

# CLINICAL PHARMACOLOGY REVIEW

Division of Hematology  
Office of Blood Review & Research

STN 125430

Sponsor: Cangene

Product: Varizig (Varicella Zoster Immune Globulin Intravenous (Human))

Indication: Passive immunization of exposed, susceptible individuals who are at risk of complications from varicella

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## INTRODUCTION

Varicella zoster virus (VZV) infection (chickenpox) typically causes a benign but highly contagious disease. From initial exposure, the incubation period for VZV is usually 14-15 days until vesicle eruption; 95% of patients develop a rash between 11 and 20 days after exposure. Systemic symptoms such as fever, chills, myalgia and arthralgia are present for 2 to 3 days prior to vesicle eruption. Infected individuals are considered contagious during the first 48 hours of vesicle eruption. High risk groups include immune-compromised children and adults, newborns of mothers with varicella shortly before or after delivery, infants less than 1 year of age and premature infants, normal susceptible adults, and pregnant women.

Varizig (Varicella Zoster Immune Globulin (Human)) is a gamma globulin fraction that contains antibodies to varicella zoster virus. The administration of Varizig prevents or reduces the severity of maternal infections when administered within 4 days of first contact. Upon absorption into the circulation, varicella zoster antibodies persist for 6 weeks or longer. The precise

concentrations of antibodies that must be achieved or maintained to attenuate varicella are not known.

A Varicella Zoster Immune Globulin product (VZIG) was licensed in the USA since 1980 for the passive immunization of exposed, susceptible individuals to reduce the incidence/severity of VZV infections. The manufacturer of VZIG, Massachusetts Public Health Biological Laboratories (MPHBL) decided to discontinue production of VZIG, and the last remaining lot of VZIG expired on March 12, 2007. This VZIG product lot was utilized as the comparator product for this clinical trial since it was the only licensed VZV human immune globulin product available in the USA.

Varizig was approved in Canada on January 18, 2001 for the prevention or reduction in severity of maternal infections within 4 days of exposure to the varicella-zoster virus.

For licensure of Varizig in the USA, a pharmacokinetic study comparing Varizig and VZIG was recommended by the FDA in pre- BLA meetings on November 30, 1999 and September 26, 2005. As a result, the intent of this clinical study is to demonstrate comparative bioavailability between Varizig and VZIG based on bioequivalence criteria. Cangene has utilized a validated assay that correlates with -----b(4)-----  
----- for determination of product potency and serum anti-VZV levels (per FDA recommendation January 17, 2006 letter).

VZIG is supplied as a sterile solution of human IgG in 0.3 M glycine that contains 625 IU of anti-VZV (volume of ~6.25 mL) and contains no preservative. The product contains 100 to 180 mg protein/mL, which is primarily IgG. All VZIG product used in the study was from a ---b(4)---  
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The reconstituted Varizig is formulated with glycine (0.1 M), sodium chloride (0.04 M), and polysorbate 80 (0.01%) and contains no preservative. The volume of each Varizig vial is 6 mL containing 125 IU of freeze-dried Varizig. Each vial contains 60-200 mg human IgG.

The sponsor has submitted a comparative pharmacokinetic study as part of the Biological License Application (BLA) package to obtain licensure of Varizig in the USA.

The following is the review of the comparative pharmacokinetic study of Varizig and VZIG in healthy volunteers.

## CLINICAL PHARMACOLOGY LABELING COMMENTS

The sponsor has modified the clinical pharmacology labeling section as requested by the FDA and the revised version is acceptable. The following is the revised clinical pharmacology labeling:

In a comparative pharmacokinetic clinical trial, 35 volunteers were administered an intramuscular dose of 12.5 IU/kg of VARIZIG (n=18) or the comparator product VZIG™ (n=17). The dose of 12.5 IU/kg of VZIG or VARIZIG given to the subjects was based on the assumption that the potency was similar for both products. For the bioequivalence analysis, a potency correction factor was applied (concentrations of VARIZIG were multiplied by 2.3) to account for higher measured potency of the comparator product. The mean peak concentration ( $C_{max}$ ) of varicella antibodies occurred within five days of administration for both products (Table 4). In the trial, baseline levels of anti-VZV antibodies ranged from 0 to 720 mIU/mL, therefore baseline levels were taken into account for pharmacokinetic calculations, to better represent the indicated population. After potency correction, baseline correction, and elimination of subjects with baseline values of anti-VZV antibody levels of >200 mIU/mL, the two products were pharmacokinetically comparable.

**Table 4 Pharmacokinetic Comparison of VARIZIG and VZIG**

PK Parameters*	VARIZIG	VZIG	Ratio 90% confidence interval
AUC <sub>0-28</sub> (mIUxDay/mL)	2472 ± 970	2347 ± 535	84.1 – 124.6
AUC <sub>0-84</sub> (mIUxDay/mL)	4087 ± 1620	3916 ± 964	82.0 – 125.6
C <sub>max</sub> (mIU/mL)	136 ± 66	138 ± 22	76.5 – 112.8
T <sub>max</sub> (Days)	4.5 ± 2.8	3.3 ± 1.5	Not applicable
t <sub>1/2</sub> ** (Days)	26.2 ± 4.6	23.1 ± 8.6	Not applicable
CL/F (mL/Day)	0.204 ± 0.045	0.199 ± 0.087	Not applicable

\* Potency and subgroup analysis were implemented for pharmacokinetic calculations. Study subjects with elevated baseline anti-VZV levels (>200 mIU/mL) from both treatment groups were excluded from pharmacokinetic calculations.

\*\* The half-life is expected to vary from patient to patient.

## RECOMMENDATION

- Although Varizig in terms of  $C_{\max}$  and  $AUC_{(0-84)}$  is not statistically bioequivalent with VZIG, the two products are pharmacokinetically comparable when subjects with high baseline values ( $\geq 200$  mIU/mL) are excluded from the analysis. Therefore, the license to market this product in the USA should not be denied because there is an un-met need of the product since currently there is no product available in the USA for passive immunization of individuals who are at risk of complications from varicella virus.

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**Study Title:** Comparative bioavailability of Varizig and VZIG in normal healthy volunteers.

The primary objective of this study was to establish the comparative bioavailability of two different varicella zoster human immune globulin products, Varizig (test product, Cangene Corporation, Canada) and VZIG (reference product, Massachusetts Public Health Biological Laboratories (MPHBL), USA), following intramuscular administration to normal healthy volunteers. The secondary objective was to demonstrate the comparative safety of Varizig and VZIG.

This study was originally designed as a double blind, randomized, parallel arm trial comparing Varizig and VZIG in 60 healthy adult subjects. Due to the circumstances, the sponsor was forced to alter the protocol. Regulatory approval for investigational product importation from the Drug Controller General, India (DCGI) was not received until just prior to expiry of the final lot of VZIG. Therefore, only 35 subjects were enrolled and randomized to receive treatment before VZIG was no longer available for the trial. Varizig was administered to 18 subjects, while VZIG was given to 17 subjects, and all subjects were included in the safety analysis (n=35).

The product potency was expressed in IU by comparison to the World Health Organization (WHO) international anti-VZV reference preparation. The potency of Varizig and VZIG was tested by a validated method [---b(4)-----] two days prior to the start of dosing. The measured potency for Varizig was  $33.22 \pm 6.56$  IU/mL (mean  $\pm$  SD, n=30) with a CV for the assay of 19.53%. For VZIG, the measured potency was  $78.78 \pm 13.03$  IU/mL (mean  $\pm$  SD, n=30) with a CV for the assay of 16.54%. Thus, the VZIG product was 2.29 times more potent than the Varizig product. The actual potency measurements were utilized for potency correction during PK statistical analysis.

This was a Phase 1 single-center double-blind randomized study with two parallel arms. Male healthy volunteers between the ages of 19 and 39 received either Varizig or VZIG by intramuscular injection. The subjects received both the test and reference product at a dose of 12.5 IU/kg of body weight. There was no pre-determined maximum dose. The dose was split into two equal injections of 3-6 mL (100 IU/mL) each for an injection into the right, and an injection into the left deltoid muscle. The two injections occurred within 3 minutes of each other. The subjects were followed for 84 days after drug administration for safety and pharmacokinetic analyses. It should be noted that the dose of 12.5 IU/kg of VZIG or Varizig given to the subjects was based on the assumption that the potency was similar for both products. For the bioequivalence analysis, the potency was adjusted (concentrations of Varizig were multiplied by 2.3).

One of the inclusion criteria was a negative anti-VZV screening test. However, subjects with positive baseline anti-VZV antibodies were enrolled into the study for reasons described below. An initial screening test was performed by the local lab, followed by a confirmatory test by the central lab. The local lab anti-VZV screening test results were negative for 15 subjects, while 20 subjects tested positive. Confirmatory screening anti-VZV tests were concurrently performed since the comparator product was nearing the expiry date; all subjects tested negative by the

central lab anti-VZV test. Cangene decided to use the central lab anti-VZV test results for subject inclusion criteria. Further anti-VZV sample testing (post-study) performed with Cangene's validated pharmacokinetic anti-VZV assay revealed that 17/35 subjects were positive at screening and baseline. Therefore, the screening anti-VZV testing did not correlate with the pharmacokinetic assay (b(4)---), resulting in 17 enrolled subjects having higher than expected baseline anti-VZV levels. One subject was considered a clinical outlier and was not included in the comparative bioavailability analyses (n=34).

At baseline 18 subjects had low/undetectable anti-VZV (<5 mIU/mL), 6 subjects had moderate levels (10 to < 200 mIU/mL) and 11 subjects had high anti-VZV titers ( $\geq 200$  mIU/mL), as determined by validated b(4)----- method. Subjects with anti-VZV levels  $\geq 200$  mIU/mL were excluded (n=11) from a post-hoc analysis that was subsequently conducted (n=24).

Blood samples (15 mL) for pharmacokinetic study were collected after Varizig or VZIG administration for anti-VZV analysis at the following time-points: 12 hours, day 1, 2, 3, 4, 5, 7, 9, 11, 14, 21, 28, 42, 56 and 84. The 90% confidence interval (CI) for the assessment of comparability was applied on log transformed  $C_{max}$  and  $AUC_{(0-28 \text{ or } 0-84)}$ . Drug concentrations were measured by a validated -----b(4)----- at Cangene Corporation.

## RESULTS

### Potency and Baseline Uncorrected:

The results of the PK analysis are summarized in Table 1 and concentration-time plot is shown in Figure 1. From Table 1, it appears that the inter-subject variability for both formulations is substantially high. The percent coefficient of variation (%CV) for Varizig is more than 100% on all PK parameters as shown in Table 1. For VZIG (reference), %CV was lower than Varizig (63% on  $C_{max}$  and approximately 90% on AUC). This high variability in both test and reference formulations may have resulted in the failure of 90% CI.

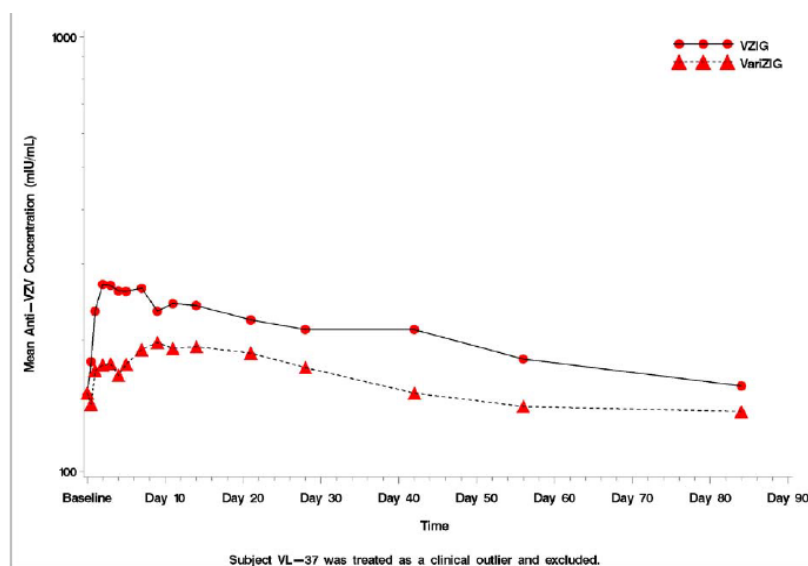
**Table 1: Pharmacokinetic parameters and 90% Confidence Interval (CI) for Varizig and Vzig (Potency uncorrected)**

Parameters	VZIG (reference)	Varizig (test)	% difference	90% CI
$C_{max}$ (mIU/mL)	297 $\pm$ 186 (63)	221 $\pm$ 266 (120)	26	26.4-77.7
$AUC_{(0-28)}$	10605 $\pm$ 9366 (88)	9182 $\pm$ 13090 (142)	13	18.9-89.1
$AUC_{(0-84)}$	19952 $\pm$ 19012 (95)	14460 $\pm$ 21420 (148)	28	17.1-84.3

AUC unit is (mIU\*day/mL); n = 17 for both formulations

Numbers in parenthesis are percent coefficient of variation (%CV)

**Figure 1: Potency and baseline uncorrected Anti-VZV concentration versus time plot**



**Potency Corrected (but not baseline):**

When potency was not corrected for Varizig both  $C_{\max}$  (26%) and  $AUC_{(0-84)}$  (28%) were lower than VZIG (Table 1). When potency was corrected, the difference in  $C_{\max}$  and  $AUC_{(0-84)}$  between test and reference formulations became wider (Table 2). A potency correction was used because Vzig is 2.29 times more potent than Varizig and the dosing was not based on the potency of the two formulations. Potency corrected  $C_{\max}$  and  $AUC_{(0-84)}$  for Varizig were higher by 76% and 72%, respectively than VZIG (Table 2). In both cases (potency corrected and uncorrected), the 90% CI was outside the limit of bioequivalence acceptance criteria of 80% to 125% (Tables 1 and 2).

**Table 2: Pharmacokinetic parameters and 90% Confidence Interval (CI) for Varizig and Vzig (Potency corrected but not baseline)**

Parameters	VZIG (reference)	Varizig (test)	% difference	90% CI
$C_{\max}$ (mIU/mL)	297 ± 186 (63)	523 ± 632 (121)	76	62.5-184.2
$AUC_{(0-28)}$	10605 ± 9366 (88)	21537±31042 (144)	103	44.7-211.4
$AUC_{(0-84)}$	19952 ± 19012 (95)	34292±50796 (148)	72	40.5-199.9

AUC unit is (mIU\*day/mL)

**Baseline and Potency Corrected: (baseline correction for all subjects):**

Due to high variability in the baseline, both AUC and  $C_{\max}$  values were corrected for baseline and the potency of the products. In Table 3, the results of the analysis are summarized. Concentration-time plot after baseline and potency correction is shown in Figure 2. Even after baseline and potency correction the products were not bioequivalent (Table 3).

**Table 3: Pharmacokinetic parameters and 90% Confidence Interval (CI) for Varizig and Vzig (Baseline and Potency corrected for all subjects)**

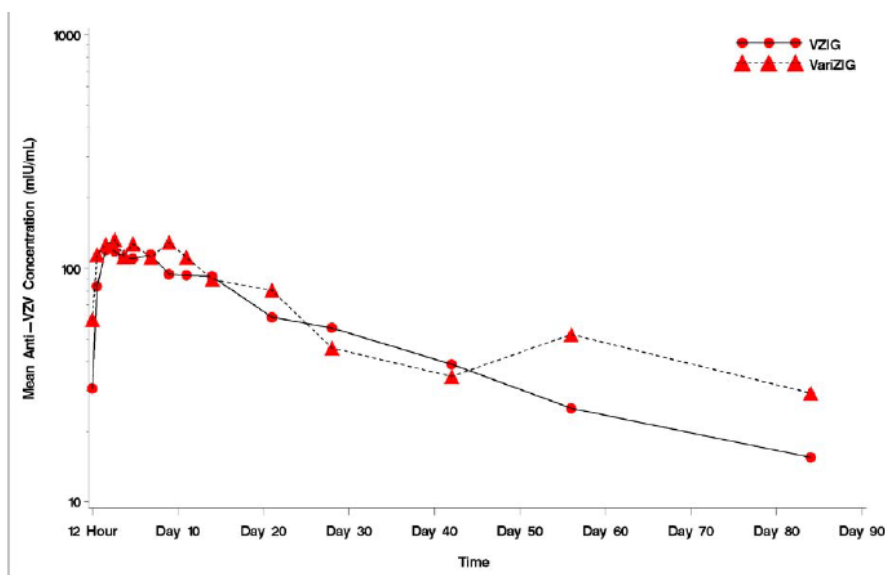
Parameters	VZIG (reference)	Varizig (test)	% difference	90% CI
$C_{\max}$ (mIU/mL)	$147 \pm 40$ (27)	$164 \pm 135$ (82)	12	77.9-122.1
$AUC_{(0-28)}$	$2335 \pm 896$ (38)	$3044 \pm 2900$ (95)	30	82.2-154.3

N = 17 for VZIG and n = 14 for  $AUC_{(0-28)}$  calculation for Varizig; three subjects from Varizig treatment group were excluded due to negative anti-VZV concentrations after baseline correction. Numbers in parenthesis are percent coefficient of variation (%CV)

Baseline = Varizig =  $155 \pm 240$  (mIU/mL); (range = 0-712 mIU/mL)

Vzig =  $143 \pm 160$  (mIU/mL); (range = 0-492 mIU/mL)

**Figure 2: Anti-VZV concentration versus time (baseline and potency corrected; all subjects)**

**Baseline and Potency Corrected (only subjects with baseline <200 mIU/mL were included in this analysis):**

Following the baseline correction, a post-hoc analysis was performed excluding 11 subjects (VZIG treatment group: n=5; Varizig treatment group: n=6) with high baseline anti-VZV concentrations ( $\geq 200$  mIU/mL). There were 12 subjects per treatment group in the post-hoc PK analysis. The values for post-hoc baseline and potency corrected Varizig and VZIG PK

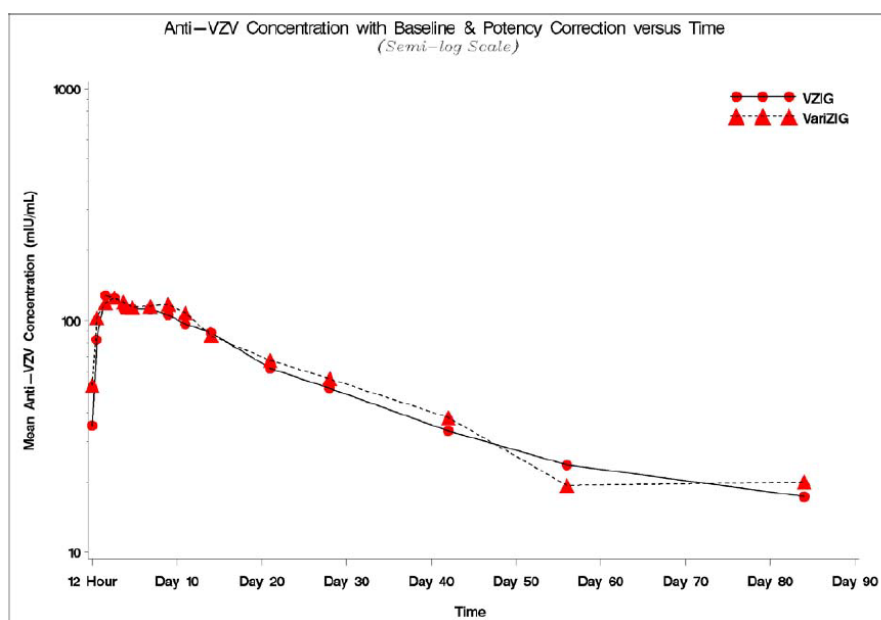
parameters, and the 90% confidence intervals are presented in Table 4. The results indicate that after excluding subjects with very high baseline values ( $\geq 200$  mIU/mL),  $AUC_{(0-28)}$  meets the bioequivalent criteria but  $C_{max}$  and  $AUC_{(0-84)}$  narrowly fails.

**Table 4: Pharmacokinetic parameters and 90% Confidence Interval (CI) for Varizig and Vzig (Baseline and potency corrected for subjects <200 mIU/mL)**

Parameters	VZIG (reference)	Varizig (test)	% difference	90% CI
$C_{max}$ (mIU/mL)	$138 \pm 22$ (16)	$136 \pm 66$ (49)	1	76.4-112.8
$AUC_{(0-28)}$	$2347 \pm 535$ (23)	$2472 \pm 970$ (39)	5	84.1-124.6
$AUC_{(0-84)}$	$3916 \pm 964$ (25)	$4087 \pm 1620$ (40)	4	82.0-125.6

AUC unit is (mIU\*day/mL); n = 12 per arm

**Figure 3: Anti-VZV concentration versus time (baseline and potency corrected)**  
Only subjects with baseline value of (<200 mIU/mL); n =12 per arm



## COMMENTS

1. Based on the bioequivalence (BE) criteria (CI = 80% to 125%), the two formulations are not bioequivalent (with or without potency adjusted) since both  $C_{max}$  and AUC fail to meet the 90% confidence interval (CI) of 80% to 125%.
2. In a post-hoc PK analysis, 10 subjects with high baseline anti-VZV levels ( $\geq 200$  mIU/mL) and one clinical outlier also with high baseline anti-VZV levels were excluded.

Thus, in the post-hoc PK analysis there were 12 subjects per treatment group. Although,  $AUC_{(0-28)}$  meets the bioequivalence criteria of 80 to 125%,  $C_{max}$  and  $AUC_{(0-84)}$  fails to meet this limit. It should be however, noted that since both the formulations were given by extra-vascular route (intramuscular) both  $C_{max}$  and AUC must meet the 90% CI of 80% to 125%.

3. It appears that both formulations are highly variable (coefficient of variation >30% on both  $C_{max}$  and AUC) and for such a high variable drug the sample size is too small to pass the bioequivalent criteria. The high variability in the product may be due to the fact that both negative and positive anti-VZV subjects were included in the analysis.

## CONCLUSIONS

Based on the bioequivalence (BE) criteria (CI = 80% to 125%), the two formulations are not bioequivalent (with or without baseline and potency corrected) since both  $C_{max}$  and AUC fail to meet the 90% confidence interval (CI) of 80% to 125%. However, when 11 subjects with high baseline anti-VZV levels ( $\geq 200$  mIU/mL) were excluded,  $AUC_{(0-28)}$  met the bioequivalence criteria of 80 to 125%, but  $C_{max}$  and  $AUC_{(0-84)}$  failed to meet this limit.

Overall, even after applying three different approaches, the two products are not bioequivalent. The two products can be termed as 'pharmacokinetically comparable' after excluding subjects with high baseline anti-VZV levels ( $\geq 200$  mIU/mL).