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ORIGINAL ARTICLE

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

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ABSTRACT

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Background. Dialyzers should be designed to efficiently eliminate uraemic toxins during dialysis treatment, given that the accumulation of small and middle molecular weight uraemic 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 performance during online hemodiafiltration (HDF) in a clinical setting.

Methods. comPERFORM was a prospective, open, controlled, multicentric, interventional, crossover study with randomized treatment sequences. It randomized stable patients receiving regular post-dilution online HDF to FX CorAL 600 (Fresenius Medical Care Deutschland), xevonta Hi 15 (B. Braun) and ELISIO 150H (Nipro) each for 1 week. The primary outcome was β2-m 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 versus comparators were tested.

Results. Fifty-two patients were included and analysed. 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 comparators was statistically significant ($P = 0.0216$ and $P < 0.0001$, respectively). Secondary endpoints related to middle molecules affirmed these results. FX CorAL 600

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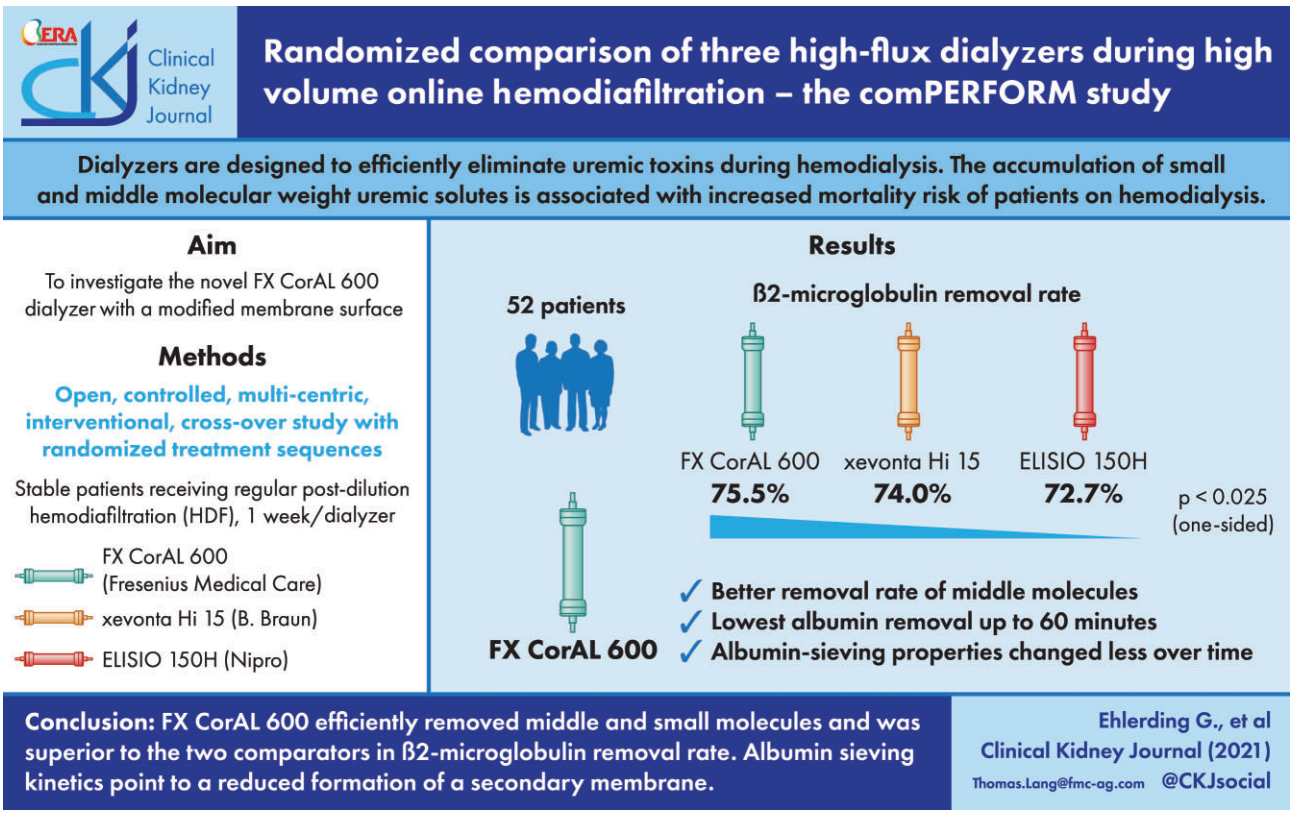
demonstrated the lowest albumin removal up to 60 minutes and its sieving properties changed less over time than with comparators.

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 reduced formation of a secondary membrane.

GRAPHICAL ABSTRACT



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

INTRODUCTION

Uraemic solutes are removed from the blood of haemodialysis patients via a haemodialyzer. 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 uraemic 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-m (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 large amounts of uraemic toxins of middle-molecule size. In parallel, a permeability cut-off should be maintained that limits the loss of essential proteins such as albumin (66 kDa) during haemodialysis or hemodiafiltration (HDF) [1]. Albumin commonly serves as a marker for protein leakage into the dialysate when using high-flux dialysis membranes. Hypoalbuminaemia, a key parameter of nutritional status of haemodialysis 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 with cellulose-based membranes and were a major historical milestone in the improvement of haemodialysis and HDF. The FX series of Fresenius Medical Care (FMC; Bad Homburg, Germany) and the comparators in this study use these polymers [ELISIO by Nipro (Osaka, Japan): PES; xevonta by B. Braun (Melsungen, Germany): 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 the safety and performance of FX CorAL [13]. The first compared FX CorAL with two other dialyzers of the FX series (FMC) while the second

compared FX CorAL to SUREFLUX by Nipro and Polyflux by Baxter/Gambro (Deerfield, IL, USA). In these studies, FX CorAL was numerically superior to FX CorDiax in removing β2-m, non-inferior to Polyflux and superior to SUREFLUX. Moreover, haemocompatibility analyses showed significantly lower C5a and sC5b-9 complement activation for FX CorAL than for two comparators from the FX series. Compared with 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 Hemodiafiltration) was to generate clinical data on clearances and removal rates (RRs) of β2-m and other uraemic toxins of FX CorAL compared with two comparators, as well as on clinical adverse events of the modified PSU membrane. Furthermore, comPERFORM included a method of sampling and analysing albumin from the dialysate recently developed in-house, 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 Federal Institute for Drugs and Medical Devices (BfArM), to the centres' ethics committees and to federal authorities as required by the German Medical Device Act. Planning, conduct and analysis of the trial observed the principles of ISO 14155 (Clinical investigation of medical devices for human subjects – Good clinical practice), including the standards of the Helsinki Declaration. comPERFORM is 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 centre. Patients were recruited from four haemodialysis centres in Germany.

Adult patients with chronic kidney disease Stage 5D on high-volume post-dilution 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 products and related products were excluded.

Interventions

Three different dialyzers were compared in this trial: FX CorAL 600, xevonta Hi 15 and ELISIO 150H (also available as ELISIO 15H). 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 1 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 FMC haemodialysis systems: 5008, 5008(S) or 6008. Treatment modalities, including anticoagulation with heparin, remained unchanged between study phases, unless required for medical reasons (see Supplementary data, Table S1). 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

RR of β2-m (β2-m RR) in plasma during 4-hour sessions ($t = 0-240$ minutes after the 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 minutes and 240 minutes 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.

β2-m at 60 minutes was used for the calculation of β2-m clearance, a secondary endpoint. Further secondary endpoints were RRs and clearances for myoglobin, phosphate, creatinine, phosphate and urea. Samples were collected with the β2-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 minutes 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 ~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 Supplementary data, Table S2.

For calculating RRs and clearances of the respective molecules, blood samples were taken at the dialysis cannula (pre-HDF samples) and at the arterial and venous injection ports of the dialysis machine during HDF (heparinized Monovette). Samples were centrifuged and frozen before being sent to a central laboratory. Haematocrit was determined from arterial blood (ethylenediaminetetraacetic acid Monovette) and analysed at the site. To ensure 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 RRs, clearances or albumin amount. All laboratory analyses were performed as presented in Supplementary data, Table S2.

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

Sample size

For the primary variable β2-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]. A total of 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 $n = 4$ centres and an assumed intra class correlation (ICC) of 0.2 [15]. The adjusted number of cases under these assumptions was 21. Considering a correction for 25% dropouts, 28 patients were planned to be included.

The variability of β2-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 in 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 8–10 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 centre and a random plan was prepared before the trial by the Clinical Research Organization (CRO), using block-wise randomization via SAS for Windows version 9.4 (SAS Institute, Cary, NC, USA). Each trial centre 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 β2-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 1 error rate.

A. Non-inferiority comparison of FX CorAL 600 versus xevonta Hi 15; non-inferiority margin $\delta = -2\%$.
B. Non-inferiority comparison of FX CorAL 600 versus ELISIO 150H; non-inferiority margin $\delta = -2\%$.
C. Superiority comparison of FX CorAL 600 versus xevonta Hi 15.
D. Superiority comparison of FX CorAL 600 versus 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 'centre' and 'patient'. Non-inferiority testing was based on 95% confidence intervals (CIs), with non-inferiority confirmed, if the lower limit of the 95% CI for the β2-m RR difference was greater than $\delta = -2\%$. Superiority testing was again based on 95% CIs, with superiority confirmed, if the lower limit of the 95% CI for the β2-m RR difference was greater than $\delta = 0\%$. The described hypothesis testing procedure, based on the 95% CI, corresponds to a one-sided α level of 2.5%.

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

The formulas for calculating β2-m RR [16], blood-side clearances (K_b) [17], and albumin removal AR[9] are described in Supplementary data, Section 1.

Safety events were coded in MedDRA (https://www.meddra.org/) 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 were not replaced. Based on the 'missing at random assumption', the linear mixed model allowed the modelling of incomplete data.

RESULTS

The comPERFORM trial started on 28 October 2019. The trial enrolled, randomized and examined a total of 52 patients until 6 November 2020. None of the included patients decided to terminate participation or withdrew informed consent. The disposition of the patients is presented 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 minutes 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 and the PP population of 50 patients.

Baseline data, HDF and vital signs

Table 1 shows baseline demographic and medical history data for 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

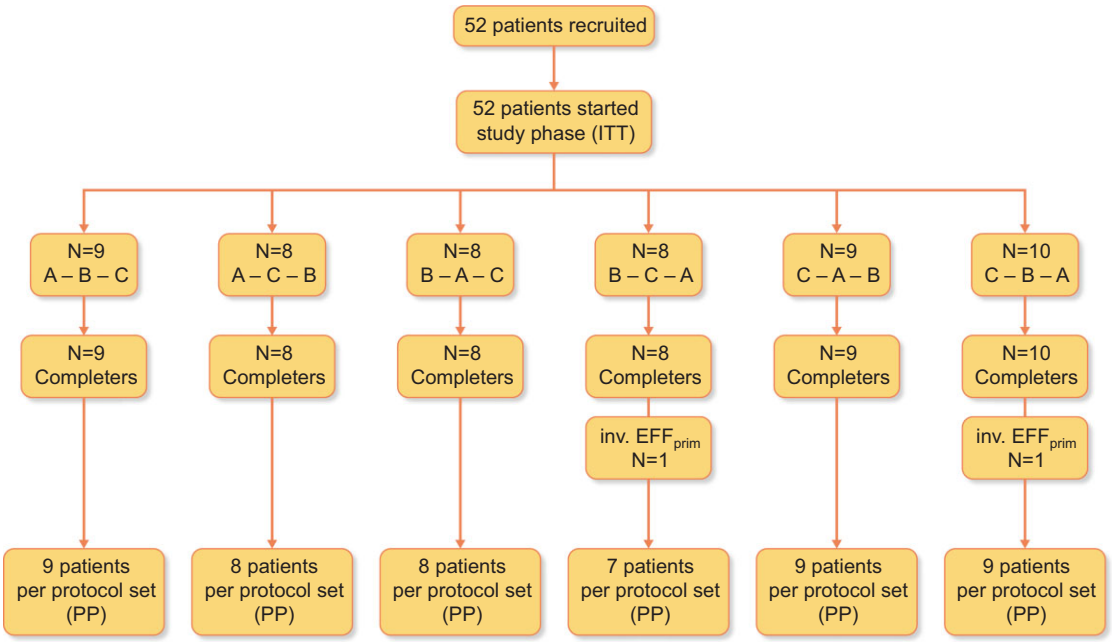
Table 3 displays β2-m RR for all dialyzers in the PP and ITT populations. The test for non-inferiority (PP population) of FX CorAL 600 versus xevonta Hi 15 and ELISIO 150H demonstrated the non-inferiority of FX CorAL 600 to both comparators (versus xevonta Hi 15: $P < 0.0001$; versus ELISIO 150H: $P < 0.0001$). 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 ELISIO 150H ($P < 0.0001$). On a descriptive scale, Supplementary data, Figure S1 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 3 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 versus its comparators.

β2-m clearance at 60 minutes after the 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 similarly.

Furthermore, the analysis found significant differences overall between the dialyzers' RRs as well as clearances for myoglobin, the second middle molecule in the analysis ($P < 0.0001$ for RR. $P = 0.0003$ for clearance). Regarding RR, 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.



A = FX CorAL 600 (FME); b = xevonta Hi 15 (B. Braun); C = ELISIO 150H (Nipro)
ITT: Intention-to-treat population; PP: per protocol population; inv. EFF_{prim}: invalid primary efficacy parameter leading to exclusion from the PP population (plasma sample collected from the venous instead of the arterial port)

FIGURE 1: Disposition of patients.

Table 1. Demographic and medical history data (ITT population N = 52)

Characteristics	Values
Age (years), mean ± SD	64.8 ± 14.46
Male %	85
BMI (kg/m^2), mean ± SD	28.2 ± 7.54
Primary renal disease[a], *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 (range)	55.5 (5–170)
Duration of current treatment modality (months), median	13.7
Plasma creatinine (mg/dL), mean ± SD	7.8 ± 2.04
Plasma urea (mg/dL), mean ± SD	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 anaemia	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

[a]More than one disease could be documented
RRT: renal replacement therapy.

RRs 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 presented in Figure 2. FX CorAL 600 demonstrated the lowest amount of albumin removal up to the 60-minutes time point, with the difference versus the other dialyzers being significant ($P < 0.03$ at 15, 30 and 60 minutes versus both comparators). After 60 minutes, the albumin RRs—i.e. the slope of the curves—decreased with all dialyzers, the least with FX CorAL 600. At the end of HDF after 240 minutes, 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 (versus xevonta Hi 15: $P = 0.1885$; versus 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 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 (six patients, eight events; six of these muscle spasms), followed by Gastrointestinal disorders (five patients, five events; three of these diarrhoea) and Nervous system disorders (four patients, five events; two 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 not considered related to a medical procedure or the 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

Table 2. Treatment parameters (safety analysis set)

Parameters	Dialyzer			P-value
	FX CorAL 600 ($n = 52$)	xevonta Hi 15 ($n = 52$)	ELISIO 150H ($n = 52$)	
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 two doses ($n = 2$)	11 000 ± 1414	11 000 ± 1414	11 000 ± 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 mean ± 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 second dose of LMWH received the second dose instead of an infusion.

Table 3. Primary endpoint β2-m RR: descriptive, non-inferiority and superiority statistics

Dialyzer	N	LS mean	Std Err	95% Confidence interval		P-value
				Lower	Upper	
PP population						
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 FX CorAL 600–xevonta Hi 15		1.46	0.69	0.08	2.83	<0.0001[a]
Difference FX CorAL 600–ELISIO 150H		2.77	0.68	1.43	4.11	<0.0001[a]
ITT population						
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 FX CorAL 600–xevonta Hi 15		1.42	0.69	0.04	2.80	0.0216[b]
Difference FX CorAL 600–ELISIO 150H		2.70	0.68	1.35	4.05	<0.0001[b]

[a]P-value to conclude non-inferiority, one-sided tests at the 2.5% level.
[b]P-value to conclude superiority, one-sided tests at the 2.5% level; LSmean:least squares mean; S.E. = standard error. The 95% confidence intervals describe differences between dialyzers. Carry-over effect between periods (type 3 test of fixed effects): P = 0.81

150H) and 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 HDF. comPERFORM was prospective, non-blinded and performed in four haemodialysis centres in Germany. Its main aim was to analyse the performance of the novel PSU-based high-flux dialyzer FX CorAL 600, including the kinetics of albumin sieving, thus giving insights into how membrane design might affect performance.

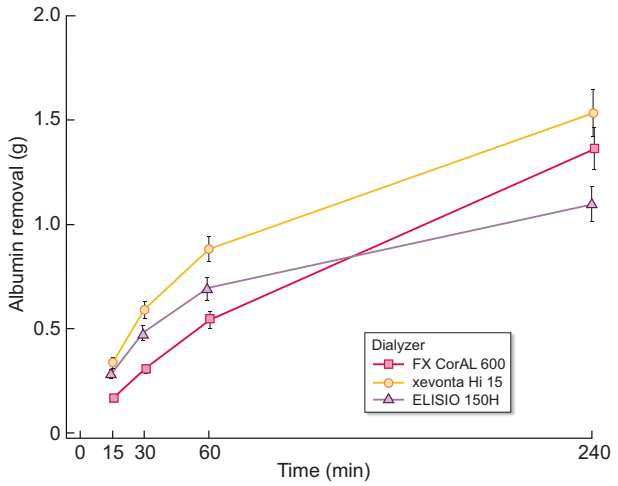
FX CorAL 600 showed the highest β2-m RR of the three dialyzers (75.47%), followed by xevonta Hi 15 (74.01%) and ELISIO 150H (72.70%), and demonstrated a statistically significant superiority to its comparators. β2-m clearance and myoglobin removal, secondary endpoints related to the middle molecules, were also significantly higher with 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 and restless legs syndrome [18]. Regarding the removal and clearance of small molecules, the FX CorAL 600 and both comparators 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 β2-m generation and release and is generally improved during haemodialysis [19, 20]. Thus metabolic acidosis reversal during dialysis may add numerically to β2-m removal via the dialyzers, but we believe it does not bias the comparison of dialyzers due to the study's cross over design.

The β2-m RRs in the comPERFORM study were somewhat higher (range 72.7–75.5%) than in an earlier study comparing FX

Table 4. Secondary endpoints: descriptive and superiority statistics

		LS mean			P-value		
Laboratory test	Parameter	FX CorAL 600	xevonta Hi 15	ELISIO 150H	Overall[a]	FX CorAL 600 versus xevonta Hi 15	FX CorAL 600 versus ELISIO 150H
β2-m (mL/min)	Clearance	105.74	97.23	97.73	**0.0011**	**0.0010**	**0.0019**
Myoglobin (%)	Removal rate	61.01	52.89	56.73	**<0.0001**	**<0.0001**	**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

LS mean: least squares mean. P-value to conclude significant differences between groups (two-sided tests at the 5% level). P-values <0.05 are in bold.
[a]Overall test includes all three dialyzers.



Dialyzer	15 min	30 min	60 min	240 min
FX CorAL 600	0.17 ± 0.11 g	0.31 ± 0.15 g	0.54 ± 0.28 g	1.36 ± 0.71 g
xevonta Hi 15	0.33 ± 0.17 g	0.59 ± 0.28 g	0.88 ± 0.40 g	1.53 ± 0.80 g
ELISIO 150H	0.28 ± 0.16 g	0.48 ± 0.27 g	0.69 ± 0.39 g	1.10 ± 0.60 g

FIGURE 2: Cumulative albumin removal to the dialysate over time by dialyzer (ITT population; mean ± standard error).

CorAL 600 with 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 RRs 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 (~325 mL/min versus 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 reached >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 150H [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 uraemic toxins over time; however, this topic was not 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 its higher PVP concentration on the inner surface, which stabilizes a membrane-protective hydro layer [12]. It is important regarding tolerability that this high PVP concentration on the FX CorAL's membrane does not lead to high elution [27]. Recent *in vitro* experiments indicated that PVP elution is different between dialyzers 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 HDF session with xevonta Hi 15—was at the low end, though within the range of data published [10, 18]: the amount of albumin removed ranged from 1 to >10 g per session, and it may be influenced by the type of haemodialysis 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 haemodialysis or HDF contributes to protein-energy wasting in patients with end-stage renal disease. As such, it leads to muscle and fat loss as well as cachexia and to increased mortality. As a consequence, low albumin removal is considered a 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 that occurred more frequently, like diarrhoea

and 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 a 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 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 haemodialysis/HDF population with generalized and advanced vascular diseases as were present in this patient, in addition to a pre-existing severe cardiovascular disease.

The study was designed to analyse short-term performance over treatment periods of 1 week per dialyzer. In this setting, the FX CorAL 600 was superior to its comparators by ∼2–4% β2-m RR. While this effect appears small, the chronic and repeated nature of dialysis treatment may multiply this effect over time. We cannot conclude from the present study whether these differences observed in one treatment session might 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 RRs observed are unlikely to be caused by inhomogeneities in residual renal function due to the study's crossover design.

CONCLUSIONS

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

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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AUTHORS' CONTRIBUTIONS

G.E., W.R., M.K.K. and E.Z. were responsible for the investigation. T.L. was responsible for
project administration and writing, reviewing and editing the manuscript. A.E. was responsible for
conceptualization and methodology. A.M.Z. and J.K. were responsible for
writing, reviewing and editing the manuscript. B.O. was responsible for
project administration and writing the manuscript. M.S.G. was responsible for
conceptualization and 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.

CONFLICT OF INTEREST STATEMENT

T.L., A.E., A.M.Z., J.K. and M.S.C. and MSG are full-time employees of Fresenius Medical Care and report personal fees from Fresenius Medical Care outside the submitted work. G.E., W.R., M.K.K. and E.Z. report grants, personal fees and non-financial support from Fresenius Medical Care during the conduct of the study. B.O. reports personal fees from Fresenius Medical Care received directly and via Institut Dr Schauerte during and after the study. The results presented in this article have not been published previously in whole or part, except in abstract format.

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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