INVESTIGATOR WORKSHEET – SCREENING / DAY 1

1. Include patient:

- ☐ Inform patient regarding the study (sign and date informed consent)
- ☐ Review inclusion and exclusion criteria (sign and date I/E criteria form)
- ☐ If patient participates in the SUBSTUDY: additional informed consent form to be signed and dated by the patient and investigator

2. Perform volume assessment (see next page)

3. Prescribe diuretic treatment:

- ☐ **Bolus IV loop diuretic** = **2 x oral home dose*** with maximum of 5 mg bumetamide/ 200 mg furosemide
- ☐ **500 mg bolus IV IMP** (Investigational Medicinal Product)

***Conversion factor:**
1 mg bumetanide po = 1 mg bumetanide IV
40 mg furosemide po = 40 mg furosemide IV
20 mg torsemide po = 40 mg furosemide IV = 1 mg bumetanide IV

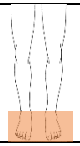
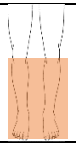
4. Ensure **urine collection** starts right after first bolus infusion and ends at the morning of day 2

VOLUME ASSESSMENT – SCREENING / DAY 1 – Date: __ / __ / ____ - Time: __ : __

Patient should have at least 1 clinical sign of volume overload **to be eligible**:
- Oedema (score 2 or more)
- Ascites confirmed by echography
- Pleural effusion confirmed by chest X-ray or echography

In case of ascites and/or pleural effusion, imaging to be repeated on day 2, 3 and 4!

Name and signature of cardiologist with heart failure expertise:

	Trace oedema: <4mm and rebounds ≤ 10sec		Clear pitting oedema: ≥ 4*mm and takes up >10sec to rebound*		
OEDEMA	☐ No oedema (score 0)	☐ Trace oedema (score 1)	 ☐ Up to ankle (score 2)	 ☐ Up to knee (score 3)	 ☐ Above knee (score 4)
PLEURAL EFFUSION	☐ No pleural effusion (score 0)	☐ Minor, non-amendable for punction (score 2)	☐ Major, amendable for punction (score 3)		
ASCITES	☐ No ascites (score 0)	☐ Minor only detected by echography (score 2)	☐ Significant ascites (score 3)		

Instruction: please indicate per row 1 field that applies.

INELIGIBLE

START STUDY TREATMENT (day 1):
- Bolus IV loop diuretic (**2x oral home dose** with max 5 mg bumetanide or 200 mg furosemide)
- 500 mg bolus IV IMP

Conversion factor: 1 mg bumetanide po = 1 mg bumetanide IV / 40 mg furosemide po = 40 mg furosemide IV / 20 mg torsemide po = 40 mg furosemide IV = 1 mg bumetanide IV

BACKGROUND THERAPY

Fluids

- 24h oral intake of fluid and sodium: restricted to 1500 mL and 1.5 g, respectively
- Maintenance infusion with 500 mL glucose 5% and 3g $MgSO_4$ administered over 24h time interval, until complete decongestion or end of the study treatment phase
- Non-protocol fluids administration (including those for administration of intravenous medication) should be limited

Potassium

- In case of serum potassium levels <4 mmol/L, 40 mmol of KCI to be added to the maintenance infusion
- Oral potassium supplements may be used at the discretion of the treating physician, but their use will be prospectively registered

Sodium bicarbonate

- In case of metabolic acidosis with serum bicarbonate levels <20 mmol/L, it is recommended to administered intravenously 100 ml of $NaHCO_3$ 8.4%

Neurohumoral blockers

- Treatment with neurohumoral blockers may be continued at the same or lower dosage at the discretion of the treating physician, until the end of the treatment phase (max 4 days) or until complete decongestion is achieved, whatever comes first
- Dose increases for any of these medications are not allowed during the screening and treatment phase with the exception of mineralocorticoid receptor antagonists in case of hypokalaemia despite intravenous potassium supplement
- Starting an SGLT2 inhibitor and a switch from renin-angiotensin system blockers to saccubutril/valsartan is not allowed during the screening and treatment phase, but might be pursued after decongestion is achieved
- After decongestion, it is strongly recommended to up-titrate doses of neurohumoral blockers according to the guidelines in the HFrEF patients

INVESTIGATOR WORKSHEET – DAY 2

1. **Perform volume assessment** (see next page)

2. **Prescribe diuretic treatment:**
   - Bolus IV loop diuretic = 1 x oral home dose*

     AND

     500 mg bolus IV IMP (Investigational Medicinal Product)
   - After 6 hours: bolus IV loop diuretic = 1 x oral home dose*

***Conversion factor:**
1 mg bumetanide po = 1 mg bumetanide IV
40 mg furosemide po = 40 mg furosemide IV
20 mg torsemide po = 40 mg furosemide IV = 1 mg bumetanide IV

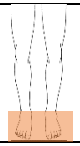
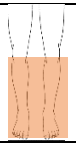
3. Ensure that **urine collection** period **1 is stopped** and that urine collection period **2 is started**

VOLUME ASSESSMENT – DAY 2 – Date: __ / __ / _____ - Time: __ : __

Urinary output 1: _____ mL

(starts immediately after first bolus administration and until the morning of day 2 prior to the morning bolus of the study medication)

Name and signature of cardiologist with heart failure expertise:

	Trace oedema: <4mm and rebounds ≤ 10sec		Clear pitting oedema: ≥ 4*mm and takes up >10sec to rebound*		
OEDEMA	☐ No oedema (score 0)	☐ Trace oedema (score 1)	 ☐ Up to ankle (score 2)	 ☐ Up to knee (score 3)	 ☐ Above knee (score 4)
PLEURAL EFFUSION	☐ No pleural effusion (score 0)	☐ Minor, non-amendable for punction (score 2)	☐ Major, amendable for punction (score 3)		
ASCITES	☐ No ascites (score 0)	☐ Minor only detected by echography (score 2)	☐ Significant ascites (score 3)		

Instruction: please indicate per row 1 field that applies.

SUCCESFULL DECONGESTION: **STOP IV STUDY TREATMENT** AND CHANGE TO ORAL REGIMEN

CONTINUE STUDY TREATMENT (day 2, 8-12 AM):
- Bolus IV loop diuretic (**1x** oral home dose)
- 500 mg bolus IV IMP

After 6 hours: bolus IV loop diuretic (**1x** oral home dose)

Conversion factor: 1 mg bumetanide po = 1 mg bumetanide IV / 40 mg furosemide po = 40 mg furosemide IV / 20 mg torsemide po = 40 mg furosemide IV = 1 mg bumetanide IV

BACKGROUND THERAPY

Fluids

- 24h oral intake of fluid and sodium: restricted to 1500 mL and 1.5 g, respectively
- Maintenance infusion with 500 mL glucose 5% and 3g $MgSO_4$ administered over 24h time interval, until complete decongestion or end of the study treatment phase
- Non-protocol fluids administration (including those for administration of intravenous medication) should be limited

Potassium

- In case of serum potassium levels <4 mmol/L, 40 mmol of KCI to be added to the maintenance infusion
- Oral potassium supplements may be used at the discretion of the treating physician, but their use will be prospectively registered

Sodium bicarbonate

- In case of metabolic acidosis with serum bicarbonate levels <20 mmol/L, it is recommended to administered intravenously 100 ml of $NaHCO_3$ 8.4%

Neurohumoral blockers

- Treatment with neurohumoral blockers may be continued at the same or lower dosage at the discretion of the treating physician, until the end of the treatment phase (max 4 days) or until complete decongestion is achieved, whatever comes first
- Dose increases for any of these medications are not allowed during the screening and treatment phase with the exception of mineralocorticoid receptor antagonists in case of hypokalaemia despite intravenous potassium supplement
- Starting an SGLT2 inhibitor and a switch from renin-angiotensin system blockers to saccubutril/valsartan is not allowed during the screening and treatment phase, but might be pursued after decongestion is achieved
- After decongestion, it is strongly recommended to up-titrate doses of neurohumoral blockers according to the guidelines in the HFrEF patient

INVESTIGATOR WORKSHEET – DAY 3

1. **Perform volume assessment** (see next page)

2. **Prescribe diuretic treatment:**
   - Bolus IV loop diuretic = 1 x oral home dose*

     AND

     500 mg bolus IV IMP (Investigational Medicinal Product)
   - After 6 hours: bolus IV loop diuretic = 1 x oral home dose*

***Conversion factor:**
1 mg bumetanide po = 1 mg bumetanide IV
40 mg furosemide po = 40 mg furosemide IV
20 mg torsemide po = 40 mg furosemide IV = 1 mg bumetanide IV

3. Ensure that **urine collection** period 2 **is stopped** and **assess TOTAL urine collection** (collection period 1 + collection period 2) for decision on ESCALATION THERAPY (if total urine collection < 3500 ml)

VOLUME ASSESSMENT – DAY 3 – Date: __ / __ / _____ - Time: __ : __

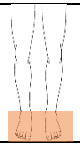
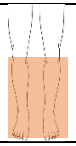
Urinary output 1: _____ **mL**

Urinary output 2: **+** _____ **mL**

_____ **mL** **= TOTAL urinary output**

Name and signature of cardiologist with heart failure expertise:

(Urinary output 2: from end of urinary collection period 1 until the morning of day 3 prior to the morning bolus of the study medication)

	Trace oedema: <4mm and rebounds ≤ 10sec		Clear pitting oedema: ≥ 4*mm and takes up >10sec to rebound*		
OEDEMA	☐ No oedema (score 0)	☐ Trace oedema (score 1)	 ☐ Up to ankle (score 2)	 ☐ Up to knee (score 3)	 ☐ Above knee (score 4)
PLEURAL EFFUSION	☐ No pleural effusion (score 0)	☐ Minor, non-amendable for punction (score 2)	☐ Major, amendable for punction (score 3)		
ASCITES	☐ No ascites (score 0)	☐ Minor only detected by echography (score 2)	☐ Significant ascites (score 3)		

Instruction: please indicate per row 1 field that applies.

SUCCESFULL DECONGESTION: **STOP IV STUDY TREATMENT** AND CHANGE TO ORAL REGIMEN

CONTINUE STUDY TREATMENT (day 3, 8-12 AM):
- Bolus IV loop diuretic (**1x** oral home dose)
- 500 mg bolus IV IMP

After 6 hours: bolus IV loop diuretic (**1x** oral home dose)

If TOTAL urinary output < 3500mL:

ESCALATION THERAPY
- ☐ Doubling IV loop diuretic dose
- ☐ Add oral chlorthalidone 50mg daily
- ☐ Ultrafiltration or renal replacement therapy

BACKGROUND THERAPY

Fluids

- 24h oral intake of fluid and sodium: restricted to 1500 mL and 1.5 g, respectively
- Maintenance infusion with 500 mL glucose 5% and 3g $MgSO_4$ administered over 24h time interval, until complete decongestion or end of the study treatment phase
- Non-protocol fluids administration (including those for administration of intravenous medication) should be limited

Potassium

- In case of serum potassium levels <4 mmol/L, 40 mmol of KCI to be added to the maintenance infusion
- Oral potassium supplements may be used at the discretion of the treating physician, but their use will be prospectively registered

Sodium bicarbonate

- In case of metabolic acidosis with serum bicarbonate levels <20 mmol/L, it is recommended to administered intravenously 100 ml of $NaHCO_3$ 8.4%

Neurohumoral blockers

- Treatment with neurohumoral blockers may be continued at the same or lower dosage at the discretion of the treating physician, until the end of the treatment phase (max 4 days) or until complete decongestion is achieved, whatever comes first
- Dose increases for any of these medications are not allowed during the screening and treatment phase with the exception of mineralocorticoid receptor antagonists in case of hypokalaemia despite intravenous potassium supplement
- Starting an SGLT2 inhibitor and a switch from renin-angiotensin system blockers to saccubutril/valsartan is not allowed during the screening and treatment phase, but might be pursued after decongestion is achieved
- After decongestion, it is strongly recommended to up-titrate doses of neurohumoral blockers according to the guidelines in the HFrEF patients

INVESTIGATOR WORKSHEET – DAY 4

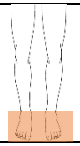
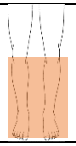
1. **Perform volume assessment** (see next page)

2. **Stop <u>study</u> diuretic treatment**

VOLUME ASSESSMENT – DAY 4 – Date: __ / __ / ____

STOP STUDY TREATMENT
After the treatment phase, you are recommended to prescribe the lowest dose of loop diuretic that you think is needed and to increase the neurohumoral blockade recommended by guidelines. Patients can be discharged as early as 24 hours after the physician concluded that the volume overload is no longer present.

Name and signature of cardiologist with heart failure expertise:

	Trace oedema: <4mm and rebounds ≤ 10sec		Clear pitting oedema: ≥ 4*mm and takes up >10sec to rebound*		
OEDEMA	☐ No oedema (score 0)	☐ Trace oedema (score 1)	 ☐ Up to ankle (score 2)	 ☐ Up to knee (score 3)	 ☐ Above knee (score 4)
PLEURAL EFFUSION	☐ No pleural effusion (score 0)	☐ Minor, non-amendable for punction (score 2)	☐ Major, amendable for punction (score 3)		
ASCITES	☐ No ascites (score 0)	☐ Minor only detected by echography (score 2)	☐ Significant ascites (score 3)		

Instruction: please indicate per row 1 field that applies.

INVESTIGATOR WORKSHEET – DISCHARGE

Only applicable when discharge later than day 4

1. **Perform volume assessment** (see next page)

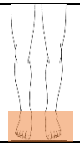
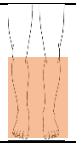
VOLUME ASSESSMENT – DISCHARGE – Date: __ / __ / ____

Only applicable when discharge later than day 4

Name and signature of cardiologist with heart failure expertise:

DISCHARGE

Patients can be discharged as early as 24 hours after the physician concluded that the volume overload is no longer present.

OEDEMA	Trace oedema: <4mm and rebounds ≤ 10sec		Clear pitting oedema: ≥ 4*mm and takes up >10sec to rebound*		
	☐ No oedema (score 0)	☐ Trace oedema (score 1)	 ☐ Up to ankle (score 2)	 ☐ Up to knee (score 3)	 ☐ Above knee (score 4)
PLEURAL EFFUSION	☐ No pleural effusion (score 0)	☐ Minor, non-amendable for punction (score 2)	☐ Major, amendable for punction (score 3)		
ASCITES	☐ No ascites (score 0)	☐ Minor only detected by echography (score 2)	☐ Significant ascites (score 3)		

Instruction: please indicate per row 1 field that applies.

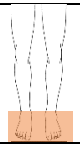
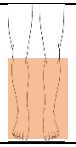
INVESTIGATOR WORKSHEET – FU MONTH 3

1. **Perform volume assessment** (see next page)

VOLUME ASSESSMENT – FU MONTH 3 – Date: __ / __ / ____

FOLLOW-UP
Patients will be followed for a maximum of 3 months for secondary/ tertiary endpoint analysis. This follow-up should not differ from standard of care for such patients.
Please make every effort to contact participants who are lost to follow-up.

Name and signature of cardiologist with heart failure expertise:

OEDEMA	Trace oedema: <4mm and rebounds ≤ 10sec		Clear pitting oedema: ≥ 4*mm and takes up >10sec to rebound*		
	☐ No oedema (score 0)	☐ Trace oedema (score 1)	 ☐ Up to ankle (score 2)	 ☐ Up to knee (score 3)	 ☐ Above knee (score 4)
PLEURAL EFFUSION	☐ No pleural effusion (score 0)	☐ Minor, non-amendable for punction (score 2)		☐ Major, amendable for punction (score 3)	
ASCITES	☐ No ascites (score 0)	☐ Minor only detected by echography (score 2)		☐ Significant ascites (score 3)	

Instruction: please indicate per row 1 field that applies.