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DSR clinical proof-of-concept study

Results presented at Heart Failure 2019

27 May 2019

Today's presenters

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Chief Executive Officer

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Director of Heart Failure Research

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- The **alfa**pump® has not yet received regulatory approval in the US and Canada. Any statement in this presentation about safety and efficacy of the **alfa**pump does not apply to the US and Canada because the device is currently undergoing clinical investigation in these territories.
- Sequana Medical's proprietary DSR therapy is under development and is developing **alfa**pump DSR (Direct Sodium Removal) to deliver a convenient and fully implanted system for DSR therapy. DSR therapy is still in development and it should be noted that any statements in this presentation regarding safety and efficacy arise from pre-clinical studies and ongoing clinical investigations which have yet to be completed. There is no link between DSR therapy and ongoing investigations with the **alfa**pump system in Europe, the US and Canada.

Agenda

- Welcome and introduction
- **alfa**pump® DSR – breakthrough approach to volume overload in Heart Failure
- Dr. Testani's presentation at Heart Failure 2019
- Conclusions and next steps
- Q&A

DSR clinical proof-of-concept study meets primary and secondary endpoints

- DSR therapy was safe & well-tolerated with no adverse events or significant discomfort
- Substantially higher sodium removal with DSR vs standard PD solution
- Minimal inter-patient variability
- Preparations underway for repeated dose **alfa**pump® DSR study to commence in H2 2019

✓ Clinical proof of concept for DSR
+
✓ Proven **alfa**pump platform
=
✓ De-risked Program in Very Large Market with Clear Unmet Clinical Needs

DSR: Direct Sodium Removal; PD: peritoneal dialysis

alfapump® DSR

Breakthrough approach to
volume overload in heart failure
built on proven device platform

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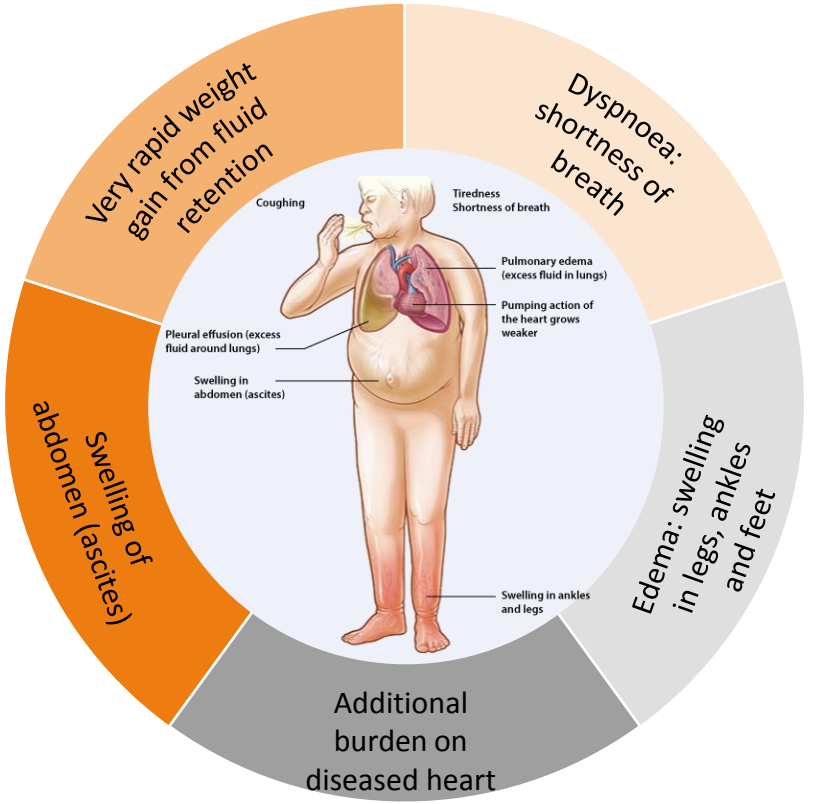
Heart Failure is a large and growing market

Nearly 6.5 million adults affected by heart failure in the US[1]

Causes of heart failure[2]

Volume overload is a key clinical consequence of heart failure with a significant impact on patient's quality of life[3]

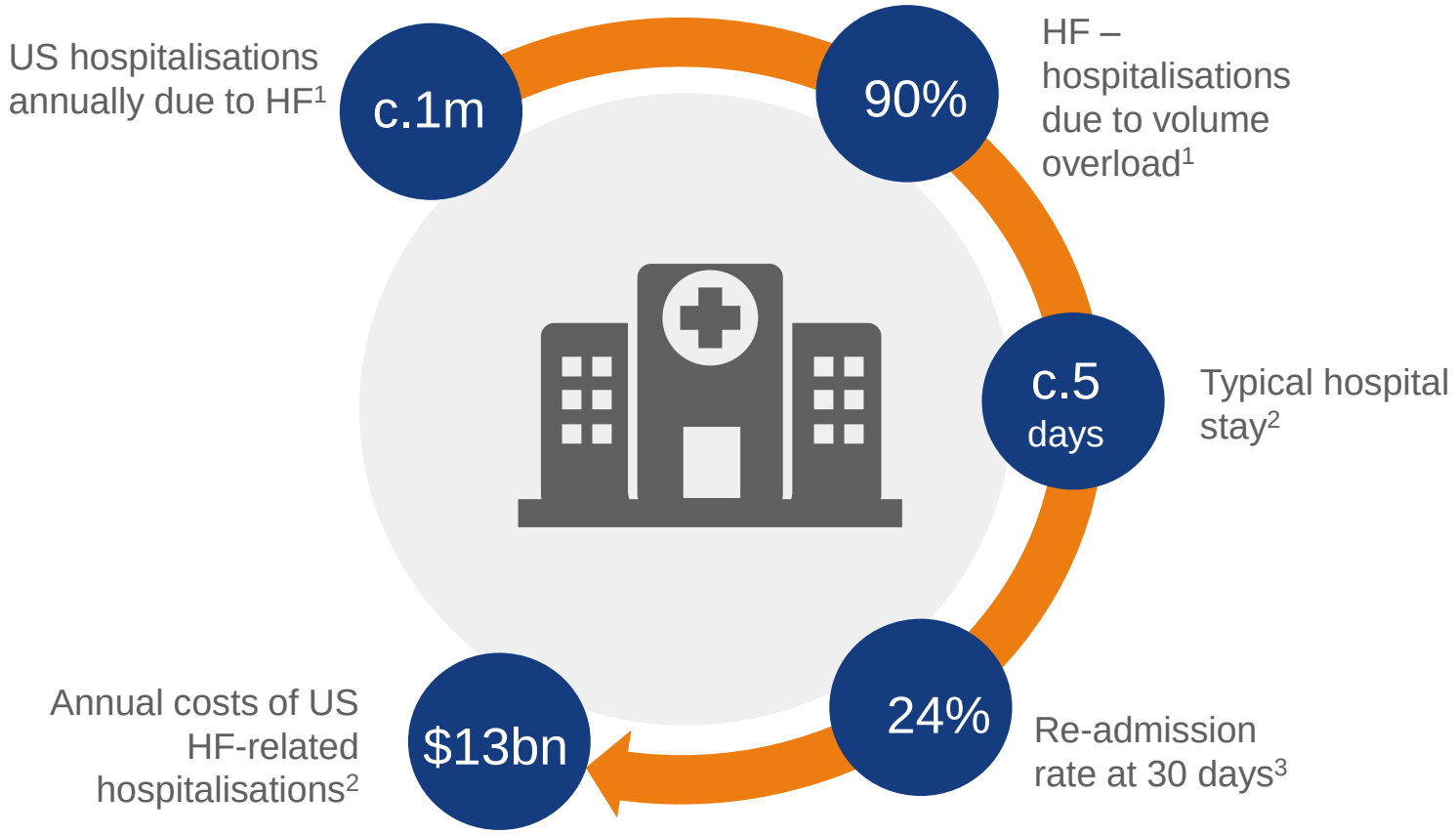


Source 1: Mozzafarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2017 update (adults: >=20 years of age); Source 2: American Heart Association; Source 3: Mayo clinical website

Volume overload in Heart Failure (HF)

$13 billion annual cost of HF-related hospitalisations; ~90% due to volume overload

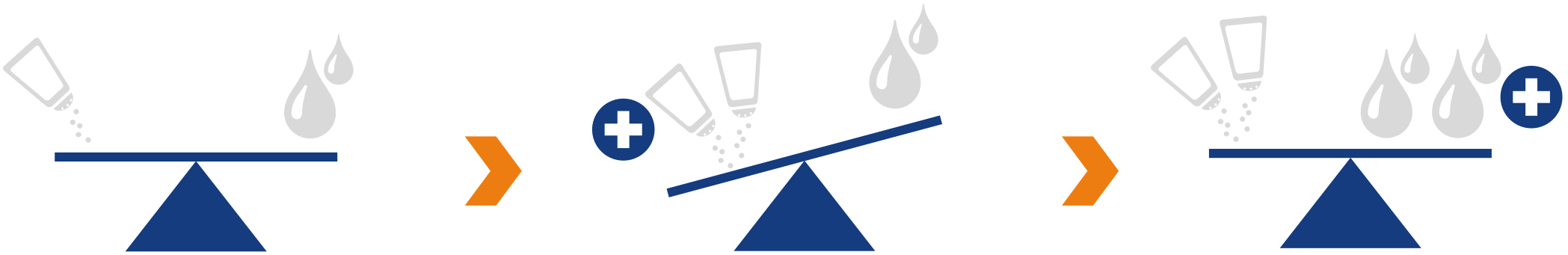
Clear unmet need to reduce hospitalisations, improve Quality of Life and reduce mortality



Source 1: Costanzo et al., J. Am. Coll., 2007; Source 2: Kilgore et al. (2017); Source 3: Ross et al. (2010)

Volume overload in Heart Failure driven by sodium

Body maintains constant sodium concentration by accumulating water



Maintaining a constant concentration of sodium in the body is essential for our health

- too high: hypernatremia
- too low: hyponatremia

The body's response to heart failure causes sodium levels to increase

To restore the balance, the body retains water, leading to volume overload and an increased burden on the heart

Key challenge of diuretic therapy

Diuretic therapy only results in a temporary reduction of fluid volumes

Diuretics cause loss of fluid (hypotonic urine) – loss of sodium is low – leading to increased sodium concentration

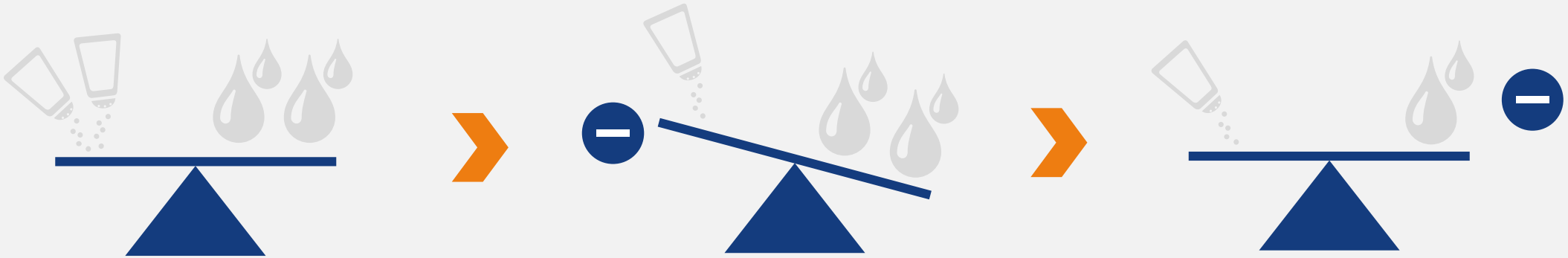
To restore the balance, the body takes on board water (thirst response) or cuts back on urination

The body does not eliminate sodium as it is “scarce” and hard to replace

Only the removal of sodium will lead to sustainable volume reduction

Direct sodium removal (DSR)

Tackling sodium removal directly



Volume overload in heart failure

Removing the sodium (DSR)

Elimination of excess fluid

Administer infusate to peritoneal cavity

Infusate extracts sodium from the body

Remove extracted sodium from peritoneal cavity

Body restores balance by eliminating excess fluid

Dr. Testani's Presentation at Heart Failure 2019

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First in human experience with direct sodium removal using a zero sodium peritoneal solution: A new candidate therapy for volume overload

Veena Rao, Jeffrey Turner, Devin Mahoney, Matthew Griffin, Jennifer Asher, Juan Ivey-Miranda, Nicole Gomez, Fredric Finkelstein, Jeffrey Testani

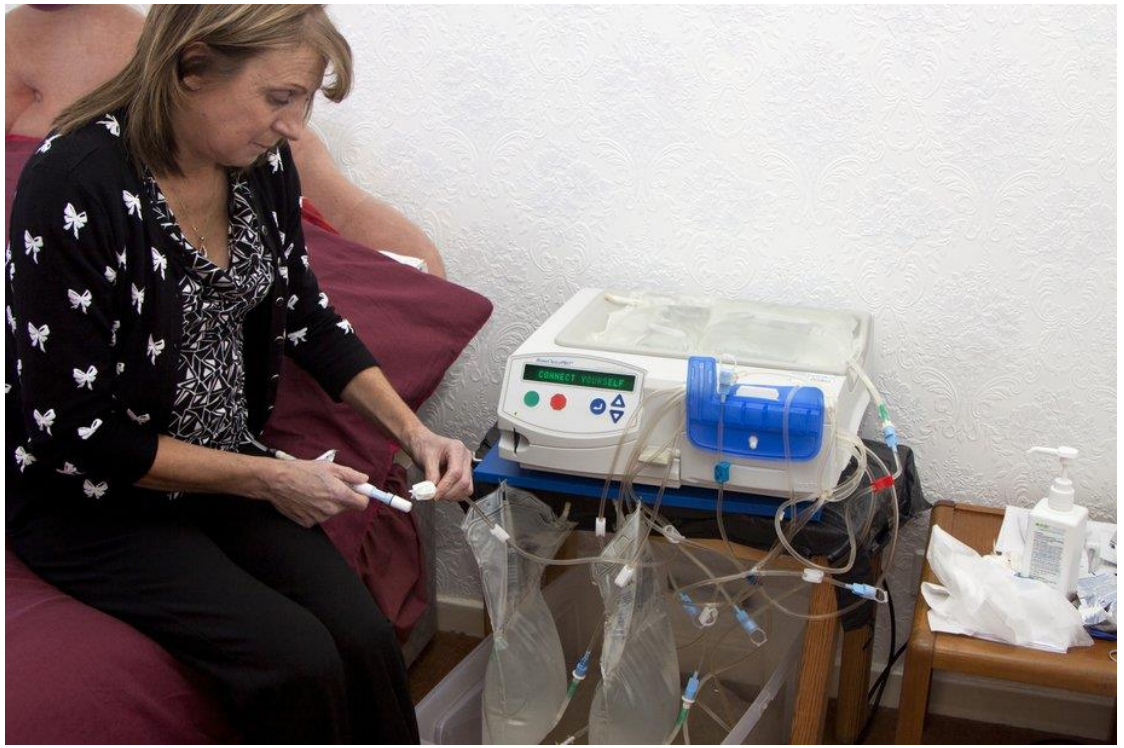
Jeffrey M. Testani, MD, MTR
Associate Professor of Medicine
Director of Heart Failure Research
Yale University

Heart Failure: Can we do better than diuretics?

- On a population level, symptoms and hospitalizations are driven by volume overload
  - Loop diuretics are the mainstay of therapy
  - Well described toxicity
  - Resistance is common
- Long list of failed cardio-renal therapeutics has accumulated over the last decade
  - A new pill that replaces the loop diuretics is not likely soon
- Sodium removal through non-renal routes is an attractive option
  - Veno-Venous ultrafiltration has been explored;
    - » Not an ideal chronic therapy
  - Peritoneal dialysis for chronic volume maintenance has had low levels of interest

Why is peritoneal dialysis (PD) not used more frequently in heart failure?

- Standard PD has several limitations:
  - Large volumes (~8 to 10 liters) and long dwell times with the patient connected to PD cycler
  - External catheter with infection risks
  - Dialysis stigma
- Only modest fluid and sodium removal with standard PD solutions
  - PD is designed primary to “clean” the blood rather than remove sodium

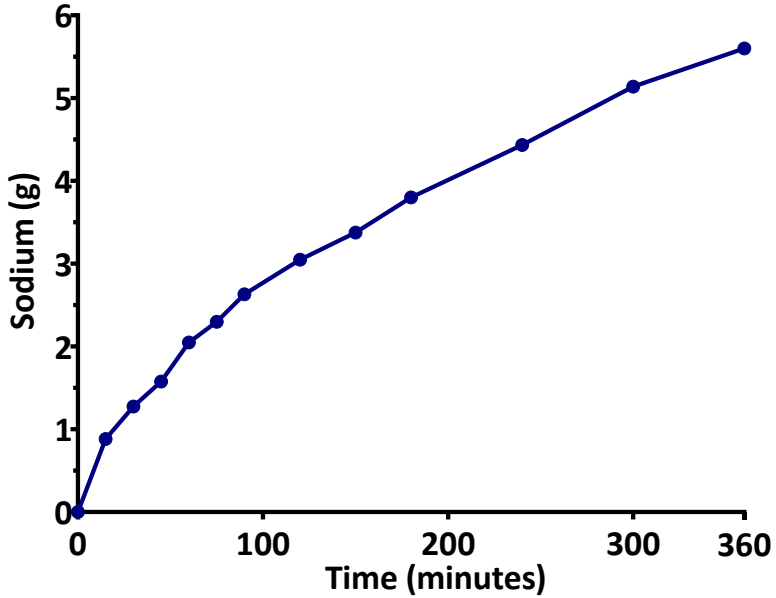


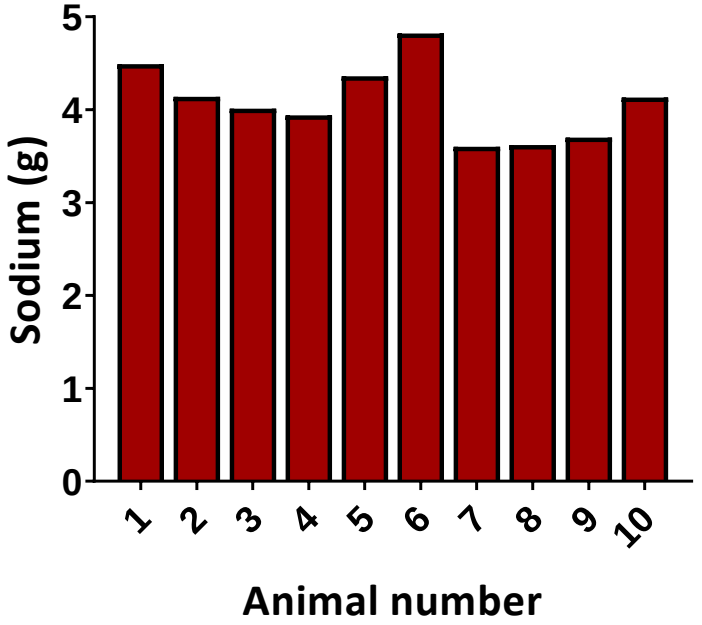
Can we use the peritoneal membrane more efficiently to directly remove sodium in HF patients?

- Most HF patients have acceptably functioning kidneys
  - No need to “clean” the blood
- Standard PD solutions have ~7.5 grams of salt per liter
  - Nearly isotonic to plasma (~132 mmol/L)
  - Very small gradient for sodium to diffuse
- By using a zero sodium osmotic solution should achieve much more efficient sodium removal
  - Standard peritoneal ultrafiltration
  - We can also capitalize on diffusion down a huge concentration gradient (~140 mmol/L to 0 mmol/L)
- More efficient sodium removal allows for smaller volume of fluid and shorter dwell times
  - Less invasive methods for filling and removal of solution from the peritoneum

Pre-clinical data: Results in normal swine

- 1 Liter of sodium free 10% dextrose in water as the Direct Sodium Removal (DSR) solution
- 6 hour dwell: (n=4)
  - 5.5 grams of sodium
  - 1.5L of ultrafiltrate
- 2 hour dwell (N=10):
  - 3.9 grams of sodium
  - 800 cc of ultrafiltrate

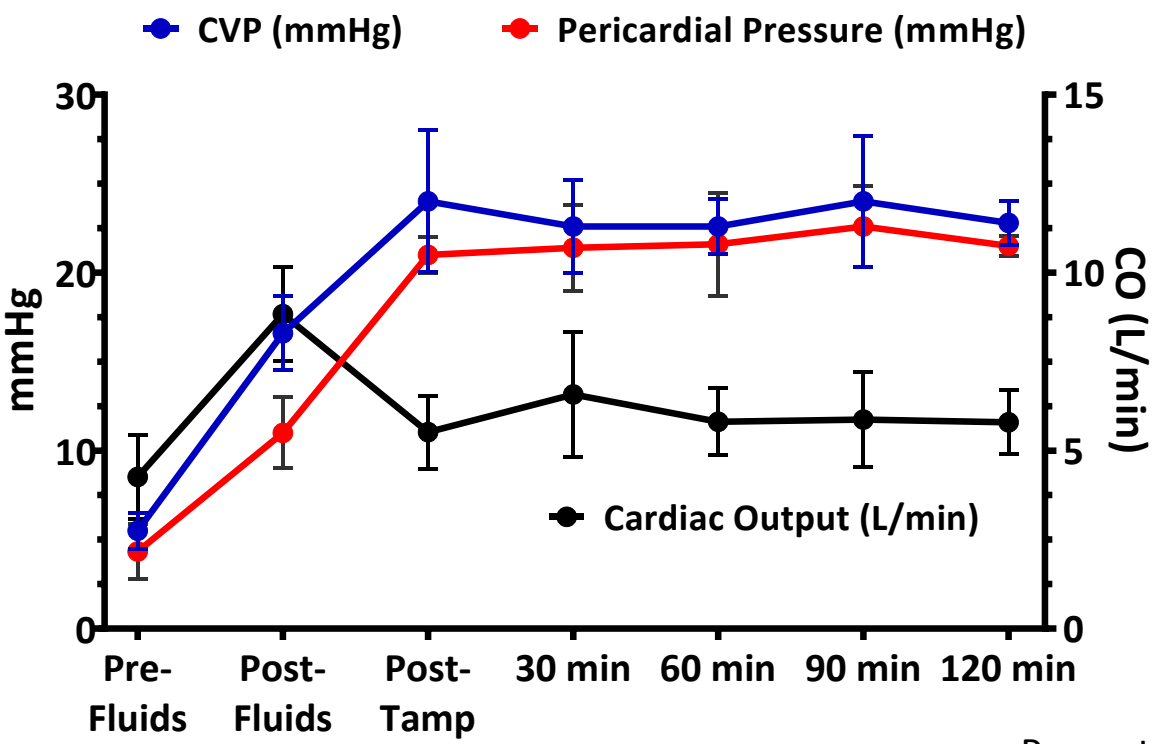


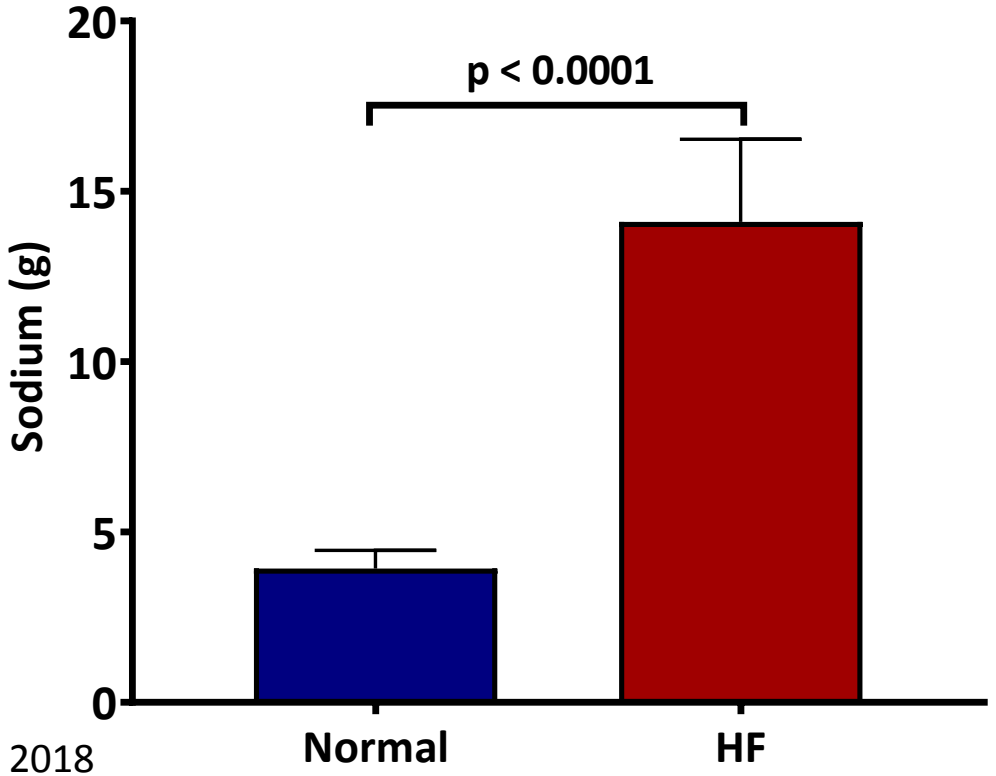


Presented HFSA 2018

Pre-clinical data: Heart Failure vs. normal pigs

- Right sided HF model with fluid loading and tamponade
- 2 hour DSR dwell





Presented HFSA 2018

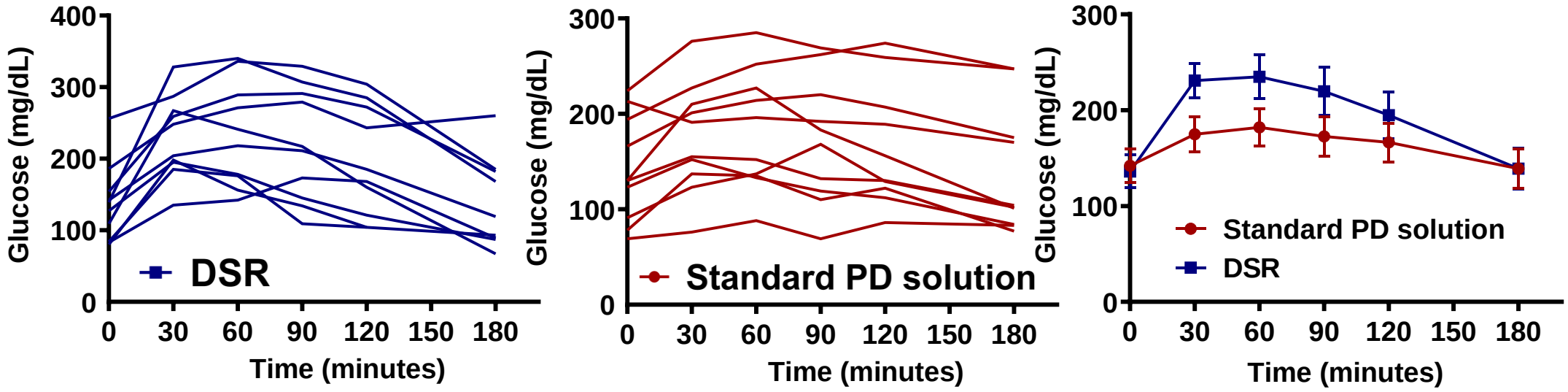
DSR first in human proof of concept: Design

- **Design:**
  - Randomized open label crossover of DSR vs. standard PD solution
  - Conducted in prevalent PD patients rather than normal subjects due to the risks of PD catheter placement
- **Intervention:**
  - DSR solution: Sodium free 10% dextrose
  - Standard PD solution: 4.25% dextrose standard PD solution (Dianeal, Baxter)
    - Both solutions are approximately 500 mOsm/L
    - 4.25% dextrose PD solution is the “strongest” commercially available product
  - One liter of either solution was infused into the peritoneum and left to dwell for 2 hours
  - Crossover to the alternate solution one week later
- **Endpoints:**
  - Primary: Safety/tolerability defined as completion of the 2-hour dwell without significant discomfort or AE
  - Secondary efficacy endpoint: Difference in sodium removal between DSR solution and standard PD solution

Primary endpoint: Safety and tolerability

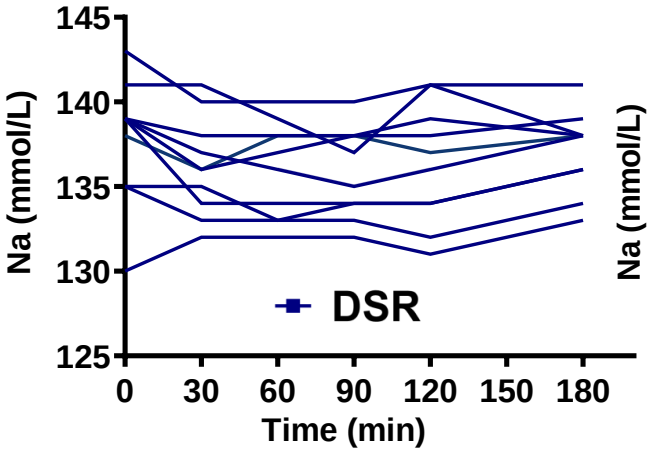
- **Primary endpoint:**
  - All patients completed the 2 hour dwell without adverse event or significant discomfort causing protocol discontinuation
- Mild cramping during fluid instillation lasting <30 minutes occurred in 2 patients
  - One had cramping with DSR solution only
  - One had cramping with both solutions
  - Most patients stated instillation of the DSR solution felt the same as their standard PD solution
- Negligible removal of non-target solutes
  - Potassium (5.7 mmol)
  - Magnesium (1.1 mmol)
  - Phosphorus (2.0 mmol)
  - Calcium (1.7 mmol)

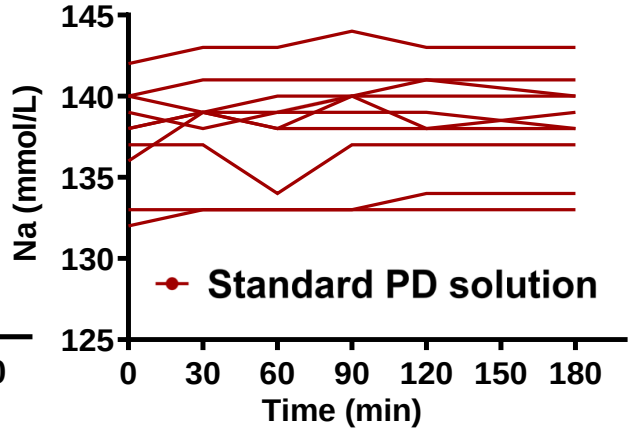
Change in plasma glucose was modest and transient

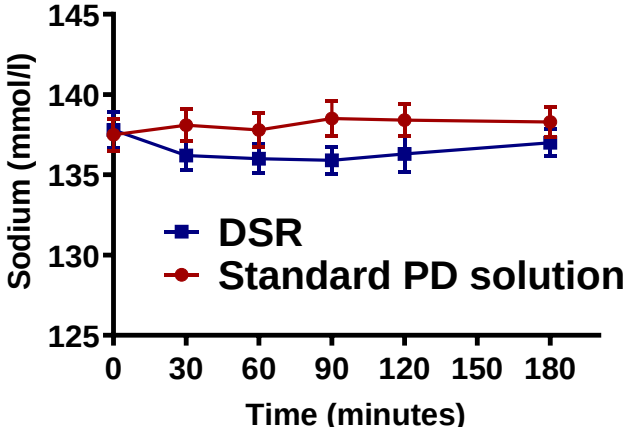


Changes in serum sodium were small

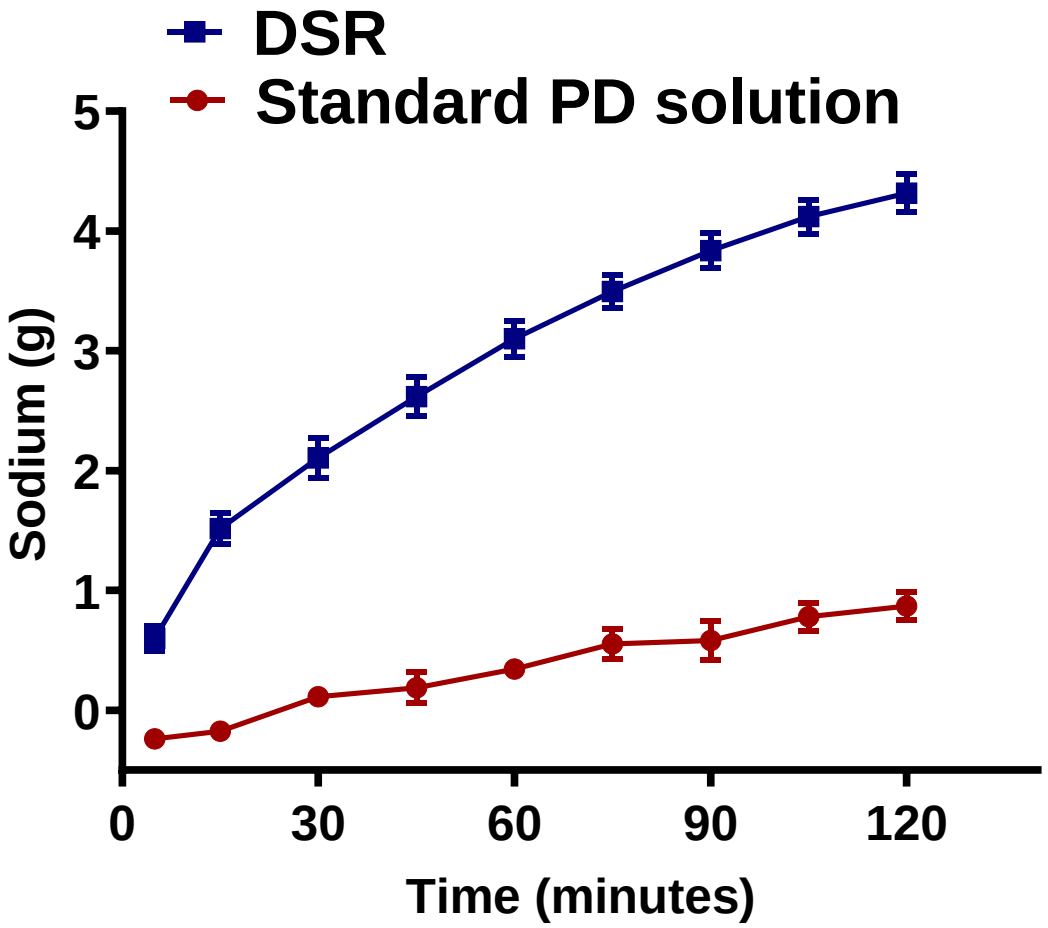
Uncorrected serum sodium

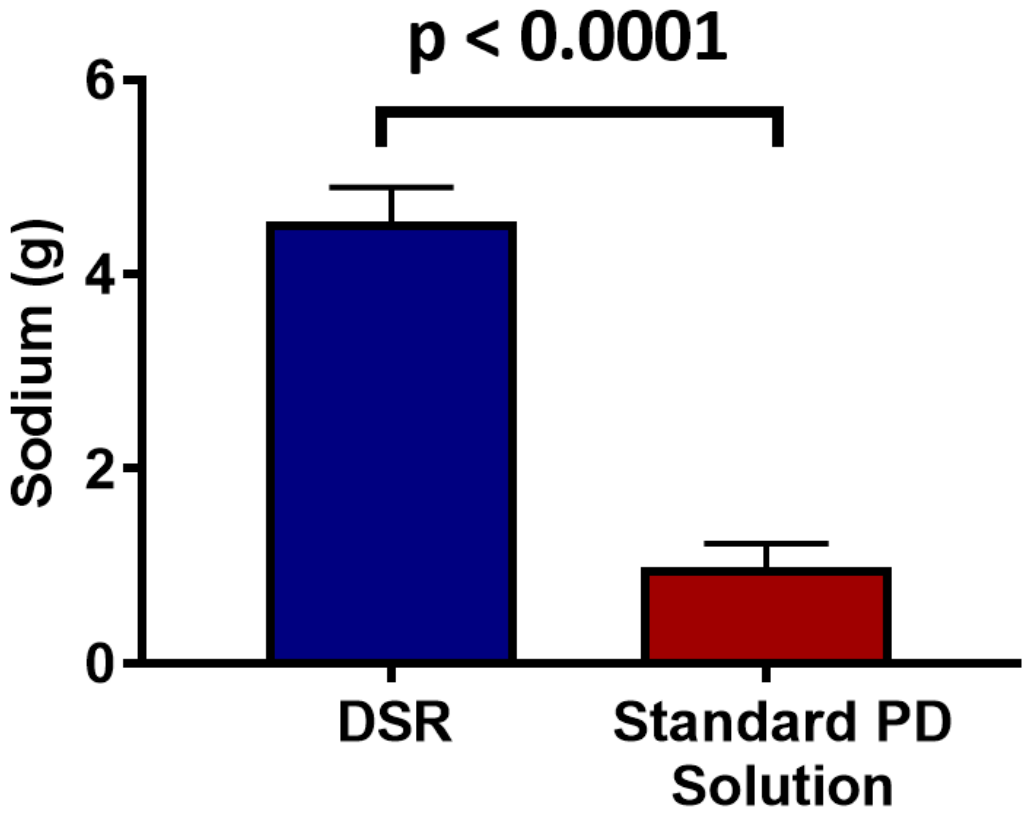






Secondary efficacy endpoint: Sodium removal was substantially greater with DSR





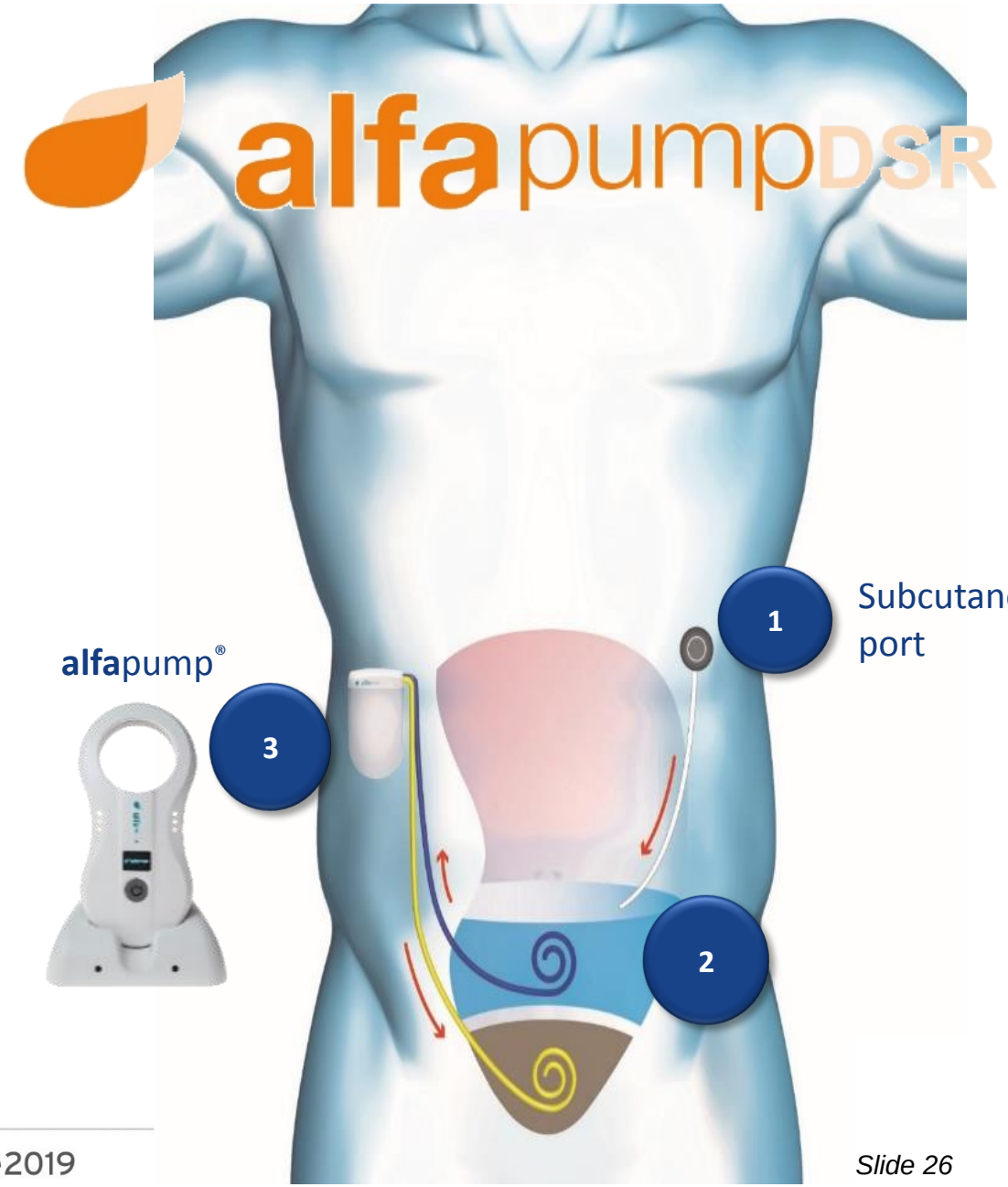
Conclusion

- These data provide proof of concept that Direct Sodium Removal with a sodium free peritoneal solution is feasible in humans
- **Safety/tolerability:**
  - Well tolerated
  - Minimal off target solute removal
  - Did not result in significant electrolyte disturbances or prolonged or severe hyperglycemia
- **Efficacy:**
  - Substantial sodium removal
    - Nearly 5 grams of sodium with a 2 hour treatment

Future directions

- Next planned study is a multidose chronic HF study using the alfapump® (Sequana Medical)
  - Fully implanted system
  - Developed for refractory ascites
  - Pump already derisked in this population
    - Over 700 systems implanted and 400 patient years experience to date

1. Administration of DSR solution into peritoneal cavity via subcutaneous port
2. Sodium enters DSR solution via diffusion and ultrafiltration
3. alfapump® clears sodium-rich fluid into the bladder which is eliminated by urination



Conclusions and next steps

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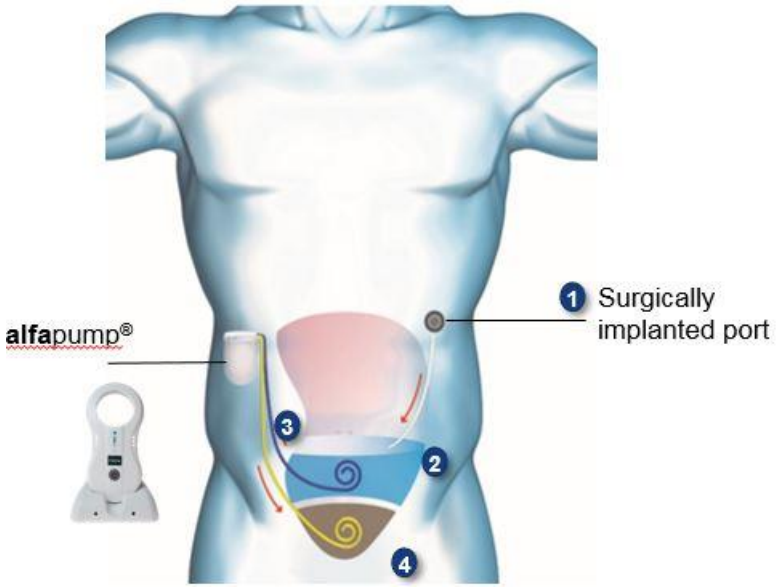
alfapump® DSR leverages on proven elements

Combining clinical proof-of-concept of DSR with validated alfapump platform



✓ **DSR**	- Safe & well-tolerated - Clinically relevant removal of sodium - Minimal patient inter-variability

✓ **alfa**pump	- Validated technical performance
	  - *eg* pumping, charging, communication, patency, monitoring
	- Extensive clinical experience
	  - Over 700 implants and 400 patient years
	- Deep understanding of implementation
	  - *eg* implantation procedure

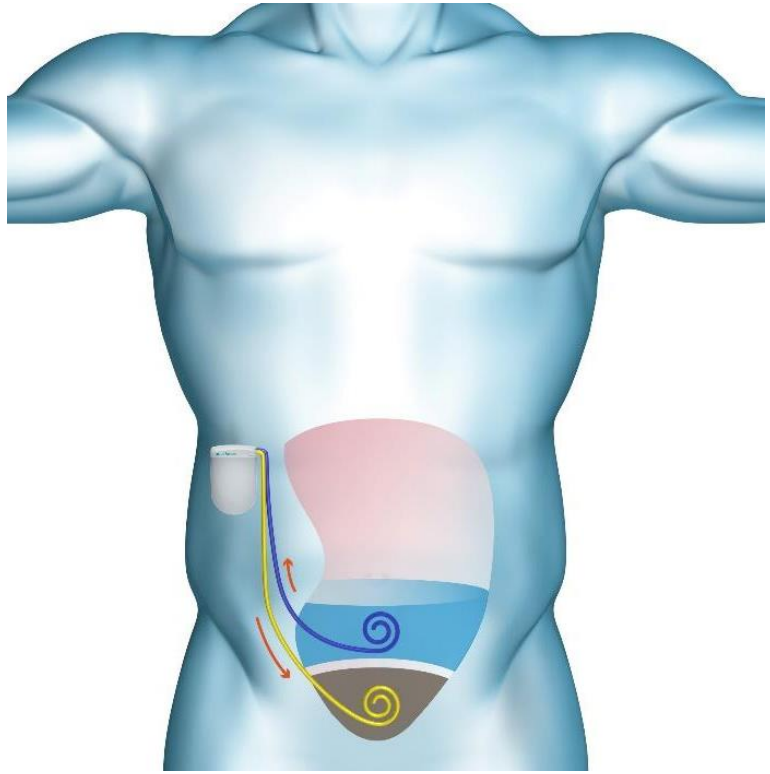
✓ **Implanted port**	- Many years of clinical experience

Today's breakthrough results pave the way for future clinical development of alfapump DSR

alfapump® platform

Unique capabilities to manage fluid imbalance

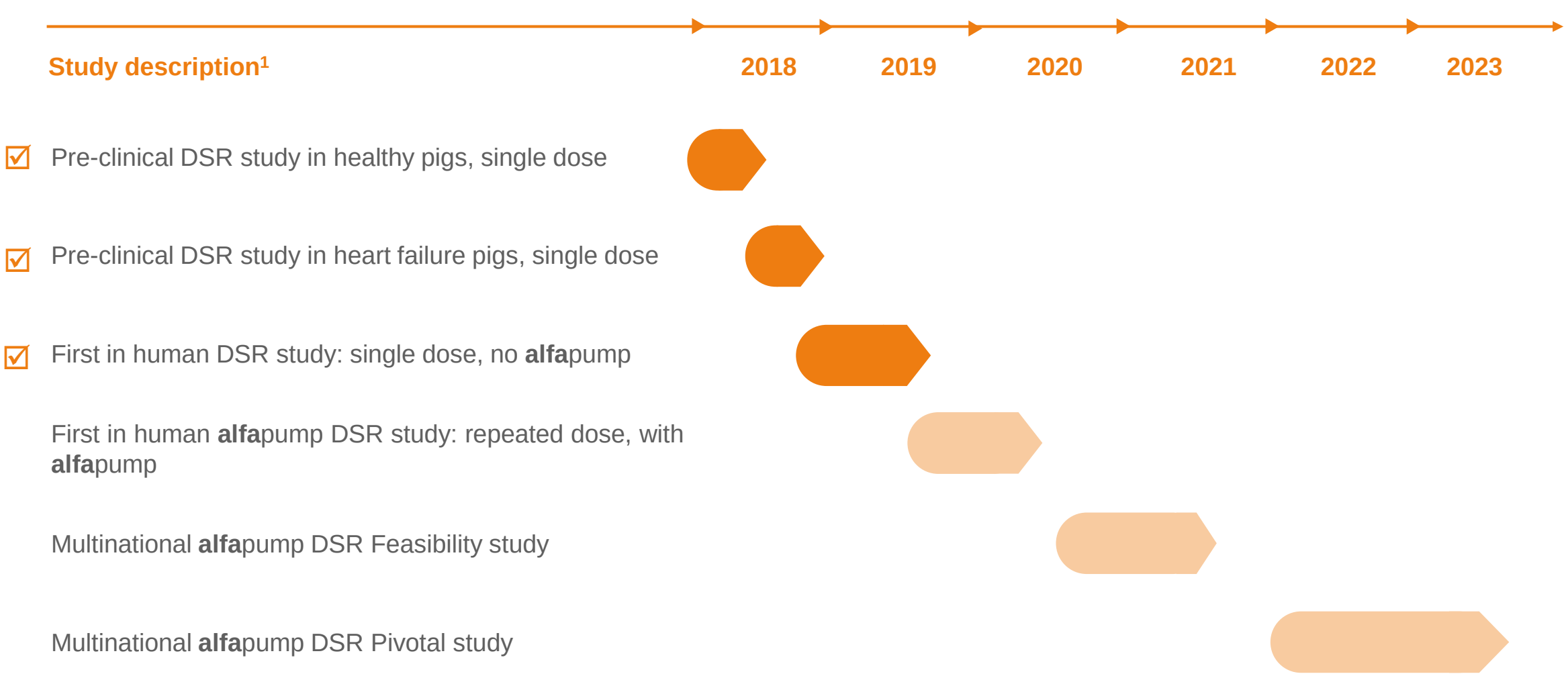
- Pump volume easily adjusted
- Fully implantable
- No significant heating during charging and operation
- Moves up to 4 litres of fluid per day
- Long-term implantation & catheter patency



- Remote data monitoring
- Battery charged through the skin
- Easy implantation
- Automatic operation
- Virtually non-clogging

Strong IP barriers through extensive patent portfolio & know-how

alfapump® DSR development overview



Note 1: study design and timelines subject to change

Strong news flow in 2019

Key anticipated milestones

H2 2018

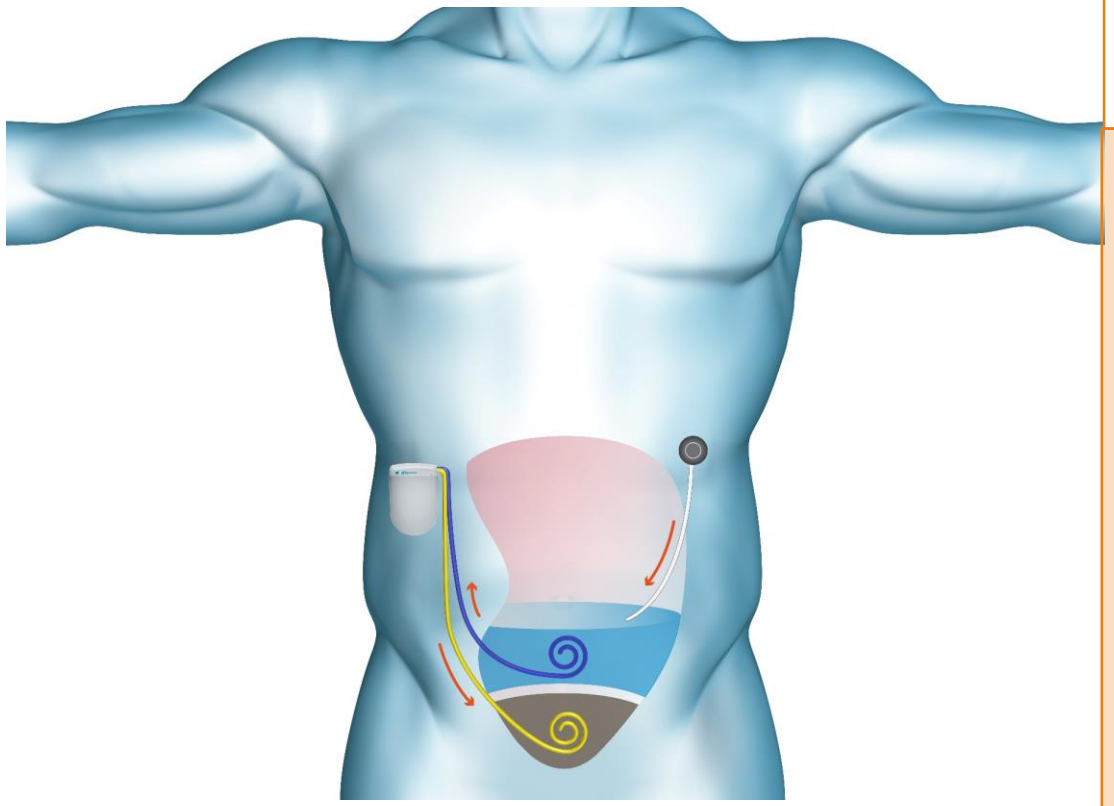
- ✓ Completion of DSR study in pig heart failure model & presentation of results
- ✓ Presentation of clinical data on 17 malignant ascites patients in retrospective clinical study
- ✓ Outcome of NICE review of **alfa**pump®
- ✓ Initiation of First in Human clinical study for heart failure, single dose
- ✓ Initiation of TOPMOST: European “Super Registry” (Reporting Data Regularly)

H1 2019

- ✓ Outcome of FDA Breakthrough Device designation
- ✓ Inclusion in German treatment guidelines (DGVS) for complications of liver cirrhosis
- ✓ Completion and presentation of results of first in human DSR proof-of-concept study, single dose
- ○ Initiation of prospective malignant ascites study
- ○ Initiation of prospective albumin study

H2 2019

- ○ Feedback FDA on protocol POSEIDON North-American pivotal study
- ○ Initiation of POSEIDON North-American pivotal study
- ○ Expected Dutch reimbursement of **alfa**pump®
- ○ Presentation of initial results of repeated dose **alfa**pump DSR clinical study



alfapumpDSR

- ✓ Volume overload in heart failure is a very large market with clear unmet clinical needs
- ✓ Results from this study demonstrate potential of our proprietary DSR therapy as a breakthrough approach
- ✓ **alfa**pump DSR leverages proven elements:

  DSR therapy, **alfa**pump & implanted port
- ✓ Preparations underway for repeated dose **alfa**pump DSR study to commence in H2 2019

Q&A