Clinical Study Protocol

PAND-004-CMD

Evaluation of the Aurora Xi New Nomogram Software 2.0

Sponsor:

Fresenius Kabi

Three Corporate Drive

Lake Zurich, Illinois USA 60047

Confidential Information

1 PROTOCOL SUMMARY

Name of Sponsor: Fresenius Kabi	**Name of Investigational Product(s):** Aurora Xi With Investigational Software 2.0	**Regulatory Identifier:** IDE 29600
CSP ID: PAND-004-CMD		
CSP Title: Evaluation of the Aurora Xi New Nomogram Software 2.0		
Estimated Duration: 6-9 Months		
Planned Number of Procedures: Approximately 51,720 procedures for the primary endpoint evaluation.		

Objective(s):

Primary:

- The primary objective of this study is to demonstrate that the overall rate of significant hypotensive adverse events (SHAEs, IQPP DAE Classification 1.2-1.6) in donors using the Aurora Xi New Nomogram algorithm is less than double the SHAE rate in donors using the Aurora Xi Optimized Nomogram algorithm.

Secondary:

- To determine if the incidence rate of SHAEs per donor status (first-time or repeat donor) observed with the New Nomogram (Test arm) is non-inferior to the incidence rate observed with the Optimized Nomogram (Control arm).
- To determine if the incidence rate of SHAEs of female donors observed with the New Nomogram (Test arm) is non-inferior to the incidence rate observed with the Optimized Nomogram (Control arm).
- To determine if the incidence rate of SHAEs for donors ≤20 years of age observed with the New Nomogram (Test arm) is non-inferior to the incidence rate observed with the Optimized Nomogram (Control arm).
- To determine if the incidence rate of SHAEs for donors weighting ≤124 lbs observed with the New Nomogram (Test arm) is non-inferior to the incidence rate observed with the Optimized Nomogram (Control arm).
- To determine if the incidence rate of hypotensive severe/injury adverse events (IQPP DAE Classification 1.5 or 1.6) observed with the New Nomogram (Test arm) is non-inferior to the incidence rate observed with the Optimized Nomogram (Control arm).
- To determine if the time from start of plasmapheresis procedure to the first SHAE observed with the New Nomogram (Test arm) is non-inferior to the time observed with the Optimized Nomogram (Control arm).

Exploratory:

- To compare the plasma volume collected with the New Nomogram (Test arm) versus the Optimized Nomogram (Control arm)
- To determine the collection time with the New Nomogram (Test arm)

Study Design: This is a multicenter, prospective randomized controlled clinical trial to evaluate the Aurora Xi New Nomogram for the collection of plasma. The Test group will utilize the Aurora Xi Plasmapheresis system with New Nomogram (software version 2.0) and the Control group will utilize the Aurora Xi Plasmapheresis System with Optimized Nomogram (software version 1.3). Subjects will be retained in the assigned study arm (Test/Control) throughout their participation in the study period. Participants will donate for up to 8 weeks for the primary endpoint analysis, resulting in at least 51,720 plasmapheresis procedures. At that point, the primary endpoint analysis will take place. If noninferiority is demonstrated for the primary endpoint, but subgroup enrollment is not judged to be sufficient, an optional extension period will begin, during which collections and enrollment will continue from specific subpopulations (first-time donors, female donors, young donors, and low body weight donors). Collections performed during the optional extension period will not be included in the primary endpoint analysis but will be included for secondary endpoint analyses / subgroup analysis.

[redacted]

It is anticipated that enrollment will take approximately 6-9 months. Prior to enrollment, all subjects will be required to provide a signed informed consent for this research study and meet all standard requirements for the plasma collection center. Subjects will be considered enrolled at the time of venipuncture for the first on-study collection procedure. Plasmapheresis subject evaluations will be completed pre-procedure, during the procedure, and post-procedure between the date of the first on-study collection and up to 2 weeks after the last on-study collection.

Inclusion/Exclusion Criteria:

Inclusion:

- All subjects must meet current safety guidelines for plasma donation as set forth by the FDA as well as those in the standard operating procedures established by the participating institution.
- Enrolled subjects who do not meet inclusion criteria at a later donation attempt are eligible to remain in the clinical trial and to subsequently donate plasma once they meet eligibility criteria again.

Exclusion:

- Subjects not able or unwilling to give consent to participate.
- Subjects withdrawn by a qualified healthcare provider due to safety concerns.
- Subjects who are employed by the clinical site or Sponsor.

Statistical Methods:

The primary objective of the study is to demonstrate that the overall rate of significant hypotensive adverse events (SHAEs, IQPP DAE Classification 1.2-1.6) in donors using the Aurora Xi New Nomogram algorithm is less than double the SHAE rate in donors using the Aurora Xi Optimized Nomogram algorithm. A non-inferiority test will be carried out based on a confidence interval approach using a two-sided 95% confidence interval for the relative rate of SHAE for the experimental versus control arms based on a log linear model.

Secondary objectives of the study will be carried out by fitting a log linear model with the same specifications as the primary objective analysis with binary procedure-specific response, log-link, identity variance function, and working independence assumptions, Once the model is fitted, a point estimate and a 95% confidence interval will be computed for the relative rate of SHAEs for the secondary endpoints.

Summary statistics (N, mean, standard deviation, median, minimum, and maximum) will be reported on continuous (numeric) parameters for each Randomization Group for the Intent-to-Treat and Per-Protocol analyses unless otherwise indicated. Summary statistics (e.g., counts and percentages) will be reported on categorical (non-numeric) parameters for each Randomization Group for the Intent-to-Treat and Per-Protocol analyses unless otherwise indicated.

TABLE OF CONTENTS

List of Tables

DOCUMENT CHANGE HISTORY

Version	Change	Reason for Change
2	Updated number of donations required for subgroup analysis.	The proportion of donors in the subgroups (female, young, low-weight) was not what was expected.

2 ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	adverse event
ASAP	as soon as possible
bpm	beats per minute
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Act
CRF	case report form
CSP	Clinical Study Protocol
CSP ID	Fresenius Kabi Study Identifier
CV	curriculum vitae
DIS	Donor Information System
DAE	Donor Adverse Event
DRS	Donor Reaction System
dL	Deciliter
DSMB	Data Safety Monitoring Board
[redacted]	[redacted]
[redacted]	[redacted]
EDC	electronic data capture
eDQ	electronic donor questionnaire
EU	European Union
F	female
°F	degrees Fahrenheit
FDA	Food and Drug Administration
FWA	Federalwide Assurance
g	gram
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
ICH	International Council for Harmonization
ICF	informed consent form
IDE	Investigational Device Exemption
in	inch
IORG	Institutional Review Board Organization
IP	investigational product
IORG	IRB Organization
IQPP	International Quality Plasma Program
IRB	Institutional Review Board
ISO	International Organization for Standardization
lb	pound
IRT	Interactive Response Technology
LOC	loss of consciousness

Abbreviation	Definition
M	Male
mL	Milliliter
mmHg	millimeters of Mercury
SAE	serious adverse event
SHAE	Significant Hypotensive Adverse Event
SOP	standard operating procedure
US	United States

3 BACKGROUND

The marketed Aurora Xi Plasmapheresis System, comprised of the Aurora Xi Instrument (hardware and software) and a Plasmacell Xi Disposable Set, is an automated plasmapheresis system intended for routine collection of plasma to be processed as Source Plasma.

The collection of plasma by the Aurora Xi system is an automated procedure with the donor connected to the Plasmacell Xi Disposable Set via an apheresis needle set throughout the collection process. The collection procedure requires a single venipuncture, which means that one access site is used to draw whole blood and return concentrated cellular components. The procedure involves sequential cycles of alternating phases: one in which blood is drawn and plasma is separated and collected and the other in which residual cellular components are returned. Venous pressure is continuously monitored to avoid exceeding the flow capacity of the donor's vein and to maintain comfortable pressures in the donor vein.

The current, three-tiered, weight-based plasma nomogram in the US does not factor in the [redacted] A New Nomogram has been configured for the Aurora Xi software (Version 2.0) [redacted] than the current Optimized Nomogram three-tier nomogram used with the Aurora Xi device. [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

3 OBJECTIVE(S)

3.1 Primary Objective

The primary objective of this study is to demonstrate that the overall rate of significant hypotensive adverse events (SHAEs, IQPP DAE Classification 1.2-1.6) in donors using the Aurora Xi New Nomogram algorithm is less than double the SHAE rate in donors using the Aurora Xi Optimized Nomogram algorithm.

3.2 Secondary Objectives

To determine if the incidence rate of SHAEs per donor status (first-time or repeat donor) observed with the New Nomogram (Test arm) is non-inferior to the incidence rate observed with the Optimized Nomogram (Control arm).

- To determine if the incidence rate of SHAEs for female donors observed with the New Nomogram (Test arm) is non-inferior to the incidence rate observed with the Optimized Nomogram (Control arm).
- To determine if the incidence rate of SHAEs for donors ≤20 years of age observed with the New Nomogram (Test arm) is non-inferior to the incidence rate observed with the Optimized Nomogram (Control arm).
- To determine if the incidence rate of SHAEs for donors weighting ≤124 lbs observed with the New Nomogram (Test arm) is non-inferior to the incidence rate observed with the Optimized Nomogram (Control arm).
- To determine if the incidence rate of hypotensive severe/injury adverse events (IQPP DAE Classification 1.5 or 1.6) observed with the New Nomogram (Test arm) is non-inferior to the incidence rate observed with the Optimized Nomogram (Control arm).
- To determine if the time from start of plasmapheresis procedure to the first SHAE observed with the New Nomogram (Test arm) is non-inferior to the time observed with the Optimized Nomogram (Control arm).

3.3 Exploratory Objectives

- To compare the plasma volume collected with the New Nomogram (Test arm) versus the Optimized Nomogram (Control arm)
- To determine the collection time with the New Nomogram (Test arm)

4 SCOPE

This is a multicenter, randomized controlled prospective IDE clinical trial to evaluate the safety of the Aurora Xi Plasmapheresis System with New Nomogram compared to a Control group undergoing plasmapheresis on the Aurora Xi system using the currently marketed Optimized Nomogram. The trial will be conducted at a minimum of 3 BioLife plasma donation centers.

5 STUDY DESIGN

5.1 Overview of Study Design

This study will enroll human subjects in accordance with this protocol, the applicable sections of the FDA Code of Federal Regulations (21 CFR Parts 50, 54, 56, 640, and 812), the principles of the World Medical Association Declaration of Helsinki (2013 version), International Council for Harmonisation (ICH), protection of human subjects in research and the execution of good clinical trials, International Organization for Standardization (ISO) 14155:2020 Clinical investigation of medical devices for human subjects – Good clinical practice, and the privacy regulation of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), as it pertains to this study.

This multicenter, prospective randomized controlled clinical trial is designed to enroll donors from at least 3 BioLife plasma donation centers to reach a minimum of 51,720 total collection procedures for the primary analysis. Prior to the initiation of study collections, there will be a two-week period when individuals may be consented for the study, prior to commencing their first on-study procedure. Prior to enrollment, all subjects will be required to provide a signed informed consent. Each subject will be randomized prior to their first procedure and repeat donors will be retained in their randomized study group (Test/Control) throughout their trial participation. Subjects will not be informed to which group they have been randomized.

For the primary endpoint analysis, individuals will be eligible to donate for a maximum of 8 weeks, a time set to minimize the effect of the date of enrollment on the number of possible procedures per participant. It is estimated that the study will enroll approximately 11,519 subjects, but fewer subjects may be enrolled if the number of procedures per subject is greater than the current estimate. Upon collection of the target number of procedures and analyzing the primary endpoint, an optional extension period may commence, during which only donors who qualify for one or more high risk subgroup (female, weight ≤124 lbs, ≤20 years of age and First-Time Donor) will be enrolled and undergo on-study collections. Individuals consented prior to the extension period may continue donating during this extension if they qualify for one or more of the relevant subgroups. The purpose of this extension period would be to generate additional data to support the secondary subgroup analysis. Collections during the extension period will not be included in the primary endpoint analysis since it represents a period of biased enrollment. After analyzing the primary endpoint, an optional extension period may commence, during which only donors who qualify for one or more high risk subgroup (female, weight ≤124 lbs, ≤20 years of age and First-Time Donor) will be enrolled and undergo on-study collections. Individuals consented prior to the extension period may continue donating during this extension if they qualify for one or more of the relevant subgroups. The purpose of this extension period would be to generate additional data to support the secondary endpoint subgroup analysis. Collections during the extension period will not be included in the primary endpoint analysis since it represents a period of biased enrollment.

Plasmapheresis subject evaluations will be completed pre-procedure. Other parameters, including adverse events, will be collected during and/or post-procedure (See section 7 - Study Procedures/Methodology).

Enrollment for the primary endpoint evaluation is anticipated to take approximately 6-9 months. The optional extension period may take up to an additional 3 months.

5.2 Subject Selection

Subjects will be recruited by the site investigator(s) or designee(s), who will discuss details of study participation with each potential subject. All recruitment material will be IRB approved. Each subject will provide signed informed consent, as approved by the IRB, before participating in the study. In accordance with the clinical site's SOPs, if a subject is unable to provide signed informed consent, his/her legally authorized representative may not sign on his or her behalf. After providing written informed consent, subjects will be verbally asked if they consent to continued study participation prior to initiation of all subsequent study procedures. After choosing to participate, the subject can withdraw from the study at any time without prejudice, penalty or loss of benefits or care that he or she would otherwise be entitled.

All subjects will be assessed for eligibility prior to any possible study procedure using the inclusion and exclusion criteria.

All subject information will be kept confidential in compliance with all applicable state and federal laws and regulations.

5.2.1 Inclusion Criteria

Potential subjects must satisfy all the following criteria prior to enrollment in the study:

- All subjects must meet current safety guidelines for frequent plasma donation as set forth by the FDA and the study sponsor, as well as those in the standard operating procedures established by the participating institution.
- Currently enrolled subjects who do not meet inclusion criteria at a later donation attempt are eligible to remain in the clinical trial and to subsequently donate plasma once they meet eligibility criteria again.

5.2.2 Exclusion Criteria

Potential subjects must NOT satisfy any of the following criteria prior to enrollment or during the study:

- Subjects not able or unwilling to give consent to participate.
- Subjects withdrawn due to safety concerns by qualified healthcare provider.
- Subjects who are employed by the clinical site or Sponsor.

5.2.3 Subject Enrollment

Subjects are enrolled/randomized at the time of consent.

The 8-week donation period begins at the time a subject undergoes venipuncture for their first procedure.

5.2.4 Subject Donation Status

First-time donors are defined as donors who have not donated plasma at BioLife within the past 6 months.

Repeat donors are defined as donors who have donated plasma at BioLife within the past 6 months.

5.2.5 Subject Withdrawal

Subjects who are withdrawn from the study, as well as the reason for withdrawal, will be recorded on a Subject Withdrawal Log located at the site.

Possible reasons for withdrawal include but are not limited to:

- Safety concerns of a qualified healthcare providerwhole blood or platelets outside of this clinical trial during the study participation period.If, after enrolling, the subject no longer satisfies Inclusion Criteria, meets any Exclusion Criteria, or otherwise withdraws from the study, any data from all previous procedures will remain in the database and be considered evaluable. However, a study procedure will be considered non-evaluable if the participant is found to have donated plasma, whole blood or platelet components outside of the study between the time of enrollment and that study procedure.

If at any point during the study a subject undergoes a procedure on the incorrect group according to their initial assigned study arm, a protocol deviation will be documented, and the subject can donate on their assigned study arm for subsequent procedures.

Subjects will not be asked prior to each visit if they want to continue to participate in the study. It will be the subject's responsibility to inform the study staff prior to a study procedure if they want to be withdrawn from the study.**STUDY PROCEDURES/METHODOLOGY**

6.1 Training

Qualified healthcare professionals and site personnel will be trained before study start, including review the Clinical Study Protocol, any conditions imposed by the IRB, and any applicable regulatory requirements. Training will be documented on training forms to verify training on the protocol, investigational software, use of case report form, and clinical trial conduct. Duties of all site personnel will be documented on the Site Signature Delegation Key.

Training will cover:

- Clinical trial objectives
- Clinical Study Protocol review
- Personnel Responsibilities
- Informed Consent requirements and process
- Case Report Form procedures

- Enrollment procedures
- Protocol deviation procedures
- AE and SAE Reporting
- Device Malfunction Reporting
- Instructions for use (e.g., Operator's Manual)
- Device training
- Good Clinical Practice (GCP) guidelines
- Regulatory requirements

Change to staff as documented on the Site Signature Delegation Key or addition of new personnel will require appropriate training and documentation.

6.2 Lead-In Consenting Period

Each site will be allowed to begin consenting subjects 2 weeks prior to the first planned study procedure at the site. During this lead-in period, plasma donors (first-time and repeat) can be presented with the opportunity to consent for this study. Any donors consented during this period will be able to continue donating whole blood, platelets, or plasma outside the study protocol, until the date that any study collection procedures begin at the site, without causing any exclusion criteria to be met.

In order to minimize potential bias, the Lead-In Consenting Period will be capped at 1,152 subjects across all study sites and 384 subjects at each of the three planned study sites (10% of the estimated total enrollment).

6.3 Roll-in Procedures

Roll-in procedures will follow all procedures/methodology detailed in this clinical study protocol and will consist of a safety evaluation by the Data Safety Monitoring Board (DSMB) after all sites have completed a minimum of 150 collection procedures.

6.4 Study Procedures

The Aurora Xi Plasmapheresis System will be operated by qualified operators who have been trained on the operation of the system. The Test group will utilize the Aurora Xi Plasmapheresis System with New Nomogram (software version 2.0) and the Control group will utilize the Aurora Xi Plasmapheresis System with Optimized Nomogram (software version 1.3). Instructions for apheresis disposable set installation, operation of the Aurora Xi system and troubleshooting procedures will be followed as described in the Aurora Xi Plasmapheresis System Operator's Manual, Software Version 1.3 (47-19-16-307) or the investigational Aurora Xi Plasmapheresis System Operator's Manual, Software Version 2.0 (REC-024378).

Prior to starting a collection procedure, each subject will be assessed for study eligibility (Inclusion and Exclusion Criteria), will be informed about the procedure and, if qualified, will be asked to sign an informed consent form (ICF). Subject height will be measured using a stadiometer and a scale will be used to verify weight. Subjects will be randomized 1:1 to the Test or Control group according to a pre-determined web-based randomization

schedule (See Section 7.6). Study arms will be coded as “Group A” or “Group B” within the collection center and within the donor information system of the site. Subjects will be assigned to the same study group (Test/Control) throughout their participation in the study.

When a subject is sent to the instrument for donation, [redacted]

All subjects (Test and Control) will receive 500 mL of saline compensation as part of the plasmapheresis procedure as the primary form of re-hydration. (If, under exceptional circumstances, saline cannot be administered as part of the automated procedure, plasma center policies will be followed).

Post-procedure, the instrument procedure data will be electronically transferred from the device itself into the center’s electronic DIS data capture system via the DXT system.

Upon completion of the procedure, the subject will schedule their next visit(s). This will ensure that the wait time prior to their next procedure is minimal and aligns with standard scheduling practices at BioLife. The scheduling will account for Group A or Group B to manage equal donor flow/wait time).

[redacted]

6.6 Study Evaluations

6.6.1 Pre-Procedure

[redacted]

[redacted]If the donor is deferred, based on BioLife standard deferral criteria, the date/time and reason will be collected. [redacted]

During the informed consent process, subjects will be asked to self-declare race and ethnicity and if they have donated whole blood, platelets or plasma at any collection center (i.e., even if not BioLife) in the past 6 months. Furthermore, prior to each potential study procedure, subjects will be asked, via the eDQ (Electronic Donor Questionnaire), if they donated whole blood, platelets, or plasma outside of the clinical trial since the last time they donated plasma.

6.6.2 During Procedure

During the procedure, the collection Date, Start and End times, procedure note ID and procedure notes will be recorded. All adverse event ID, adverse events, Start date/time, End date/time, signs and symptoms, adverse event notes and collected volume at time of AE will be collected during the procedure. The adverse events will be categorized according to the definitions outlined in the International Quality Plasma Program (IQPP) Standard for Recording Donor Adverse Events. Categories 1.2 to 1.6 Hypotensive categorization will only be analyzed for primary objective. The Operator ID at Venipuncture, Re-Stick and Disconnect will also be collected.

6.6.3 Post-Procedure

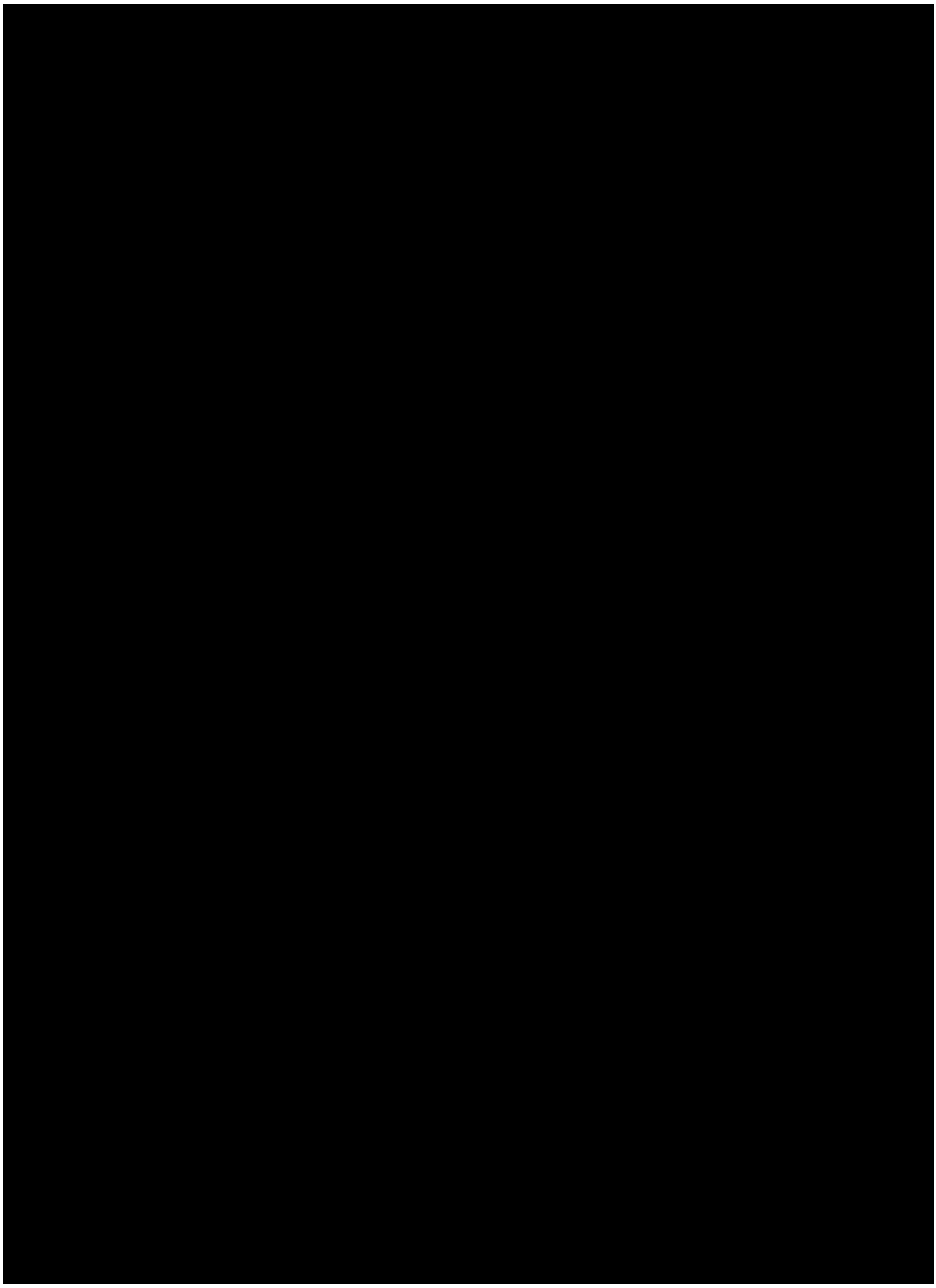
[redacted] If the donor chooses to withdraw from the study, the date and reason will be collected.

Adverse events (ID, category, sub-category, date, time) that occur within 72 hours post-procedure will be subject-reported and recorded. Subjects may report post-procedure adverse events at any time during the study. For a period of 2 weeks after the last study collection, any adverse events related to study procedures that are reported to BioLife will be included in the study dataset.

6.6.4 Study Parameters

Table 1 provides a listing of all the study parameters that will be recorded pre-procedure to post-procedure. Additional information, such as the Instrument log files, DXT data files or Disposable Set Lot Number, may be reviewed as part of a quality or complaint investigation, per standard protocol.

[redacted]



6.7 Appropriateness of Measurements

Employed test measurements are standard for the industry.

6.8 Study Completion

The Sponsor considers the study complete 2 weeks after the last procedure is completed at all clinical sites.

6.9 Site Closure

The Sponsor considers the site closed after the collection of the final data/data clarification forms, and the Sponsor has completed the Site Close-out Visit.

6.10 Discontinuation

Details of discontinuation of subjects or site(s) may include, but are not limited to:

- Failure of the investigator to comply with the study protocol, regulatory requirements or other study provisions
- Safety concerns
- Inadequate study subject enrollment by the investigator

6.11 Study Termination

Study termination may be decided at any time by the sponsor or site investigator, provided there is reasonable cause and/or sufficient notice is given in advance of the intended withdrawal. Examples include, but are not limited to:

- Safety concerns
- Failure to demonstrate non-inferiority in the primary endpoint analysis

6.12 Collected Plasma

The plasma collected on both arms of this study will be considered equivalent and approved for use as source plasma. BioLife will release Source Plasma for further manufacture compliant with 21CFR Chapter I Subchapter F to a manufacturing facility for manufacture and distribution of US licensed plasma derived therapies. The plasma and downstream products will not be labeled as investigational.

7 DESCRIPTION OF INVESTIGATIONAL PRODUCT

7.1 Intended Use

The intended use of Aurora Xi with the New Nomogram is the same as the currently cleared Aurora Xi system:

The Aurora Xi Plasmapheresis System with investigational Software Version 2.0 is intended for the automated collection of plasma by membrane filtration to be processed as Source Plasma. The Aurora Xi system is to be used with a single-use Plasmacell Xi

Disposable Set and 4% sodium citrate anticoagulant and allows for Saline and No Saline Protocol options.

7.2 General Description

[redacted]

[redacted]

[redacted] Subjects will be retained in the arm to which they were randomized for their first donation throughout the study.

In order to accommodate the larger collection container, the Test and Control devices will include a bag hanger and container shroud specifically designed for the 2000 mL plasma collection container, in order to ensure that there is no interference between the larger container and the device (power column and/or protective shroud). Both the bag hanger and container shroud are cleared for use in the United States. [redacted]

7.3 Materials and Supplies

The following investigational products are intended for use in this study:

- Aurora Xi Plasmapheresis System Investigational Software Version 2.0 with New Nomogram Enable Key, FTX 4613
- Aurora Xi Plasmapheresis System Operator's Manual, Software Version 2.0, REC-024378
- Aurora Xi Plasmapheresis System Administrator's Guide, Software Version 2.0, REC-024379

Marketed materials may include, but are not limited to:

- Aurora Xi Plasmapheresis System instrument, Code 6R4612 or 6R4612R

- Aurora Xi Plasmapheresis System, Software Version 1.3, Code 6R4612
- Plasmacell Xi Disposable Set, Code 6R2600
- Anticoagulant Sodium Citrate Solution, USP 500 mL, Code 4B7889Q or equivalent
- Sodium Chloride Injection, USP 500 mL, 0.9% Sodium Chloride, Code 6B1275 or equivalent
- Plasmalink Transfer Pack Container, 2000 mL, Code 6R2042
- Apheresis Needle, with MasterGuard protector, 17 ga (Code 4R2441)
- Rotated Plasma Collection Hanger (Code 6212599951)
- Cutback Shroud (Code 61125999949)
- Software Rev 1.2 Aurora Xi Optimized Nomogram Enable USB (Code 6112598275)

7.4 Labeling

The Aurora Xi Plasmapheresis System with investigational software 2.0 will be labeled with the following information:

> CAUTION: This device is for Investigational Use Only with Clinical Study Protocol PAND-004-CMD.

Even though the control arm is not investigational, to prevent bias, the Aurora Xi Plasmapheresis System with software 1.3 will also be labeled with the following information:

> CAUTION: This device is for Investigational Use Only with Clinical Study Protocol PAND-004-CMD.

7.5 Anticipated Changes to the Investigational Product During the Study

There are no changes anticipated to the investigation product during the study.

7.6 Method of Assignment to Investigational Product(s)

Subjects will be randomized 1:1 to the Test group (Aurora Xi Plasmapheresis System with New Nomogram) or the Control group (Aurora Xi Plasmapheresis System with Optimized Nomogram) by a qualified member of the study staff. [redacted] Upon completed entry of the required randomization parameters, the IRT system will assign the subject into either Group A or Group B. All subjects must meet all eligibility criteria and sign an ICF prior to randomization. Repeat donors will remain in the same study group (Group A/Group B) throughout their participation in the clinical trial.

The block randomization (by subject) scheme will ensure a balanced allocation of subjects in each subgroup (Test/Control), and subjects will be randomized within blocks of variable size (2, 4, or 8) within strata defined within the site according to the following criteria:

[redacted]

Variable block sizes are used to ensure that investigators cannot predict what the next assignment will be.

If at any point during the study a subject undergoes a procedure on the incorrect group according to their initial assigned study arm, a protocol deviation will be documented, and the subject can donate on their assigned study arm for subsequent procedures.

If the optional extension period were to occur, previously randomized donors will keep their original randomization assignment. Donors who are consented and enrolled during the extension period will be randomized 1:1 to test and control, as described above.

8 BIAS MITIGATION

Subjects will not be made actively aware to which group they have been randomized. To reduce potential bias, all study instruments will look visibly the same to the subject from their viewpoint, although the Test and Control instruments will be segregated from each other in each center. Test and Control groups will be de-identified as either Group A or B on center documentation and the device itself.

The following steps will be taken to help to reduce bias: all devices will be labeled for Investigational Use Only with Clinical Study Protocol PAND-004-CMD, and both groups' devices will include a commercially available bag hanger and container shroud designed for the larger volumes of saline and storage bags, and collections will be completed using 2000 mL containers and 500 mL bags of Sodium Citrate. All site documentation for the subject will be either Group A or B rather than Test or Control. Group A or B will also be visible in DIS, so staff will be unaware of group type. [redacted] The way the operators interact and question regarding AE will remain the same for both groups.

[redacted] Once all procedures are completed, Fresenius Kabi Clinical Affairs group will have access to all data.

Fresenius Kabi Data Management will have access to all data during the study. Fresenius Kabi Data Management will create the Data Management Plan that will provide details about the hidden field processes. It will include details on how the hidden data will be restricted in the EDC system based on study roles, at what point the hidden data will be made available to Clinical Affairs and the Principal Investigator, and procedures if hidden fields are incidentally revealed to unauthorized personnel.

9 RISK ANALYSIS

9.1 Risks Associated with Blood Donation

The typical risks associated with venipuncture and routine blood donation may occur. These may include bruising/hematoma formation or skin irritation at the venipuncture site, rapid heart rate due to hypovolemia, tiredness, and vasovagal-associated symptoms, such as hyperventilation, sweating, weakness, pallor, dizziness/lightheadedness, loss of consciousness, nausea, vomiting or convulsions. Although the venipuncture needles are sterile and proper aseptic technique will be used, in rare cases infections or inflammation of the vein may occur. Rare complications include arterial puncture or peripheral nerve injury.

9.2 Risks Associated with an Apheresis Procedure

Risks and discomforts that are unique to apheresis procedures may occur. Mild symptoms of hypocalcemia, such as finger or perioral discomfort (e.g., tingling), unusual smell or taste sensation, vibrations, muscle discomfort and/or headache, or paresthesia (abnormal sensation of the skin) may occur temporarily and are caused by citrate in the anticoagulant that is returned to the subject more rapidly than the subject can metabolize. Study subjects will be monitored for sign/symptoms of hypocalcemia. Adjustments to the procedure or an over-the-counter calcium carbonate supplement such as Tums may be given, if any of these symptoms occur. Continued rapid administration of citrate anticoagulant may result in more severe evidence of citrate toxicity, including tetany, convulsions or, in extremely rare occasions, cardiac arrest and death. Other symptoms, although unlikely, may include skin redness, itching, hives, bronchospasm (difficulty breathing), and abdominal cramps.

Other potential risks during apheresis include hemolysis, air embolus, blood loss, or blood clotting. Apheresis technology is designed to monitor for the presence of air, hemolysis, leaks, or blockage in the disposable kit during the procedure.

9.3 Risks Associated with Use of the Aurora Xi New Nomogram

Safety levels for all apheresis-related hazardous situations have been established in alignment with currently accepted industry practice and regulations, and these levels have been approved through a cross-functional review. Fresenius Kabi's documented design and development processes include risk management activities that assess the probability of these hazardous situations, and risk controls are established to maintain device safety. The device is verified to maintain performance within these established safety limits, with results of the verification and risk management activities reviewed through a formal cross-functional design review prior to first human use release. All changes to the device go through the same process of analysis, risk management, verification, and review prior to human use. This process ensures that the original device and all subsequent modifications to the device, do not present unacceptable risks to the subject.

Some subjects may donate more plasma than currently allowed under the established plasma volume limit, and the increase in absolute volume collected may increase the chance of adverse events.

The risk management process has been reviewed and concluded that there are no unacceptable risks, and that the benefits of this device outweigh the risks.

Stated special controls, when combined with general controls (e.g., Good Manufacturing Practice), should mitigate any risks associated with the use of Aurora Xi with New Nomogram.

10 SAFETY EVALUATIONS

10.1 Adverse Events

Adverse events that occur from venipuncture through 72 hours post-donation will be handled initially by the BioLife site's standard operating procedures. All Adverse Events (AEs) will be defined and categorized in accordance with plasma center operating procedures, which follow IQPP standards (refer to Appendix 15.2 – IQPP Standard for Recording Donor Adverse Events). Initial review and classification of adverse events will be done by the BioLife site Center Physician, using their standard procedures. Note that the collection volume at the time of an adverse event will be visible to those medical reviewers, who may indicate which arm of the study an individual was participating on. Therefore, a second, blinded Medical Review will be conducted for all SHAE Events. This medical reviewer will be blinded to study arm assignment and volume of plasma collected. If there is a discrepancy between the independent Medical Reviewer and the site's routine medical classification, the independent medical review categorization will used for the endpoint analysis.

All AEs that occur and are self-reported by the subject during or after the start of any apheresis donation through 72 hours post-donation will be recorded. The subject will have up to 2 weeks post-donation to self-report any AEs that occur through 72 hours post-donation.

For the purposes of this study only SHAE Classifications 1.2-1.6, considered significant hypertensive adverse events (SHAEs), will be analyzed for the primary objective. A blinded independent Medical Review will be conducted of the SHAE Events categorization and sub-categorization.

Table 2. IQPP Donor Adverse Event Hypotensive Classification Guide

DAE Classification	Description	Signs/Symptoms/Findings
1. Hypotensive (Vasovagal/Hypovolemia) Hypotensive reaction (vasovagal/hypovolemia) that falls into any of the following categories. *Note:* For the purposes of this IQPP Standard, "medical staff intervention" means the use of expertise from the physician or physician substitute to make decisions regarding management of the DAE.		
1.1 Hypotensive: Prefaint, No LOC (Minor)	This reaction: - Must resolve without medical staff (e.g., physician substitute) intervention, AND Involves signs and symptoms that resolved quickly (e.g. within approximately 10 minutes).	May include one or more of the following: a. Abdominal cramps; b. Auditory disturbance (e.g. sounds coming from a distance or "buzzing" in the ears); c. Chills or Shivering;

DAE Classification	Description	Signs/Symptoms/Findings
		d. Clammy; e. Cold extremities; f. Dizziness; g. Epigastric discomfort; h. Facial pallor (e.g. pale skin or lips) i. Feeling of Warmth; j. Headache or neck ache; k. Hypotension; l. Lightheadedness; m. Nausea; n. Palpitations; o. Sweating; p. Visual Disturbance (e.g. blurred or faded vision); or q. Weakness
1.2 Hypotensive: Prefaint, No LOC (Moderate):	This reaction: a. Requires medical staff (physician substitute) intervention, OR b. Involves signs/symptoms that did not resolve quickly (e.g. within 10 minutes) OR Additional signs/symptoms may be present.	May include any in 1.1 AND a. Vomiting
1.3 Hypotensive: LOC (brief)	In this reaction, LOC lasts approximately less than sixty seconds.	May include any in 1.1 or 1.2
1.4 Hypotensive: LOC (prolonged)	In this reaction, LOC lasts approximately sixty seconds or longer.	May include any in 1.1 or 1.2
1.5 Hypotensive; Severe (With or Without LOC)	This reaction may or may not include LOC.	May include any in 1.1 through 1.4 AND any of the following: a. Chest Pain; b. Convulsions/Seizures c. Loss of Bladder/Bowel Control; or d. Prolonged signs or symptoms that do not resolve.
1.6 Hypotensive; Injury	A hypotensive event that results in ANY type of injury such as: a. Closed Head Injury; b. Dental Injury; c. Fracture; d. Laceration; e. Soft Tissue Injury (not phlebotomy-related); or f. Other	May include any of 1.1 – 1.5 as well as any signs/symptoms related to the injury itself.
NOTE: If the donor exhibits symptoms of a hypotensive event (1.1 through 1.6), in addition to "anxiety," then the event should be classified according to "1.1-1.6 Hypotensive."		

10.2 Serious Adverse Events

21 CFR312.32 defines a serious adverse event (SAE) as any AE that results in any of the following outcomes:

- Death
- Life-Threatening
- Hospitalization (initial or prolonged)
- Disability or Permanent Damage
- Congenital Anomaly/Birth Defect
- Required Intervention to Prevent Permanent Impairment or Damage (Devices)
- Other Serious (Important Medical Events)

All SAEs shall be investigated, documented, managed, and reported according to this procedure and in compliance with the appropriate regulations and local authorities.

Prior to the start of the study, the monitor shall:

- Inform the investigator(s) of the definition of a serious adverse event, *and*
- Advise the investigator(s) of the time frame for reporting SAEs to the sponsor and their IRB and the regulatory requirements for reporting serious adverse events.

It is expected that the investigator(s) shall report all serious adverse events to the sponsor within 24 hours of onset or identification of an event. All UADEs must be reported to the IRB within ten working days. All SAEs must be recorded per the Sponsor Serious Adverse Event reporting process.

According to ISO 14155:2020, an Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation of the investigational medical device. This includes any malfunction of the investigational medical device, or any event resulting from user error or intentional misuse of the investigational medical device.

21CFR812.3(s) defines an Unanticipated Adverse Device Effect (UADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Table 3 Required Reports from Investigator

Report	Submit To	Time
Withdrawal of IRB approval 21 CFR 812.150(a)(2)	Sponsor	Within 5 working days
Progress Report(s) 21 CFR 812.150(a)(3)	Sponsor, Monitor, IRB	Regular intervals (at least yearly)

Report	Submit To	Time
Deviation from protocol 21 CFR 812.150(a)(4)	Sponsor, IRB	ASAP but no later than 5 working days
Failure to obtain informed consent 21 CFR 812.105(a)(5)	Sponsor, IRB	Within 5 working days
Final Report (Completed Case Report Forms constitute a Final Report from Investigator) 21 CFR 812.150(a)(6)	Sponsor, IRB	Within 3 months after termination
Both Serious and Unanticipated Adverse Device Effects 21CFR 812.150(a)(1)	Sponsor	ASAP (within 24 hours) by telephone, facsimile or email
	IRB	ASAP, but in no event later than 10 working days after the investigator first learns of the effect.

11 DATA QUALITY ASSURANCE

11.1 Data Capture System

The 21 CFR Part 11 compliant Zelta electronic data capture (EDC) system will be utilized for this study. Appropriate controls will be in place at each step at which a computerized system will be used to create, modify, maintain, archive, retrieve, or transmit source data. Technical and procedural controls will be implemented to protect information and personal data processed against unauthorized or unlawful access, disclosure, dissemination, alteration, or destruction or accidental loss, especially where the processing involves transmission over a network.

11.2 Data Flow

Fresenius Kabi Data Management will create the Data Management Plan document that will specify the procedures and controls followed at every step of the data flow from the subject to the study EDC system, including source documentation retention, file type and mode of transfer, system requirements, account and access credentials, file protection, transfer security, change controls, frequency, data storage and archiving, and reconciliation processes.

Data generated from the Advarra eConsent System, endpoint PULSE IRT System, electronic Donor Questionnaire (eDQ) System, Donor Reaction System, Donor Information System, and TrackWise System will serve as the primary data sources for the clinical trial record; all are 21 CFR Part 11 compliant. Only individuals with documented training and authorization will have access to study data.

The DXT Data Management System will send instrument data to the site's Donor Information System. Information may also be manually entered into the Donor Information System by designated and qualified site staff. Information from the Advarra eConsent System will be manually entered into the endpoint PULSE IRT System by designated and qualified site staff. Designated site staff will export data from the Donor Information System, Donor Reaction System, electronic Donor Questionnaire (eDQ) System, and

TrackWise System to a secure File Transfer Protocol site. Only Fresenius Kabi Data Management and designated and qualified site staff will have access to the secure File Transfer Protocol site. Fresenius Kabi Data Management will download the files from the secure File Transfer Protocol site onto a Fresenius Kabi closed network location protected by password access and appropriate system controls. Only Fresenius Kabi Data Management will have access to the network location. Fresenius Kabi Data Management will then import the electronic Donor Questionnaire (eDQ), Donor Information System, and Donor Reaction System data files directly into the 21 CFR Part 11 compliant Zelta EDC System. The TrackWise System data files may be directly imported into the Zelta EDC System by Fresenius Kabi Data Management, or manually entered into the Zelta EDC System by trained and authorized site personnel.

Fresenius Kabi Data Management will download data files directly from the endpoint PULSE IRT System to a closed network location protected by password access and appropriate system controls. Only Fresenius Kabi Data Management will have access to the network location. Fresenius Kabi Data Management will then send the endpoint PULSE IRT System data files over a closed password-protected network to designated site staff. Fresenius Kabi Data Management will then import the endpoint PULSE IRT System data directly into the Zelta EDC system.

[redacted]

Fresenius Kabi Data Management will have access to all data during the study. Fresenius Kabi Data Management will create the Data Management Plan that will provide details about the hidden field processes, including how the hidden data will be restricted in the Zelta EDC System based on study roles, at what point the hidden data will be made available to Fresenius Kabi Clinical Affairs and the Principal Investigator, and procedures if hidden fields are incidentally revealed to unauthorized personnel.

11.3 Data Recording

All data provided to the study sponsor will be encoded to maintain study subject confidentiality. Each data element will be associated with an authorized data originator. When data is automatically populated a data element identifier will automatically be created to identify and record the originator of the data element. Corrections to data will be tracked via an audit trail, and each correction will be identified by the person making the change. The time, date, and reason for change will all be recorded. Only those individuals who have documented training and authorization will have access to the data. Processes and procedures will be established to ensure that backup copies of data are maintained and retained for a defined period within a safe and secure location only accessible to authorized personnel.

11.4 Case Report Forms

All study data will be imported or manually entered into the EDC system by trained and authorized personnel. The data import into EDC will be a controlled, validated, secure process with supporting documentation created and implemented by Fresenius Kabi Data Management. The EDC system will record who entered or generated the data and when it

was entered or generated. Modifications and corrections to the data will include who made the change, when, and why. Authorized, trained study site personnel will receive a secure login and password from the sponsor to manually update study data if needed. Controls will be employed to ensure the security and integrity of all authorized users.

The EDC system will automatically generate data quality queries as data is added. Fresenius Kabi clinical monitors, Data Management, or Statistics personnel may also generate manual queries as necessary. The study site will need to address each query in a timely matter.

11.5 Monitoring Procedures

Details will be outlined in the Study Monitoring Plan. Key risk indicators may include, but are not limited to, adverse event reporting, compliance to the protocol, enrollment, and the Investigator Site File. In the event where a particular site is not performing as expected, appropriate intervention may be made. Interventions may include, but are not limited to, retraining, site audits, enrollment suspension or site termination.

Safety monitoring on a real-time basis will be implemented, such that the sponsor, and independently the Principal Investigator, will be able to take appropriate steps to manage emergent safety signals, e.g., to put on hold or stop the clinical trial in case a safety signal is observed. In addition, an external Data Safety Monitoring Board will perform a review of the safety data after the roll-in procedures and if a safety event is triggered.

11.6 Maintenance of Records

Documents that must be provided to the Sponsor prior to any study Site Initiation include:

- Medical Device Agreement
- Financial Disclosure and Arrangements of Clinical Investigator
- Investigator’s Signed Protocol Signature Sheet
- Study Site Personnel CVs and Medical Licenses
- A copy of the IRB-approved informed consent form (ICF) and other adjunctive material (e.g., marketing flyers) to be used in the study, including written documentation of IRB approval for these materials
- Name and address of the IRB and a statement/document that attests that it is organized and operates according to GCPs and applicable laws and regulations (i.e., the FWA number and/or IORG number and/or a list of the IRB's current members)

11.7 Record Retention

During or after the study, the appropriate regulatory agency may inspect study records at the investigational site. Since inspection may arise at any time, records should be kept current at all times. The Sponsor must be advised of any request by a regulatory agency to visit or inspect the laboratory.

Records must be maintained for:

- A period of at least 2 years after the last approval of a marketing application in an ICH region when there are no pending or contemplated marketing applications in an ICH region.
- A period of at least 2 years after the formal discontinuation of development of the investigational product(s).

These documents should be retained for a longer period of time if required by the applicable regulatory requirement(s) or if required by the Sponsor.

11.8 Publications

The protocol, procedures, and data pertaining to this study will be treated as confidential information. Publication of data and/or information derived from these studies must be done with the prior review and approval of the Sponsor. Scientific personnel may share authorship with investigators on abstracts, oral presentations and manuscripts. The first author will be the person assuming primary responsibility for the abstract or manuscript.

12 STATISTICAL METHODS AND SAMPLE SIZE

12.1 General Overview

All of the data will be verified and archived by Fresenius Kabi, USA, Lake Zurich, IL. Any change to the data analysis methods described in this protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any change to the data analysis methods described in the protocol, and the justification for making the change will be described in the final study report.

The primary objective of this study is to demonstrate that the per procedure rate of significant hypotensive adverse events (SHAEs) using the Aurora Xi New Nomogram algorithm is less than double the SHAE rate under the Aurora Xi Optimized Nomogram algorithm. This is a multi-center randomized controlled trial in which plasma donors at three centers will be recruited and randomized in a 1:1 ratio to use the Aurora Xi New Nomogram algorithm or the Aurora Xi Optimized Nomogram algorithm.

Standard summary statistics (e.g., count, mean, standard deviation, minimum, median, and maximum values) will be reported for subject and procedure parameters.

One secondary objective is to demonstrate that the per procedure rate of severe hypotensive adverse events (IQPP DAE Classification 1.5 or 1.6) under the Aurora Xi New Nomogram algorithm is non-inferior to the per procedure severe hypotensive adverse event rate using the Aurora Xi Optimized Nomogram algorithm. Analyses will be carried out as in the primary analysis with this binary donation-specific response, log-link, identity variance function, and working independence assumption. A robust variance estimate will be used for inference to provide protection against a within-donor association in responses of successive procedures within clusters defined by donor identifying numbers.

The Statistical Analysis Plan will expand on the data analysis to be conducted for the remaining endpoints.

12.2 Determination of Sample Size

The sample size requirement is calculated based on a model for correlated binary data in which the marginal mean is modelled with a log-link function and set by

$$log\ \mu_{ij} = \beta_0 + \beta_1 X_i$$

where X_i= 1 for an individual assigned to the experimental arm and X_i= 0 otherwise. Note that center is not controlled for in the sample size calculation. Controlling for center is anticipated to improve power by explaining variation in the response, so this is a conservative approach to estimating the sample size since the power is anticipated to be at least the desired power. For the sample size derivation, the fitted model uses the identity variance function and a working independence assumption with a robust variance derived from a joint model to account for the association in the responses from serial donations from the same donor. The calculations require specification of the mean $\mu_x = E(Y_{ij}|X_i = x)$ and the variance $V_x = \text{var}(Y_{ij}|X_i = x)$ of the response Y_{ij} to procedure j from donor i as well as the within-donor correlation. If κ_x and μ_x is the mean and variance for the number of procedures for a donor in arm x and n is the total number of donors to be recruited, then the asymptotic (large sample) variance (*asvar)* of the estimator of the log relative rate satisfies

$$asvar\left\{\sqrt{n}\left(\hat{\beta}_1 - \beta_1\right)\right\} \simeq \frac{2V_0}{\kappa_0\mu_0^2}\left(1 + \frac{\delta_0\rho}{\kappa_0}\right) + \frac{2V_1}{\kappa_1\mu_1^2}\left(1 + \frac{\delta_1\rho}{\kappa_1}\right)$$

where $\delta_x = v_x + \kappa_x^2 - \kappa_x$ and ρ is the within-donor correlation in the responses over successive procedures from the same donor. The sample size involves computation of an asymptotic robust variance estimate for the estimator based on a multivariate binary probability mass function with specified marginal event rates of SHAE for the Test and Control arms and a specified exchangeable correlation for responses over successive procedures within the same donor, using the conditional linear family (Preisser and Qaqish, 2014) of multivariate binary models. In addition to the response model, a zero-truncated negative binomial model is used for the number of donation procedures over time from each donor which accommodates between-donor heterogeneity in the procedure rate. The number of required donors is computed based on the constraint

$$P\left(\hat{\beta}_1 + 1.96\sqrt{asvar_A\left(\hat{\beta}_1\right)} < \beta_{1M} | \beta_1 = \beta_{1A}\right) = 0.80$$

which ensures that the probability that the upper limit of a two-sided 95% confidence interval for the relative risk is below $RR_M = \exp(\beta_{1M}) = 2$ with 80% power if the true log relative rate is determined by β_{1A}. Based on historical data, the event rate in the control arm is expected to be 0.221% thus setting $p_C = 0.00221$ or equivalently $\log \mu_0 = \beta_0 = \log(0.00221)$. The margin of non-inferiority is specified as $\exp(\beta_{1M}) = 2$. To accommodate a slight elevation in the SHAE rate under the alternative hypothesis of non-inferiority, the sample size calculations will be carried out with $\exp(\beta_{1A}) = 1.2$, corresponding to a 20% relative increase in the SHAE rate (still within the region of non-inferiority). Accommodating a slight increase helps ensure that the power objectives are met to demonstrate non-inferiority even if there is a 20% relative increase in the SHAE rate using the Aurora Xi New Nomogram. In order to achieve 80% power when $\exp(\beta_{1A})$ equals 1.2,

when donations are taken over an 8-week follow-up period, a sample size of n = 11,519 donors may be required. The total number of procedures across all trial participants of $n \times \kappa$ will target 51,720 for the primary endpoint evaluation.

12.3 Analysis Data Sets

The study endpoints include the primary and secondary objectives. The Intent-to-Treat Analysis (All Subjects Enrolled) will consist of individuals who signed an informed consent form, were randomized, and had at least one procedure initiated during the study. Outcomes for all procedures will be analyzed and responses attributed to the arm to which donors were randomized. The Per-Protocol Analysis will restrict attention to procedures in which the device used (Test or Control) matched the arm to which the donor was randomized.

The hypothesis for the primary endpoint for the Intent-to-Treat and Per Protocol analyses is shown as

$$H_0 : RR \geq RR_M \text{ (inferiority)} \quad vs. \quad H_A : RR < RR_M \text{ (non-inferiority)}$$

Summary statistics (mean, standard deviation, median, minimum, maximum and count) will be presented for continuous parameters with their 95% confidence limits as applicable. Discrete parameters will be presented by total number and percentage. Summary statistics will be presented for continuous parameters or descriptive statistics for discrete parameters.

12.4 Analyses

Standard summary statistics (e.g., number, mean, standard deviation, minimum, median, and maximum values) will be reported for subject and procedure parameters. Analyses will be performed to evaluate the primary objective to demonstrate that the per procedure rate of significant hypotensive adverse events (SHAEs) using the Aurora Xi New Nomogram algorithm is less than double the rate of SHAE rate under the Aurora Xi Optimized Nomogram algorithm in Section 12.2.

Additional analysis will be performed to demonstrate that the per procedure rate of severe hypotensive adverse events (IQPP DAE Classification 1.5 or 1.6) under the Aurora Xi New Nomogram algorithm is non-inferior to the per procedure severe hypotensive adverse event rate using the Aurora Xi Optimized Nomogram algorithm. Analyses will be carried out as in the primary analysis with this binary procedure-specific response, log-link, identity variance function, and working independence assumption. A robust variance estimate will be used for inference to provide protection against a within-donor association in responses of successive procedures with clusters defined by donor identifying numbers. The same non-inferiority margin will be used as for the primary response.

A detailed statistical procedure will be outlined in the Statistical Analysis Plan for the other secondary endpoints.

12.4.1 Efficacy Analysis

There are no Efficacy Analysis planned as the purpose of this study is to demonstrate safety. A variety of secondary analyses (described in Section 3.2) will be carried out to assess the effectiveness of the Test procedure for the collection of greater volume, etc.

12.4.2 Additional Analyses

Once the minimum number of procedures has been achieved for the primary endpoint analysis, a review of the data will occur. The primary endpoint will be evaluated based on the population/procedures up to this point. If this analysis demonstrates non-inferiority of the Test arm relative to the Control (i.e., the primary objective), then a specific analysis of subgroup sample sizes will be conducted. If any subgroup targets have not been achieved, the sites will be asked to specifically enroll and collect procedures from the target subgroup(s) only, until the subgroups in question meet their target minimum number of procedures. Each participant can donate for up to 8 weeks. The subgroup analysis will be conducted once a sufficient number of procedures for each subgroup is recorded. The primary endpoint will not be re-evaluated with the additional collections performed during this target enrollment and donation period to ensure that the primary analyses are based on a representative sample of donors and procedures.

12.5 Roll-in Procedures

Upon completion of the Roll-in procedures at each site (minimum of 150 procedures at each clinical site), summary statistics of Adverse Events (category and sub-category) will be evaluated by the DSMB. The summary statistics listing will have the randomization category, device serial number, device software version, collection volume at time of adverse event, total plasma volume and total collection volume fields hidden from reviewers. If deemed acceptable, the study enrollment will remain unaffected and will continue. Roll-in procedures will be included in the evaluable population. Enrollment will not be paused during the safety evaluation.

12.6 Data Safety Monitoring Board Review

A Data Safety Monitoring Board (DSMB) may conduct one or more safety analyses based on the Criteria for DSMB Review (Section 12.10) to review safety-related data. All members of the DSMB will be external to Fresenius Kabi. The DSMB will meet as required and will monitor the safety of the trial, according to the DSMB charter.

The Criteria for DSMB Review will be shared with the DSMB, which will determine, based on these or alternative criteria that they may independently develop, the safety of continuing with the study. This evaluation will be based on a comprehensive review of the available safety information as the clinical trial progresses. The DSMB may have access to additional information in its review, e.g., from a requested unblinded data review, that may allow them to come to a more informed decision. Their independent assessment will be shared with the sponsor team.

The DSMB will also review data related to the Criteria for DSMB Review, as defined in section 12.10. The DSMB will determine if it is safe to continue the trial or will decide to terminate the study. This decision is binding for the sponsor.

12.7 Subject Disposition

Subject disposition and reasons for study procedure/drug discontinuation will be summarized for inclusion in the final report.

12.8 Subject Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be collected and summarized for inclusion in the final report.

12.9 Protocol Deviations

A protocol deviation is defined as any change or alteration from the procedure stated in the study plan, consent form or clinical trial materials that were originally provided by the sponsor and approved by the IRB.

All protocol deviations must be reported to Fresenius Kabi through the TrackWise System data files. All deviations, regardless of whether medically justifiable (e.g., the subject's safety), shall be reported. In addition, the qualified healthcare professional is required to adhere to the IRB's reporting requirements for protocol deviations.

Qualified healthcare professionals are required to maintain accurate, complete and current records, including documentation showing the dates of, and reasons for, each deviation from the protocol. Failure to comply with the protocol may result in qualified healthcare professional termination of participation in the clinical trial.

12.10 Criteria for DSMB Review

In addition to safety monitoring after the roll-in procedures, the following criteria for DSMB review will apply for possible study termination due to safety concerns:

<u>Rule 1: Subject Death</u>

If at any time during the study there are:

- One or more subject deaths reported.

<u>Rule 2: Occurrence of Severe Hypotensive Events</u>

If at any point in the first 50% of planned procedures, there are:

- 6 or more severe hypotensive events [1.5 (Hypotensive; Severe (With or Without LOC)) or 1.6 (Hypotensive; Injury)] of the IQPP definition.

Within 24 hours of sponsor notification, the DSMB will be notified of the event(s) and perform an unblinded review of the event(s). If the event(s) is determined to be related to

the Investigational Product and affects the safety profile, the study will be put on hold and the information will be transmitted to the FDA immediately.

If the event(s) is determined not to be related to the Investigational Product and has no effect on the safety profile, the study may continue and all DSMB documentation of the event(s) and decision will be immediately transmitted to the FDA for further review.

12.11 Stopping Rules

After the primary endpoint evaluation period, the extension period, if needed, will end at the discretion of the sponsor, when a sufficient sampling of each high-risk subgroup has been achieved. Due to potential difficulty recruiting participants from each high-risk subgroup, the sponsor reserves the option to stop the study prior to or at any time during this optional extension period.

- If the primary endpoint fails, then the extension phase will not occur.
- If enrollment during the extension period for any of the subgroups is not sufficient to complete the study in a reasonable time period (up to 3 months), then the extension period could be stopped at the discretion of the sponsor.

13 ADMINISTRATIVE RULES

13.1 Investigators' Responsibilities

The study will be conducted in a manner designed to assure the acceptability of the data by regulatory authorities. All Investigators, Sub-investigators, and DSMB members are required to complete a Disclosure of Financial Interest supplied by the Sponsor. This section contains a summary of Investigator responsibilities that will help ensure the study is performed in compliance with regulations. Specific mechanisms and procedures are described to maintain the compliance of both the Investigator and the Sponsor.

The PI may delegate tasks to qualified members of the investigation site team but retains responsibility for the clinical investigation. This also applies when activities are outsourced to an external organization by the Principal Investigator, in which case he/she shall implement procedures to ensure the integrity of all tasks performed and any data generated by this external organization.

Certain events in the performance of the study require particular reports from the Investigator within prescribed time frames. A summary of the required Investigators' reports follows:

Table 44. Required Reports from Investigator

Report	Submit To	Time
Withdrawal of IRB approval 21 CFR 812.150(a)(2)	Sponsor	Within 5 working days
Progress Report(s) 21 CFR 812.150(a)(3)	Sponsor, Monitor, IRB	Regular intervals (at least yearly)

Report	Submit To	Time
Deviation from protocol 21 CFR 812.150(a)(4)	Sponsor, IRB	ASAP but no later than 5 working days
Failure to obtain informed consent 21 CFR 812.105(a)(5)	Sponsor, IRB	Within 5 working days
Final Report (Completed Case Report Forms constitute a Final Report from Investigator) 21 CFR 812.150(a)(6)	Sponsor, IRB	Within 3 months after termination
Both Serious and Unanticipated Adverse Device Effects 21 CFR 812.150(a)(1)	Sponsor	ASAP (within 24 hours) by telephone, facsimile or email
	IRB	ASAP, but in no event later than 10 working days after the investigator first learns of the effect.

Note: Requirements for Investigator-required reports may vary, depending on local regulatory requirements.

13.1.1 Confidentiality

The Investigator and his/her staff will agree to treat all aspects of the study in a confidential manner. All documents and data pertaining to the study can only be released with the consent of the Sponsor or as required by federal or state law or authorized regulatory agencies. Each Investigator agrees to permit review of all pertinent data by the Sponsor or its agents as well as representatives of the US FDA or other appropriate regulatory agencies during and/or following performance of the study.

13.1.2 Protocol Modifications

All protocol revisions must be issued by the Sponsor. The investigator will acknowledge the change by signing and dating the Investigator Signature Page. Protocol modifications should not be implemented prior to any required IRB approval, except where necessary to eliminate hazards to subjects when the change(s) involve only logistical or administrative details (example: address or telephone change).

13.1.3 Protocol Deviations

In situations regarding a departure from the protocol, the investigator will contact the appropriate Sponsor representative as soon as possible but no later than 5 working days. Notification to the Sponsor should be made prior to implementing a departure from the protocol, if at all feasible. In all cases, contact with the Sponsor should be made as soon as possible in order to discuss the situation and agree on an appropriate course of action. Protocol deviation(s) will be documented and describe any departure from the protocol and the circumstances that necessitated the departure.

13.1.4 On-Site Audits

The investigator agrees to allow representatives of the sponsor to visit the investigational site to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source

documents, for inspection and comparison with CRFs. Subject privacy will be respected at all times and will be in accordance with any local or country-specific requirements. Sufficient prior notice will be provided by the sponsor to allow the investigator time to prepare for the audit.

The governing IRB may conduct an on-site audit during the course of the study. The investigator should notify the Sponsor if he has been contacted by the IRB regarding an audit.

Similar auditing procedures may be conducted by agents of any regulatory body reviewing the results or procedures of this study. The investigator should immediately notify the Sponsor if they are contacted by a regulatory agency concerning an inspection.

13.1.5 Institutional Review Board

The Investigator will be responsible for obtaining IRB approval for the study and for providing the Federalwide Assurance (FWA) and/or Institutional Review Board Organization (IORG) number(s) to the Sponsor, as appropriate. All study-related plasma facility SOPs and work aids will be submitted to the IRB, as required. After approval of the protocol, informed consent form, and any other adjunctive material (e.g., marketing flyers) by the IRB, the investigator must provide a copy of the IRB approval document to the Sponsor. Copies of these documents are to be maintained at the study site.

The written notification must be signed by the Chairman of the IRB, or his/her designee, and must identify the specific protocol. In cases where an IRB member has a specific conflict of interest, abstention of the individual from the vote should be documented. An investigator or sub-investigator may be a member of the IRB but may not participate in the deliberation or vote on any research in which he/she is involved.

13.1.6 Informed Consent

The ICF will be in accordance with the Declaration of Helsinki, principles of GCP, applicable regulatory requirements, subject privacy requirements and the Sponsor's policies. The ICF must be reviewed by the Sponsor and approved by the IRB.

Each subject must provide signed informed consent according to local requirements, after the nature of the study has been fully explained, in order to participate in the study. The ICF must be signed prior to performance of any study-related activity.

The investigator, or designee, must explain to potential subjects the aims, methods, reasonably anticipated benefits, potential hazards and risks of the study, right to refuse participation and right to withdraw without affecting the subject's medical care. The other elements of the informed consent will be explained, and subjects will be given the opportunity to ask questions. After this explanation, but before entry into the study, consent should be appropriately documented by the subject's dated signature. If a subject is unable to read or requires a translator, an impartial witness must be present during the entire informed consent discussion and process. The signature of the impartial witness will certify

the subject's consent. The subject will be given a signed and dated copy of the informed consent form.

Subjects will not be asked prior to each visit if they want to continue to participate in the study. It will be the subject's responsibility to inform the study staff prior to a procedure if they want to be withdrawn from the study.

13.1.7 Investigational Product(s)

Any investigational product (IP) under evaluation must be kept under strict control and used only as described in the protocol. The Investigator will be asked to ensure that IP(s) is stored and returned/destroyed appropriately and to provide documentation in support of this.

All IP(s) will be labeled according to regulatory requirements. IP(s) must be stored under conditions set forth by the Sponsor in this protocol, on the product label, and/or communicated in writing. The IP(s) must be installed in a segregated area of the BioLife collection centers, which are expected to maintain their standard security protocols and access restrictions throughout the duration of the study. BioLife shall establish site-specific standard operating procedures that instruct staff to only use study devices (Test and Control) for on-study collections.

If an IP(s) fails to perform in the expected manner, the Investigator will notify the Sponsor immediately.

14 REFERENCES

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15 APPENDICES

15.1 Investigator Signature

INVESTIGATOR SIGNATURE PAGE

I have reviewed the Clinical Study Protocol PAND-004-CMD, Evaluation of the Aurora Xi New Nomogram Software 2.0, Version 2.

I have fully discussed the objective of this study and the contents of this protocol with the Sponsor's representatives.

I confirm that I have read and understand this protocol. I agree to conduct this study in accordance with this protocol, the applicable FDA Code of Federal Regulations (21 CFR Parts 50, 54, 56, 640, and 812) and the principles of the World Medical Association Declaration of Helsinki (2013 Version), protection of human subjects in research and the execution of good clinical trials, the privacy regulation of the Health Insurance Portability and Accountability Act of 1996 (45 CFR Parts 160 and 164), any local regulations and with the terms outlined in the Study Agreement.

I will accept the Sponsor's oversight of the study. I have read and understand all related information and guides provided by the Sponsor, as applicable. I will abide by the publication plan set forth in my agreement with Fresenius Kabi and will promptly submit the protocol to the applicable IRB.

Principal Investigator (Print Name)	Signature	Date

Institution

15.2 IQPP Standard for Recording Donor Adverse Events

Embedded PDF	 IQPP_DAERS_V2.pdf
URL	IQPP Standard for Recording Donor Adverse Events