Statistical Analysis Plan

A randomized, controlled, open-label, parallel, multicenter study in kidney failure patients on hemodialysis comparing the Theranova Dialyzer to hemodiafiltration

Author: [redacted]

Version Number and Date: V1.0, 28Jun2022

Statistical Analysis Plan Signature Page

Statistical Analysis Plan V1.0(**28Jun2022**) for Protocol BXU561424.

	Name	Signature	Date
Author:	[redacted]		2022-07-08
Position:	[redacted]		
Company:			

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	[redacted]	[redacted]	08 July 2022 | 04:23:15 CDT
Position:	[redacted]		
Company:	Baxter Medical Products Trading [redacted]		
Approved By:	[redacted]	[redacted]	11 July 2022 | 02:48:39 CDT
Position:	[redacted]		
Company:	Baxter Medical Products Trading [redacted]		
Approved By:	[redacted]	[redacted]	08 July 2022 | 08:10:24 CDT
Position:	[redacted]		
Company:	Baxter Medical Products Trading [redacted]		

Modification History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	28Jun2022	[redacted]	Not Applicable – First Version

1 Introduction

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol **BXU561424**. It describes the data to be summarized and analysed, including specifics of statistical analyses to be performed.

This statistical analysis plan (SAP) is based on Protocol **BXU561424**, V1.0, Amendment 1, dated 01-December-2021.

2 Study Objectives

2.1 Primary Objective

To demonstrate non-inferiority of the Theranova 400 Dialyzer in hemodialysis (HD) mode (hereinafter referred to as Theranova 400) compared to hemodiafiltration (HDF), using FX 800 in HDF mode (hereinafter referred to as FX 800 HDF), in regard to the reduction ratio (RR) of lambda free light chains (λ FLC), and Beta-2 microglobulin (β2-MG) at the mid-week treatment day dialysis session.

2.2 Secondary Objective

- To evaluate Theranova 400 compared to FX 800 in regard to assessments of Kt/Vurea, Urea Reduction Ratio (URR) at the mid-week treatment day dialysis session.
- To evaluate the RRs of α1-microglobulin (α1-MG), Chitinase-3-like protein 1 (YKL-40), complement factor D (CFD), myoglobin and kappa free light chains (κ FLC) at the mid-week treatment day dialysis session.

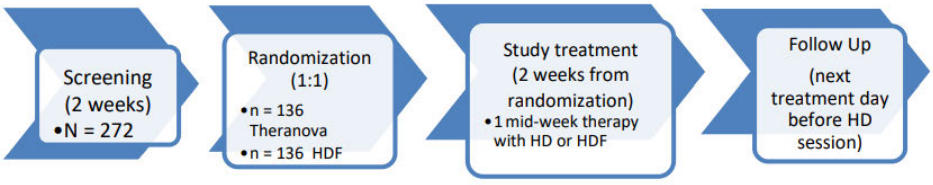
3 Study Design

3.1 General Description

A randomized, controlled, open-label, parallel, multicenter study.
The study population consists of patients with kidney failure on a stable HD and/or HDF prescription. A sufficient number of patients will be enrolled to ensure 272 patients are randomized 1:1 to either Theranova 400 (136 patients) or FX 800 (136 patients). All patients will receive one (1) session of mid-week therapy with either Theranova 400 or FX 800. A follow-up session is scheduled at the next treatment (end-week) session, but prior to

treatment commencement (See Figure 1).

Figure 1: Clinical Trial Design Flow



3.2 Sample Size Calculation

3.2.1 Total Sample Size

The goal of this study is to demonstrate non-inferiority of Theranova 400 compared to FX 800 in the 2 primary endpoints and the non-inferiority margins selected are considered clinically acceptable. The sample size calculation is performed using PASS procedure Mann-Whitney U or Wilcoxon Rank-Sum Tests for Non-Inferiority. A separate sample size calculation is performed for both primary endpoints using a specified non-inferiority margin of 10% and a one-sided alpha level of 0.025, where the true difference in means is assumed to be zero (0).

3.2.2 Sample Size Calculation In Regard To λ FLC Reduction Ratio

A previously conducted Theranova HDF study [1] was used to obtain λ FLC RR mean and standard deviation (SD) of 37.83 and 8.26; a higher estimate for SD of 9.09 is used by adding an additional +10% error to calculate sample size to account for a potential increase in variability. Based on a 1:1 randomization, with a sample size of 129 patients in the Theranova 400 group and 129 patients in the FX 800 group (total N = 258), a Wilcoxon Rank-Sum test with a 0.025 one-sided significance level will have 90% power to demonstrate non-inferiority of the Theranova 400 Dialyzer compared to the FX 800 Dialyzer as assessed by λ FLC RR with a non-inferiority margin of 10% (i.e. 3.783).

3.2.3 Sample Size Calculation In Regard To ß2-MG Reduction Ratio

A previously conducted Theranova HDF study [1] was used to obtain ß2-MG RR mean and SD of 78.48 and 6.75; a higher estimate for SD of 14.28 is used to calculate sample size to

account for a potential increase in variability based on a literature review of studies conducted in China. Based on a 1:1 randomization, with a sample size of 75 patients in the Theranova 400 group and 75 patients in the FX 800 group (total N = 150), a Wilcoxon Rank-Sum test α with a 0.025 one-sided significance level will have 90% power to demonstrate non-inferiority of the Theranova 400 Dialyzer compared to the FX 800 Dialyzer as assessed by β2-MG RR with a non-inferiority margin of 10% (i.e. 7.848).

3.2.4 Sample Size For This Study

Consequently, in order to demonstrate non-inferiority between Theranova 400 and FX 800 in both primary endpoints, a sample size of 129 patients in the Theranova 400 group and 129 patients in the FX800 group is required to guarantee 90% power for the analysis of λ FLC and > 90% power for the analyses of ß2-MG. To allow for 5% of patients to drop out or be excluded from the Per-protocol population as a result of patient classification, a total of 272 patients will be randomized 1:1 to treatment with the Theranova 400 Dialyzer (136 patients) or treatment with the FX 800 Dialyzer (136 patients).

3.3 Schedule Of Activities

Schedule of activities can be found in Figure 2 in the protocol.

4 Changes to Analysis from Protocol

1. In protocol, continuous and categorical demographic and baseline characteristics will be summarized by treatment groups. A t-test or Wilcoxon Rank-Sum test, as applicable, will be used to assess differences between treatment groups in continuous variables and Fisher's exact test will be used to assess differences between treatment groups in categorical variables. Considering this study is a randomnized study, patients will be randomly assigned to the different treatment groups. The baseline characteristics will be balanced between different treatment groups. As a result, statisitcal tests will not be used to assess differences between treatment groups in SAP.
2. In protocol, a sensitivity analysis was to be performed for the primary efficacy endpoints using the full analysis set (FAS), after utilize last observation carried forward (LOCF) to impute the missing values of the λ FLC and β2-MG RRs. The primary endpoint is the reduction ratio, and there are only 2 measurements being taken per patient. If LOCF was applied, then the reduction ratio = 0.The imputed result will be favorabily bias towards

non-inferiority. Therefore, LOCF will no longer be used and multiple imputation (missing at random) and tipping point approaches (missing not at random) will be utilized to explore the robustness of analysis result for missing data.

5 Planned Analyses

The following analyses will be performed for this study:

- Interim Analysis
- Final Analysis

5.1 Data Monitoring Committee (DMC)

There will be no DMC for this study.

5.2 Interim Analysis

A blinded interim analysis for sample size re-estimation will be conducted when approximately 50% of patients complete their mid-week treatment day dialysis session and corresponding λ FLC and β2-MG RRs are available.

This interim analysis allows for modifying the sample size while the study is ongoing and is based on a blinded estimate of the variance. The one-sample estimator which will be calculated from the pooled data maintains trial integrity, shows good performance and is therefore recommended for application [2] .

The data utilized during the interim analysis will be based on the FAS and statistics will be limited to the calculated one-sample variance estimator (not split by treatment group) of the λ FLC and β2-MG RRs measured at the mid-week treatment day dialysis session. For sample size re-estimation, for each primary endpoint, the same sample size calculation as outlined in Section 3.2 will be carried out using the one-sample variance estimator which is based on the pooled variance (across both treatment groups) of the RRs as observed in the patients included in the interim analysis. In case the re-estimation for the sample size of λ FLC or β2-MG yields a patient number > 272 (including 5% drop out), the sample size of the study will be increased to this re-calculated number but will not exceed 350. In case the sample size reassessment for λ FLC or β2-MG yields a patient number ≤ 272 (including 5% drop out), the sample size of the study will not be adjusted and the original sample size of 272 will be maintained. Due to this blinded and pooled (non-treatment group based) approach in re-estimation of the sample size and the absence of early stopping for futility and efficacy, no

alpha adjustment is required for the final analysis.

The steps of re-estimating the sample size are described as follows:

1. For each primary endpoint:
    - Regard the collected data (approximately 50% of all patients) as one sample, and estimate the mean and standard deviation (SD);
    - Based on a 1:1 randomization, use the normal approximation;
    - Use the one-sided significance level as 0.025 and the power of 90% to calculate the sample size;
2. Choose the larger re-estimated sample sizes of the two endpoints, and enlarge it with the 5% drop-off rate. If the re-estimate is smaller than 272, the study will stick on the original 272-sample design, and if the re-estimate is greater than 272, the new sample size will be used to recruit patients.
3. In case the re-estimation for the sample size of λ FLC or β2-MG yields a patient number > 272 (including 5% drop out), the sample size of the study will be increased to this re-calculated number but will not exceed 350. In case the sample size reassessment for λ FLC or β2-MG yields a patient number ≤ 272 (including 5% drop out), the sample size of the study will not be adjusted and the original sample size of 272 will be maintained. Due to this blinded and pooled (non-treatment group based) approach in re-estimation of the sample size and the absence of early stopping for futility and efficacy, no alpha adjustment is required for the final analysis.

5.3 Final Analysis

All final, planned analyses identified in this SAP will be performed by Kun Tuo Biostatistics following Sponsor Authorization of this Statistical Analysis Plan and Database Lock.

6 Analysis Sets

Agreement and authorization of patients included/ excluded from each analysis set will be conducted prior to database lock.

6.1 Intention-To-Treat Full Analysis Set (FAS)

Includes all randomized patients. Patient assignment will be based on the treatment randomized.

6.2 Per Protocol Set (PPS)

PPS is a subset of the FAS and meets the following requirements: Patients were randomized to the respective treatment at the mid-week treatment day dialysis session and did not have any major protocol deviations that could affect the assessment of the primary endpoint when dividing the patient population.

Major protocol deviations when dividing the patient population are defined as follows:

- The actual QB of the patient is < 220 mL/minute for a duration of more than 30 min or for a total duration of > 60 minute at the mid-week treatment day dialysis session; patients in control group who actually do not achieve at least 16 L convective volume (including UF)
- The actual dialysis time of the patient is < 210 minute at the mid-week treatment day dialysis session.

6.3 Safety Set (SS)

Includes all enrolled patients (ICF signed) that have been treated. Patient assignment will be based on actual treatment received.

7 General Considerations

7.1 Reference Start Date And Study Day

Study Day will be calculated from the reference start date, and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first application of study device and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then: Study Day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date then: Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear partial or missing in the listings.

7.2 Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement (including unscheduled assessments) taken prior to the first application of study device. In the case where Adverse Events (AEs) and medications without onset time record commencing on the reference start date will be considered post-baseline.

7.3 Retests , Unscheduled Visits and Early Termination Data

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries.

In the case of a retest (same visit number assigned), the last available measurement for that visit will be used for by-visit summaries.

Data of 'early termination' visit will not be included in by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

7.4 Windowing Conventions

No visit windowing will be performed for this study.

7.5 Statistical Tests

Unless specified, all statistical tests will be performed at a significance level of 5% with two-sided 95% confidence interval (CI).

7.6 Common Calulations

Descriptive statistics for continuous variables include number of cases, the number of missing cases, arithmetic mean, standard deviation, median, Q1, Q3, minimum, and maximum. Class variables will be described by frequency and percentage.

The level of precision for each continuous parameter statistic will be presented as follows:

- minimum/maximum in same precision as in the data or database, as appropriate,
- mean/median/Q1/Q3 in one more level of precision than minimum/maximum,
- SD in one more level of precision than mean/median,
- n will be presented as an integer.

For class variables, the percentage retains one decimal place. When the frequency is 0, the percentage will not be displayed; when the percentage is 100%, the percentage will be

displayed as 100%. If there is no special explanation, the denominator of the percentage is the number of cases in the corresponding analysis set. If there are missing values, the number of missing cases will be presented in a separate 'missing' line, unless otherwise specified.
For quantitative measurements, change from baseline will be calculated as:

- Test Value at Treatment Interval X – Baseline Value

7.7 Software Version

All analyses will be conducted using SAS version e.g. 8.2 or higher.

8 Statistical Considerations

8.1 Missing Data

For the primary efficacy endpoints, multiple imputation and tipping point analysis will be used to impute missing values of the λ FLC and β2-MG RRs using the Intention-to-treat FAS for the sensitivity analysis. Imputation method are detailed in section 17.1.3.
No additional data will be imputed.

8.2 Multiple Comparisons / Multiplicity

The two primary endpoints will be tested simultaneously. Only when both primary endpoints pass is the study declared successful. Therefore, no multiplicity adjustment are necessary for this portion. Hierarchical structure will be used for the testing for both non-inferiority and superiority. Superiority will only be tested if non-inferiority passes.
There are no other multiplicity adjustments are made for the study. The secondary endpoint is not assigned to alpha, so it not refers to alpha adjustment. All secondary endpoints, all p values are descriptive in nature only.

9 Output Presentations

Appendix 1 Partial Date Conventionsshows conventions for presentation of data in outputs.

The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures and listings to be provided by Kun Tuo Biostatistics. All data collected will be listed. When the content of this SAP does not match the template, the template will take priority.

10 Disposition and Withdrawals

All patients who provide informed consent will be accounted for in this study.
Patient disposition and withdrawals including inclusion and exclusion criteria will be presented for all patients. The numbers and percentages of patients who were randomized, completed procedure within two weeks of randomization, completed and discontinued from the study will be summarized by treatment and overall. Reasons for discontinuation from the study will be summarized.
The numbers and percentages of patients in each analysis set will be provided by treatment group and overall. A listing of patients who are excluded from analysis sets, with reason for excluded from analysis set will be produced.

11 Protocol Deviations

Any act of intentional or unintentional variation of the protocol is defined as protocol deviation (PD). The numbers and percentages of patients in the FAS with any protocol deviation will be summarized by treatment, deviation category and overall. All protocol deviations will be listed. Protocol deviations will be summarized by categories and overall.

12 Demographic and other Baseline Characteristics

Demographic data and other baseline characteristics will be presented for Intention-to-treat FAS and be summarized by treatment and categories. A listing will be provided.

The following demographic and other baseline characteristics will be reported for this study:

- Age (years) ,defined as Age(Years)=(Date of signed ICF – Date of birth)/365.25, round down to integer
- Sex
- Child-bearing potential, only for female
- Ethnicity
- Dialysis Vintage (years)
- Weight (kg) at baseline
- Height (cm) at baseline
- BMI ($kg/m^{2)}$ at baseline, defined as BMI (kg/ m^2) = weight (kg)/ height (m) ^{2}

13 Renal Disease Baseline Characteristics

Renal baseline characteristics will be presented for Intention-to-treat FAS and be summarized by treatment and categories. A listing will be provided.

- Renal diagnosis etiology
- Type of first chronic dialysis treatment
- Received Renal Transplantation

14 Previous Treatment Parameter

Previous Treatment Parameter will be presented for Intention-to-treat FAS and be summarized by treatment and categories. The average over 6 times dialysis for continuous variables will be summarized by six previous treatment types. A listing will be provided using all data from the last 6 times.

The following previous treatment parameter will be reported for this study:

- Total duration of hemodialysis(years)
- Dialysis frequency in latest 6 times
- Total dialysis time(min)
- Dialyzer used
- QB(mL/min)
- QD(mL/min)
- Type of vascular access
- Treatment Type
- Scheduled replacement volume(L)
- Actual replacement volume(L)
- Treatment interruption, interruption time will also be summarized when treatment interruption exists.
- Anticoagulation Type,if having Anticoagulation,
- Anticoagulation supplement during the treatment, total supplement dose will also be summarized when anticoagulation supplement during the treatment exist.
- Dry weight(kg)

15 Medical History /Concomitant Illnesses

SS will be used for Medical History/Concomitant Illnesses, unless otherwise specified. No inferential statistics will be provided.

- Medical History/Concomitant Illnesses will be coded using Medical Dictionary for Regulatory Activities (MedDRA XXX) terminology.
- Medical History are defined as those conditions prior to or at the day of the first application of study device.
- Concomitant Illnesses are conditions which started prior to the first application of study device and are ongoing after the first application of study device.
- Medical History/Concomitant Illnesses will be presented by primary system organ class (SOC) and preferred term (PT).

The illness will be regarded as concomitant Illnesses, if Medical History or Concomitant Illnesses cannot be classified according to the relationship between the date of the first application of study device and the start date of an illness.

16 Prior Medications and Concomitant Medications

Prior and concomitant medications will be presented for SS, and coded using WHO Drug Global Dictionary: XXXX.

- Concomitant medication will be listed and summarized by Anatomical Therapeutic Chemical (ATC) level 3 and preferred chemical substance, a listing will be presented for prior medication. If a patient had more than one concomitant medication within ATC, the patient will be counted only once within a ATC Term.
- Prior medications are medications that started and stopped prior to the first application of study device within the observation.
- Concomitant medications are medications which are ended on or after the date of the first application of study device within the observation or were ongoing at the end of the study.
- The medication will be regarded as concomitant medication, if medication and concomitant medication cannot be classified according to the relationship between the date of first application of study device and the end date of a medication.

17 Efficacy Analysis

The analysis of primary endpoints will be based on the PPS. Sensitivity analysis of the primary endpoints and analysis of secondary endpoints will be based on the FAS. All the efficacy endpoints will be assessed at the mid-week treatment day dialysis session.

17.1 Primary Efficacy

17.1.1 Primaty Efficacy Variables & Derivations

Primary efficacy endpoints:

The reduction ratios of λ FLC and β2-MG at the mid-week treatment day dialysis session.

Derivations of analysis variables:

Reduction ratio (unit: %) = $\left(1-\frac{Cpost}{\mathrm{Cpre}}\right) \times 100\%$

C_{Pre} and C_{Post} are the measured arterial plasma concentrations of the solute before and after themid-week treatment day dialysis session, respectively [3].

However, for the middle molecules (λ FLC and β2- MG) C_{Post} will be first corrected ($C_{Post-corr}$) for the decrease in total extracellular volume due to fluid removal as follows:

$C_{Post-corr} = \left(\frac{cpost}{1+\frac{BWPre-BWPost}{0.2\times BWPost}}\right)$

C_{Post} is the measured plasma concentration of the solute after dialysis; and BW_{Pre} and BW_{Post} are the patient's body weight before and after dialysis, respectively[4] .

Data of the variables above will be collected from the Central Lab .

17.1.2 Primary Analysis Of Primary Efficacy Variables

PPS population is the primary efficacy analysis population. Descriptive statistics of reduction ratios of λ FLC and β2-MG will be provided by treatment group.

Listings of reduction ratio will be presented and sorted by patient id and treatment group.

The statistical hypothesis for testing the treatment group difference for reduction ratios of λ FLC is presented as follows:

- Ho: $\mu_T-\mu_R \leq -3.783$ tested against the alternative hypothesis
- Ha: $\mu_T-\mu_R > -3.783$

where:

μ_T is the means of RRs of λ FLC in Theranova 400 treatment and μ_R is the means of RRs of λ

FLC in the FX 800 treatment.

A two-sample t-test will be utilized to generate a two-sided 95% confidence interval (CI) for the difference in means (μ_T - μ_R). If the lower bound of the CI is greater than -3.783, then non-inferiority between the Theranova 400 and FX 800 treatment group can be demonstrated for λ FLC RR. If the lower bound of the CI is greater than zero, then superiority of Theranova 400 treatment over FX 800 treatment can be concluded.

The statistical hypothesis for testing the treatment group difference for reduction ratios of β2-MG is presented as follows:

- Ho: μ_T-$\mu_R \leq$ -7.848 tested against the alternative hypothesis
- Ha: μ_T-$\mu_R >$ -7.848

where:

μ_T is the means of RRs of β2-MG in Theranova 400 treatment and μ_R is the means of RRs of β2-MG in the FX 800 treatment.

A two-sample t-test will be utilized to generate a two-sided 95% confidence interval (CI) for the difference in means (μ_T - μ_R). If the lower bound of the CI is greater than -7.848, then non-inferiority between the Theranova 400 and FX 800 treatment group can be demonstrated for β2-MG RR. If the lower bound of the CI is greater than zero, then superiority of Theranova 400 treatment over FX 800 treatment can be concluded.

The two hypothesis tests are hierarchically structured so that the second test (superiority) will only be considered if the first test (non-inferiority) is rejected. There is no alpha adjustment for the second test as a result of the hierarchical testing.

17.1.3 Sensitivity Analysis Of Primary Efficacy Variables

In order to addressing robustness of the primary analysis results of primary efficacy endpoint, three sensitivity analysis approaches are proposed:

- **Sensitivity 1:** It will be conduct based on PPS. An ANOVA model on primary efficacy endpoints (reduction ratios of λ FLC and β2-MG) with fixed effects for treatment group and study site to evaluate differences between the treatment groups

will be analyzed and corresponding two-sided 95% CIs derived. An interaction term between treatment group and study site will be tested. If the interaction between treatment group and study site is not significant (P>0.05), then the interaction term will be removed from the model. Data will also be tested for normality using a Quantile-Quantile (Q-Q) plot. If data are not normally distributed, a log transformation will be used and if normality holds, the Cox method[5] will be used to estimated two-sided 95% CIs. If after log transformation, measurements do still not follow a normal distribution, then the Kruskal Wallis test will be used in place of the ANOVA.

- **Sensitivity 2:** It will be conduct based on PPS. A non-parametric method: Wilcoxon Rank-Sum Test will be used to analyze the primary endpoints. Hodges-Lehmann estimate will be used to calculate the 95%CI.

- **Sensitivity 3:** Above statistical analysis method will be conducted using the FAS population with multiple imputation method based on missing at random (MAR) to impute the missing values of the λ FLC and β2-MG RRs. A two-sample t-test will be utilized to generate a two-sided 95% confidence interval (CI) for the difference in means (μ_T - μ_R). the imputing step is as follow:
  1. Handling baseline missing data. Baseline missing data will be imputed using regression imputation. Baseline value of age, gender, serum creatinine and bun will be incorporated into the model as covariates to predict and impute missing baseline values.
  2. The missing data are imputed by group in 20 times to generate 20 complete datasets using PROC MI procedure(seed=6162022) by monotone imputation.
  3. The primary endpoint will be calculated according to each imputed complete datasets.
  4. Two sample t-test as specified for primary analysis will be applied to each complete datasets and the inference drawn using Rubin's combination rules using PROC MIANALYZE.

- **Sensitiviy 4:** tipping point approach will be used to assess the robutness of analysis result under missing not at random (MNAR) assumption. It will perform a series of

analyses with a range of different values of the shift parameter δ only applied to the imputed datasets of Theranova 400 group at which the conclusion about the statistical significance of the estimated treatment effect will be altered. All step is same to Sensitivity 3 except that the shift parameter δ will be added to the imputed datasets at the Theranova 400 group.

17.2 Secondary Efficacy

17.2.1 Secondary Efficacy Variables & Derivations

Secondary efficacy endpoints:

Kt/V_{urea}, Urea Reduction Ratio and the reduction ratios of α1-MG, YKL-40, CFD, myoglobin and κ FLC obtained at the mid-week treatment day dialysis session.

Derivations of analysis variables:

For this single hemodialysis treatment study, $spKt/V_{urea}$ is adopted to calculated Kt/V_{urea}.

$SpKt/V_{urea}$ refers to single pool Kt/V. The single pool Kt/V will be calculated as:

$spKt/V_{urea}$= -ln[(post dialysis Urea)/(pre dialysis Urea) − 0.008 × total dialysis time(h)] + [4 − 3.5 × (post dialysis Urea)/(pre dialysis Urea)] × (ultrafiltration volume (in liters))/(post dialysis weight)

Reduction ratio (unit: %) = $\left(1-\frac{Cpost}{\mathrm{Cpre}}\right) \times 100\%$

C_{Pre} and C_{Post} are the measured arterial plasma concentrations of the solute before and after the mid-week treatment day dialysis session, respectively [3].

However, for the middle molecules (κ FLC, α1-MG, CFD, YKL-40, myoglobin) C_{Post} will be first corrected ($C_{Post\text{-}corr}$) for the decrease in total extracellular volume due to fluid removal as follows:

$C_{Post\text{-}corr} = \left(\frac{cpost}{1+\frac{BWPre-BWPost}{0.2\times BWPost}}\right)$

C_{Post} is the measured plasma concentration of the solute after dialysis; and BW_{Pre} and BW_{Post} are the patient's body weight before and after dialysis, respectively[4] .

17.2.2 Analysis Of Secondary Efficacy Variables

FAS population will be used for secondary efficacy variables.

Quantile-Quantile (Q-Q) plot will be drawn to testify the normality distribution of the

Kt/Vurea and URR. If the variable follows the normality distribution, a t-test will be used to evaluate differences between treatment groups in Kt/Vurea and URR. Otherwise, Wilcoxon Rank-Sum test will be used.

Quantile-Quantile (Q-Q) plot will be drawn to testify the normality distribution of the RRs of α1-MG, YKL-40, CFD, myoglobin and κ FLC. If the variable follows the normality distribution, a t-test will be used to evaluate differences between treatment groups for the RRs of α1-MG, YKL-40, CFD, myoglobin and κ FLC obtained at the mid-week treatment day dialysis session. Otherwise, Wilcoxon Rank-Sum test will be used.

18 Safety Analysis

All outputs for safety outcomes will be based on safety set, and presented by treatment groups.

18.1 Treatment parameters

Treatment parameter will be presented for safety set and be summarized by treatment and categories. A listing will be provided.
The following treatment parameter will be reported for this study:

- Total dialysis time(min)
- Programmed QB(mL/min)
- Programmed QUF(mL/min)
- QB adjusted during the dialysis treatment
- Type of vascular access
- Treatment type
- Dialysate type
- Scheduled replacement volume (L)
- Actual replacement volume (L)
- Treatment interruption, interruption time will also be summarized when treatment interruption exists.
- Anticoagulation type
- Anticoagulation supplement during the treatment, total supplement dose will also be summarized when anticoagulation supplement during the treatment exist.

- Dry weight(kg)

18.2 Adverse Events

An AE is any untoward medical occurrence in a clinical study and which does not necessarily have to have a causal relationship with the investigational medical device *Chinese medical device GCPArticle 93*. Adverse Events (AEs) will be coded using MedDRA and presented by System Organ Class (SOC) and Preferred Term (PT). Treatment-emergent AE (TEAE) will include AEs that occur on the day of or after the study treatment and will be summarized in the safety summaries. Pre-treatment AEs including AEs reported at Screening and Randomization will be recorded in the eCRF but will not be summarized in the safety summaries.

In AE summaries, the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency. Treatment group comparability in the incidence of AEs will be evaluated using Fisher's exact test.

Severity of AE

Severity is classed as mild/ moderate/ severe. If severity is missing, the AE will be considered servere.

Relationship with Study Device/ Study Procedure

Relationship, as indicated by the Investigator, is classed as “Unable to Judge”, “Definitely Unrelated”, “Possibly Unrelated”, “Possibly Related”, “Probably Related”, “Definitely Related” (increasing severity of relationship).

Relationship with Study Device

Treatment-related AE is defined as a AE with a relationship as “Possibly Related”, “Probably Related” or “Definitely Related” or “Unable to Judge” to the study treatment. AEs with a missing relationship to study treatment will be regarded as “Definitely Related” to study treatment. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

Relationship with study procedure

AEs related to study procedure is defined as a AE with a relationship to the study procedure as “possibly related”, “probably related” or “definitely related” or “unable to judge” to study procedure. If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medication will be used in the corresponding relationship summaries.

18.2.1 All Adverse Events

The following AE summaries will be described frequency and percentage by treatment group and overall in an overview summary table:

- TEAEs
- Severity of AE (mild, moderate, severe)
- Treatment-Related AE
- Procedure-Realated AE
- Serious AEs
- Treatment-Related SAE
- Deaths
- AEs leading to withdraw from the study
- Treatment-Related AEs leading to withdrawal
- TEAE in ≥5% of patients
- Treatment-Related TEAE in ≥5% of patients

If a patient experienced more than one adverse event, the AE with the worst severity will be used in the corresponding summaries.

In addition, all AEs will be listed and presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity of event. If a patient reports an AE more than once within that SOC/ PT, the AE with the worst severity will be used in the corresponding severity summaries.

18.2.2 Adverse Events Leading to Withdraw From The Study

AEs leading enrolled patients removed or withdraw from the study will be listed and summaries by SOC and PT.

18.2.3 Treatment-Related Adverse Events Leading to Withdraw From The Study

Treatment-Related TEAEs leading enrolled patients removed or withdraw from the study will be listed and summaries by SOC and PT.

18.2.4 The Most Common (≥5% Incidence) Adverse Events

The most common(which total incidence is ≥5% or incidence of either treatment group is ≥5%) adverse events will be listed and presented by SOC, PT and severity.

18.2.5 The Most Common (≥5% Incidence) Treatment-Related Adverse Events

The most common(which total incidence is ≥5% or incidence of either treatment group is ≥5%) treatment-related adverse events will be listed and presented by SOC, PT and severity.

18.2.6 Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as 'yes' in "Serious" item on the Adverse Events page of the CRF. A listing and summary of SAEs by SOC and PT will be prepared.

18.2.7 Treatment-Related Serious Adverse Events

A listing and summary of treatment-related SAEs by SOC and PT will be prepared.

18.2.8 Adverse Events Leading to Death

AEs leading to Death are those events which are recorded as 'Death' on the Adverse Events page of the CRF. A listing and summary of AEs leading to death by SOC and PT will be prepared.

18.2.9 Treatment-Related Adverse Events Leading to Death

A listing and summary of treatment-related AEs leading to death by SOC and PT will be prepared.

18.3 Device Deficiency

Device deficiency, device deficiency resulted in an adverse event, and device deficiency resulted in a serious adverse event will be listed separately.

The following Device deficiency summaries will be described frequency and percentage by treatment group and overall in an overview summary table:

- Device deficiency

- Device deficiency reported to Baxter as a product complaint
- Device deficiency resulted in AE
- Device deficiency resulted in SAE

Device deficiency, device deficiency resulted in an adverse event, and device deficiency resulted in a serious adverse event will be listed separately.

18.4 Laboratory Evaluations

Results from the laboratory will be included in the reporting of this study for Blood routine, Serum Creatinine, Blood urea nitrogen/Blood urea, Blood electrolytes, Liver function, C-reactive protein. A list of laboratory assessments to be included in the outputs is included in Appendix 1 Partial Date Conventions.

Presentations will use SI Units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Actual outcomes from the CRF and the change from baseline will be listed and summarized descriptively by timepoint, treatment group and overall.

Listing of actual outcomes will be provided.

The following summaries will be provided for laboratory data:

- Change from basline by visit (for quantitative measurements).
- Shift from baseline according to investigator's judgment by worst post-baseline(for quantitative measurements and categorical measurements).
- Listing of all laboratory results and change from baseline results.
- Listing of patients meeting markedly abnormal criteria according to investigator's judgment.

18.5 Vital Signs

The following Vital Signs measurements will be reported for this study:

- Body Temperature(°C)
- Respiratory Rate (Beats/Min)

- Pulse (bmp)
- Diastolic Blood Pressure(mmHg)
- Systolic Blood Pressure(mmHg)

Change from baseline will be summarized by visit, treatment group and overall. Listing of actual outcomes will be provided.

18.6 Body Weight and dry weight

Pre-dialysis and post-dialysis body weight, Pre-dialysis dry weight will be summarize by group and overall.

18.7 Other Safety Evaluations

The other safety evaluations including virology, pregnancy blood test will be listed.

Reference

[redacted]

[2] Tim Friedea, Meinhard Kieser. Blinded sample size re-estimation in superiority and noninferiority trials: bias versus variance in variance estimation. Pharmaceutical Statistics 2013;12(3):141-6.

[3] Guidelines for Technical Review of Disposable Dialyzer Registration (SYJBXH [2013] No. 3), January 4, 2013

[4] Bergström J, Wehle B. No change in corrected ß2-microglobulin concentration after cuprophane haemodialysis [letter]. Lancet. 1987; 1:628-629.

[5] Olsson U. Confidence intervals for the mean of a log-normal distribution[J]. Journal of Statistics Education, 2005, 13(1).

Appendix 1 Partial Date Conventions

Imputed dates will NOT be presented in the listings.

Algorithm for prior / concomitant medications:

Start date	Stop date	Action
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant

Start date	Stop date	Action
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant
	Missing	Assign as concomitant

Appendix 2 Laboratory Evaluation Test Name

Laboratory Category		Laboratory Test Name
Blood routine		Erythrocytes(RBC)、Hemoglobin(HB)、Mean corpuscular volume(MCV)、Mean corpuscular hemoglobin(MCH)、Mean corpuscular hemoglobin concentration(MCHC)、Leukocytes(WBC)、Platelets(PLT)、Eosinophils Percentage(EOS%)、Hematocrit(HCT)
Chemistry	Liver function	Direct bilirubin(DBIL)、Total bilirubin(TBIL)、Aspartate aminotransferase (AST)、Alanine aminotransferase (ALT)、Gamma glutamyl transferase (GGT)、Alkaline phosphate (ALP)、Total Protein(TP)、Albumin (ALB)、Globulin
	Blood glucose, cholesterol, triglyceride	Glucose (GLU、Triglycerides (TG)、Total Cholesterol (CHOL)
	Serum Creatinine	Serum Creatinine(CR)
	BUN/BU	BU、BUN
	Electrolyte	Potassium (K)、Sodium (Na)、Chlorine (Cl)、Calcium (Ca)、Phosphorus (P)
Coagulation functions		International normalized ratio(INR)、Activated partial thromboplastin time(APTT)、Prothombin time(PT)