

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

Intended Use: As platelet additive solution for the storage of hyperconcentrated platelets

Applicant: B-Braun Medical Inc.

Product Name: Isoplate Solution

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Concur _____ Not Concur _____

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1. EXECUTIVE SUMMARY

The Isoplate Solution is identical in formulation, packaging, sterilization, and manufacturing as the Isolyte® S, pH 7.4 (Multi-Electrolyte Injection) which is a FDA approved sterile, nonpyrogenic intravenous injection. The only difference between these two is the indication. The company performed three studies: platelet Leukoreduction and yield (Protocol I), in vitro (Protocol II), and in vivo (Protocol III) studies under IND 13684 to support a new indication of Isolyte® S, pH 7.4 as an alkalinizing agent for the storage of hyperconcentrated platelets. However, as agreed with FDA, the protocol I in the original study plan does not support this NDA. Only the results of Protocols II and III are submitted to seek approval of Isoplate Solution as platelet additive solution. The sponsor should provide the detailed information of analyzed results including the confidence intervals to determine if the acceptable criteria are met.

2. BACKGROUND

The Isoplate Solution is identical in formulation, packaging, sterilization, and manufacturing as the Isolyte® S, pH 7.4 (Multi-Electrolyte Injection) which is a FDA approved sterile, nonpyrogenic intravenous injection. The only difference between these two is the indication. The company performed three studies: platelet Leukoreduction and yield (Protocol I), in vitro (Protocol II), and in vivo (Protocol III) studies under IND 13684 to support a new indication of Isolyte® S, pH 7.4 as an alkalinizing agent for the storage of hyperconcentrated platelets. However, as agreed with FDA, the protocol I in the original study plan does not support this NDA. Only the results of Protocols II and III are submitted to seek approval of Isoplate Solution.

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.

The test statistic, to be evaluated in a paired t-test for the assay, is defined as:

$$\Delta X_i = \frac{(X_{Ti} - X_{Ci})}{X_{Ci}} \quad \mu = \frac{\sum \Delta X_i}{N}$$

Where X_{Ti} is the test measurement, and X_{Ci} is the control measurement. The estimated mean of the N paired data points is a statistics for the parameter stated in the hypothesis statements.

For factors where a lower value is considered to indicate better platelet quality (e.g. Pselectin)

Null Hypothesis $H_0: \mu \geq 0.2$; Alternate Hypothesis $H_1: \mu < 0.2$

For factors where a higher value is considered to indicated better platelet quality (e.g. ESC, HSR, morphology score)

Null Hypothesis $H_0: \mu \leq -0.2$; Alternate Hypothesis $H_1: \mu > -0.2$

For a given assay, the test (P.A.S. stored platelets) outcome will be determined to be non-inferior to the control (plasma stored platelets) outcome, if the null hypothesis is rejected with a one-sided 97.5% confidence limit. The confidence limit will be determined by a standard one-sided t-test with $\alpha = 0.025$.

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.

The acceptance criteria for the primary outcomes of recovery and survival were to demonstrate non-inferiority via rejection of the Null Hypotheses. No adjustments were made for multiple comparisons. (1) For radiolabeled platelet recovery: Test minus 66% Control is equal to or greater than zero with one-sided 97.5% confidence limit; and (2) For radiolabeled platelet survival: Test minus 58% Control is equal to or greater than zero with one-sided 97.5% confidence limit. Below is an outline of the statistical approach used to analyze the primary outcomes, which was communicated to FDA in an amendment to IND 13684 on September 2, 2008.

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.

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

3. STATISTICAL EVALUATION

In the early statistical review stage, SAS transport data files were requested. An amendment (# 0001) with XPT files was submitted on June 18, 2010. However, the detailed description of the dataset names and the variables definitions were not included in the amendment.

For both in vitro (protocol II) and in vivo (protocol III) studies, the detailed information of analyzed results to be compared with acceptable criteria are not included in the sponsor's Reports of Efficacy and Safety Studies. Instead, the results are reported in the clinical overview document as:

For In Vitro Platelet Quality Study, there was one primary outcome: 95% or more of the Test units have Day 5 pH greater than 6.2 with one-sided confidence limit of 95% (0/60 failures). There were four secondary outcomes: the difference between Test and Control on Day 5 was less than 20%, with a one-sided upper 97.5% confidence limit for P-selectin, and a one-sided lower 97.5% confidence limit for extent of shape change (ESC), hypotonic shock response (HSR), and morphology. Hyperconcentrated platelets stored in Isoplate Solution for five days met the acceptance criteria for pH, ESC, HSR and morphology. Pselectin, a secondary outcome, did not meet the statistical acceptance criterion; however, the P-selectin values for the Test platelets were well within the range of commonly transfused platelet products in the United States.

For In Vivo Platelet Study, there were two primary outcomes: i) Test minus 66% Control is equal to or greater than zero with one-sided 97.5% confidence limit for radiolabeled platelet recovery; ii) Test minus 58% Control is equal to or greater than zero with one-sided 97.5% confidence limit for radiolabeled platelet survival. Hyperconcentrated platelets stored in Isoplate Solution for five days met both primary outcomes. There were no secondary outcomes.

Comments to Review Committee

1) In order to verify the results with acceptance criteria of the studies, the sponsor needs to provide the detailed information of statistical analyses including the computed confidence intervals, the computation software and programs to generate the results.

2) As agreed with FDA, the study conducted under Protocol I in the original study plan is not included in this NDA submission. However, from IND 13684/26, we realized that this study has failed and a new study (Protocol IV) was proposed in IND 13684/28. Would it be a concern to CBER for clearing this NDA with a failed protocol I study of platelet Leukoreduction and yield?

Letter Ready Comments

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