



# Presentation

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Member of the Management Board

September 16, 2024

**Expert call | HDF**  
**High-volume hemodiafiltration**

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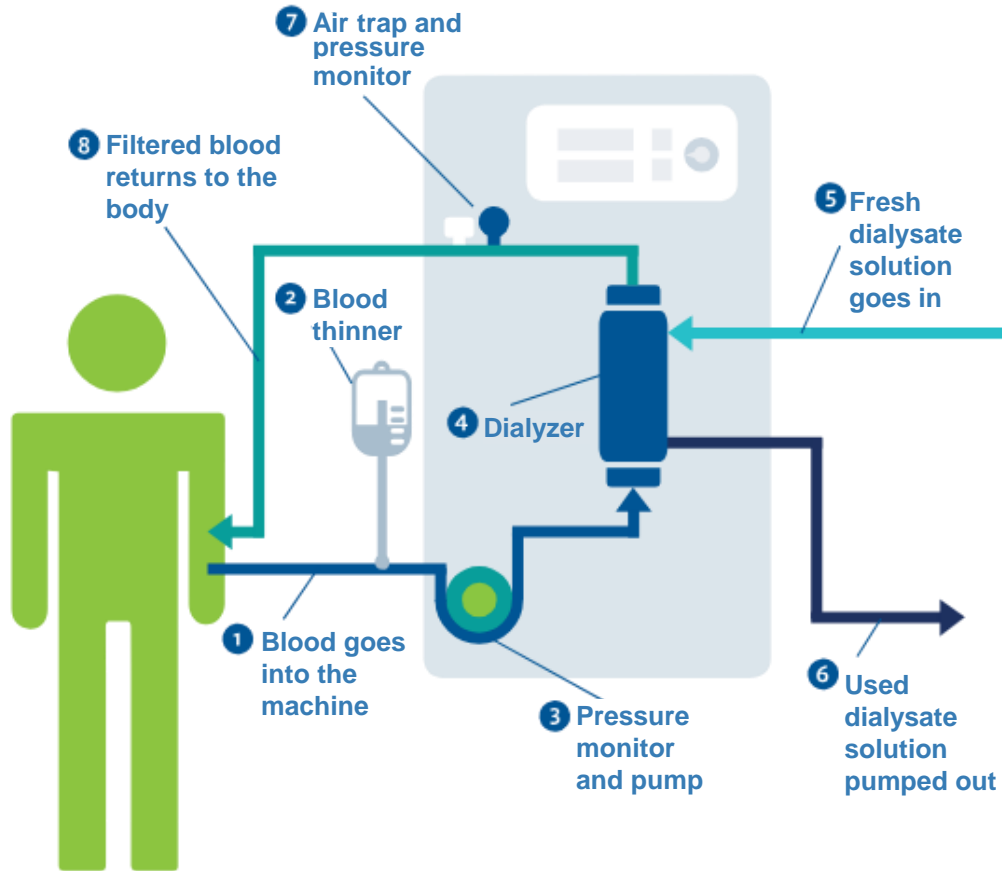


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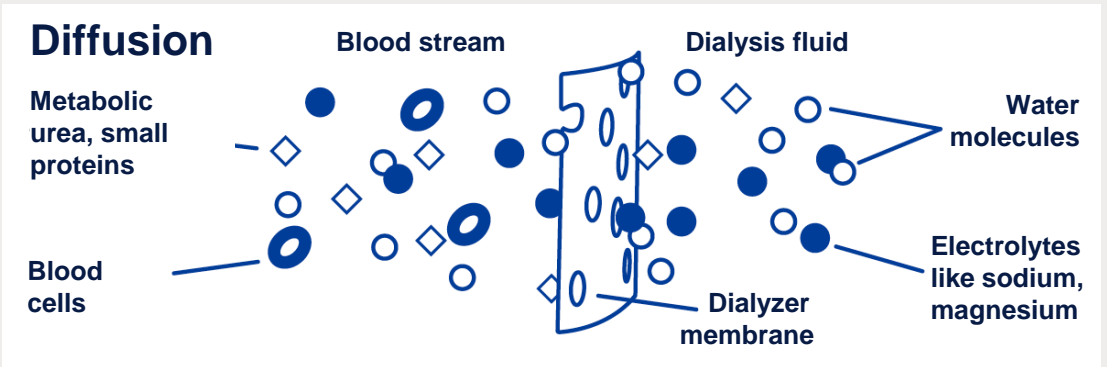
- 1 How it works: HD vs. HDF**
- 2 FME product innovation**
- 3 Clinical benefits**
- 4 CONVINCe Study**
- 5 FME real-world experience**
- 6 Bringing HDF to the U.S.**

# Basic principle of hemodialysis (HD) | Diffusion

## Hemodialysis



- In HD, blood is filtered outside of the body through a dialyzer (“artificial kidney”) that comprises a large number of hollow fibers
- Blood flows into the fibers while dialysis fluid (“dialysate”) is added into the dialyzer and bathes the fibers
- **Diffusion** is the main form of solute removal in HD
  - Diffusion describes the movement of particles down a concentration gradient from blood to dialysate



# Different types of hemodialysis (HD) treatments

## Typical HD | All based on diffusion

### Low Flux

- Small pores and low water permeability
- Good for diffusive clearance and often used for intermittent HD

### High Flux

- Larger pores and increased water permeability
- Can remove moderate-sized molecules, such as uremic toxins, inflammatory proteins, and lipoproteins

Standard High Flux

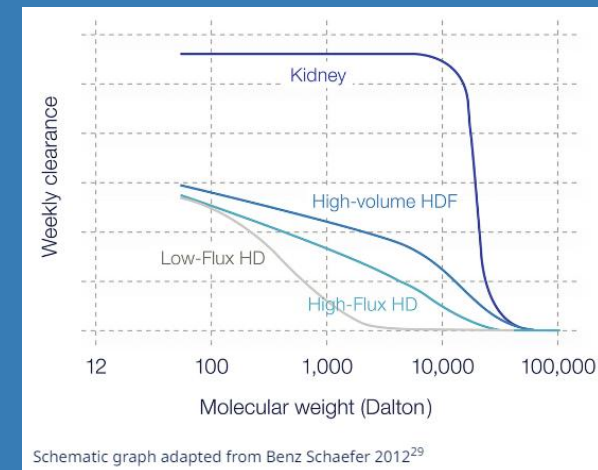
MCO High Flux

Super High Flux

- Back-filtration in a dialyzer with a more open pore structure
- Designed to increase clearance of conventional and large middle molecules through medium cutoff membranes (MCO)

## HDF | A distinct, innovative therapy

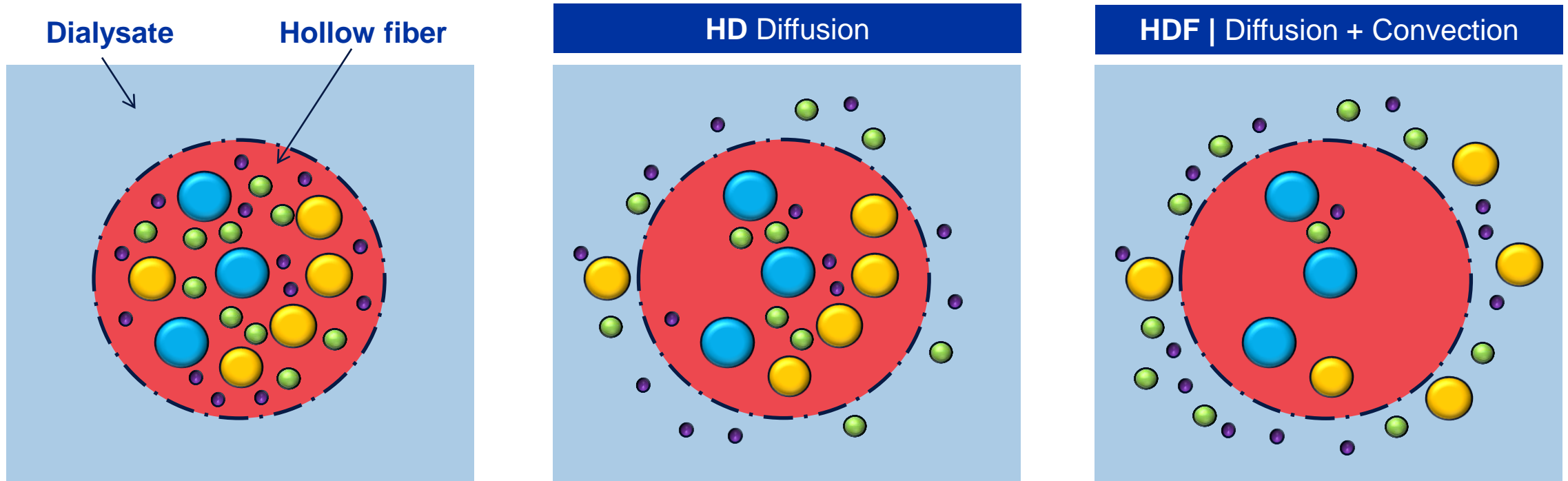
- **Hemodiafiltration (HDF)** brings the clearance profile closer to natural kidney function
- Addition of **convection** helps to eliminate middle and larger unwanted uremic molecules
- In machines equipped to perform HDF, systems re-designed to manage a safe and flawless application, including replacement fluid



# HDF | Diffusion and convection act together to improve solute removal

Goal to remove key toxins while maintaining albumin levels

## Fiber cross section view



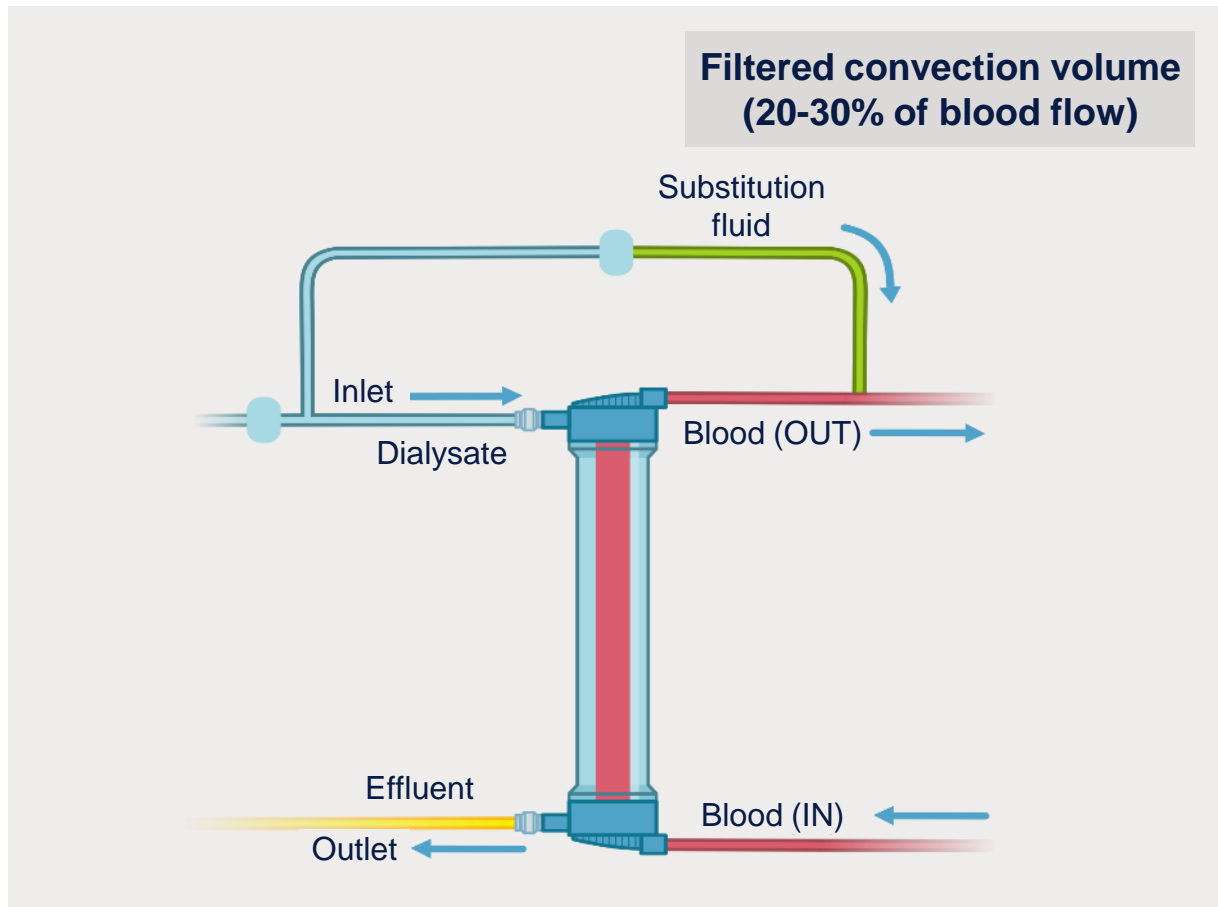
● Urea (60 Dalton) ● Creatinine (113 Dalton) ● Beta 2 Microglobulin (11,800 Dalton) ● Albumin (66,500 Dalton)

- A **dalton (Da)** is a measure of molecular weight also known as an atomic mass unit; average weight of a strand of hair =  $1.2044 \times 10^{19}$  Da
- **Albumin** is an important protein in the blood that aids with fluid balance

# Different forms of HDF

## Post-dilution, high-volume HDF most efficient with proven benefits

### What difference does the form of HDF make?



Imamović G et al. In: Karkar A, ed. Advances in Hemodiafiltration. InTech Open. 2016;5-23.

- Different forms of HDF exist: pre-, mid-, mixed- and post-dilution
- Post-dilution is the most efficient
- Post-dilution at high volumes ( $\geq 23$  liters achieved) demonstrated proven benefits in CONVINCE Study and FME real-world experience of more than a decade
- Lower volumes not found to provide similar benefits
- Post-dilution, high-volume HDF predominant form in Europe for more than a decade and proposed for the U.S.

# FME has led the world in innovation making high-volume HDF practical, safe, and effective

## Requirements for high-volume HDF

Machine designed for high-volume HDF

Appropriate dialyzers

Vascular access

Ultrapure water for high-quality replacement fluid

HDF-capable machines and dialyzers the latest in a long history of FME innovation in renal space





# Clinical benefits of high-volume HDF



# History of trials comparing HD vs. HDF

## Randomized clinical trials history

2012

**Contrast Study<sup>1</sup>**

2013

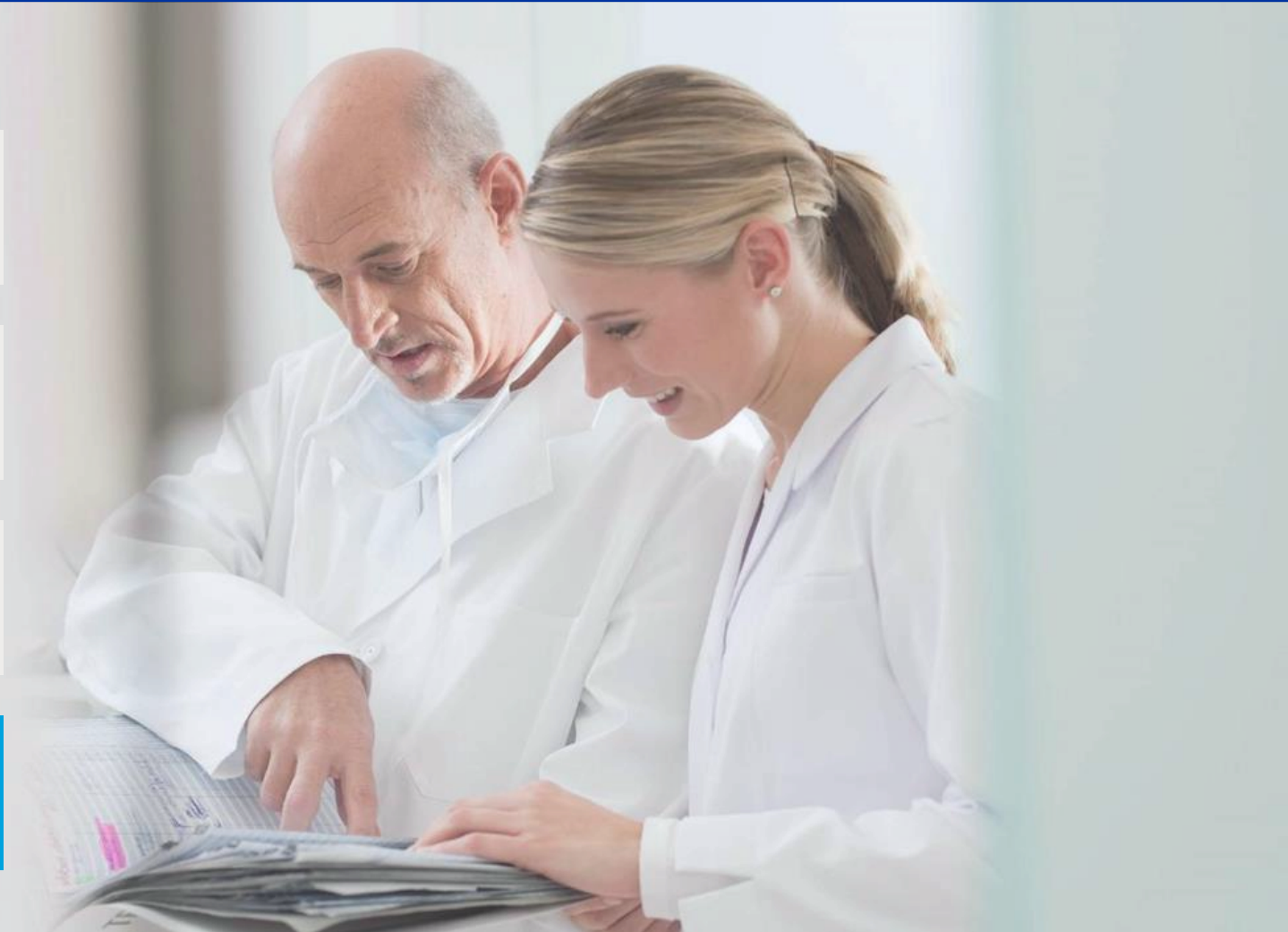
**Turkish HDF Study<sup>2</sup>**  
**ESHOL Study<sup>3</sup>**

2017

**FRENCHIE Study<sup>4</sup>**

2023

**CONVINCE Study<sup>5</sup>**



1 Grooteman et al. JASN (2012) 23: 1087-1096, 2 Ok E et al. NDT (2013) 28: 192-202, 3 Maduell et al. JASN (2013) 24(3) :487-97 1495-1509, 4 Morena M et al. Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly. Kidney Int. 2017 Jun;91(6):1495-1509., 5 Blankestijn P et al. Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure. N Engl J Med. 2023 Aug 24;389(8):700-709.

# CONVINCE Study | High-volume HDF reduces mortality

A pragmatic, multinational, randomized, controlled trial

## Primary objective

To **compare HDF** when delivered consistently in high-dose (volume), with high flux **HD** treatment in terms of **all-cause mortality**

1,360  
patients



61 dialysis  
centers



8 European  
countries



## Primary outcome

23%

mortality rate reduction



This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 754803.

Blankestijn PJ, et al.. Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure. N Engl J Med. 2023 Aug 24;389(8):700-709.

# CONVINCE Study | High-volume HDF improves quality of life

## Health-related quality of life

### Secondary objective

To **compare HDF** when delivered consistently in high-dose (volume) with high flux **HD** treatment regarding **health-related quality of life**

### Patient-reported outcome measurement information system

<i>Cognitive function</i>	<i>Physical function</i>	<i>Fatigue</i>	<i>Sleep disturbance</i>
<i>Anxiety</i>	<i>Depression</i>	<i>Pain interference</i>	<i>Social participation</i>

### Secondary outcome

- HDF **positively affects the health-related quality of life** perceived by patients in the study
- It is most pronounced in their **cognitive function**
- Like the observed better survival, the effect became **more relevant over time**



This project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 754803.



Rose M, et al. The CONVINCE randomized trial found positive effects on quality of life for patients with chronic kidney disease treated with hemodiafiltration. *Kidney Int.* 2024 Jul 30:S0085-2538(24)00534-9.

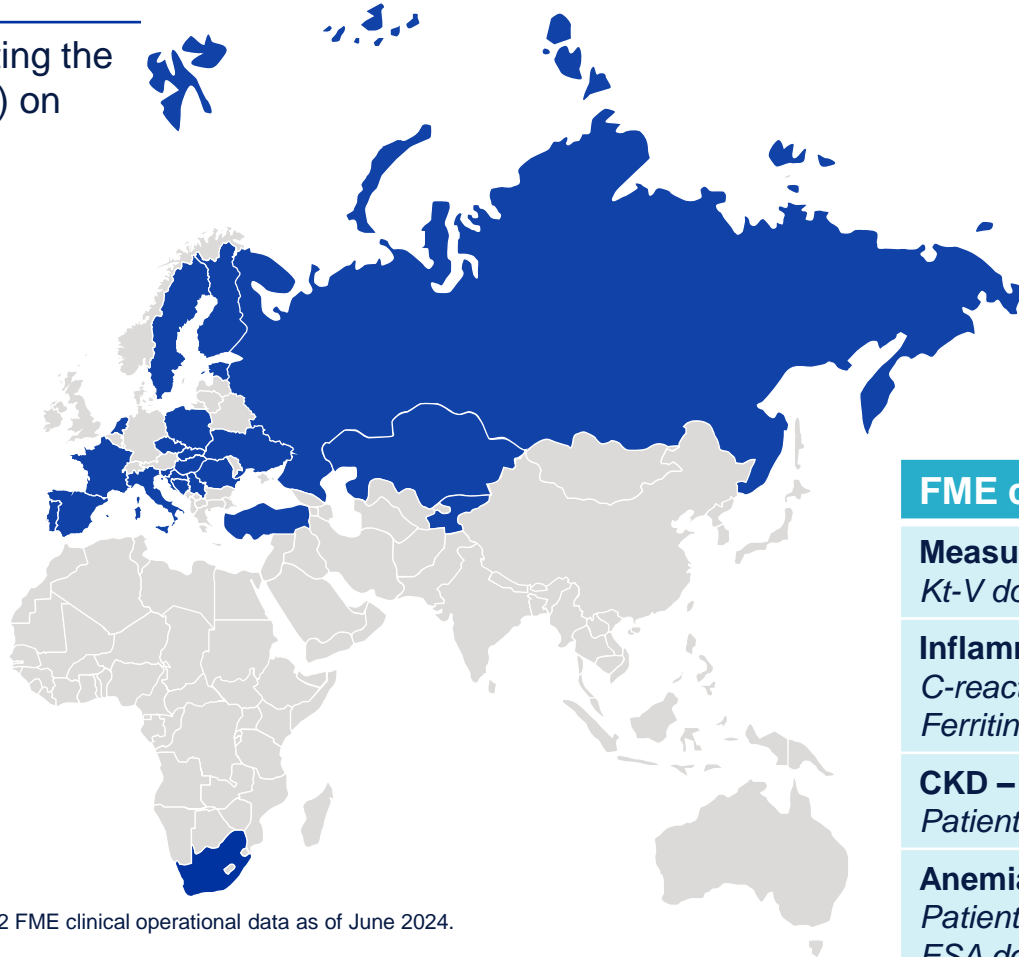
# FME experience with HDF for >20 years

## Real-world experience confirms CONVINCE findings

### FME clinical data

Real-world data analysis evaluating the impact of HDF (compared to HD) on mortality outcomes

-  23 countries
-  661 FME centers
-  85,117 patients<sup>1</sup>
-  25,527,806 treatments
-  4 years of data



### FME clinical operational data<sup>2</sup> – real time

<b>Measure of dialysis adequacy</b> <i>Kt-V dose</i>	+8.0%
<b>Inflammation</b> <i>C-reactive protein</i> <i>Ferritin</i>	-19.6% -8.2%
<b>CKD – MBD (Mineral and Bone Disorder)</b> <i>Patients with phosphate binders</i>	-17.4%
<b>Anemia</b> <i>Patients with ESA (Erythropoiesis-stimulating agents)</i> <i>ESA dosage</i>	-7.2% -8.2%

<sup>1</sup> Patients treated over the course of the 4-year study, <sup>2</sup> FME clinical operational data as of June 2024.  
CVD = Cardiovascular disease

# Globally, HDF has grown more than any other therapy in the last 10 years

## HDF patient development globally (in K)<sup>1</sup>



<sup>1</sup> HDF patient numbers include intermittent HDF patients.

- HDF is available in more than **90** countries, but not yet the U.S.
- More than **4,000** scientific publications available on the therapy
- In Europe and other countries HDF has become an **established treatment modality**
- The National Institute for Health and Clinical Excellence (NICE) in England recommends **considering HDF as the first option** vs. HD

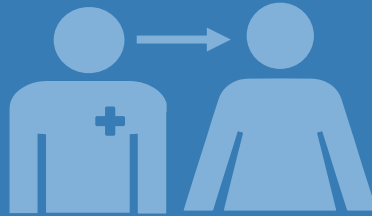


# HDF expansion | FME bringing a new standard of care to the U.S.

## Leveraging benefits of an integrated company

### Care Delivery

- Opportunity to positively affect quality of life, improve outcomes, and meaningfully reduce mortality rate in dialysis patient population



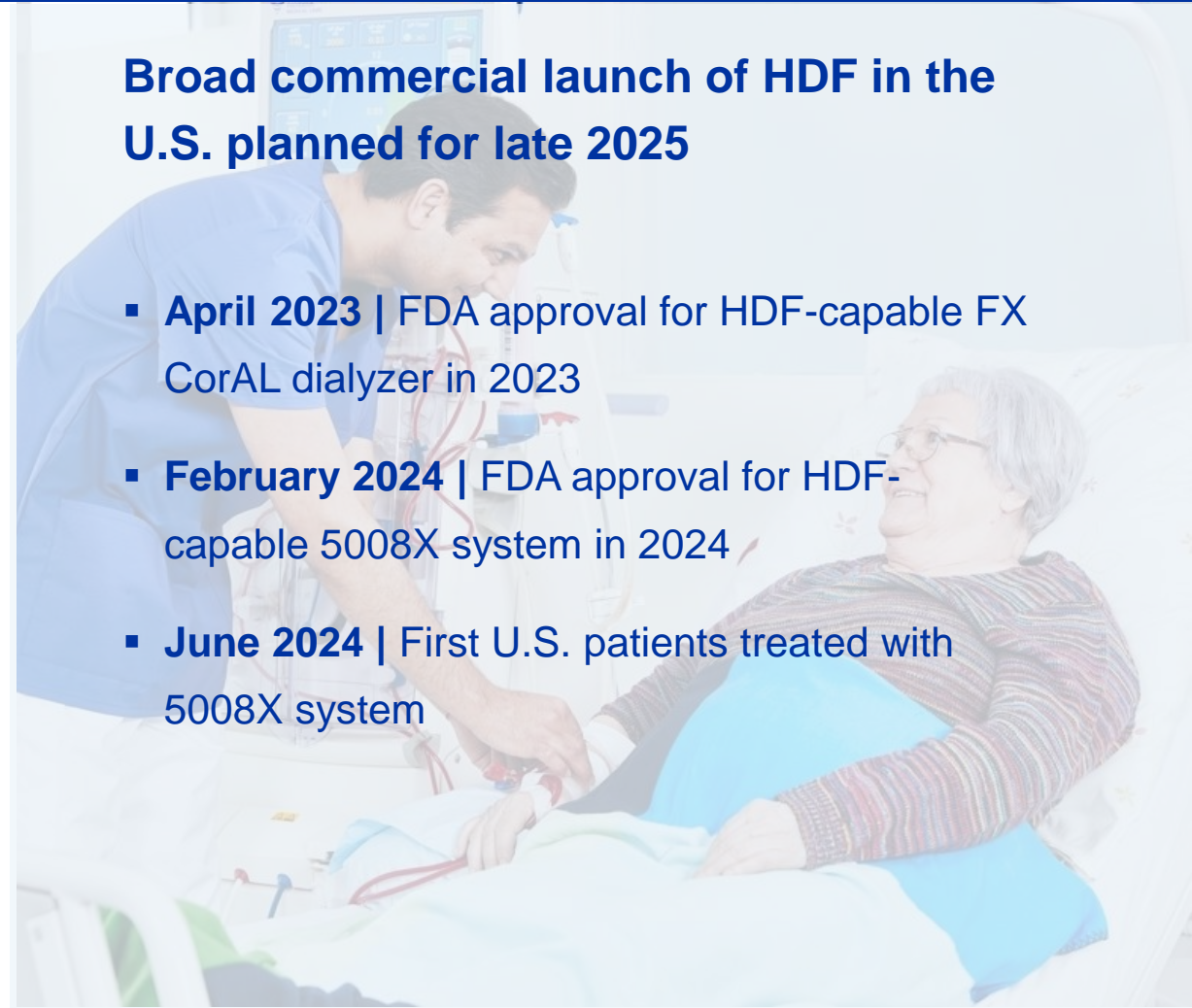
### Care Enablement

- Opportunity to bring a novel advanced therapy to the U.S. market
- Installed base of 160,000 machines in the U.S.



## Broad commercial launch of HDF in the U.S. planned for late 2025

- **April 2023** | FDA approval for HDF-capable FX CorAL dialyzer in 2023
- **February 2024** | FDA approval for HDF-capable 5008X system in 2024
- **June 2024** | First U.S. patients treated with 5008X system





**Your questions are welcome**



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