Efficacy and Safety of Expanded Hemodialysis with the Theranova 400 Dialyzer

A Randomized Controlled Trial

Daniel E. Weiner,[1] Luke Falzon,[2] Line Skoufos,[3] Angelito Bernardo,[3] Werner Beck,[4] Mengqi Xiao,[3] and Ha Tran[3]

Abstract

Background and objectives Expanded hemodialysis therapy enabled by medium cut-off membranes may promote greater clearance of larger middle molecules that comprise putative uremic solutes than conventional high-flux dialysis. This randomized trial evaluated the efficacy and safety of hemodialysis treatment with a medium cut-off dialyzer.

Design, setting, participants, & measurements Clinically stable patients on maintenance hemodialysis were randomized to receive dialysis with either a medium cut-off dialyzer (Theranova 400) or a high-flux dialyzer (Elisio-17H) over 24 weeks of treatment. The primary safety end point was the predialysis serum albumin level after 24 weeks of treatment. The primary efficacy end point was the reduction ratio of free λ light chains at 24 weeks of treatment.

Results Among 172 patients on maintenance hemodialysis, mean age was 59±13 years, 61% were men, 40% were Black, and mean dialysis vintage was 5±4 years. Of the 86 patients randomized to each dialyzer, 65 completed the trial in each group. The reduction ratio for the removal of free λ light chains was significantly higher in the Theranova 400 group compared with the Elisio-17H group after 4 weeks (39% versus 20%) and 24 weeks (33% versus 17%; both $P<0.001$). Among secondary end points, the Theranova 400 group demonstrated significantly larger reduction ratios at 4 and 24 weeks for complement factor D, free κ light chains, TNFα, and β2-microglobulin ($P<0.001$ for all), but not for IL-6. Predialysis serum albumin levels were similar between groups after 24 weeks (4 g/dl with the Theranova 400 and 4.1 g/dl with the Elisio-17H), consistent with noninferiority of the Theranova 400 dialyzer in maintaining predialysis serum albumin levels after 24 weeks of treatment.

Conclusions Hemodialysis therapy with the Theranova 400 dialyzer provides superior removal of larger middle molecules, as exemplified by free λ light chains, compared with a similar size high-flux dialyzer, while maintaining serum albumin level.

Clinical Trial registry name and registration number A Multi-Center, Prospective, Randomized, Controlled, Open-Label, Parallel Study to Evaluate the Safety and Efficacy of the Theranova 400 Dialyzer in End Stage Renal Disease (ESRD) Patients, NCT03257410.

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[1]Tufts Medical Center, Medicine, Nephrology, Boston, Massachusetts
[2]Baxter Healthcare Corporation, Worldwide Medical, San Gwann, Malta
[3]Baxter Healthcare Corporation, Worldwide Medical, Deerfield, Illinois
[4]Baxter International Inc., Worldwide Medical, Hechingen, Germany

Correspondence: Mr. Luke Falzon, Baxter Healthcare Corporation, Malta Life Sciences Park, San Gwann SGN3000, Malta. Email: luke_falzon@baxter.com

Introduction

The loss of kidney function in patients with kidney failure causes accumulation of solutes termed uremic toxins because of their negative effect on patient health (1). The uremic syndrome is attributed to the progressive retention of a large number of compounds, which under normal conditions, are excreted by the healthy kidneys. These compounds are called uremic retention solutes or uremic toxins when they interact negatively with biologic functions (2).

These toxins can be grouped into small-molecular-weight water-soluble molecules, middle molecules, and protein-bound solutes. Although smaller molecules with a molecular mass <0.5 kD are effectively removed by dialysis, conventional dialysis has more difficulty in clearing middle molecules ranging from 0.5 to 60 kD (2). Middle molecules can be further subdivided into two groups on the basis of their molecular mass: conventional middle molecules of 0.5–25 kD and larger middle molecules of >25 kD. The former group includes β2-microglobulin (11.8 kD), historically considered the standard representative of a middle molecule (3), whereas the latter includes free Ig light chains including free λ light chains (45 kD) (4). Larger middle molecules are associated with inflammation, cardiovascular events, and other dialysis-related comorbidities in patients with comorbid cardiovascular disease, mineral and bone disorders, and infectious diseases (5,6).

Hemodialysis (HD) is the most common dialysis modality worldwide, and it removes solutes, including

small molecules (<0.5 kD) and conventional middle molecules (0.5–25 kD), primarily by diffusion, with very limited convection. Highly porous membranes, such as those featured in high-flux dialyzers, allow some middle molecules like β2-microglobulin to pass through the membrane, but these membranes do not readily clear larger solutes. Larger middle molecules (>25 kD) need to be removed either by convection or through the use of highly permeable membranes.

The incidence and prevalence of CKD and kidney failure are increasing worldwide. In the United States, the number of people receiving dialysis has risen by about 20,000 cases per year (7). Innovation is essential in pushing dialysis treatment forward to enable better patient care. The Theranova 400 dialyzer, through its innovative design, combines the functional features of enhanced permeability, increased selectivity, controlled retention, and improved internal filtration into a single dialyzer. The term expanded HD has been proposed to define a treatment where diffusion and convection are technically integrated inside a hollow-fiber dialyzer equipped with a medium cut-off membrane (8–10), enabling removal of small, conventional middle molecules and large middle molecule uremic toxins. Theranova is a hollow-fiber, single-use dialyzer, with improved removal of large proteins >25 kD, as well as selective maintenance of essential proteins such as albumin (11,12).

Existing data on the performance of medium cut-off dialyzers are on the basis of short-term, nonrandomized clinical trials (13–19). Accordingly, this randomized, controlled trial was conducted to evaluate the efficacy of expanded HD with the Theranova 400 membrane for larger middle molecule removal with acceptable serum albumin loss and safety profile over a 6-month period.

Materials and Methods

This multicenter, randomized, controlled trial was conducted in 21 centers in the United States from September 2017 to October 2018, in accordance with the International Conference on Harmonization Guideline on Good Clinical Practice (ICH GCP E6) and the Declaration of Helsinki. The protocol was registered in Clinicaltrials.gov (identifier NCT03257410) on August 18, 2017, and approved by an institutional review board. Patients or their legally authorized representative signed an informed consent form to participate in the study. No changes were made to the procedures and study outcomes after trial commencement.

Participants

Patients receiving thrice weekly in-center maintenance HD, aged ≥22 years, who met the following criteria were included in the study: (*1*) clinically stable without acute medical events for 30 days prior, (*2*) receiving HD with a high-flux dialyzer for at least 3 months prior, (*3*) expected to maintain an acceptable urea clearance (Kt/V) with a dialyzer of an approximate surface area of 1.7 m^2, and (*4*) have stable functioning vascular access. Key exclusion criteria were history of acute infection ≤4 weeks before randomization and patients with chronic liver disease, paraprotein-associated disease, hepatitis, HIV, bleeding disorders, active cancer, or monoclonal or polyclonal gammopathy. Patients with known serum free κ/λ light chain ratio <0.37 or >3.1, suggestive of monoclonal plasma diseases, were also excluded.

Methods

This was an open-label study without concealment of the dialyzer used to patients or site personnel; the allocation was concealed to the central laboratory and study sponsor. Patients were randomized to receive treatment with either Theranova 400 (Baxter Healthcare International) or Elisio-17H (Nipro Corporation). Randomization to Theranova 400 or Elisio-17H, a high-flux dialyzer with a similar surface area (1.7 m^2), was stratified by site with dynamic allocation. Participants were assigned a unique study identifier, and the dialyzer each participant was assigned to was determined according to a central randomization scheme provided by the electronic data capture system. Randomization was performed *via* Medidata Balance, which is fully integrated into the electronic data capture system Medidata Rave. Within Medidata Balance, dynamic allocation with second best probability was used to ensure equal distribution of randomized patients between treatment arms overall and within study centers; an unblinded statistician was responsible for study randomization set-up. Dialysis prescription and management were performed per institutional practice. Monthly microbiologic water/dialysate quality testing according to current Centers for Medicare and Medicaid Services regulations for dialysis water (ANSI/AAMI RD62:2001, https://dialysiswatersolution.com/regulations-and-guidelines/ansiaami/rd-62-water-for-dialysis/) and conventional dialysate (ANSI/AAMI RD52, https://dialysiswatersolution.com/regulations-and-guidelines/ansiaami/rd-52-dialysate-for-hemodialysis/) was required. HD treatment duration per session for each individual participant varied on the basis of clinical requirements determined by the clinician, according to the participants' needs. Medications were administered according to each center's standard practice.

Outcomes

The objective of the study was to compare expanded HD with Theranova 400 versus HD with Elisio-17H, a similar size high-flux dialyzer. The primary end points were the level of predialysis serum albumin measured after 24 weeks of treatment and the removal of free λ light chains (45 kD), measured at 24 weeks of treatment and expressed as a reduction ratio (RR).

Secondary end points included the RR of free λ light chains at 4 weeks and other middle to large molecules (complement factor D, 24 kD; free κ light chains, 23 kD; IL-6, 25 kD; TNFα, 17 kD; and β2-microglobulin, 11.8 kD) at 4 weeks and at 24 weeks of treatment. Other outcomes included the predialysis levels and change from baseline of factor 7 (50 kD), protein C (53–62 kD), factor 2 (72 kD), vitamin A, and normalized protein equivalent of nitrogen appearance and normalized protein catabolic rate (nPNA [nPCR]). Adverse events (AEs) were monitored through study completion. Exploratory end points consisted of patient reported quality of life using the Kidney Disease Quality of Life instrument (KDQOL-36) and the EuroQol instrument (EQ-5D-5L), as well as inflammation assessment by high-sensitivity C-reactive protein.

Statistical Analyses

The sample size was driven by the primary safety end point. The sample size was calculated using the PASS 15.0.1 software procedure "Noninferiority Tests for the Difference between Two Means."

On the basis of prior data (20), the mean and SD of predialysis albumin levels were 3.53±0.37 g/dl after 1 month of therapy. In calculating sample size, it was presumed that comparable predialysis albumin levels were expected with both Theranova 400 and Elisio-17H dialyzers. A 5% noninferiority margin was selected on the basis of the conclusion that less than a 5% variation in serum albumin has no clinical significance, as evidenced from two observational studies examining the association between serum albumin levels and mortality in large US cohorts of patients on HD and peritoneal dialysis, respectively (21,22). In both studies, variations in serum albumin of ±0.1 g/dl over 6 months were defined as "stable serum albumin levels." With a sample size of 70 patients per group, a *t* test with a 0.025 one-sided significance level would have 80% power to demonstrate noninferiority of the Theranova 400 dialyzer compared with the Elisio-17H dialyzer, as assessed by predialysis serum albumin with a noninferiority margin of 5% (the noninferiority margin was calculated as −0.1765 g/dl). To allow for a dropout rate of 15%, a total sample size of 166 was calculated.

For the primary safety end point, an analysis of covariance model with fixed effects of treatment and site and the continuous fixed covariate of baseline predialysis serum albumin was used to generate a two-sided 95% confidence interval for the difference in treatment means (μT–μR). With a lower bound of >-1.765 g/L (equivalent to −0.1765 g/dl), noninferiority would be demonstrated. Similarly, an analysis of covariance model was used for the primary efficacy end point. The testing of the RR of free λ light chains at 24 weeks of treatment was contingent upon the outcome of the analysis of the primary safety end point and was only conducted once noninferiority could be established for the primary safety end point. This hierarchical testing approach guaranteed that the overall type 1 error was controlled at a two-sided 0.05 significance level.

A mixed-effects repeated measures model was used to evaluate differences between treatment groups in the RR of free λ light chains, complement factor D, free κ light chains, IL-6, TNFα, and β2-microglobulin at 4 weeks and at 24 weeks of treatment. The model included the fixed effect of treatment, visit, and the random effect of patient. A mixed-effects repeated measures model was also used to evaluate the differences between treatment groups in Kt/V_{urea}, and the difference in the change from baseline for the tested molecules.

Multiple imputation was used to account for missing data for the RR of free λ light chains and the predialysis serum albumin assessment after 24 weeks of treatment (Supplemental Tables 1 and 2). Primary analyses were intention to treat. The change from baseline of the tested molecules was also measured (results are provided in the Supplemental Material). All analyses were performed using SAS/GRAPH 9.4 software, SAS/STAT 14.1 software, and Base SAS 9.4.

The end points were analyzed in a hierarchical manner, starting from the primary safety end point. *Post hoc* analyses were conducted to assess the statistical significance of all outcomes, regardless of the predetermined hierarchical manner of testing. Additionally, the measured arterial plasma concentrations after dialysis were corrected for the decrease in total extracellular volume owing to fluid removal.

Results

Patient Population

Twenty-one centers in the United States participated in this clinical study. Of the 282 patients meeting the inclusion criteria who underwent laboratory screening, 172 participants were randomized, with 86 in each group (Figure 1). Age, weight, sex, race, cause of kidney failure diagnoses, and elements of the dialysis prescription were similar between groups, although more participants in the Theranova 400 group used a catheter for vascular access at randomization (Table 1). Dialysis treatment parameters are provided in Supplemental Table 3. All analyses were performed on patient groups as originally assigned.

Safety Outcomes

Primary Safety Outcome. At baseline, the mean predialysis level of serum albumin in the Theranova 400 group (4.0±0.3 g/dl) was comparable with the Elisio-17H group (4.0±0.3 g/dl). Likewise, after 24 weeks of treatment (primary safety end point), the mean predialysis serum albumin level was 4.0±0.3 g/dl in the Theranova 400 group and 4.1±0.4 g/dl in the Elisio-17H group, demonstrating noninferiority of the Theranova 400 in maintaining serum albumin levels (Table 2). Sensitivity analysis using last value carried forward confirmed this result (Supplemental Table 4).

Secondary Safety Outcomes. The change in serum albumin from baseline was significantly different between the two groups only after weeks 4 and 8 (Table 3). After week 4, the mean level was 4.0±0.3 g/dl with a −0.1±0.2 mean change from baseline in the Theranova 400 group, whereas in the Elisio-17H group, the mean level was 4.0±0.3 with a 0.0±0.2 mean change from baseline ($P=0.03$). After week 8, the mean level was 3.9±0.3 g/dl with a −0.1±0.3 mean change from baseline in the Theranova 400 group, whereas in the Elisio-17H group, the mean level was 4.0±0.3 g/dl with a 0.0±0.2 mean change from baseline ($P=0.004$). Although the differences in change from baseline between the two groups after weeks 4 and 8 were statistically significant, the observed changes were well below 5%, and the mean levels were still within normal laboratory ranges. Supplemental Table 5 shows serum albumin changes across clinically relevant thresholds.

Results of clinical laboratory assessments, including comprehensive metabolic panel and hematology results, vitamin A levels, and lipid levels, were generally similar between groups (Supplemental Tables 6–14). There was a statistically significant difference in the mean change in glucose, serum calcium, and serum potassium levels from baseline between the study groups; however, values remained consistent with those seen in patients on HD. Additionally, no significant differences between the groups were seen in clinical laboratory assessments of coagulation factors or liver function. nPNA(nPCR) was

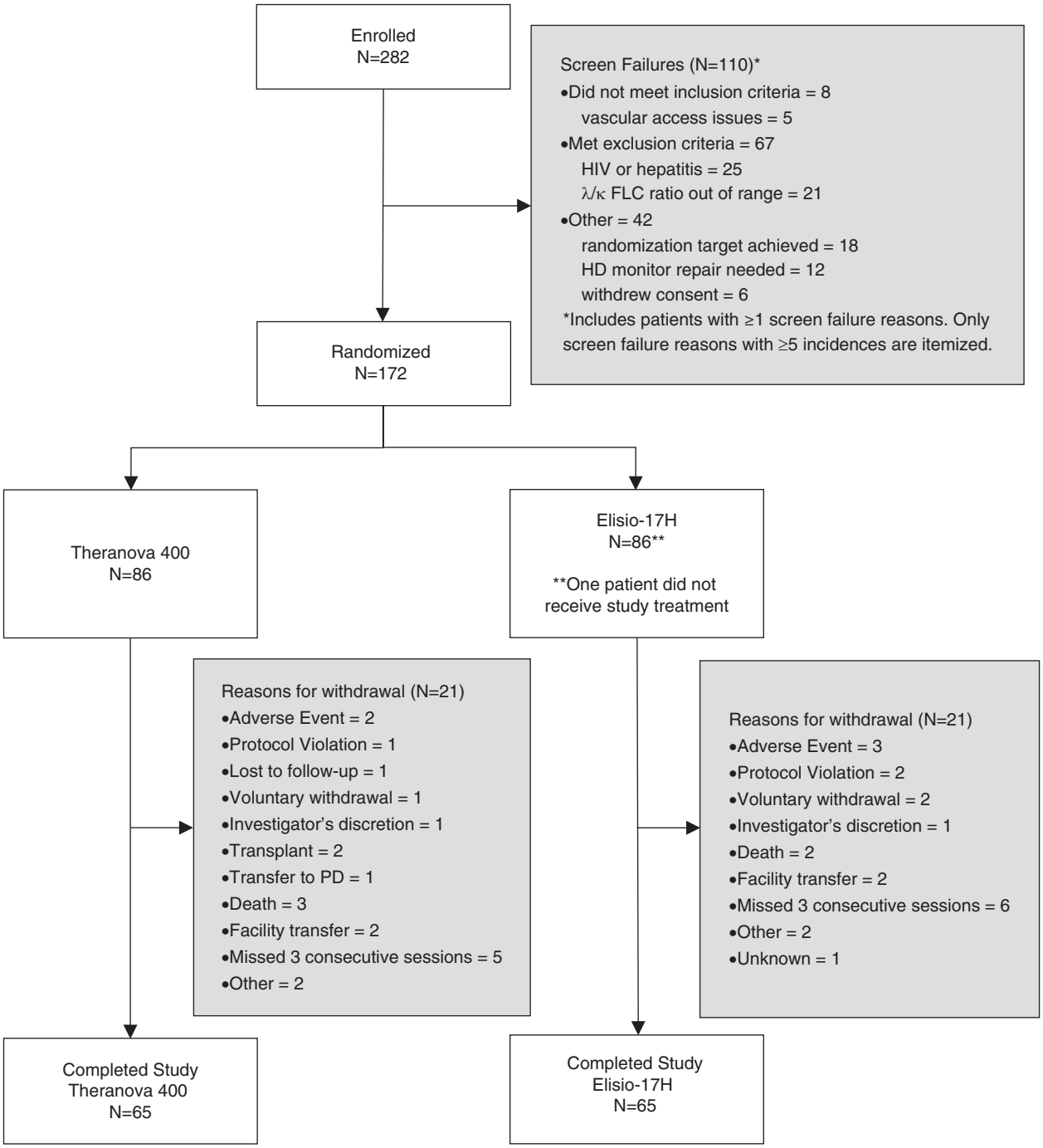

Figure 1. | **Patient disposition**. Enrollment, randomization, and completion of the clinical trial, including reasons for not completing the 24-week per protocol trial intervention, showing similar completion between the Theranova 400 and Elisio-17H randomization strata. FLC, free light chain; HD, hemodialysis; PD, peritoneal dialysis.

measured after every 4 weeks of treatment. There was no statistically significant difference in the level of nPNA(nPCR) at all 4-week intervals between the two groups.

Efficacy Outcomes

Primary Efficacy Outcome. The Theranova 400 showed significantly larger removal of free λ light chains at 24 weeks of treatment than the Elisio-17H dialyzer (mean RR of 33%±11% versus 17%±13% at 24 weeks; $P<0.001$; Figure 2, Table 4). Significantly larger removal of free λ light chains was also observed with the Theranova 400 at 4 weeks of treatment than with the Elisio-17H dialyzer (mean RR of 39%±14% versus 20%±11%; $P<0.001$). Sensitivity analysis using last value carried forward confirmed these results (Supplemental Table 15).

Secondary Efficacy Outcomes. The Theranova 400 demonstrated superior removal of middle to large molecules as

Table 1. Demographics, medical history, and dialysis settings

Characteristic	Value	Theranova 400, $n=86$	Control, $n=86$	Total, $n=172$
Age, yr	Mean (SD)	59 (14)	60 (12)	59 (13)
Weight, kg	Mean (SD)	90 (24)	95 (26)	92 (25)
Height, cm	Mean (SD)	170 (11)	170 (11)	170 (11)
Predialysis weight at first treatment day, kg	*n*	86	85	171
	Mean (SD)	90 (24)	95 (27)	92 (26)
Postdialysis weight at first treatment day, kg	*n*	86	85	171
	Mean (SD)	88 (24)	93 (26)	92 (25)
Sex, *n* (%)	Female	32 (37%)	35 (41%)	67 (39%)
	Male	54 (63%)	51 (59%)	105 (61%)
Race, *n* (%)	American Indian or Alaska Native	0	0	0
	Asian	5 (6%)	2 (2%)	7 (4%)
	Black	33 (38%)	35 (41%)	68 (40%)
	Native Hawaiian or other Pacific Islander	3 (4%)	3 (4%)	6 (4%)
	White	40 (47%)	42 (49%)	82 (48%)
	Other	5 (6%)	4 (5%)	9 (5%)
Primary kidney diagnoses (top 4), *n* (%)	Diabetic kidney disease	34 (40%)	43 (50%)	77 (45%)
	Hypertensive nephropathy	36 (42%)	24 (28%)	60 (35%)
	Polycystic kidney disease	3 (4%)	5 (6%)	8 (5%)
	GN	5 (6%)	3 (4%)	8 (5%)
Medical history	Hypertension, *n* (%)	78 (91%)	75 (87%)	153 (89%)
	Diabetes mellitus type 2, *n* (%)	47 (55%)	55 (64%)	102 (59%)
	Years on dialysis			
	n	79	74	153
	Mean (SD)	5.4 (5)	4.7 (4)	5.1 (4)
Type of current vascular access, *n* (%)	Arteriovenous fistula	68 (79%)	74 (86%)	142 (83%)
	Arteriovenous graft	12 (14%)	12 (14%)	24 (14%)
	Dual lumen catheter	6 (7%)	0	6 (4%)
Heparin type, *n* (%)	Unfractionated heparin	68 (79%)	61 (71%)	129 (75%)
	Low-molecular-weight heparin	15 (17%)	15 (17%)	30 (17%)
	Missing	3 (4%)	10 (12%)	13 (8%)

demonstrated by RRs measured at 4 and 24 weeks: complement factor D, free κ light chains, TNFα, and β2-microglobulin ($P<0.001$ for all; Figure 2, Table 4). The level of IL-6 at the end of the study was lower than at the start of treatment for the Theranova 400 group. The RR of IL-6 was negative for the control at both 4 (5%±46% versus −9%±61%; $P=0.09$) and 24 weeks of treatment (11%±38% versus −3%±39%; $P=0.05$); these differences were not statistically significant. Additional information regarding the change in absolute values of the above parameters can be found in Supplemental Table 16.

Single-pool Kt/V (spKt/V) was assessed after every 4 weeks of treatment. There were no significant differences in the mean spKt/V values at all measured time points, except for week 8 (Supplemental Table 17), where the spKt/V for the Theranova 400 was 1.62±0.29 and the value for the Elisio-17H was 1.51±0.32 ($P=0.02$). The value of spKt/V was within adequacy standards at all measured time points.

Exploratory Outcomes

There were no significant differences in the mean high-sensitivity C-reactive protein at all trial time points. Additionally, no significant differences were observed in the KDQOL-36 survey and EQ-5D-5L questionnaire results between the two groups. Quality of life results are presented in Supplemental Tables 18–20.

Adverse Outcomes

No significant differences were observed between the Theranova 400 and the Elisio-17H groups in incidence ($P=0.87$) and incidence rate ($P=0.32$) of AEs. There were 19 serious adverse events (SAEs) in 15 participants in the

Table 2. Primary safety outcome: Predialysis serum albumin assessment after 24 weeks

Parameter	Dialyzer	n	Mean (SD)	Median	Minimum, Maximum	Two-Sided 95% Confidence Interval[a]
Predialysis serum albumin after 24 wk, g/dl	Theranova 400	64	4.0 (0.3)	4.0	3.5, 4.7	−0.12 to 0.05
	Control	65	4.1 (0.4)	4.0	3.2, 4.9	

[a]If the lower bound of the two-sided 95% confidence interval around the mean estimated treatment difference between Theranova 400 and the control is >-0.1765, then noninferiority can be claimed. If the lower bound of the two-sided 95% confidence interval is >0, then superiority may be concluded.

Table 3. Secondary safety outcomes: Baseline and change from baseline of predialysis serum albumin

Parameter	Time Point	Theranova 400					Control					P Value
		n	Mean (SD)	Median	Minimum, Maximum	95% Confidence Interval	n	Mean (SD)	Median	Minimum, Maximum	95% Confidence Interval	
Predialysis serum albumin, g/dl	Baseline	86	4.0 (0.3)	4.0	3.4, 4.9	NA	86	4.0 (0.3)	4.0	3.3, 4.7	NA	NA
Change in predialysis serum albumin from baseline, g/dl	4 wk	80	−0.1 (0.2)	−0.1	−0.8, 0.6	−0.14 to −0.03	77	0.0 (0.2)	0.0	−0.7, 0.5	−0.04 to 0.05	0.03
	8 wk	78	−0.1 (0.3)	−0.1	−0.8, 0.5	−0.17 to −0.05	77	0.0 (0.2)	0.0	−0.6, 0.5	−0.05 to 0.05	0.004
	12 wk	77	−0.1 (0.3)	−0.1	−1.2, 0.6	−0.19 to −0.06	72	−0.0 (0.2)	0.0	−0.8, 0.5	−0.10 to 0.01	0.13
	16 wk	72	−0.1 (0.3)	−0.1	−1.3, 0.7	−0.21 to −0.05	71	−0.0 (0.3)	0.0	−1.6, 0.5	−0.10 to 0.05	0.11
	20 wk	66	−0.1 (0.3)	−0.1	−0.7, 0.5	−0.15 to −0.02	69	0.0 (0.3)	0.0	−0.9, 0.5	−0.05 to 0.08	0.07
	24 wk	64	0.0 (0.3)	0.0	−0.6, 0.4	−0.06 to 0.07	65	0.0 (0.3)	0.1	−0.6, 0.8	−0.02 to 0.11	0.61

Theranova 400 group, and 39 SAEs in 23 participants in the Elisio-17H group. This difference was not statistically significant. There were no SAEs associated with either device. None of the AEs were unanticipated; all were AEs typically seen in patients on maintenance HD. Six patients died during the study (three in each group), with one death in the Elisio-17H group occurring after participant withdrawal from the study. None of the deaths were assessed as related to either device.

Discussion

Among patients on maintenance HD, treatment with the Theranova 400 dialyzer maintained serum albumin level while providing superior removal of larger middle molecules as compared with a similar size high-flux dialyzer over 24 weeks. Prior studies have examined the effects of expanded HD, a mechanism whereby diffusion and convection are combined within a medium cut-off, hollow-fiber membrane; however, most were relatively small and exploratory, with limited follow-up duration (15,20,23). Recently, the Trial Evaluating Mid Cut-Off Value Membrane Clearance of Albumin and Light Chains in Hemodialysis Patients (REMOVAL-HD) was reported (24). REMOVAL-HD, a nonrandomized study in which 89 patients in Australia and New Zealand received 24 weeks of treatment with expanded HD, demonstrated no reduction in serum albumin as well as a durable reduction in free κ and λ light chains. Levels of free light chains significantly increased after cessation of HD with the medium cut-off dialyzer during a 4-week postintervention wash-out phase. Our findings greatly expand on these results, with a larger population and a randomized, controlled design.

Given the potential association of retained solutes with worse clinical outcomes in patients receiving dialysis, these results suggest that there may be a role for expanded HD to improve clinical outcomes. Of note, in this trial, free λ light chains were studied as a representative large middle molecule that is easily measured rather than as a presumptive "uremic toxin," with this study critically focusing on both clearance of these molecules as well as predialysis levels of large middle molecules. The latter is notable because if there is toxicity associated with retained uremic solutes, therapeutic management will require sustained reduction in the levels of these solutes. In parallel, no sustained reduction was seen in serum albumin level—an important finding given the association between higher serum albumin concentration and better outcomes in patients on HD.

Optimal removal of uremic solutes has been a goal of HD since its inception. High-flux dialysis membranes improved clearance of smaller middle molecules that were retained with older low-flux membranes, such as β2-microglobulin, resulting in improved outcomes for patients receiving dialysis, including a dramatic reduction in dialysis-associated amyloid; however, high-flux membranes provide limited clearance of larger solutes (>25 kD). Although hemodiafiltration may enhance clearance of many of these middle molecules, hemodiafiltration is not standard practice in the United States and is far more complex and costly than current high-flux HD. Given the potential role of these large uremic toxins in

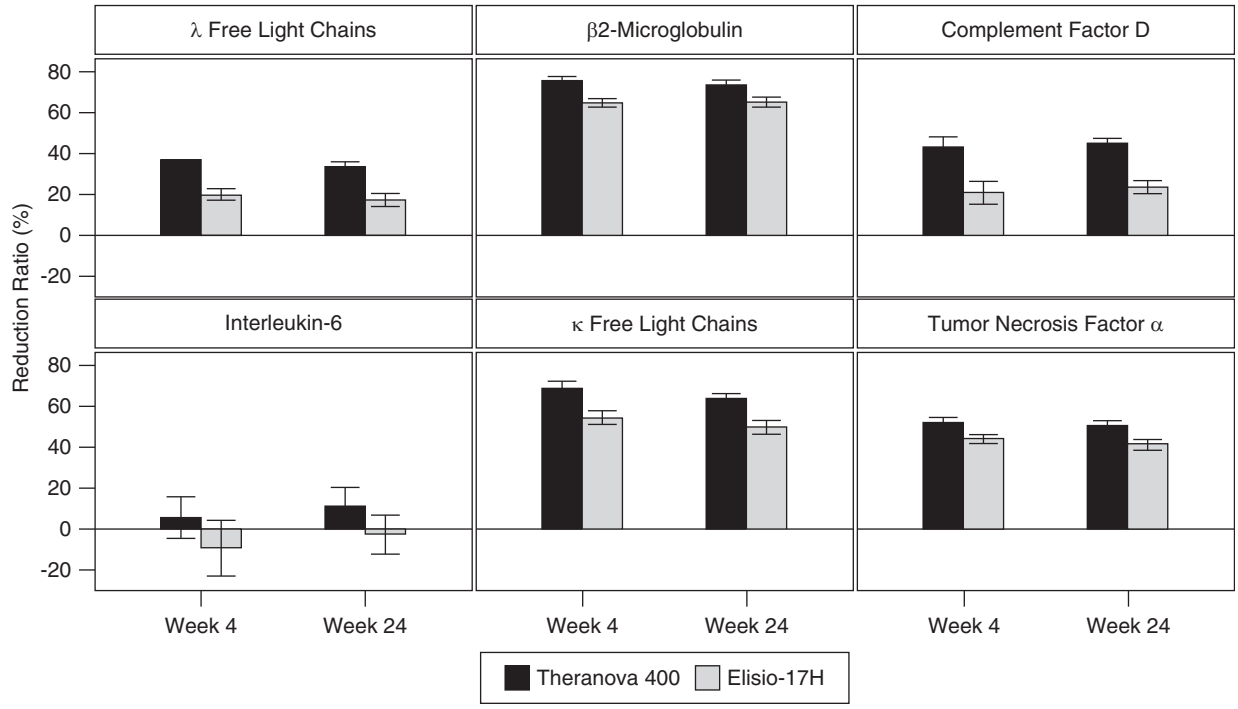

Figure 2. | **Removal of middle molecules at 4 and 24 weeks.** The reduction ratios of free λ light chains, complement factor D, free κ light chains, TNFα, and β2-microglobulin were significantly higher in the Theranova group compared with the Elisio-17H group ($P<0.001$ for all). For IL-6, the difference was not statistically significant.

cardiovascular disease and inflammation in patients with kidney failure, newer technologies enhancing clearance of middle molecules while limiting loss of important proteins, such as albumin, may have an important role in improving the health of patients on dialysis.

Multiple middle molecules are present at higher levels in patients on dialysis and have been associated with adverse outcomes (25). These include several of the solutes measured as a part of our study, although the primary efficacy solute, free λ light chains, was assessed as a representative large middle molecule. Notably, significantly greater RRs for TNF-α were measured with the Theranova 400 than with the Elisio-17H. TNF-α, a 17-kD cytokine, is present at levels four- to five-fold higher among patients on dialysis and may contribute to atherosclerosis. Similarly, IL-6 is associated with inflammation (26); although trending to a greater reduction among those randomized to the Theranova 400 arm, the RR difference in IL-6 concentration did not achieve statistical significance and predialysis levels of IL-6 and TNF-α did not change substantially with either dialyzer over the course of the trial. The modestly lesser increase during dialysis in IL-6 levels among those randomized to the Theranova 400 membrane could be consequential. In a study of 45 patients on HD, serum IL-6 levels increased by 14% during a dialysis session, whereas in a study of 57 patients on HD, 60% of patients experienced an increase in IL-6 levels during a dialysis session (27,28). In the latter trial, a greater increase in IL-6 level during the HD session was associated with an increased mortality risk, although the number of study participants was insufficient to have confidence in this conclusion.

Interestingly, despite significantly larger RRs observed for free λ and κ light chains, complement factor D, TNF-α, and β2-microglobulin, only predialysis levels of free λ and κ light chains declined significantly more in the Theranova 400 group versus control over the course of the trial. Intradialytic removal kinetics during HD using medium cut-off membranes has recently been analyzed for selected middle molecules (complement factor D, myoglobin, and β2-microglobulin) (29). However, there is still limited knowledge on kinetics of removal, intercompartmental distribution, and generation of all individual molecules investigated in our study, which did not include solute kinetics. Additionally, removal will not affect generation, and, if acute clinical settings result in higher generation, increased clearance from a prior dialysis session may not have a durable effect on future predialysis levels. This may be particularly true for TNF-α, which has a short $t_{1/2}$ (30). Therefore, it remains unclear whether the observed differential behavior among molecules within the same molecular weight spectrum might be related to differences in their pharmacokinetic properties or different intradialytic removal kinetics.

Although there were no observed significant differences in the quality of life assessments, the trial was not powered to evaluate differences in patient-reported outcomes. The KDQOL-36 survey is widely used in dialysis, but it is a broad survey that has particular value in screening for patient-perceived symptoms and is dependent on patient expectations (31). Additionally, although the EQ-5D-5L comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and is utilized across many chronic conditions, the ability to detect

Table 4. Primary and secondary efficacy outcomes: Reduction ratios (%) of middle molecules at 4 wk and 24 wk

Parameter[a]	Dialyzer	Wk 4, *n*	Mean (SD)	Median	Minimum, Maximum	*P* Value	Wk 24, *n*	Mean (SD)	Median	Minimum, Maximum	*P* Value
Primary efficacy outcome											
Reduction ratio of free λ light chains[b] (45 kD)	Theranova 400	80	39.3 (14.5)	42.4	−46.2, 71.1	<0.001	63	33.3 (11.0)	32.8	8.1, 54.1	<0.001
	Control	75	19.9 (11.4)	18.9	−4.5, 41.6		65	17.2 (12.9)	15.9	−10.7, 74.2	
Secondary efficacy outcomes											
Reduction ratio of complement factor D (24 kD)	Theranova 400	83	43.0 (23.9)	48.0	−58.1, 78.5	<0.001	62	45.0 (10.4)	46.0	11.0, 68.0	<0.001
	Control	76	20.9 (23.7)	22.5	−110.9, 77.8		65	23.6 (12.1)	23.9	−47.0, 45.5	
Reduction ratio of free κ light chains (23 kD)	Theranova 400	80	68.8 (17.3)	72.1	−57.9, 94.6	<0.001	63	63.8 (11.8)	65.8	27.8, 87.4	<0.001
	Control	75	54.8 (14.5)	56.0	−29.1, 77.6		65	50.0 (13.2)	49.4	2.3, 74.1	
Reduction ratio of IL-6 (25 kD)	Theranova 400	80	5.5 (45.9)	19.6	−155.4, 66.1	0.09	63	11.0 (37.8)	20.8	−128.5, 66.2	0.05
	Control	78	−9.2 (60.6)	3.9	−341.2, 55.6		65	−2.6 (39.4)	7.8	−162.2, 46.2	
Reduction ratio of TNFα (17 kD)	Theranova 400	80	52.5 (9.4)	54.3	16.3, 72.4	<0.001	63	50.7 (9.3)	52.2	23.8, 68.5	<0.001
	Control	78	44.1 (9.3)	45.3	11.0, 58.1		65	41.5 (10.2)	41.9	−0.9, 57.9	
Reduction ratio of β2-microglobulin (11.8 kD)	Theranova 400	78	75.7 (8.2)	77.2	46.6, 98.9	<0.001	63	73.6 (10.4)	75.9	30.3, 96.7	<0.001
	Control	76	64.9 (8.9)	65.6	24.1, 83.2		65	65.4 (9.4)	65.9	36.8, 90.0	

[a]Baseline, predialysis, and postdialysis concentrations can be found in Supplemental Table 13.
[b]The reduction ratio of free λ light chains at 4 weeks of treatment was a secondary efficacy outcome.

clinically meaningful change in the HD population is uncertain.

This trial has several limitations. First, the screen failure rate was high (Figure 1); of note, the decision to exclude patients with indeterminant or positive HIV/hepatitis serology was conservative and, in practice, this exclusion criteria should not substantially limit the use of expanded HD given the relatively low prevalence of HIV and viral hepatitis in the HD population. Additionally, excluding patients with known serum free κ/λ light chain ratio <0.37 or >3.1 (n=21) was implemented with the intention of excluding patients with conditions suggestive of monoclonal plasma diseases, which are rare, as including patients with baseline serum free κ/λ light chain ratio beyond the prespecified range may have confounded the results of the study. Second, although overall participant retention was good, several participants were missing follow-up solute measures and approximately one quarter of participants did not complete the study; however, sensitivity analyses *via* multiple imputation and last observation carried forward demonstrated similar results. Third, as a trial designed to show changes in clearance and levels of large middle molecules, the study was insufficient in duration and sample size to comment on key clinical outcomes such as cardiovascular events and mortality. Fourth, although the Theranova 400 membrane more effectively cleared large middle molecules than a similar size high-flux membrane, the Elisio-17H, we lack data on residual kidney function and kidney clearance; however, given the mean dialysis duration of 4 years among participants, it is likely that most participants had minimal residual clearance, if any. The trial also has multiple strengths, including the randomized design, high rates of adherence, minimal loss to follow-up, and consistent results across solutes analyzed.

Serum laboratory values of uremic toxins that would be considered normal values in patients on HD are unknown. Existing studies that examined the association of higher levels of free κ and λ light chains with poorer outcomes were conducted in patients with CKD, excluding patients on dialysis. One early study of 142 patients with CKD found free κ and λ light chains (especially in patients on dialysis) was associated with inflammation, vascular calcification, and levels of other uremic toxins such a β2-microglobulin (32). Elevated serum free κ light chains and free λ light chains levels appeared to be associated with mortality; however, the association disappeared after adjustment for a propensity score including age, CKD stage, and aortic calcification. Furthermore, one meta-analysis pooling data from five prospective cohort studies showed that serum free κ and λ light chains levels were independently associated with mortality (33). The serum free κ and λ light chains values above the upper limit of normal (43.3 mg/L) were independently associated with mortality (hazard ratio, 1.45; 95% confidence interval, 1.14 to 1.85). In our randomized pivotal trial, the absolute values of free κ and λ light chains, as expected, were markedly higher than in the literature referenced above (Supplemental Table 13). With lower absolute values of both free κ and λ light chains in the Theranova 400 arm compared with the control arm after 24 weeks of treatment, it is possible that expanded HD may potentially

demonstrate improved mortality with long-term treatment because of better clearance of larger middle molecules.

Morbidity and mortality remain high among patients on dialysis, and there have been limited changes in dialysis technologies over the past several decades. Recognizing the critical need to advance dialysis therapy, new initiatives are evolving to support and fund innovation in the kidney space (34). These include changes in dialysis technology, such as those potentially enabled by the Theranova 400 membrane, as well as paradigm shifts in the provision of kidney care as envisioned by the Kidney Innovation Accelerator (KidneyX).

In conclusion, expanded HD with the Theranova 400 dialyzer is safe and efficacious, providing superior removal of larger middle molecules, including several putative uremic toxins, compared with a similar size high-flux dialyzer, while maintaining serum albumin. Although this study demonstrated greater removal of large middle molecules among patients on prevalent HD, larger studies of longer duration are needed to assess long-term potential beneficial effects related to more effective removal of these middle molecules, including improvements in cardiovascular disease, inflammation, mortality, and key patient-reported outcomes.

Disclosures

W. Beck has patents WO2015/118045 and WO2015/118046 issued and is a full-time employee of Baxter International Inc. L. Falzon and A. Bernardo are employees of Baxter Healthcare Corporation. H. Tran, L. Skoufos, and M. Xiao are employees of Baxter Healthcare Corporation and own stock in the company. D.E. Weiner receives salary support paid to his institution for clinical research efforts by Dialysis Clinic Inc. He was a site principal investigator in this clinical trial and received no funding from Baxter Healthcare International beyond this role, with trial support paid to his institution. He has consulted for Akebia, Janssen, and Tricida. He reports receiving personal fees from Cara Therapeutics. All remaining authors have nothing to disclose.

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Data Sharing Statement

Deidentified individual participant data (including data dictionaries) will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Data will be made available beginning 9 months and ending 36 months after publication. Proposals should be submitted to luke_falzon@baxter.com.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.01210120/-/DCSupplemental.

Supplemental Table 1. Reduction ratio of λ FLC at 24 weeks–multiple imputation.

Supplemental Table 2. Predialysis serum albumin assessment after 24 weeks–Multiple imputation.

Supplemental Table 3. Dialysis treatment parameters.

Supplemental Table 4. Sensitivity analysis-Predialysis serum albumin assessment after 24 weeks. Last observation carried forward.

Supplemental Table 5. Shift table of predialysis serum albumin by visit.

Supplemental Table 6. Predialysis coagulation factors summary and change from baseline.

Supplemental Table 7. Summary of normalized protein equivalent of nitrogen appearance.

Supplemental Table 8. Comprehensive metabolic panel summary and change from baseline.

Supplemental Table 9. Coagulation summary and change from screening.

Supplemental Table 10. Hematology laboratory summary and change from baseline.

Supplemental Table 11. Small uremic solutes summary and change from baseline.

Supplemental Table 12. Vitamin A and lipids summary and change from baseline.

Supplemental Table 13. Liver function summary and change from screening.

Supplemental Table 14. Proteins summary and change from baseline.

Supplemental Table 15. Sensitivity analysis–Reduction ratio of λ FLC at 24 weeks. Last observation carried forward.

Supplemental Table 16. Change from baseline of predialysis levels of middle molecules after 4 and 24 weeks.

Supplemental Table 17. Monthly single-pool Kt/V_{urea}.

Supplemental Table 18. Patients' self-rated health on a vertical visual analogue scale.

Supplemental Table 19. Exploratory analysis-Patient-reported outcome measures EQ-5D-5L your health today and index value.

Supplemental Table 20. Exploratory analysis-Patient-reported outcome measures EQ-5D-5L dimensions.

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