Furosemide sc2Wear micro-pump patch for oedema in heart failure

LAY SUMMARY

Heart failure is a common and disabling condition that affects the heart's ability to pump blood around the body. The heart muscle doesn't receive enough oxygen to work properly and a blood vessel may completely block off, leading to a heart attack (myocardial infarction), where a section of heart muscle dies completely forming a scar. A sudden worsening of heart failure symptoms can cause fluid to enter the lungs and surrounding tissue.

Furosemide sc2Wear micro-pump patch is intended to treat patients with heart failure who have increased fluid in their lungs and other tissues. This treatment aims to reduce hospital stay for patients who suffer a worsening of their heart failure. The sc2Wear micro-pump delivers the drug just under the skin by a wearable patch, rather than requiring hospital treatment where drugs are given directly into the blood by a drip.

If furosemide sc2Wear micro-pump is licensed for use in the UK, it could be a new treatment option for patients with heart failure and could reduce their hospital stay. Furosemide sc2Wear micro-pump has the potential to reduce symptoms of heart failure and increase survival in this group of patients.

NIHR HSRIC ID: 11808
TARGET GROUP

- Heart failure: with oedema – to reverse deterioration in heart failure following symptoms of decompensation; to allow completion of the treatment for an episode of acute decompensated heart failure at home; and for the periodic treatment of advanced heart failure to maintain euvolemia.

TECHNOLOGY

DESCRIPTION

Sc2Wear furosemide micro-pump patch (furosemide micropump; SCP-101) is a proprietary controlled-release reformulation of the diuretic furosemide for the treatment of heart failure. Furosemide is a diuretic widely-used to treat oedema; swelling due to excess extracellular fluid that is most often associated with congestive heart failure, kidney diseases and liver disease. The sc2Wear micro-pump patch, delivers the drug subcutaneously (SC) via a wearable patch device; a rotation of the pump shaft results in a very precise, small volume (10µL) release of the drug, via a 27G needle that is inserted following placement and activation, and automatically withdraws back into the device following completion of delivery. The furosemide formulation is optimised for SC delivery by reducing the pH to avoid skin reactions and discomforta. The product is expected to provide therapy for home use (under medical guidance). It is suggested that use of the product will reduce the need for emergency or in-hospital care, shorten hospital stay and improve outcomes in patients who still require hospitalisation. In phase III clinical trials, 80mg of furosemide was administered SC over 5 hours1.

Furosemide is licensed as an oral and parenterally administered diuretic for many indications including cardiac, pulmonary, hepatic and renal oedema, as well as peripheral oedema due to mechanical obstruction, venous insufficiency or hypertension2. Furosemide is generally well-tolerated and there are no commonly reported adverse events2. As with other diuretics, electrolytes and water balance may be disturbed as a result of diuresis after prolonged therapy. Furosemide leads to increased excretion of sodium and chloride, and consequently increases excretion of water. In addition, excretion of other electrolytes (in particular potassium, calcium and magnesium) is increased2.

Sc2Wear furosemide micro-pump patch is not in clinical trials for any other indication.

INNOVATION and/or ADVANTAGES

If licensed, sc2Wear furosemide micro-pump patch will offer an additional treatment option to treat oedema in heart failure; to reverse deterioration in heart failure following symptoms of decompensation; to allow completion of treatment for an episode of acute decompensated heart failure at home; and for the periodic treatment in advanced heart failure to maintain euvolemia. Sc2Wear furosemide micro-pump patch has the potential to reduce inpatient care for patients with heart failure by preventing hospitals admissions or reducing length of stay when they do occur.

DEVELOPER

ScPharmaceuticals.

a Company provided information.
Heart failure is a common condition that can result from any structural or functional cardiac or non-cardiac disorder that impairs the ability of the heart to respond to physiological demands for increased cardiac output. It may arise as a consequence of a myocardial, valvular, pericardial, endocardial or electrical problem. It has a considerable impact on affected patients with a high mortality and reduced quality of life.

Acute decompensated heart failure (ADHF) is defined as a sudden worsening of heart failure symptoms and is usually caused by cardiogenic pulmonary oedema with rapid fluid accumulation in the lungs, although it can occur without pulmonary oedema. Acute decompensated heart failure occurs as the sudden or gradual onset of the signs or symptoms of heart failure requiring unplanned emergency primary care appointments, visits to accident emergency departments, or hospitalisation. Regardless of the underlying precipitant of the exacerbation, pulmonary and systemic congestion due to increased left- and right-heart filling pressures is a nearly universal finding in ADHF.

Heart failure currently affects approximately 900,000 people in the UK, with around 68,000 new cases diagnosed each year. It has a poor prognosis; 30-40% of patients diagnosed with heart failure die within a year. Acute heart failure is a common cause of admission to hospital, with over 67,000 admissions in England and Wales per year, and it is the leading cause of hospital admissions in people 65 years or older in the UK. The most common cause of heart failure is coronary artery disease. Patients are regarded as being in end-stage heart failure if they are at high risk of dying within about 6 months. In 2013, heart failure (ICD-10 I50) accounted for 5,525 deaths in England. In 2014-15, 70,890 patients in England were admitted with heart failure (ICD-10 I50) requiring 146,150 finished consultant episodes and accounting for 792,041 bed days.

Heart failure hospitalisations account for approximately 5% of all emergency admissions and 2% of all NHS inpatient bed-days. Heart failure also accounts for almost 2% of the total
NHS budget, with approximately 70% of these costs due to HF admissions\textsuperscript{16}. The company suggest that one major contributing factor to this cost is length of stay. Unlike other similar conditions that have adopted an early-discharge or ambulatory care model (for example myocardial infarction, infective endocarditis, or chronic obstructive pulmonary disease), the organisation of inpatient treatment for heart failure has not significantly changed over the past few decades\textsuperscript{5}. Reducing length of stay has been proposed by the company as a way of not only improving patients’ quality of life and reducing hospital-related patient harm, but also providing substantial cost savings to the NHS\textsuperscript{6}.

**CURRENT TREATMENT OPTIONS**

For most people, heart failure is a long-term condition that cannot be cured. In most cases of heart failure, the aim is to find a combination of management approaches including lifestyle changes, medicines, devices, or surgery that will help restore heart functionality, reduce symptoms, prevent further coronary artery disease progression and improve quality of life\textsuperscript{19}.

Pharmacological treatments available include\textsuperscript{3,9,10}:
- Angiotensin converting enzyme (ACE) inhibitors as first-line treatment.
- Beta-blockers – bisoprolol, metoprolol, nebivolol or carvedilol; can be in combination with ACE inhibitors as first-line treatment.
- Aldosterone antagonists such as spironolactone or eplerenone as an add-on therapy.
- Angiotensin II receptor antagonists as second line treatment as an alternative to ACE inhibitors\textsuperscript{5}.
- Hydralazine in combination with nitrate.
- Diuretics – such as furosemide, bumetanide or thiazide diuretics; should be considered for patients with dyspnoea or oedema. Patients with ADHF are treated with a higher dose of diuretics via bolus or infusion strategies.

\textsuperscript{5} Expert personal communication.
Calcium channel-blockers – such as amlodipine, which may be used in patients for the treatment of co-existing hypertension or symptomatic ischaemic heart disease\(^d\).

Anticoagulants – for patients with a history of thromboembolism.

Aspirin – for patients with a history of atherosclerotic arterial disease.

Intravenous (IV) inotropic agents – such as dobutamine, dopamine, milrinone or enoximone; should only be considered for the short-term treatment of ADHF.

Clinical strategies aimed at reversing the worsening of heart failure include an increase in the oral dose of furosemide, changing to another oral loop diuretic such as bumetanide or torsemide, the addition of a thiazide diuretic such as bendroflumethiazide or metolazone, or the use of IV furosemide. A clinical expert has stated SC furosemide is currently used in a number of localities in the USA, UK, Switzerland and Spain in the palliative management of patients with advanced heart failure but the published evidence is limited to only small prospective and retrospective cohort studies\(^d\).

Patients may ultimately require heart transplantation. Apart from the shortage of donor hearts, the main challenges in transplantation are the consequences of the limited effectiveness and complications of immunosuppressive therapy in the long term, including antibody-mediated rejection, infection, hypertension, renal failure, malignancy, and coronary artery vasculopathy\(^18\).

The company report that in a patient with heart failure, pre-acute hypervolemia may occur as a result of poor medication compliance, dietary transgression and poor absorption. This hypervolaemic state further interferes with oral absorption leading to the worsening of fluid overload. Hospital administration of IV furosemide is the cornerstone of the current acute management of ADHF, resulting in prompt diuresis and relief of congestion. Treatment of hypervolaemia restores absorption, allowing for transition back to oral therapy\(^d\). However, a clinical expert notes that although this may be true in some patients, many decompensated heart failure patients do remain sensitive to oral diuretics throughout their treatment\(^d\).

The company suggest that during the pre-acute stage leading to ADHF, patients often develop progressive subclinical and clinical signs followed by a progressive increase in symptoms. Clinical strategies aimed at reversing the worsening of heart failure include an increase in the oral dose of furosemide, changing to another oral loop diuretic or addition of a second oral diuretic, or the use of IV furosemide. In the acute patient, IV furosemide is used to provide relief of severe symptoms while, in the post-acute stage, it continues to improve the clinical condition of the patient, preparing them for the transition to oral therapy and discharge\(^e\). However, a clinical expert has reported that IV furosemide is not widely used in the UK and is not part of the pathway laid out in the NICE acute heart failure guidelines\(^d\).

### EFFICACY and SAFETY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>NCT02329834, scP-01-002; IV furosemide vs SC furosemide; phase II/III.</td>
<td>ScPharmaceuticals.</td>
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<tr>
<td>NCT02579057, 2015-01; IV furosemide vs SC furosemide; phase II/III.</td>
<td>John Hopkins University.</td>
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<tr>
<td>SUBQ-HF; SC furosemide.</td>
<td>National Heart, Lung, and Blood Institute, National Institutes of Health (USA).</td>
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</table>

\(^d\) Company provided information.
<table>
<thead>
<tr>
<th>Source of information</th>
<th>Trial registry¹, manufacturer.</th>
<th>Trial registry², manufacturer.</th>
<th>Manufacturer.</th>
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<tbody>
<tr>
<td>Location</td>
<td>USA.</td>
<td>USA.</td>
<td>USA.</td>
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<tr>
<td>Participants</td>
<td>n=16; aged 18 years and older; history of ≥3 months treated NYHA class II/III heart failure with presence of symptoms of chronic volume overload requiring ongoing treatment with oral furosemide at a dose of ≥40mg per day for ≥20 days prior to baseline; body weight &lt;130kg and body mass index &lt;38 kg/m²; NT-proBNP &gt;300 pg/ml or BNP &gt;100 pg/mL; no ADHF or hospitalisation for heart failure in the last 4 weeks; no worsening of signs or symptoms of heart failure in the 2 weeks prior to screening; no patients with requirement for IV loop diuretics or in-patient treatment for heart failure; no systolic blood pressure &lt;90mmHg; no serum sodium &lt;130 mEq/L and no serum potassium &lt;3.0 mEq/L; no diagnosis of type I or type II diabetes mellitus; no presence or need for urinary catheterisation, urinary tract abnormality or disorder interfering with urination; no glomerular filtration rate on admission &lt;45 mL/min/1.73m²; no moderate to severe hepatic dysfunction.</td>
<td>n=40 (planned); aged 18 to 100 years; history of at least 3 months treated NYHA class II/III/IV heart failure or recent hospitalisation for heart failure; presenting to Heart Failure Bridge Clinic with decompensated heart failure with signs/symptoms including elevated jugular venous pressure (JVP), dyspnea and peripheral oedema where the decision is made to give IV diuretics; no presence or need for urinary catheterisation, urinary tract abnormality or disorder interfering with urination.</td>
<td>Age 18 years or older; hospitalisation for acute heart failure with at least 1 symptom out of dyspnoea, orthopnoea, or oedema and 1 sign out of rales on auscultation, peripheral oedema, ascites, pulmonary vascular congestion on chest radiography, BNP &gt;250 ng/mL or NTproBNP &gt;1,000 ng/mL; persistent congestion despite at least 24 hours of IV therapy, defined by the presence of at least 2 or more of peripheral oedema, rales, elevated JVP, ascites or BNP &gt;250 ng/mL or NTproBNP &gt;1000 ng/mL; total anticipated daily IV furosemide dose (at time of screening) 80-160 mg (or equivalent)/day; anticipated need for at least 48 more hours of parenteral diuretic therapy.</td>
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<tr>
<td>Schedule</td>
<td>Randomised to furosemide 80mg SC administered over 5 hours followed by furosemide 80mg IV bolus in second period; or furosemide 80mg IV bolus followed by furosemide 80mg SC administered over 5 hours in second period. Treatment periods were separated by a 10 days wash-out period.</td>
<td>Randomised to furosemide 80mg SC administered as 30mg over the first hour and then as 12.5mg per hour over the subsequent 4 hours; or furosemide single dose determined by investigator (maximum dose 160mg) administered by IV bolus over 2 minutes.</td>
<td>Randomised to standard care in hospital vs early supported discharge with SC furosemide pump, patient administered at 80mg SC over 5 hours and applied up to twice daily for up to 7 days.</td>
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<td>Follow-up</td>
<td>Day 7, days post treatment.</td>
<td>Day 7 and day 30 clinic visit or telephone follow-up.</td>
<td>Day 7 and day 30 clinic visit.</td>
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<tr>
<td>Primary outcome/s</td>
<td>Pharmacokinetic parameters.</td>
<td>Urine output.</td>
<td>Days alive and out of the hospital between randomisation and day 30.</td>
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<td>Secondary outcome/s</td>
<td>Adverse events; clinical laboratory, urinalysis, vital signs, ECG parameters, physical exam findings.</td>
<td>Heart failure symptom scoring/symptom improvement measured by Kansas City Cardiomyopathy Questionnaire; adverse effects and urine sodium.</td>
<td>Composite safety endpoint of death, sustained ventricular arrhythmias, and severe hypokalaemia (potassium level &lt;3.0 mmol/L); costs from randomisation through 30 days; days alive and outside the hospital through 14 days; 30 day heart failure readmission, emergency department visit for heart failure, or death; symptoms through day 75; renal function and NT-proBNP to 30 days; safety.</td>
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**Key results**

Bioavailability of SC furosemide was equivalent to IV. For SC furosemide vs IV furosemide, diuresis was 2.65L vs 2.61L at 8hrs and 3.63L vs 3.56L at 24hrs.

**Adverse effects (AEs)**

SC treatment was reportedly well-tolerated.

**Expected reporting date**

The study completion date was reported as April 2015. The company state the results are currently being prepared for publishing. The estimated primary completion date is reported as June 2016. The study is expected to be completed in 2018.

### ESTIMATED COST and IMPACT

#### COST

The target price for the drug-device combination including the novel furosemide formulation and all device components will be the equivalent of €150.00. A typical patient may use 1.25 of these units.

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° Company provided information.
IMPACT - SPECULATIVE

Impact on Patients and Carers

- Reduced mortality/increased length of survival: a clinical expert has expressed doubts that this technology will be associated with mortality benefit. Only one of the three studies described has mortality as part of an endpoint, and this only measures survival up to 30 days.

- Reduced symptoms or disability

- No impact identified

- Other

Impact on Health and Social Care Services

- Increased use of existing services

- Decreased use of existing services: the company has stated that heart failure patients commonly deteriorate over 2-3 weeks and when they are admitted they have approximately 8.4L of extra fluid. They claim that approximately 50% of admissions can be prevented and that in approximately half of the patients who are admitted, the length of stay can be reduced in the order of 4 days in the UK with the patient finishing the treatment at home.

- Re-organisation of existing services: an expert notes that this patient group has a high mortality (around 10% when hospitalised). Further research is needed to demonstrate safety and effectiveness in the home setting as none of the listed studies will specifically address this subgroup of patients. Furthermore, before using this treatment in clinical practice, each patient and home environment would need to be risk assessed. The expert also stated the technology indication could lead to a reduction in length of stay for patients once they have been admitted to hospital; and although reduced length of stay is desirable there are other requirements during an admission for heart failure (confirmation of diagnosis with echocardiogram, assessment by the multidisciplinary heart failure team, follow-up within two weeks of discharge by the community heart failure team) that would still need to be processed prior to safe discharge (as set out in the NICE Acute Heart Failure Guidelines).

- Need for new services

- Other

- None identified

1 Expert personal communication.
2 Expert personal communication.
Impact on Costs and Other Resource Use

- Increased drug treatment costs
- Reduced drug treatment costs
- Other increase in costs
- Other reduction in costs
- Other

Other Issues

- Clinical uncertainty or other research question identified: An expert commented that the Sc2Wear furosemide micro-pump patch is an interesting potential option in the management of acute decompensated heart failure but the evidence base needs to be built. The pathway for patient management with this treatment would need to be very carefully defined and depend on the listed indication. The expert also commented it is likely to have a positive effect on patient experience. It may also be useful in the palliative care setting.
- None identified

REFERENCES

1 ClinicalTrials.gov. Crossover Study to Compare the Pharmacokinetics and Bioavailability of a Novel Furosemide Regimen Administered Subcutaneously vs. the Same Dose Administered Intravenously in Subjects with Chronic Heart Failure. www.clinicaltrials.gov/show/NCT02329834 Accessed 3 March 2016.


