Statistical Analysis and Reporting Plan (SARP)

Endexo-002

A Randomized, Open Label, Cross-over Feasibility Study for Heparin-free Hemodialysis with the Dialyzer with Endexo™ in End-Stage Renal Disease (ESRD) Subjects

Statistical Analysis and Reporting Plan

Version 2.0
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1. STUDY OBJECTIVES

1.1. Primary Objective

The primary objective of the study is to explore the feasibility of heparin-free hemodialysis (HFHD) with two extracorporeal dialysis circuits (A) and (B) in ESRD subjects who are maintained on conventional hemodialysis (HD) with Citrasate dialysate and regularly prescribed heparin. Circuit (A) includes the dialyzer with Endexo and Combiset bloodline; and Circuit (B) includes the dialyzer with Endexo and Streamline bloodline.

1.2. Secondary Objective

The secondary objective is to collect and summarize adverse events with both dialysis circuits.

2. STUDY DESIGN

2.1. General Description

This is a randomized, open-label, cross-over study with subjects on thrice-weekly (in-center) hemodialysis. The study consists of a Screening Period, study Period 1, Washout Period, study Period 2, and a Follow-up Visit.

- **Screening Period:**

  The Screening Period begins with signing of the informed consent form (ICF) and can extend up to 4 weeks in duration. After completing all required tests/procedures and determining/verifying the eligibility, the subject is randomly assigned to one of the circuit sequences, either AB or BA. The randomization is done in the electronic data capture (EDC) system.

  Circuit A consists of the dialyzer with Endexo and CombiSet bloodline and Circuit B consists of the dialyzer with Endexo and Streamline bloodline.

- **Period 1:**

  Period 1 consists of 5 HD sessions (Visits 1 to 5) on the dialyzer with Endexo with the CombiSet bloodline for sequence AB and Streamline bloodline for sequence BA according to the randomization, and different heparin doses shown below:

  Visit 1: 100% of heparin as prescribed

  Visit 2: 50% of heparin as prescribed

  Visits 3, 4, 5: 0% of heparin

  This period lasts for approximately two weeks per subject.

- **Washout Period:**

  The Washout Period occurs between Period 1 and Period 2. It consists of three conventional HD sessions (Visits 6, 7, and 8). This period lasts approximately one week per subject.

- **Period 2:**

  Period 2 consists of 5 HD sessions (Visits 9 to 13) on the dialyzer with Endexo with Streamline bloodline for sequence AB and CombiSet bloodline for sequence BA according to the randomization, and different heparin doses shown below:

  Visit 9: 100% of heparin as prescribed,

  Visit 10: 50% of heparin as prescribed,

  Visits 11, 12, 13: 0% of heparin

- **Follow-up Visit:**

  An in-center Follow-up Visit is to be conducted within 1 week of the subject's last scheduled study HD treatment. This visit cannot be combined with the last study HD visit.

2.2. Method of Assigning Subjects to Treatment Groups

Eligible subjects will be randomly assigned to one of the 2 sequences AB or BA as follows:

	Period 1	**Period 2**
Sequence AB	Circuit (A)	Circuit (B)
Sequence BA	Circuit (B)	Circuit (A)

The study planned to recruit subjects at two sites. To keep the balance, a randomization block of 2 was used. The randomization chart was generated in 10 randomization blocks, a total of 20 subjects for each site. The chart was loaded to Medidata RAVE Randomization and Trial Supply Management (RTSM).

2.3. Blinding

N/A

2.4. Determination of Sample Size

A sample size was not calculated. A total of 12 to 16 subjects with three heparin free HD treatments for each circuit for each subject or 36 to 48 HD sessions per circuit was considered appropriate for a feasibility study.

3. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

3.1. Changes in the Conduct of the Study

Concurring with FDA's comments/suggestions, the withdrawal criteria when clotting score (CS) = 4 in a HD treatment are as follows:

- If CS=4 in dialyzer, the subject will be withdrawn from the study
- If CS=4 in circuit A bloodline (CombiSet), Period 1, the subject will proceed to washout
- If CS=4 in circuit A bloodline (CombiSet), Period 2, the subject will be withdrawn from the study, and
- If CS=4 in circuit B bloodline (Streamline) in any period, the subject will be withdrawn from the study.

3.2. Changes in the Planned Analyses

Concurring with FDA's comments/suggestions, the secondary endpoint of adverse events, and device-related adverse events, became the primary safety endpoint.

4. EFFICACY AND SAFETY ENDPOINTS

4.1 Primary Endpoint

The primary endpoint is the number and percent (%) of successful heparin-free HD sessions for each subject in each circuit. A successful HD session must meet all the following criteria:

1. Absence of complete HD circuit occlusion (Grade 4) rendering dialysis impossible
2. Absence of the need to replace dialyzers or bloodlines due to clotting
3. Absence of saline flushes to maintain blood flow through the circuit during the HD session
4. Absence of any additional heparin beyond what is allowed per study visits
5. Single pool Kt/V (spKt/V) ≥ 1.2

4.2 Primary Safety Endpoint

The primary safety endpoint includes adverse events and device-related adverse events.

4.3 Additional Assessments

The following data will be collected on the dialyzer with Endexo during Periods 1 and 2:

- Number and percentage (%) of dialyzers and blood lines for each clotting grade using the visual inspection clotting grade scale
- HD treatment duration or time to complete circuit occlusion (Grade 4)
- Blood volume processed per dialysis session
- The volume, the time of saline administered, and the reason for administration per subject per HD session (other than for circuit priming or rinse back)
- Urea Reduction Ratio (URR) and spKt/V for all HD sessions

5. STATISTICAL METHODS

5.1 General Methodology

There are multiple observations of one measurement for each subject in each period. Unless specified, all analyses will be performed at the subject level, i.e., take average of multiple observations first of the measurement for each subject then analyze/summarize on subject averages.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for continuous endpoints. Frequency and percent will be presented for categorical endpoints. Any missing values of an endpoint will not be imputed. All data entered and collected will be listed.

5.2 Analysis Methods for Endpoints

If adequate, 95% confidence interval will be calculated for each dialysis circuits (A) and (B). For comparisons, if adequate, paired-t tests may be performed between dialysis circuits (A) and (B) for continuous endpoints, McNemar's tests may be employed for categorical endpoints.

For 0% heparin, the average of a continuous endpoint from multiple HD treatments will be calculated for each subject, then descriptive statistics will be summarized at subject level.

For β_2-microglobulin, the laboratory results for post dialysis will be corrected for ultrafiltration using the formula in Bergström and Wehle (1987).

$$\text{Corrected value} = \frac{\text{Uncorrected value}}{1 + \Delta W/(0.2PW)},$$

where ΔW = pre-dialysis weight – post dialysis weight, PW is the post dialysis weight.

5.3 Analysis Populations

- **Safety Population (SPOP):** The SPOP includes subjects who signed the ICF, met inclusion criteria, did not meet any exclusion criteria, were enrolled and randomized in the study.
- **Analysis population (APOP):** The APOP includes subjects who are in the SPOP and have at least one heparin reduction HD treatment in the study.

5.4 Adjustments for Covariates

N/A

5.5 Handling of Dropouts or Missing Data

Any missing values at dialysis treatment level of an endpoint will not be imputed.

If a subject missed a HD treatment but was able to have an unplanned HD treatment with the same requirements, the results from the unplanned HD treatment will replace the missed one.

5.6 Interim Analyses

No interim analysis is planned.

5.7 Multicenter Studies

One to two study sites were planned as stated in the protocol. One site enrolled subjects for the study.

5.8 Multiple Comparisons/Multiplicity

N/A

5.9 Use of an "Efficacy Subset" of Subjects

N/A

5.10 Active-Control Studies Intended to Show Equivalence/Non-inferiority

N/A

5.11 Examination of Subgroups

Due to small numbers of subjects in the study, subgroup analyses were not performed.

6 STATISTICAL ANALYSES

6.1 Patient Disposition

The subject disposition table will include the items below:

- The number of subjects who signed the informed consent and were screened.
- The number of subjects who failed screening with reasons.
- The number of subjects who were eligible.
- The number of subjects who were randomized.
- The numbers of subjects who completed the following stages: Period 1, Washout, Period 2, and end of study.
- The number of subjects and percent by category of major reasons for early discontinuation.
- The numbers of subjects in the safety and in the analysis populations.

Subject inclusion in the different analysis sets will be listed for all subjects. Subject disposition data will be presented in a listing for all subjects.

6.2 Protocol Deviations

Any protocol deviation will be listed. Summaries by category of protocol deviations will be presented if the number of protocol deviations is sufficiently large.

6.3 Demographic and Other Baseline Characteristics

- Demographic characteristics: descriptive statistics will be presented for age, frequency, and percent will be presented for sex, race, and ethnicity.
- Dialysis history: frequency, and percent of primary cause of ESRD, and current vascular access will be presented. In addition, descriptive statistics for dialysis vintage will be presented.
- Medical history: all medical history and non-pharmacological treatment/therapies recorded will be listed for each subject.
- Initial HD prescriptions and any prescription changes other than heparin dose and bloodline will be listed for each subject.

6.4 Concomitant Medications/Therapies

Concomitant medications will be listed.

Medications used for hemodialysis or during dialysis treatments will be summarized and listed separately for concomitant medications.

6.5 Treatment Compliance

N/A

6.6 Analysis of Primary Endpoint

The frequency for subjects with possible successful heparin-free sessions (0, 1, 2, or 3) will be displayed for each circuit. The descriptive statistics of subject's percent of successful heparin-free sessions will be presented for each dialysis circuits (A) and (B).

6.7 Analysis of Primary Safety Endpoint

Adverse events will be coded for system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA), Version 23.1. For all AEs and device related AEs, the number and percent of subjects with at least one occurrence, and the number of all occurrences under one preferred term, as well as under one system organ class, will be presented by circuit and % heparin.

6.8 Analysis of Additional Assessments

These additional assessments will be analyzed under the analysis population.

- Distributions of clotting scores by circuit, by % heparin will be presented for dialyzer arterial end cap, venous end cap, venous chamber for each bloodline, arterial chamber for Combiset, and arterial pod and venous pod for Streamline.
- For HD delivered, arterial pressure, venous pressure, blood flow rate, dialysate flow rate, HD treatment duration, mean KECN, ultrafiltration volume, and blood volume process, descriptive statistics will be presented by circuit, and % heparin.
- For β_2-microglobulin, the removal rate {((pre-HD – post-HD)/pre-HD) x 100} will be calculated. Descriptive statistics will be presented by circuit, and % heparin for the pre-HD, post-HD and corrected post-HD β_2-microglobulin concentrations, as well as removal rates from post-HD and corrected post-HD.
- For total volume of saline administered, descriptive statistics will be presented by circuit, and % heparin. Total volume for treating clotting, total volume for treating intradialytic symptoms, and total volume for medication delivery will be presented in the same manner. In addition, the total number of saline flushes and the total number of HD sessions received by subjects will be presented by circuit and % heparin for treating clotting, treating intradialytic symptoms, and for medication delivery.

- For URR and spKt/V, descriptive statistics will be presented by circuit, and % heparin.

6.9 Analysis of Safety

All safety measurements will be analyzed under the safety population.

6.9.1 Adverse Events

See Section 6.7.

6.9.2 Clinical Laboratory Evaluation

Descriptive statistics for each test, and changes (absolute and relative from post-HD to pre-HD will be presented by circuit and % heparin for hematology and for serum chemistry. In addition, descriptive statistics of changes of pre-HD of 50% heparin session and pre-HD of all 0% heparin sessions from baseline, which is defined as the pre-HD tests of 100% heparin session, will be presented.

6.9.3 Vital Signs

Descriptive statistics for vital signs at screening and follow up will be presented. Descriptive statistics for pre-HD, post-HD vital signs, and changes will be presented by circuit and % heparin.

6.9.4 Physical Findings, and Other Observations Related to Safety

Physical examinations at screening and follow-up will be listed.

7 REFERENCES

Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. J Am Soc Nephrol. 1993 Nov; 4(5:1205-13.

Bergström J, Wehle B. No change in corrected β_2-microglobulin concentration after cuprophane hemodialysis. Lancet. 1987 Mar 14; 1(8533):628-9.