risk Children

- **Shu-Huey, et. al., *Pediatr Hematol and Oncology*, 1992:**
  - 5 VZV susceptible leukemic children
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  - Varicella was mild, recovered after ACV (IV 7 days + PO 7 days)
  - Only 11% of patients developed varicella
- **Ferdman (i.e. Feldman), et. al., *PID*, 2000:**
  - 3 patients who developed varicella despite IGIV therapy (7, 11, 30 days before exposure)
  - Varicella was mild (IGIV, CD4 count, acyclovir therapy)
  - IGIV-treated individuals with profound T cell deficiency or dysfunction may not respond as well and VZIG prophylaxis should be considered

So, unfortunately, the data are really very, very slim in being able to interpret this as being evidence that it works.

You might expect, perhaps you might guess, that the attack rate might be 20 to 30 percent. So, in fact, you may have a half or a two-thirds reduction, but there isn't any control group.

DR. LA RUSSA: This really needs to be studied. It makes sense to me that, if you give the right amount, it should work.

The other problem you should be cautious about in looking at studies in immunocompromised patients is that lots of those patients now get prophylactic acyclovir to prevent CMV infection and other things, or they may get prophylactic gancyclovir, which is highly active against varicella. So, you really need to look at all of these things.

MS. SEWARD: My other question is, I know the recommendations are for use of VZIG in healthy adults, but realistically, do you use it for that?

I get questions -- at CDC we get lots of weekend and night questions about pregnant women exposures, but we never get a question about a healthy adult. So, I suspect it is not being used for that purpose much.

DR. LA RUSSA: I see all the disasters, and I actually think it should be used for healthy adults. My adult colleagues are sometimes of the opinion that, why don't we just wait and see what happens and treat the individual.

I have just seen too many people on respirators with varicella pneumonia to think it is worthwhile saving a couple hundred bucks to see if that is going to happen, but you are right, a lot of people don't do that.

DR. DOPPELT: From a practical standpoint, getting back to the vaccine, how easy or difficult is it to administer within 36 hours of exposure?

[Type text]

DR. LA RUSSA: The question is, how easy or difficult to administer within 36 hours. That is tough. It really depends. The study that I showed you was done in a closed population in a shelter. Right, Jane?

DR. SEWARD: Yes, but there is plenty of data from Japan and other first exposure data in children, very nice, controlled data showing that, within 72 hours, the vaccine prevents 90 percent severe disease, and sort of maybe even up to 70 percent out to five days.

I think if somebody presents within three days, you can give it. As Phil said, with adults there isn't the same data.

I think the currently formulated varicella vaccine, about 90 percent of adults respond after one dose. So, we might expect that it is not going to be bad, and I think it is a pretty good option for healthy adults.

DR. ALLEN: What about immunocompromized children, though?

DR. SEWARD: No, you can't give it. They are the big problem group.

DR. LA RUSSA: The thing with the immunocompromised children is that we really -- well, that also is a landscape that is going to change.

If you think about what is happening now, we have had vaccines since about 1996 and, since most of the use of VZIG for immunocompromised children was in kids with leukemia, the mean age of leukemia, onset of leukemia, is about four to six years of age.

In a sense, we have already sort of tempered that problem, I hope, because now we are going to have a bunch of kids who are vaccinated as healthy kids, who are becoming immunocompromised some years after, and I think we are going to have to look at what happens to them. No, I would not vaccinate a severely immunocompromised patient at the time of exposure.

The other point, obviously, is that neonates would not have had a chance to get the vaccine. On the other hand, if the vaccine is used in the upcoming cohort, we should, we hope, have fewer and fewer susceptible women who would become infected late in pregnancy.

DR. SEWARD: I am not sure that is the case. Pre-vaccine era, only about five percent of adults were susceptible. We will be lucky to achieve that with the vaccination program as well.

MR. LA RUSSA: As I mentioned, in New York City, most of our susceptible women come from areas of the world where the vaccine is not available, and the rate of seropositivity for young adults is much lower than it is in the States. I think we are going to have an ample supply of those.

DR. ALLEN: Dr. LaRussa, let me ask you, what is used for VZIG in Europe, other countries around the world? At least I assume that the supply for Massachusetts is predominantly distributed and used within the United States.

DR. LA RUSSA: I don't know that I could answer that question. I know VZIG-like products are available in Europe, and in Canada there is a manufacturer.

In parts of Southeast Asia, nothing is available. People either do nothing or they use antivirals as an option, nothing that becomes a potential alternative source to be used within the United States, however.

DR. SCOTT: I think I can answer that question. If you look at the web and you look at some of the papers that are available that have been published, what you can see is that current licenses are held by Commonwealth Serum Laboratories in Australia, by Cangene in Canada, by Biatest, by Behringwerke AG in Europe, and by BPL in the United Kingdom.

[Type text]

So, there are other companies that are licensed for this, and it is my belief that some of these are making lots at a low rate.

Some of these certainly could use U.S. plasma, if that became a question and, as everybody knows here, the United Kingdom is already using U.S. plasma for its products, and certainly so are some other manufacturers.

DR. SEWARD: I have another question on IVIG. What would be the procedures for the FDA to change requirements, to require a certain level of varicella immune globulin in there, as they do currently for measles and some other parts of the product?

DR. SCOTT: The purpose of requiring those titers in the products originally was lot to lot consistency and looking at the biological function of antibodies, to make sure that it was intact.

The purpose wasn't really per se to prevent measles or diphtheria, although obviously those would be desirable.

So, back when that lot release testing decision was made for the CFR, people looked at titers of antibodies that you would expect to be in immune globulins, and selected some of those to use for lot to lot consistency, and for antibody function.

Now, in terms of what would we -- what is one of the approaches? The typical approach for licensing for an indication now is to have a clinical study, and rather not to just titer a product and say it is okay for this.

DR. ALLEN: Okay, other questions or comments for Dr. LaRussa? We will have a chance to come back and discuss this more broadly later. Thank you very much, a very nice overview.

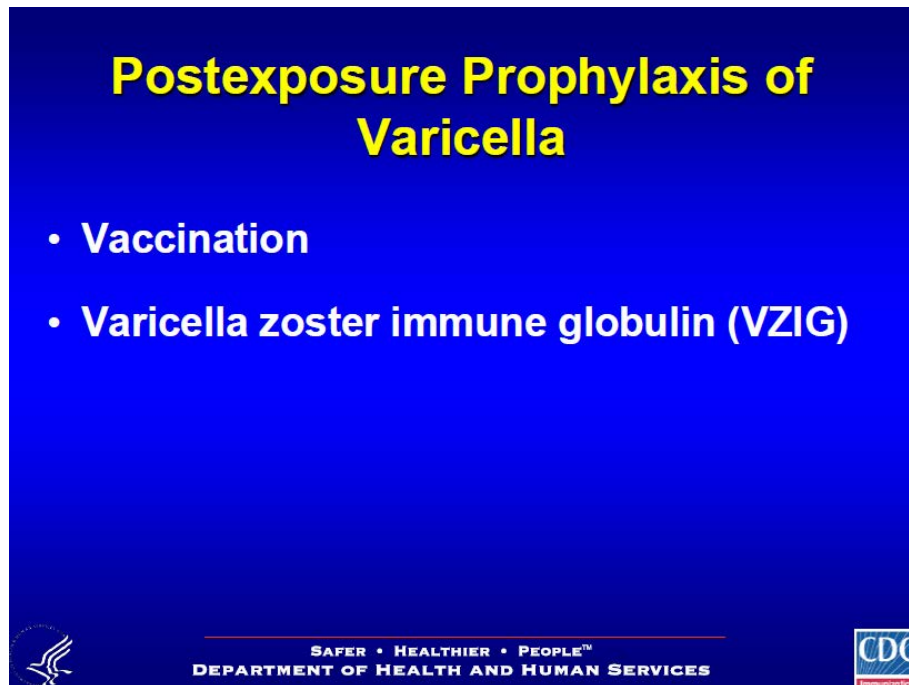
Our next presentation is by Dr. Mona Marin, medical epidemiologist with the national immunization program at the Centers for Disease Control. The topic is advisory committee -- well, ACIP, advisory committee for immunization practices, recommendations for post-exposure prophylaxis of severe varicella infections. Dr. Marin.

**Agenda Item: Advisory Committee for Immunization Practices  
Recommendations for Post-Exposure Prophylaxis of Severe Varicella Infections.**

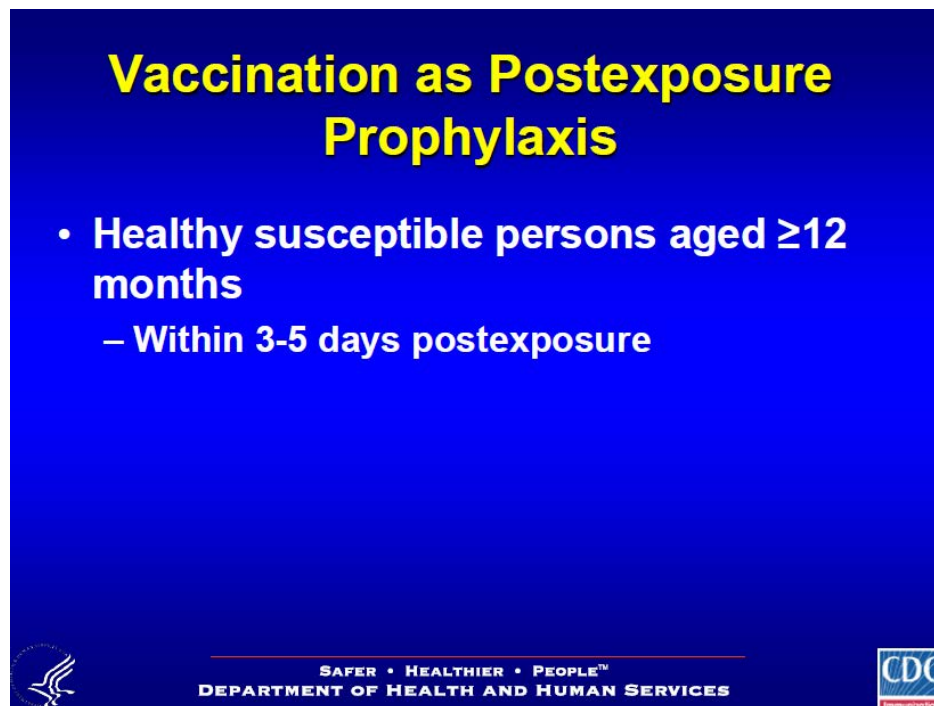
DR. MARIN: Good afternoon. So, I will be presenting today the current recommendations for post-exposure prophylaxis in varicella infection.

I will start with two slides that are not in your handout, and I apologize for that, but I want to give you a broader perspective of what we can use for post-exposure prophylaxis.

So, there are two interventions, vaccination and varicella zoster immune globulin.



Only shortly about vaccination, varicella vaccine is recommended for healthy, susceptible persons aged 12 months or older.



It should be administered within three to five days post-exposure, and there was here quite a discussion regarding its effectiveness in preventing disease within three days, but it can be administered up to five days, being effective in modifying the severity of the disease.

Now, regarding recommendations for VZIG, I will first present general indications for the use of VZIG, and then the recommendations of the advisory committee on immunization practices.

## **Outline VZIG Recommendations**

- **General indications for the use of VZIG**
- **Advisory Committee on Immunization Practices (ACIP) recommendations**
- **American Academy of Pediatrics (AAP), Committee on Infectious Diseases additional recommendations (Red Book)**
- **Other recommendations**



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I will go over some special situations that are mentioned in the recommendations of the committee on infectious diseases of the American Academy of Pediatrics, published in the red book, and I will end with some recommendations of other expert groups.

## **General Indications for the Use of VZIG**




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## Indications for the Use of VZIG

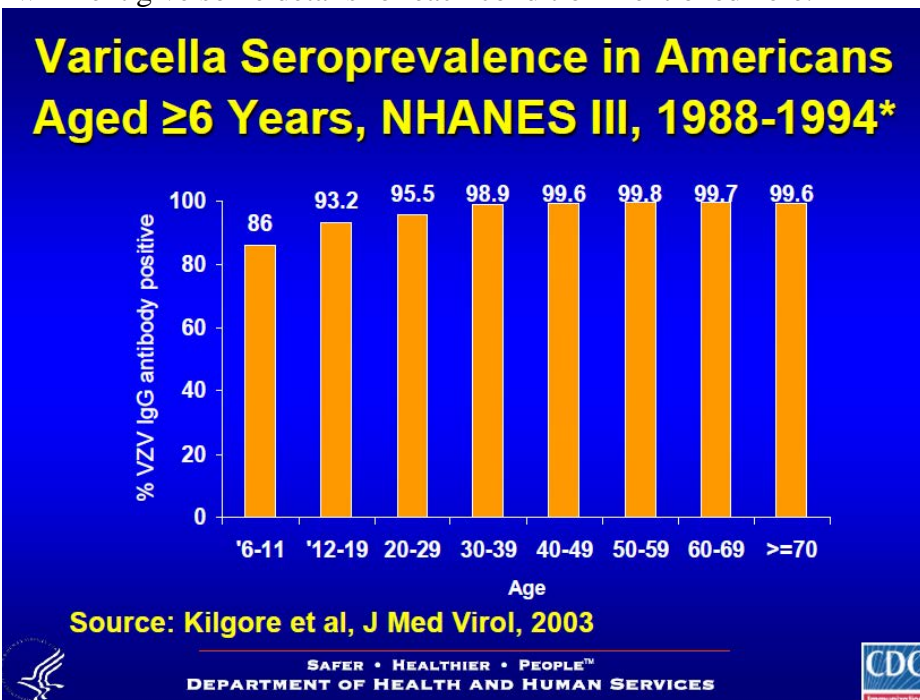
- The decision to administer VZIG to a person exposed to varicella-zoster virus (VZV) should be based on whether:
  - The patient is susceptible
  - The exposure is likely to result in infection
  - The patient is at greater risk for complications than the general population



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As far as general indications for the use of VZIG, ACIP and AAP (*American Academy of Pediatrics*) indicate that the decision to administer VZIG post exposure to varicella zoster virus should be based on whether the patient is susceptible, either by lacking recommendation of vaccination or by having a negative history of disease, the exposure is likely to result in infection, and the patient is at greater risk for complications than the general population. I will next give some details for each condition mentioned here.



As far as susceptibility to varicella, the most recent available data are from seroprevalence studies from the pre-vaccine era, NHANES, which is the national health and nutrition examines survey.

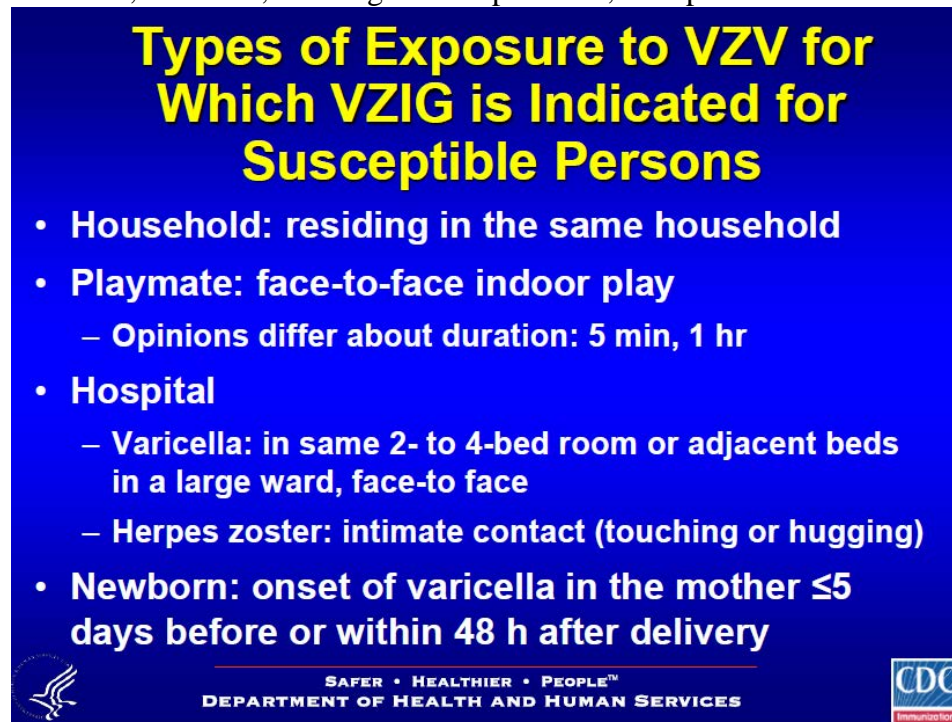
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They used an immune assay to detect the IgG, but the epidemiology of disease since then makes us believe that these data are still accurate, especially for adults.

So, by age group, for children age six to 11 years, 86 percent of them are immune, and for those 12 to 19 years, 93 percent of them were immune.

As far as adults, as you can see, five percent of those age 20 to 29 years were susceptible. One percent of those, 30 to 39 years, and an average about .5 percent of those aged 40 years and older.

Another key element in assessing the need for VZIG indication is exposure to a varicella zoster virus, therefore, defining what exposure is, is important.



**Types of Exposure to VZV for Which VZIG is Indicated for Susceptible Persons**

- **Household:** residing in the same household
- **Playmate:** face-to-face indoor play
  - Opinions differ about duration: 5 min, 1 hr
- **Hospital**
  - **Varicella:** in same 2- to 4-bed room or adjacent beds in a large ward, face-to face
  - **Herpes zoster:** intimate contact (touching or hugging)
- **Newborn:** onset of varicella in the mother  $\leq 5$  days before or within 48 h after delivery

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Unfortunately, the literature data do not support an absolute definition of exposure. In the ACIP guidelines, in the red book, there are included the following types of exposure for which VZIG is indicated for susceptible persons.

Households, that is, residing in the same household with a patient, employment, face to face indoor play, and here experts differ in opinion about the duration of face to face contact that warrants administration of VZIG.

Some suggest a contact of five minutes or more constitutes a significant exposure for this purpose. Other experts consider a close contact at least one hour.

Hospital exposure to a case of varicella is considered being in the same two or four bed room, or adjacent beds on a large ward, or face to face contact with an infected staff member or patient, or a visit by a person deemed infectious.

Exposure to a herpes zoster case is considered as having an intimate contact, such as hugging or touching with an infectious person.

For newborns, exposure is considered onset of varicella in the mothers five days before, or less, or within 48 days after delivery. VZIG is not indicated if the mother has zoster.

## ACIP Recommendations



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### Use of VZIG for Postexposure Prophylaxis

- **Persons aged <13 years**
  - **Immunocompromised children**
    - **Primary and acquired immunodeficiency disorders**
    - **Neoplastic diseases**
    - **Immunosuppressive treatment**
  - **Neonates whose mothers become infected with varicella 5 days before and 2 days after delivery**
  - **Neonates exposed postnatally - premature infants**
    - **Hospitalized**
    - **<28 weeks' gestation or weigh  $\leq 1,000$  g**



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The groups identified to be of greater risk of varicella complications, and for which ACIP recommends VZIG are for persons aged less than 13 years, immunocompromised children, including children who have primary and acquired immunodeficiency disorders, neuroplastic diseases, and receiving immunosuppressive treatments.

Data are limited regarding whether routine therapy with immune globulin intravenous yields the persistence of a sufficient passively acquired VZV antibody to protect susceptible immunocompromised persons who become exposed to VZV.

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ACIP recommends that these persons, or immunocompromised persons who receive regular IGIV should be administered with VZIG if exposed to wild type varicella zoster virus.

Other recommended groups are neonates whose mothers have signs and symptoms of varicella within five days before to two days after delivery.

Neonates exposed postnatally, specifically, premature infants born to susceptible mothers, because their immune system may be compromised.

These infants should be considered at risk as long as they are hospitalized, and premature infants who are less than 28 weeks gestation or weigh less than 1,000 grams at birth, and who are exposed to VZV should receive VZIG regardless of the maternal history.

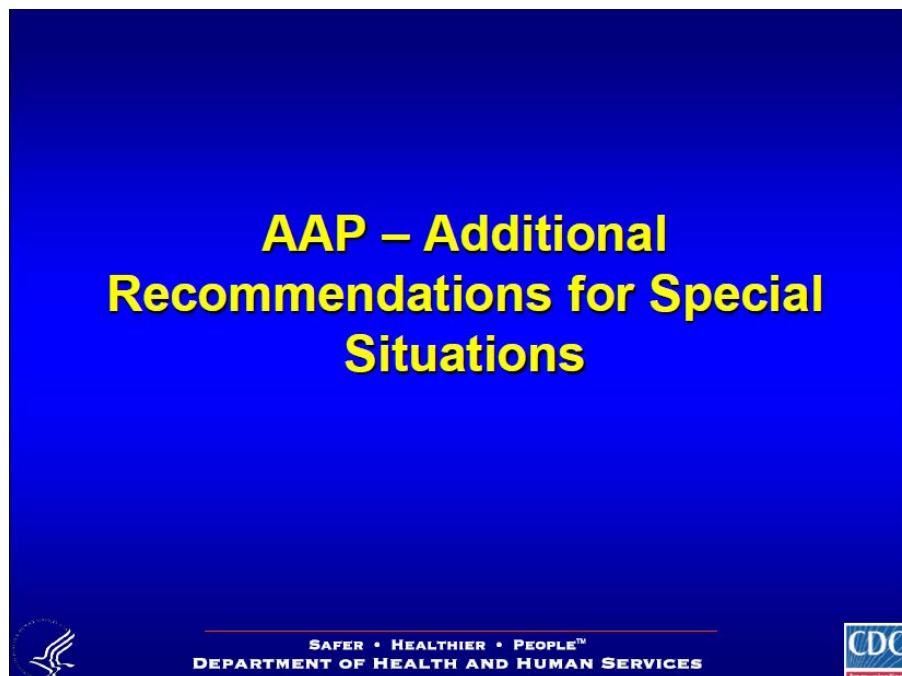
VZIG is not recommended for healthy, full term babies who are exposed postnatally, even if the mothers do not have a history of varicella disease.

For persons aged 13 years or older, VZIG is indicated for immunocompromised adolescents and adults. For healthy, susceptible adolescents and adults, although varicella disease is more severe than in children, the decision to administer VZIG should be made on an individual basis.

In this case, VZIG is administered mainly for modifying, rather than preventing, the disease, hoping to induce a life-long immunity. Other high risk groups are susceptible pregnant women and hospital personnel.

In addition to this recommendation, as they are listed here, they are ACIP recommendations, but we can find them quite in the same way in the AAP guidelines.

The AAP mentions in their guidelines some special situations, and these situations refer to patients receiving immune globulin intravenous.



## **Patients on High-dose IGIV**

- **Patients receiving monthly high-dose IGIV ( $\geq 400$  mg/kg) are likely to be protected and probably do not require VZIG if the last dose of IGIV was given 3 weeks or less before exposure**



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AAP considers that patients receiving high dose IGIV, 400 milligrams per kilogram or greater, are likely to be protected, and probably do not require VZIG if the last dose of IGIV was given three weeks or less before exposure.

## **Patients with a Bleeding Diathesis**

- **Use of VZIG for patients with a bleeding diathesis should be avoided, if possible. IGIV would be an acceptable alternative in this situation.**




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Another special situation is that of patients with bleeding diathesis, and AAP recommends that use of VZIG for patients with a bleeding diathesis should be avoided if possible, and IVIG would be an acceptable alternative in this situation.

## Healthy Adults

- **VZIG can be given to healthy susceptible adults after exposure to varicella, but VZIG is not recommended routinely. A 7-day course of Acyclovir may be given to susceptible adults beginning 7 to 9 days after varicella exposure if vaccine is contraindicated or more than 72 hours elapsed from the time of exposure.**




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As far as prophylaxis of healthy adults, AAP considers that VZIG can be given to healthy, susceptible adults after exposure to varicella, but their discussions were here.

VZIG is not routinely recommended. For this situation, AAP would favor administration of vaccine, and if the vaccine is contraindicated, or more than 72 hours have elapsed since exposure, then a seven-day course of acyclovir administered late in the incubation period, seven to nine days after exposure, is recommended by AAP.

## Other Recommendations



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## Recipients of Stem Cell Transplant

- Postexposure prophylaxis with valacyclovir or acyclovir (between days 3-28 postexposure) be considered in addition to VZIG for all VZV-seronegative recipients of hematopoietic stem cell transplant\*

\*Source: Weinstock et al, Infect Contr & Hosp Epidemiol, 2004



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In the end, recommendations made by a group of experts regarding post-exposure prophylaxis of recipients of stem cell transplants, varicella zoster virus causes high morbidity in these patients.

There are some recommendations of ACIP regarding prophylaxis or prevention of opportunistic infections in recipients of stem cell transplants, but there are some issues that were not addressed. So, a group of experts was formed to come with consensus recommendations regarding some issues.

One of them is post-exposure prophylaxis against VZV infection in these patients. In their recommendation, the experts stated that extensive clinical experience indicates that acyclovir and valacyclovir are highly effective in preventing VCV activation in transplant recipients, and recommended that, because VZV infection is severe, and VZIG is not 100 percent effective, post exposure prophylaxis with valacyclovir or acyclovir, as you can see, between days three to 28 post-exposure be considered, in addition to VZIG to all VZIG sero-negative recipients of hematopoietic stem cell transplants. That is all I have.

DR. ALLEN: Thank you very much. Questions or comments for Dr. Marin's presentation? Okay, no specific questions, thank you very much. Please, if you can, stay for the discussion. We may ask for some clarification.

At this point, we have finished our formal presentations. We are supposed to move to the open public hearing. I do not have a list of any speakers who have requested to speak. Does anyone wish to speak at the open public hearing? Would you identify yourself, please. This is pertinent to this topic?

### **Agenda Item: Open Public Hearing.**

MR. SINCLAIR: Chris Sinclair, Cangene Corporation. I would like to partially address Dr. Case's question initially.

Cangene is the manufacturer of the varicella zoster immune globulin product in Canada, and we are currently moving forward to fill the unmet need in the Canadian market place, and we are looking at, and evaluating at this point in time, to filling the unmet need of the varicella zoster immune globulin in the United States.

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I just wanted to maybe address or make comments to each of the three points of discussion, if I could. With regard to the surrogate markers of efficacy, we do believe that a surrogate marker of efficacy, such as antibody levels in patients following administration, would be an appropriate way of evaluating varicella zoster immune globulins in clinical studies, especially given the difficulties in conducting these studies, as we have heard many times over and over here, that varicella zoster immune globulin does not prevent infection, it just will reduce the severity of infection.

With regard to the true definition of the surrogate end point, I am not sure that bioequivalence per se would be an appropriate measure, possibly because of the fact that some alternative products are available for IV administration as well as IM, and being able to demonstrate bioequivalence is not necessarily going to occur when you are giving a product IV compared to IM.

With regard to the patient populations, we have heard quite a bit about the immunocompromised patients. I think that Dr. LaRussa also talked about the pregnant women and the severity of the varicella infection during pregnancy, especially with regard to pneumonia, and potentially with regard to congenital varicella disease, and I think this would be an alternative patient population that would also be advantage for a demonstration of efficacy of use through a surrogate marker of efficacy.

Finally, with regard to whether or not IVIG or acyclovir would be an appropriate alternative, I think that Dr. LaRussa's presentation demonstrated that VZIG would probably be an alternative, but the preferred alternative, if it is available, and I think that he well defined the risk associated with IVIG as well as acyclovir. Thanks.

DR. ALLEN: A quick question. Can you briefly comment on major differences in manufacturing process between your product and what you heard described from the Massachusetts Health Department?

MR. SINCLAIR: I am not from the manufacturing side. I am from the clinical side. I know that we use the same manufacturing process that we use for our WinRho product, as well as our immune globulin products that are currently licensed in the United States, and we use an ion exchange chromatography method as opposed to the ethanol fractionation method.

The potency of the product, we use the Mass State product as our in-house potency standard. So, we have comparable potencies. However, the product manufactured is a five percent product for either IM or IV administration.

DR. ALLEN: Thank you. Let me get Dr. Epstein, and then we will come back.

DR. EPSTEIN: I would like to clarify a regulatory point on the term surrogate marker. There really are two types of surrogate markers, ones that have been validated, and ones that are likely to be valid, but have not been validated.

There is a distinction to be made. If the committee feels that there are validated markers, then we could give final approvals on that basis, but generally the studies would still have to be clinical to show end points based on a validated surrogate.

If the surrogate is likely to be valid, but has not been validated, then the FDA would only be giving what we call an accelerated approval, which is conditional, and the condition being that it would be validated later in clinical studies.

Whichever way you go, you do end up with some level of clinical studies. There is also the subtle point that it would be rather unusual for the agency to give approval to the product based on accelerated approval with an unvalidated surrogate in the situation where clinical studies, in fact, are feasible.

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Dr. Scott did make that point. On the other hand, we may have an unusual situation here, if product were otherwise to become unavailable.

Of course, the products could potentially remain available under IND, but that is a more cumbersome mechanism to provide products. I don't know if I made things clearer or more murky, but the term has two contexts.

DR. KLEIN: Since you are on the clinical side, can you tell the committee what clinical studies were done in Canada in order to license it, and whether your product is licensed in any other countries?

MR. SINCLAIR: The last one first, we are not licensed in any other countries, and we have performed a study in pregnant women that have been exposed through household exposures for the majority of cases within, I believe, 96 hours for the majority of patients, as the mother at risk program in Toronto.

We compared the study that was published by Gideon Koren a couple of years ago (2002), and it (*i.e. the Cangene study*) involved 60 subjects, whereby they were randomized to receive either an IM or IV dose of our product, or an IM dose of the licensed U.S. product, and they had similar rates of infection.

As I guess was discussed previously, the infection rates of natural disease progression, in the absence of therapy, is not well defined.

DR. ALLEN: Dr. LaRussa?

DR. LA RUSSA: Just a few comments. I would be very careful about throwing congenital varicella into the mix there, because you are never ever going to design a study that is going to show that any product is effective in preventing that, since the rates are so low.

I guess the other comment I would make is, I am trying to think of how we would design an efficacy study in the United States to test efficacy against clinical diseases and infection with the rate of varicella falling so much.

We might be able to look at antibody end points but, since we are not really sure what those mean in the patients, unless you looked at a very, very restricted, well-described population, what would it mean to have a FAMA titer or a GP ELISA titer of greater than five?

I don't know what that means, and it seems to me that what you have done in the past is, everybody sort of piggy backed on the titer of the first ZIG product, and then gone and said, well, my product has equivalent titers to ZIG.

I am not sure how you get out of that bind now, unless you are going to do the studies in some other country.

DR. SCOTT: If I could just clarify that the ZIG product titers may or may not have been linked to the VZIG titers, but the clinical efficacy was linked. I think we don't feel we are relying still on those archaic ZIG titers, as it were, for the current product, although the product may have been selected based on the VIG (*ZIG*) titers originally.

DR. LA RUSSA: I just don't see how we could do a study now.

DR. KATZ: A question for one of the pediatricians around the table. I presume there is somebody's accumulated experience with agammaglobulinemic kids receiving replacement doses of intravenous immune globulin that might be informative regarding their risk from varicella exposures.

Apparently the American Academy thought there was enough to make a recommendation. Can I be enlightened on that?

DR. LA RUSSA: The situation with the kids with agammaglobulinemia was that they developed chicken pox at the same rate and at the same severity as normal kids.

[Type text]

I don't know that anybody has looked at whether the addition of giving them intravenous gammaglobulin actually reduce that risk, but we could run it.

DR. SEWARD: They are now eligible to get varicella vaccine.

DR. ALLEN: Okay, at this point I think we are about ready to move into general discussion. So, I am going to close the open public hearing section, and ruefully acknowledge that I didn't read the open public hearing announcement for general matters meetings that I was supposed to, but our speaker did identify that he did have industry ties. So, perhaps my oversight will be excused.

We will move at this point into the open committee discussions. Dr. Scott, did you want to come and present us -- they are listed, I guess, formally as questions. They really aren't questions so much as requests for discussion. Do you want to present the questions to us formally, for consideration?

**Agenda Item: FDA Perspective and Questions for the Committee.**

DR. SCOTT: So, the first question is, to please discuss what laboratory and clinical data would be sufficient to demonstrate efficacy of a new anti-varicella antibody preparation for prophylaxis of severe infection.

Comment, please, especially on which target populations would be more informative and, actually, most important to study, most relevant.

What surrogate markers, if any, would be appropriate for an assessment of efficacy, and what other considerations you have for clinical trials.

DR. ALLEN: Okay, A, B and C are open for discussion.

**Agenda Item: Committee Discussion and Recommendations.**

DR. DiMICHELE: Actually, I don't want to discuss them so much as actually ask just a few more questions, particularly of our experts around the table.

I guess, in trying to think about this, obviously clinical and laboratory correlates would be good, to have both of them together.

So, based on what we heard so far we had sort of the clinical correlate study with the VZIG versus ZIG studies from the 1970s and 1980s, and it seemed like they looked at things like pox count, pneumonia, hepatitis and stuff.

Looking at severe disease, it looked like that seemed to be some reasonable clinical criteria by which we could maybe look at a clinical trial going forward, but I would like the experts to kind of comment on that, to see if, indeed, my interpretation is correct.

Secondly, I am a little confused, understanding the fact that titers don't mean everything, but I am a little bit confused -- and maybe Dr. LaRussa can clarify that -- because certainly it seems like there are some criteria by which people are considered to be immune, based on FAMA and GP ELISA titers.

I guess maybe I am still a little confused about where those come. Then my third question, actually, is for Dr. Ambrosino, in terms of wondering whether there would ever be enough VZIG for a comparison trial, were we to think about licensing another product.

Lastly, I just want to say that IVIG appears to have some efficacy but, given what we have heard earlier today, and certainly the fact that we may have to be curtailing use rather than expanding use, I am a little concerned about just generally recommending gammaglobulin at this time.

DR. LA RUSSA: I will make a couple comments. I didn't want to give you the impression that antibody is not protective, but you have to realize that most of what we know

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about antibody is in the context of either natural infection or vaccine, where you are also stimulating a cell mediated immune response.

So, to separate out what actually is an protective antibody titer gets to be a tough problem. That is why looking back -- I was a little surprised, looking back at all the old studies, to see how little data had been accumulated and actually what antibody titer the individual developed, which really would have helped you with this problem.

If you could have said, CF titer one to 50 at 48 hours assured you of protection, then you could have a surrogate marker for a clinical study, and that data is just not there now.

The other thing that you have to realize about varicella is that it is a tightly cell associated virus and, although there are these viremias, most of the spread of virus is from cell to cell.

So, if your antibody gets there quick, it hopefully sops up virus before it gets into lymphocytes and monocytes, but if it gets there too late, then there is going to be this passage of RS from cell to cell, that you can't really do anything about.

That is where I think the antivirals come in, because there are a high intracellular triphosphate levels that work on an intracellular level, and not on an extracellular level.

DR. DI MICHELE: Let's say that, given that, yes, endogenous immunity and titers achieved by endogenous immunity are very different than passive acquisition of titers, but let's say you just take the titers, and you give them passively or you acquire them endogenously.

Of course, the whole cellular immunity issue is not discussed. Certainly, might that not be a good place to start in terms of saying, at least, okay, this is what you get with passive immunity, it is something similar to what you might generate in an endogenous situation.

Let's say you are talking about the immunocompromised pediatric population, which I think I am going to get to a little bit later in terms of being potentially a target for clinical trials.

I mean, yes, that would leave out the cellular immune issue, but it might give us a starting point. Is that not valid at all?

DR. LA RUSSA: I think, unfortunately, in that group, the cellular immune response is so important that looking at antibody titers is going to be very misleading.

Again, if you look at a lot of the older data, the attack rates are pretty high, even in the presence of antibody in the immunized individual.

So, it might actually be cleaner to look at a totally immunocompetent population where you didn't have to worry about -- let me pose a scenario for you.

Let's say you decide you want to study children with leukemia. Well, you then have to think about what kind of regimens they are on, you have to think about what kind of periodic blood products they get, whether they are using effective antivirals as prophylactic agents.

There are so many variables in that situation, that you are either going to have to do a huge study in a place where there is a lot of varicella, or you are not going to really be able to answer your question.

DR. DI MICHELE: Even if, for instance, VZIG, which has been the standard of care -- I mean, VZIG is the standard of care in this population. I mean, we have been giving VZIG to kids with all sorts of cancers, on all sorts of regimens, this whole time. I guess my impression is it has been relatively effective.

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DR. LA RUSSA: Yes, so then what you are saying is, we are going to do a comparative trial looking at antibody end points, but we don't even know what to make of the VZIG end points.

I mean, we can say that, if you use VZIG of a certain titer, and give it within an appropriate time, you are going to get a certain amount of efficacy and, if we get similar titers, then we can make the supposition that this stuff should work just as well.

I think that is what we were talking about when we said, when you want to compare it to VZIG, you can do that, but if you are looking for clinical end points, I think that is going to be very hard to do. There is just not enough disease around.

DR. ALLEN: I think those are very good points, and looking in particular at our opening presentations about what has happened to the demand for product over the last couple of years, the clinical situations demanding its use, apparently, aren't there nearly as frequently.

I suspect, therefore, that the disease outcomes are going to be much more difficult to assess because it is just not going to occur that frequently.

I think we are going to have to use some degree of surrogate markers looking at antibody levels and that sort of thing, perhaps as you said, in immunocompetent populations, although I have got some immediate questions that come up about the ethics of doing those kinds of studies.

I think this is going to have to be looked at very carefully, and I think we are going to have to accept some degree of surrogate markers, at least as an initial step, while we are trying to get clinical end points.

DR. LA RUSSA: Just one other point. To compound the problem even more, we are doing such a good job of vaccinating kids that your pool of susceptible kids that potentially you could use for these kinds of studies is decreasing as time goes on.

So, unless you are willing to accept as a pool of immunocompromised kids those that have previously received vaccine, you don't really have a pure susceptible population. It is going to be a very small number.

DR. DI MICHELE: Does that mean that we are using equivalency in terms of FAMA titers? Let's say a child get leukemia and we are looking at FAMA titers for immunity. Are we using vaccination and endogenous infection FAMA titers are equivalent, in terms of protection? Are you saying that this child is protected, or are you giving these kids VZIG?

DR. LA RUSSA: You should ask me that question in another year. We were just talking about this over lunch, that essentially we have got this partially immune population of kids that are aging into the age of leukemia, and we are going to have to watch very carefully.

I can say anecdotally that I haven't gotten a lot of calls from frantic oncologists saying I have got kids with leukemia who have been vaccinated and now they have disease. That, again, the problem there is that the burden of disease to be exposed to is much less, too.

DR. KATZ: A question I think is probably for the FDA. As I look at the incidence of varicella and the apparent decline in use of VZIG, I am just wondering if the IVIG manufacturers are, in some way, shape or form, clamoring for this indication, i.e., to do the requisite trials.

DR. SCOTT: I hadn't noticed any clamoring at all. That said, there have been maybe mild degrees of interest expressed when this problem became known.

DR. SEWARD: I just wanted to make a comment on the correlate issues. I mean, studies -- the vaccine trials, you know, the best correlate marker that has been described is an antibody level six weeks post-vaccination.

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A year out, or two years out from that, there seems to be some marker set that measures something. It might be the cell mediated immune response.

So, you can't look at a child two to three years after vaccination and make any sense of that antibody titer in terms of protection, and we are not measuring kids six weeks post-vaccination out there in the community. So, we don't really have a correlate that is applicable to community use.

DR. ALLEN: Not seeing any other hands, I am going to ask another question of the FDA. Dr. Scott or Dr. Epstein, what about other manufacturers that might take on exactly the same process that has been used?

I mean, we are not talking about a process that necessarily has, you know, been found not to work, or to be inapplicable in current technology. Are there other manufacturers that could be invited or induced in some way to assume responsibility for creating a product, which might at least simplify the licensure requirements?

DR. SCOTT: In theory, it is possible to accomplish this kind of technology transfer. I think, in practice, for somebody to want to go into relatively small scale fractionation with virtually identical equipment and procedures, would be considered a fairly high undertaking, given the potential financial benefits of this kind of product.

I am just pointing out, there is a fairly high threshold that it wouldn't be impossible from a regulatory point of view at all.

DR. ALLEN: I mean, it certainly qualifies classically. It is not a drug. It is a biological, but it is an orphan biological situation.

There is a need for it. There are kids and adults that potentially are going to be harmed by the absence of the product. There is a national interest to have it available, it would seem to me. Payment for it in our current structure may be more difficult.

DR. AMBROSINO: I will make a relevant comment, I think. Our other product, Cytogam, that is a larger market, and our partners there are Medimmune, and Medimmune is actually the distributor of that product, and are looking to transfer the exact same process to a contract manufacturer and, in fact, we are assisting in any way we can.

The trouble is -- and we are glad to give our batch records away, we are glad to say, here, make it. I want to be helpful here. It just isn't enough patients out there that don't have an alternative that anyone would do that, at least everybody we have talked to, that it would make sense, and that is our problem, but boy, we would be glad to do a tech transfer in terms of offering this to anyone.

DR. ALLEN: In some regards, that seems like that may not be the least costly option but it may be the simplest option, even though I think we would agree VZIG isn't an ideal biological.

If it were to be formulated from scratch today, it at least seems to have a reasonable degree of efficacy and utility that has not been supplanted either by antivirals or by the standard IVIG.

So, there seems to be a continued role for it, even though it is still very much an orphan biological at this point.

DR. SEWARD: My comment to the second question, following on from that, is that it remains to be proven whether IVIG could substitute. I don't think the data is there right now.

It may well be able to do that, but the current scientific data isn't strong enough to make the statement now that it does, and the same small numbers, difficultly with exposures in

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the immunocompromised, acyclovir, the data is in healthy children, and not enough data in the immunocompromised children, and they are the main target group for this product, I think.

DR. KATZ: As I recall the vaccine in healthy children publication, the antibody levels are lower after immunization than natural infection, which I guess is no surprise whatsoever.

The other concern I have, I actually, as I look at the data, and if I had to guess, I would say that IGIV will, in fact, be effective if we figure out a reasonable dose to use.

I think a lot of authoritative people not concerned with licensure are intimating that in the recommendations that come down, but what is going to happen to the ability to maintain anything like the antibody levels that we see now as the immunized population ages and becomes our donors.

DR. LA RUSSA: I think those are good points, and perhaps the issue then becomes one of how do you stimulate and pay for a clinical trial that would compare IVIG appropriately with VZIG in an appropriate population.

DR. HARVATH: The question I had would be to propose an alternative to a randomized trial, because I think a randomized trial is, in terms of what we are hearing in terms of sheer numbers of people who would even be eligible, it doesn't sound like it is a likely possibility.

What we have done, an alternative approach we have taken, at least at NHLBI, for orphan diseases or really rare conditions for which we are trying to facilitate clinical studies of therapies -- for example, populations such as thalassemia patients -- is to first think about a registry or a reporting of cases.

CDC would probably be a great place to start in terms of reported cases where you have taken various approaches to treat patients who have these complications from this infection, and then what approaches we are taking to treat those patients.

It is not anywhere near as gratifying as doing a prospectively designed trial, but if you set a registry up appropriately, and you know the kind of questions that you would like to answer, you can at least get closer to the type of information you need, especially in the situation where it is going to be very difficult to come up with sufficient numbers to conduct a prospectively designed clinical trial.

The other question I had is for the folks who work -- like Dr. LaRussa and Dr. Seward -- what types of cell mediated immune in vitro tests have been done along the way to evaluate the responsiveness to therapy.

For example, if someone has had an exposure to the virus, and then they are given passive immunization with VZIG, has anyone done studies subsequently to find out whether they do develop cell mediated immunity?

DR. LA RUSSA: I can make a couple of comments. First, to go back to the issue of the randomized trial, I think -- just before I forget this point -- if you were willing to accept equivalency with VZIG, you could take a situation like, let's say, health care workers, where most health care workers are screened with varicella, for varicella antibodies. So, you would at least find an ongoing population of susceptibles.

Then do a study where you gave half of them VZIG and half of them IVIG at the appropriate dose, or this other product, whatever it is, and show that you got similar antibody titers. You might accept that type of equivalency.

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That might be the kind of trial that you could do, but it would only be in terms of looking at antibody titers, and not any kind of efficacy, and obviously you would have to look at safety, too, if you were going to do IVIG.

To answer your question about cell mediated immune responses, actually the best tests that we had is one that is no longer available.

There were a number of skin test antigens that were really wonderful for testing cell mediated immunity. The only problem with those is that they can also be immunogenic at the same time that you are testing.

We, in one small study, we saw antibody rises after skin test antigen testing. So, that clouds the water a little.

There are plenty of tests. There are in vitro lymphocyte stimulation, there are LE spot assay, there are interferon release, there is a lot of stuff. It just depends how much money the CDC is willing to spend. You could look at that.

To answer your question, though, with VZIG, people have looked for both infection rate, in terms of long-term persistence of antibody and cell mediated immunity, despite getting VZIG, and those things do happen. That is part of the problem. It doesn't prevent infection.

DR. KLEIN: Before we spend too much time talking about randomized trials, is there anyone here who believes we have enough product available to design a randomized trial, get it off the ground and completed? It sounds to me like there is not a prayer of doing that.

DR. SEWARD: Certainly not time, let alone if product is the problem. CDC, if we put an RFA out for the next fiscal year, we will be funding it next August, and the results will be in a year or two after that. We are out of this product by next year.

DR. KLEIN: I think we will look at something else then; right?

DR. SCOTT: From a practical standpoint, though, if you have a product under IND and you have an associated treatment IND for people who aren't eligible for the IND product under the IND study, there is a potential -- far less than ideal, but there is a possible short term solution there.

DR. LA RUSSA: I am just curious, from the FDA standpoint, how many patients in each group would you need to see in order to say that antibody titers were equivalent at 48 hours or one week? Would you be happy with 20 or 30 in a group, or would you need to see more than that?

DR. SCOTT: Something on the order of that number, and PK studies, for example, that were pivotal to licensure were done with the vaccinia immune globulins. You are looking at less than 100 people, and they had several different doses in each group.

DR. ALLEN: Let me just take a moment to point out that question number two is, please comment on whether the available scientific data support use of IVIG or acyclovir as a substitute for VZIG for prophylaxis of severe varicella zoster virus infection in any clinical settings.

We have skirted on some of these issues. Dr. LaRussa addressed it from his perspective in some of his concluding statements, but that question is open for discussion also.

DR. LA RUSSA: I think the answer has to be no, in the absence of further study.

DR. KATZ: If the word scientific was taken out of the question, would you change your answer?

[Type text]

DR. LA RUSSA: Well, no, I don't think I would. I think I would want to know how much antibody is in the different IVIG preparations, so that I could figure out the right amount to give.

I really want to know if I am causing other problems that we haven't talked about. I have seen the kids who get rapid infusions of IVIG and white out their lungs and do other things. So, I need to see some safety data.

If I am backed up against a wall and I don't have any VZIG, yes, I am going to do that, but that is purely non-scientific.

DR. SEWARD: I see a difference between supporting use of, or recommending use of. So, if scientific were taken out, I could say, yes. I mean, if you are up against a wall and you don't have anything, I think most clinicians are going to give IGIV or use acyclovir, because they don't want to sit there.

If the scientific data isn't available, I think everybody imagines these things are going to provide some benefit, but it is not strong enough scientific data now to say that it is going to be equivalent and should be recommended. So, I see a difference with those words.

DR. ALLEN: And I guess I would be a little happier if we actually had 2-A and 2-B, with 2-A being IGIV and 2-B being acyclovir.

I think they are quite separate issues. I mean, acyclovir as an antiviral has got certain very appropriate uses, but it is not a substitute in any way for the immune globulins, and I think you presented sufficient overall data, Dr. LaRussa, to indicate that each has got its own appropriate role in this, but there is certainly not going to ever be equivalence or used as substitutes for one another.

The issue with IVIG, I think, has been laid out separately in terms of identifying antibody levels, targeted antibody levels, appropriate dosage, and looking at safety and efficacy under different clinical situations, and there we need additional data.

DR. KUEHNERT: I think, going back again to a clinical standpoint, I think that if you look at question two and add to it, versus doing nothing and watchful waiting, I think you have a very different answer than if you are looking at a rigorous scientific data. So, it depends what your standpoint is, I think.

DR. SCOTT: I think it would be fair to say -- and Jay can correct me if I am wrong -- that the point of question two, really the underlying point is to ask, do we need VZIG.

I think that we have talked about this a lot, and what I have heard is that there are some circumstances still, even though you don't meet it very often, where it is felt that you need it, and that is what the clinicians think, and that seems to be supported also by the kinds of patients that we know are out there.

DR. KLEIN: It just seems to me, from hearing this discussion and trying to absorb all this information, that you need it until you can demonstrate that there is something else as good.

Right now you have a gold standard. It appears to be effective. There are loads of studies. They aren't all perfect but they support the use of this drug.

We don't have anything that says, given the absence of this drug, there is something equivalent. Maybe IVIG is going to be terrific if we figure out what dose, but we simply don't know, and we are not going to have a chance to find out before the supply runs out.

DR. DI MICHELE: The only thing I would add to Dr. Klein's statement, which I agree with, is that unfortunately the issue of need is a moving target, and one that we don't completely understand.

[Type text]

DR. ALLEN: To add onto that, the point that Dr. Katz and others have raised earlier is the fact that our donor population is changing also, in terms of the type and titer of antibody.

We will be switching over time from people whose immune response is caused by wild type virus infection to people who will have vaccine titer antibody, or vaccine antibody, and what we will need to do and how, under future circumstances, very carefully needs to be monitored over time.

It sounds to me like the IVIG, if that is to be the substitute pending further studies, that, again, we need to continue to assess that over time, because the IVIG of the future, with regard to this antibody, is not likely to be equivalent to what we have available today.

DR. LA RUSSA: Just one last comment. If you had said to me, here is the data that shows that IVIG is of equivalent immunogenicity, let's say, as VZIG, I can come up with -- I will give you the dose, and you will get the proper antibody titers, it is still going to be a much more difficult product for the clinician to use, and will essentially take what is a very short interaction with the health care system and turn it into a much longer one.

I guess I would say that, if I had a choice, and you asked me, should we continue to find a source of VZIG, I would say, that is my preference.

If that is not an option, I can live with IVIG with all the caveats that we have talked about, but that would certainly not be my preference.

DR. ALLEN: Dr. Marin, can I ask you a question? Has the ACIP addressed this question and the issue of the declining availability of VZIG in the future, in any of its deliberations?

DR. MARIN: This issue was discussed in the ACIP VZIG working group, and the decision was to postpone it for the August discussions, and to go to a recommendation for the end of October meeting of the ACIP.

So, we presented to the working group a review of available data on efficacy and effectiveness of IVIG, some data about antivirals used as post-exposure prophylaxis. Most of the discussions will be in the August meeting of the working group.

DR. SEWARD: I wouldn't anticipate, based on my experience with working groups and the data that you have all seen, that they are going to be having any different discussion than we are having here. Same data, same limitations, no other available product.

DR. AMBROSINO: May I add about the red book? Dr. Reynolds asked me to mention to you -- the chairman of the red book -- that they will have recommendations in the fall for alternative use, just so there will be recommendations out there.

They are hoping that ACIP and red book, as usual, will be harmonized. Sometimes that happens in the beginning and sometimes later.

DR. ALLEN: Dr. Epstein and Dr. Scott, I wonder if there shouldn't be communications with the ACIP and with the red book staff also, just to let them know about this discussion here and the FDA's concerns and issues in terms of approaching it.

DR. SCOTT: Thanks to the session, and also to the preceding telecoms, I think we have established ties through CDC to ACIP and we should connect with the red book folks as well.

DR. KLEIN: It just seems to me that, given the discussion that we heard and the limited amount of information, that you can always get an expert panel together and, given the inferior products, you will get a recommendation about how to use them until data is available.

[Type text]

It seems to me, from what I have heard, that you would like to look for an alternative source of manufacture, and it seems to me that that should be the number one thing to do.

Once you have found someone, whether it is inside this country or outside this country, who is willing to do so, then you should make it financially reasonable for them to produce it.

It also seems to me that we have talked a lot about the declining need in the United States, but from what I heard, with the immigration issues that we have, this need is not going to go away for a very, very long time.

So, we shouldn't assume that, with vaccination, that this is not going to be an issue in the United States in five years or ten years. It will be.

DR. ALLEN: I think that is a very good point, and in particular, if we go back to our early presentations on what has happened, yes, there has been a fairly dramatic decline over the last several years in terms of the need for the product.

Nonetheless, if you are looking at pediatric doses, you were still producing, what, 10,000 doses a year, and in adults the equivalent would be 2,000 a year.

That is a fair number of patients overall that have some need of the product. I understand that is what is being produced, may not be what is being administered and used.

Still, we are talking about something that is needed by thousands of people a year in this country alone, and I agree with Dr. Klein that my immediate take is that, while we do need to fund some additional studies, we do need to look at what will be happening over time, we do need some good comparisons, that trying to find an alternative source for VZIG at the present time is clearly the preferable way to go.

Again, one hesitates to bring some of these issues up to congress, which has the appropriations responsibility for the federal government, because they will tend to beat government people around the ears, claiming that they have created a crisis and didn't pay attention to this early enough. The issue somehow does need to be brought to other levels of the administration, and congress also.

DR. SCOTT: I just wanted to mention there are some incentives. Clearly on the numbers of people treated, this would qualify as an orphan product.

I say that, obviously, without a formal submission, and there are tax credits as well for the study, as well as study grants, which are not enormous, but it is more than nothing, perhaps. There is also the potential for cost recovery for an IND product like this.

DR. ALLEN: Dr. Holmberg, I am sure you have paid attention to the discussion also, and will take it back with regard to your committee responsibilities.

DR. HOLMBERG: I have a lot of concern about this, primarily because, when we talk about the supply of -- I think the information you gave us was that in January you would be running out of supply.

On the other hand, trying to use the IVIG as an alternative without the scientific data to support it, we are in the same situation that we are currently with IVIG, where we have anywhere from 40 to 100 percent of the hospital use being off label, which just exacerbates the problem.

So, we are aware of this, and we will be working closely with all the other agencies -- CDC and FDA along with this -- to try to work out of a problem, of a solution to this.

I think some of the issues that we have, and some of the suggestions that have already been made, as far as going outside the country, with a product that may be made in

[Type text]

Canada with U.S. plasma, definitely in the United Kingdom with U.S. plasma being used over there, there is some great potential of expanding beyond our borders here.

I think I hear the message loud and clear, and I agree with Dr. Klein, that this is not going to go away. We have a growing immigration rate and we do have some real concerns here, to protect those people, to protect the American population.

DR. ALLEN: Dr. Epstein and Dr. Scott, have you received the discussion that you need? Do you want further clarification or explication in any area?

DR. EPSTEIN: I think it would be helpful to have a specific discussion about surrogate markers. Do committee members, either individually or collective, think that PK comparison with VZIG ideally, prospectively, and otherwise, retrospectively, would be a valid approach, plus or minus whatever review we can do of the Canadian clinical trial, because it has been pointed out that the product in Canada was, in fact, approved there based on a clinical trial.

I would also comment that, if we think PK is a suitable approach -- that is to say, antibody levels -- would it be suitable to do those studies in normal, healthy individuals, or do you really have to look for these rarer, susceptible populations to do PK studies, or could you simply look at the evolution of titers in healthy normals.

I think that is kind of the crux. I think we have heard enough about question two. The general sense appears to be that there is a need for a VZIG product and that, although clinicians might use whatever is available otherwise, they would certainly want the continued availability of VZIG, which is established. I am simply summarizing what I thought I heard. I think I haven't heard as clear an answer on question one, particularly 1-B, surrogates.

DR. DI MICHELE: I think there are two issues here. One of them is titers, but the other is clinical efficacy in the patients who need it most.

I just -- I am going to go back to what I said before, the VZIG pivotal trial for licensure that was done in the 1980s seemed to at least look at presence or absence of the worst systemic complications of disease, plus a pox count.

That, combined with something like titers, I think might be the best approach, if it is doable. Again, depending on what the FDA was willing to accept in terms of an equivalency trial.

I think that issue is not just has import when you ask us, what population do you want to study, because if you want to just look at PK, you can probably look at it in any population.

If you want to look at PK combined with efficacy, then I think you have to look at it in the most susceptible populations.

So, it just depends on the issue of whether you want a clinical end point, either compared to historical controls or in addition to the surrogate marker. I think that will determine what population you use.

DR. LA RUSSA: I guess what we could do in the short term is maybe design a very quick study that we could send around to pediatric oncologists and see how much varicella they are still seeing, to see whether it is even feasible to do what you are asking.

We have a pretty large pediatric oncology group at Columbia, and I am saying, I haven't gotten a call about a varicella case in the leukemic probably in the last year or so.

DR. DI MICHELE: That is because they are still getting VZIG.

DR. LA RUSSA: I don't think so, because we have to approve VZIG.

[Type text]

DR. SEWARD: I mean, varicella disease is 80 to 90 percent declined. So, you are not seeing it in schools and in day care centers and, if we do, it is modified mild disease, breakthrough in vaccinees, which is not as infectious.

So, I think the amount of varicella around is going to make it a lot more challenging to do the clinical efficacy study now in the United States. You could do it in Canada, although Canada is now vaccinating for varicella as well, but they don't have as fully implemented a program. You could do it in Europe, in the United Kingdom.

DR. LA RUSSA: The other thing I would say is, if you wanted to do just a PK study, I suppose you could do it in people that were seropositive, but that is really going to muck up the analysis stage, because then you are going to have to normalize for their pre-VZIG antibody titer.

I guess what I was proposing is that, let's say that you believe that five percent of the adult population is susceptible and, since health care workers in many cities have a disproportionate number of people from outside the country, who may have a higher rate of susceptibility, you may, in fact, end up with a pool of health care workers, susceptible health care workers that you could do a quick PK study on and answer at least the equivalency question. I really don't think you are going to be able to answer the clinical question.

DR. KATZ: I don't know about health care workers. I know that, at my hospital system, we require proof of immunity, history or proof of immunity, and we immunize if they can't provide one or the other. So, health care workers may be tough.

I have a question and that is, is using normals, immune or susceptible, appropriate? Are the highest risk people in any way more catabolic? Do we know anything about PK in these particularly sick kiddies and what not, that would be different from normals?

DR. LA RUSSA: My problem there, as I pointed out before, is that there are a lot more variables. The kids that you would like to give it to all get blood products. They get either acyclovir, sometimes gancyclovir prophylaxis, and there are lots of other things going on.

You will have to look at renal function and liver function and other things. I think it just becomes a much more complicated study. I agree, that that would be the best population to do it in, but I think it is problematic.

DR. ALLEN: I agree. For a baseline, I really would like to see a comparable trial between IVIG at several different doses, and VZIG in a well-defined normal population, preferably kids.

It is probably not ethical, it can't be done very easily, but it would be nice to have that kind of baseline data.

The other variable that it doesn't begin to address in any way is cell mediated immunity, which is an important component of the response to this infection. At least that would begin to answer one initial set of questions with regard to the pharmacokinetics.

DR. LEW: I just want to make one comment, though. I know that, technically, we always like to first do trials on the healthy folks and then you move on down.

The truth is, this is going to be a product that really is for the immunocompromised child that we are really trying to target.

When you get the most severe, we are talking about bone marrow transplant kids. In a way, I have mixed feeling, that they are truly the target with all the caveats that you have, Phil, that yes, they have renal problems, they have every sort of problems, are on many different medications, but that is really the target group. I am curious as to whether -- it seems like that is the group we really do want to study.

[Type text]

DR. LA RUSSA: And again, I would agree with you. I just don't know what to do about their blood product use and the other things that are going to complicate the analysis.

I would be happy, if we had the time, the money, to get enough to sort out the variables. I would be very happy to do it in that population.

DR. DI MICHELE: On the other hand, the cancer patient isn't the only immunocompromised pediatric patient as well. There are transplant recipients, the renal disease population, and there are a few others.

DR. QUIROLO: I have one question about using IVIG as a treatment. Even if you did devise a study, you would have to know what the titer is in the IVIG you are giving and then you would have to depend on the manufacturer to tell you what the titer was in every dose of IVIG, which I don't know if they would be willing to do. It is expensive.

DR. ALLEN: That is certainly one other caveat with regard to the use of that product, and it is certainly one that wasn't there with VZIG because every lot was titered to within a very narrow range.

If IVIG is going to be used in the future, if there is an established efficacy and it is used as a routine in the future, you probably are going to have to know what the range is for each lot that is used.

It may be that certain lots should be set aside, if you will, for this particular use as opposed to other lots. I don't know.

DR. SEWARD: I am trying to ask the question whether immunological equivalency, as demonstrated just in the lab, and then safety data, in immunocompromised children, would be sufficient for licensing an orphan product.

DR. ALLEN: I think it does need to be addressed. I think that is a good point.

DR. LAAL: Is there information about correlates for protection, surrogate markers for protection, that we can get out of the studies that must have been done when the vaccine was licensed?

All that I am hearing about is the antibody part of the immune response, and I don't know enough about the literature, but when the vaccines were made, what kind of studies were done?

DR. LA RUSSA: The reason why we try to separate these two things out is because it is one thing to immunize someone with an antigen that stimulates both antibody and cell mediated immunity, but that is not really applicable to the question of prophylaxis, where you are relying purely on antibody to do the protection.

So, unfortunately, since those two arms of the immune system are so wound together that the data from the vaccine trials, frankly, is irrelevant to the question that you are asking.

DR. LAAL: Even if one was to look at the antibody responses in children who were protected versus the breakthrough children who were not so well protected.

DR. SEWARD: You can't separate the antibody responses from the cell mediated immune responses. I mean, they are highly correlated and interrelated.

DR. LA RUSSA: You know, in some ways, the antibody responses are really a reflection of a good cell mediated immune response and not a separate response.

Here you are saying we want to use antibodies, pure antibodies, as protection. So, the vaccine studies really don't help you. If anything, they confuse the situation.

DR. ALLEN: Other comments or discussion on this issue?

[Type text]

DR. SCOTT: I wanted to thank the committee, and I want to paraphrase some ideas that I heard into a possible approach.

If PK studies could be done in normal people that are not immune, and there was comparability shown between the current VZIG product and another VZIG product, that wouldn't answer the clinical question, but it could be considered reasonably likely, which is actually the wording of the CFR for accelerated approval to be connected, or connectable to efficacy in the immune compromised people.

Now, that kind of a study comes with a major caveat, that there is a post-marketing study as well, which could actually be some way of monitoring some of these immune deficient patients, or the first X number of patients that receive the product in a certain category.

That is just an example. I am not saying that is an imprimatur, but that is something that comes to my mind, and I wonder what the committee thinks about that kind of an approach.

DR. SEWARD: I think it is a good start.

DR. KLEIN: I would be very comfortable with that. I think, unfortunately, the good news is that, with the rate of disease, and with any kind of a product that is any good at all, it will probably take 100 years to demonstrate that you have more disease than your historical controls.

So, you are probably never going to find that out, but certainly this would be a reasonable approach with a post-marketing survey.

DR. SCOTT: I point out 1984, when the CDC looked at the distribution of this product. They had about 10,000 vials a year distributed, and the clinical trials were undertaken just a few years before that.

So, whether or not there are enough people out there to do a study, or to collect the data and do a post-marketing study, I think there is a possibility. We don't know how the current VZIG is being used. That is one of the hurdles, coming up with a design.

DR. KATZ: We keep supplies in my hospital, where I am responsible for this issue, and we outdate it all, two or three doses for a 70 kilo guy. We buy it once or twice a year - not a 70 kilo guy, I apologize for my sexism, a 70 kilo person. We are outdating it. We haven't used any for three years.

DR. LA RUSSA: One thing you could do is make receipt of VZIG contingent upon completing the results of whatever study, go back to the way we used to distribute VZIG before it was a licensed product. That way you could get that information.

DR. ALLEN: Yes, it would be good if that kind of information were routinely available in many circumstances, but it is not, but that is a good suggestion.

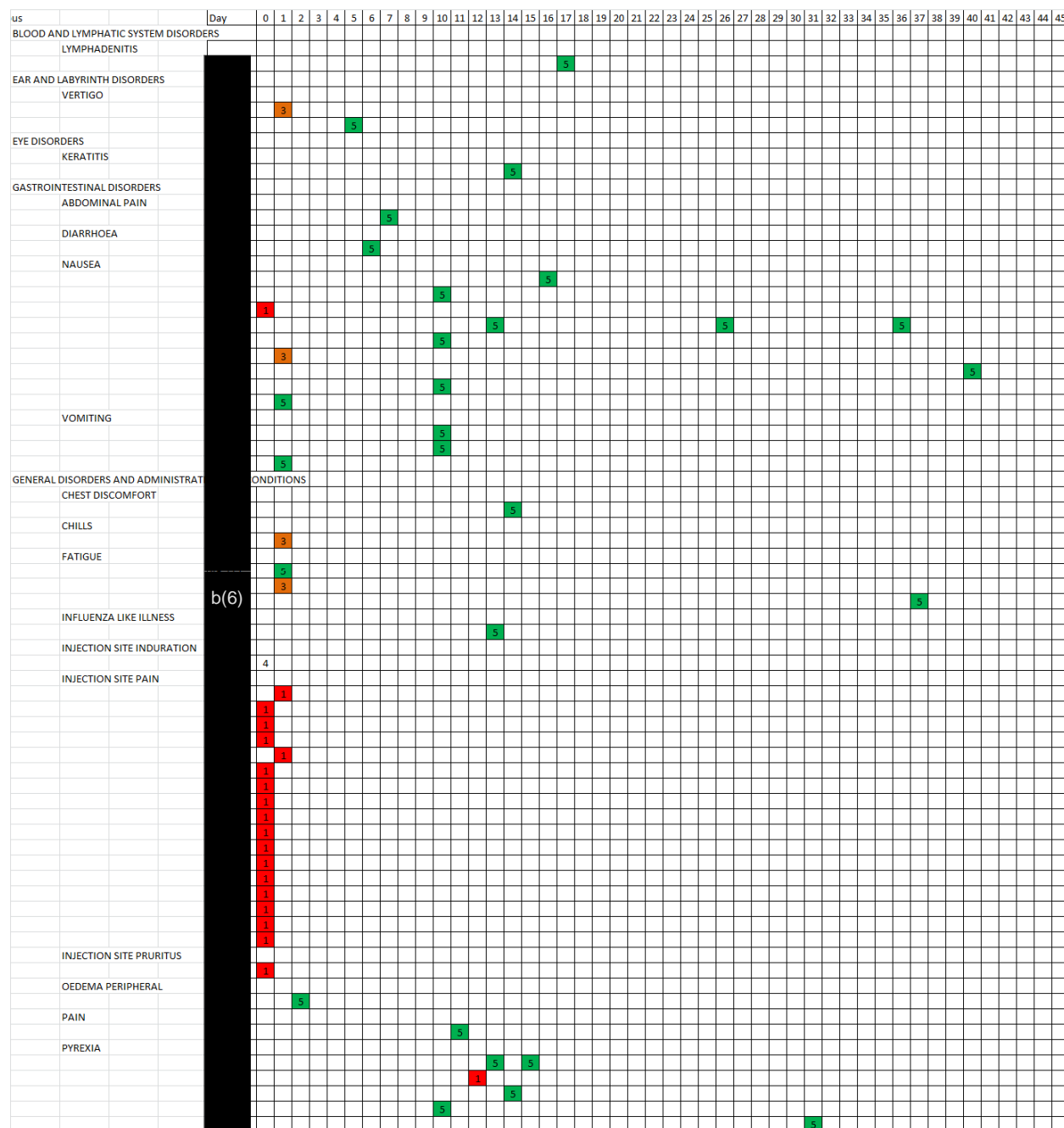
Other comments or discussion? Okay, I want to thank the committee. I think this has been a difficult discussion, but very exciting.

I want to thank the special members who have joined us, and our presenters, who came in for their part of it. It has been very helpful. Thank you all, and that will close section two. We will go ahead and have the break now, and I would like to have people back and ready to start at 3:45, please.

[Brief recess.]

1 = judged definitely related	3 = judged possibly related
4 = judged conditional (more information needed)	5 = judged doubtfully related

### APPENDIX 3. NON-SERIOUS ADVERSE EVENTS IN STUDY VZ-006 BY DAY AFTER VARIZIG ADMINISTRATION



1 = judged definitely related	3 = judged possibly related
4 = judged conditional (more information needed)	5 = judged doubtfully related

[illegible]

1 = judged definitely related	3 = judged possibly related
4 = judged conditional (more information needed)	5 = judged doubtfully related

[illegible]

1 = judged definitely related	3 = judged possibly related
4 = judged conditional (more information needed)	5 = judged doubtfully related

## APPENDIX 4. STUDY VZ-006: SERIOUS ADVERSE EVENTS BY DAY AFTER PREVIOUS ADMINISTRATION OF VARIZIG®

[illegible]

## Causality Code

Red background → Subjects with thrombosis/coagulopathy	1 = definitely related	2 = probably related
Pink → subject with similar coag. concern		
3 = possibly related	4 = unlikely related	5 = conditional (more information needed)

### Study VZ-009: Non-Serious Adverse Events by Day after Previous Administration of VariZIG<sup>®</sup>

## APPENDIX 5. STUDY VZ-009: NON-SERIOUS ADVERSE EVENTS BY DAY AFTER PREVIOUS ADMINISTRATION OF VARIZIG®

[illegible]

## Causality Code

Red background → Subjects with thrombosis/coagulopathy	1 = definitely related	2 = probably related
Pink → subject with similar coag. concern		
3 = possibly related	4 = unlikely related	5 = conditional (more information needed)

### Study VZ-009: Non-Serious Adverse Events by Day after Previous Administration of VariZIG®

[illegible]

## Causality Code

Red background → Subjects with thrombosis/coagulopathy	1 = definitely related	2 = probably related
Pink → subject with similar coag. concern		
3 = possibly related	4 = unlikely related	5 = conditional (more information needed)

### Study VZ-009: Non-Serious Adverse Events by Day after Previous Administration of VariZIG®

# Causality Code

Red background → Subjects with thrombosis/coagulopathy	1 = definitely related	2 = probably related
Pink → subject with similar coag. concern		
3 = possibly related	4 = unlikely related	5 = conditional (more information needed)

## Study VZ-009: Non-Serious Adverse Events by Day after Previous Administration of VariZIG®

		Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45		
INVESTIGATIONS	ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED	VM-00995							4																																									
	ALANINE AMINOTRANSFERASE INCREASED	VM-00063																					4																											
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	ASPARTATE AMINOTRANSFERASE INCREASED	VM-00059						5																																										
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	BLOOD ALKALINE PHOSPHATASE INCREASED	VM-00997																																																
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	HAEMOGLOBIN DECREASED	VM-00059																																																
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	PLATELET COUNT DECREASED	VM-00059																																																
		VM-00168																																																
	TRANSAMINASES INCREASED	VM-00560																																																
	WEIGHT INCREASED	VM-00995																																																
		VM-00997																																																
	WHITE BLOOD CELL COUNT DECREASED	VM-00059																																																
		VM-00063																																																



# Causality Code

Red background → Subjects with thrombosis/coagulopathy	1 = definitely related	2 = probably related
Pink → subject with similar coag. concern		
3 = possibly related	4 = unlikely related	5 = conditional (more information needed)

## Study VZ-009: Non-Serious Adverse Events by Day after Previous Administration of VariZIG®

	Day	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)																																																		
TUMOUR PAIN	VM-00994					4																																												
NERVOUS SYSTEM DISORDERS																																																		
CONVULSION	VM-00091					4																																												
DIZZINESS	VM-00361																	4																																
HEADACHE	VM-00238																						4																											
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	VM-00283																								4																									
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MIGRAINE	VM-00361																																																	
NEUROPATHY PERIPHERAL	VM-00995					4																																												
SOMNOLENCE	VM-00168																																																	
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS																																																		
UMBILICAL GRANULOMA	VM-00217																																																	
PSYCHIATRIC DISORDERS																																																		
ANXIETY	VM-00361																																																	
NERVOUSNESS	VM-00361																																																	
RENAL AND URINARY DISORDERS																																																		
HAEMOGLOBINURIA	VM-00063																																																	
HYDRONEPHROSIS	VM-00091																																																	



### Color Code for SAE type

Red background → Subjects with thrombosis/ coagulopathy	1 = Death	2 = Life Threatening
Pink → subject with similar coag.concern		
3 = Significantly disabling/ incapacitating	4 = Required or prolonged hospitalization	6 = Medically serious

**Study VZ-009: Serious Adverse Events by Day after Previous Administration of VariZIG®**  
[subjects who experienced a thrombotic/coagulopathic adverse event have a red background]

## APPENDIX 6. STUDY VZ-009: SERIOUS ADVERSE EVENTS BY DAY AFTER PREVIOUS ADMINISTRATION OF VARIZIG®

[illegible]

### Color Code for SAE type

Red background → Subjects with thrombosis/ coagulopathy	1 = Death	2 = Life Threatening
Pink → subject with similar coag.concern		
3 = Significantly disabling/ incapacitating	4 = Required or prolonged hospitalization	6 = Medically serious

**Study VZ-009: Serious Adverse Events by Day after Previous Administration of VariZIG®**  
[subjects who experienced a thrombotic/coagulopathic adverse event have a red background]

[illegible]

### Color Code for SAE type

Red background → Subjects with thrombosis/ coagulopathy	1 = Death	2 = Life Threatening
Pink → subject with similar coag.concern		
3 = Significantly disabling/ incapacitating	4 = Required or prolonged hospitalization	6 = Medically serious

**Study VZ-009: Serious Adverse Events by Day after Previous Administration of VariZIG®**  
[subjects who experienced a thrombotic/coagulopathic adverse event have a red background]

[illegible]

**APPENDIX 7. CANGENE'S RESPONSE TO THE CLINICAL ITEMS IN THE OCTOBER 4, 2012, INFORMATION REQUEST**

[The response has been put into outline format by the reviewer.]

**CLINICAL**

*16. Antibodies against human protein S of the coagulation system have been observed in patients who experienced post-infectious purpura fulminans after varicella infection (e.g., see Journal of Thrombosis and Haemostasis 3: 1243–1249 (2005).*

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**Cangene Response:**

- 1) Cangene has not tested the VariZIG product for the levels of anti-protein S antibodies.
  - a) However, we have reviewed the literature available on the development of antibodies to protein S after varicella infection and can discuss this literature in the context of plasma collection for the production of VariZIG.
- 2) Autoimmune protein S deficiency can develop following varicella infections,
  - a) although other organisms have also been implicated (1).
  - b) Post-infectious protein S deficiency is caused by the development of neutralizing antibodies to protein S that increase clearance of protein S from the circulation (2).
  - c) Development of anti-protein S antibodies has been reported primarily in children, and
    - i) can result in thrombotic manifestations such as purpura fulminans within a few days or weeks after the onset of the precipitating infection (1).
  - d) The autoimmune response is transient;
    - i) the anti-protein S antibodies return to low/undetectable levels following resolution of the infection (3).
  - e) Nevertheless, the transient protein S deficiency has effects on the anticoagulation process and may lead to thromboembolic complications,
    - i) such as purpura fulminans, in individuals with varicella (3).
    - ii) It is noteworthy to mention that post-infectious purpura fulminans is a rare complication that mainly manifests in children (1,4).
    - iii) The reports of purpura fulminans in adults are limited to a handful of case reports (1) that were not associated with antibody- mediated protein S deficiency (5, 6, 7).
- 3) VariZIG is manufactured using plasma that is collected at FDA-approved plasma collection centers.
  - a) To donate plasma, donors must be healthy adults as per 21 CFR, Subpart G – 640.63 – Suitability of Donor (8).
  - b) Each donor is screened prior to every plasma donation in accordance with the plasma supplier's FDA-approved questionnaire. The questionnaire includes donor confirmation

- of feeling “well and healthy” on the day of donation.
  - c) Donors must also have a suitable temperature (99.6°F or less) on the day of donation.
  - d) Lastly, donors are asked if they have been to a doctor or clinic or if they are using new prescribed medications (including antibiotics, antivirals and/or antifungals) since their last donation.
    - i) If answered yes, the reason for doctor visit/use of medication(s) is evaluated to determine if there is an underlying medical condition (e.g., varicella or varicella-related complication such as purpura fulminans) that would require a deferral.
- 4) Symptoms of varicella include fever and malaise which may occur 1 to 2 days before rash onset, particularly in adults (9).
- a) Therefore, plasma donors presenting with early or acute-phase symptoms of varicella or other infections would be temporarily deferred from donating plasma.
  - b) Since post infectious protein S autoantibodies are transient (i.e., with the resolution of varicella infection anti-protein S antibodies dramatically decrease to undetectable/low levels (3);
    - i) a donor that was temporarily deferred because of a potential varicella or any other infection would have undetectable or low levels of anti- protein S antibodies following recovery from infection and at subsequent plasma donation visits.
- 5) Overall, donor deferral measures at plasma collection centers ensure quality and safety of plasma used for VariZIG manufacture.
- a) In cases where donors present with symptoms of varicella, deferrals would be in place until resolution of the infection.
  - b) Due to
    - i) rarity of post-infectious purpura fulminans in adults (i.e., potential plasma donors),
    - ii) the transient nature of post-infectious anti-protein S antibodies and
    - iii) deferral measures for symptoms of infection at plasma collection centers,
  - c) anti-protein S antibodies are unlikely to be a safety concern for the VariZIG product.

**Reviewer’s Comment:** ---b(4)-----  
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***17. Adverse event monitoring and causality categorization appears to be inconsistent between studies VZ-006 and VZ-009. Following are examples of these inconsistencies:***

***a. On June 22, 2006, there was a varicella exposure incident in the NICU at Wesley Medical Center in Wichita, KS. Thirteen (13) premature infants were treated with VariZIG i.m. There were 21 non-serious adverse events in 6 subjects, and 10 serious adverse events (including 2 deaths) in 3 subjects, as shown in the following table:***

SUBJID	Non-Serious AE	Serious AE	Day after last dose
-b(6)---b(6)---			
-b(6)----- -	Dermatitis Diaper		4
	Haematochezia		5
-b(6)----- -			
-b(6)----- -			
-b(6)----- -			
-b(6)----- -			
-b(6)----- -	Metabolic Acidosis		2
	Hypoalbuminaemia		6
-b(6)----- -	Hypothermia		5
	Sepsis		5
-b(6)----- -	Haematochezia		3
		Death [Bronchopulmonary Dysplasia]	6
-b(6)----- -		Intraventricular Haemorrhage	1
		Disseminated Intravascular Coagulation	2
		Convulsion	2
		Pulmonary Haemorrhage	2
		Death	3
-b(6)----- -	Sepsis		4
	Metabolic Acidosis		15
	Skin Disorder “Skin Breakdown”		21
-b(6)----- -		Staphylococcal Sepsis	3
		Coagulopathy	6
		Thrombocytopenia	6
	Convulsion		6
	Hypotension		8

SUBJID	Non-Serious AE	Serious AE	Day after last dose
	Pneumonia		9
	Metabolic Acidosis		9
	Adrenal Insufficiency		13
	Dermatitis Diaper		14
	Hydronephrosis		22
	Bronchopulmonary Dysplasia		25
	Staphylococcal Sepsis		25
	Pneumonia		28
	Necrotising Enterocolitis Neonatal		36
-b(6)----- -			

*In contrast to this, the VZ-009 study report (page 47 of 306) states “9 pre-term infants (VM-00510 to VM-00518) exposed in the neonatal intensive care unit at Winthrop University Hospital in Mineola, NY; and five immunocompromised pediatric patients exposed at Children’s Hospital at Montefiore Bronx, NY were amongst 10 patients exposed to an immunocompromised host with zoster lesions.”*

*The ADMIN database shows that these premature infants were treated with VariZIG on March 18, 2008; however, the AE database contains no adverse events for these subjects.*

#### **Cangene Response:**

- 1) The VZ-009 interim clinical study report was generated based on case report forms submitted to Cangene prior to the report cut-off date of September 1, 2011.
  - a) Due to both
    - i) the interim nature of the study report, and
    - ii) the expanded access program itself,
  - b) not all data was complete.
  - c) Specifically, as discussed in the interim study report,
    - i) since the VZ-009 study is an expanded access study and subjects were treated under urgent or emergency scenarios,
      - (1) not all case report forms were returned to the sponsor and
      - (2) those which were returned did not always have all fields completed.
      - (3) Investigational sites were queried regarding missing data,

- (a) but when queries were not addressed, data was accepted as missing.
- d) The handling of missing data is discussed in the interim study report in section 11.4.2.2.
- 2) As part of the data review and report writing activities,
  - a) it was noted that no adverse events were reported from Winthrop University Hospital in Mineola, NY and that
  - b) adverse event pages were not submitted for Children's Hospital at Montefiore Bronx, NY,
  - c) whereas safety data reported from Wesley Medical Center appeared to be complete.
  - d) After submission of the interim report,
    - i) Cangene initiated on site monitoring activities to determine if adverse event data was available at the two sites in New York.
    - ii) Cangene's intention was to include any updated information from these clinical trial sites in the final clinical study report.
    - iii) As a result of onsite visits in September 2012,
      - (1) Cangene determined that adverse event data was available for these subjects and a second visit in October 2012 was schedule to train investigational site staff on adverse event reporting and data collection and to aid in reporting of this data.
- 3) As a result of these monitoring activities,
  - a) adverse event data from these two sites has been collected.
  - b) This data has not yet been entered into the VZ-009 database,
    - i) and has not been through internal querying or medical coding.
  - c) In the case of SAE data,
    - i) as Cangene just received this data starting the week of October 9th, these cases are still open,
    - ii) clarifications are being collected from the investigators and sponsor medical assessment is ongoing.
    - iii) As such, preliminary data has been tabulated for response to this question (Table 9).

Table 9 Adverse Event Data for Three VZ-009 Expanded Access Protocol Sites with Multiple Patients Exposed in a Hospital Setting

Subject ID	Site	Non-Serious AE	Serious AE	Day after last dose
VM-00080	Wesley			
VM-00081	Wesley	Dermatitis Diaper		4
		Haematochezia		5
VM-00082	Wesley			
VM-00083	Wesley			
VM-00084	Wesley			
VM-00085	Wesley			
VM-00086	Wesley	Metabolic Acidosis		2
		Hypoalbuminaemia		6
VM-00087	Wesley	Hypothermia		5
		Sepsis		5
VM-00088	Wesley	Haematochezia		3
			Death [Bronchopulmonary Dysplasia]	6
VM-00089	Wesley		Death [Intraventricular Haemorrhage]	1
			Disseminated Intravascular Coagulation	2
			Convulsion	1
			Pulmonary Haemorrhage	1
VM-00090	Wesley	Sepsis		4
		Metabolic Acidosis		15
		Skin Disorder "Skin Breakdown"		21

Subject ID	Site	Non-Serious AE	Serious AE	Day after last dose
VM-00091	Wesley		Staphylococcal Sepsis	3
			Coagulopathy	6
			Thrombocytopenia	6
		Convulsion		6
		Hypotension		8
		Pneumonia		9
		Metabolic Acidosis		9
		Adrenal Insufficiency		13
		Dermatitis Diaper		14
		Hydronephrosis		22
		Bronchopulmonary Dysplasia		25
		Staphylococcal Sepsis		25
		Pneumonia		28
		Necrotising Enterocolitis Neonatal		36
VM-00092	Wesley			
VM-00510	Winthrop			
VM-00511	Winthrop	Left lower quadrant lesion		8
			Tachycardia	12
		Retinopathy of Prematurity		20
		Gastroesophageal reflux		29
VM-00512	Winthrop	s/p Status post PDA ligation		9
		Retinopathy of Prematurity		27
VM-00513	Winthrop			
VM-00514	Winthrop	Status post bilateral inguinal hernia repair		3

Subject ID	Site	Non-Serious AE	Serious AE	Day after last dose
VM-00515	Winthrop	Hyperpigmented macule on 1 parietal scalp, 2 cm diameter		0
		Inguinal hernia		8
			Pedal Edema <sup>a</sup>	29
		Gastroesophageal reflux/esophageal dysmotility		31
		Retinopathy of Prematurity Stage 1 Zone 3		27
VM-00516	Winthrop	Gastroesophageal reflux		0
			Sepsis <sup>a</sup>	10
			Urinary tract infection <sup>a</sup>	13
			Patent foramen ovale <sup>a</sup>	14
		Tremors		35
VM-00517	Winthrop		Apnea of prematurity <sup>a</sup>	5
		Left lower quadrant lesion		8
		Retinopathy of Prematurity		20
		Circumcision		28
VM-00518	Winthrop			
VM-00782	Montefiore	Rhinorrhea		11
		2 petechiae on right upper eyelid		18
		Arm pain		31
		URI last week that is improving		39
			Lesions on back, chest [Varicella]	4
VM-00783	Montefiore	URI previous week		11
		Right leg pain		18
		Right sided abdominal pain		18

Subject ID	Site	Non-Serious AE	Serious AE	Day after last dose
		Headache		25
			Varicella	4
VM-00785	Montefiore	Throat pain		21
		Bleeding from lip due to lesion		25
			relapsed AML	11
VM-00789	Montefiore	Leg pain		11
		Sore throat		15
		Constipation		17
		Bilateral preauricular ear tags		18
			Sepsis	29
VM-00790	Montefiore	Fever		6
		Mild body aches		6
		Buises on shins and knees		11
		Thrombocytopenia		11
		Rash throughout face		14
		Puffy eyes		41

<sup>a</sup> SAEs from Winthrop University Hospital are currently being queried by Cangene's Pharmacovigilance department. Each of the SAEs were categorized as Medically Serious by the investigator and the seriousness of the events are still being reviewed by Cangene.

- 4) At Winthrop University Hospital, 9 preterm infants were exposed to varicella in the neonatal intensive care unit in March 2008.
  - a) All 9 infants received VariZIG and were entered into the VZ-009 expanded access study.
  - b) Initially, no adverse events were reported for these infants in the case report forms (an adverse event page was provided indicating no adverse events).
    - i) However, upon further discussions with the investigator, the case histories for these patients have been reviewed and adverse events have been captured for 6 out of 9 of the preterm infants.
    - ii) The remaining three infants were released from hospital days after study drug administration and no adverse events were reported.

- iii) Although none of the infants had prolonged hospitalization or re-hospitalization recorded in the study,
      - (1) a number of adverse events were categorized as medically serious by the investigator.
      - (2) These adverse events are still being queried by Cangene's pharmacovigilance unit and are noted in Table 9.
    - c) Serious adverse events similar in nature to those reported at Wesley Medical Center did not occur at this center.
    - d) The investigator at Winthrop indicated that all preterm infants treated had stabilized prior to administration of VariZIG.
    - e) All of the reported events have an unlikely causality relationship to the study drug, as assessed by the investigator.
- 5) At Children's Hospital at Montefiore, VariZIG was requested for ten immunocompromised pediatric patients exposed to a host with zoster lesions in October 2009.
  - a) Five of these patients did receive VariZIG (Subjects VM-00782, 783, 785, 789 and 790) and case report form data was returned.
  - b) The remaining five subjects for whom VariZIG was requested did not receive study drug or participate in the expanded access program.
  - c) Of the five patients participating in the expanded access program,
    - i) two subjects did develop varicella lesions and these patients were included in the efficacy analysis of the interim study report.
  - d) The site was initially queried for missing data including adverse event case report form pages,
    - i) however, responses to queries were not received.
    - ii) More recently, a new investigator assigned to this study
      - (1) has been responsive, and
      - (2) has reviewed the case histories for these patients and provided Cangene with both serious adverse event reports and non-serious adverse event listings.
    - iii) Serious adverse event reports have been received for the two subjects with varicella, subjects VM-00782 and VM-00783.
    - iv) Two additional serious adverse event cases have been reported for patient VM-00785 with recurrent bone marrow failure, reported as residual bone marrow disease (relapsed AML) resulting in death post-study on –b(6)-----
    - v) A serious adverse event of sepsis has been reported for subject VM-00789.
    - vi) Adverse events for all five subjects have now been reported to Cangene and are tabulated in Table 9.
    - vii) All of the reported events have an unlikely causality relationship to the study drug, as assessed by the investigator.
- 6) Cangene plans to include this updated safety data as well as any additional data received from other VZ-009 expanded access patients in the final clinical study report.
  - a) Data query and monitoring activities are still underway in this ongoing expanded access program.

***b. The following table shows the causality profile across all reported adverse events in studies VZ-006 (maternal exposure) and VZ-009 (expanded access for high risk):***

	<b>Definitely Related</b>	<b>Probably Related</b>	<b>Possibly Related</b>	<b>Unlikely Related</b>	<b>Conditional</b>
<b>VZ-006</b> (N = 133 AEs)	26 (20%)	0 (0%)	13 (10%)	93 (70%)	1 (1%)
<b>VZ-009</b> (N = 341 AEs)	4 (1%)	4 (1%)	17 (5%)	287 (84%)	27 (8%)

*It can be seen that adverse events in study VZ-009 were only rarely categorized as “probably” or “definitely” related to NP001 administrations, whereas adverse events judged “definitely” related accounted for 20% of the adverse events, perhaps including adverse events that other might categorize as “probably” related.*

*For example in study VZ-006 (N = 60), the adverse events “Injection Site Pain”, “Injection Site Haematoma”, “Injection Site Induration”, or “Injection Site Pruritus” occur in 20 subjects receiving intramuscular administration, and for 19 of these 20 cases the event is judged “definitely” related to the product. However, in study VZ-009 (N = 372), the adverse events “Injection Site Paraesthesia” and “Injection Site Haematoma” occur in just 2 subjects, judged “definitely” and “probably” related, respectively. Study VZ-009 predominantly used the intramuscular route of administration, rendering these differences difficult to interpret.*

*Attribution of causality is a judgment arrived at by the investigator, followed by a re-assessment by the sponsor. It is clear that different assessment procedures were followed in these two studies, thereby confounding the analysis of the safety profile of this product.*

*Therefore, please revise the adverse events databases for 1) completeness, 2) appropriate seriousness categorization, and 3) causality assessment, and submit the revised adverse events databases to this BLA.*

### **Cangene Response:**

- 1) Cangene confirms that adverse event data provided in the BLA for all completed studies (VZ-001, VZ-003, VZ-006 and VZ-008) is complete, including causality and seriousness categorization.
  - a) The VZ-009 study is an ongoing expanded access program.
  - b) The datasets provided for the VZ-009 study represent the data available at the cut off date of September 1, 2011, and are complete for that time period.
  - c) As discussed in the response to question 17a, a final study report is planned to capture all data for this study and a more complete dataset is anticipated at the time of final report.
  - d) New data is being reported to the IND according to expedited and annual reporting requirements.
  - e) As data for this study is currently being entered and reviewed, new datasets are not provided at this time.
- 2) An examination of the overall adverse event profile for each study is discussed in the study

reports submitted in the BLA.

- a) In addition, adverse events by population are discussed in the **Overview of Safety** (Module 2.5.5) and the **Summary of Clinical Safety** (Module 2.7.4) of the BLA submission.
  - b) Adverse reactions captured in the clinical studies are consistent with the profile for intramuscular immune globulin products.
- 3) To address the above FDA points, Cangene will describe the process for assessment of causality for non serious and serious adverse events in the two studies, and how these were reported in the BLA.
- a) A further breakdown of the adverse events by study will be included, to allow discussion of observed differences.
  - b) Cangene medical assessment of causality and seriousness will be discussed. At this point, a revision of the adverse event database is not planned.

#### **Adverse Event Database for VZ-006 and VZ-009**

- 1) Adverse events, in both the VZ-006 and VZ-009 studies, were initially assessed by the investigator for intensity, causality and seriousness.
  - a) In both studies, causality was assessed in the case report form based on WHO causality definitions which were defined in the study protocols.
  - b) The definitions of definite, probable, possible, conditional, and doubtful (VZ-006) or unlikely (VZ-009), were similarly defined in each study, with some minor differences (see **Appendix I**).
- 2) Consistent with Cangene's current practice, the VZ-009 (version 3.0) study protocol further defined Cangene's mapping of WHO causality to ICH relatedness for clinical trials, where a related event is one where there is a reasonable possibility that the AE was caused by the product in question.
  - a) AEs assessed as having a "definite", "probable", "possible" or "conditional" association with the study drug according to the WHO definitions will be reported as related.
    - i) Whereas, an unrelated adverse event is clearly or most probably caused by other etiology such as the patient's underlying condition, therapeutic intervention or concomitant therapy, or the delay between the administration of the product and the onset of the AE is incompatible with a causal relation, or the AE started before the administration of the product.
  - b) AEs assessed as having an "unlikely" association with the study drug according to the WHO definitions will be reported as not- related/no relationship.
  - c) These definitions were used to map the causality to related and unrelated for the VZ-009 interim study report.
  - d) The same definitions were applied in retrospect for interpreting adverse event data from the VZ-006 study, as discussed further below.
  - e) Overall, a similar approach was taken with both studies.
- 3) Study VZ-006 in pregnant women exposed to varicella was a controlled, open label clinical trial with three treatment arms, an IM commercial VZIG arm, an IM NP-001 (VariZIG) treatment arm and an IV treatment arm. During the VZ-006 clinical trial, a total of 133

adverse events were reported.

- a) Forty-one events (31%) were reported in the IM VZIG group,
- b) 41 events (31%) were reported in the IM NP-001 group and
- c) 51 events (38%) were reported in the IV NP-001 group.
- d) Breakdown by causality (WHO and ICH) by treatment group is presented in Table 10.

**Table 10 VZ-006 Adverse Events Summary by Causality and Treatment Group**

Treatment group	Number of adverse events reported (% total AEs)					Total AEs (N patients)
	Definitely Related	Probably Related	Possibly Related	Conditional	Doubtful Related	
IM Commercial VZIG (N=19 patients)	14 (34%)	0 (0 %)	2 (5%)	0 (0 %)	25 (61%)	41 (16)
IM NP-001 (VariZIG) (N=19 patients)	8 (20%)	0 (0 %)	7 (17%)	0 (0 %)	26 (63%)	41(15)
IV NP-001 (VariZIG) (N=22 patients)	4 (8%)	0 (0 %)	4 (8%)	1 (2%)	42 (82%)	51 (16)
Total all treatment groups	26 (20%)	0 (0%)	13 (10%)	1 (1%)	93 (70%)	133 (47)
	Related AEs (N patients)					Unrelated AEs (N patients)
IM Commercial VZIG (N=19 patients)	16 (12) <sup>a</sup>					25 (10)
IM NP-001 (VariZIG) (N=19 patients)	15 (10) <sup>b</sup>					26 (9)
IV NP-001 (VariZIG) (N=22 patients)	9 (5) <sup>c</sup>					42 (16)
Total all treatment groups	40 (27)					93 (35)

<sup>a</sup> 9 related adverse events in 9 patients were due to injection site pain. The remaining 7 related adverse events occurred in 4 patients

<sup>b</sup> 8 related adverse events in 8 patients were due to injection site pain. The remaining 7 related adverse events occurred in 5 patients

<sup>c</sup> 3 related adverse events in 3 patients were due to injection site reactions. The remaining 6 related adverse events occurred in 3 patients.

Removal of the 20 injection site reactions, results in 20 (18%) related adverse events and 93 (82%) unrelated adverse events

- e) In the VZ-006 study, there were a similar number of related events in both the IM commercial VZIG and the IM NP-001 (VariZIG) arms. Although distribution of definitely and possibly related events did vary, all definite and possible events were mapped to related causality.
- 4) Study VZ-009 was an open labeled expanded access program to provide VariZIG to patients at risk of severe complications of varicella, including pregnant women, immunocompromised or immunosuppressed children and adults, infants (including pre-term infants, newborns to mothers with varicella shortly before or after birth) and non-immune healthy adults.
- a) In the interim report, a total of 353 adverse events were reported by 96 subjects (28.5%) prior to the cut-off date of September 1, 2011.
  - b) As discussed in response to 17 a above, due to both the interim nature of the study report, and the expanded access program itself, not all data was complete.
  - c) Additional data collected will be incorporated into the final study report.
  - d) Breakdown of the interim report adverse event data by causality (WHO and ICH) by patient group is presented in Table 11.

**Table 11 VZ-009 Adverse Events Summary by Causality and Patient Group**

Patient group	Number of adverse events reported (% total AEs) <sup>a</sup>					Total AEs (N patients)
	Definitely Related	Probably Related	Possibly Related	Conditional	Unlikely Related	
Immunocompromised children and adults (N=159)	4 (2%)	0 (0%)	11 (4%)	27 (11%)	207 (83%)	249 (61)
Infants (N=103)	0 (0%)	2 (4%)	2 (4%)	0 (0%)	52 (93%)	56 (23)
Pregnant Women (N=71)	1 (3%)	2 (5%)	3 (8%)	0 (0%)	34 (85%)	40 (10)
Healthy Adults (N=4)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	3 (75%)	4 (2)
Total all patient groups (N=337)	5 (1%)	4 (1%)	17(5%)	27 (8%)	296 (85%)	349 (96)
	Related AEs (N patients)					Unrelated AEs (N patients)
Immunocompromised children and adults (N=159)	42 (10)					207 (53)
Infants (N=103)	4 (4)					52 (20)
Pregnant Women (N=71)	6 (5)					34 (6)
Healthy Adults (N=4)	1 (1)					3 (1)
Total all patient groups (N=337)	53 (20)					296 (80)

<sup>a</sup> Causality was not assessed by the investigator for 4 adverse events, including diaper dermatitis in an infant, an underdose in a preterm infant and facial swelling and pruritis in an immunocompromised adult.

**Table 11 VZ-009 Adverse Events Summary by Causality and Patient Group**

Patient group	Number of adverse events reported (% total AEs) <sup>a</sup>					Total AEs (N patients)
	Definitely Related	Probably Related	Possibly Related	Conditional	Unlikely Related	
Immunocompromised children and adults (N=159)	4 (2%)	0 (0%)	11 (4%)	27 (11%)	207 (83%)	249 (61)
Infants (N=103)	0 (0%)	2 (4%)	2 (4%)	0 (0%)	52 (93%)	56 (23)
Pregnant Women (N=71)	1 (3%)	2 (5%)	3 (8%)	0 (0%)	34 (85%)	40 (10)
Healthy Adults (N=4)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	3 (75%)	4 (2)
Total all patient groups (N=337)	5 (1%)	4 (1%)	17(5%)	27 (8%)	296 (85%)	349 (96)
	Related AEs (N patients)					Unrelated AEs (N patients)
Immunocompromised children and adults (N=159)	42 (10)					207 (53)
Infants (N=103)	4 (4)					52 (20)
Pregnant Women (N=71)	6 (5)					34 (6)
Healthy Adults (N=4)	1 (1)					3 (1)
Total all patient groups (N=337)	53 (20)					296 (80)

<sup>a</sup> Causality was not assessed by the investigator for 4 adverse events, including diaper dermatitis in an infant, an underdose in a preterm infant and facial swelling and pruritis in an immunocompromised adult.

**Table 11 VZ-009 Adverse Events Summary by Causality and Patient Group**

Patient group	Number of adverse events reported (% total AEs) <sup>a</sup>					Total AEs (N patients)
	Definitely Related	Probably Related	Possibly Related	Conditional	Unlikely Related	
Immunocompromised children and adults (N=159)	4 (2%)	0 (0%)	11 (4%)	27 (11%)	207 (83%)	249 (61)
Infants (N=103)	0 (0%)	2 (4%)	2 (4%)	0 (0%)	52 (93%)	56 (23)
Pregnant Women (N=71)	1 (3%)	2 (5%)	3 (8%)	0 (0%)	34 (85%)	40 (10)
Healthy Adults (N=4)	0 (0%)	0 (0%)	1 (25%)	0 (0%)	3 (75%)	4 (2)
Total all patient groups (N=337)	5 (1%)	4 (1%)	17(5%)	27 (8%)	296 (85%)	349 (96)
	Related AEs (N patients)					Unrelated AEs (N patients)
Immunocompromised children and adults (N=159)	42 (10)					207 (53)
Infants (N=103)	4 (4)					52 (20)
Pregnant Women (N=71)	6 (5)					34 (6)
Healthy Adults (N=4)	1 (1)					3 (1)
Total all patient groups (N=337)	53 (20)					296 (80)

<sup>a</sup> Causality was not assessed by the investigator for 4 adverse events, including diaper dermatitis in an infant, an underdose in a preterm infant and facial swelling and pruritis in an immunocompromised adult.

### Assessment of Causality for Adverse Events

- 1) It is Cangene's current practice to report and summarize adverse event data based on investigator assessment of causality in the study report.
  - a) Cangene is in agreement with the current draft FDA guidance for Industry and Investigators – Safety Reporting Requirements for INDs and BA/BE Studies (10) stating,
    - i) “the investigator is knowledgeable about the human subject (e.g., medical history, concomitant medications), administers the investigational drug, monitors the subject's response to the drug, is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be drug-related, and may have observed the event.”
  - b) While investigator assessment of causality may be queried during case report form review, it is not the current practice to provide a separate sponsor assessment of causality for every non-serious adverse event.
- 2) While the investigator assessment of causality of adverse events is utilized for the purposes of tabulating data in the clinical study reports, by current practice,
  - a) all serious adverse events undergo internal medical assessment by the pharmacovigilance department.
  - b) In cases where there is disagreement in causality assessed by the investigator and the sponsor,

- i) Cangene would expedite a case judged as related by the sponsor but assessed as unrelated by the investigator,
    - (1) but for the purposes of reporting, an event considered related by the investigator would not be downgraded by the sponsor.
  - c) Cangene does rely on investigators to make the initial assessment of seriousness and to report the serious adverse event.
- 3) For the VZ-006 study, conducted between September 1996 and April 1999,
  - a) Cangene did initially assess relatedness of adverse events for both non-serious and serious adverse events in the original study report.
  - b) As discussed in the VZ-006 addendum report, when the initial VZ-006 clinical study report was prepared, an assessment of relatedness of the events was made by the sponsor based on the investigator's assessment of causation, as captured on the CRF, and past experience with the study drug.
  - c) Whereas the investigator utilized WHO causality (definite, probable, possible, conditional, doubtful) for causality, the sponsor reassessment utilized related or unrelated.
  - d) This relatedness is captured in the body of the original study report, but is not present in the datasets.
- 4) To remove the potential for bias, the revised summary tables presented in the BLA submission in the VZ-006 addendum report assign relatedness of events based solely on the opinion of the investigator.
  - a) In the addendum report, if causality was assessed as definite, probable, possible or conditional, the event was mapped as related to study drug.
  - b) When causality was assessed as doubtful, the event was mapped as unrelated to study drug.
  - c) Summary data presented in the addendum report for related and unrelated adverse events are based on this mapping.
  - d) Consideration of investigator assessment and the mapping of causality are consistent with Cangene's current practice and reporting in the VZ-009 interim study report.

### **Causality Differences in the VZ-006 and the VZ-009 Adverse Events Databases**

- 1) A discrepancy in the number of definitely related adverse events has been noted between the two clinical studies VZ-006 and VZ-009.
  - a) This discrepancy related primarily to the FDA observation regarding injection site reactions.
    - i) In particular, there were a large number of injection site reactions captured during the VZ-006 study, as summarized in Table 12.

**Table 12 Injection Site Reactions by Treatment Group in VZ-006**

Adverse event term	Number of Injection Site Reactions by Treatment Group		
	IM Commerical VZIG (N=19 patients)	IM NP-001 (VariZIG) (N=19 Patients)	IV (VariZIG) (N=22 patients)
Pain Injection Site	9	8	0
Injection Site Reaction	0	0	2
Ecchymosis (at injection site)	0	0	1

- ii) Of note, all adverse events of injection site pain were reported at a single clinical trial site (Dr. Koren, Toronto).
  - iii) Injection site pain was reported in
    - (1) 9/15 (60%) patients in the IM Commercial VZIG group and
    - (2) 8/15 (53%) patients in the IM NP-001 (VariZIG) group at this clinical trial site.
  - iv) No adverse reactions of injection site pain were reported in the 4 patients in the IM Commercial VZIG group or the 4 patients enrolled in the IM NP-001 (VariZIG) group at the three remaining sites.
  - v) In the IV NP-001 (VariZIG) treatment group, there were 2 injection site reactions (injection site induration and pruritis at injection site) and 1 ecchymosis (bruising at the injection site) in the 22 patients enrolled in this group.
  - vi) In total, injection site reactions account for 19 of the definitely related events and the single conditionally related event in VZ-006.
- 2) In contrast to VZ-006, in VZ-009
- a) only two injection site reactions (Injection Site Hematoma and Injection Site Pain) were reported out of the 337 patients summarized in the interim report.
  - b) Similarly, in the pharmacokinetic study VZ-008, there were no reports of injection site reactions in 35 healthy volunteers administered VariZIG (N=18) or VZIG (N=17) intramuscularly.
  - c) The product label for the previous licensed varicella immune globulin (VZIG) reported that adverse drug reactions related to discomfort at the injection site (pain, redness, or swelling at the injection site) occurred in approximately 1 in 100 patients (11).
  - d) This incidence is similar to that observed for other intramuscular immune globulin products.
    - i) For example, in clinical trials for Rhophylac, Rho(D) Immune Globulin (Human), in 447 Rho(D)-negative pregnant women administered either intravenous or intramuscular Rhophylac, injection site reactions occurred in 0.5% of study participants (12).
    - ii) In clinical trials for HepaGam B, Hepatitis B Immune Globulin (Human), in newborn infants (N=253) or adults (N=42) exposed to hepatitis B and treated with an intramuscular injection of HepaGam B, only 1 injection site reaction, induration of the right and left thighs in a newborn infant was observed (13).
    - iii) While injection site reactions are expected for intramuscularly administered immune globulin products, the rates observed in the VZ-009 study are consistent with that reported for other IM immune globulin products.
    - iv) This data suggests that the large number of injection site reactions reported in VZ-006 may have been related to practices at a single investigational site.

- 3) While Cangene is not suggesting that the injection site reactions in VZ-006 should be disregarded,
  - a) if the data is examined without injection site reactions,
    - i) not only does the percentage of related adverse events decrease,
    - ii) but the percentage of unrelated adverse events in the VZ-006 study,
    - iii) increases to 82%,
      - (1) which is more in line with VZ-009 data (see Table 10 footer).
    - iv) As Cangene considers all adverse events with definite, probable and possible causality to be related, minor differences in investigator assessment of these causalities are not further discussed.
- 4) However, there were a large number of conditionally related adverse events reported in the VZ-009 study.
  - a) These differences may have been related to differences in definition of conditional or it could be a result of individual investigator assessment.
  - b) The VZ-006 study defined conditional as “A reaction that follows a reasonable temporal sequence in relation to the administration of the drug; that does not follow a known response pattern to the suspected drug; but could not be reasonably explained by the known characteristics of the subject’s clinical status.”
  - c) The VZ-009 study defined conditional as “A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination” (**Appendix I**).
- 5) A single adverse event in the VZ-006 study was classified as conditional.
  - a) A pregnant woman randomized to receive intravenous VariZIG (NP-001) had injection site induration, starting on the day of study drug administration.
    - i) This event was classified as conditional by the investigator. ,
  - b) In the original study VZ-006 study report, Cangene assessed this event as unrelated.
    - i) However, a more conservative assessment would be to consider the injection site reaction as related.
- 6) In the VZ-009 study,
  - a) the 27 adverse events classified as conditionally related to VariZIG occurred in two patients.
    - i) For one patient, VM-00031, a 5 year old immunocompromised child with acute lymphocytic leukemia,
      - (1) a serious adverse event of neutropenia was captured in the case report form as conditionally related (SAE Case VZ009-00031
      - (2) In the SAE database, clarification was provided by the investigator that the event was considered unlikely related to VariZIG and due to chemotherapy.
      - (3) The seriousness of the event was assessed as medically significant.
      - (4) As the case report form recorded conditional causality,
        - (a) the clinical trial adverse event data includes this case of neutropenia to be related.
        - (b) This case may be further queried for reconciliation in the final study report.
      - (5) However, as an isolated case, this related neutropenia does not have a large impact on the overall safety data for the drug product.

- (6) In addition, a more plausible reason for the neutropenia has been provided in the case narrative in the interim study report.
- (7) As the study population included immunocompromised patients, a total of 11 events of neutropenia in 10 subjects were captured in the VZ-009 study. All other cases of neutropenia had an unlikely causation (unrelated to study drug).
- ii) In a second patient in the VZ-009 study, VM-00059, a 3 year old immunocompromised child with neuroblastoma and bone marrow failure,
  - (1) the investigator captured 26 lab abnormalities as adverse events with a conditional relationship to the study drug.
  - (2) This subject received VariZIG on May 26, 2006 and events of haemoglobin decreased (3 events), hyponatraemia (2 events), hyperglycaemia (6 events), aspartate aminotransferase increased (3 events), hypocalcaemia (3 events), hypokalaemia (3 events), white blood cells decreased (2 events), platelet count decreased (3 events) and hypomagnesaemia (1 event) between May 26, 2006 and July 3, 2006.
  - (3) These events were reviewed by Cangene pharmacovigilance after corresponding with the investigator and a memo in the case report form suggests that the events are more likely related to concomitant therapy with concomitant chemotherapy treatment, etoposide and cisplatin.
    - (a) Although this is a more likely causality, the adverse events with causality of conditional are captured as related.
  - (4) Overall, these conditionally related lab abnormalities are isolated to a single patient and do not have a large impact on the safety profile of VariZIG.
- b) Other lab abnormalities, including 17 investigations in 8 patients and 31 metabolism and nutrition disorders in 13 patients, were captured as adverse events in the VZ-009 interim clinical study report and had an unlikely causation (unrelated to study drug).
- 7) Over all, the adverse reactions captured in the clinical studies are consistent with the profile for intramuscular immune globulin products.
  - a) The most common adverse reactions were injection site pain, headache, chills, fatigue and rash.
  - b) Less common adverse reactions expected for an immune globulin product were reported including nausea, arthralgia and myalgia.
  - c) A single case of serum sickness is discussed further in question the response to question 20.

### **Seriousness Categorization**

- 1) Cangene does rely on the investigators to report serious adverse events, through both expedited reporting and on the case report form.
  - a) Both studies utilized similar reporting criteria for determining whether an adverse event was serious.
  - b) Differences in the number of serious adverse events in the two studies relate primarily to the differences in the study populations, as VZ-009 included immunocompromised patients, infants and preterm infants, healthy adults and pregnant women, while VZ-006 was limited to pregnant women.
- 2) In VZ-006, out of 60 pregnant women,

- a) 4 serious adverse events were reported in 4 patients, specifically
    - i) two spontaneous abortions,
    - ii) a therapeutic abortion and
    - iii) an asthma exacerbation.
  - b) All serious adverse events were assessed as having doubtful causality by the investigator and as not related to the study drug by the sponsor in the original VZ-006 study report.
- 3) In VZ-009, out of 71 pregnant women,
- a) two serious adverse events were reported in two patients,
    - i) a premature separation of the placenta and
    - ii) a congenital anomaly.
  - b) In both cases the investigator and Cangene assessed these events as unrelated to VariZIG.
  - c) As VZ-009 is an ongoing expanded access program,
    - i) additional serious adverse events will be captured in the final study report.
- 4) It is Cangene's current practice to provide an internal medical assessment of all serious adverse events.
- a) The interim clinical study report for VZ-009 did not include the company's medical assessment.
  - b) Two tables with serious adverse event narratives from the interim clinical study report are appended (**Appendix II**), to include Cangene's medical assessment of each case.
  - c) Overall, the Cangene assessment is in agreement with the investigator assessment of seriousness and relatedness or causality

## Summary

- 1) In summary, Cangene provided complete adverse event databases for the VariZIG studies in the BLA up to and including the data lock for VZ-009.
  - a) Similar definitions were used to map the causality to related and unrelated for the VZ-009 interim study report and applied in retrospect for interpreting adverse event data from the VZ-006 study addendum.
  - b) Similarly, Cangene applied the same approach for including the Investigator's assessment for seriousness and causality, as per FDA guideline.
- 2) Therefore, Cangene considered similar assessment procedures to be followed in general for both studies.
  - a) However, in the case of 'Definitely Related' categorization for VZ-006 having a higher reporting frequency,
    - i) this has been attributed to the 19 injection site reactions reported by a single site, discussed in further detailed above,
      - (1) which is not consistent with the reporting from other sites.
    - ii) This apparent discrepancy is therefore considered to have been related to practices at a single investigational site and does not represent a difference in interpretation of the safety database across studies in general.
  - b) The differences in the causality and seriousness interpretations highlighted by the FDA

are explained in further detail in this response.

- c) The existing datasets are not provided in this response, Cangene has not needed to add or change data in the BLA adverse event database to address these points.

**Reviewer's Comment:** The responses is acceptable. The applicant acknowledges that the databases for VZ-009 are not analyzable for demonstration of safety or efficacy. The applicant intends to update the VZ-009 database and submit reports with due diligence.

**18. Please submit the 95% confidence intervals for the infection rates observed in study VZ-006 for stratum 1 (1-4 days since exposure) and for stratum 2 (5-14 days since exposure).**

**Cangene Response:**

- 1) The infection rates and corresponding 95% confidence intervals were calculated using the exact binomial distribution for each stratum.
- a) In addition, a two-sided Fisher's exact test was performed to test the null hypothesis that there is no difference between the two strata. The results are provided in the table below:

**Table 13 Infection Rates and 95% Confidence Interval Observed in Study VZ-006 for the Two Strata**

Stratum <sup>a</sup>	Infection Rate	95% Confidence Interval	p-value <sup>b</sup>
1 – 4 days	0.3529 (12/34)	(0.1975, 0.5351)	0. 7798
5 – 14 days	0.3043 (7/23)	(0.1321, 0.5292)	

<sup>a</sup> All treatment groups (IM VariZIG, IV VariZIG, and IM VZIG) are included in the analysis.

<sup>b</sup> Fisher's exact test.

- 2) Based on the above results, there does not appear to be a statistically significant difference in the rate of varicella infections observed in patients treated within 4 days of exposure compared to patients treated between 5 and 14 days of exposure to VZV.

**Reviewer's Comment:** The response is acceptable. Other analyses of the outcomes in VZ-006 are discussed in this review.

**PVP**

**19. You list 'signal detection' as a planned action (e.g., in the context of potential risks such as hypersensitivity reactions) in your pharmacovigilance plan. Can you please clarify/elaborate on your specific signal detection methods?**

**Cangene Response:**

- 1) As part of the Pharmacovigilance Plan (PVP) for Varicella Zoster Immune Globulin (Human) (VariZIG) Cangene intends on employing traditional methods for the detection of safety signals related to VariZIG exposure in patients receiving the product for the following indications:
  - Intramuscular (IM) or Intravenous (IV) administration for the prevention or reduction in severity of maternal infections within 4 days of exposure to the Varicella Zoster Virus (VZV) (approved in Canada only)
  - Post-exposure prophylaxis (IM administration proposed in US) in high risk individuals including:
    - Immunocompromised children and adults,
    - Newborns of mothers with varicella shortly before or after delivery,
    - Premature infants,
    - Infants less than one year of age,
    - Adults without evidence of immunity, and
    - Pregnant women.
- 2) Signal detection activities will be performed on a quarterly basis and will include traditional methods such as
  - a) reviews of individual case safety report (ICSRs),
  - b) case series reviews, and
  - c) analyses of individual AE reporting frequencies (RFs) for any unusual or striking features that may be interpreted as a signal.
- 3) At this time, Cangene does not anticipate the need to employ complex statistical methods for signal detection.
  - a) Such methods are typically used to evaluate large datasets.
  - b) Based on case information received since March 2006,
    - i) Cangene does not expect a large number of cases (large dataset) for evaluation at this time;
    - ii) between March 2006 (approval in Canada) and 17 January 2012 (end of the last Periodic Safety Update reporting period),
      - (1) Cangene did not receive any post-marketing cases reporting adverse events (AEs) involving VariZIG.
    - iii) In addition, Cangene received a total of 41 new serious AE reports involving VariZIG since March 2006 through clinical trial VZ-009 entitled 'Safety and Efficacy of Varicella Zoster Immune Globulin (Human) (VariZIG) in Patients at-Risk of Varicella Infection.
- 4) As part of Cangene's signal detection activities, the following cases involving VariZIG received by Cangene will be evaluated:
  - Cases reporting new serious unexpected/unlisted AEs,
  - Cases reporting new non-serious unexpected/unlisted AEs,

- Cases reporting the occurrence of serious events thought to be extremely rare in the general population;
  - Cases reporting a possible lack of efficacy,
  - Fatal cases,
  - Cases reporting an abnormal/unexpected outcome in the fetus following use of VariZIG in pregnant women,
  - Cases reporting off-label use of VariZIG including,
  - Cases reporting a medication error with VariZIG,
- 5) Reviews of ICSRs and case series will focus on the evaluation of
- (1) designated medical events (DMEs) such as AEs which are rare, serious and have a pharmacological class-attributable risk (i.e. risks associated with immunoglobulin products),
  - (2) targeted medical events (TMEs) that are associated with immunoglobulin products (i.e. thrombotic events, coagulation disorders, hypersensitivity etc.), and/or
  - (3) the patient populations requiring treatment with VariZIG.
- a) In addition, the following will also be considered/evaluated as part of Cangene's signal detection activities:
- Identification of a previously unrecognized at-risk population (e.g., populations with specific racial or genetic predispositions or co-morbidities),
  - Confusion about a product's name, labeling, packaging or use,
  - New pre-clinical safety findings of human relevance,
  - Other concerns identified by the Health Authorities,
  - An apparent increase in the severity and frequency of an expected/listed event.
- 6) Analyses of case information will include mapping signals according to
- a) System Organ Class (SOC),
  - b) AE preferred term (PT),
  - c) age and/or range,
  - d) gender,
  - e) country (as a surrogate for race),
  - f) VariZIG dose administered,
  - g) time to onset, treatment and
  - h) AE duration, outcome,
  - i) cause of death,
  - j) concomitant medications and
  - k) co-morbid conditions (relevant medical history).
- 7) If three or more case reports involve the onset of a given AE following exposure to VariZIG,
- a) the signal will be considered validated (signal validation) and

- b) Clinical judgement will be used to evaluate clinical relevance of the signal.
    - i) Clinical relevance may include
      - (1) strength of evidence for a causal effect,
      - (2) severity of the reaction and
      - (3) its outcome,
      - (4) novelty of the reaction (e.g. new or serious),
      - (5) clinical context,
      - (6) possible drug-drug reactions.
  - c) In the event that a given AE is considered clinically relevant (validated),
    - i) it will be considered as a potential signal requiring further evaluation including:
      - An evaluation of the signal for public health impact,
      - Assessment of the signal including determining its reporting frequency and determining whether the signal represents a potential or identified risk.
- 8) A safety signal will then be classified as
- a) high, medium or low priority and
  - b) managed according to internal Cangene procedures including
    - i) updating product information (i.e. labelling) and
    - ii) the development of risk mitigation strategies where applicable.
  - c) Signals that are considered as identified risks and may impact public health will be classified as high priority and will require the development of risk mitigation strategies.
  - d) Signals identified as potential risks that may impact public health will be classified medium priority.
    - i) For such signals, additional risk characterization activities may be considered based on clinical relevance.
  - e) Signals that do not constitute a public health risk will be considered low priority and will be monitored for clinical relevance.

**Reviewer's Comment:** Item 19 was submitted by the pharmacovigilance reviewer, David Menschik, M.D. (See the pharmacovigilance review).

**20. Subject VM-00995 is a 14 year old female with T-cell acute lymphoblastic anemia in consolidation who received 625 IU VariZIG on June 11, 2011, and on June 16, 2011, experienced extreme fatigue with a hematocrit of 20% accompanied by pain and swelling in her left wrist, right elbow, and both hip joints. The following day she was hospitalized. She became febrile, and a chest x-ray showed "showed new medial retrocardiac opacity/infiltrate, not well-seen on lateral view, possibly representing atelectasis, infection or Mycoplasma pneumonia." An infectious disease work-up was negative. After receiving one packed red blood cell transfusion, she was discharged on June 18, 2011. The investigator recorded 13 non-serious adverse events for this subject, and one serious adverse event, "serum sickness", judged to be severe and related to the VariZIG administration. "Arthritis" on day 12 after VariZIG administration was judged to be "possibly" related, and the remaining adverse events were all judged to be "unlikely" to be related. The following table shows these 14 adverse events by day after VariZIG administration:**

MED_TERM	Day after last administration
Leukopenia	2
Neuropathy Peripheral	2
Neutropenia	2
Anaemia	5
Activated Partial Thromboplastin Time Prolonged	6
Serum Sickness	6
Weight Increased	9
Anaemia	10
Neutropenia	11
Arthritis	12
Hypomagnesaemia	16
Alanine Aminotransferase Increased	24
Hyperphosphataemia	24
Thrombocytopenia	27

*The adverse event “serum sickness” is not a common adverse event after administration of a human immune globulin product, such as VariZIG*

*Please submit additional information on subject VM-00995 that explains why you conclude that each of the reported “unlikely related” adverse events are not related to the administration of VariZIG. In particular, what information supports the conclusion that the prolonged activated partial thromboplastin time on day 6 is unrelated to VariZIG administration?*

**Cangene Response:**

- 1) As requested, Cangene is providing additional information on subject VM-00995/b(6) (Cangene Case US 145211) from clinical trial VZ-009 “Safety and Efficacy of Varicella Zoster Immune Globulin (Human) (VariZIG™) in Patients At-Risk of Varicella Infection”.
  - a) A case summary is provided below.
  - b) Since the case was considered serious and related to VariZIG exposure,
    - i) the case was submitted on 28 June 2011 as a 15-day expedited report to the Regulatory Health Authorities (RHAs) according to ICH E2A.
  - c) Case US-145211 involves a 14 year-old female subject with a history of T-cell acute lymphoblastic leukemia (T-cell ALL) and asthma who was diagnosed with serum sickness associated with VariZIG exposure with symptoms initially being described as polyarthritis and fever.
  - d) Additional AEs reported for this subject include
    - i) leukopenia,

- ii) peripheral neuropathy,
  - iii) neutropenia,
  - iv) anaemia,
  - v) prolonged activated partial promboplastin time,
  - vi) increase weight,
  - vii) hypomagnesaemia,
  - viii) increase alanine aminotransferase,
  - ix) hyperphosphataemia and
  - x) thrombocytopenia.
- 2) All AEs experienced by this subject were reported by the investigator on the Case Report Form (CRF) provided as part of clinical trial VZ-009.
    - a) Although causality assessments for non-serious AEs are not required by clinical trial investigators (as outlined in the “Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies. September 2010”),
      - i) the investigator did provide assessments for all serious and non-serious AEs reported for this subject.
    - b) While serum sickness was considered serious and related to VariZIG exposure,
      - i) all non-serious AEs were considered to be unlikely related (not related).
  - 3) It should be noted that investigator causality assessments for AEs reported in clinical trial subjects are critically important as the investigators are better able to assess the clinical relevance of the reported AE based on participant medical histories, clinical laboratory findings, concomitant disease and/or medications, as well as an overall clinical picture of the subject at the time of AE onset.
    - a) As a result, we assume that the causality assessments of “unrelated” assigned by the investigator to AEs leukopenia, peripheral neuropathy, neutropenia, anaemia, prolonged activated partial promboplastin time (aPTT), increased weight, hypomagnesaemia, increased alanine aminotransferase (ALT), hyperphosphataemia and thrombocytopenia are based on sound clinical judgment that has taken into account the subject’s medical condition and the potential for a causal relationship to concomitant diseases and/or other medical treatments (concomitant) received at the time of VariZIG exposure.
  - 4) Based on a review of the case information provided for this subject, the subject’s T-cell ALL, as well as other underlying medical conditions may have contributed to the onset of those AEs assessed by the clinical trial investigator as “unlikely unrelated” to VariZIG exposure.
    - a) In addition the subject was receiving concomitant medications for a variety of medical conditions at the time of VariZIG dosing.
    - b) It is possible that the medications may have contributed to the onset of specific AEs in this subject.
    - c) A review of the subject’s medical history indicates that the the subject received mercaptopurine, cytarabine and methotrexate for the treatment of her T-cell ALL.
  - 5) The subject also received sulfamethoxazole/trimethoprim for the prevention of pneumonia and Lovenox (enoxaparin) for deep vein thrombosis (DVT).
    - a) In addition, the subject was receiving loratidine, prednisone and diphenhydramine for allergies including seasonal allergies, and docusate and polyethylene glycol for constipation concomitantly.

- b) Additional concomitant medications include allopurinol, ondansetron, oxycodone, vancomycin, heparin flush, morphine, and normal saline bolus.
  - c) Therefore, an association between the onset of the non-serious AEs reported for this subject and concomitant disease and/or medications cannot be ruled out.
- 6) A review of the subject's medical history suggests that the onset of leukopenia, neutropenia, anemia and thrombocytopenia in this subject is likely due to the direct effect of chemotherapy received for her T-cell ALL.
- a) The subject began treatment on 17 May 2011 with nelaribine, followed by Cytosan on 24 May 2011 and weekly vincristine administration (previous cycle before VariZIG: 13 June 2011).
  - b) As it is well known that chemotherapy depresses the hematopoietic system,
    - i) it is expected that the chemotherapeutic treatments administered to this subject would play a role in the onset of said AEs.
    - ii) While anemia, leukopenia and thrombocytopenia have been reported following administration of vincristine,
      - (1) the use of other chemotherapeutic agents such as Cytosan, nelaribine and mercaptopurine used in this subject may have also contributed to the development of anemia, leukopenia and thrombocytopenia.
  - c) The AEs anemia and neutropenia have been reported twice in this subject: Day 2 and again on Days 10 and 11 following VariZIG administration.
    - i) While chemotherapeutic products such as vincristine and Cytosan are administered to patients in one week cycles, mercaptopurine is administered daily for several weeks.
    - ii) Based on the dosing regimens of the chemotherapeutic medications administered to this subject at the time of VariZIG exposure
      - (1) it is expected that specific AEs, namely anemia and neutropenia, are likely to be reported more than once.
- 7) In addition, neuromuscular effects have been reported with Vincristine use in patients with ALL;
- a) with peripheral neuropathy being the most frequently reported manifestation.
  - b) The peripheral neuropathy reported in this subject was manifested by numbness in the fingertips and may be related to vincristine administration rather than VariZIG exposure.
  - c) Note, the subject was already being monitored for mild vincristine neuropathy at the time of VariZIG administration.
- 8) The reported AE hypomagnesemia is an electrolyte disturbance in which there is an abnormally low level of magnesium in the blood and is usually caused by a variety of conditions including
- i) inadequate intake of magnesium,
  - ii) chronic diarrhea,
  - iii) malabsorption,
  - iv) alcoholism,
  - v) chronic stress,
  - vi) loss of magnesium due to diuretics or
  - vii) the redistribution of magnesium within the body due to steroids,
  - viii) volume overload or

- ix) increased carbohydrate infusions including hyperglycemia.
  - a) At the time of VariZIG administration, this subject experienced steroid induced hyperglycemia which would have contributed to the onset of hypomagnesemia.
  - b) In addition, the increase in weight reported for this subject may have been the result of fluid overload rather than VariZIG administration.
- 9) The reported hyperphosphatemia is an electrolyte disturbance in which there is an abnormally elevated level of phosphate in the blood.
- a) At the time of VariZIG administration, the subject was receiving cytotoxic therapy that causes by cell lysis and may have contributed to the onset of hyperphosphatemia.
  - b) The subject was also receiving Vancomycin and allupurinol for prophylaxis of infection and chemotherapeutic effects, respectively.
  - c) While nephrotoxic medications such as Vancomycin may impact renal function and impair phosphate elimination, allopurinol increases the production of xanthine which can lead to elevated blood phosphate levels.
  - d) In this subject both medications likely contributed to the increase in blood phosphate levels rather than VariZIG.
- 10) The increase in ALT levels observed in this subject following VariZIG exposure may be due to normal fluctuations in levels over the course of the day.
- a) While testing ALT levels is routine for the diagnostic evaluation of hepatocellular injury,
    - i) there are other causes including chemotherapy.
  - b) The ALT increase without other abnormal liver enzymes levels or other liver function tests (Alk Phos 94 U/L, total bilirubin 0.9 mg/dL) is considered insignificant.
  - c) This abnormal laboratory value reported at day 24 following VariZIG exposure was borderline, thus the relationship to VariZIG is unlikely.
- 11) At the time of VariZIG administration, the subject was receiving Lovenox for the treatment of DVT (confirmed as thrombus from right mid-femoral vein of thigh to proximal/mid posterior tibial and peroneal veins by ultrasound).
- a) On 16 June 2011 the subject's platelet count was 30 k/mm<sup>3</sup>.
  - b) Because the subject was already thrombocytopenic, the benefit/risk of using Lovenox was evaluated as the medicinal product would likely lead to prolonged coagulation.
  - c) In addition, heparin was administered to this subject to flush a catheter line the same day the test was done.
  - d) Both Lovenox and heparin are known to interfere with the coagulation system and may have contributed to the prolonged aPTT observed in this subject six days following VariZIG exposure.
  - e) In addition, elevated aPTT levels associated with just below normal PT levels (12.3 sec; with normal levels at 12.5 sec) and a normal International Normalization Ratio (INR) could be an incidental finding.
  - f) Thus the prolonged aPTT observed is not likely related to VariZIG exposure.

**Reviewer's Comment:** The response is acceptable.

**21. Subject VM-00301 is a 37 year old immunocompromised female with a history of lupus**

*erythematous, with a biliary stent for an unknown reason and chronic abdominal pain. Eight (8) days after receiving 625 IU VariZIG she became febrile with acute abdominal pain, arthralgia, weakness and loss of appetite. She did not develop varicella, and a lupus flare was ruled out. The investigator considered these events to be significantly disabling, but not related to VariZIG*

*Please submit additional information on subject VM-301 that explains why you conclude that the serious adverse events “abdominal pain,” “arthralgia,” “asthenia,” “decreased appetite,” “fatigue,” and “pyrexia,” – all recorded as occurring on day 8 after administration of VariZIG – were unrelated to VariZIG administration.*

**Cangene Response:**

- 1) As requested, Cangene is providing additional information on subject VM-00301/b(6) (Cangene Case VZ009\_00017) from clinical trial VZ-009 “Safety and Efficacy of Varicella Zoster Immune Globulin (Human) (VariZIG™) in Patients At-Risk of Varicella Infection”.
  - a) A case summary is provided below.
  - b) The case was not reported to the Regulatory Health Authorities (RHAs)
    - i) as it did not meet the ICHE2A criteria for expedited reporting;
      - (1) the case was considered serious BUT unrelated to VariZIG exposure.
- 2) The case involves a 37 year old female patient with a history of lupus, chronic abdominal pain associated with a biliary stent.
  - a) She was enrolled in clinical trial VZ-009 after she was exposed to her child's varicella.
  - b) Following administration of a single 625 IU intramuscular (IM) dose of VariZIG™ (lot 00405011 expiry date October 2008) on 23 April 2007,
    - i) the patient experienced
      - (1) fever,
      - (2) acute abdominal pain,
      - (3) weakness,
      - (4) arthralgia and
      - (5) decreased appetite
    - ii) eight days post-administration.
  - c) The subject’s liver enzymes were reported as elevated;
    - i) a similar event was reported in the subject’s past medical history and was considered related to her biliary stent.
- 3) While the subject was not hospitalized, the investigator did consider the reported AEs as severe and significantly disabling/incapacitating such that the subject required assistance from her family with activities of daily living (ADL).
  - a) Causality was reported by the investigator as unlikely related VariZIG exposure.
- 4) While a temporal relationship appears to exist between the onset of the reported events and the administration of VariZIG exposure administration,
  - a) the onset of fever and arthralgia occurred 10 days following VariZIG administration.
  - b) Since most delayed allergic reactions occur within 7 days of immunoglobulin administration,
    - i) the AEs of fever and arthralgia could not be due to a delayed allergic reaction.

- ii) In addition, these AEs are not typically associated with such reactions.
- 5) A review of the case information suggests that there are other contributing factors that may be responsible for the onset of the reported AEs in this subject.
  - a) The subject's previous history of a biliary stent and chronic abdominal pain
    - i) may be associated to the reported AEs of fatigue and poor appetite, and
    - ii) may have had an impact on the subject's ADL.
- 6) Patients with systemic lupus erythematosus (SLE) often develop arthralgia and sometimes arthritis as part of the condition.
  - a) Fever, although multifactorial, is also a typical symptom of SLE.
    - i) Therefore, the subject's underlying SLE may provide a more plausible explanation for the reported AEs of arthralgia and fever than an immune response to VariZIG exposure.
  - b) While the Investigator did not think it was lupus flare up,
    - i) this possibility cannot be ruled out.
  - c) In addition, the subject had an elevated sedimentation rate and an increase in C reactive protein levels.
    - i) These clinical laboratory findings suggest an inflammatory response or infection supporting the conclusion that the reported AEs may be associated with SLE rather than an immune response to VariZIG exposure.
- 7) Based on this review Cangene agrees with the Investigator's causality assessment of the reported AEs;
  - a) the onset of fever, abdominal pain, decreased appetite, arthralgia and fatigue were unlikely related to VariZIG exposure in this case.
- 8) The corresponding Medwatch report is provided in **Appendix III**.

**Reviewer's Comment:** The response is acceptable.

**22. The INDICATIONS AND USAGE section of the proposed package insert includes the following statement:**

***Administer VariZIG as soon as possible following varicella zoster virus (VZV) exposure, ideally within 96 hours for greatest effectiveness, but not later than 10 days after VZV exposure.***

***Please submit the clinical data, and the considerations, that support the advice to give Varizig beyond the 96 hour time point.***

### **Cangene Response**

- 1) Clinical data on administration of VariZIG beyond the 96 hour (4 day) time point is derived from the clinical trial VZ-006.
  - a) In this study, VZV non-immune pregnant women were randomized to receive 625 IU of

- VariZIG IM, VariZIG IV or commercial VZIG IM, following exposure to VZV.
- b) The pregnant women were stratified into two groups depending on the timing of VZV exposure;
    - i) 1-4 days since exposure (n=34) and
    - ii) 5-14 days since exposure (n=23).
  - c) Of the women stratified to the 5-14 days since exposure group,
    - i) only 2 of 23 were greater than 10 days from varicella exposure.
    - ii) Table 14 presents a summary of each stratum by treatment group and varicella outcome.

**Table 14 Characteristics of Subject Strata in Study VZ-006**

<b>Strata (Time since VZV exposure)</b>	<b>Treatment (No. of subjects)</b>	<b>No. of pregnant women that developed varicella posttreatment</b>
Stratum 1 (1-4 days)	VariZIG IM (n=11)	5
	VariZIG IV (n=12)	2 (3)
	VZIG IM (n=11)	5 (6)
	<b>Total, n=34</b>	<b>12 (14)</b>
Stratum 2 (5-14 days)	VariZIG IM (n=6)	1
	VariZIG IV (n=9)	3 (4)
	VZIG IM (n=8)	3 (4)
	<b>Total, n=23</b>	<b>7 (9)</b>

**Reviewer's comment:** The blue font numbers in parentheses show the numbers if subjects with presumed subclinical VZ infections are included. Subclinical VZ infection is assumed in the absence of Clinical Varicella (defined as presence of VZ skin lesions or CIS positive scores), but with greater than 100-fold increase in anti-VZ titer at "Closeout" (day 42) compared to baseline (day 0). These subjects with presumed subclinical VZ infections are –b(6)- VariZIG IV stratum 1; –b(6)- VZIG IM stratum 1; –b(6)- VariZIG IV stratum 2; and –b(6)- VZIG IM stratum 2.

- 2) The rate of varicella infection was
  - a) 35.29% (12/34) and 30.43% (7/23) in stratum 1 and stratum 2, respectively.

- b) As presented in the response to question 18,
  - i) the difference in incidence of varicella between the two strata is not statistically significant Table 13.
  - (1) However, a review of the safety data collected over the course of study VZ-006 demonstrated that
    - (a) those subjects receiving treatment within 1-4 days of VZV exposure had milder symptoms as compared to those who were exposed 5-14 days prior to treatment,
      - (i) which may translate in a reduction of infection severity and therefore a better clinical outcome.
- 3) In addition to the Cangene data, other studies with varicella zoster immune globulin-treated pregnant women demonstrated that
  - a) the rates of varicella infection were similar between pregnant women treated
    - i) within 3 days and
    - ii) within 4-10 days [ref. 14; Enders & Miller (2000)].
  - b) In particular, results presented by Enders and Miller showing the outcome of varicella exposure in 212 seronegative pregnant women treated with varicella zoster immune globulin are reproduced below (Table 15).

<b>Table 15 Varicella Zoster Immune Globulin Efficacy Data presented in Enders and</b>							
<b>VZIG administration following days after exposure</b>	<b>Total n</b>	<b>Outcome</b>					
		<b>No infection</b>		<b>Subclinical infection</b>		<b>Modified / normal varicella</b>	
		n	%	n	%	n	%
1-2-3 days	153	83	(54)	7	(5)	63	(41)
4-5 days	46	27	(59)	1	(2)	18	(39)
6-10 days	13	4	(31)	3	(23)	6	(46)
Total	212	144	(54)	11	(5)	87	(41)

**Reviewer's Comment:** Blue background added by the reviewer (C.M.) to emphasize the small sample size on which the applicant's conclusion is based.

- c) In addition, Miller et al cite similar data in pregnant women as well as a study using BPL varicella zoster immune globulin in immunosuppressed household contacts.
  - i) The clinical attack rate of varicella in the immunosuppressed patients was found to be 54%
    - (1) compared to an expected rate of 90% varicella [ref. 15; Miller et al. (1993)].
  - ii) The authors concluded that VZIG can attenuate varicella infection up to 10 days after exposure.

**Reviewer's Comment:** The following is Table 5 of Miller et al. (1993):

**Table 5** Outcome in 44 seronegative pregnant women given 1000 mg of VZIG within 10 days of close contact with chickenpox

	<b>Interval between contact and giving VZIG</b>	
	<b>Up to 3 days</b>	<b>4-10 days</b>

Outcome	No.	(%)	No.	(%)
Not infected	6	(29)	6	(26)
Asymptomatic infection	5	(24)	6	(26)
Mild chickenpox	6	(48)	8	(48)
Severe chickenpox	4		3	
Total	21		23	

**Reviewer’s Comment (continued):** This study was smaller than Cangene’s VZ-006 study, but unlike study VZ-006, it included subjects with subclinical infection (denoted “asymptomatic infection”). It differs from VZ-006 by grouping day 4 subjects with the late treatment group; study VZ-006 grouped day 4 subjects into stratum 1 (days 1-4). The extent of exposure for Table 5 cannot be discerned; but if the study included subjects with less than 24 hours exposure, then it is reasonable to assume that some exposures were minimal and should be excluded from the analysis (as shown in this review of study VZ-006). If subjects with minimal contact are excluded from the analysis, the denominators in this small study decrease, and the observed attack rates increase (as shown in this review of study VZ-006). In this case, the question of the clinical benefit of VZIG administration remains open.

- d) These studies appear to be the basis for EMA core labeling recommendations on varicella zoster immune globulin use which are “as soon as possible” after exposure, “ideally within 3 days but within 10 days maximum” (16) (EMA – Core SPC for human Varicella immunoglobulin for intramuscular use, 2005).
- 4) Although initially designed for VariZIG treatment within 96 hours of exposure,
  - a) study VZ-009 study protocol was revised (February 2011) to allow inclusion of subjects who had been exposed to VZV up to 10 days prior to VariZIG administration.
  - b) Out of 297 subjects included in interim efficacy analysis,
    - i) only nine subjects with VariZIG treatment up to 10 days from VZV exposure were identified in the interim VZ-009 dataset.
      - (1) Of these 9 subjects with VariZIG administration up to 10 days from VZV exposure,
        - (a) only one subject developed clinical varicella.
  - c) An additional six individuals were administered VariZIG greater than 96 hours after VZV exposure under emergency use IND.
    - i) From data supplied to Cangene,
      - (1) none of the individuals developed clinical varicella.
    - ii) These individuals would have been eligible for study VZ-009,
      - (1) but at the time of subject enrollment, the VZ-009 protocol stipulated VariZIG administration within the 96 hour time point.
  - d) A larger sample size of subjects treated between 5-10 days post-exposure is anticipated for the final study report.
- 5) Overall, the recommendation to administer VariZIG beyond the 96 hour time point is based primarily on
  - a) clinical data from study VZ-006.
  - b) Limited data from the interim report for study VZ-009 and emergency use IND cases as

- well as other historical studies provide additional support.,
- c) Cangene proposes that VariZIG be administered as soon as possible following VZV exposure, ideally within 96 hours for greatest effectiveness,
    - i) but not later than 10 days after VZV exposure.

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