Randomized comparison of three high-flux dialyzers during high volume online hemodiafiltration – the comPERFORM study

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Background. Dialyzers shall be designed to efficiently eliminate uremic toxins during a dialysis treatment, given that the accumulation of small and middle molecular weight uremic solutes is associated with increased mortality risk of patients with end-stage renal disease. In the present study we investigated the novel FX CorAL dialyzer with a modified membrane surface for the performance during online-hemodiafiltration in a clinical setting.

Methods. comPERFORM was a prospective, open, controlled, multi-centric, interventional, cross-over study with randomized treatment sequences. It randomized stable patients receiving regular post-dilution online hemodiafiltration (HDF) to FX CorAL 600 (Fresenius Medical Care Deutschland GmbH), xevonta Hi 15 (B. Braun), and ELISIO 150H (Nipro), each for one week. The primary outcome was β2-microglobulin removal rate (β2-m RR) during online-HDF. Secondary endpoints were RR and/or clearance of β2-m and other molecules. Albumin removal over time was an exploratory endpoint. Non-inferiority and superiority of FX CorAL 600 vs. competitors were tested.

Results. 52 patients were included and analyzed. FX CorAL 600 showed the highest β2-m RR (75.47%), followed by xevonta Hi 15 (74.01%) and ELISIO 150H (72.70%). Superiority to its competitors was statistically significant (p=0.0216 and p<0.0001, respectively). Secondary endpoints related to middle molecules affirmed these results. FX CorAL 600 demonstrated the lowest albumin removal up to 60 min, and its sieving properties changed less over time than with competitors.
**Conclusions.** FX CorAL 600 efficiently removed middle and small molecules and was superior to the two comparators in β2-m RR. Albumin sieving kinetics point to a reduced formation of a secondary membrane.

**Keywords:** albumin sieving, FX CorAL, hemodiafiltration, membrane design, performance

**INTRODUCTION**

Uremic solutes are removed from the blood of hemodialysis patients via a hemodialyzer. The dialyzer’s membrane is mainly responsible for the selective sieving of molecules; the overall goal is a system that approaches the clearance capability of a healthy kidney (1,2).

One important issue is the removal of middle-molecule size uremic toxins (0.5 – 15 kDa). Studies have shown that there is a positive correlation between survival and middle-molecule clearance in chronic dialysis patients (3–6). β2-microglobulin (β2-m; 11.8 kDa) is described as a surrogate for middle-molecules in this context. In addition to their possible influence on survival, an accumulation of middle-size molecules like β2-m is a precursor to amyloidosis, resulting in a further decline of organ function. The increase in β2-m levels in plasma is thought to be due to a reduction or loss of residual kidney function (7,8). Thus, it is important that dialyzers clear high amounts of uremic toxins of middle-molecule size. In parallel, a permeability cut-off should be maintained, which limits the loss of essential proteins such as albumin (66 kDa) during hemodialysis or hemodiafiltration (HDF) (1). Albumin commonly serves as marker for protein leakage into the dialysate when using high-flux dialysis membranes. Hypoalbuminemia, a key parameter of nutritional status of hemodialysis patients, is associated with increased mortality in end-stage renal disease (9,10).

To improve biocompatibility while maintaining or improving performance, synthetic dialyzer membranes are constantly undergoing further development. Today, the most widely used polymers in these membranes are polysulfone (PSU) and polyethersulfone (PES). Both polymers show a better biocompatibility compared to cellulose-based membranes and were a major historical milestone in the improvement of dialysis and HDF. The FX series of Fresenius Medical Care Deutschland GmbH (FME) and the comparators in this study use these polymers (ELISIO by Nipro: PES; xevonta by B. Braun: PSU). FX CorAL (PSU), the investigational device in this study, is a further development of FX CorDiax to improve membrane biocompatibility. Its membrane has an increased polyvinylpyrrolidone (PVP) content on its blood side surface. To prevent PVP oxidation and elution, it is stabilized with a small amount of α-tocopherol (11,12).

Two earlier clinical trials evaluated safety and performance of FX CorAL (13). The first compared FX CorAL with two other dialyzers of the FX-Series (FME) while the second compared FX CorAL to SUREFLUX by Nipro and Polyflux by Baxter/Gambro. In these studies, FX CorAL was numerically superior to FX CorDiax in removing β2-m, non-inferior to Polyflux, and superior to SUREFLUX. Moreover, hemocompatibility analyses showed significantly lower C5a and sC5b-9 complement activation for FX CorAL than for two comparators from the FX-Series. Compared to Polyflux and SUREFLUX, FX CorAL activated complement sC5b-9 significantly less (13).

The aim of comPERFORM (Comparative clinical performance of dialyzers applied during high volume online haemodiafiltration) was to generate clinical data on clearances and removal rates (RR) of β2-m and other uremic toxins of FX CorAL in comparison to two comparators, as well as on clinical adverse events of the modified PSU membrane. Furthermore, comPERFORM included a method of sampling...
and analyzing albumin from the dialysate recently developed inhouse, with the intention to characterize the dialyzers’ albumin sieving properties.

MATERIALS AND METHODS

Trial design

comPERFORM followed a multi-centric, prospective, open, controlled, interventional, cross-over study design with randomized treatment sequences.

Prior to initiation, the trial was submitted to the German regulatory authority BfArM, to the centers’ Ethics Committees, and the federal authorities as required by the German Medical Device Act. Planning, conduct, and analysis of the trial observed the principles of ISO 14155, the Good Clinical Practice Guidelines for clinical trials with medical devices, including the standards of the Helsinki Declaration. comPERFORM was registered at ClinicalTrials.gov (NCT04102280).

Participants

comPERFORM recruited stable patients receiving regular post-dilution online HDF in accordance with the established routine procedures at the study center. Patients were recruited from four hemodialysis centers in Germany.

Adult patients with chronic kidney disease stage 5D on high-volume postdilution online HDF (>21 L/session substitution volume), treatment three times weekly and vascular access permitting high flow could be enrolled in the study after having provided written informed consent. Patients with concurrent major illnesses or considered clinically unstable by the investigator, with recurrent episodes of vascular access failure, and with known or suspected allergy to trial product and related products were excluded.

Interventions

Three different dialyzers were compared in this trial: FX CorAL 600, xevonta Hi 15, and ELISIO 150H. To avoid bias, all dialyzers possessed a synthetic membrane suitable for HDF treatments as well as a comparable surface size. Patients were treated with each dialyzer for one week. In the follow-up week (Week 4), each patient was re-assigned to the same type of dialyzer used before the study. All treatments were performed with one of the following FME hemodialysis systems: 5008, 5008(S) or 6008. Treatment modalities, including anticoagulation with heparin, remained unchanged between study phases, unless required for medical reasons (see Supplemental Table 1). All application of medication during the study, as well as in the 6 months prior to study start, was documented.

Outcome variables and laboratory methods

Removal rate of β2-microglobulin (β2-m RR) in plasma during 4-hour sessions (t=0 min to t=240 min after start of HDF) was defined as the primary endpoint. β2-m was determined at the mid-week dialysis session of each trial period pre-HDF and 60 min and 240 min after its start. In every period, outcome and other laboratory variables were determined in the mid-week session (second session) to exclude potential carry-over effects.
ß2-m at 60 min was used for the calculation of ß2-m clearance, a secondary endpoint. Further secondary endpoints were removal rates and clearances for myoglobin, phosphate, creatinine, phosphate, and urea. Samples were collected with the ß2-m samples.

Albumin removal into the dialysate over time was an exploratory endpoint calculated from albumin concentrations determined pre-HDF and 15, 30, 60, and 240 min during HDF. In the drop distance for used dialysate after the dialysis machine, a tailormade cuvette was integrated and connected to a sampling pump collecting used dialysate at a rate of approx. 300 mL/h into a sampling bag. Before samples were taken, the bag was mixed manually to dissolve any albumin gradients. Albumin concentrations in dialysate were determined at a central laboratory as described in Supplemental Table 2.

For calculating removal rates and clearances of the respective molecules, blood samples were taken at the dialysis cannula (pre-HDF samples) and at the arterial and the venous injection port of the dialysis machine during HDF (heparinized Monovette®). Samples were centrifuged and frozen before being sent to a central laboratory. Hematocrit was determined from arterial blood (EDTA Monovette®) and analyzed at the site. To assure correct filling of the Monovettes® for arterial samples, the blood flow was transiently reduced to 100 mL/min during sampling. Furthermore, blood flow rate, dialysate flow, dialysate amount, substitution volume, and ultrafiltration volume were documented at the times required for the calculation of removal rates, clearances, or albumin amount. All laboratory analyses were performed as presented in Supplemental Table 2.

Safety events were reported to BfArM, ethics committees, and sponsor according to requirements of the German MPSV (Medizinprodukte-Sicherheitsplanverordnung). The patients’ safety was continuously monitored by the investigator during the clinical investigation.

**Sample size**

For the primary variable ß2-m RR, the non-inferiority margin of -2% and the standard deviation were taken from earlier studies with FX CorAL 600 dialyzer and the number of patients needed for this cross-over study was estimated accordingly (13, 14). \( N_{ind}=14 \) independent patients were required, fixing the error level at \( \alpha=2.5\% \) for a one-sided test, and aiming at a power of \( 1-\beta=80\% \). This patient number was corrected for design effects, with \( n=4 \) centers and an assumed intra-class correlation (ICC) of 0.2 (15). The adjusted number of cases under these assumptions corresponded to \( N_{adj}=21 \). Considering a correction for 25% dropouts, \( N=28 \) patients were planned to be included.

The variability of ß2-m RR was monitored in two pre-planned blinded interim analyses for the purpose of sample size adjustment, with the first analysis after 16 patients had completed the study (15). This interim analysis suggested that at least 48 patients should be included into the study to achieve the primary objective with a power of ≥80%. A second pre-planned interim analysis was performed after 40 patients to check the assumptions of the first interim analysis. Accounting for dropouts/missing values, it was decided that the study should recruit 8 to 10 additional patients.

**Randomization**

The cross-over design of the study permitted six possible treatment sequences: ABC, ACB, BCA, BAC, CBA, and CAB. Randomization of patients to these sequences was stratified by trial center, and a random plan was prepared before the trial by the Clinical Research Organization (CRO), using block-wise randomization via SAS. Each trial center assigned eligible patients sequentially to the next
available patient number and requested the corresponding treatment sequence from the CRO by randomization request fax.

**Statistical methods**

The primary objective of this clinical investigation was to show that FX CorAL 600 is non-inferior or superior to xevonta Hi 15 and ELISIO 150H in terms of the mean \( \beta_2 \)-m RR. The primary analysis consisted of four hierarchically ordered hypotheses, where the next hypothesis can only be tested if the hypothesis before has been passed successfully. This procedure prevents inflation of the type one error rate.

A. Non-inferiority comparison of FX CorAL 600 vs. xevonta Hi 15; non-inferiority margin \( \delta = -2\% \).

B. Non-inferiority comparison of FX CorAL 600 vs. ELISIO 150H; non-inferiority margin \( \delta = -2\% \).

C. Superiority comparison of FX CorAL 600 vs. xevonta Hi 15.

D. Superiority comparison of FX CorAL 600 vs. ELISIO 150H.

Assuming no carry over effect, a linear mixed model was used for statistical analysis. This model included the fixed effects “period” and “dialyzer” and the random effects “center” and “patient”. Non-inferiority testing was based on 95% confidence intervals (CI), with non-inferiority confirmed, if the lower limit of the 95% CI for the \( \beta_2 \)-m RR difference was larger than \( \delta = -2\% \). Superiority testing was based on 95% CIs again, with superiority confirmed, if the lower limit of the 95% CI for the \( \beta_2 \)-m RR difference was larger than \( \delta = 0\% \). The described hypothesis testing procedure, based on the 95% CI, corresponds to a one-sided \( \alpha \) level of 2.5%.

For the non-inferiority tests, the primary analysis used the per protocol (PP) population, for superiority tests the intention-to-treat (ITT) population. For validation purposes, the non-inferiority and the superiority analyses were performed on the ITT and the PP population, respectively.

The formulas for calculating \( \beta_2 \)-m RR(16), blood side clearances \( K_b \)(17), and albumin removal AR(9) are described in Supplemental Section 1.

Safety events were coded in MedDRA and tabulated by Preferred Term (PT), System Organ Class (SOC), seriousness, and relatedness to HDF or dialyzer employed at the time the event occurred.

Missing data was not replaced. Based on the ‘missing at random assumption’, the linear mixed model allowed the modeling of incomplete data.

**RESULTS**

The comPERFORM trial started on 28 October 2019. The trial enrolled, randomized, and examined a total of 52 patients until 06 November 2020. None of the included patients decided to terminate participation or withdrew informed consent. The disposition of the patients is displayed in Figure 1.

Two patients in two sequences were excluded from the PP analysis set, because plasma samples were taken from the venous instead of the arterial port of the dialyzer at 240 min in Weeks 2 and 3. For four additional patients, the primary endpoint was not calculated in single periods, because treatment parameters (flow rates) differed to a relevant extent from the other periods. Loss of a single period did not affect inclusion to the PP population. Thus, the Safety population as well as the ITT population consisted of 52 patients, the PP population of 50 patients.
Baseline data, HDF and vital signs

Table 1 shows baseline demographic and medical history data of the trial population, as well as plasma creatinine and urea. Table 2 presents information on treatment parameters, including anticoagulation (per dialyzer). There were no major differences between dialyzers.

Outcomes – primary endpoint

Table 3 displays β2-m RR for all dialyzers in the PP and in the ITT population. The test for non-inferiority (PP population) of FX CorAL 600 versus xevonta Hi 15 and ELISIO 150H demonstrated the non-inferiority of FX CorAL 600 to both comparators (vs. xevonta Hi 15: p < 0.0001; vs. ELISIO 150H: p < 0.0001). In addition, superiority of FX CorAL 600 versus the comparators was tested (ITT population) and found that FX CorAL 600 was superior to xevonta Hi 15 (p = 0.0216) and to ELISIO 150H (p < 0.0001). On a descriptive scale, Supplemental Figure 1 displays the course of β2-m plasma concentration over time for the ITT population. With all three dialyzers, the plasma concentrations of β2-m decreased at a higher rate in the first 60 minutes of the session compared to the remaining three hours. There were no carry-over effects (p=0.81; see Table 3).

Outcomes – secondary endpoints

Table 4 shows descriptive statistics of the secondary endpoints as well as the p-values for superiority tests of FX CorAL 600 vs. its comparators.

β2-m clearance at 60 min after start of HDF showed significant differences overall between the three dialyzers (p = 0.0011), with the detailed analysis finding a significant superiority of FX CorAL 600 versus both comparators, which between themselves performed highly similar.

Furthermore, the analysis found significant differences overall between the dialyzers' removal rates as well as clearances for myoglobin, the second middle molecule in the analysis (p < 0.0001 for removal rate; p = 0.0003 for clearance). Regarding removal rate, FX CorAL 600 was significantly superior to both comparators; regarding clearance, FX CorAL 600 was superior to xevonta Hi 15 and performed comparably to ELISIO 150H.

Removal rates and clearances of the small molecules creatinine, phosphate, and urea were similar between dialyzers, with neither statistically significant nor clinically conspicuous differences.

Outcomes – exploratory endpoint

Removal of albumin over time is displayed in Figure 2. FX CorAL 600 demonstrated the lowest amount of albumin removal up to the 60 min timepoint, with the difference vs. the other dialyzers being significant (p < 0.03 at 15, 30, and 60 min vs. both comparators). After 60 min, the albumin removal rates — i.e., the slope of the curves — decreased with all dialyzers, the least with FX CorAL 600. At the end of HDF after 240 min, the albumin removal was highest with xevonta Hi 15 (mean ± SE: 1.55 ± 0.16 g; ITT population), followed by FX CorAL 600 (1.38 ± 0.17 g) and ELISIO 150H (1.13 ± 0.17 g). These differences were not statistically significant (vs xevonta Hi 15: p = 0.1885; vs ELISIO 150H: p = 0.0504).
**Adverse events**

Eighteen (34.6%) patients experienced adverse events during the study, and an overall total of 45 adverse events were reported. Adverse events were distributed to the dialyzers used when the events occurred as follows: FX CorAL 600: 7 patients, 8 events; xevonta Hi 15: 6 patients, 9 events; ELISIO 150H: 9 patients, 16 events.

The most frequently reported events belonged to the MedDRA SOC Musculoskeletal and connective tissue disorders (6 patients, 8 events; 6 of these muscle spasms), followed by Gastrointestinal disorders (5 patients, 5 events; 3 of these diarrhea) and Nervous system disorders (4 patients, 5 events; 2 of these headaches). One case of coronary artery disease with a fatal outcome occurred in the follow-up week on the patient's standard, i.e., non-investigational dialyzer. The event was neither considered related to medical procedure nor dialyzer. Investigators classified three other non-serious adverse events as possibly related to a dialyzer: head discomfort (FX CorAL 600); ear pain, headache, and influenza like illness (ELISIO 150H); abdominal pain (ELISIO 150H). No clotting within dialyzers occurred.

**DISCUSSION**

The clinical investigation comPERFORM was an interventional three-period randomized sequence cross-over study with 52 patients undergoing high-volume online post-dilution hemodiafiltration (HDF). comPERFORM was prospective, non-blinded, and performed in four hemodialysis centers in Germany. Its main aim was to analyze the performance of the novel polysulfone-based high-flux dialyzer FX CorAL 600, including the kinetics of albumin sieving, thus giving insights into how membrane design might affect performance.

FX CorAL 600 showed the highest $\beta_2$-microglobulin removal rate of the three dialyzers (75.47%), followed by xevonta Hi 15 (74.01%) and ELISIO 150H (72.70%), and demonstrated a statistically significant superiority to its competitors. $\beta_2$-microglobulin clearance and myoglobin removal, secondary endpoints related to the middle molecules, were also significantly higher with the FX CorAL than with both comparators. The removal of middle molecules has repeatedly been examined and found relevant as a surrogate marker for clinical endpoints like mortality (4–6) and possibly also for symptoms affecting quality of life in end-stage renal disease, like sleep disturbance, itching, or restless legs syndrome (18). Regarding the removal and clearance of small molecules, the FX CorAL 600 and both competitors had a comparably high performance. When interpreting middle molecule removal, the role of metabolic acidosis should be kept in mind. Metabolic acidosis may increase cellular $\beta_2$-microglobulin generation and release and is generally improved during hemodialysis (19,20). Thus, metabolic acidosis reversal during dialysis may add numerically to $\beta_2$-microglobulin removal via the dialyzers, but we believe it does not bias the comparison of dialyzers due to the study’s cross-over design.

The $\beta_2$-microglobulin removal rates in the comPERFORM study were somewhat higher (range: 72.7% to 75.5%) than in an earlier study comparing FX CorAL 600 to Polyflux 170H and SUREFLUX-17UX (70.3% and 67.7% for the two dialyzers with synthetic membranes; 51.3% for the cellulose-based dialyzer) (13). This difference is explained by different treatment modalities and confirms observations of other authors, that higher removal rates can be obtained with higher substitution and blood flow rates (16,21,22): In the study reported by Ehlerding et al. (13), substitution flow rates were set manually to around 70 mL/min, whereas in comPERFORM they were automatically set by the dialysis machines and reached a mean of 92 mL/min. In addition, blood flow was slightly higher in the comPERFORM study (approx. 325 mL/min vs. 305 mL/min). Considering these differences in HDF
procedures, the comparison to other studies confirms the external validity of the comPERFORM data. These data also show the range of operation of novel dialyzers. Convective volumes, i.e., the sum of substitution and ultrafiltrate volume, were between 26 and 27 L per session and thus reach the range >23 L which has been suggested to achieve optimum dialysis results with post-dilution online HDF (2,18,23–26).

Data on albumin removal into the dialysate showed that FX CorAL 600 removed significantly less albumin than its comparators over the first hour of HDF, and that sieving remained almost constant thereafter, whereas the comparators’ sieving rates declined until the end of the HDF session, shown by a flattened curve. These data are qualitatively and quantitatively in line with in vitro examinations on FX CorAL 600 and other dialyzers, including xevonta Hi 15 and ELISIO-15H (12). The declining albumin loss rate seen with the comparators may indicate increased secondary membrane formation by protein adsorption (‘fouling’). Secondary membrane formation may reduce the clearance and removal of other uremic toxins over time; however, this topic has not been addressed in comPERFORM and warrants future examination. The reduced albumin adsorption seen over the first hour with FX CorAL 600 is thought to originate from the dialyzer membrane’s almost neutral surface charge, and by its higher PVP concentration on the inner surface, which stabilizes a membrane protective hydro-layer (12). It is important under tolerability aspects, that this high PVP concentration on the FX CorAL’s membrane does not lead to a high elution (27). Recent in vitro experiments indicated that PVP elution is different between dialyzers on the market and depends on membrane material and method of sterilization (27).

Overall and considering the high blood flow and convective volume, the absolute removal of albumin with all three dialyzers – the highest mean being 1.6 g over a 4-hour hemodiafiltration session with xevonta Hi 15 – was at the low end, though within the range of data published(10,18): albumin amount removed ranged from 1 g to >10 g per session, and it may be influenced by type of hemodialysis or HDF, treatment modalities, type of dialyzer (high-flux, protein-leaking, or medium cut-off), and the method of sampling and quantifying albumin. Protein and specifically albumin loss during dialysis or HDF contributes to protein-energy wasting (PEW) in patients with end-stage renal disease. As such, it leads to muscle and fat loss as well as cachexia and to increased mortality, and, as a consequence, low albumin removal is considered as useful clinical surrogate (10).

Looking at the safety side, the comPERFORM study did not elicit any signals. Most adverse events occurred only once, and the adverse events occurring more frequently, like diarrhea or muscle spasms, are unspecific and/or typical for the population and procedure under study. Most adverse events were of mild intensity, virtually all resolved without sequelae during the study, and only very few adverse events had consequences on the continuation of study treatment. Furthermore, the number, nature and severity of adverse events did not reveal relevant differences between the three dialyzers investigated in this study; therefore, their safety profile is considered as comparable. The only serious adverse event (death due to coronary artery disease) was unrelated to the procedure or device; it is considered a frequent outcome in a hemodialysis / HDF population with generalized and advanced vascular diseases as were present in this patient, in addition to a preexisting severe cardiovascular disease.

The study had been designed to analyze short-term performance over treatment periods of one week per dialyzer. In this setting, the FX CorAL 600 was superior to its comparators by approx. 2-4% B2-m RR. While this effect appears small, the chronic and repeated nature of the dialysis treatment may multiply this effect over time. We cannot conclude from the present study whether these differences observed in one treatment session may translate into a clinically significant long-term effect. A further limitation is that comPERFORM did not collect data on residual renal function, which is a determinant of middle-molecule removal. However, differences in middle molecule removal
rates observed are unlikely to be caused by inhomogeneities in residual renal function due to the study's cross-over design.

CONCLUSIONS

FX CorAL 600 was superior to the two comparator dialyzers in removing β2-microglobulin over 4-hour online hemodiafiltration (HDF) sessions (primary endpoint) and in β2-microglobulin clearance, measured 60 min after start of HDF. It efficiently removed and cleared myoglobin as well as small molecules and was well tolerated. Further studies are planned, which will investigate long-term effects of the FX CorAL 600 on patient outcomes.

DATA AVAILABILITY STATEMENT

Aggregated data underlying this article are available in the article and in its online supplementary material. Personal data underlying this article cannot be shared publicly to maintain the privacy of individuals that participated in the study.

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CONFLICT OF INTEREST STATEMENT

TL, AE, AMZ, JK, and MSG are full-time employees of Fresenius Medical Care and report personal fees from Fresenius Medical Care, outside the submitted work.

GE, WR, MKK, and EZ report grants, personal fees, and non-financial support from Fresenius Medical Care, during the conduct of the study; BO reports personal fees from Fresenius Medical Care received directly and via Institut Dr. Schauerte during and after the study.

The results presented in this paper have not been published previously in whole or part, except in abstract format.

AUTHORS' CONTRIBUTIONS

GE, WR, MKK, EZ: Investigation
TL: Project Administration, Writing, Review & Editing
AE: Conceptualization, Methodology
AMZ: Writing, Review & Editing
JK: Writing, Review & Editing
BO: Project Administration, Writing
MSG: Conceptualization, Project Administration

The interpretation of study results and revision of this manuscript was conducted by all authors. The decision to submit this manuscript for publication was jointly made by all authors and the manuscript was confirmed to be accurate and approved by all authors.

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### Table 1. Demographic and medical history data (ITT population)

|                          | Total (N=52)                  |
|--------------------------|-------------------------------|
| Age [years]              | 64.8±14.46                    |
| Gender [% male]          | 85                            |
| BMI [kg/m²]              | 28.2±7.54                     |
| Primary renal disease* [n (%)] |                          |
| Hypertensive / large vessel disease | 25 (48.1%)             |
| Diabetes mellitus        | 11 (21.2%)                    |
| Cystic / hereditary / congenital diseases | 9 (17.3%)             |
| Glomerulonephritis       | 7 (13.5%)                     |
| Time on RRT [median months (range)] | 55.5 (5-170)               |
| Duration of current treatment modality [median months] | 13.7            |
| Plasma creatinine [mg/dL] | 7.8±2.04                      |
| Plasma urea [mg/dL]      | 99.8±31.92                    |
| Concomitant diseases (MedDRA SOC / most frequent PT) [% affected] |                          |
| Metabolism and nutrition disorders | 92.3%                         |
| Metabolic acidosis       | 46.2%                         |
| Blood and lymphatic system disorders | 88.5%                         |
| Nephrogenic anemia       | 82.7%                         |
| Vascular disorders       | 86.5%                         |
| Hypertension             | 75.0%                         |
| Endocrine disorders      | 71.2%                         |
| Secondary hyperparathyroidism | 65.4%                       |
| Cardiac disorders        | 63.5%                         |
| Coronary artery disease  | 28.8%                         |

*More than one disease could be documented; RRT: Renal replacement therapy; data are given as mean ± SD, median [Range] or number (percentage), as appropriate.
Table 2. Treatment parameters (Safety Analysis Set)

|                               | FX CorAL 600 (N=52) | xevonta Hi 15 (N=52) | ELISIO 150H (N=52) | p value |
|-------------------------------|----------------------|----------------------|---------------------|---------|
| Mean blood flow rate (effective) [mL/min] | 331±11.6             | 330±11.6             | 329±11.6            | p=0.816 |
| Mean dialysate flow rate [mL/min]     | 529±18.6             | 528±18.6             | 529±18.6            | p=0.844 |
| Substitution volume [L]            | 25.4±2.8             | 26.2±2.8             | 25.8±2.8            | p=0.226 |
| Mean substitution flow rate [mL/min] | 93.3±5.7             | 95.0±5.7             | 93.3±5.7            | p=0.419 |
| Ultrafiltrate volume [L]           | 1959±244             | 2113±244             | 2138±244            | p=0.091 |
| Effective treatment time [min]     | 273±13.6             | 270±13.6             | 275±13.6            | p=0.051 |
| Anticoagulation (Bolus [IU])       |                      |                      |                     |         |
| Clexane (n=4)                    | 6625±2562            | 6625±2562            | 6625±2562           | *       |
| LMWH (n=1)                       | 3000                 | 3000                 | 3000                | *       |
| LMWH 2 doses (n=2)               | 11000±1414           | 11000±1414           | 11000±1414          | *       |
| Unfractionated heparin (n=45)     | 3389±1719            | 3389±1719            | 3389±1719           |         |
| Anticoagulation (Infusion [IU/h])  |                      |                      |                     |         |
| LMWH (n=1)                       | 1000                 | 1000                 | 1000                | *       |
| Unfractionated heparin (n=45)     | 1014±126             | 1019±126             | 1019±126            | p=0.397 |

LMWH: Low Molecular Weight Heparin; Results are Least Squares means ± Standard Error; p values relate to the descriptive significance of differences between the means of the three treatment groups (two-sided tests).

*: Not calculated, as datasets were identical between groups (p=1.00). Patients receiving a Clexane bolus did not receive heparin infusions. Patients with a 2nd dose of LMWH received the 2nd dose instead of an infusion.
Table 3. Primary endpoint β2-m RR: descriptive, non-inferiority and superiority statistics

| PP population | Dialyzer    | n  | LS mean | Std Err | Lower  | Upper  | p-value |
|---------------|-------------|----|---------|---------|--------|--------|---------|
|               | FX CorAL 600| 49 | 75.47   | 0.93    | 73.62  | 77.32  |         |
|               | xevonta Hi 15| 47 | 74.01   | 0.94    | 72.14  | 75.88  |         |
|               | ELISIO 150H | 50 | 72.70   | 0.93    | 70.86  | 74.54  |         |

|                | Difference  |    | 1.46    | 0.69    | 0.08   | 2.83   | <.0001 |
|                | FX CorAL 600- xevonta Hi 15 |    |         |         |        |        |        |
|                | Difference  |    | 2.77    | 0.68    | 1.43   | 4.11   | <.0001 |
|                | FX CorAL 600- ELISIO 150H    |    |         |         |        |        |        |

| ITT population | Dialyzer    | n  | LS mean | Std Err | Lower  | Upper  | p-value |
|---------------|-------------|----|---------|---------|--------|--------|---------|
|               | FX CorAL 600| 49 | 75.66   | 0.89    | 73.89  | 77.43  |         |
|               | xevonta Hi 15| 48 | 74.24   | 0.89    | 72.47  | 76.01  |         |
|               | ELISIO 150H | 51 | 72.96   | 0.88    | 71.21  | 74.71  |         |

|                | Difference  |    | 1.42    | 0.69    | 0.04   | 2.80   | 0.0216 |
|                | FX CorAL 600- xevonta Hi 15 |    |         |         |        |        |        |
|                | Difference  |    | 2.70    | 0.68    | 1.35   | 4.05   | <.0001 |
|                | FX CorAL 600- ELISIO 150H    |    |         |         |        |        |        |

1 p-value to conclude non-inferiority, one-sided tests at the 2.5% level; 2 p-value to conclude superiority, one-sided tests at the 2.5% level; LSMean=Least squares mean; StdErr=Standard error; 95% confidence intervals describe differences between dialyzers. Carry-over effect between periods (Type 3 test of fixed effects): p=0.81
Table 4. Secondary endpoints: descriptive and superiority statistics

| Laboratory test | Parameter   | LSMEAN FX CorAL 600 | LSMEAN xevonta Hi 15 | LSMEAN ELISIO 150H | p-value overall* | p-value FX CorAL 600 vs xevonta Hi 15 | p-value FX CorAL 600 vs ELISIO 150H |
|----------------|-------------|----------------------|----------------------|---------------------|------------------|---------------------------------------|-------------------------------------|
| 82-microglobulin [mL/min] | Clearance   | 105.74               | 97.23                | 97.73               | 0.0011           | 0.0010                                | 0.0019                              |
| Myoglobin [%] | Removal rate | 61.01               | 52.89                | 56.73               | <.0001           | <.0001                                | 0.0015                              |
| Myoglobin [mL/min] | Clearance   | 50.43                | 39.42                | 50.60               | 0.0003           | 0.0004                                | 0.9574                              |
| Creatinine [%] | Removal rate | 67.24               | 66.68                | 66.27               | 0.6929           | 0.6304                                | 0.3944                              |
| Creatinine [mL/min] | Clearance   | 177.70               | 176.75               | 176.73              | 0.8926           | 0.6856                                | 0.6771                              |
| Phosphate [%] | Removal rate | 61.18               | 60.32                | 59.95               | 0.7987           | 0.6561                                | 0.5129                              |
| Phosphate [mL/min] | Clearance   | 184.55               | 184.24               | 184.45              | 0.9909           | 0.8951                                | 0.9683                              |
| Urea [%] | Removal rate | 73.93                | 73.89                | 73.49               | 0.8986           | 0.9658                                | 0.6745                              |
| Urea [mL/min] | Clearance   | 191.91               | 192.85               | 192.90              | 0.8792           | 0.6693                                | 0.6551                              |

LSMean=Least squares mean; p-value to conclude significant differences between groups (two-sided tests at the 5% level), p-values < 0.05 are printed in bold; *: overall test includes all three dialyzers.
**FIGURE 1:** Disposition of patients.
FIGURE 2: Cumulative albumin removal to the dialysate over time by dialyzer (ITT population; means ± SE).