Protocol No.: BXU561424

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

Medical Device Clinical Study Protocol

Name of medical device: Hollow fiber dialyzers with medium cut-off membrane

Model and Specification: Theranova 400

Category of experimental medical device:

Class III medical device subject to clinical study approval:

Yes □ No √

Similar products in China: Yes □ No √

Protocol version number and date: V1.1 Amendment 1.1, May 30, 2022

Clinical study institution: [redacted]

Investigator: [redacted] **(Principal Investigator)**

Sponsor: Gambro dialysatoren GmbH

Agency: Baxter Medical Products Trading (Shanghai) Co., Ltd.

[redacted]

Instructions:

1. For multicenter clinical studies, only the leading site is filled in the cover, and other institutions of the clinical study are listed in the protocol content.
2. For multicenter clinical studies, the coordinating investigator is filled in as the investigator in the cover.

	Date
Original Protocol:	2021 MAY 19
Amendment 1.0	2021 DEC 01
Amendment 1.1	2022 MAY 30

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SYNOPSIS

Study Title:	A randomized, controlled, open-label, parallel, multicenter study in kidney failure patients on hemodialysis comparing the Theranova Dialyzer to hemodiafiltration
Study Objectives	**Primary Objective:** The primary objective is 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), 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. **Secondary Objectives:** 1. To evaluate the Theranova 400 compared to FX 800 in regard to assessments of Kt/V_{urea}, Urea Reduction Ratio (URR) at the mid-week treatment day dialysis session. 2. 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.
Study Design	A randomized, controlled, open-label, parallel, multicenter study.
Device in the Test Group	Product name: Hollow fiber dialyzers with medium cut-off membrane Model and Specification: Theranova 400 Registrant: Gambro Dialysatoren GmbH
Device in the Control Group	Product name: Hollow fiber hemodialysis filter Model and Specification: FX 800 HDF Registrant: Fresenius Medical Care AG & Co. KGaA.
Study Population	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 receive 1 mid-week therapy with either Theranova 400 (136 patients) or FX 800 (136 patients).
Inclusion Criteria	All of the following criteria must be met for the patient to be eligible for participation. 1. Patients aged ≥18 years old and ≤80 years old, regardless of gender; 2. Patients who are able to sign informed consent form (ICF) after an explanation of the proposed study; 3. Patients who receive in-center HD treatment at a site that routinely implements high

	flux dialysis and HDF; 4. Patients who have been stable receiving in-center HD/HDF for >3 months prior to study enrollment; 5. Patients with kidney failure receiving maintained HD treatment with a history of thrice weekly HD, and at least 1 HDF session within 1 month prior to the study shall be judged by the investigator; 6. Patients who have an adequate arteriovenous (AV) fistula or graft, or dual-lumen tunneled catheter capable of providing a blood flow rate (QB) of at least 250 mL/min; 7. Patients have no changes in dialysis prescription (dialyzer, time, dialysis fluid flow rate (QD), QB, sufficient dialysis anticoagulation, and stable prescribed doses) over last 6 treatments as judged by investigator. The dialysis treatment time should be 3.5 to 4.5 hours per session with a minimum QB of 250 mL/min and QD of 500 mL/min; 8. Patients with a minimum total convective volume (including ultrafiltration [UF]) of 16 L post-dilution for the most recent HDF treatment; 9. Patients who have Kt/V_{urea} > 1.2 for the last 2 measurements, with the most recent Kt/V_{urea} measurement taken within 4 weeks before or during study screening.
Exclusion Criteria	Patients who meet any of the following criteria will be excluded from the study: 1. Patients who have acute kidney injury with the chance for recovery; 2. Pregnant and lactating women; 3. Patients diagnosed with a New York Heart Association (NYHA) Class IV congestive heart failure, or acute coronary syndrome, and/or who have suffered a myocardial infarction within 3 months prior to the start of the study; 4. Patients with known hemodynamic instability, anemia (hemoglobin <90 g/L), and/or patients with hemoglobin >130 g/L for coagulation risk; 5. Patients with active or ongoing infection as per investigator's judgement (eg. C-reactive protein [CRP] level more than 5 folds of normal); 6. Patients who are severely malnourished or with significant disease that interferes with liver synthetic function (e.g. with serum albumin <30 g/L); 7. Patients with positive serology tests for Hepatitis B surface antigen, Hepatitis C total antibody, and advanced liver, or pulmonary disease as judged by the investigator; 8. Patients with positive serology tests for human immunodeficiency virus (HIV), Syphilis; 9. Patients receiving immunosuppressive treatment or with autoimmune disease;

	10. Patients with a history of solid tumors requiring anti-cancer therapy in the past or next 6 months, or with a life expectancy of <1 year, or patients with a history of hematology neoplasm; 11. Patients who are pre-scheduled for a living donor kidney transplant within the next 1 year, who plan a change to peritoneal dialysis (PD) within the next 1 year, or who require single-needle dialysis therapy; 12. Patients who have had an allergic response to polyarylethersulfone (PAES) or polysulfone (PS) membrane or have a history of poor tolerance to dialyzers with synthetic membranes; 13. Patients with a history of severe mental disorders who are unable to provide consent or comply with study procedures as assessed by the investigator; 14. Patients who are currently participating in or have previously participated in other interventional clinical studies during the past 30 days; 15. Patients with any comorbidity possibly conflicting with the study as judged by the investigator.
Duration of Treatment	The study will have a duration of 3 weeks per per patient in total. The study will consist of: 1) Screening Period: 2 weeks; 2) Treatment Period: 1 week, 1 session in mid-week therapy with either Theranova 400 or FX 800; (Note: visit ought to be conducted within 2 weeks after randomization). Follow-up: review of treatment-related AEs conducted at the next dialysis session (end-week therapy session), but prior to treatment commencement.
Study Medical Device, Frequency and Mode of Administration	In-center HD mid-week therapy with the Theranova 400 Dialyzer in HD mode, or with the FX 800 Dialyzer in HDF mode, 1 mid- week session as per patient randomization.
Efficacy Endpoints	**Primary Endpoints:** 1. RR of λ FLC; 2. RR of β2-MG. **Secondary Endpoints:** At the mid-week treatment day dialysis session 1. Kt/V_{urea}; 2. URR; 3. RR of α1-MG; 4. RR of YKL-40; 5. RR of CFD;

	6. RR of myoglobin; 7. RR of κ FLC.
Safety Assessments	**Safety Assessments** − Adverse events (AEs) and serious adverse event (SAEs). − CRP analysis − Routine serum chemistry and hematology assessments − Vital signs pre-and post-dialysis per treatment − Device deficiencies (during use of the investigational product; which would include functional characteristics [e.g., leaks, tubing separations, etc.])

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). **Sample size calculation in regard to λ FLC reduction ratio:** A previously conducted Theranova HDF study was used to obtain λ FLC RR mean and standard deviation (SD) of 37.83 and 8.26. 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, 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). **Sample size calculation in regard to ß2- microglobulin reduction ratio:** A previously conducted Theranova HDF study 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 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). **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).
Statistical Analysis	The analysis details of the planned statistical methods will be provided in the study statistical analysis plan (SAP). The draft SAP is formed after determination of the study protocol and electronic case report form (eCRF). It will be finalized prior to database lock. **Analysis of Primary Endpoints:** For λ FLC and ß2-MG RR, a 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 for the 2 endpoints are greater than the predefined noninferiority margins, then non-inferiority between the Theranova 400 and FX 800 treatment group can be demonstrated. In case the assumption of a normal distribution is not justified, RRs can be log transformed in order for the measurements to follow a normal distribution. If, after transformation, measurements still do not follow a normal distribution, the above statistical analyses methods will be replaced with their non-parametric equivalents. The Wilcoxon Rank-Sum Test will be used in place of the t-test while the Kruskal Wallis test will be used in place of the ANOVA. **Analysis of Secondary Endpoints:** Secondary endpoints will be evaluated as follows: A t-test or Wilcoxon Rank-Sum test, as applicable, will be used to evaluate differences between treatment groups in Kt/V_{urea} and URR. A t-test or Wilcoxon Rank-Sum test, as applicable, 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. **Analysis of Safety Endpoints:** Safety endpoints will be evaluated as follows: The summary of AEs will include AEs that occur on the day of or after the study treatment. Pre-treatment AEs including AEs reported at Screening and Randomization will be recorded in the eCRF but will not be summarized in the safety tables. Adverse events will be mapped to a Primary SOC and Preferred Term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA) and summarized descriptively by SOC, PT and treatment group. Treatment group comparability in the incidence of AEs will be evaluated using Fisher's exact test. Investigational device related product defects will be summarized descriptively. Comparator related product defects will not by collected or analyzed by Baxter. Serum chemistry, hematology assessments, patient vital signs and CRP will be

	summarized descriptively per measurement time point using n, mean, median, standard deviation, minimum, and maximum. **Other Assessments:** 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. **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. For sample size re-estimation, for each primary endpoint, the same sample size calculation 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 $\leqslant$ 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.
Visit Schedule	Refer to 7.2.1.1 Study Flow.

LIST OF ABBREVIATIONS

Abbreviation	Definition of Term
AE	adverse events
α1-MG	alpha-1 microglobulin
AV	arteriovenous
β2-MG	beta-2 microglobulin
BP	blood pressure
Ca	calcium
Cl	chlorine
CFD	complement factor D
CRP	c-reactive protein
eCRF	electronic case report form
DD	device deficienies
DMP	Data Management Plan
EDC	electronic data capture system
FAS	full analysis set
GCP	good clinical practice
HD	hemodialysis
HDF	hemodiafiltration
HF	high flux
HIV	human immunodeficiency virus
ICF	informed consent form
κ FLC	kappa free light chain
K	potassium
Kt/V_{urea}	formula used to quantify hemodialysis and peritoneal dialysis adequacy
λ FLC	lambda free light chain
Na	sodium
NMPA	National Medical Products Administration
P	phosphorus
QB	blood flow rate
QD	dialysis fluid flow rate

RR	reduction ratio
SAE	serious adverse event
SAP	statistical analysis plan
SOP	standard operating procedure
UF	ultrafiltration
URR	urea reduction ratio
YKL-40	chitinase-3-like protein 1

1. Sponsor

Company name	Gambro dialysatoren GmbH
Address	Holger-Crafoord-Strasse 26, 72379 Hechingen, Germany
Tel	+49 7471171227
Fax	+49 7471171227
Qualification	Production license

Agent	Baxter Medical Products Trading (Shanghai) Co., Ltd.
Address	12 floor, Changle Road 989#, Xuhui District, Shanghai
Tel	+86 21 24012366
Fax	+86 21 24012466
Qualification	Business license

2. List of Clinical Study Institutions and Investigators

Clinical study institution code	Address	Clinical study institution name	Investigator	Technical title	Contact
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

3. Study Objectives

3.1 Objectives

Primary Objective:
The primary objective is 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), 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.

Secondary Objectives:

1. To evaluate the Theranova 400 compared to FX 800 in regard to assessments of Kt/V_{urea}' Urea Reduction Ratio (URR) at the mid-week treatment day dialysis session.
2. To evaluate the RRs of urea, 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.

3.2 Content

The clinical study is conducted in accordance with relevant regulations of National Medical Products Administration (NMPA).

To ensure approximately 272 patients with kidney failure on a stable HD and/or HDF prescription will be enrolled in this study.

The investigational product is hollow fiber dialyzers with medium cut-off volume of Gambro Dialysatoren GmbH (model: Theranova 400), and the control product is hollow fiber HD filter (model: FX 800 HDF) of Fresenius Medical Care AG & Co. KGaA.

This study is a randomized, controlled, open-label, parallel multicenter study. Ensure to recruit a sufficient number of patients, 272 patients are randomized at a 1:1 ratio to receive treatment

with Theranova 400 (136 patients) or FX 800 (136 patients) at the mid-week treatment day dialysis session. A follow-up visit to assess treatment related AEs is to be conducted at the next end-week dialysis session, but prior to treatment commencement. The RRs of large middle-molecular-weight toxins are observed and compared in the 2 groups. The indicators such as adverse events (AEs), laboratory tests and vital signs of patients and the device defects are monitored to evaluate the safety and efficacy of Theranova 400.

4. Background

The incidence of chronic kidney disease is increasing worldwide, and if it is not controlled and treated in time, it may develop into kidney failure, previously referred to as end-stage kidney disease (ESRD). In China, there are more than 2.9 million kidney failure patients[1]; however, given the limited supply of donor kidneys, dialysis remains the mainstay treatment. There are about 700,000 patients receiving dialysis treatment in China [1]. Although HD has been implemented for over 50 years, the all-cause mortality of patients receiving HD is still increasing, with poor long-term prognosis[2].

Uremic toxins accumulated in patients with kidney failure include: low-molecular-weight (<500 Da) and middle-molecular-weight (500~60 KDa) water-soluble toxins and protein-binding toxins[3]. Cardiovascular disease is the leading cause for death of dialysis patients, accounting for 55.2% of deaths[4]. Traditional HD therapy is very effective in clearing urea and smaller middle molecules, but is limited in clearing larger middle molecules. These accumulated large middle-molecular-weight uremic toxins may cause and aggravate inflammation, atherosclerosis and calcification, which indirectly lead to the death of patients[5]. Studies have shown that, compared to conventional high-flux HD (HF-HD), HDF that combines diffusion and convection can reduce the all-cause mortality. Compared to the conventional HF-HD, HDF can more effectively clear larger molecular toxins in one session, which may be related to the better clearance effect of HDF on middle-molecular-weight toxins[6,7]. The high-convection online hemodiafiltration (OL-HDF) is not suitable for all patients due to the problems such as vascular access dysfunction, inability of the water treatment system to provide ultrapure water, and expenses[8].

Theranova's innovative Medium Cut-Off® membranes has high permeability and selectivity to uremic toxins (clearance of a molecular weight of up to 45 kDa) and can retain essential proteins, to maintain patient's albumin level during the HD treatment[9]. Its unique membrane and high cut-off characteristics expand the clearance range beyond those of flux membrane dialyzers. Theranova 400 can be widely used in most blood purification centers under conventional HD equipment and treatment modes, with the effect similar to HDF[10].

Theranova 400 has been marketed in European Union (EU) since 2016, and accredited De Novo certification in the United States of America (US) in 2020. At present, a large amount of research data on the efficacy and safety has been accumulated. The PerCOM study laying the foundation for Theranova's marking in EU [11,12] showed that, Theranova is superior to HF-HD in terms of clearance of middle molecular weight toxins, and is equivalent or superior to high-convection HDF; Theranova and HDF have almost the same clearance for low molecular weight toxins. The pivot study [13] laying a foundation for Theranova's approval by US FDA (Food and Drug Administration) showed that, Theranova is much better than HF-HD in clearing large middle molecules (λ FLC), and there is no significant change in serum albumin level of patients after 24 weeks of observation. The preclinical data and in vitro performance data provided by Boschetti de Fierro et al. (2015), Hulko et al. (2015), Voigt et al. (2016) confirmed that the performance of Theranova 400 was similar to HDF. In addition, a number of studies on Theranova 400 that are published in international journals have proven its safety and efficacy.

Presently, it is proposed to conduct clinical studies to evaluate the safety and efficacy of Theranova 400 in China. The dialyzer has been tested by the Guangdong Medical Device Quality Surveillance and Test Institute and is qualified for clinical studies. Therefore, this clinical trial protocol is formulated and implemented after approval of the hospital's ethics committee. The clinical study summary report will be submitted to the NMPA for product registration application.

5. Product Features, Structural Composition, Operating Principle, Action Mechanism and Test Scope

5.1 Product Features

Expanded hemodialysis (HDx), enabled by the Theranova dialyzer, expands the range of uremic solutes (up to 45,000 Da) efficiently removed during intermittent HD.

The Theranova dialyzer provides removal of small molecules (<500 Da, such as urea) equivalent to high flux membranes used in HD and HDF. Removal of conventional middle molecules (500 - <25,000 Da, such as κ FLC) is increased compared to high flux membranes used in HD. Removal of large middle molecules (25,000 – 45,000 Da, such as λ FLCs) is increased compared to high flux membranes used in HD and HDF.

Expanded hemodialysis, enabled by the Theranova dialyzer, achieves its performance using existing HD workflow and infrastructure[13,14].

5.2 Product Structure

The membrane material used in Theranova 400 is a composite of polyaryl ether sulfone (PAES) and polyvinylpyrrolidone (PVP). Both ends of the dialyzer are filled with polyurethane (PUR) hollow fibers to separate the blood chamber from the dialysate chamber. The inner diameter of each hollow fiber is approximately 180 μm, and the wall thickness is approximately 35 μm. The effective length of the membrane is 236 mm. The number of hollow fibers of Theranova 400 is about 13,000, and the surface area of Theranova 400 is 1.7 m^2. The material of the shell and end cap of the dialyzer is polycarbonate.

5.3 Operating Principle

The blood (after anticoagulation treatment) is transported from the patient's blood channel to the dialyzer through the extracorporeal circulation pipeline system through the HD machine. The blood enters the blood inlet and is dispersed into the cavity containing hollow fibers.
The Theranova dialyzer uses the principle of countercurrent concentration difference to enhance solute exchange. The dialysate pumped by the HD machine flows through the dialysate chamber through the dialysate inlet from the opposite direction to the blood flow in the extracorporeal circulation (reverse flow).
Hydrostatic pressure or transmembrane pressure (TMP) is produced by the combination of positive and negative pressure across the membrane. The pressure difference between the blood chamber and the dialysate chamber causes solute-dissolved plasma and certain lower molecular weight molecules to pass through the membrane and enter the dialysate chamber of the device (convection). At the same time, the solute dissolved in the plasma diffuses into the dialysate chamber along the concentration gradient between the plasma and the dialysate. During treatment, in these devices, uremic toxins and waste products enter the reverse-flowing dialysate through transmembrane convection and diffusion to achieve the effect of being removed from the patient's blood. The dialysate flows out of the device through the dialysate outlet.

Due to its larger membrane pore size, Theranova 400 has a significantly higher permeability for middle molecules in the molecular weight range of 15-45 kDa in comparison to conventional HF membranes. A narrow pore size distribution in the Theranova 400 membrane ensures that during HD there is an effective retention of larger proteins with molecular weights greater than 60 kDa such as albumin, coagulation factors or immunoglobulins. For certain molecules like β2-MG, myoglobin, κ-FLC, Interleukin-6 (IL-6), CFD, α1-MG, YKL-40 and λ- FLC, Theranova 400 has been reported to provide equivalent or superior solute clearance than HDF. [15]
Use of HF membranes, such as the FX 800 HDF allows the removal of uremic toxins, particularly middle molecules such as β2-MG. Theranova 400 and FX 800 HDF use the same principles of operation, i.e. diffusive and convective transport when performing HF-HD.

5.4 Action Mechanism

Same as the operating principle.

5.5 Scope of Study

It is proposed to conduct this study in 11 medical institutions with qualifications for clinical studies.

6. Intended Use, Contraindications and Precautions of Product

6.1 Intended Use

THERANOVA dialyzers are indicated for treatment of chronic and acute kidney failure by HD.

6.2 Contraindications

There are no known contraindications for the use of the Theranova 400.

6.3 Precautions

The dialyzers are for single use only.

Follow the product instructions to use the product.

The quality of the product is guaranteed for first use only,and only when prepared and used according to the procedures described. Reprocessing this dialyzer may cause serious damage to the product resulting in patient hazard.

Treatment parameters should be chosen within the limitations given in the specification table.

The dialyzer is used together with a dialysis device that can precisely control and monitor the ultrafiltration rate and blood in the dialysate circuit (leakage detector).

Expanded removal of molecules may lead to increased removal of certain drugs. Clinicians should consider this when prescribing the device and make any necessary dosing adjustments.

Do not apply isolated/sequential ultrafiltration when using THERANOVA dialyzers, due to higher permeability for larger plasma proteins such as free haemoglobin. In dialysis patients, plasma free haemoglobin is usually present in low concentrations (up to 239 mg/L [16]). During isolated/sequential ultrafiltration, free haemoglobin is filtered and concentrated in the dialysate compartment. This leads to a reddish coloration of the ultrafiltrate which may trigger the internal blood leak detector.

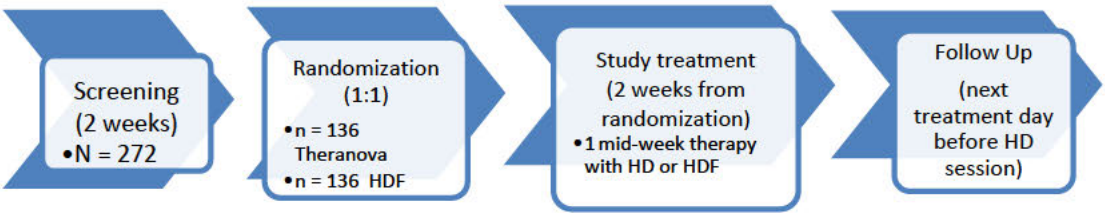
7. Overall Design

7.1 Study Design

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



7.1.1 Study Purpose

To demonstrate non-inferiority of Theranova 400 compared to FX 800 HDF, in regard to the RR of λ FLC, and β2-MG.

7.1.2 Rationale of Study Design

(1) Selection of clinical study methods: randomized, parallel-controlled, open-label, multicenter study.

(2) Randomization: In this trial, central randomization system is used for randomization, and stratified block randomization method is selected. Using the center as a stratification factor, all screened patients are randomly assigned to the test group or the control group at a ratio of 1:1.

(3) Open-label: Investigators and patients are not blinded due to differences in the appearance and operation between investigational products and control products. In

addition, the RRs of β2-MG and λ FLC in this trial are not affected by subjectivity of investigators or patients, so an open-label design is utilized in this trial.

(4) Parallel control: There is no similar product available yet. The hollow fiber HD/filter (model: FX 800 HDF) is similar to the investigational product in intended uses, structures and performances as the control product in this trial.

7.1.3 Measures to Reduce and Avoid Bias

(1) Multicenter clinical study: Patients are from multiple study sites, avoiding the bias of test results caused by systematic errors in a single study site.

(2) A randomized design is utilized in this study to ensure comparability between groups and reduce selection bias.

(3) Participating investigators and operators in various sub-sites will be trained on the use of the Theranova 400 Dialyzer; the study must be conducted in strict accordance with the clinical study protocol and China's standard operating procedures for HD.

7.1.4 Study Medical Device and Control Device

(1) Study Medical Device

Product name	Hollow fiber dialyzers with medium cut-off membrane
Model and Specification	Theranova 400
Registrant	Gambro Dialysatoren GmbH
Shelf Life	Refer to IFU
Storage	<30ºC/86ºF
Structural composition	The membrane material used in Theranova 400 is a composite of polyaryl ether sulfone (PAES) and polyvinylpyrrolidone (PVP). Both ends of the dialyzer are filled with polyurethane (PUR) hollow fibers to separate the blood chamber from the dialysate chamber. The inner diameter of each hollow fiber is approximately 180 μm, and the wall thickness is approximately 35 μm. The effective length of the membrane is 236 mm. The number of hollow fibers of Theranova 400 is about 13,000, and the surface area of Theranova 400 is 1.7 m^2. The material used for the dialyzer housing and end caps is polycarbonate.
Scope/Intended Use	THERANOVA dialyzers are indicated for treatment of chronic and acute kidney failure by HD.

(2) Control Device:

Product name	Hollow fiber hemodialysis filter
Model and Specification	FX 800 HDF
Registrant	Fresenius Medical Care AG & Co., KGaA.
Registration No.	GXZJ 20193101929
Shelf Life	Refer to IFU
Storage	Refer to IFU
Structural composition	This product consists of fiber membrane, housing, packaging material, top cover, sealing ring, blood protective cap and dialysate protective cap. The materials of hollow fiber membrane, housing, packaging, topcover, sealing ring, blood protective cap and dialysate protective cap are a mixture of polysulfone fiber-polyvinylpyrrolidone, polypropylene, polyurethane, polypropylene, silicon resin and polypropylene, respectively. This product is sterilized by flowing steam, and it is disposable.
Scope/Intended Use	The product is indicated for conventional HD or HDF treatment.

7.1.5 Patient Selection

7.1.5.1 Inclusion Criteria

All of the following criteria must be met for the patient to be eligible for participation.

1. Patients aged ≥18 years old and ≤80 years old, regardless of gender;

2. Patients who are able to sign informed consent form (ICF) after an explanation of the proposed study;

3. Patients who receive in-center HD treatment at a site that routinely implements high flux dialysis and HDF;

4. Patients who have been stable receiving in-center HD/HDF for >3 months prior to study enrollment;

5. Patients with kidney failure receiving maintained HD treatment with a history of thrice weekly HD, and at least 1 HDF session within 1 month prior to the study shall be judged by the investigator;

6. Patients who have an adequate arteriovenous (AV) fistula or graft, or dual-lumen tunneled catheter capable of providing a blood flow rate (QB) of at least 250 mL/min;

7. Patients have no changes in dialysis prescription (dialyzer, time, dialysis fluid flow rate (QD), QB, sufficient dialysis anticoagulation, and stable prescribed doses) over last 6 treatments as judged by the investigator. The dialysis treatment time should be 3.5 to 4.5 hours per session with minimum QB of 250 mL/min and QD of 500 mL/min;

8. Patients with a minimum total convective volume (including ultrafiltration (UF)) of 16 L post-dilution for the most recent HDF treatment;

9. Patients who have $Kt/V_{urea} > 1.2$ for the last 2 measurements, with the most recent Kt/V_{urea} measurement taken within 4 weeks before or during study screening.

7.1.5.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study:

1. Patients who have acute kidney injury with the chance for recovery;

2. Pregnant and lactating women;

3. Patients diagnosed with a New York Heart Association (NYHA) Class IV congestive heart failure, or acute coronary syndrome, and/or who have suffered a myocardial infarction within 3 months prior to the start of the study;

4. Patients with known hemodynamic instability, anemia (hemoglobin <90 g/L), and/or patients with hemoglobin >130g/L for coagulation risk;

5. Patients with active or ongoing infection as per investigator's judgement (e.g C-reactive protein [CRP] level more than 5 folds of normal);

6. Patients who are severely malnourished or with significant disease that interferes with liver synthetic function (e.g. with serum albumin <30 g/L);

7. Patients with positive serology tests for Hepatitis B surface antigen, Hepatitis C total antibody, and advanced liver, or pulmonary disease as judged by the investigator;

8. Patients with positive serology tests for human immunodeficiency virus (HIV), Syphilis;

9. Patients receiving immunosuppressive treatment or with autoimmune disease;

10. Patients with a history of solid tumors requiring anti-cancer therapy in the past or next 6 months, or with a life expectancy of <1 year, or patients with history of hematology neoplasm;

11. Patients who are pre-scheduled for a living donor kidney transplant within the next 1 year, who plan a change to peritoneal dialysis (PD) within the next 1 year, or who require single-needle dialysis therapy;

12. Patients who have had an allergic response to polyarylethersulfone (PAES) or polysulfone (PS) membrane or have history of poor tolerance to dialyzers with synthetic membranes;

13. Patients with a history of severe mental disorders who are unable to provide consent or comply with study procedures as assessed by the investigator;

14. Patients who are currently participating in or have previously participated in other interventional clinical studies during the past 30 days;

15. Patients with any comorbidity possibly conflicting with the study as judged by the investigator.

7.1.5.3 Study Suspension and Discontinuation

7.1.5.3.1 Criteria for Study Suspension and Discontinuation

The main purpose of study suspension or discontinuation is to protect rights and interests of patients, ensure the study quality and avoid unnecessary economic losses. Study suspension or discontinuation will be performed in case of the following circumstances (including without limitation):

（1） Clinical study institutions and investigators assess that the risks outweigh the benefits if the study continued;

（2） The Ethics Committee finds that the rights and interests of patients cannot be guaranteed;

（3） Discontinuation of study is required by the Sponsor for various reasons;

（4） Discontinuation of study is instructed by regulatory authorities.

7.1.5.3.2 Procedure for Study Suspension and Discontinuation

When deciding to suspend or discontinue the study, the Sponsor shall promptly inform the study management departments of the clinical study institutions who will inform the investigators and the Ethics Committee, and provide them with relevant data supporting this decision. The resumption of the clinical study needs approval of the Ethics Committee. After the end of the clinical study, the sponsor shall inform the Shanghai Medical Products Administration in writing.

7.1.5.4 Patient Withdrawal

7.1.5.4.1 Criteria for Patient Withdrawal:

All patients are entitled to withdraw at any time throughout the study. Patients will withdraw from the study under the following circumstances:

（1） Withdrawal of ICF;

（2） AEs/serious adverse events (SAEs) occur that make treatment inapplicable;

（3） Serious protocol violation;

（4） Death;

（5） Pregnancy;

（6） Kidney transplantation;

（7） Switch to PD;

（8） Other reason.

Process of Withdrawal from the Study:

（1） Details of the time and reasons for withdrawal from the study are recorded in the electronic case report form (eCRF);

（2） Patients' data will not be collected after their withdrawal from the study, but patients who withdraw from the study due to AEs must be followed up until the AEs are stable or resolved or are deemed no need of further follow-up by investigators.

7.1.5.5 Time of Enrollment

All patients who sign the ICF will be enrolled into the study after judged to meet the inclusion criteria but not to meet the exclusion criteria by the investigators.

The enrollment period is expected to be approximately 8 months, which will be adjusted according to the actual enrollment situation.

7.1.5.6 The Expected Overall Duration of Clinical Study and Justification

It is expected that the overall duration of the clinical study is approximately 31 months. The overall duration of this clinical study from preliminary preparation, initiation of sub-site, enrollment of patients to last patient out is approximately 19 months. The database lock, statistical analysis, writing of summary reports and closing of centers will take approximately 12 months. The duration of the study may be adjusted according to the actual progress. If the study is not completed as scheduled, it will be extended accordingly until completion of the study.

7.1.5.7 Expected Duration per Patient

The study will have a duration of 3 weeks at maximum per patient in total see Figure 1). The study will consist of:

（1） Screening Period: 2 weeks;

（2） Treatment Period : 1 week, 1 session in mid-week therapy with either Theranova 400 or FX 800; (Note: visit ought to be conducted within 2 weeks after randomization)

Follow-up review of treatment-related AEs conducted at the next dialysis session (end-week therapy session), but prior to treatment commencement.

7.1.5.8 Sample Size for this Clinical Study

Based on statistical calculation, the effective sample sizes for the test group and the control group are at least 129 and 129 cases, respectively. Taking 5% dropout rate and loss due to major protocol violation into account, the sample size in the test group is 136 cases and that in the control group is 136 cases, 272 cases in total.

7.1.6 Evaluation of Efficacy

7.1.6.1 Endpoints

The following endpoints will be assessed at the mid-week treatment day dialysis session .

(1) Primary Endpoints:

1) RR of λ FLC;
2) RR of β2-MG.

(2) Secondary Endpoints:

1) Kt/V_{urea};
2) Urea Reduction Ratio (URR);
3) RR of α1-MG;
4) RR of YKL-40;
5) RR of CFD;
6) RR of myoglobin;
7) RR of κ FLC.

7.1.6.2 Method for Evaluation, Recording and Analysis of Efficacy Endpoints and Time Selection

7.1.6.2.1 Evaluation Methods

(1) Reduction ratio (RR):

The RR for each solute, based on the change in the arterial plasma concentration over the dialysis session, will be calculated as:

$$RR(\%) = \left(1 - \frac{Cpost}{Cpre}\right) \times 100\%$$

Where C_{Pre} and C_{Post} are the measured arterial plasma concentrations of the solute before and after dialysis, respectively [17].

However, for the middle molecules (λ FLC, κ FLC, α1-MG, CFD, YKL-40, myoglobin and β2-MG) C_{Post} will be first corrected ($C_{Post\text{-}corr}$) for the decrease in total extracellular volume due to fluid removal as follows:

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

Where 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[18].

(2) $spKt/V_{urea}$ refers to single pool Kt/V. The single pool Kt/V will be calculated as[1]:

$$spKt/V_{urea} = -\ln\left[\frac{\text{post dialysis Urea}}{\text{pre dialysis Urea}} - 0.008 \times \text{total dialysis time(h)}\right] + \left[4 - 3.5 \times \frac{\text{post dialysis Urea}}{\text{pre dialysis Urea}}\right] \times \frac{\text{ultrafiltration volume (in liters)}}{\text{post dialysis Weight}}$$

7.1.6.2.2 Time Selection

Blood samples will be taken for testing before and after the dialysis treatment at themid-week treatment day dialysis session.

7.1.6.2.3 Analysis Method

For the statistical analysis method, refer to Section 8.7.

7.1.7. Safety Assessments

1) AEs and SAEs;

2) CRP analysis;

3) Routine serum chemistry and hematology assessments;

4) Vital signs pre- and post-dialysis per treatment.

5) Device deficiencies (DDs) (during use of the investigational product; which would include functional characteristics [e.g., leaks, tubing separations, etc.])

7.1.7.2 Method for Evaluation, Recording and Analysis of Safety Endpoints and Time Selection

7.1.7.2.1 Method for Evaluation and Recording and Time Selection

(1) Endpoints:

1) Adverse events (AEs) and SAEs: All AEs and SAEs occurring in the duration of ICF signing and the end of the trial will be recorded, and SAEs will be reported according to regulatory requirements;

2) C-reactive protein (CRP): Blood will be taken for testing before themid-week treatment day dialysis session

3) Blood routine, electrolytes :

- Blood routine: Hematocrit, hemoglobin , mean corpuscular hemoglobin , mean corpuscular hemoglobin concentration , mean corpuscular volume , platelet count, red blood cell count, white blood cell count, percentage of eosinophils;
- Blood electrolytes: Phosphorus (P), potassium (K), sodium (Na), calcium (Ca), chlorine (Cl).

Blood will be taken for testing before and after the dialysis treatment at the mid-week treatment day dialysis session;

4) Liver function: Blood will be taken for testing before the dialysis treatment at the mid-week treatment day dialysis session;

5) Collecting vital signs (according to various standard operation procedure):

Blood pressure (BP), pulse rate: Before and after the mid-week HD treatment

Respiratory rate and body temperature: Before the mid-week HD treatment;

6) Device deficiencies (DDs) (during use of the investigational product; which would include functional characteristics [e.g., leaks, tubing separations, etc.]). All DDs occurring in the treatment period will be recorded.

7.1.7.2.2 Analysis Method

For the statistical analysis method, refer to Section 8.7.

7.2 Study Process

7.2.1 Study Flow

7.2.1.1 Study Flowchart and Schedule of Events

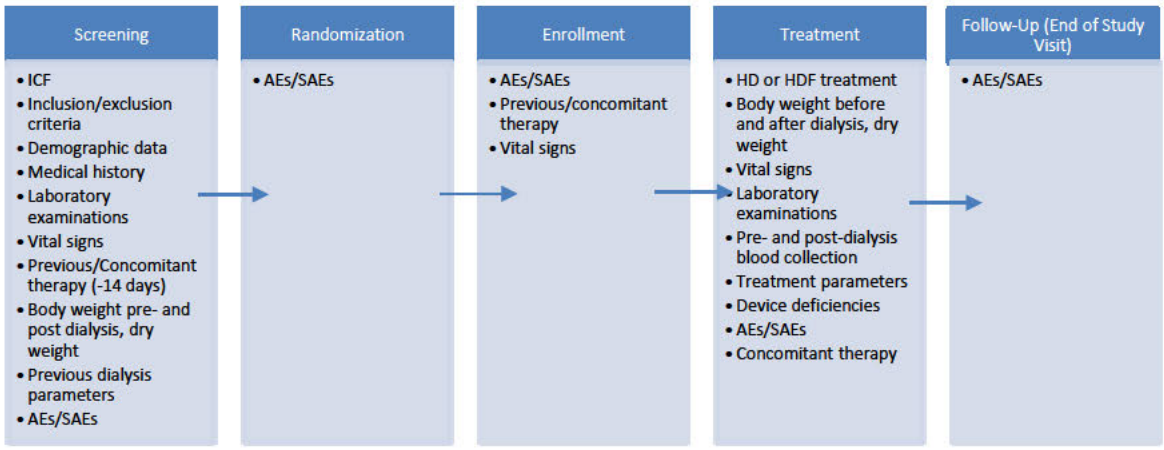


Figure 2: Study Flowchart

Schedule of Events:

Time of visit / Content of visit	Screening Period		Randomization	Enrollment	Visit 1 (Note: Must be conducted in 2 weeks after randomization)		
	Day -14～ Day -1				Mid-week 1		
	Pre-regular Dialysis	Post-regular Dialysis			Pre-Intervention Dialysis (Theranova/ HDF)	Post-Intervention Dialysis (Theranova/ HDF)	Follow-Up
ICF	X						
Inclusion/Exclusion criteria	X						
Demographics[1]	X						
Medical history [2]	X						

Previous dialysis treatment parameters [3]	X						
Laboratory tests (Clinical Laboratory of Study Center)							
Coagulation function [4]	X						
Blood glucose, cholesterol, triglyceride;	X						
Hepatitis B surface antigen,Hepatitis C virus antibody,HIV,syphilis;	X						
Pregnancy blood test [5]	X						
Liver function [6]	X				X		
Blood routine[7]	X				X	X	
Serum Creatinine	X				X	X	
Blood urea nitrogen/Blood urea	X	X			X	X	
CRP	X				X		
Electrolytes [8]	X				X	X	
Laboratory tests (Central laboratory)							
β2-MG					X	X	
α1-MG					X	X	
λ FLC					X	X	
κ FLC					X	X	
YKL-4					X	X	
CFD					X	X	
Myoglobin					X	X	
Serum Albumin					X		
Others							
Vital signs [9]	X			X	X	X	
Pre-dialysis and post-dialysis body weight, dry weight	X	X			X	X	
Treatment parameters [10]					X		
Device Deficiencies[11]					X	X	
Adverse Events	X	X	X	X	X	X	X
Previous/Concomitant medication	X[12]	X		X	X	X	

Note:

1) Demographics: age, sex, height, ethnicity, dialysis vintage
2) Medical history: Including history of kidney disease, presence or absence of complicated tumors, mental disorders, cardio-cerebrovascular diseases, severe liver or lung diseases, history of bleeding, abnormal blood coagulation, and any other medical history referred to inpatient records, history of allergies, frequency of

previous HD treatment, presence of side effects, history of dialysis-related hypotension during dialysis, history of previous infectious diseases (hepatitis, HIV and syphilis, etc.);

3) Previous dialysis parameters: Prescriptions of the last 6 HD treatments [QD, QB, replacement volume, treatment time, type of vascular access, anticoagulant prescription and dosage], dry weight and dialysis initiation time.
4) Coagulation function: Activated partial thromboplastin time (APTT), prothrombin time (PT) and international normalized ratio (INR);
5) Pregnancy blood test (human chorionic gonadotropin): Applicable to women of childbearing age and within 1 year of menopause;
6) Liver function: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, glutamyltransferase (GGT), bilirubin, total bilirubin, total protein, globulin, albumin;
7) Blood routine: Hematocrit, hemoglobin , mean corpuscular hemoglobin , mean corpuscular hemoglobin concentration , mean corpuscular volume , platelet count, red blood cell count, white blood cell count, percentage of eosinophils;
8) Electrolytes: Phosphorus (P), potassium (K), sodium (Na), calcium (Ca), chlorine (Cl);
9) Vital signs: Blood pressure (BP), pulse rate, respiratory rate and body temperature; BP, pulse rate: Before and after the mid-week HD treatment. Respiratory rate and body temperature: Before the mid-week HD treatment ;
10) Treatment parameters: Dialysis date, start time and end time of each HD/HDF session, dialyzer used, the name of dialysate, dialysate type and composition (sodium, bicarbonate, A-concentrate used), programmed QB, QD and ultrafiltration flow rate (QUF; all in mL/min), Initial ultrafiltration volume (unit: L); actual total ultrafiltration volume at the end of treatment (unit:L); supplementary additional collection: scheduled replacement fluid volume and actual replacement volume (unit: L); during the study visit , It needs to be recorded at the beginning of treatment and when QB needs to be adjusted during treatment; QD (mL/min) at the end of treatment, total dialysis time; duration and reason of any treatment interruption;
11) Product complaints will be recorded along with device deficiencies
12) Previous/ Concomitant medications: Previous medications (name of medication, start time of medication, treatment of disease, medication dose and frequency) 14 days before signing the ICF.

7.2.1.2 Screening Phase (day -14 to -1) , Randomization and Enrollment

Patients will enter the screening period only after the ICF has been signed. The maximum duration of the screening period is 2 weeks. Signing of the ICF and the screening visit may take place on the same day, if necessary. The following visit activities should be carried out before dialysis. (Assessment of blood urea nitrogen/blood urea will be conducted after dialysis as well.)

1) The screening number of the enrolled patients will be registered and the inclusion and exclusion criteria reviewed for patients;

2) If the patient meets all inclusion and none of the exclusion criteria, the patient will be assigned random numbers from small to large according to the order in which they are enrolled in the group.

The following data will be collected:

1) Demographic data: Age, sex, height, ethnicity, dialysis vintage;

2) Medical history: including history of kidney disease, presence or absence of combined tumors, mental disorders, cardio cerebrovascular diseases and severe liver and lung diseases, history of bleeding, abnormal blood coagulation, and any other medical history referred to inpatient records , history of allergies, the frequency of previous HD treatments, history of dialysis-related hypotension, and the last 6 diabetes treatments Prescription [QD, QB, replacement volume, treatment time, vascular access type, anticoagulation prescription and dose, dry weight, and dialysis initiation time], presence

of side effects, history of insulin-related hypotension episodes, history of past infectious diseases (Hepatitis, HIV, syphilis, etc.);

3) Coagulation function: Activated partial thromboplastin time (APTT), PT, and INR;

4) Liver function: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, glutamyltransferase (GGT), bilirubin, total bilirubin, total protein, globulin, albumin;

5) Blood glucose, cholesterol, triglyceride;

6) Hepatits B surface antigen,hepatitis C virus antibody, HIV,syphilis;

7) Pregnancy blood test: human chorionic gonadotropin (HCG) blood test, for women of childbearing age and within 1 year of menopause;

8) Blood routine: Hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, white blood cell count, eosinophil percentage;

9) Creatinine;

10) Blood urea nitrogen/blood urea;

11) CRP;

12) Electrolytes: P, K, Na, Ca, Cl;

13) Vital signs: BP, pulse rate, respiratory rate and body temperature;

14) Pre- and Post- dialysis body weight, dry weight;

15) Recording of previous/concomitant medications: Previous medications (name of medcation, start time of medication, disease treatment, medication dosage and frequency) within the 14 days before signing the ICF and concomitant medications after signing the ICF are recorded as previous/concomitant medications in the eCRF;

16) Documented AEs/SAEs.

7.2.1.3 Treatment Period (mid-week session)

（Note: Must be conducted within 2 weeks after randomization）

During the mid-week treatment, the patient will undergo HD/HDF treatment, according to the according to the randomization number corresponding to the treatment group. Blood samples before dialysis should be collected as baseline data for patients. See Section 7.2.3 for detailed requirements for blood sample collection. All the following visit contents need to be collected before and after dialysis except for 24-h urine protein, which needs to be collected only before dialysis.

Parameter setting of HD/HDF treatment: QB ⩾250 mL/min, QD ⩾500 mL/min, QR (including UF)⩾16 L, treatment time: 4 hours.

Items tested at the Clinical Lab of Research Center.

1) Blood routine: Hematocrit , hemoglobin , mean corpuscular hemoglobin , mean corpuscular hemoglobin concentration , mean corpuscular volume , platelet count, red blood cell count, white blood cell count, eosinophil percentage;

2) Creatinine;

3) Blood urea nitrogen/blood urea;

4) CRP;

5) Electrolytes: P, K, Na, Ca, Cl

6) Liver function: ALT, AST, GGT, bilirubin, total bilirubin, total protein, globulin, albumin;

Items need to be tested at the Central Laboratory:

1) β2-MG;

2) α1-MG;

3) λ FLC;

4) κ FLC;

5) YKL-4;

6) CFD;

7) Myoglobin;

8) Serum Albumin

Other visit assessments:

1) Vital signs: collect vital signs pre- and post-dialysis (according to various standard operating procedures): BP, pulse: pre- and post-dialysis; breathing rate and axillary temperature: Before dialysis treatment.

2) Body weight, dry weight (pre- and post-dialysis) ;

3) Treatment parameters: Dialysis date, start time and end time of each HD/HDF treatment, dialysis machine used, name of dialyzer, dialysate type and composition (sodium, bicarbonate, A concentrate used), preset QB, QD and ultrafiltration rate (QUF) (in mL/min), preset ultrafiltration volume (in L); actual total ultrafiltration volume at the end of treatment (unit: L); additional collection in control group: The preset amount of replacement fluid and the actual amount of replacement (unit: L); during the study visit, the QB should be recorded at the beginning of treatment and if there is any adjustment during the treatment; QD (mL/min) at the end of the treatment, and total dialysis time; The duration and reason of any treatment interruption;

4） Device deficiencies.

5) Documented concomitant medications;

6) Documented AEsSAEs.

7.2.1.4 Follow-Up

A follow-up session is to be conducted at the next (end-week dialysis) treatment session. Adverse events which would have occurred on the mid-week treatment day or the day after will be collected during this session.

7.2.1.5 Missed Visits

Under normal circumstances, missed visits will not be rescheduled.

If the patient misses a planned mid-week dialysis treatment, the missed mid-week dialysis treatment will be replaced in the following week, and subsequent visits and follow-ups will be carried out as planned. If the patient cannot make up for the missed mid-week dialysis treatment in the following week, the patient will be withdrawn from the study.

The reason for the missed visit must be recorded on the eCRF.

7.2.1.6 Concomitant Medications during Study Participation

No medicine is forbidden during the participation in the study. Detailed information on any concomitant medication must be documented. Any changes in concomitant medications must be documented in corresponding visits. The information collected on concomitant medications should (or at least) include the trade name or common name of the drug, indications, usage and dosage, start date and discontinuation or persistence state.

7.2.2 Specification on Device Usage

7.2.2.1 Training

People designated by the Sponsor will provide trainings on the use of Theranova 400 dialyzer for investigators participating in the study, including doctors, nurses in the dialysis room, and other operators. The training dates and training materials will be saved in the folders in the research center.

7.2.2.2 Labeling

The Sponsor shall properly mark the medical devices for the study in accordance with the *Regulations on the Administration of Medical Device Insert Sheet and Labeling*, and the labeled contents include: Name of the medical device for the clinical study (marked " for clinical only study"), specification and model, unique number, storage, period of validity, and provider.

7.2.2.3 Reception, Storage and Safekeeping

During this clinical study, the Sponsor will provide a sufficient number of medical devices for each research center. Each research center shall designate special people to be responsible for the reception, storage and safekeeping of medical devices for the study, and fill in the relevant records as required.

The clinical study institutions and investigators shall be responsible for the use of medical devices for the study, and shall not transfer them to any non-participant of the clinical study. The investigators should ensure that all devices for the study are used only for the patients of this clinical study.

7.2.2.4 Disposal and Recovery

All medical devices used in the research center must be disposed of according to the requirements of the research center.

When the research is completed, all unused medical devices of the treatment group shall be returned to the Sponsor or Sponsor's designee.

7.2.2.5 Documentation

The investigators shall save the disposal records of relevant medical devices for the study, mainly including but not limited to:

（1） Reception date of the research center;

（2） Quantities of medical devices received;

（3） Label of medical devices (batch/lot numbers or unique code number); ;

（4） Date of use;

（5） Patient identifier (unique identification number);

（6） Date of return of unused, expired or malfunctioning medical devices (if applicable).

The Sponsor shall be responsible for the production and inspection records such as the production date, batch number, serial number and inspection report of the devices for the study, as well as the transportation and use records when the device is delivered to the clinical study institutions and the records of recovery and disposal after the study.

7.2.3 Operating Procedure

7.2.3.1 Hemodialysis Operation

See Appendix 2 for this operating procedure. It is prepared with reference to *Blood Purification Standard Operating Procedure (2021 Edition)* and only provides suggestions for the operations in this study. If the centers have relevant standard operating procedures (SOP), they can also operate in accordance with the SOP of this center.

7.2.3.2 Hemodiafiltration Operation

See Appendix 3 for this operating procedure. It is prepared with reference to *Blood Purification Standard Operating Procedure (2021 Edition)* and only provides suggestions for the operations in this study. If the centers have relevant SOP, they can also operate in accordance with the SOP of this center.

7.2.3.3 Blood Sampling

The research center or central laboratory will collect, store, transport, and process all blood samples in accordance with the requirements and operating procedures of the clinical trial center. The special requirements related to blood sample collection specified in this test protocol shall be subject to the description of this test protocol. Before the start of the study, the relevant parameter detection methods, units and normal ranges involved will be provided to the Sponsor.

Patients will be in supine position during blood collection. No puncture of the patient is necessary, as the blood samples will be taken from the fistula needle or from the sampling port of the blood line. The specific requirements are as follows:

Figure 3: Blood Sample Requirements

	Pre-Dialysis	Post-Dialysis

Sampling location	Blood samples from fistula needle or central venous catheter.	Blood samples from arterial sampling port of bloodline.
Sample tube	Prepare the sample tube according to substance to be analyzed.	Prepare the sample tube according to substance to be analyzed.
Sampling method	□ Patients withAV fistula: Blood samples are taken from the access needle immediately following needle insertion. The pre-dialysis blood sample must be drawn before injecting saline, heparin, or other potential diluents. □ For patients with a central venous catheter, the first 10 mL of blood drawn before dialysis must be discarded before sampling. This is done to avoid dilution by the heparin tube sealing solution.	□ The post-dialysis blood sample should be drawn from the arterial end using a slow-flow method (ultrafiltration flow rate [QUF] is first set to 0 mL/min, followed by a QB of 100 mL/min. Sampling can then be carried out after 15-30 seconds). □ Post-dialysis blood sampling will be done within 240 ± 5 minutes of treatment time. □ For patients in whom the dialysis treatment stops earlier due to reasons other than the dialyzer: blood sampling can be completed at the end of the dialysis treatment if the actual treatment duration is at least 210 minutes.

7.2.4 Possible Adverse Reactions from use of Dialyzer and their Management [20]

（1） If blood leakage is found inside the dialyzer, the operator must stop the treatment and replace the dialyzer. Do not return the blood to the patient since it may have become contaminated by the dialysis fluid. If necessary, administer adequate replacement solution to the patient to compensate for the blood loss.

（2） If an external blood leak is observed, secure connections or replace the dialyzer. If necessary, an adequate replacement solution should be administered to the patient to compensate for the blood loss.

（3） If a dialysate compartment leak is observed the operator has to check the correct placement of the dialysate connectors or to stop the treatment and replace the dialyzer. If necessary, administer adequate replacement solution to the patient to compensate fluid imbalance.

（4） If air enters the extracorporeal blood circuit, an air embolism may occur. This can be hazardous to the patient. To minimize the risk of air embolism, constant monitoring of the extracorporeal blood circuit, both visually and with an air detector, is recommended. Strict adherence to the manufacturer's recommended activities will facilitate the removal and prevent the accumulation of air in the dialyzer before the treatment session. If air

enters or is identified in the dialyzer during priming and cannot be removed with the use of additional priming, the dialyzer must be replaced.

（5） If clotting occurs in the dialyzer, both the dialyzer and the blood lines must be replaced. Flush the vascular access devices according to clinic procedure. Discard the dialyzer and the blood lines. Do not return the blood to the patient.

7.2.5 Adverse Reactions of Hemodialysis and Handling [1]

The following are adverse reactions that have been reported related to HD therapy: hypotension, muscle cramps, nausea, vomiting, and headache, etc. For details, refer to Appendix 4.

7.2.6 Adverse Reactions of Hemodiafiltration and Handling [1]

Patients may experience similar complicationsas those related toHD and hemofiltration during HDF, in addition to the following: reverse ultrafiltration and wasting syndrome. For details, refer to Appendix 5.

8. Statistical Considerations

8.1 Statistical Design, Methods and Analysis Procedures

The analysis details of the planned statistical methods will be provided in the study statistical analysis plan (SAP). The draft SAP is formed after determination of the study protocol and eCRF. It will be finalized prior to database lock.

8.2 Determination of Sample Size

8.2.1. 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).

8.2.1.1 Sample Size Calculation in regard to λ FLC Reduction Ratio

A previously conducted Theranova HDF study [21] 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).

8.2.1.2 Sample Size Calculation in regard to ß2- MG Reduction Ratio

A previously conducted Theranova HDF study [21] 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).

8.2.1.3 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).

8.2.2 Sample Size for each Disease and Justification

This clinical study does not involve the determination of sample size for each disease.

8.3 Significance Level and Power of Clinical Study

A 0.025 one-sided significance level and a power of 90% were used in planning this study.

8.4 Expected Dropout Rate

It is estimated that the expected ratio of cases with dropout or serious protocol violations is about 5%.

This ratio refers to the proportion of patients who ultimately cannot be evaluated for primary efficacy on the per-protocol analysis set. This part of patients are those who have been dropped out or have serious protocol violation (affecting the evaluation of primary endpoints) after confirmed by the principal investigator (PI).

8.5 Eligibility/Fail Criteria for Clinical Study Results

Let μ_T denote the Theranova 400 treatment mean and let μ_R denote the FX 800 treatment mean. The statistical hypothesis of the study can be written as:

Ho: $\mu_T-\mu_R \leq -\delta$

Ha: $\mu_T-\mu_R > -\delta$

When evaluating the primary endpoint of λ FLC, the non-inferiority margin is -3.783 (10% of assumed mean RR of 37.83%). When evaluating the primary endpoint of ß2-MG RR, the non-inferiority margin is -7.848 (10% of assumed mean reduction ratio of 78.48%). When the non-inferiority of the two primary endpoints of λ FLC and β2-MG RRs are both established, the non-inferiority of this study is established.

8.6 Criteria for Discontinuation of Study Based on Statistical Reasons and Justification

No statistical stopping rules are stipulated for this study.

8.7 Statistical Methods of all Data, together with Processing of Missing, Unused or Erroneous data (including midway exit and withdrawal) and Unreasonable Data

8.7.1 Data Statistical Analysis

8.7.1.1Analysis of Primary Endpoints

For the λ FLC and ß2-MG RR endpoints, let μ_T denote the Theranova 400 treatment mean and let μ_R denote the FX 800 treatment mean. Then the null hypothesis to demonstrate non-inferiority using a 10% margin for λ FLC RR can be expressed as: Ho: μT-μR≤-3.783. The alternative hypothesis is expressed as: Ha: μ_T-μ_R>-3.783. A 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 > -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 > 0, then superiority of Theranova 400 treatment over FX 800 treatment can be concluded.

Equivalently the null hypothesis to demonstrate non-inferiority using a 10% margin for ß2-MG RR can be expressed as Ho: μ_T-μ_R⩽-7.848. The alternative hypothesis is expressed as: μ_T-μ_R >-7.848. A 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 > -7.848, then non-inferiority between the Theranova 400 and FX 800 treatment group can be demonstrated for ß2-microglobulin RR. If the lower bound of the CI > 0, then superiority of Theranova 400 treatment over FX 800 treatment can be concluded.

Two sensitivity analysis will be conducted for both endpoints:

1. An ANOVA model 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.

A non-parametric method: Wilcoxon Rank-Sum Test will be used to analyze the primary endpoints.

In case the assumption of a normal distribution is not justified, RRs can be log transformed in order for the measurements to follow a normal distribution. If, after transformation, measurements do still not follow a normal distribution, above statistical analyses methods will be replaced with their non-parametric equivalents. The Wilcoxon Rank-Sum Test will be used in place of the t-test while the Kruskal Wallis test will be used in place of the ANOVA.

8.7.1.2 Analysis of Secondary Endpoints

Secondary endpoints will be evaluated as follows:

A t-test or Wilcoxon Rank-Sum test, as applicable, will be used to evaluate differences between treatment groups in Kt/V_{urea} and URR.

A t-test orWilcoxon Rank-Sum test, as applicable, 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.

8.7.1.3 Analysis of Safety Endpoints

Safety endpoints will be evaluated as follows:

1. The summary of AEs will include AEs that occur on the day of or after the study treatment. Pre-treatment AEs including AEs reported at Screening and Randomization will be recorded in the eCRF but will not be summarized in the safety tables. Adverse events will be mapped to a Primary System Organ Class (SOC) and Preferred Term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA) and summarized descriptively by SOC, PT and treatment group. Treatment group comparability in the incidence of AEs will be evaluated using Fisher's exact test. An overview (overall) summary table of all AEs will be generated that includes the total number of AEs, number and percentage of patients with at least one AE, number and percentage of patients with at least one SAE, number and percentage of patients with at least one severe AE, number and percentage of patients with at least one AE probably associated with study treatment, number and percentage of patients with an AE leading to study discontinuation and number and percentage of patients with an AE leading to death. This summary will be presented by treatment group and combining both groups (Total). In addition, two separate AE summary tables will be provided, one for analysis by severity and relationship to the study dialyzer, and the other will provide a separate AE summary table for SAEs and AEs that led to withdrawal from the study.
2. Device deficiencies (DD) will be summarized descriptively.
3. Serum chemistry, hematology assessments, liver function, patient vital signs, and CRP will be summarized descriptively per measurement time point using n, mean, median, standard deviation, minimum, and maximum.

8.7.1.4 Other Assessments

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.

8.7.2. Processing of Missing, Unused or Erroneous Data (including midway exit and withdrawal) and Unreasonable Data

All missing, unused or erroneous data (including midway exit and withdrawal) and unreasonable data will be discussed and finalized determined by the investigators and biostatisticians during the data review phase. The basic statistical principles of these data processing are as follows:

（1） Describe the details of each dropout case, and compare the dropout between the test group and the control group by using χ^2 or Fisher's exact probability method;

（2） Missing data at baseline will not be imputed;

（3） Missing values of primary efficacy endpoints of λ FLC and β2-MG RRs will not be imputed.

（4） Missing values of the secondary efficacy endpoints and safety endpoints will not be filled;

（5） Erroneous and unreasonable data will be processed as missing values;

（6） Sensitivity analysis will 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.

8.8 Procedures for Reporting Deviations from the Original Statistical Program

Generally, only the statistical analysis content stipulated in advance in the statistical analysis plan can be presented in the clinical study report of this study. The additional statistical analysis due to various uncertain reasons is only for exploratory purpose.

Any deviations from the statistical analysis plan will be documented and described with details.

8.9 Criteria for Selection of Patients Included in the Analysis and Justification

(1) Intention-to-treat FAS: Includes all randomized patients. Patient assignment will be based on the treatment randomized.

(2) Per-Protocol Set (PPS): Is a subset of the FAS and meets the following requirements: Patients were randomized to the respective treatment at themid-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: :

1) 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 themid-week treatment day dialysis session; patients in control group who actually do not achieve at least 16 L convective volume (including UF)

2) The actual dialysis time of the patient is < 210 minute at themid-week treatment day dialysis session.

(3) Safety analysis set (SS): Includes all enrolled patients (ICF signed) that have been treated. Patient assignment will be based on actual treatment received.

The analysis of the primary endpoint will be based on the PPS, with a supportive analysis of the primary endpoint based on the FAS. Unless otherwise specified, the remaining analyses will be based on the FAS. All safety related analyses will be based on the SS.

8.10 Exclusion of Special Information when Verifying Assumptions and Justification, if applicable

Not applicable.

8.11 Interim Analysis

A blinded interim analysis for sample size re-estimation will be conducted when approximately 50% of patients complete theirmid-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 [22].

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 themid-week treatment day dialysis session. For sample size re-estimation, for each primary endpoint, the same sample size calculation as outlined in Section 8.2 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.

This interim analysis does not involve comparison of efficacy between groups, and will be performed by the sponsor or a Contract Research Organization (CRO) or a third party authorized by the sponsor. The details will be described in the Statistical Analysis Plan.

9. Data Management

In principle, the Sponsor and the initiating unit are jointly responsible for data management and analysis in the clinical study. In this study, data management will be carried out by the data management specialist from the CRO with the approval of the Sponsor. The data management specialist will develop the Data Management Plan (DMP) according to the project requirements and carry out data management based on the DMP to ensure the authenticity, integrity and traceability of clinical study data.

9.1 Original Documentation Forms

The original materials can prove the authenticity of the patients and the integrity and authenticity of the data. All data recorded in the electronic data capture (EDC) system are derived from the original data and should be consistent with the original materials. If the data in EDC system is inconsistent with the original materials, it is necessary to make modifications according to the original materials or provide reasonable explanations. The original materials are stored in each study site. The original materials include but are not limited to the following documents:

- Outpatient medical records and medical records for HD treatment;
- HD (filtration) treatment record sheets;
- Laboratory test reports;
- Other medical examination reports;
- ICFs;
- Medical device use records, etc.

9.2 Electronic Data Capture System

In this study, data will be collected by using an EDC system, which is well validated to enable preservation of audit trails and good management of accounts and authorities.

The EDC system will automatically retain the audit trail of data, including the time of data entry and change, operator, data operator's name, reason for change, data value before the change, and data value after change, so as to ensure the traceability of data.

The system administrator creates accounts for different roles, grants different access permissions, and strictly manages and controls the application and cancellation of accounts.

9.3 Design of Electronic Case Report Form

The data management specialist firstly designs the eCRF according to the study protocol and the Clinical Data Acquisition Standard Harmonization (CDASH), and then the database designer establishes the eCRF in EDC and sets the procedure for logic verification of the data to be collected; The database can be only launched upon the test by t the data management specialist.

9.4 Electronic Case Report Form Completion

The eCRF will be completed by the investigator or authorized clinical research coordinator (CRC) according to the source documents (including original medical records, examination reports, etc.). The investigator is responsible for timely and accurately entering the study data into the EDC system. The clinical research associate (CRA) approved by the Sponsor is responsible for confirming that all data records and reports are correct and complete, and that all data in the EDC system are consistent with the original materials.

9.5 Data Verification and Query Management

The reliability, completeness and accuracy of data in the EDC system will be verified according to the Data Verification Plan (DVP) which mainly includes logic verification and manual verification. Data entry into the EDC system will be performed by the investigator or the staff designated by the investigator with their accounts. The data management specialist is responsible for data validation. If questionable data are found, queries could be raised in the system. The investigator or the staff designated by the investigator will verify and corrected the data or respond to the queries. All data modifications would have modification trace in the system. If CRA may also raise queries in the system if questionable data are found when performing source data verification (SDV).

9.6 Medical Monitoring

Medical monitoring will be completed by the medical monitor throughout the study, including but not limited to review of eligibility, protocol violations, periodic clinical study data, and treatment data.

9.7 Data Quality Assurance

This study will use quality control and data validation processes to ensure the reliability and accuracy of the clinical database. The Monitoring Plan and DMP will detail the data entry, verification, clarification and validation processes to be followed by all relevant study personnel

to ensure compliance with Good Clinical Practice.

9.8 Data Management Plan

The medical coder will be responsible for medical coding in this study. The MedDRA will be used for coding of AEs and past medical history, while WHO (World Health Organisation) Drug Dictionary will be used for that of concomitant medications. The medical coding will follow the *Medical Coding Plan*, which specifies in detail the contents of medical coding entries, dictionary version, dictionary update, coding review, etc.

9.9 External Data Management

The external data for this study are test results from the central laboratory and will be managed according to the External Data Transmission Agreement.

9.10 Blind Review

Before locking the clinical study database, the Sponsor's representative, PI, statistical analyst and data management specialist blindly review the data, jointly review the questionable data, divide the statistical analysis population according to the clinical study protocol and sign the decision on the division of the statistical analysis population.

9.11 Database Locking

After all the queries are answered and the data in the database are confirmed to be complete and accurate, the database will be locked by the database management specialist with the joint approval of the Sponsor's representative, PI, statistical analyst and data management specialist.

9.12 Submission and Archiving of Data Management Documents

After the database is locked, the data administrator shall write Data Management Report based on the actual implementation of the project, and complete the submission and archiving of paper and electronic documents according to the project document management requirements.

The data management specialist submits the data to the statistical analyst. The statistical analyst will perform statistical analysis according to SAP.

10. Feasibility Analysis

10.1 Analysis of the Possibility of Success

(1) This study will be conducted in accordance with the study protocol developed in accordance with the Declaration of Helsinki (the 64th WMA General Assembly, Fortaleza, Brazil, October 2013), the *Good Clinical Practice for Medical Devices (GCP)* (CFDA, NHFPC Order No. 25), the *Provisions for Medical Device Registration* (CFDA Order No. 4) and other relevant regulations.

(2) The Ethics Committee of the initiating unit is responsible for reviewing the ethics and scientificity of the study protocol. The Ethics Committee of each clinical study institution reviews the feasibility of the study, the qualification and experience of the investigators, and the equipment and conditions. Patients will be recruited volunteers who understand the objectives of the study and have adequate compliance with the study protocol. By

signing the ICF, the rights and interests of the patients will be fully guaranteed, which provides a guarantee for the completion of the clinical study.

(3) Before the start of this study, the Sponsor or its designee will conduct unified training on the investigational medical device, study protocol and study-related data, unified recording method and evaluation criteria for the relevant personnel participating in this clinical study.

(4) Theranova 400 has been marketed in 44 countries or regions around the world with more than 3.5 million devices used, and some clinical efficacy and safety data have been accumulated. Moreover, its composition structure and technical standards comply with the requirements of relevant national and indusstudy standards, and all the technical requirements for product safety and performance have passed the relevant tests by Guangdong Medical Device Quality Supervision and Inspection Institute.

(5) The participating units of this clinical study are qualified as national clinical study institutions for drugs/medical devices, and have rich clinical study experience and good quality control system.

(6) All the staff participating in this study have received unified training and have a high standard of GCP regulations, which can ensure that all the original data such as observation results and laboratory tests in the clinical study are carefully recorded and verified, and finally ensure that all the conclusions drawn after the completion of the clinical study are derived from the real original data.

In summary, the success of this clinical study is highly controllable.

10.2 Analysis of the Possibility of Failure

(1) Failure to strictly implement the clinical study protocol, failure to operate, inspect and evaluate in accordance with the specifications, failure to reach approximately 308 valid cases and other factors may cause the failure of this study, but these factors are still controllable.

(2) The patients enrolled in this study are patients with chronic kidney failure requiring HD/HDF treatment. The patient may have other complications. The improvement of various indicators after treatment is related to the patient's underlying diseases and treatment compliance, not completely dependent on the investigational product. During this study, the investigator will complete the relevant examinations according to the requirements of the protocol, strictly implement the inclusion and exclusion criteria of cases and carry out the treatment in strict accordance with the requirements of the protocol, avoiding the inclusion of patients who cannot finish the expected treatment and have poor compliance, so as to reduce the interference factors as far as possible.

(3) The investigators participating in this clinical study shall be trained in product knowledge and operating procedures by the personnel designated by the Sponsor to ensure that the treatment operators are skilled. During the operation, the occurrence of AEs will be closely observed and a detailed treatment plan will be developed to prevent the occurrence of AEs.

In conclusion, this clinical study is less likely to fail.

11. Quality Control of Clinical Study

11.1 Site Quality Control

In order to ensure the quality of the study, the PIs participating in the study jointly discuss and develop the clinical study protocol before the study is officially initiated.

The Sponsor or person who's assigned shall organize the trainings on relevant laws and regulations, study protocol, principle of the investigational medical device, scope of application, product performance and treatment instructions for the personnel participating in the clinical study prior to the initiation of the clinical study, so as to improve each participant's understanding of relevant laws and regulations, study protocol and investigational medical device and to master and strictly implement the clinical study protocol to ensure the study quality.

It is necessary to ensure the accuracy, consistency, completeness and credibility of the data collected during the study. All the observed results and abnormal findings in clinical studyies shall be timely and carefully verified and recorded to ensure the reliability of data. During the clinical study, the study site and central laboratory should provide laboratory qualification certificates (such as inter-laboratory quality assessment certificate) for regular quality control.

11.2 Monitoring

The CRA approved by the Sponsor shall perform regular and irregular monitoring during the study. The CRA shall fulfill the responsibilities specified in GCP and be responsible for monitoring whether the study personnel follow the study protocol and accurately record the study results; During each monitoring, the CRA must compare the eCRFs with original CRFs and inform the investigator of any omissions or errors. Moreover, the CRA should also verify that all AEs are recorded and that SAEs or device deficiencies are reported and recorded within the required time. The CRA should submit a written report to the Sponsor in a timely manner after monitoring.

11.3 Audit and Inspection

The study site must also be subject to audits by auditors appointed by the Sponsor in accordance with GCP requirements. The auditors conduct systematic and independent inspection on clinical study-related activities and documents to evaluate and determine whether the study is conducted in accordance with the study protocol, standard operating procedures and relevant regulatory requirements, and whether the study data are recorded in a timely, true, accurate and complete manner. The audit does not directly involve the personnel conducting the clinical study.

The regulatory authority may inspect the documents, facilities, records and other aspects related to the clinical study.

12. Ethical Review and Informed Consent

12.1 Ethical Considerations

(1) Ethical review and informed consent are the main measures to ensure the rights and interests of patients. The parties participating in this study shall assume corresponding ethical responsibilities according to their responsibilities in the study.

(2) This clinical study conforms to the ethical principles in the Declaration of Helsinki (the 64th WMA General Assembly, Fortaleza, Brazil, October 2013) and GCP and other relevant regulations, and the clinical protocol has been designed with full consideration of the rights and interests of patients.

(3) The Ethics Committee of a medical device clinical study institution shall be composed of at least 5 members, including medical professionals and non-medical professionals, of which there shall be members of different genders. At least one of the non-medical professional members is a legal worker and one is a person other than the site. The members of the Ethics Committee shall have the qualification or experience in assessing and evaluating the science, medicine and ethics of the clinical study. All the members shall be familiar with the ethical guidelines and relevant regulations for medical device clinical studys and abide by the articles of association of the Ethics Committee.

(4) Before the start of the study, the study protocol, ICF, patient recruitment procedures, and other written documents provided to the patients should be reviewed and approved by the Ethics Committee. Any amendment to the above documents should be re-approved by the Ethics Committee. The investigator may start screening a patient only after the written approval of consent has been given by the Ethics Committee.

12.2 Informed Consent

Before a patient participates in the study, the investigator should fully explain the details of the clinical study to the patient or the guardian of the patient with no or limited civil capacity, including known and foreseeable risks and possible AEs.

The patient or his/her guardian shall sign and date the ICF upon the investigator's full and detailed explanation, and the investigator shall also sign and date the ICF. For the incapacitated patients, if the Ethics Committee agrees in principle and the investigator believes that the patients' participation in the clinical study is in their own interests, they may participate in the clinical study upon the signature of their guardians before the study. If either the patient or his/her guardian cannot read, a witness should be present in the process of being informed. If important information or unexpected clinical effect involving the investigational medical device is found, the investigator and Sponsor should modify the Informed Consent Form. After the revised Informed Consent Form is approved by the Ethics Committee, the affected patients or their guardians should sign for confirmation again. A copy of the signed and dated Informed Consent Form shall be kept by the investigator and patient, respectively.

By signing the Informed Consent Form, the patient agrees the CRA/Auditor/Ethics Committee/regulatory authorities to verify the obtained original data of the clinical study to determine the reliability of such data.

13. Provisions for Reporting Adverse Events and Product Complaints

13.1 Adverse Events

13.1.1 Definition of Adverse Events

Table 1. Adverse Event Term Definitions

Adverse Event (AE)	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*
Serious Adverse Event (SAE)	An SAE is any untoward medical occurrence in the clinical study that is life-threatening or leads to serious deterioration in health including: Fatal illness or injury; Persistent impairment of any body structure or body function; Hospitalization or prolongation of existing hospitalization; Medical or surgical intervention to preclude permanent impairment to any body structure or body function; Fetal distress, fetal death, or congenital abnormalities, congenital defects and other events. *Chinese medical device GCP Article 93*
Device Deficiency (DD)	DDs refer to unreasonable risks of medical devices under normal use during the process of clinical trial that may endanger human health and life safety, such as label error, quality problem and fault. *Chinese medical device GCP Article 93*

13.1.2 Safety Reporting

All AEs observed by the study personnel or reported by the patient during the course of the study will be documented from the time of signing the ICF (i.e., enrollment) through the final assessment visit (i.e., End of Study Visit). All device deficiencies (DD) observed by the study personnel or reported by the patient during the treatment period will be documented.

Any medical condition that is present at the time that the participant is screened will be considered medical history and not recorded as an AE or SAE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE or SAE in the eCRF.

If a definitive diagnosis has been medically established by the physician caring for the patient or by the investigator, this diagnosis should be recorded as the AE or SAE. If a definitive diagnosis has not been medically established, the signs and symptoms should be recorded as the AEs or SAEs. Once the diagnosis is confirmed, the eCRF should be updated from signs and symptoms to the diagnosis.

If a patient is given a diagnosis and also experiences a complication of the diagnosis (e.g., myocardial infarction with congestive heart failure), both the diagnosis and the medical complication should be collected and recorded as separate events.

Adverse events or SAEs that change in severity will be documented only once with the highest degree of severity.

An elective procedure/surgery that occurs during the course of the study but is being performed for a documented pre-existing condition and was pre-planned prior to study entry will not qualify as an AE or SAE. If, however, the pre-existing condition unexpectedly deteriorates during the study requiring the procedure/surgery to be performed earlier than planned, the condition for which the procedure/surgery is being performed will qualify as an AE or SAE (refer to Table 1).

Laboratory and vital sign abnormalities qualify as AEs if medical intervention is required to treat or address the abnormality, if the patient must be discontinued from the study due to the abnormality, or if the investigator determines the value is clinically significant.

For all AEs associated with patients, a full description of the event should be recorded in the eCRF including the date and time of onset (when the signs and symptoms of the event began), outcome, seriousness, severity, event description, actions taken, and causal relationship of the AE or SAE. Investigators should review and reference the severity (refer to Table 2) and causality definitions (refer to Table 3) when determining relationship of the AE or SAE to the study device and procedure. The investigator may also discuss the event(s) with the Sponsor's Medical Monitor or designee.

For all AEs associated with users or other persons (not the study patient), a full description of the event should be recorded on the paper AE form and sent via email to Sponsor designee and Baxter Global Patient Safety Medical Device Vigilance [redacted].

All AEs and SAEs should be actively solicited and documented in the eCRFs, no matter how common they are for a patient and regardless of the causality assigned by the investigator. Additionally, any AE and SAEs voluntarily reported by the patient should be recorded in the eCRF and verified by the investigator or designee with the relevant source documents.

The outcome/resolution of all AEs and SAEs will be determined by the investigator and documented in the eCRF. Investigators will follow all unrelated AEs and SAEs until resolution, stable, or the end of the study, whichever occurs first, and follow all study device-related and procedure-related AEs and SAEs until resolution or stable, including following the patient after the end of the study if necessary. Outcomes and other relevant information obtained after the end of the study will be reported via the paper AE form and sent via email to Baxter Global Patient Safety Medical Device Vigilance [redacted].

For the outcome categories that can be used in the eCRF by the investigator refer to Table 4.

During the study period, if a patient experiences an AE which is considered causally related to a Baxter medicinal/drug product (not the study medical device or comparator), the event shall be forwarded by the investigator or designee within 24 hours of becoming aware of the AE to Baxter

Global Patient Safety [redacted] for assessment as per Baxter's process for case processing of spontaneous reports.

Table 2. Severity Assessment *

Criterion	Definition
Mild	Transient, mild, no influence on daily life and activities, no special measures or treatment required.
Moderate	Slight influence on daily life and activities, and measures or treatment should be taken when necessary.
Severe	Seriously affecting daily life and activities, special measures or treatment must be taken, and hospitalization is required when necessary, which may be life-threatening.

**Severity assessment based on the Chinese medical device GCP*

Table 3. Causality Assessment *

Classification	Causality Criteria	Causal Association
Definitely Related	The AE occurs in a temporal sequence consistent with the use of the medical device, and the AE is consistent with the known type of AE of the device. The improvement occurred after stopping the use of the device, and the AE could not be explained by other reasons.	YES
Probably Related	The AE occurs in a temporal sequence consistent with the use of the medical device, and the AEis consistent with the known type of AE of the device. Improvement after discontinuation of the device, the patient's clinical status, or other modes of treatment may also contribute to the AE.	YES
Possibly Related	The AE occurs in a temporal sequence consistent with the use of the medical device, and the AE is consistent with the known type of AE of the device. The AE may also occur due to the patient's clinical status or other treatment.	YES
Possibly Unrelated	The AE does not occur in a temporal sequence consistent with the use of the medical device, and the AE is not consistent with the known type of AE of the device. The patient's clinical status or other treatment modality may have contributed to the AE.	NO
Definitely Unrelated	The AE does not occur in a temporal sequence consistent with the use of the medical device, the AE is not consistent with the known type of AE of the device, and the AEs does not disappear after stop using the device. The AE may be caused by the patient's clinical status or other	NO

Table 3. Causality Assessment *

	treatment methods. The AE is resolved when the disease status is improved or other treatment methods are stopped. The AE occurs when other treatment methods are reused.	
Unable to Judge	It cannot be assessed with the above rationale.	YES

**Causality assessment based on the Chinese medical device GCP*

Causality: Performed by a medical professional and is a determination of whether there is a reasonable possibility that a medical device/procedure is etiologically related to/associated with an AE. Causality assessment includes, for example, assessment of temporal relationships, underlying disease, presence (or absence) of a more likely cause, and physiologic plausibility. Investigator shall provide an alternative etiology for SAEs that are definitely unrelated or possibly unrelated to use of study medical device. If the alternative etiology is unknown, investigator shall document "unknown."

For AEs with causal relationship (Definitely Related, Probably Related, Possibly Related or Unable to Judge) to Theranova 400, the AE must also be reported as a device deficiency to the Sponsor.

Table 4. Outcome Conclusion *

Symptoms disappear (with or without sequelae, record sequelae).
The symptoms were improved.
Persistent symptoms.
Death (direct cause of death and time of death are recorded).
Unknown (record reason).

**Outcome conclusion based on the Chinese medical device GCP*

13.1.2.1 Adverse Events, Serious Adverse Events and Device Deficiency Reporting

The principal investigator shall:

a. Record every AE, SAE and DD including assessment and full description of each event.

b. Report to the Sponsor or designee within 5 business days of awareness, all non-serious AEs.

c. Report to the Sponsor or designee within 24 hours of awareness, all SAEs and DDs. Each SAE should be documented on a separate SAE eCRF. Each DD should be documented on a separate DD eCRF. In addition, SAEs should be reported to Sponsor or designee in written form.

d. Report to the Ethics Committee, SAEs and DDs, if required by national or local regulations or by the Ethics Committee.

e. Supply the Sponsor or designee, upon Sponsor's or designee's request, with any additional information related to the safety reporting of a particular event.

f. After study completion, report any SAEs within 24 hours after awareness on the paper AE form to the Sponsor [redacted]

13.1.2.2 Pregnancy Reporting

If a female study patient or a study patient's partner becomes pregnant during the study patient's participation in the trial, the pregnancy must be reported by investigator to Sponsor designee and Baxter Global Patient Safety Medical Device Vigilance [redacted] within one business day of awareness using the Pregnancy Report Form. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) irrespective of relatedness to the study medical device or procedure are considered SAEs, and the reporting time period is the same as it is for SAEs.

13.2 Product Complaints

A Product Complaint (PC) includes any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product after it is released for distribution or related to a service that affects the performance of such product. A complaint may involve the possible failure of the product itself, its packaging, or its labeling (i.e., product label, package insert, or any instructions for use).

Reports of off-label use (in the absence of a device allegation or associated AE) are considered use error and need to be reported as complaints.

When a product complaint is encountered with a Post-Marketed Baxter product, the information should be reported to Baxter by the investigator to [redacted] within 24 hours of awareness of the event using the Product Complaint form. This should also include AEs with a positive causal relationship to a Post-Marketed Baxter device.

When a DD for the pre-marketed investigational device (Theranova dialyzer) is encountered, the information should be reported on the DD eCRF form and analysed by Baxter PMS (via [redacted]). Product complaints reported for the comparator product will be collected based on each study site's established PC reporting processes and sent to the product manufacturer. Baxter will not analyze comparator-related PCs.

13.3 Safety Reporting to Authorities and Ethics Committee

It is the responsibility of the investigator to report any SAEs and DDs to Ethics Committee, according to national or local regulatory requirements. Sponsor or designee will report applicable AEs and DDs to regulatory authorities according to written guidelines, including timelines.

14. Determination, Deviation and Amendment of Clinical Study Protocol

14.1 Determination of the Clinical Study Protocol

The clinical study protocol shall be reported to the Ethics Committee of the clinical study institution for review and approval after discussion, and filed at the provincial regulatory authority in the place where the Sponsor or its designee is located in accordance with the requirements in CFDA Announcement [2015] No. 87. The clinical study can only be conducted after filing.

14.2 Deviations from the Clinical Study Protocol

The investigator should strictly follow the clinical trial protocol and should not intentionally deviate from the protocol or materially change the protocol. However, in the event of an emergency that requires emergency treatment, such as when the patient is at immediate risk, a written report may be made afterwards.

If the investigator unintentionally fails to follow the clinical study protocol, the investigator should timely report to the competent medical device clinical study administration, and notify the Sponsor and the Ethics Committee in time.

For any protocol deviation, the investigator must record the reason, date and in major / minor deviation deviation in the original documents.

Protocol deviations include but are not limited to:

(1) The selected patients do not meet the inclusion criteria or meet the exclusion criteria;

(2) Failure to perform or accurately perform the treatment specified in this clinical study protocol, such as:

   1) The actual QB of the patient is less than 220 mL/minute for a duration of more than 30 minute or for a total duration of more than 60 minute at themid-week treatment day dialysis session;

   2) The actual dialysis time of the patient is less than 210 minute at themid-week treatment day dialysis session;

(3) Failing to report AEs within the time limit specified in the clinical study protocol.

The investigator should classify the severity of protocol deviations as follows:

(1) Major protocol deviation: Protocol deviations that affect the study data and results, or jeopardize the rights, safety or health of the patients.

(2) Minor protocol deviations: Protocol deviations that will not affect the study data and results or jeopardize the rights, safety or health of patients.

Protocol deviations will be reviewed and evaluated on an ongoing basis by the Sponsor and appropriate corrective and preventive actions will be taken as necessary, including but not limited to: Notify, re-train the site or investigator, terminate the qualification of the study site, and report to local drug regulatory authority and national health regulatory authority.

14.3 Amendments to the Clinical Study Protocol

The clinical study protocol must be strictly implemented after being approved by the Ethics Committee. If it is necessary to supplement or revise the study protocol after the start of the study, the investigator and the Sponsor should make revisions upon negotiation and submit the revised study protocol to the Ethics Committee again for approval before implementation. Amendments to the clinical study protocol should be documented in detail, including: the specific contents of and reasons for the amendments, the letter of submission to the Ethics Committee for re-approval and the approval document of the Ethics Committee, etc.

15. Direct Access to Source Data and Documents

Source data and documents are defined in GCP as follows:

Source data refer to all information in original records and their approved copies of clinical findings, observations and other activities in a clinical study that can be used for reconstruction and evaluation of the clinical study.

Source documents are printed, visible, or electronic documents that contain source data.

Original medical records and laboratory test data of patients. The investigator should truthfully and accurately record and preserve the source data and documents related to the clinical study. The regulatory authority, CRA and inspector can directly access the source data and documents of this clinical study for inspection, monitoring and verification.

16. Finance and Insurance

See the Clinical Study Agreement for details. In this study, insurance will be purchased in accordance with the requirements of GCP.

17. Assessments Covered in the Clinical Study Report

The investigator shall verify or validate the safety and efficacy of the investigational medical device according to the design requirements of the Clinical Study Protocol, and complete the Clinical Study Report. The Clinical Study Report shall comply with the relevant requirements of GCP and be consistent with the Clinical Study Protocol, with its contents including but not limited to:

（1） General information;

（2） Abstract;

（3） Introduction;

（4） Clinical study objectives;

（5） Clinical study methods;

（6） Clinical study content;

（7） General clinical data;

（8） Investigational medical device and control medical device or control diagnosis and treatment method;

（9） Statistical analysis methods and evaluation methods adopted;

（10） Clinical evaluation criteria;

（11）Organizational structure of clinical study;

（12） Ethical statement;

（13） Clinical study results;

（14） Adverse events identified in the clinical study and treatment;

（15） Analysis and discussion of clinical study results, especially indications, scope of application, contraindications and precautions;

（16） Clinical study conclusions;

（17） Existing problems and suggestions for improvement;

（18） List of study personnel;

（19） Other situations requiring explanation;

（20） Comments from the investigator and the competent medical device clinical study administration.

18. Confidentiality

This clinical study protocol contains trade secrets that are privileged or strictly confidential and may not be disclosed without legal permission. It is only exposed to the investigators of the clinical study, and no further distribution is allowed. This disclosure policy applies to all other confidential information that will be provided in the future.

In case that the parties terminate the cooperation, each party shall still have the obligation to keep the technical secrets and trade secrets of the product agreed in this clinical protocol known to or obtained by the other party confidential, that is: Not to be disclosed to or known by any third party. However, the disclosure caused by submitting the information to the competent product approval authority, filing authority and/or experts for review and discussion demonstration shall be excluded.

18.1 Trade Secrets

The technical secrets and trade secrets of the product as agreed herein refer to: ① Clinical data and trial data; ② Product specification, technical requirements and test methods; ③ All relevant technical data and literatures.

19. Agreement on Publishing Study Results

The ownership of all the data and study results of this clinical study shall be in accordance with GCP.

Any trial-related information (including this research plan) shared by the sponsor is proprietary information and should be kept confidential. The data generated during this clinical study belongs to the sponsor. Whether it is now or in the future, sponsors can decide to use the data for presentations or publications or submit them to regulatory agencies. In addition, the sponsor reserves the right to review and approve the research data before any publication or any presentation may release proprietary information.

20. Responsibilities Assumed by Each Party

20.1 Responsibilities of Clinical Study Institutions and Investigators

Clinical study institutions and investigators shall strictly fulfill their responsibilities in GCP and carry out this clinical study in accordance with this study protocol and clinical study agreement.

Before a clinical study, the competent medical device clinical study administration shall cooperate with the Sponsor in submitting an application to the Ethics Committee and submitting the relevant documents as required. The investigator shall truthfully explain the details of the investigational product to the patients, and give the patients sufficient time to consider whether to participate in the clinical study before the study; Faithfully record the side effects and AEs and product complaints. In case of any AE, it is necessary to timely make clinical judgment, take measures and truthfully and timely report them level by level to protect the rights and interests of patients; After the clinical study, the clinical study personnel shall sign, and the competent medical device clinical study administration shall sign, date and sign, and issue the clinical study report to the investigator. Keep the patient data and the data provided by the implementer confidential.

The investigator should strictly follow the clinical study protocol, and should not deviate from the protocol or materially change the protocol without the approval of the Sponsor and the Ethics Committee, or failing to obtain the approval from the NMPA as required.. However, in the event of an emergency that requires immediate removal, such as when the patient is at immediate risk, a written report may be made afterwards.

The investigator should ensure that the clinical study data are accurately, completely, clearly and timely recorded in the eCRF. Any change of data should be signed and dated by the investigator, and original records should be kept, which should be clear and identifiable.

The clinical study institution and investigator should accept the monitoring and verification by the Sponsor and the supervision by the Ethics Committee, and provide all required records related to the study. Where drug regulatory authorities and health regulatory authorities send inspectors to carry out verification, clinical study institutions and investigators shall cooperate.

20.2 Sponsor’s Responsibilities

The Sponsor should strictly perform the responsibilities specified in GCP, including but not limited to:

The Sponsor is responsible for organizing the development and revision of the Investigator’s Brochure, clinical study protocol, Informed Consent Form, eCRF and other relevant documents,

and organizing the training necessary for the clinical study.

The Sponsor shall ensure that all investigators conducting clinical studies strictly follow the clinical study protocol, and timely point out and correct the failure of clinical study institutions and investigators to comply with relevant laws and regulations, this Practice and clinical study protocol; In case of serious situation or continuous failure to change, the study shall be terminated and reported to the food and drug regulatory authority of the province, autonomous region or municipality directly under the central government where the clinical study institution is located and China Food and Drug Administration.

The Sponsor shall bear the treatment cost and corresponding economic compensation for the patients who suffer from injury or death due to the clinical study, except for the damage caused by the faults of medical institution and its medical staff in the diagnosis and treatment.

21. Appendices

3) [redacted]

[redacted]

Appendix 3 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 4

[redacted]

[redacted]

[redacted]

[redacted]

Appendix 5

(V) Depletion syndrome

[redacted]

22. References

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Investigator's Statement

I agree:

1. To conduct this clinical study in strict compliance with *Declaration of Helsinki*, current laws and regulations of China, and the requirements of the clinical study protocol.
2. To accurately record all data required into the eCRF and complete the final report of the clinical study on time.
3. The investigational medical device is only used in this clinical study. The receipt and use of the study device will be completely and accurately recorded and the records will be kept during the clinical study.
4. To allow the CRA and inspector authorized or designated by the Sponsor and supervision department to conduct inspection, verification and examination on the clinical study.
5. To strictly perform the clinical study contract and articles of agreement signed by all parties.

I have already read the clinical trail protocol, including above Statement and fully agree all requirements above.

Comments of the Sponsor

Signature (Seal)

Date

Comments of the Investigator

Signature

Date

Comments of the Medical Device Clinical Study Institution

Signature (Seal)

Date