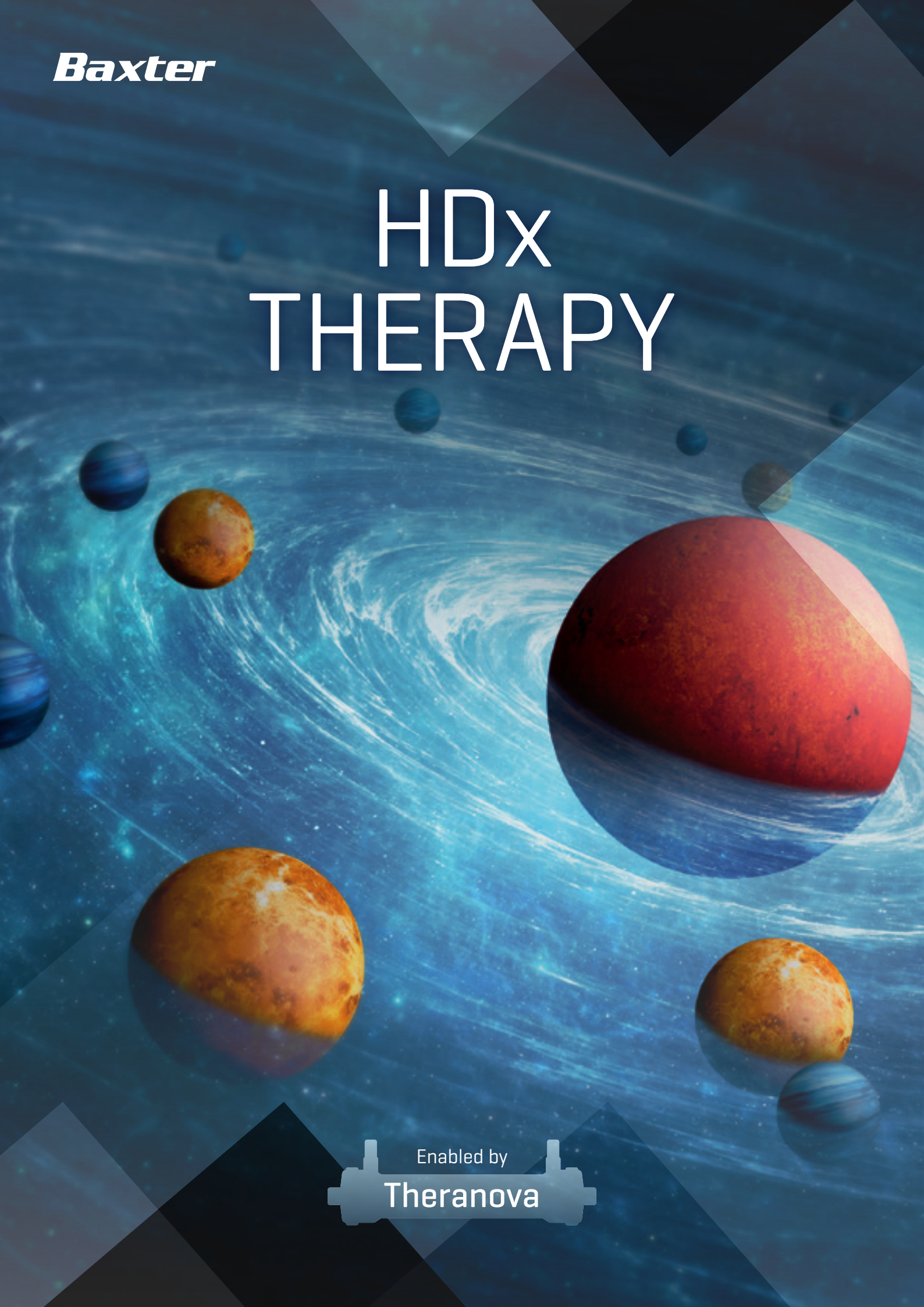
Baxter

HDx THERAPY



Enabled by

Theranova

THE NEXT HORIZON IN DIALYSIS IS CLOSER THAN YOU THINK

HDx by **Theranova*** expands your renal possibilities for all HD patients

HDx therapy (expanded HD) is the next evolution in hemodialysis. It targets the efficient removal of large middle molecules (25 kDa to <60 kDa), many of which are linked to the development of inflammation, cardiovascular disease and other co-morbidities in dialysis patients.[1,2]

With HDx therapy, **Theranova** can provide superior removal of large middle molecules compared to HD and HDF and it can do so using regular HD workflow and infrastructure.[3]

HDx is enabled by the **Theranova** dialyzer, which features an innovative membrane that combines a higher permeability than regular high-flux dialyzers with effective selectivity for larger proteins.[4,5]

This therapy opens a new door for dialysis patients, who are believed to benefit from the effective removal of large uremic toxins, as well as for clinics who want expanded dialysis performance without the added burden of HDF.[6]

PHOSPHATE

BETA 2 MICROGLOBULIN

INTERLEUKIN-6

YKL-40

CREATININE

LAMBDA FREE LIGHT CHAIN

*Do not use **Theranova** dialyzers in HDF or HF mode

CHANGE ONE THING, CHANGE EVERYTHING

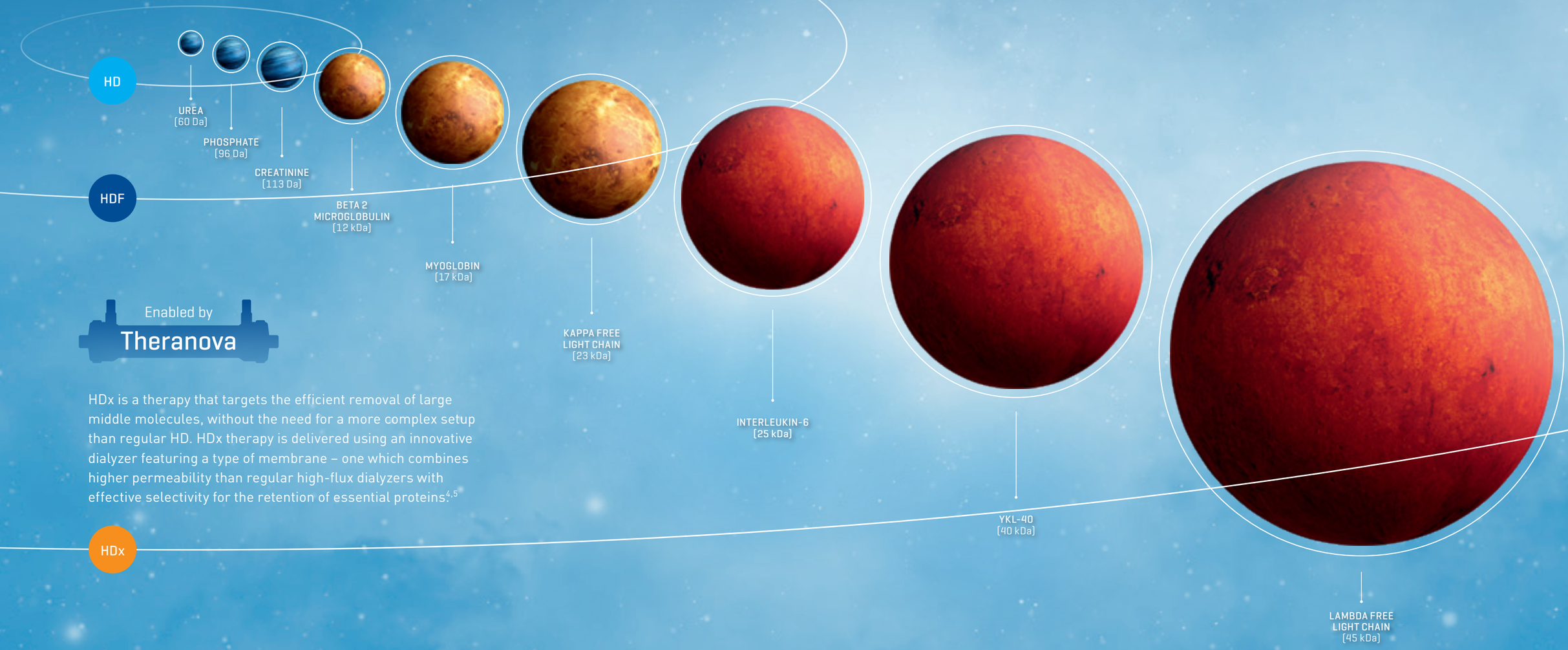
Explore HDx Therapy by **Theranova**

Mortality from cardiovascular and infectious events in HD remains unsatisfactorily high with current dialytic therapies.[7] Large middle molecules have been associated with inflammation, cardiovascular events and other dialysis-related co-morbidities.[2] Current dialytic therapies, though efficient in removing small solutes, have limited capability to remove large middle molecules.[8]

CATEGORIZATION OF UREMIC SOLUTES

Non-protein bound uremic solutes accumulating in chronic kidney disease can be divided into three main categories.[5]

- **Small molecules (< 500 Da)**
  Effective removal by diffusion
- **Conventional middle molecules (> 500 Da - < 25 kDa)**
  Limited removal by diffusion, compensated by applying convection
- **Large middle molecules (25 kDa - < 60 kDa)**
  Require higher permeability membranes for effective removal



Enabled by **Theranova**

HDx is a therapy that targets the efficient removal of large middle molecules, without the need for a more complex setup than regular HD. HDx therapy is delivered using an innovative dialyzer featuring a type of membrane – one which combines higher permeability than regular high-flux dialyzers with effective selectivity for the retention of essential proteins.[4,5]

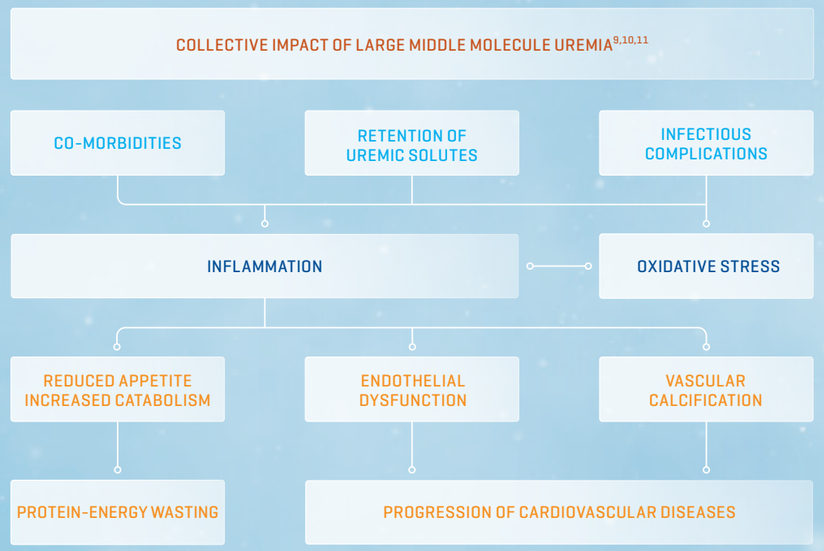
SHIFTING FOCUS TO LARGE MIDDLE MOLECULES

Examining Middle Molecules Beyond Beta 2 Microglobulin

Uremia related to the retention of large middle molecules is associated with inflammation, cardiovascular events and several co-morbidities.[9,10,11]

CO-MORBIDITIES ASSOCIATED WITH SPECIFIC LARGE MIDDLE MOLECULES[8,12]

Solute	MW (kDa)	Relevance
Interleukin-6	21-28	Pro-inflammatory, immune modulation, atherosclerosis
Pentraxin-3	40	Acute phase reactant; implicated as inducer of endothelial damage
YKL-40	40	Novel marker; up-regulated in inflammation-associated diseases; associated with outcome
α1-acid glycoprotein	43	Acute phase reactant
Lambda free light chain	45	Pro-inflammatory; plasma levels correlate with outcome such as survival in CKD patients, immune modulation
Advanced glycation end products	30-60	Associated with inflammation, malnutrition, atherosclerosis, CV disease, and survival



A STEP CLOSER TO THE NATURAL KIDNEY

HDx therapy is made possible thanks to the combination of 4 principles in a single dialyzer device design.

1. HIGHER PERMEABILITY

With an increased nominal pore size, the **Theranova** dialyzer has significantly higher permeability for large middle molecules compared to regular high-flux membranes, both before and after blood contact.

2. EFFECTIVE SELECTIVITY FOR LARGER PROTEINS

By combining a unique, asymmetric 3-layer structure with a carefully controlled pore size distribution, the **Theranova** dialyzer appears to be a stable separation profile and selectivity throughout treatment, keeping albumin removal limited.

3. RETENTION

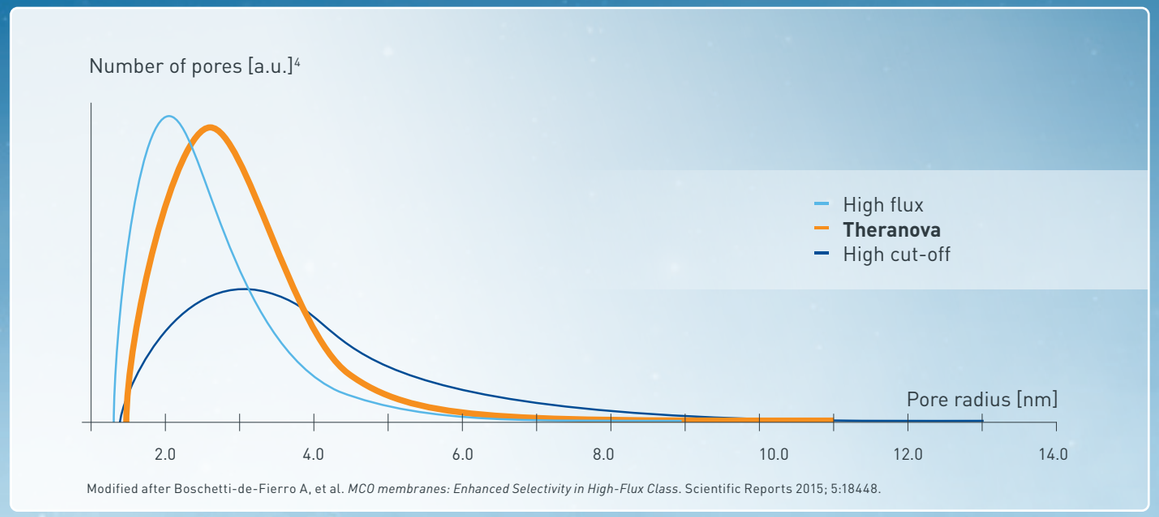
The adsorptive properties of the **Theranova** membrane maintain the same level of bacteria and endotoxin retention as other standard dialysis membranes.[13] Despite its higher permeability, the **Theranova** membrane appears to be a safe and effective barrier to potential dialysis fluid contaminants. It is compatible with standard fluid quality (ISO 11663 or ANSI/AAMI RD62) and does not require any additional fluid quality control measures.[14]

4. INTERNAL FILTRATION

The inner diameter of the **Theranova** membrane has been carefully reduced in order to increase convective transport along the membrane and, consequently, enhance the effectiveness of large middle molecule removal.

FILTRATION PROFILE CLOSER TO THE NATURAL KIDNEY

These 4 principles result in a membrane design unique to the **Theranova** dialyzer. Its innovative **medium cut-off (MCO)** membrane expands the range of solutes removed during regular dialysis while retaining essential proteins at a safe level. This unique cut-off and retention onset profile allows for filtration closer to that of the natural kidney.[4,5]



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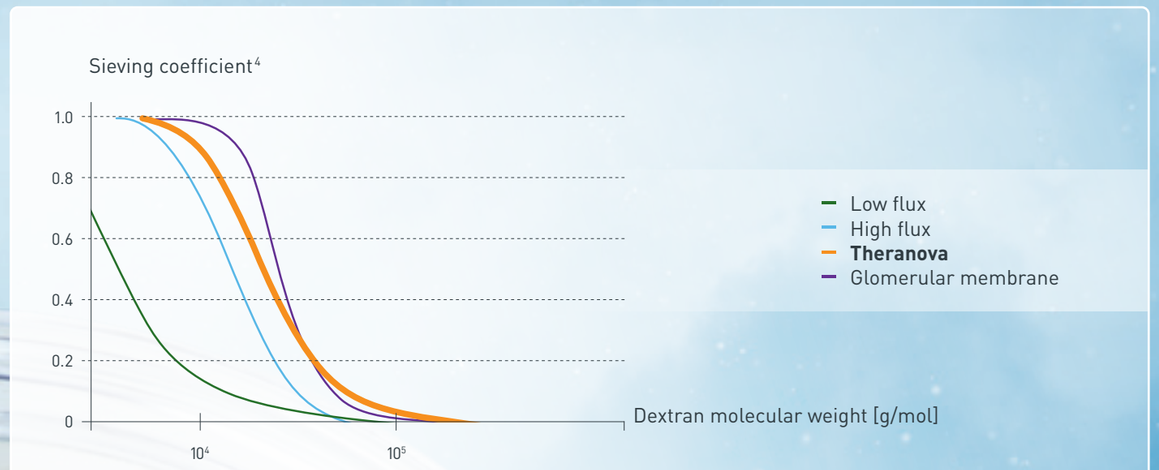
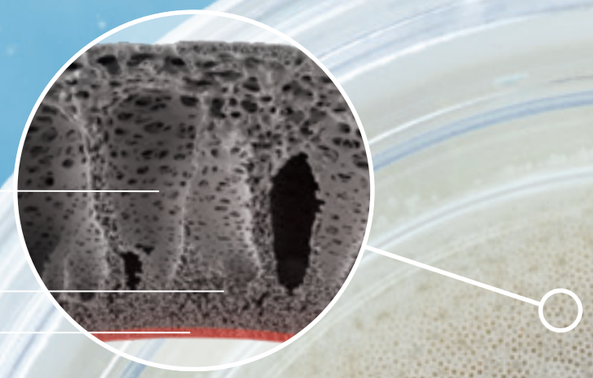


Modified after Boschetti-de-Fierro A, et al. *MCO membranes: Enhanced Selectivity in High-Flux Class*. Scientific Reports 2015; 5:18448.

The membrane structure is asymmetric and can be seen in cross section as three distinct layers:

- A finger-like macro-porous outer layer
- A sponge-like intermediate layer
- A very thin inner layer (skin)



EXPANDED HEMODIALYSIS (HDx): SUPERIOR LARGE MIDDLE MOLECULE REMOVAL

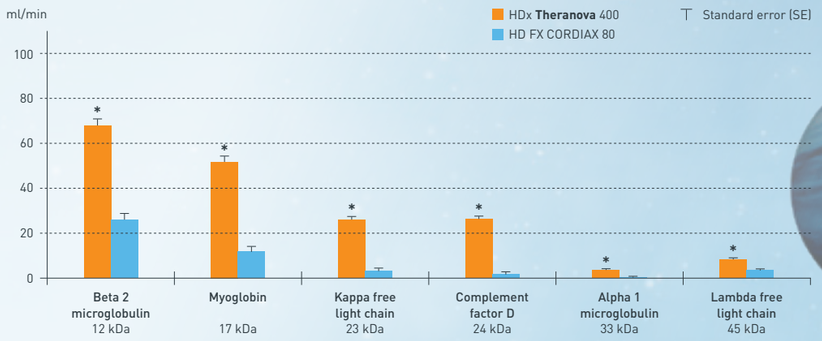
Treatment Effects and Therapy Implications (vs. HD)[3]

HD therapies have been the treatment of choice for many years – both for many patients and many clinics. The design and operating mode of the **Theranova** dialyzer enables HDx therapy to be easily implemented on any HD monitor.[15] This means by simply changing the dialyzer, any clinic can provide markedly greater clearances and intradialytic reduction ratios than regular HD – all at ordinary blood flow rates.

OVERALL CLEARANCE HDx vs. HD

HDx with **Theranova** 400 dialyzer
HD with latest generation high-flux dialyzer
Q_B = 300 ml/min – Treatment Time = 4 h (Mean) – n = 19

* p<0.001 vs high-flux HD

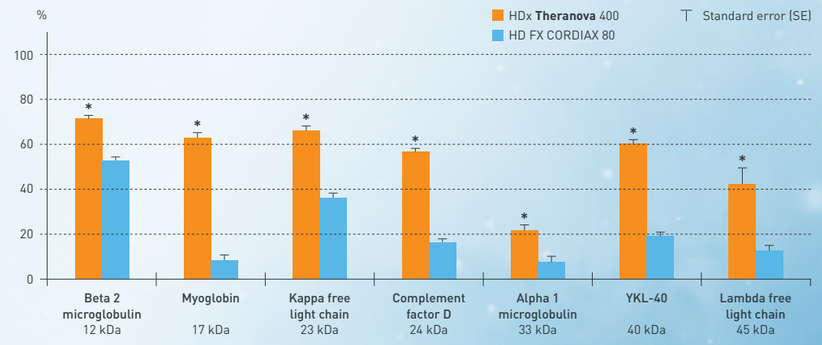


Modified after Kirsch AH, et al. *Performance of hemodialysis with novel medium cut-off dialyzers.* Nephrol Dial Transpl 2017; 32(1):165-72.

REDUCTION RATIO HDx vs. HD

HDx with **Theranova** 400 dialyzer
HD with latest generation high-flux dialyzer
Q_B = 300 ml/min – Treatment Time = 4 h (Mean) – n = 19

* p<0.001 vs high-flux HD



Modified after Kirsch AH, et al. *Performance of hemodialysis with novel medium cut-off dialyzers.* Nephrol Dial Transpl 2017; 32(1):165-72.

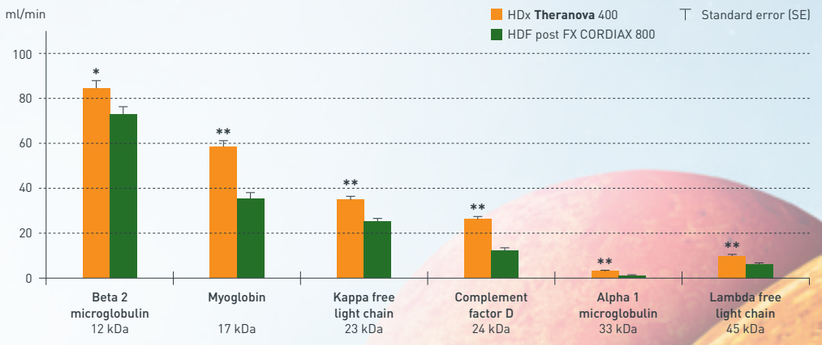
Treatment Effects and Therapy Implications (vs. HDF)[3]

Theranova provides superior removal of large middle molecules in comparison to high-volume HDF.[3] This performance can be achieved in all regular HD environments: HDx simplicity removes the potential burden of patient eligibility or therapy-specific delivery systems.

OVERALL CLEARANCE HDx vs. HDF

HDx with **Theranova** 400 dialyzer
HDF with latest generation high-flux dialyzer for HDF
Q_B = 400 ml/min – Treatment Time = 4.4 h – Vconv = 24L (Mean) – n = 20

* p<0.01 vs HDF
** p<0.001 vs HDF

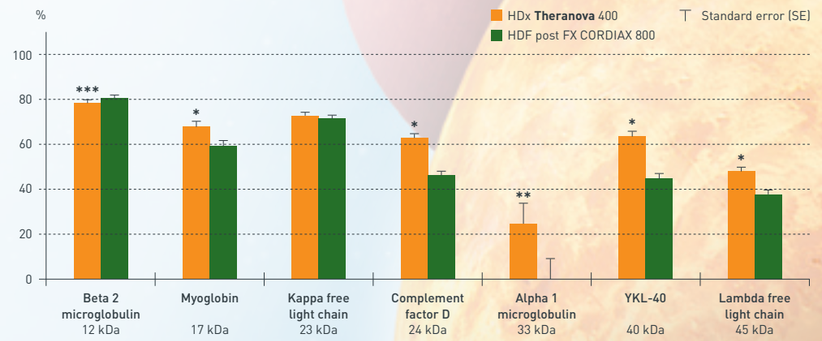


Modified after Kirsch AH, et al. *Performance of hemodialysis with novel medium cut-off dialyzers.* Nephrol Dial Transpl 2017; 32(1):165-72.

REDUCTION RATIO HDx vs. HDF

HDx with **Theranova** 400 dialyzer
HDF with latest generation high-flux dialyzer for HDF
Q_B = 400 ml/min – Treatment Time = 4.4 h – Vconv = 24L (Mean) – n = 20

* p<0.001 vs HDF
** p<0.01 vs HDF
*** p<0.05 vs HDF



Modified after Kirsch AH, et al. *Performance of hemodialysis with novel medium cut-off dialyzers.* Nephrol Dial Transpl 2017; 32(1):165-72.

TODAY'S KNOWLEDGE TOMORROW'S DISCOVERY

ALBUMIN REMOVAL PER SESSION

Limited and consistent albumin removal – to between 1 and 4 grams per treatment.

ALBUMIN REMOVAL DURING DIALYSIS SESSIONS, IN GRAMS (N=39)[3]

	Q_b = 300 mL/min T = 4 h	Q_b = 400 mL/min T = 4.4 h
Mean (± SD)	2.7±0.7	3.0±0.7
Median	2.9	3.2
Range	1.5-3.9	1.9-3.9

ALBUMIN LEVEL STABILITY AFTER 6 MONTHS

HDx treatment, enabled by **Theranova**, shows limited removal of albumin demonstrating that after 6 months plasma albumin level is stable (within 5% change only).[16,17,*]

ALBUMINEMIA EVOLUTION OVER TIME (N=524)[17,*]

	Albumin g/dl (mean ± SD)	Difference g/dl	Difference %	95% CI Difference %
Baseline	4.05±0.32			
Week 2	3.98±0.32	-0.07	-1.7	-1.2 to -2.2
Month 1	3.97±0.31	-0.08	-1.9	-1.4 to -2.4
Month 3	3.93±0.29	-0.12	-2.9	-2.2 to -3.4
Month 6	3.95±0.33	-0.11	-2.4	-1.9 to -3.4

CHANGING DIALYSIS ONE STUDY AT A TIME

HDx is constantly generating new evidence supporting therapy efficacy.

LATEST FINDINGS

- In a multi-centric observational study of 41 HD patients, pre-dialysis levels of beta 2 microglobulin and kappa and lambda free light chains were reduced after 3 and 6 months with HDx therapy using the **Theranova** dialyzer.[18,*]
- A large observational registry study in prevalent HD patients found an approximate 50% reduction in the number of patients meeting Restless Leg Syndrome (RLS) criteria after 6 months on HDx therapy.[19,**] A smaller before-after study found no difference in patient-reported symptom burden[16,*]

UPCOMING STUDIES

- Analyzing real world data of patients on HDx therapy.
- Exploring morbidity and mortality in patients dialyzed with the HDx therapy.
- Determining and comparing hard clinical end points of HDx.
- Understanding the effects of HDx therapy with other therapies.

* Based on data presented in a congress abstract – see reference for details.
** Based on data presented in a congress abstract – see reference for details. Restless leg syndrome was only one of several secondary endpoints.

PROVIDE EXPANDED HD

- Superior removal of large middle molecules (25 kDa to <60 kDa) compared with HD and HDF modalities is delivered with **Theranova**, with limited albumin removal.[3]
- Pre-dialysis levels of beta 2 microglobulin and kappa and lambda free light chains were reduced after 3 and 6 months with HDx therapy using the **Theranova** dialyzer in a multi-centric observational study of 41 HD patients.[18,*]
- Restless Leg Syndrome criteria are reduced approximately 50% after 6 months for prevalent HD patients in a large observational study by Baxter.[19,**] A smaller before-after study found no difference in patient-reported symptom burden.[16,*]
- Applicable to all HD patients.

RETAIN HD SIMPLICITY

- HD infrastructure: no need for HDF capable monitors nor specific water quality and fluid quality assurance measures.[6]
- HDx therapy is enabled simply by the use of **Theranova** in HD mode.

* Based on data presented in a congress abstract – see reference for details.
** Based on data presented in a congress abstract – see reference for details. Restless leg syndrome was only one of several secondary endpoints.

For safe and proper use of the device, please refer to the Instructions for Use.

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The products meet the applicable provisions of Annex I (Essential Requirements) and Annex II (Full quality assurance system of the Council Directive 93/42/EEC of 14 June 1993, amended by Directive 2007/47/EC)

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