

An In Vivo Recovery and Survival Study of Platelets Collected on the Trima Accel System and Stored in InterSol Solution

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Syne qua non Ltd Study No: EAS17002

Statistical Analysis Plan

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For Syne qua non Ltd – Lead Statistician

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LIST OF ABBREVIATIONS

| | |
|-------------------|--|
| ¹¹¹ In | Indium 111 |
| ⁵¹ Cr | Chromium 51 |
| AE | Adverse Event |
| CIP | Clinical Investigation Plan |
| CRF | Case Report Form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| FAS | Full Analysis Set |
| FDA | United States Food and Drug Administration |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PT | Preferred Term |
| SAE | Serious Adverse Event |
| SAF | Safety Analysis Set |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SE | Standard Error |
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Event |
| UADE | Unanticipated Adverse Device Effect |
| WHO Drug | World Health Organization Drug Dictionary |

1 INTRODUCTION

This document details the statistical analysis that will be performed for the Terumo BCT, Inc study: An In Vivo Recovery and Survival Study of Platelets Collected on the Trima Accel System and Stored in InterSol Solution.

The proposed analysis is based on the contents of the final version of the Clinical Investigation Plan (CIP) (dated 10JUL2017) and case report form (CRF) (dated 17AUG2017). In the event of future amendments to the CIP, this statistical analysis plan (SAP) may be modified to account for changes relevant to the statistical analysis.

The table, listing, and figure shells are supplied in a separate document (CTS-5066 (EAS17002) Amendment 1 TFL Shells Draft Final [dated 06DEC2017]).

2 STUDY OBJECTIVES AND DESIGN

2.1 Study Objectives

The primary objective of the study is to determine the in vivo recovery and survival of radiolabeled platelets collected on the Trima Accel system, diluted in InterSol, and stored for 5 days.

2.2 Study Endpoints

The primary endpoint of the study is the recovery and survival of platelets as calculated using the COST software. Recovery (at 24 hours) is expressed as a percentage of the extrapolated platelet count at time 0. Survival is expressed in hours and is approximated using linear regression.

Safety endpoints will include the collection of adverse events (AEs), serious adverse events (SAEs), and unanticipated adverse device effects (UADEs) from the start of the apheresis procedure until study completion.

2.3 Study Design

This is a prospective, open-label, multicenter, controlled study to determine the in vivo recovery and survival of radiolabeled hyperconcentrated platelets in healthy adults. Hyperconcentrated platelets will be collected on the Trima Accel system and stored for 5 days in 65% InterSol/35% plasma. There will be 2 investigational sites located within the United States. Full details of the design are detailed in CIP Section 9.1.

2.4 Visit Structure

The visit structure and scheduled assessments are detailed in CIP Section 11.

3 SAMPLE SIZE

Assuming an approximate 40% screen fail/early termination rate, up to 40 healthy adult participants will be enrolled in this study to ensure 24 evaluable data points across 2 investigational sites in the United States.

4 RANDOMIZATION

Randomization of test and control samples to be radiolabeled with either Indium 111 (^{111}In) or Chromium 51 (^{51}Cr) will be carried out for each participant based on a randomization scheme provided by Terumo BCT, Inc. Details of this randomization will not be covered in this SAP.

5 INTERIM ANALYSIS

No interim analysis is planned.

6 ANALYSIS PLAN

6.1 General

Summary statistics for continuous variables will consist of number of non-missing observations (n), mean, standard deviation (SD), minimum, median and maximum, unless specified otherwise. The precision of these variables is defined in the table, figure, and listing shells document.

For categorical variables, the number and percentage of participants in each category will be presented, based on the number of non-missing observations apart from disposition of participants, background and demographic characteristics, and adverse events where the percentage will be based on the number of participants in the analysis set.

6.2 Derived Data

- Incomplete dates

For calculation purposes, incomplete dates will be completed using worst case. Further details are detailed in the relevant sections as required.

- Numeric variables that have been recorded as non-numeric values

In the case where a variable is recorded as ">x", "≥x", "<x" or "≤x", then for *analysis purposes*, a value of x will be taken. Where a range of values is quoted, the midpoint of the range will be taken. For example, if a laboratory safety parameter is reported as being below the limit of quantification, the value of the limit will be used in the calculation of summary statistics. The recorded value will be reported in listings.

- Methods for handling withdrawals and missing data

No data will be imputed; only observed data will be reported.

6.3 Analysis Sets

The **Enrolled Analysis Set** includes all participants who signed informed consent irrespective of whether they underwent any study related apheresis procedure.

The **Safety Analysis Set (SAF)** will include all participants enrolled in this trial who undergo any study related apheresis procedure, defined as having had venipuncture for apheresis.

The **Full Analysis Set (FAS)** will consist of all completed procedures/products where the corresponding test and control values for the primary endpoint are valid. If any of the criteria outlined in CIP Section 16.4 are met, the product will not be included in the FAS.

The list of participants included in the FAS will be agreed upon prior to database lock once all study data are available. The definitions for Enrolled Analysis Set and SAF are sufficient to determine the participants included within these analysis sets and so do not require review and agreement prior to database lock.

6.4 Data Presentations

The data will be summarized in tabular form over all participants.

Disposition of participants will be summarized using the enrolled set. Background and demographic characteristics will be summarized using the FAS and SAF. The primary endpoint will be summarized using the FAS. Safety data will be summarized using the SAF.

All listings, apart from those relating to the Trima Accel System, infusion, blood sampling, pregnancy testing and vital signs will be based on the enrolled set. Those relating to the Trima Accel System, infusion, blood sampling, pregnancy testing and vital signs will be based on the SAF. Listings will be sorted by site, participant number and visit.

6.5 Disposition of Participants

The number and percentage of all participants enrolled, failed screening, included in the FAS and SAF, who completed the study and prematurely discontinued study procedure will be summarized by site and overall. The number and percentage of participants will be summarized by their reasons for discontinuation. Eligibility for each of the analysis sets along with reasons for exclusion will be listed. Study completion/discontinuation data will be listed.

6.6 CIP Deviations

Details of all CIP deviations (date, deviation category and specific details) and participant eligibility will be listed.

6.7 Background and Demographic Characteristics

6.7.1 Demography

Any height recorded in cm will be converted to inches using the following formula:

$$\text{Height(in)} = \text{height(cm)} / 2.54$$

Any weight recorded in kg will be converted to pounds using the following formula:

$$\text{Weight(lb)} = \text{weight(kg)} * 2.2046226218$$

Demographic characteristics (age, gender, race and ethnicity) and body measurements (height and weight) collected at 'Screening' will be summarized. Height will be reported in inches and weight in pounds. All participant demographic data including informed consent and whether any study related procedures were conducted prior to informed consent form being signed will be listed.

6.7.2 Medical History

Medical history events will be recorded. All events including specific diagnosis will be listed, which will include a flag for ongoing and previous conditions.

6.7.3 Pregnancy Test

Details of the pregnancy test conducted at 'Day 5/Infusion day' will be listed.

6.7.4 Vital Signs

Any temperature recorded in Celsius will be converted to Fahrenheit using the formula below:

$$T_{(^{\circ}\text{F})} = T_{(^{\circ}\text{C})} \times 1.8 + 32$$

All vital signs data including derived variables will be listed.

6.8 Concomitant Medications/Medical Interventions

Medications will be coded using the World Health Organization Drug dictionary (WHO Drug) Version Mar17.

Any medication taken in the 7 days prior to apheresis procedure through study completion will be recorded as a concomitant medication. Prior concomitant medications are defined as those that started prior to apheresis procedure (time of venipuncture) including ongoing medications. Medications that started after venipuncture will be deemed to be concomitant medications after venipuncture. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed concomitant after venipuncture.

Only medical interventions for adverse events following apheresis procedure (time of venipuncture) will be recorded.

Prior concomitant medications and concomitant medications/medical interventions started after venipuncture for apheresis procedure will be listed separately.

6.9 Administration of Study Procedure and Exposure

Details of the Trima Accel System used and Trima end run summary report details will be listed.

Start and end time of infusion will be listed.

6.10 Primary Endpoint

The acceptance criterion for the recovery of platelets (%) is the demonstration of non-inferiority by the rejection of the Null Hypothesis (H_0) defined by the following hypotheses:

$$\text{Null Hypothesis} \quad H_0: \mu_d \leq 0 \text{ where } \mu_d = \mu_T - 0.66 * \mu_C$$

Alternative Hypothesis $H_1: \mu_d > 0$

Let $\Delta X_i = (X_{Ti} - 0.66 * X_{Ci})$ be a difference in recovery (%) for participant i . The sample mean and standard deviations of these observed differences will be used to construct the lower limit of a one-sided 97.5% confidence interval for μ_d assuming a t-distribution with $n-1$ degrees of freedom. If the lower limit of the confidence interval is greater than 0, the Null Hypothesis will be rejected in favor of the Alternative Hypothesis suggesting the test product meets the United States Food and Drug Administration (FDA) acceptance criteria for platelet recovery.

The acceptance criterion for the survival of platelets (days) is the demonstration of non-inferiority by the rejection of the Null Hypothesis (H_0) defined by the following hypotheses:

Null Hypothesis $H_0: \mu_d \leq 0$ where $\mu_d = (\mu_T/24) - 0.58 * (\mu_C/24)$

Alternative Hypothesis $H_1: \mu_d > 0$

Let $\Delta X_i = ((X_{Ti}/24) - 0.58 * (X_{Ci}/24))$ be a difference in survival of platelet (days) for participant i . The sample mean and standard deviations of these observed differences will be used to construct the lower limit of a one-sided 97.5% confidence interval for μ_d assuming a t-distribution with $n-1$ degrees of freedom. If the lower limit of the confidence interval is greater than 0, the Null Hypothesis will be rejected in favor of the Alternative Hypothesis suggesting the test product meets the FDA acceptance criteria for platelet survival.

6.10.1 Primary Analysis

The mean and standard deviation for i) the recovery of platelets (%) and ii) survival of platelets (days) for the test and control samples and mean difference between test and control samples (using difference as defined in acceptance criteria, see Section 6.10) will be calculated over all participants and presented with the lower limit of the one-sided 97.5% confidence interval for the mean difference. Confidence intervals will be calculated using the formula below:

$$\text{Lower 97.5\% CI} = \bar{\Delta X} - t_{n-1, 0.975} * SE(\bar{\Delta X}) \quad \text{where} \quad \bar{\Delta X} = \frac{\sum_{i=1}^n (X_{Ti} - F * X_{Ci})}{n}$$

n is the total number of participants

X_{Ti} = Test primary endpoint measurement for participant i

X_{Ci} = Control primary endpoint measurement for participant i

i

F is 0.66 for recovery of platelets (%) and 0.58 for survival of platelets (days)

$SE(\bar{\Delta X})$ is standard error (SE) of $\bar{\Delta X}$

The following code will be used in SAS:

```
PROC MEANS data=test alpha=0.025 lclm;
```

```
VAR delta_x;
```

```
OUTPUT OUT=xbarstat N=n MEAN=mean STD=std LCLM=lclm;
```

```
run;
```

Assumptions of normality will be assessed visually using box and whisker plots, histograms and normal probability plots. If assumption of normality cannot be made, then confidence intervals will be generated using bootstrapping methods.

The test product will be declared to meet the FDA standard if the lower limit of a one-sided 97.5% confidence interval for the difference is greater than 0 for both endpoints (recovery of platelets (%) and survival of platelets (days)), using difference as defined in acceptance criteria (see Section 6.10).

6.10.2 Summaries

The difference between test and control recovery of platelets (%) and survival of platelets (days) will be summarized.

The number and percentage of participants whose test sample was randomized to ^{111}In radiolabel (and control sample to ^{51}Cr) and whose test sample was randomized to ^{51}Cr (and control sample to ^{111}In) will be summarized in a table.

All radioactivity measurement data will be listed.

Date and time of the blood sample collections will be listed.

6.11 Safety Evaluation

6.11.1 Adverse Events

Adverse events (AEs) will be coded using MedDRA dictionary Version 20.

A treatment-emergent adverse event (TEAE) is defined as an AE that started on or after the start of the apheresis procedure (time of venipuncture) until study completion. If adverse event dates are incomplete and it is not clear whether the adverse event was treatment-emergent, it will be assumed to be treatment-emergent.

A device/procedure-related TEAE is defined as a TEAE that is possibly, probably or definitely related to the study device/procedure. If the TEAE has a missing relationship it is assumed to be related to the study device/procedure for analysis purposes.

A summary table will present the following:

- TEAEs (events and participants).
- Serious TEAEs (events and participants).
- Unanticipated adverse device effects (UADEs) (events and participants).
- TEAEs leading to discontinuation of study (participants only).
- Study device related TEAEs leading to discontinuation of study (participants only).
- Study procedure related TEAEs leading to discontinuation of study (participants only).
- TEAEs leading to death (participants only).

In the above summaries, if a participant experienced more than one TEAE, the participant will be counted once using the most related event for the “related to study device/procedure” summaries.

The following tables will be presented:

- TEAEs by system Organ Class (SOC) and Preferred Term (PT).

- TEAEs by SOC, PT and CTCAE grade.
- TEAEs by SOC, PT and related (related/unrelated) to study device and also relationship (definitely/probable/possible/unrelated).
- TEAEs by SOC, PT and related (related/unrelated) to study procedure and also relationship (definitely/probable/possible/unrelated).

For all of the above, SOC and PT will be presented in decreasing frequency of the total number of participants with TEAEs.

Further details of the above four tables are given below:

1. If a participant experienced more than one TEAE, the participant will be counted once for each SOC and once for each PT. The number of events will also be presented.
2. If a participant experienced more than one TEAE, the participant will be counted once for each SOC and once for each PT at the worst CTCAE grade.
3. If a participant experienced more than one TEAE, the participant will be counted once for each SOC and once for each PT using the most related (this applies to summaries of relationship to study device and relationship to study procedure).

Adverse event data will be listed in full and this will also include a treatment-emergent flag.

Serious TEAEs and UADEs will also be listed separately.

6.12 Clinical Laboratory Evaluation

Laboratory measurements will be presented in the same order as in the CRF.

Laboratory results from the fingerstick test (hemoglobin/hematocrit) will be listed.

Laboratory results from the venous whole blood sample from diversion pouch at apheresis visit (hemoglobin/hematocrit and platelet count) will be listed.

Laboratory results from stored product including platelet concentration, yield and pH, bacterial test result and type of bacterial test used will be listed.

6.13 Device Deficiency

All device deficiency data will be listed.

6.14 Changes from the CIP Planned Analysis

The primary endpoint survival of platelets will now be reported in days rather than hours.