Direct Sodium Removal with the Sequana medical alfapump DSR® system

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Disclosures

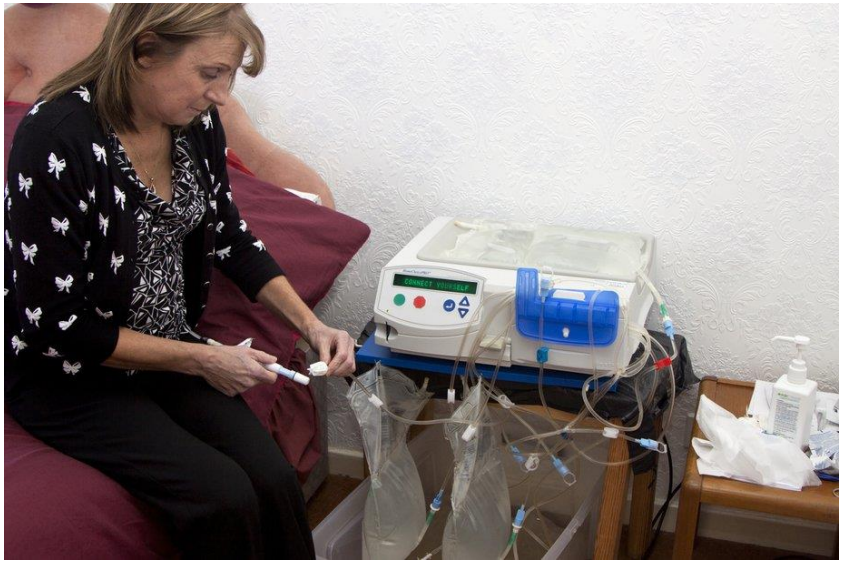
- Related to the presentation: Research funding and personal fees from Sequana Medical
- Unrelated to the presentation: Grants and personal fees from 3ive labs, personal fees from Bayer, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Bristol Myers Squibb, personal fees from Astra Zeneca, personal fees from Novartis, personal fees from Cardionomic, personal fees from MagentaMed, grants and personal fees from Reprieve medical, grants and personal fees from FIRE1, personal fees from W.L. Gore, grants and personal fees from Sanofi, grants from Otsuka, grants from Abbott, grants and personal fees from Merck, personal fees from Windtree Therapeutics, personal fees from Lexicon pharmaceuticals, personal fees from Precardia, personal fees from Edwards, Personal fees from BD; In addition, Dr. Testani has a patent Treatment of diuretic resistance issued to Yale and Corvidia Therapeutics Inc, a patent Methods for measuring renalase issued to Yale, and a patent Treatment of diuretic resistance submitted by Reprieve Medical

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?

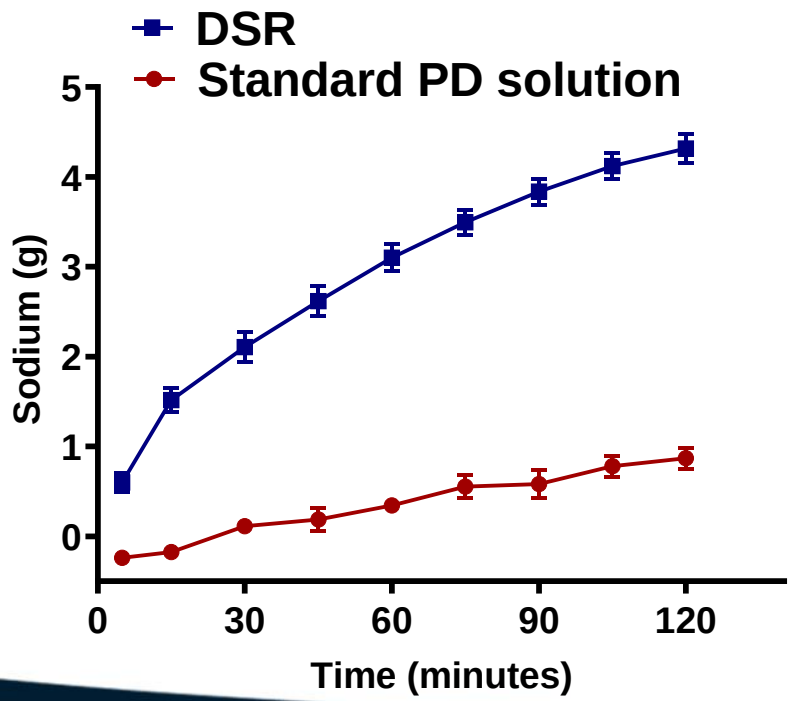
- Standard PD has several limitations:
  - Large volumes (~8 to 10 liters) and long dwell times with the patient connected to PD cycler
  - External catheter with infection risks
  - Dialysis stigma
- Many of these limitations stem from the fact that PD is designed primary to “clean” the blood rather than control volume

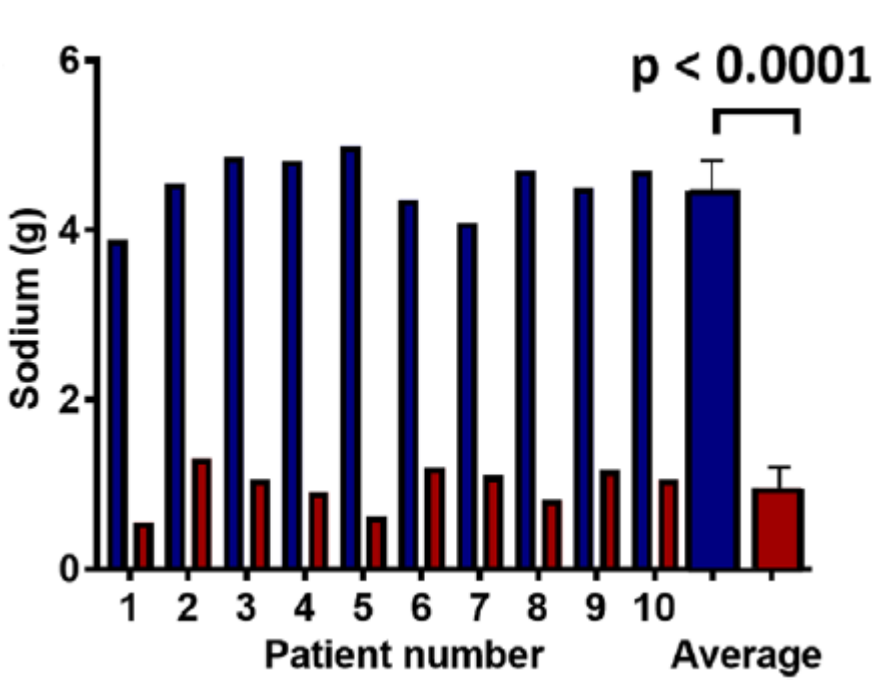


Can we use the peritoneal membrane more efficiently to directly remove sodium in HF patients?

- 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) thus a small gradient for sodium to diffuse
- By using a zero sodium osmotic solution we can achieve much more efficient sodium removal
  - Large concentration gradient driving diffusion of sodium (~140 mmol/L to 0 mmol/L)

Proof of concept study: DSR vs. Standard PD solution

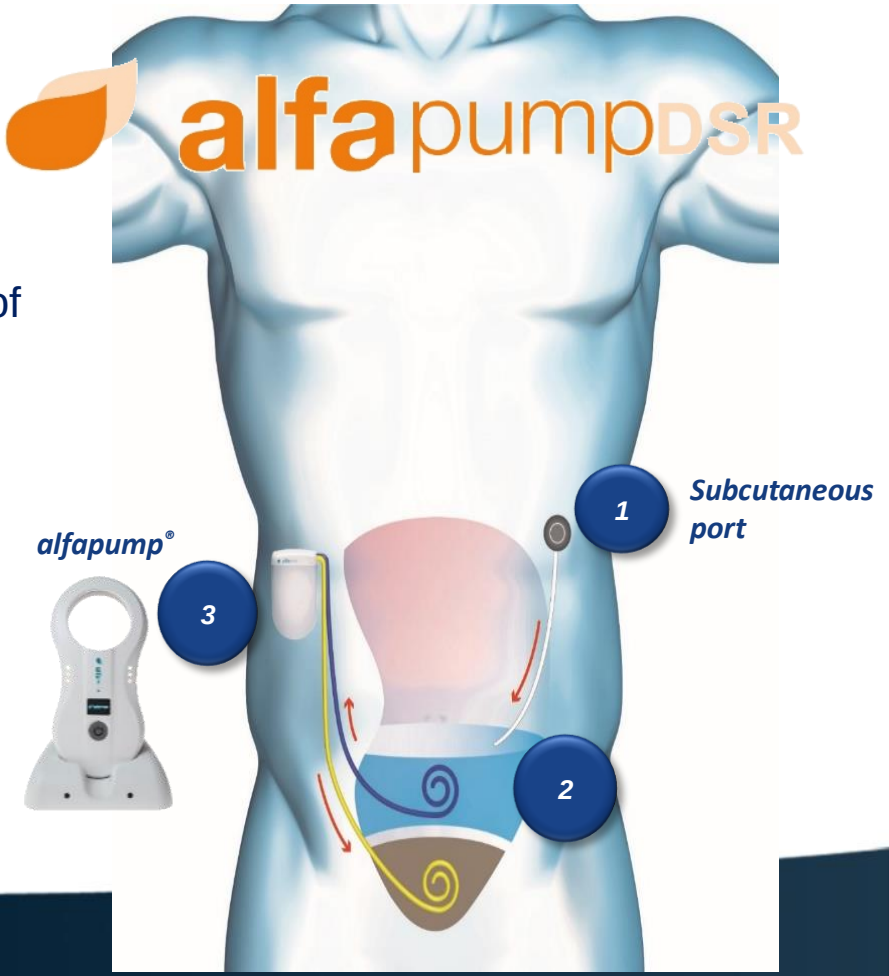




The alfapump Device:

- Fully implanted transcutaneously chargeable system developed for refractory and malignant ascites
  - Over 800 systems implanted and hundreds of 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***



Proof of concept: RED-DESERT study (NCT04116034)

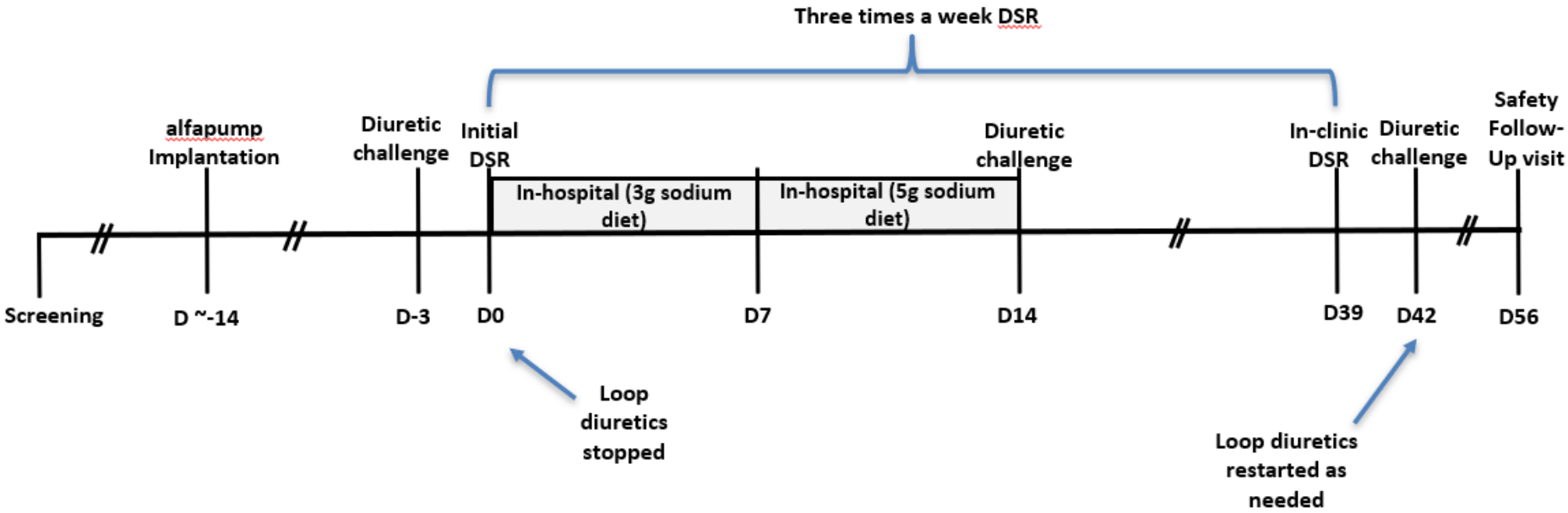
Primary objective: To understand the safety and tolerability of *serial* treatment with alfapump® DSR therapy in chronic stable diuretic resistant HF patients

Secondary objective: To understand the impact of serial treatment with alfapump DSR therapy on parameters of cardio-renal function and diuretic response

Study Design: Prospective first in human feasibility study in up to 10 participants

Number of centers: 2

Study Timeline



Key inclusion/exclusion criteria

Inclusion:

1. eGFR > 30ml/min/1.73m^2
2. Diagnosis of heart failure with one of the following: nt-proBNP > 400 pg/ml (or BNP > 100 pg/ml) and oral diuretic dose ≥ 80mg furosemide equivalents OR Oral diuretic dose ≥ 120mg furosemide equivalents
3. Stable diuretic dose for 30 days
4. Systolic blood pressure ≥ 100 mmHg
5. Determined by treating provider to be at optimal volume status

Exclusion:

1. Serum sodium < 135 mEq/L
2. Severe hyperkalemia or baseline plasma potassium > 4.5 mEq/L
3. History of significant bladder dysfunction expected to interfere with ability of subject to tolerate DSR pumping into bladder
4. Uncontrolled diabetes with frequent hyperglycemia or Type 1 diabetes

Baseline characteristics

N=8	Result	Min : Max
Age – Years (Mean ±SD)	61.9 ±8.5	49 : 77
Male - %	100	N/A
Height – cm (Mean ±SD)	172.8 ± 5.7	163 : 182
Weight – kg (Mean ±SD)	75.4 ± 17.7	53.0: 107.8
BMI – kg/m² (Mean ±SD)	25.2± 4.8	19.1 : 32.6
Ejection Fraction - % (Mean ±SD)	24.4 ± 3.1	20 : 28
Nt-proBNP - pg/mL (Mean ±SD)	4589 ± 2945	1536 : 8831
eGFR – ml/min/1.73 m² (Mean ±SD)	68 ± 19	37 : 96
Hematocrit - % (Mean±SD)	43.9 ± 7.48	32.5 : 55.2
Furosemide equivalents – mg (Mean ±SD)	322.5 ± 263.3	80 : 800

Safety and tolerability

Tolerability:

- Overall the serial DSR procedure was well tolerated aside from mild discomfort in one patient toward the end of pumping

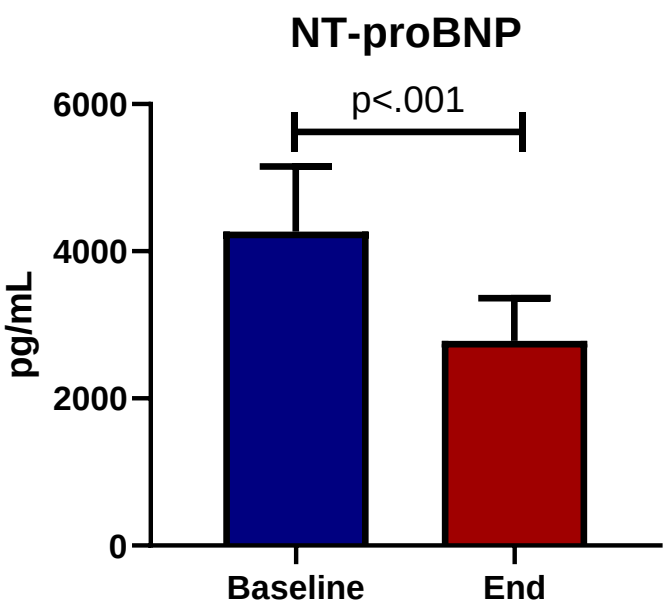
Adverse events of relevance to DSR therapy:

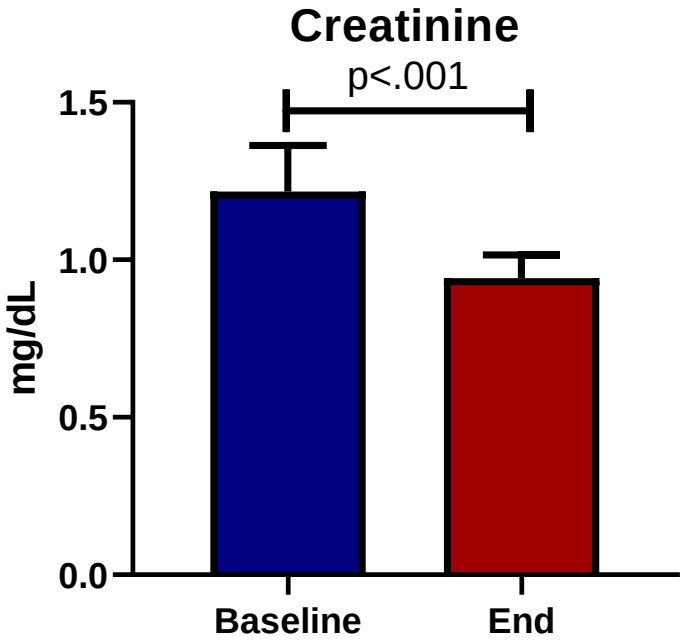
- There were no heart failure, renal, or electrolyte related adverse events

Efficacy:

- All patients were able to remain off loop diuretics for the entire 6-week study period
- A neutral sodium balance during the 2 week in-hospital period was achieved (-1.3 grams)
- Stable weight over the duration of the study was achieved (75.6 to 75.5 kg)
- Most patients had down titration of DSR therapy to maintain constant weight
  - Average 10% dextrose volume 750 ± 348 ml/treatment

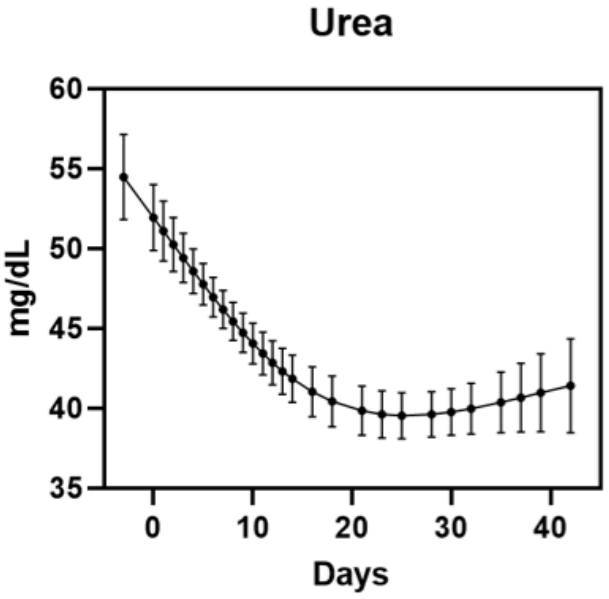
Significant improvement in cardio-renal function

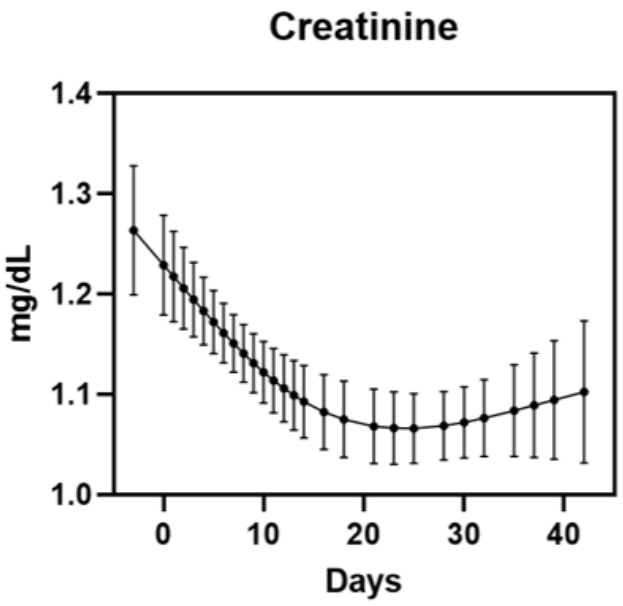


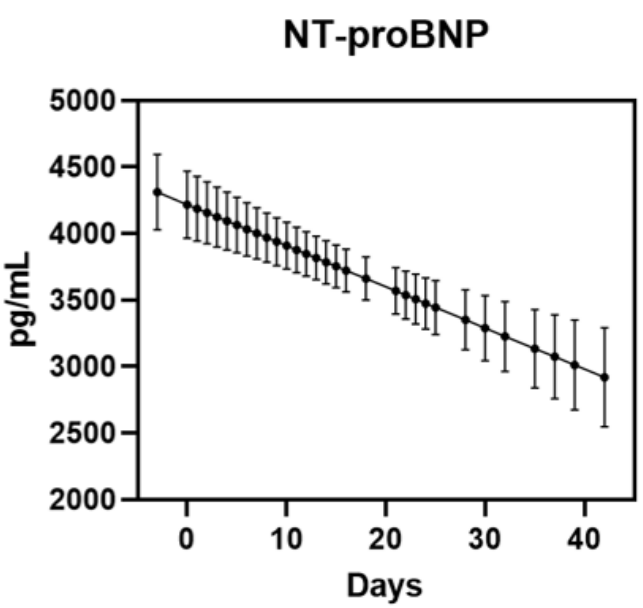


** P value from mixed models using serial measures over study (N=7)*

Temporal trends of improvement

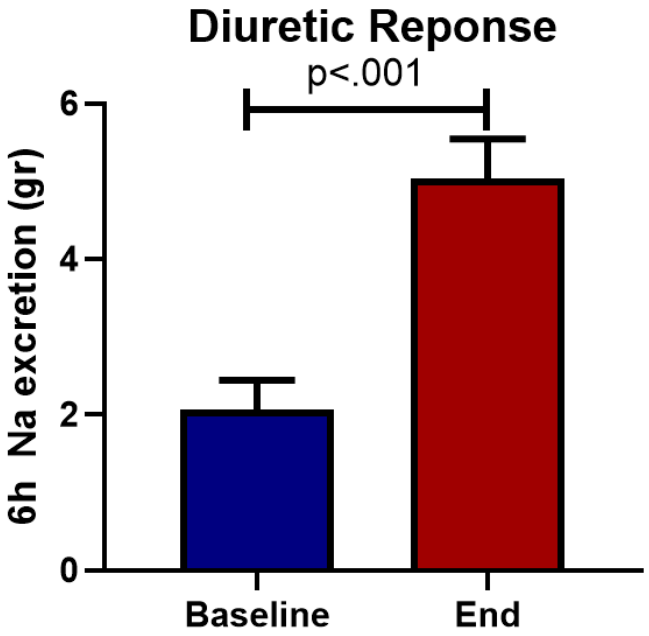






Dramatic improvement in diuretic response:

- Diuretic response was formally queried with a 40mg IV furosemide administration followed by a 6-hour timed urine collection

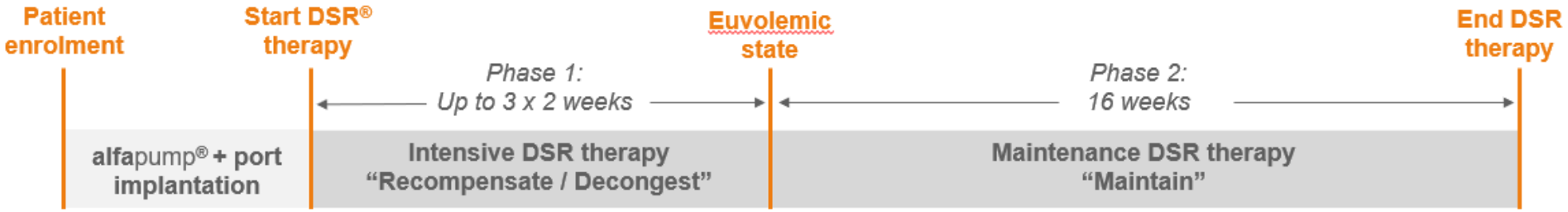


The improvement in diuretic response was durable:

Subject	Daily Dose of loop diuretics (mg)***		Time since last DSR study treatment**	Current Daily dose (mg)***	Reduction in diuretic dosage
	At screening	During DSR Treatment (D0 - 42)			
101-001	80	0	12.5 months	40	-50 %
101-002	200	0	12.5 months	80	-60 %
101-003	400	0	10 months	80	-80 %
101-005	120	0	10.5 months	40 every 3rd day	-89 %
101-006*	80	0	8.5 months	0	-100 %
101-007*	300	0	2 months	40 three times a week	-94 %
101-008*	600	0	2 months	80	-87 %
101-009†	800	0	NA	NA	NA

Ongoing studies: SAHARA DESERT

20 decompensated heart failure patients with persistent congestion on high dose diuretics



Study Endpoints

- ***Primary:*** ***safety and tolerability of alfapump DSR® therapy***
- ***Secondary:*** ***feasibility of DSR therapy to restore and maintain euvolemia without additional loop diuretics***
- ***Exploratory:*** ***evaluate potential impact of SGLT-2 inhibitors on DSR therapy****

SAHARA interim results:

- N=10 enrolled to date
  - Baseline loop diuretic dose ~250 mg/day
  - Baseline NT-proBNP >6000
- Thus far:
  - All patients have achieved euvolemia with DSR therapy
  - Improvement in natriuretic peptides and renal function
  - Dramatic and durable improvement in diuretic response

Future directions

- Current DSR studies utilize 10% dextrose as the DSR solution
  - Each 1L produces ~700cc UF
- Ongoing animal experiments to develop a superior solution
  - Icodextrin/dextrose based solution
  - Each 500cc produces ~1500 cc UF
    - ~4X as powerful as 10% dextrose
- First in human planning underway

Conclusion

- alfapump DSR therapy may represent a powerful new tool to address volume overload and cardio-renal dysfunction
- Unlike IV loop diuretics which often have a negative impact on renal function and diuretic response
  - 2-6 weeks of DSR therapy leads to a dramatic improvement in diuretic response
  - Most patients can be maintained on low dose or no loop diuretic for months after intensive DSR therapy
- A new DSR solution is under development that will offer greater UF capability with smaller volumes
- Additional research is warranted to better understand the cardio-renal benefits of alfapump DSR therapy and the application to HF patients