Statistical Analysis and Reporting Plan (SARP)

Endexo-001

An Open-label clinical study to assess the performance of the dialyzer with Endexo™ in End-Stage Renal Disease Subjects

NCT03536663

Statistical Analysis and Reporting Plan

8/5/2019

1. STUDY OBJECTIVES

1.1. Primary Objective

The primary objective of the study is to collect data on the performance of the dialyzer with Endexo when used to perform hemodialysis (HD) in end stage renal disease (ESRD) subjects.

1.2. Secondary Objective

The secondary objective is to collect and summarize adverse events with the dialyzer with Endexo when used to perform HD in ESRD subjects.

2. STUDY DESIGN

2.1. General Description

This is a prospective, sequential, multi-center, open-label study with subjects on thrice-weekly (in-center) hemodialysis treatment.

Each subject will participate in a screening period, Optiflux period, Endexo period, and a follow-up visit.

- Screening Period
  Screening, which will be up to 4 weeks in duration, begins with signing of the informed consent form (ICF). After the Screening Period is completed (with eligibility verified), the subject is enrolled and can proceed to the Optiflux Period.

- Optiflux period
  The Optiflux Period is 12 HD treatments (visits 1 to 12) on the Optiflux dialyzer (4 weeks in duration)). A maximum of two missed treatments are permitted within visits 2 to 11. The visit 12 cannot be missed during the Optiflux period.

- Endexo period
  The Endexo period is 38 HD treatments on the dialyzer with Endexo (approximately 13 weeks in duration). The visit 13 cannot be missed. A maximum of four missed treatments are permitted within Visits 14-50.

- Follow-up visit
  An in-center Follow-up visit is to be conducted within 1 week of the last scheduled study HD treatment.

2.2. Discussion of Study Design, Including the Choice of Control Groups

The design is based on FDA's Guidance for Industry and CDRH Reviewers: *Guidance for the Content of Premarket Notifications for Conventional and High Permeability Hemodialyzer* (August 7, 1998). A period of 4 weeks using Optiflux, which was prescribed currently, are added in prior to the use of the test product. The measurements in Optiflux period for each subject can serve as the control for comparisons as needed.

2.3. Method of Assigning Subjects to Treatment Groups

N/A

2.4. Blinding

N/A

2.5. Determination of Sample Size

The sample size of 15-24 subjects is based on FDA's Guidance for Industry and CDRH Reviewers: *Guidance for the Content of Premarket Notifications for Conventional and High Permeability Hemodialyzer* (August 7, 1998), which recommends that data be collected for a minimum of 12 subjects receiving 36 treatments each.

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

3.1. Changes in the Conduct of the Study

Protocol amendment 2:

- Added in the time of administration and reason for saline flush, and
- Collected TMP and UFR at 15 minutes (±5 minutes) after the recorded start of HD during visits 24, 27 and 30.

3.2. Changes in the Planned Analyses

- Additional listing for reasons of saline flush. The percent of using saline to treat clotting or clotting related will be calculated if applicable.
- Additional K_{uf} will be calculated and summarized for visits 24, 27 and 30.

4. EFFICACY AND SAFETY ENDPOINTS

4.1. Primary Endpoint(s)

The primary endpoint is to collect data on the *in vivo* K_{uf} of the dialyzer with Endexo during the first use at 15 minutes (±5 minutes) after the recorded start of HD. K_{uf} can be derived from the Ultrafiltration Rate and the Transmembrane Pressure (TMP) as follows:

K_{uf} (mL/hr/mmHg) = UF Rate (mL/hr) / TMP (mmHg)

4.2. Secondary Endpoint(s)

The secondary endpoints include collecting the following data on the dialyzer with Endexo and the Optiflux dialyzer:

- The number of any adverse events and device-related adverse events.
- Urea Reduction Ratio (URR) and spKt/V (calculated from pre- and post-dialysis BUN) for the first study use of the dialyzers
- Pre- and post-HD serum albumin and β_2-microglobulin for the first use of dialyzers, visit 1 for Optiflux and visit 13 for dialyzer with Endexo.

4.3. Additional Assessments

The following data will be collected on the dialyzer with Endexo and the Optiflux dialyzer.

- Complement activation (C3a, C5a, SC5b-9) during the first study use of the dialyzer, collected pre-HD and at 30 minutes (±10 minutes) after the recorded start of HD,
- Thrombus scoring, performed at the end of dialyzer use for every dialyzer used in the study,
- Urea Reduction Ratio (URR) and spKt/V every 3-4 weeks,
- Total volume (mL) of saline flush for each treatment, frequency and rate per HD treatment when using to treat clotting during HD.

5. STATISTICAL METHODS

5.1. General Methodology

There are multiple observations of one measurement for each subject in each period. 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 collected will be listed.

5.2. Analysis Methods for Endpoints

If adequate, 95% confidence interval will be calculated for each period (Optiflux or Endexo). For comparisons, if adequate, paired-t tests may be performed between periods (Optiflux vs. Endexo) for continuous endpoints, McNemar's tests may be employed for categorical endpoints.

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. Adjustments for Covariates

N/A

5.4. Handling of Dropouts or Missing Data

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

5.5. Interim Analyses

No interim analysis is planned.

5.6. Multicenter Studies

This is a multi-centers study. Due the similarity of hemodialysis treatments among the dialysis clinics, the center effect will not be considered in this study.

5.7. Multiple Comparisons/Multiplicity

N/A

5.8. Use of an "Efficacy Subset" of Subjects

N/A

5.9. Active-Control Studies Intended to Show Equivalence/Non-inferiority

N/A

5.10. Examination of Subgroups

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

6. STATISTICAL ANALYSES

6.1. Disposition of Subjects

Frequencies will be for overall, by center, and for the treatment period.

The subject disposition table will include:

- The number of subjects who signed the informed consent.
- The number of subjects with screen failure.
- The number of subjects who were eligible.
- The number of subjects who were enrolled.
- The number of subjects who were discontinued in Optiflux, or in Endexo periods.
- The numbers of safety and analysis populations.
- The number of subjects and percent by category of major reasons for early discontinuation.

6.2. Protocol Deviations

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

6.3. Analysis Populations

- **Safety Population (spop):** The spop (safety population) will include subjects who sign the ICF, are eligible, are enrolled in the study, and have at least one HD treatment with the dialyzer with Endexo.

- **Analysis population (apop):** The apop (analysis population) will include subjects who are in the spop, and have a minimum of 36 HD treatments with the dialyzer with Endexo.

6.4. Demographic and Other Baseline Characteristics

- Demographics, 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 will be presented.
- Medical history, all medical history recorded will be listed for each subject.

- Physical examinations, all recorded systems examined at the screening and follow-up will be listed.
- Vital signs, descriptive statistics will be presented for vitals recorded in the screening and follow-up.
- Initial prescriptions, the prescription will be listed for each subject.

6.5. Compliance

N/A

6.6. Analysis of Primary Endpoint

Descriptive statistics for ultrafiltration rate, TMP and ultrafiltration coefficient K_{uf} of the first study use (visit 13) of the dialyzer with Endexo will be presented under analysis population. A 95% confidence interval will be calculated if appropriate. These measurements observed/calculated for other timepoints (visits 24, 27 and 30) will be also presented with descriptive statistics.

6.7. Analysis of Secondary Endpoints

All secondary endpoints will be analyzed under the analysis population.

For URR and spKt/V for the first study use of both dialyzers, descriptive statistics will be presented, and 95% confidence intervals will be calculated if appropriate. These measurements observed/calculated for other timepoints (every 3-4 weeks) will be also presented with descriptive statistics.

For serum albumin and β_2-microglobulin, the relative percent change {((pre-HD – post-HD)/pre-HD) x 100} will be calculated. Descriptive statistics will be presented for the pre-HD and post-HD laboratory values and the relative percent change. Percent changes will also be calculated using corrected β_2-microglobulin concentrations based on the equation published by Bergström and Wehle. The 95% confidence interval will be derived if appropriate.

Adverse events will be coded for system organ class (SOC) and preferred term using Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. Adverse events and device-related events per treatment will be calculated. The 95% confidence intervals will be derived if appropriate.

6.8. Analysis of Exploratory Assessments

All exploratory assessments will be analyzed under analysis population.

For the measurements of complement activation, the relative percent change {((30 minutes after the recorded start of HD – pre-HD)/pre-dialysis) x 100} will be calculated. Descriptive statistics

will be presented for the "pre-dialysis" and "30 minutes after the recorded start of HD" laboratory values and the relative percent change. The 95% confidence intervals will be calculated if appropriate.

For thrombus formation:

- the number of subjects and percentages, and the number of dialysis treatments in each period for each grade category will be presented, and,
- the proportion of treatments with full dialyzer clotting will be calculated for each subject in each period. Descriptive statistics of the proportions will be presented. A 95% confidence interval of the proportions will be calculated if appropriate.

6.9. Analysis of Safety

All safety measurements will be analyzed under safety population

6.9.1 Adverse Events

See Section 6.7.

6.9.2 Clinical Laboratory Evaluation

Descriptive statistics will be presented for reach test and timepoint required by the protocol. Changes between test results from pre-dialysis and post dialysis will also be presented for blood samples collected pre- and post-dialysis.

6.9.3 Vital Signs

Descriptive statistics will be presented for timepoints required by the protocol. Changes between blood pressure (systolic and diastolic) from pre-dialysis and post dialysis will also be presented.

6.9.4 Physical Findings, and Other Observations Related to Safety

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

6.9.5 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.

7. REFERENCES

FDA Guidance for Industry and CDRH Reviewers (1998), Guidance for the Content of Premarket Notifications for Conventional and High Permeability Hemodialyzer.

Daugirdas JT: Second generation logarithmic estimates of single-pool variable volume Kt/V: An analysis of error. J Am Soc Nephrol. 4:1205-1213, 1993.

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