

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
Division of Biostatistics (HFM-215)

STATISTICAL REVIEW AND EVALUATION

(Mid-cycle)

Type/Application ID/Amendment #: NDA/BN 090067/0011

Indication: For use in adults as a source of electrolytes and water for hydration, and as an alkalinizing agent

Applicant: B-Braun Medical, Inc.

Product Name: Isolyte S, pH 7.4

Primary Statistical Reviewer: Chinying Wang, Ph. D. (HFM-219)

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Concur _____ Not Concur _____

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EXECUTIVE SUMMARY

The Isoplate Solution is identical to the Isolyte® S, pH 7.4 (Multi-Electrolyte Injection) that is a FDA approved sterile, nonpyrogenic intravenous injection. In the original submission, the company performed *in vitro* (Protocol II) and *in vivo* (Protocol III) studies to seek a new indication as platelet additive solution for the storage of hyperconcentrated platelets. Due to the deficiencies of the original submission, FDA issued a Non-Approval letter dated February 4, 2011 to the sponsor. This amendment includes the sponsor's complete response to the CR letter. The sponsor's response to statistical request (item 6) in the CR letter is acceptable. The *in Vivo* platelet survival/recovery study showed satisfactory results. The *in Vitro* platelet quality study met the primary endpoint of pH > 6.2, but failed in one secondary endpoint, namely, the surface P-selectin expression.

BACKGROUND

The Isoplate Solution is identical to the Isolyte® S, pH 7.4 (Multi-Electrolyte Injection) that is a FDA approved sterile, nonpyrogenic intravenous injection. The company performed *in vitro* (Protocol II) and *in vivo* (Protocol III) studies under IND 13684 for a new indication as platelet additive solution for the storage of hyperconcentrated platelets. In the original submission, the two studies with the corresponding statistical analyses are as follows.

Protocol II study

This was a paired study comparing the *in vitro* platelet quality of the Test Product (hyperconcentrated platelets collected on Trima Accel system, Version 6.0, diluted to 35% plasma carryover and stored for 5 Days) to the Control Product (standard platelets collected on Trima Accel and stored in plasma). Up to 100 research donors will be enrolled in this study to ensure N=60 paired evaluable data points.

Acceptance Criteria for Efficacy Outcomes:

1) Primary Outcomes

The primary outcome for this study is that 95% or more of the platelet Test units have Day 5 pH greater than 6.2 with one-sided confidence limit of 95% (0/60 failures).

2) Secondary Outcomes

For P-selectin expression, ESC, HSR, and Morphology score the difference between Test and Control on Day 5 is less than 20% with one-sided 97.5% confidence limit.

(a) For factors where a smaller value corresponds to a better outcome (P-selectin):

Test Statistic $\hat{\mu} / S$ where $\hat{\mu} = \text{Average } (T_i - 1.2 * C_i)$

S = standard error of $\hat{\mu} = S_d / (N)^{1/2}$

S_d = standard deviation of $\hat{\mu}$

Null Hypothesis $H_0: \mu \geq 0$

Alternate Hypothesis $H_1: \mu < 0$

(b) For factors where a larger value corresponds to a better outcome (ESC, HSR, Morphology):

Test Statistic $\hat{\mu} / S$ where $\hat{\mu} = \text{Average} (T_i - 0.8 * C_i)$

S = standard error of $\hat{\mu} = S_d / (N)^{1/2}$

S_d = standard deviation of $\hat{\mu}$

Null Hypothesis $H_0: \mu \leq 0$

Alternate Hypothesis $H_1: \mu > 0$

The one-sided 97.5% upper and lower confidence limits for μ will be calculated using Equations 1 and 2, respectively, given below with t-statistic.

$$x(\alpha) = \hat{\mu} + t(1 - \alpha, N - 1) S_d / (N)^{1/2} \quad \text{Equation 1 – Upper Limit}$$

$$x(\alpha) = \hat{\mu} - t(1 - \alpha, N - 1) S_d / (N)^{1/2} \quad \text{Equation 2 – Lower Limit}$$

Protocol III study

This was a paired study comparing *in vivo* radiolabeled recovery and survival of Test platelets to the Control product (fresh autologous platelets prepared from whole blood). A total of 43 subjects were enrolled in this study to achieve 23 paired evaluable data points for recovery and survival.

Acceptance Criteria for Efficacy Outcomes:

The recovery and survival were to demonstrate non-inferiority. No adjustments were made for multiple comparisons.

a) Radiolabeled platelet recovery: Test minus 66% Control is equal to or greater than zero with one-sided 97.5% confidence limit.

b) Radiolabeled platelet survival: Test minus 58% Control is equal to or greater than zero with one-sided 97.5% confidence limit.

For factors where a larger value corresponds to a better outcome (recovery, survival):

Recovery	$\hat{\mu}_{rec} = \text{Average}(T_i - 0.66 * C_i)$
Survival	$\hat{\mu}_{sur} = \text{Average}(T_i - 0.58 * C_i)$
where	$T_i = \text{Test arm values}$
	$C_i = \text{Control arm values}$
Test Statistic	$\hat{\mu}_X / s$
where	$\hat{\mu}_X = \hat{\mu}_{rec}$ for recovery or $\hat{\mu}_{sur}$ for survival
	$s = \text{standard error of } \hat{\mu}_X = S_d / (N)^{1/2}$
	$S_d = \text{standard deviation of } \hat{\mu}_X$
Null Hypothesis	$H_0: \mu_X \leq 0$
Alternate Hypothesis	$H_1: \mu_X > 0$

The one-sided limit 97.5% ($\alpha = 0.025$) confidence interval will be calculated for the test statistic $\hat{\mu}_X$ with sample standard deviation s_d and size N, using Equation 1 below and the t statistic. Equation 1 below correlates to the lower limit for recovery and survival.

$$x(\alpha) = (\hat{\mu}_X) - t(1-\alpha, N - 1) s_d / (N)^{1/2} \quad \text{Equation 1 – Lower Limit}$$

Conclusions of Efficacy Results for the Two Studies

1. The protocol III study (*in Vivo* platelet survival/recovery study of Isoplate stored platelets) showed satisfactory results.
2. However, the protocol II study (*in Vitro* platelet quality study) met the primary endpoint of $pH > 6.2$, but failed in one secondary endpoint, the surface P-selectin expression, which is more than 20% higher in the test group ($22 \pm 15.4\%$) compared to control ($15.1 \pm 9.1\%$).

CR letter issued by FDA

Due to the deficiencies of the original submission as indicated by different disciplines of the review committee, FDA issued a-Non-Approval Letter dated February 4, 2011 to the sponsor. The sponsor's response to the CR letter is included in this amendment. The statistics related item 6 in the CR letter and the sponsor's response are shown below:

STATISTICAL:

6. For both studies conducted under Protocols II and III, please provide the computed confidence intervals to determine whether the acceptance criteria are met. In addition, please include the computer programs and datasets used in your analyses.

SPONSOR'S RESPONSE

The sponsor included the confidence intervals for the outcome endpoints for both studies of protocol II and protocol III (shown below). The datasets in the original NDA application and the additional datasets for the response in the amendment are provided in SAS (in .xpt format) and Excel file format.

i) For Protocol II

Table 3 presents the confidence interval calculated for pooled in vitro data from HOX, BCW and ARC. The data of protocol II study are the same as what was submitted in the original NDA.

Table 3- Confidence Intervals for Protocol II –In Vitro Outcome

	P-selectin	ESC	HSR	Morphology
$\hat{\mu}$	4.7	3.2	8.6	55
S_d	9.8	3.9	6.1	16
N	66	66	66	66
t	1.9964	1.9964	1.9964	1.9964
$x(\alpha)^*$	7.1	2.2	7.1	51
Success if	$x(\alpha) < 0$	$x(\alpha) > 0$	$x(\alpha) > 0$	$x(\alpha) > 0$
	Failed	Passed	Passed	Passed

* One-sided 97.5% upper confidence limit for P-selectin and one-sided 97.5% lower confidence limit for ESC, HSR, Morphology score

ii) For Protocol III

In the CR letter, FDA requested that the clinical data collected at the Yale study site be excluded from analysis (see Appendix). This study was repeated at a third study site, Hoxworth Blood Center (HOX), to collect an additional N=12 data points for inclusion in analysis. Consequently, Table 4 (shown below) in the amendment presents the confidence interval calculated for pooled in vivo data from Darmouth (DAR) and Hoxworth Blood Center (HOX). The data in Table 4 are different from that were presented in the original NDA submission but the conclusions of efficacy outcome for protocol III remain unchanged.

Table 4- Confidence Intervals for Protocol III –In Vivo Outcome

	Recovery	Survival
$\hat{\mu}$	13.0	1.7
S_d	6.9	0.8
N	25	25
t	2.060	2.060
$x(\alpha)^*$	10.14	1.34
Success if	> 0	> 0
	Passed	Passed

* One-sided 97.5% lower confidence limit

STATISTICAL REVIEWER’S COMMENTS

Based on the information provided in this amendment, the sponsor's response to statistical request (item 6) in the CR letter is acceptable.

Appendix

FDA requested to exclude the data of subjects at the Yale site in CR letter

Protocol III: In Vivo Platelet Study:

4. FDA has a serious concern about your results from the Protocol III *In Vivo* Platelet Study. In the paragraph 5.3.5.1.162.1 Discontinued Subjects, you stated that fifteen subjects from the Yale site were excluded from analysis in Protocol III: *In Vivo* Platelet Study. For 11 evaluated subjects at the Yale clinical site 28 subjects were enrolled, two of them did not meet the inclusion criteria and 15 subjects were excluded from evaluation for various reasons. The "low day 5 pH for test platelets" (b)(6) should be regarded as a product failure. The frequency of exclusion such as "radiolabel anomalies" -----(b)(6)----- or "isotope not received" -(b)(6)--, were much higher than those seen in comparable studies. In contrast, there was no subject exclusion from analysis at the Dartmouth clinical site, which reported only three volunteer screening failures. The marked difference in exclusion rates between Yale and Dartmouth clinical sites demonstrates that the study quality was not equivalent at these two sites. The exclusion of 15 subjects at the Yale site may represent a bias in a statistical evaluation of results.

Please provide additional data on a group of 12 donors evaluated with the *In Vivo* Platelet Study with the same design as in the Protocol III and performed at a third independent clinical site.

Sponsor's response

In communication from the Agency dated February 4, 2011, FDA requested that the clinical data collected at the Yale study site be excluded from analysis. This study was repeated at a third study site, Hoxworth Blood Center (HOX), to collect an additional N=12 data points for inclusion in analysis.

Consequently, all data collected at Yale was excluded from analysis. The new results met the FDAs acceptance criteria that:

- Test minus 66% Control is equal to or greater than zero with one-sided 97.5% confidence limit for recovery.
- Test minus 58% Control is equal to or greater than zero with one-sided 97.5% confidence limit for survival.