scPharmaceuticals

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Performance Reliability of the scFurosemide Infusor for Subcutaneous Administration of a Novel Formulation of Furosemide in Patients with Heart Failure

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Background

Heart failure (HF) affects 6.5 million adults in the United States and expected to grow to greater than 8 million by 2030. Sodium retention leading to volume overload is attributed to 59% of hospital admissions and 90% of patients admitted for acute decompensated heart failure (ADHF) are treated with loop diuretics. The use of IV furosemide is recommended universally in international guidelines for the management of ADHF due to the highly variable and overall reduction in the bioavailability of oral furosemide formulations.

Subcutaneous (SC) administration of furosemide would enable administration outside of the acute care setting. However, the current commercially available furosemide injectable products have an alkaline pH making them unsuitable for SC administration. A novel, pH neutral formulation of furosemide (scFurosemide) was developed to minimize burning and discomfort with SC administration and is delivered via a proprietary, wearable, pre-programmed Infusor (Figure 1A).

The *Infusor* is a two-component system consisting of a reusable *Activator* controller containing the electronics and a disposable, single-use *Cartridge* including a proprietary micropiston pump, needle, drug reservoir and adhesive backing that holds the system onto the user's abdomen (Figure 1B). For the administration of scFurosemide, the Activator is pre-programmed with a bi-phasic delivery profile to infuse 30 mg in the first hour, followed by 12.5 mg per hour for the subsequent 4 hours.

In a previous study, a SC infusion of 80 mg of scFurosemide using the same biphasic profile and a commercial infusion pump was shown to be bioequivalent and achieved comparable diuresis and natriuresis when compared to 80 mg IV furosemide (1). The purpose of this study was to evaluate the on-body performance and patient acceptance of the administration of scFurosemide formulation via the Infusor (scFurosemide Infusor) in patients with HF.

Objectives

- To assess the overall performance reliability of the scFurosemide Infusor
- To evaluate the ability of the scFurosemide Infusor to deliver 80 mg of scFurosemide subcutaneously
- To assess safety and local tolerance tolerability of the scFurosemide Infusor

Methods

- Patients with HF (NYHA Class II-IV) were enrolled in an open label, single dose study
- scFurosemide Infusor was filled with 80 mg (10 ml) of scFurosemide and placed on the subjects abdomen after the application of a protective skin barrier (Cavilon™ No Sting Barrier Film)
- The primary endpoint was to evaluate the overall performance reliability of the scFurosemide Infusor, measured by absence of major product failures leading to under-infusion as defined as
  - Failure of scFurosemide Infusor to deliver 80 mg ± 10% of scFurosemide based of fill and residual volumes, OR a combination of
  - Obvious leakage of scFurosemide
  - Failure to achieve furosemide plasma concentration of > 250 ng/ml during the plateau phase of delivery (1-5 hours after start of infusion)
- Pain was assessed using an 11 point numeric rating scale of pain (0= no pain; 10= worst pain imaginable), at 3 time points
  - During needle insertion
  - Maximum pain during use
  - Upon removal from the skin

Methods (cont'd)

- Visual inspection on adhesive site application was assessed for erythema, edema and other local skin reactions
- Device dislodgement score was determined by assessing the % device lifts from the skin
- Comfort of wear and interference of activity of daily living were determined using a questionnaire

Figure 1.

Results

- Eighty-one subjects were screened and 74 were enrolled across 5 sites. Baseline characteristics of the subjects in the ITT and MITT populations are shown in Table 1.
- Sixty-seven (83%) of enrolled subject completed the 5-hour infusion and comprised the MITT population
  - Six infusions were disrupted due to a known pre-production software malfunction
  - 1 patient discontinued the infusion due to discomfort with 15 minutes of the infusion remaining

Table 1. Baseline Characteristics

	ITT Population* (N=74)	MITT Population† (N=67)
Age, y (mean ± SD)	61.8 (12.2)	61.3 (12.3)
Gender, n (%)		
Male	47 (63.5)	42 (62.7)
Race, n (%)		
Black or African American	35 (47.3)	32 (47.8)
White	37 (50.0)	33 (49.3)
Other	2 (2.8)	2 (3)
Body mass index, kg/m^2 (mean ± SD)	35.7 (8.5)	35.6 (8.4)
Severity of heart failure		
NYHA Class II	59 (79.7)	54 (80.6)
NYHA Class III	15 (20.3)	13 (19.4)
Treatment history, n (%)		
ACEi/ARB	62/74 (83.8)	-
Beta-blocker	68/74 (91.9)	-
Loop diuretic	73/74 (98.6)	-
MRA	36/74 (48.6)	-

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ITT, intent-to-treat; MITT, modified intent-to-treat; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; SD, standard deviation.
*ITT population represents all enrolled participants.
†MITT population represents participants who completed the full 5-hour test treatment.

Results (cont'd)

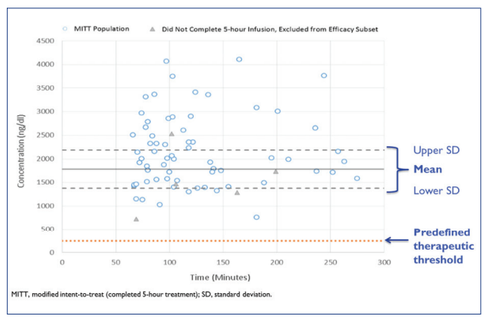
- The overall absence of major failures (primary endpoint) by the scFurosemide Infusor was 63/67 (94%; 95% CI: 85.4%, 98.4%). see Table 2.
- When the scFurosemide Infusor was adequately filled and placed on the subjects' abdomen, the specified dose was delivered in 63/64 (98%; 95% CI: 92% 100%) subjects (Table 2)
- In the MITT population, all subjects (67/67) achieved a plasma furosemide levels > 250 ng/ml during the plateau phase (mean: 2160 ng/ml; range: 763-4104 ng/ml) (Figure 2)
- There were no needle/insertion failures, complete device dislodgements or leaks observed during delivery

Table 2. Primary Endpoint Analysis

	Success/Failure			
	Absence of Major Product Failures	95% CI	P-Value	Type of Failures
Initial Assessment	63/67 (94%)	(85.4, 98.4%)	0.642	Fill, Dispense** and Use Error
Resolved Assessment*	63/66 (95.5%)	(87.3, 99.1%)	0.433	Fill, Dispense**
Dispense errors in Adequately filled Infusors	63/64 (98.4%)	(91.6,100%)	0.103	Dispense**

*Resolved data, removal of one subject due to use error
** Dispense error was in 1 subject that received 67 mg (8.4 ml) of scFurosemide which was less than the pre-defined lower bounds of minimal administration threshold of 72 mg (9.0 ml) [80 mg (10 ml) ± 10%]
Use Error =1; Fill Error= 3; Dispense Error =1

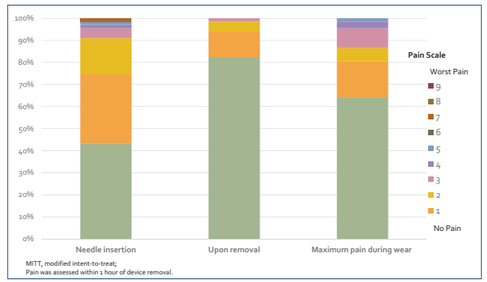
Figure 2. Plasma Furosemide Concentrations



MITT, modified intent-to-treat (completed 5-hour treatment); SD, standard deviation.

- 64/67 (95.5%) of MITT subjects reported an overall maximum pain score of < 3 (Figure 3)
- In the MITT population, skin irritation was either absent (45/67; 67.2%) or barely perceptible (16/67; 23/9%) in 91% immediately on removal of the scFurosemide Infusor (Figure 4)
- 55/56 (82%) of MITT subjects reported being either very comfortable or moderately comfortable wearing the scFurosemide Infusor (Figure 5)

Figure 3. Subject-Reported Pain



MITT, modified intent-to-treat;
Pain was assessed within 1 hour of device removal.

Figure 4. Adhesive Site Skin Response

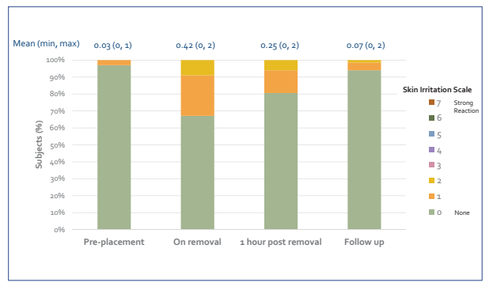
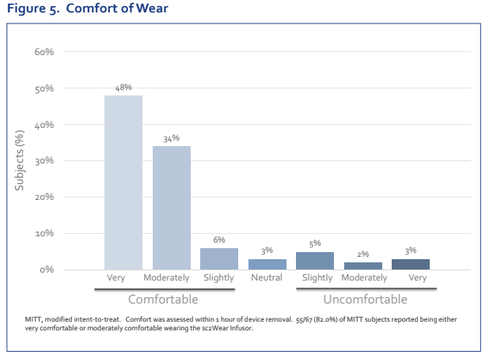


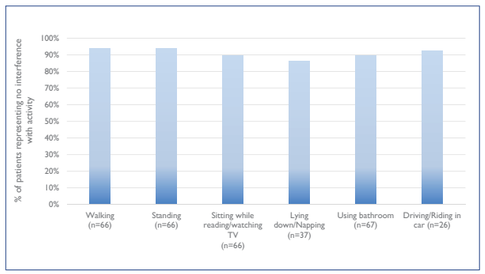
Figure 5. Comfort of Wear



MITT, modified intent-to-treat. Comfort was assessed within 1 hour of device removal. 55/67 (82.0%) of MITT subjects reported being either very comfortable or moderately comfortable wearing the sc1Wear Infusor.

- Of the subjects who attempted a daily living activity, 86%-94% of subjects stated that the scFurosemide Infusor did not interfere with the activity (Figure 6)
- Greater than 90% adherence of the scFurosemide Infusor to the skin was observed in 64/67 (95.5%) of subjects
- The most frequently observed adverse events were local skin effects, such as erythema, bruising and pain which were mild or moderate in severity, appeared to be related to the adhesive and not the drug formulation and were transient.
- Upon device removal, 67.2% had no signs of skin irritation, while 23.9% had minimal signs of erythema. These numbers improved to 80.6% (54/67) and 94% (63/67) with no evidence of irritation at 1 hour and 5-7 days post removal, respectively

Figure 6. Interference with Activities of Daily Living



Conclusions

- The scFurosemide Infusor demonstrated reliable performance without serious or significant adverse events
- All subjects (100%) achieved a plasma furosemide concentrations above the predefined therapeutic threshold
- The scFurosemide Infusor was safe and well tolerated with minimal interference on subjects activities of daily living
- The scFurosemide Infusor met the specifications with respect to needle placement and retraction, adherence to the abdominal skin and absence of device leakage
- The scFurosemide Infusor is a potential alternative to IV administration in patients with heart failure

References

1. Sica, D.A.; Muntendam, P.; Myers, R.L.; ter Maaten, J.M.; Sale, M.E.; de Boer, R.A., Pitt, B. Subcutaneous Furosemide in Hear Failure: Pharmacokinetic Characteristics of a Newly Buffered Solution. JACC: Basic to Translational Science; 2017. In Press.

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