CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209988Orig1s000

CLINICAL REVIEW(S)

NDA209988/64

Drug: Furoscix (furosemide SQ)

Safety Update

Conclusion

No unexpected safety issues are presented in this 505 b2 product safety update report. Reported adverse events seem related to the use of the device.

Introduction

Product Background

scPharmaceuticals has developed Furoscix®, a novel, pH neutral formulation of furosemide for subcutaneous administration. Furoscix is being developed for administration via a proprietary, single-use, user-loaded, pre-programmed on-body drug delivery system (Furoscix Infusor). In support of the 505(b)(2) New Drug Application (NDA) for the Furoscix Ifusor, scPharmaceuticals is relying upon the FDA's previous findings of safety and efficacy for the proposed listed drug, Furosemide Injection (Hospira, NDA 18667), in conjunction with information from Sponsor-conducted studies (Hospira 2019). The Furoscix Infusor is a drug device combination product consisting of Furoscix (Furosemide Injection, 80 mg per 10 mL) contained in a prefilled, 10 mL Crystal Zenith® (CZ) cartridge with FluroTec® coated (b) (4) rubber septum and piston, and a proprietary, single-use, user-loaded, pre-programmed on-body subcutaneous delivery system, the Infusor.

Patient Population

The proposed indication for the Furoscix Infusor is for the treatment of congestion due to fluid overload in adult patients with NYHA (New York Heart Association) Class II and Class III chronic heart failure who display reduced responsiveness to oral diuretics and who do not require hospitalization. Furoscix is not indicated for use in emergency situations or in patients with acute pulmonary edema.

In the original NDA submission (SN0001), the Sponsor included four studies in patients with heart failure using subcutaneous administration of Furoscix via a delivery device:

1) Pivotal PK/PD bridging study (scP-01-002).

2) Exploratory PK/PD study (scP-01-001) administered Furoscix subcutaneously using a commercial infusion pump (the Perfusor Space Infusion Pump, manufactured by B. Braun).

3) Clinical validation PDCV study (CP-00001).

4) Pilot study (CP-00002) administered Furoscix via the pre-change device.

In addition, the sponsor conducted a study to validate adhesive effectiveness and evaluate local skin tolerability of the (b) (4) Tape with the Furoscix Infusor (Pilot Infusor) (scP-00-003).

Since the Complete Response letter issued in December 2020, the Sponsor completed the following three studies:

1) An open label, non-randomized simulated use clinical study in healthy adult subjects aged 45-79 (scP-00-004) to evaluate the effectiveness of a software change and two different modifications to the safety latch on a simulated 5-hour drug delivery (Pilot Infusor).

2) An open label, non-randomized, single-center study (scP-01-007) to evaluate safety and local tolerability of shortened subcutaneous infusions of Furoscix (furosemide injection, 80 mg/10 mL).

3) An open label, multicenter clinical trial that evaluated the overall and heart failure related healthcare costs and safety of the Furoscix Infusor 30 days post discharge from the emergency department (scP-01-005) (Pilot Infusor).

Common adverse events by pump used.

Studies Using a Commercial Pump (Study scP-01-001)

In study scP-01-001, 10 subjects with heart failure presenting with chronic fluid overload were treated with a 5-hour subcutaneous infusion of Furoscix 80 mg via the Perfusor Space Infusion Pump, manufactured by B. Braun or oral furosemide 80 mg in a crossover design. Six subjects (60%; 6/10) reported a total of 12 AEs following subcutaneous infusion of Furoscix (bruise at injection site, burning/stinging sensation at/around injection site (4), exhausted, red discharge, flu, cramps both legs, exacerbated COPD, bronchitis and stroke), all of which were of mild severity. The only AE that was reported by more than 1 subject following subcutaneous infusion of Furoscix was “burning/stinging sensation at/around injection site”, which was reported by 4/10 (40%) subjects.

Study scP-01-002

Eight subjects in the subcutaneous group experienced application site erythema, and 7 subjects experienced application site edema. One subject in the IV group experienced application site erythema. The following AEs were related to study infusion or other study procedure (adhesive):

• 7 AEs (erythema) were related to adhesive ((b) (4) subcutaneous) – all were mild severity

• 1 AE (erythema at area of (b) (4) placement, subcutaneous) – mild severity

• 1 AE (erythema related to adhesive (b) (4) used to secure IV site) – moderate severity

• 1 AE (elevated CK secondary to higher-than-normal amount of physical activity occurring during the washout period) – moderate severity.

There were no reports of SAEs or deaths leading to discontinuation of infusion. One AE, General disorders and administration site conditions/Infusion site pain/infusion site pain, experienced by

Subject (b) (6) in Cohort 2a, led to discontinuation of infusion. The subject reported a pain score of 6 at 0.17 hours following the initiation of infusion. The subject also reported injection site pain of 6 prior to the pain assessment scheduled at 0.5 hours after the start of the infusion and asked to stop the infusion. The subject discontinued therapy because of the infusion site pain.

One subject (b) (6) Cohort 2a) experienced moderate hypotensive changes in blood pressure during the 8-hour follow-up period at approximately five (5) hours after the end of infusion. The hypotension resolved following oral rehydration.

Studies Using the Pre-change Device

Study CP-00001

In study CP-00001, Furoscix was administered subcutaneously via an on-body delivery system (pre-change device) in 74 subjects. The most frequently observed AEs in the study were application site erythema (21/74 subjects, 28.4%) and application site bruising (11/74 subjects, 14.9%). Two other AEs were implantable cardioverter defibrillator pocket infection and ventricular tachycardia (SAE, the subject had prior incidents of VT. The subject's amiodarone was increased from 200mg to 400mg daily. A right and left heart catheterization was reported to have shown non-obstructive coronary artery disease with patent stents.

Study CP-00002

In study CP-00002, Furoscix was administered via an on-body subcutaneous delivery system (pre-change device) in 27 subjects. There was one serious adverse event (non-cardiac chest pain). Non serious AEs included application site bruising [1/27, 3.7%] and application site erythema [1/27, 3.7%]). Other reported AEs were diarrhea/vomiting, dizziness, skin irritation, pruritus, facial and extremity pain).

Studies Using the Furoscix Infusor Combination Product

Study scP-01-005

A prospective single treatment arm (N= 24) (i.e., Furoscix administered via the Furoscix Infusor) managed outside the hospital was compared to a matched historical control arm that consisted of patients admitted to the hospital for ≤ 72 hours. There were 6 subjects (25.0%) that experienced at least 1 SAE (cardiac failure congestive (4.2%), food poisoning (4.2%), tibia fracture (4.2%), diabetic ketoacidosis (4.2%), hyperosmolar state (4.2%), hypovolemia (4.2%), acute kidney injury (4.2%), polyuria (4.2%), and lymphedema (4.2%). There were no deaths or any reported AE that led to premature study discontinuation.

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JOINT CLINICAL and STATISTICAL REVIEW

Application Type	NDA
Application Number(s)	209988
Priority or Standard	Standard
Submit Date(s)	August 23, 2017
Received Date(s)	August 23, 2017
PDUFA Goal Date	June 23, 2017
Division/Office	DCRP/ ODE 1/ OND
Reviewer Name(s)	Melanie Blank, MD (clinical); Steven Bai, PhD (statistics)
Review Completion Date	May 16, 2018
Established/Proper Name	Furosemide injection (a novel pH neutral furosemide formulation (SCP-101); and a proprietary subcutaneous delivery system, the Infusor
(Proposed) Trade Name	Furoscix (b) (4)
Applicant	SC Pharmaceuticals
Dosage Form(s)	Solution for subcutaneous administration
Applicant Proposed Dosing Regimen(s)	8 mg/ mL, 80 mg one time dose
Applicant Proposed Indication(s)/Population(s)	FUROSCIX for subcutaneous administration is indicated in adult patients for the treatment of edema associated with congestive heart failure, (b) (4) . (b) (4) **Limitations of Use** (b) (4) FUROSCIX is not indicated for use in emergency situations or in patients with pulmonary edema. (b) (4)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	N/A

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

There are currently no approved furosemide products for subcutaneous administration. The product under review is a drug-device combination product, the Furoscix Infusor, consisting of SCP-101, a novel pH-neutral formulation for subcutaneous infusion via scPharmaceuticals' proprietary, wearable, pre-programmed drug delivery system, "the Infusor" (also called sc2Wear Infusor). Furosemide is a loop diuretic that was discovered in 1962 and approved in 1966. It is currently approved for oral, IV and IM administration. The Furoscix Infusor's proposed indication is for the treatment of edema associated with congestive heart failure, (b) (4) Different from IV or IM furosemide, the Furoscix Infusor combination product is not indicated for use in emergency situations/ acute pulmonary edema. Different from oral furosemide, the Furoscix Infusor is not indicated for chronic use. The use of Furoscix should be reserved for patients who temporarily require a greater diuretic potential than can be achieved with oral medication alone or when gastrointestinal absorption is impaired or not practical for any reason. Parenteral therapy should be replaced with oral furosemide as soon as practical.

To support the 505(b)(2) New Drug Application (NDA) for the Furoscix Infusor, scPharmaceuticals is relying upon the FDA's previous findings of safety and efficacy for the proposed listed drug (LD), Furosemide Injection (Hospira, NDA 18667), in conjunction with information from multiple sponsor-conducted studies, including a PK bridging study using another CDRH-cleared infusion device to establish the biosimilarity between the subcutaneous and intravenous routes of delivery, and a clinical validation study to establish safety and efficacy of the combination product.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The application does not contain substantial evidence of effectiveness. The pivotal clinical trial, the Product Design Clinical Validation Study (PDCV study; study CP-00001) wasn't designed to assess the heart failure patient's ability to self-administer because it was administered by trained study staff. In addition, the primary endpoint of the study (meeting performance acceptance criteria in ≥ 95% completed infusions with the lower bound of the 95% confidence interval for the actual success > 95%) was not met. Instead, the success rate was 94% (95% CI: (b) (4)). The failures were due to decreased drug delivery (b) (4) (b) (4) (b) (4). Understanding the effectiveness of this product is not feasible when the drug was administered in the trial by study staff instead of the patients themselves. The clinical

reviewer thinks that 94% is an optimistic success rate because heart failure patients would probably have greater difficulty self-administering the product than trained study staff. As such, if Furoscix had been tested with heart failure patient self-administration, the success rate might have been considerably lower than the 94% observed in the PDCV study. Because of this uncertainty, and the risks of unknowingly undertreating edema (because of inadequate drug delivery) in the vulnerable heart failure, (b) (4) populations who would be prescribed this product, the clinical and statistical reviewers recommend against approval and recommend that the sponsor be advised to repeat the PDCV study with a reengineered device (b) (4) Furthermore, the repeat PDCV study should require patients to self-administer without a video prompt, unless the video is planned to be part of labeling.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Edema may cause considerable pain and discomfort. It is widely-held that edema of the gastrointestinal system can result in reduction of medication absorption, inadequate response to oral diuretics and requirement for parenteral diuretics. IV loop diuretics are the mainstay treatment for worsening edema unresponsive to oral diuretics and are usually administered in the hospital. A therapeutic option that allows patients or lay care-givers to self-administer parenteral furosemide would be useful for the occasional management of the edematous patient who is unresponsive to oral diuretics. This could potentially reduce hospitalization and hospital days and as such, might benefit patients.

The sc2Wear Furoscix Infusor is a device-drug combination product that was designed to deliver a fixed dose (80mg) of subcutaneous furosemide to edematous patients who are unresponsive to oral diuretics but who are not requiring rapid diuresis. The new formulation of furosemide (SCP-101) has a neutral pH, lower than the pH of the LD furosemide for IV and IM use. The Sponsor intends for the product to be used on an occasional, not chronic, basis and has stated that it is not a substitute for intravenous furosemide in emergency situations like acute pulmonary edema. In the NDA submission, the sponsor explained that there are three scenarios where the device would likely be used; when trying to avoid hospitalization in the out-patient setting, when trying to avoid hospitalization in the emergency room setting and when trying to send a patient home early from the hospital when parenteral diuretics are still thought to be necessary. The premise is that parenteral diuretics are better than oral diuretics in these settings. The studies to support approval were not designed to demonstrate that parenteral diuretics are superior to oral diuretics in these 3 clinical settings, but rather they were designed to show in a step-wise fashion that the novel furosemide solution (SCP-101) is (1) biosimilar to intravenous (IV) furosemide in stable heart failure patients (Study sCP-01-002), that the Furoscix infusor can (2) reliably infuse SCP-101 when administered by trained study staff Study CP-00001), and that (3) stable heart failure patients and care givers can self-administer the product reliably (Human Factors Studies).

The pivotal Clinical Pharmacology Study (scP-01-002) performed in stable heart failure patients was designed to bridge the proposed product [the pH neutral furosemide formulation, (SCP-101)] to the to the labeled drug (LD), IV furosemide (Hospira, NDA 18667) by demonstrating biosimilarity between the two products. The study indicated that the extent of systemic furosemide exposure is comparable between SCP-101 administered as a subcutaneous infusion using a different device than the to-be-marketed device (the B. Braun Perfusor® Pump, CDRH cleared for subcutaneous infusion) and the LD administered as an IV injection. However, the Cmax was lower and took longer to achieve for subcutaneous SCP-101 compared to IV

furosemide. Compared to IV furosemide, the time to onset of diuresis was longer for the subcutaneous SCP-101. However, the pharmacodynamic effect on urinary volume and sodium excretion was similar when measured at the end of the 24-hour study period. This study successfully bridged the two products and showed that ***if*** the sc2Wear Furoscix Infusor could deliver SCP-101 reliably, it would produce similar PK and PD effects to IV furosemide, except for rapidity of effect which would lag by ~1-2 hours. Therefore, in nonemergency clinical situations where patients require IV diuretics, an 80-mg subcutaneous infusion of SCP-101 would result in similar exposure to furosemide and produce a diuresis at 24 hours equivalent to an equivalent IV dose of the RLD.

The Product Design Clinical Validation (PDCV) Study (CP-00001) was the pivotal clinical trial designed to demonstrate the reliability of the sc2Wear Furoscix Infusor and was the bridging study for the drug/device product. According to prespecified performance criteria, the sc2Wear Furoscix Infusor did not reliably deliver SCP-101. Of the 67 subjects in the mITT population, 4 had major system-related failures leading to under-infusion of SCP-101. Because of these failures, the primary endpoint of the study was not met (meeting predefined performance acceptance criteria in ≥ 95% completed infusions with the lower bound of the 95% confidence interval for the actual success > 95%). A major system-related failure was defined as failure to dispense 80 mg ± 10% furosemide (calculated from fill volume and residual volume measurements despite completing the full 5-hour infusion or a combination of obvious leakage AND failure to achieve furosemide plasma levels > 250 ng/mL during the plateau phase of delivery). Three of the 4 failures occurred because of dispensing failures related to inadequate preparation of the device and device design flaws (b) (4) (b) (4). The other dispensing failure resulted from (b) (4) (b) (4). The devices were prepared, applied and removed at end of the 5 -hour treatment by trained study staff. In the post-marketing setting, because heart failure patients and lay caregivers will be responsible for the preparation, attachment and removal of the device, the results from study CP-00001 should be considered a best-case scenario. Looking at the results from a positive perspective, the success rate was 94% (b) (4) (b) (4) Therefore, under ideal conditions, the device probably would work reliably on average ~94% of the time. One must consider that a 94% success rate, while not meeting the prespecified endpoint, signals a potential benefit and if the product were to be approved, could translate into fewer hospital days for many patients with heart failure. (b) (4) (b) (4)

(b) (4)

The only safety signal was skin-related adverse events. There were mild to moderate skin-related adverse effects that resolved. Secondary endpoints that assessed comfort of wear, skin irritation, pain, and device dislodgement provided no concerning results.

To fairly analyze the results of study CP-00001, one must consider that the failure rate seen in the study is most likely lower than what it would be in the post-marketing setting. Because patients with edema from heart failure, (b) (4) (b) (4) are often elderly and infirm and may suffer from decreased eyesight, coordination and/or intellectual function, they may not be able to follow the instructions for use and the device failure rate would be expected to be considerably higher than in an ideal clinical study setting where trained study staff is administering the treatment. Furthermore, there will be long lag times between the time when patients first receive instruction on use of the Infusor, possibly by a nurse in the doctor's office and the time when they need to self-administer, making risk for failure even higher. It is not possible to know what the failure rate would be if heart failure patients in a more realistic clinical setting had self-administered the Furoscix Infusor in study CP-00001, thus leading to uncertainty about the true major system-related device failure rate.

Furthermore, the risks of the Furoscix Infusor cannot be evaluated simply based on a device failure rate. To do a thorough benefit-risk assessment one must consider worst case scenarios, when patients do not receive adequate doses of parenteral diuretics when needed and are unaware of it.

In clinical practice, the decision to initiate treatment with the Furoscix Infusor would be based on an assessment that a patient is refractory to oral loop diuretics and thus requires treatment with a parenteral loop diuretic. To avoid or shorten hospitalization, the patient would be prescribed Furoscix. If a patient were aware of device failure, this would prompt a call or visit to the physician who might reasonably decide that the patient needs to be admitted for IV furosemide. The largest safety concern is that the failures of delivery can occur with no awareness on the part of the patient. (b) (4) . The clinical reviewer thinks that it is quite possible that most patients will not readily determine if they are having an appropriate diuresis. One can imagine a scenario where a patient is prescribed 3-5 days of the Furoscix Infusor with instructions to return to the office after the course of treatment.

If this patient is unaware of device failure, he/she could worsen and develop acute decompensated heart failure. Heart failure patients are a particularly vulnerable population and have an increased risk of death for months after each hospitalization. A reliable device that could signal major system failures would be necessary to feel confident about safety. A human factors study, (0074) enrolled 16 stable heart failure patients and 16 lay caregivers. The participants were instructed on the use of the device by a proprietary video and there was a nurse assistant available. After ~ 24 hours the participants were asked to go to a home-simulated environment where they were instructed to prepare the device, place it on their abdomens, start it and, after 5 hours, remove it per the instructions for use (IFU) or video. There was a help line available for the participants. According to the study report, all participants except one patient (6.3% of the patients) successfully prepared the device (but this patient knew he was unable to prepare the device). The other steps were completed adequately by all participants. However, the vials were not checked by investigators to make sure that they were empty after cartridge filling, the cartridges weren't checked by investigators to make sure that they were filled completely and no serum levels were checked to ensure that the device delivered the full dose of drug. Hence, this human factors study does not provide confidence that heart failure patients and their care givers can administer the product reliably. Moreover, the video is not part of the labeling, and as such should not be included in the human factors study. The CDRH review included the following important comments:

- "The device needs an (b) (4) alarm. If the patient does not receive their dose, and is not aware that they did not receive their dose, their symptoms may worsen because of the device malfunction, which is a safety concern."

- "Due to the deficient reports, the evidence does not support that acceptable mitigations have been implemented and verified to support the top-level goal of safety."

- "The evidence does not support that acceptable mitigations have been implemented and verified to reduce the risk of under-dosing to an acceptable level. This information is needed to ensure safe and reliable care.

- "If the [video] training in [the] Human Factors study does not mimic the actual use scenario, the results of the study cannot be used to predict how future patients will interact with [the] device."

- "The Sponsor may need to make changes to the IFU to be more explicit in directing cleaning of the device and infusion site."

In summary, the PDCV study (CP-00001) probably underestimated the failure rate because of vision, coordination and/or intellectual function challenges of mildly -moderately decompensated edematous patients AND the worst-case scenario risk from device malfunction is that some patients may develop acute exacerbations of heart failure which increases risk of death.

In deciding about whether to approve Furoscix one must weigh the potential benefit of reducing hospital days in most patients (probably most, though unknown, because the PDCV study wasn't designed to assess the heart failure patient's ability to self-administer) against the unknown real-world risk of acute exacerbations of heart failure that might occur when the device fails and the patient is unaware of it. A precise risk-benefit analysis is difficult when the device failure rate when the product is administered the way it would be in the real world is unknown. i.e., 94% would be an optimistic success rate because heart failure patients would probably have greater difficulty self-administering than trained study staff. In the real-world the failure rate would be expected to be higher than the 6% seen in the PDCV study, maybe considerably higher. An accurate risk-benefit analysis is not feasible without knowing the device failure rate. Because of this uncertainty, the clinical and statistical reviewers recommend against approval and recommend that the sponsor be advised to repeat the PDCV study with a reengineered device (b) (4) Furthermore, the repeat PDCV study should require patients to self-administer without a video prompt, unless the video is planned to be part of labeling.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Edema from congestive heart failure, nephrotic syndrome and cirrhosis (NOT including pulmonary edema) causes symptoms of heaviness, abdominal bloating and increased abdominal girth, foot swelling, decreased mobility, shortness of breath,	Edema can cause considerable pain, discomfort, shortness of breath and exercise intolerance even in the absence of acute pulmonary edema. It is widely-held that

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	exercise intolerance and pain. It is widely-held that edema of the gastrointestinal system can result in reduction of medication absorption and inadequate response to oral diuretics and requirement for parenteral diuretics.	edema of the gastrointestinal system can result in reduction of medication absorption and inadequate response to oral diuretics and requirement for parenteral diuretics.
Current Treatment Options	• The therapeutic effects of diuretics have been known for decades. • Diuretics improve hemodynamic parameters and symptoms in edematous conditions • IV loop diuretics are the mainstay of treatment for worsening edema unresponsive to oral diuretics and these are usually administered in the hospital.	IV loop diuretics are the mainstay treatment for worsening edema unresponsive to oral diuretics and these are usually administered in the hospital.
Benefit	• Reducing hospitalization and reducing hospital days would be a benefit for patients. • The sc2Wear Furoscix Infusor was designed to deliver subcutaneous furosemide to edematous patients who are unresponsive to oral diuretics but who are not having a need for a rapid acute diuresis (for instance, pulmonary edema) with the aim of reducing need for IV diuretics and hospitalization. • In the Clinical Pharmacology Study (scP-01-002) performed in stable heart failure patients, the subcutaneous infusion of SCP-101 using a different device than the to-be-marketed device (the B. Braun Perfusor® Pump, CDRH cleared for	The sc2Wear Furoscix infusor was designed to deliver subcutaneous furosemide to edematous patients who are unresponsive to oral diuretics but who are not requiring a rapid acute diuresis (for instance, pulmonary edema). The potential benefit of the device is to deliver parenteral diuretics while avoiding hospitalization. The Clinical Pharmacology study (scP-01-002) performed in stable heart failure patients showed that SCP-101

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	subcutaneous infusion) showed that SCP-101 administered subcutaneously is biosimilar to IV furosemide. The time of onset of diuresis was shorter for the IV furosemide than the subcutaneous SCP-101, but the effect was the same when measured at the end of the 24-hour study period. • The sc2Wear Furoscix Infusor, tested in the Product Design Clinical Validation study (CP-00001), did not meeting its primary endpoint (meeting predefined performance acceptance criteria in ≥ 95% of completed infusions with the lower bound of the 95% confidence interval for the actual success > 95%). There were 4/67 major system-related failures leading to under-infusion of SCP-101. A major system-related failure was defined as failure to dispense 80 mg ± 10% furosemide (calculated from fill volume and residual volume measurements despite completing the full 5-hour infusion or a combination of obvious leakage AND failure to achieve furosemide plasma levels > 250 ng/mL during the plateau phase of delivery). The device was prepared, applied and removed at end of the 5 -hour treatment by study staff and therefore did not test the patient's ability to learn how to use the device from the instructions for use. Because heart failure patients and lay caregivers will be responsible for the preparation, attachment and removal of the device in the post-marketing setting, the results from study CP-00001 should be considered a best-case scenario. The success rate,	administered subcutaneously (via another FDA-cleared device, not the Furoscix Infusor) is biosimilar to IV furosemide. The time of onset of diuresis was shorter for the IV furosemide than the subcutaneous SCP-101, but the effect was the same when measured at the end of the 24-hour study period. Study CP-00001 did not meet its primary endpoint (meeting predefined performance acceptance criteria in ≥ 95% of completed infusions with the lower bound of the 95% confidence interval for the actual success > 95%) because of 4 device failures that met the sponsor's prespecified definition of a major system-related failure. A major system-related failure was defined as failure to dispense 80 mg ± 10% furosemide (calculated from fill volume and residual volume measurements despite completing the full 5-hour infusion or a combination of obvious leakage AND failure to achieve furosemide plasma levels > 250 ng/mL

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	nevertheless, was 94% (b) (4) (b) (4). Therefore, under ideal conditions, the device probably works reliably on average about 94% of the time.	during the plateau phase of delivery). Three of the 4 failures occurred because of dispensing failures related to inadequate preparation of the device and device design flaws (b) (4) (b) (4) (b) (4). One delivery failure resulted from (b) (4) (b) (4) (b) (4). No alarm indicated this failure. In study CP-00001, the device was prepared, applied and removed at end of the 5 -hour treatment by study staff and therefore did not test the patient's ability to learn how to use the device from the instructions for use. Because heart failure patients and lay caregivers will be responsible for the preparation, attachment and removal of the device in the post-marketing setting, the results from study CP-00001 should be considered a best-case scenario. The success rate, nevertheless, was 94% (b) (4) (b) (4) Therefore, under ideal

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		circumstances, the device probably works reliably on average 94% of the time. In a post-hoc analysis, one plateau furosemide level in each of the 4 subjects despite major system-related device failure was within therapeutic range (average of 1319 ng/dL). (b) (4) (b) (4) A therapeutic option that allows patients or lay care-givers to self-administer parenteral furosemide would be useful for the occasional management of the edematous patient who is unresponsive to oral diuretics. This could reduce hospitalization and hospital days and as such, could benefit patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• In the Product Design, Clinical Validation study (CP-00001), the type of delivery errors that occurred resulted from device preparation errors (b) (4) . While the average dose reduction in the 4 failures was 25% (subjects received on average 60 mg/80 mg dose), in practice, substantial reductions in administered drug volume resulting in insufficient or absent diuretic response would be expected to occur; and patients would be unaware of being under-dosed. • The device success rate in study CP-00001 is most likely considerably higher than what it would be in the real world. Because patients with edema from heart failure, (b) (4) are often elderly and/or infirm and may suffer from decreased eyesight, coordination and intellectual function, they may not be able to effectively interpret the instructions for use and the device failure rate would be expected to be considerably higher than in an ideal clinical study setting where trained study staff was administering the	The device success rate in study CP-00001 is most likely considerably higher than what it would be in the real world. Because patients with edema from heart failure, (b) (4) (b) (4) are often elderly and/or infirm and may suffer from decreased eyesight, coordination and intellectual function, they may not be able to effectively interpret the instructions for use and the device failure rate would be expected to be considerably higher than in an ideal clinical study setting where trained study staff was administering the treatment. Furthermore, there will sometimes be long lag times between when patients first receive instruction on use of the Infusor, possibly by a nurse in the doctor's office and having to self-administer, making risk for failure even higher. The failures that occurred in the Product Design Clinical Validation Study (CP-

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treatment. Furthermore, there will sometimes be long lag times between when patients first receive instruction on use of the Infusor, possibly by a nurse in the doctor's office and having to self-administer, making risk for failure even higher. • We must consider the risk to patients who do not receive adequate doses of parenteral diuretics when needed and are unaware of the device failure. • If patients are aware of device failure, this would prompt a call or visit to the physician who would likely decide that the patient needs to be admitted for IV furosemide. The largest safety concern is that the failures of delivery can occur with no indication to the patient. (b) (4) I think most patients will not be able to tell if their urine volume is higher or lower than average. One can imagine a scenario where a patient is prescribed 3-5 days of the Furoscix Infusor with instructions to return to the office after the course of treatment. If this patient is unaware that he or she is not getting a therapeutic dose, they could worsen and develop acute decompensated heart failure. Heart failure patients are a particularly vulnerable population and have a high risk of dying for months after each heart failure hospitalization. A	00001) went unnoticed by the study staff and subjects. If failures such as these occurred in the outpatient setting, it would result in delay of therapy and could result in patients going into acute decompensated heart failure. Validation studies of the revised IFU and reengineered device following failed study CP-00001 have not been satisfactorily conducted according to the CDRH review, thus failing to ensure that the Furoscix infusor would reliably deliver drug or alert patients of major system failures should they occur. In the PDCV study, there were mild to moderate skin-related adverse effects that resolved. Secondary endpoints that assessed comfort of wear, skin irritation, pain, and device dislodgement provided no concerning results.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

	reliable device that would signal major system failures would be necessary to feel confident about safety.
	• Another risk that could probably be addressed with better labeling would be the risk of infection if skin is not prepared properly before application.
	• Another risk is the potential to use the device with another drug. This occurrence is unlikely because:
	  ○ There is a prominent warning labeling against use with other drugs in the IFU
	  ○ There is an adaptor that is made specifically for the SCP-101 vial, and
	  ○ The cartridges are single use only.
	• Validation studies of the revised IFU and reengineered device following failed study CP-00001 have not been satisfactorily conducted to ensure safe use per the CDRH review.
	• There were mild to moderate skin-related adverse effects that resolved. Secondary endpoints that assessed comfort of wear, skin irritation, pain, and device dislodgement showed that for the majority of patients, there are no serious concerns regarding skin-related safety.
	• Other Common adverse effects of parenteral diuresis are electrolyte imbalances, metabolic alkalosis, worsening renal function, hyperuricemia, gout, arrhythmia, volume depletion, dry mouth, tachycardia, alterations in blood glucose and	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	glucose tolerance tests, and dizziness. These adverse effects occur with IV furosemide and are not expected to occur with any increased frequency with subcutaneous administration. The Furoscix Infusor does not pose any excess risk vis-à-vis these common adverse effects compared to IV furosemide.	

1.4. Patient Experience Data

In the pre-IND and IND period the Agency advised the sponsor to include in the clinical validation study an assessment of comfort and a targeted assessment of AEs of interest such as pain, rash, and itching at the site of the device connection with the skin, which they did.

The sponsor also conducted a user interview study that was reviewed in the CDRH review. The "users", however were health care professionals and not caregivers or heart failure patients. The results of study findings prompted several changes to the product: clarification of the workflow in the IFU, increase size of device markings, addition of indicators regarding when it is time to initiate a new step, ensurance that adhesive selection minimizes patient reactions.

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	CP-00001 and CP-00002 (secondary endpoints) and cp00003 (comfort questionnaire – saline via sc2wear device)
		x	Observer reported outcome (ObsRO)	CP-00001, scP-01-002, CP-00002
		□	Clinician reported outcome (ClinRO)	
		x	Performance outcome (PerfO)	CP-00001 and the human factors studies)
	x	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		Study 1-User Interviews (See CDRH review)
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		

	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Edema from congestive heart failure, nephrotic syndrome and cirrhosis (NOT including pulmonary edema) causes symptoms of heaviness, abdominal bloating and increased in abdominal girth, foot swelling, decreased mobility, and pain. Even in the absence of frank pulmonary edema, in patients with heart failure with other signs of fluid overload, there is usually congestion in the lungs due to elevated left atrial pressure. Pulmonary congestion contributes to shortness of breath and exercise intolerance. It is widely held that edema of the gastrointestinal system can result in reduction of medication absorption, inadequate response to oral diuretics and requirement for parenteral diuretics.

2.2 Analysis of Current Treatment Options

There are several diuretic drug products approved for edema that can be given by the IV, IM or p.o. route depending upon the severity of the condition. As of yet, no diuretics for subcutaneous administration have been approved. See Table 1 for a tabular listing of treatment options for edema.

Table 1: Table of Current Treatment Options

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Important Safety and Tolerability Issues
FDA Approved Treatments [Combine by Pharmacologic Class, if relevant]				
Furosemide IV	Edema associated with CHF, cirrhosis and renal disease, including the nephrotic syndrome. Furosemide is particularly useful when an agent with greater diuretic potential is desired. Furosemide is indicated as adjunctive therapy in acute pulmonary edema. The intravenous administration of furosemide is indicated when a rapid onset of diuresis is desired, e.g., in acute pulmonary edema.	1966	20-80 mg IV given by IV push over 2 minutes or IM. May be repeated as needed.	The safety profile of furosemide and other loop diuretics is well known. Main safety concerns are electrolyte disorders, dehydration and hypersensitivity reactions. See package insert for a complete list of AEs.
Torsemide IV	indicated when a rapid onset of diuresis is desired or when oral administration is impractical.	1993	5-200 mg by IV push over 2 minutes or by infusion (diluted). May be repeated as needed	See safety profile for furosemide

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Important Safety and Tolerability Issues
Bumetanide IV	Treatment of edema associated with congestive heart failure, hepatic and renal disease, including the nephrotic syndrome. Almost equal diuretic response occurs after oral and parenteral administration of bumetanide. Therefore, if impaired gastrointestinal absorption is suspected or oral administration is not practical, bumetanide should be given by the intramuscular or intravenous route.	1983	0.5mg -2 mg by IV push over 2 minutes and may be repeated as needed.	See safety profile for furosemide
Other Treatments				
Metolazone	Treatment of edema associated with congestive heart failure, (b) (4) renal disease, including the nephrotic syndrome.	1973	Oral use: 5-20 mg QD (titrated as needed)	Similar to safety profile for IV furosemide. See package insert for a complete list of AEs.
Thiazide diuretics (example: Hydrochloro -thiazide)	Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis and corticosteroid and estrogen therapy.	1959	Oral use: 25 mg to 100 mg daily	Similar to safety profile for IV furosemide. See package insert for a complete list of AEs.

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Important Safety and Tolerability Issues
Aldactone	Edema in cirrhosis when it is not responsive to fluid and sodium restrictions ad in nephrotic syndrome when treatment of the underlying disease, restriction of fluid and sodium intake and the use of other diuretics produce an inadequate response. And to manage edema in heart failure class III-IV	1960	100 mg daily and titrate slowly	Similar to safety profile for IV furosemide. See package insert for a complete list of AEs.
p.o. loop diuretics (example: furosemide)	Edema associated with congestive heart failure, renal disease, or hepatic disease.	1966	20mg- 80mg daily and titrate as necessary up to 600 mg/day.	Similar to safety profile for IV furosemide. See package insert for a complete list of AEs.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

SCP-101 has a neutral pH, lower than the basic pH of the RLD formulation. The active moiety is the same as the LD, furosemide which has been used for edema since its discovery in 1962. Furosemide was FDA approved in 1966 and is marketed worldwide.

3.2. Summary of Presubmission/Submission Regulatory Activity

There were 2 pre-IND meetings in 2014 to discuss the development plan. The sponsor informed the division of their plans to submit a 505(b)(2) application relying on the LD NDA 18579. It was agreed at the pre-IND meetings that the IND opening PK study could use a commercial 510k cleared infusion pump, the B. Braun Perfusor®. On January 14, 2015, the IND (No. 118919) was submitted. In a subsequent meeting, 4/27/15, the Agency clarified that for the pivotal clinical validation study to test the "to-be-marketed" device, safety endpoints needed to be prespecified and would factor prominently in our regulatory decision. The statistical plan was also discussed. FDA objected to the sponsor's sample size proposal which assumed no failures and 95% confidence that the non-failure rate would be at least (b)(4)%. The Agency stated that a

(b) (4)% non-failure rate was unacceptable and suggested that a 95% non-failure rate would be more appropriate for the intended use of the product. In the 6/1/17 pre-NDA meeting, FDA was informed of the failure of the Product Development Clinical Validation (PDCV) study in the pre-meeting package. In our preliminary comments, we stated, "While the type of data collected in the PDCV study appears adequate, the actual data do not appear to support approval… The study did not achieve its prespecified aim, which was demonstrating that ≥ 95% of products were free of major system failure. You report 63/67 or 94% (95% CI; 85% - 98%) of products were free of major system failure. Additionally, you report several device-related adverse events, including skin irritation, as well as device-related malfunctions and failures in the PDCV study, including device dislodgement, under delivery, unintended alarms and software issues."

During the meeting, scPharmaceuticals acknowledged that the PDCV study did not meet specified performance goals. They stated that software changes had been made to address issues seen in the PDCV study that resulted in noncompletion or incomplete dosing and bench testing had been conducted to replicate errors seen in the study. Based on the human errors that resulted in most of the failures in the PDCV study, scPharmaceuticals stated that they had improved graphics and updated the IFU to include instructions for patients/caregivers (b) (4) (b) (4) The sponsor reported that in a subsequent human factors study (0074), the frequency of undetected errors was 0%.

Based on the information provided, the Agency agreed that the proposed package seemed capable of supporting a review but stated that, "we are concerned that device malfunctions and failures observed in the studies may not be adequately mitigated by simply changing the IFU and conducting additional Human Factor studies."

3.3. Foreign Regulatory Actions and Marketing History

Furoscix is not marketed in the U.S. or elsewhere.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit was not requested because there were no specific concerns regarding study site misconduct, financial disclosures, protocol violations, clinical trial discontinuations, or unusual patterns in the safety or efficacy results.

4.2. Product Quality

The drug substance is Furosemide USP manufactured by (b) (4) with (b) (4) the Holder of the Drug Master File (DMF# (b) (4) Type II filed on February 01, 1996). A letter of authorization was provided.

The International Nonproprietary Name (INN) is Furosemide

The Chemical name is 4-chloro-N-furfuryl-5-sulfamoylanthranilic acid; 5-(aminosulfonyl)-4-chloro-2[(2-furanylmethyl)-amino]-benzoic acid.

See the CMC review for detailed description of product quality and product quality review issues.

4.3. Clinical Microbiology

According to the Sterility review completed by Steven Elliott, the validation activities appear to be consistent with the intended claims and are sufficient to support the indicated sterility assurance level (b) (4) following exposure to the intended validation protocol. The package integrity test methods are sufficient to demonstrate that the sealed trays used as primary packaging are effective sterile barriers for the tested shelf life, after simulated shipping and storage stresses.

4.4. Nonclinical Pharmacology/Toxicology

The nonclinical review relied largely upon the previously approved furosemide drug products. The only novel issues were the neutral pH and the subcutaneous route of administration. Hence, the review of the novel formulation for subcutaneous administration (SCP-101) was supplemented by studies in rabbits. At a dose level of 60 mg/kg (720 mg/m^2, HED 19.5 mg/kg) in the rabbit, approximately 15-fold higher than human dosage of furosemide 80 mg (49 mg/m^2, 1.33 mg/kg) injection, there were no gross or microscopic evidence of local irritation at the infusion site. There were also no SCP-101-related changes in coagulation parameters compared to control group animals. Furthermore, leachables and extractables from the infusor device were below thresholds for toxicological concern. No studies were done on the adhesive. Dr. Belay concluded that the nonclinical pharmacology/toxicology studies were adequately performed to evaluate safety and that there were no pharmacology/toxicology review issues.

4.5. Clinical Pharmacology

In the Clinical Pharmacology Study (scP-01-002) performed in 16 adults with compensated NYHA Class II/III heart failure, the subcutaneous infusion of SCP-101 using

a different device than the to-be-marketed device (the B. Braun Perfusor® Pump, CDRH cleared for subcutaneous infusion) showed that SCP-101 administered subcutaneously is biosimilar to IV furosemide. SCP-101 produced equivalent AUCs and PD effects (Na+ excretion and diuresis) to the LD, IV furosemide (Hospira, NDA 18667). The time of onset of diuresis was shorter for the IV furosemide than the subcutaneous SCP-101, but the PD effects were the same when measured at the end of the 24-hour study period. This study supports approval of the SCP-101 component of the combination product but does not provide any information on the new delivery method (the sc2Wear infusor). Please refer to the Clinical Pharmacology review by Dr. Girish Bende for an in-depth review of Study scP-01-002.

4.6. Devices and Companion Diagnostic Issues

The sc2Wear Furosemide Infusor consists of a pumping mechanism, needle insertion/retraction system, drug reservoir, and battery-operated electromotor and electronics. The device is adhered to the body using medical grade adhesive (b) (4) (b) (4) (b) (4). The device that was used in the pivotal clinical validation study (CP-00001) is representative of the to-be-marketed product regarding design and all functions and features. However, pre-production software was used with certain known defects resulting in possible false-positive error detection and programmed interruption of drug delivery. Participants who experienced this known software malfunction were excluded from the mITT analysis. The device components were packaged together as individual patient kits that included a disposable cartridge Kit and a potentially reusable activator Kit.

The failure of the Product Design Clinical Validation Study (CP-00001) to reach its primary efficacy endpoint is related to the faulty device design and inadequate IFU. The most concerning defect in the design of the device from a safety perspective (b) (4) (b) (4) are major system errors that can reduce delivery of drug. The reengineering and modifications of instructions may reduce the rate of device errors (although follow-up studies did not provide confidence of this), but (b) (4) when there is delivery failure (b) (4) (as occurred in study CP-(b) (4) has not been addressed.

There were two additional identified risks:

- The risk of infection if skin is not prepared properly before application. This could be addressed with better labeling.

- The potential to use the device with another drug. This occurrence is unlikely

because:

- There is a prominent warning labeling against use with other drugs in the IFU
- There is an adaptor that is made specifically for the SCP-101 vial, and
- The cartridges are single use only.

CDRH identified multiple deficiencies in the Safety Assurance Case reports and the Performance Testing- Engineering/ System and Software reports supporting verification and validation of the performance criteria of the device. CDRH also identified deficiencies that would need to be addressed by performing further Human Factors testing. See Dr. Carolyn Dorgan's CDRH review for a detailed description of all device and Human Factors Study issues.

4.7. Consumer Study Reviews

N/A.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Table of Studies Relevant to this NDA

Trial ID	Study Design	Subject population	Study Endpoints	Pertinent Dates
	Clinical Pharmacological Study to establish biosimilarity to LD (furosemide, Hospira, NDA 18667)			
scP-01-002	Open-label (OL), Randomized, 2-way, 2-period, X-over study to compare the PK and bioavailability of 80 mg SCP-101 administered with a Braun Infusion pump SQ compared to IV furosemide 80 mg (Hospira, NDA 18667) provided in two split doses	16 adults with NYHA Class II/III heart failure	PK and PD	Study initiation date (first subject first screening visit): 4/20/15 Study completion date (last subject last visit): 9/25/15
	PK Pilot Study			
scP-01-001	OL, pilot study comparing oral furosemide to 80 mg SCP-101 administered with a Braun Infusion pump SQ	10 adults with NYHA Class II/III heart failure	PK and PD	Study initiation date (first subject first screening visit): 12/17/14 Study completion date (last subject last visit): 4/8/15
	Clinical Validation Study			
CP-00001	OL study to evaluate the product design and clinical performance of the Furoscix Infusor combination product in subjects with chronic heart failure via the Furoscix Infusor	74 adults with NYHA Class II/III heart failure	Device Failure Rate.	Study initiation date (first subject first screening visit): 10/10/16 Study completion date (last subject last visit): 11/8/16
	PDCV Pilot Study			

Trial ID	Study Design	Subject population	Study Endpoints	Pertinent Dates
CP-00002	OL, pilot study of Furoscix Infusor combination product in subjects with congestive heart failure administered 80 mg dose of SCP-101 via Infusor	27 adults with NYHA Class II/III heart failure	Safety	Study initiation date (first subject first screening visit): 7/21/16 Study completion date (last subject last visit): 8/15/16
	Human Factors Studies			
0040 Report-0123	Human factors validation study of heart failure patients and lay caregivers using the Furoscix Infusor combination product	18 adults with Class II, III and IV heart failure and 15 adult lay caregivers	See CDRH review	See CDRH review
0041 Report 0128	Human factors validation study of heart failure clinicians using the Furoscix Infusor combination product	17 doctors, 18 nurses and 17 pharmacists	See CDRH review	See CDRH review
0072 Report-0126	Human factors validation study of heart failure patients and lay caregivers using the Furoscix Infusor combination product – post summative retest	7 adults with heart failure and 8 adult lay caregivers	See CDRH review	See CDRH review
0074 Report-0133	Human factors validation study of heart failure patients and lay caregivers using the Furoscix Infusor combination product at home	16 adults with heart failure and 16 lay caregivers	See CDRH review	See CDRH review

5.2. Review Strategy

This is a joint review between the clinical reviewer (Melanie Blank, MD) and the statistical reviewer (Steven Bai, PhD). Our approach to this NDA review was to focus on the study design and efficacy results of the pivotal trial, the Product Design Clinical Validation Trial (CP-00001) for the assessment of efficacy. The efficacy results from the sponsor will be presented as well as the approach taken by Dr. Bai with his rationale for analyzing the results differently from that taken by the sponsor. The safety review was performed by Dr. Blank. All safety data from CP-00001 and all other submitted clinical studies were included in the safety assessment. We relied heavily upon the CDRH review for assessments of the device and IFU, and human factor studies to help us evaluate the sponsor's position that post-CP-00001 modifications of the device and IFU have made the device reliable and that the product should be approved despite failure on the primary endpoint of Study CP-00001. We relied upon the Clinical Pharmacology Review for the analysis of the pharmacokinetic and pharmacodynamic study (Study SCP-01-002) that was done with another previously cleared device, the B. Braun infusor.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study CP-00001; Open Label Study to Evaluate Product Design Clinical Performance of a To-Be-Marketed Drug-Device Combination Product (sc2Wear ™ Furosemide Combination Product) in Subjects with Chronic Heart Failure

6.1.1. Study Design

Overview and Objective

Study Name and Number: Open Label Study to Evaluate Product Design Clinical Performance of a To-Be-Marketed Drug-Device Combination Product (sc2WearTM Furosemide Combination Product) in Subjects with Chronic Heart Failure (Study Number: CP-00001)

Purpose and Objectives: This study was an open label, single-dose, multicenter (all US) study to evaluate product design clinical performance of a to-be-marketed drug-device combination product (sc2Wear Furosemide Combination Product) in up to 70 adult male and female subjects previously diagnosed with mild to advanced heart failure, NYHA Class II-IV.

The objectives of the study were:

- To demonstrate that the Furoscix + Infusor combination product performs as intended and delivers 80 mg of furosemide subcutaneously in the abdominal area

- To assess safety and local tolerance of the drug-device combination product

Trial Design

Study Design: This was a multicenter (5 U.S. centers) single arm, open-label, single dose uncontrolled study designed to evaluate the product design and performance of the Furoscix infusor in ~70 male and female subjects with mild to advanced heart failure (NYHA Class II-IV). There was a 0-3-day screening period followed by a treatment phase.

Procedures and schedule:

1. Drug administration was either started on the day of enrollment or scheduled within 3 days of completion of Screening assessments. If the treatment visit did not occur within 3 days of the assessment, baseline assessments were performed prior to start of treatment on the treatment day. Screening assessments included physical examination, recording of vital signs, and recording of prescription and non-prescription medications.
2. Treatment Day observations commenced with preplacement assessments and continued through device removal. The treatment was begun by adhering the device to the study subject's abdomen using medical grade adhesive. Device preparation, placement, and removal were all performed by trained study staff. Device removal occurred within 3 hours of completion of drug delivery (8 hours of the start of administration). After device placement, the device was to perform a preprogrammed bi-phasic 5- hour subcutaneous drug administration. Of the total 80 mg dose of Furoscix, 30 mg was to be administered subcutaneously over the first hour followed by 12.5 mg/hour over the subsequent 4 hours.
3. Subjects returned 5-7 days after the Treatment Day for a post treatment follow-up and photography.
4. The following study assessments and procedures were performed:
    a. Assessment of Drug Delivery; Steady state plasma levels of furosemide during the plateau phase (1-5 hr) were to be assessed. Plasma samples were collected from all study participants and analyzed for furosemide concentrations using a validated LC-MS/MS bioanalytical method.
    b. Assessments of Product:
        i. Weight measurement of Vial and attached Adapter before and after filling the Cartridge (performed by study staff)
        ii. Evidence of complete proper device filling (photography of filled device, ready for placement)
        iii. Inspection for sharps prior to device placement and immediately after device removal
        iv. Needle insertion (subject-reported and recorded by staff)
        v. Inspection for obvious leakage

vi. Photography of device after delivery and removal (complete drug delivery)
vii. 5-point device dislodgment scale was used to assess device adherence
viii. Weight measurement of residual volumes by outside lab (b) (4) to calculate volume dispensed.
ix. Other device indications observed, outside of the normal use indications, including, but not limited to:
    1. Interruption of delivery during operation ((b) (4))
    2. Low battery alert during delivery

c. Assessments of Safety and Local Tolerability
    i. AEs and SAES, reported and observed
    ii. Local Skin Tolerance: using an 8-point skin irritation scale and photography
    iii. Subject reported pain on an 11- point numeric rating scale
    iv. Device placement photography
    v. Activity recording during wear
    vi. Subject Comfort of Wear Questionnaire

Reviewer's Comment*: *This device is designed for patients to use without assistance. Because trained study staff prepared, administered and removed the device, this protocol did not test patient performance. A more informative study design would be to require patients and care givers to prepare the device according to IFU and self-administer.

Enrollment Criteria:
Main inclusion criteria were that the patients were:

1. Adult men and women age 18 or more with NYHA Class II-IV heart failure.
2. On chronic oral diuretics and willing to suspend oral furosemide or other loop diuretic treatment on the day of treatment (use of oral diuretic within 8 hours of start of treatment was not permitted).
3. Willing to shave the area where the device would be placed prior to treatment
4. Had none of the following conditions: contraindications to furosemide, skin reactions to medical adhesives, hypokalemia (K < 3.6 mmol/L, systolic blood pressure < 90 mmHg, or pregnancy or lactation.

Study Endpoints

Primary Endpoint:
The primary endpoint was defined as the absence of major product failures and freedom from

major system-related failures leading to under-infusion (performance criteria of ≥ 95%). Major system-related failure leading to under-infusion was defined as:

1. Failure to dispense 80 mg ± 10% furosemide (calculated from fill volume and residual volume measurements), OR
2. A combination of:
    a. Obvious leakage (leakage that results in a noticeable area of wetness visible on Subjects' garment and/or any dripping of fluid from the device or on abdomen), AND
    b. Failure to achieve furosemide plasma levels > 250 ng/mL during plateau phase of delivery – 1-5 hours following activation as reported by analytical laboratory.

Secondary Endpoints:

1. Patient-reported pain (11-point numeric rating scale of 0 to 10)
    a. Pain upon needle insertion
    b. Maximum pain during use
    c. Pain upon removal (removing of adhesive from the skin)

2. Local Skin Tolerance
    a. Adhesive site skin inspection for erythema, edema and other local reactions including papular response and vesicular eruption.

3. Device Dislodgement Scoring
4. Comfort of Wear Questionnaire

Statistical Analysis Plan

The mITT population to be used for the primary analysis was all enrolled patients who received study product and completed the 5-hour infusion.

The primary endpoint was "success" if subjects did not have any of the critical failures described in the "Primary Endpoint" section above.

The null and alternative hypotheses were:

- H_0: $\pi <= 0.95$ vs. H_1: $\pi > 0.95$,

where π was the true success rate. It was to be tested according to the statistical plan using a one-sided, exact binomial test to compare the actual success rate to a target rate of 95%. If the lower 95% confidence interval for the actual success rate exceeded 0.95, then the null hypothesis would have been rejected.

There was to be no interim analysis and missing values were not to be imputed. The sponsor assumed a 15% withdrawal rate and thus planned to enroll 70 subjects to ensure a minimum of

59 subjects with evaluable drug delivery. Assuming a true success rate of 99.98% or greater, a sample size of 59 yielded at least 95% probability that they would have proven that the true success rate was > 95% using a one-sided 0.05 level of significance.

Of note, it was prespecified that participants who experienced the known Furoscix software defect in study CP-00001 were to be excluded from the sponsor's modified intent to treat (mITT) analysis.

Reviewer's Comment: If a subject had a major device failure from a leak and low serum levels of furosemide and had the infusion stopped prior to the 5 hours because of discomfort, the subject would have been excluded from the mITT. If the PDCV study is repeated, a major system failure from a leak should be included in the mITT regardless of whether the subject completes the 5-hour infusion.

Protocol Amendment

The original protocol was submitted on August 1, 2016. There was one protocol amendment submitted on August 29, 2016. Important changes were:

- Redefinition of "Ineffective Drug Delivery in primary endpoint" from "failure to adequately empty drug reservoir" to "failure to dispense 80 mg + 10% furosemide (calculated from fill volume and residual volume measurements).
- Added text to describe the method of determining volume measurements by weight
- Redefined "obvious leakage" to "leakage that results in noticeable area of wetness visible on subject's undershirt or other garment, and/or dripping of fluid from the device or rolling droplets on the subject's abdomen.

Reviewer's Comment: The changes in the one protocol amendment provided a specific definition and quantifiable measure for the endpoint of "ineffective drug delivery" and described the measurements required for the calculation. There amendment also included a more concrete definition of "obvious leakage". These changes to the protocol were intended to reduce ambiguity and improving interpretation of study results.

6.1.2. Study Results

Compliance with Good Clinical Practices

The studies were conducted in accordance with all applicable regulatory requirements including a U.S. IND. The studies were conducted in accordance with "good clinical practices" (GCP), all applicable subject privacy requirements, and the guiding principles of the Declaration of Helsinki including IRB/IEC review and approval to conduct the study.

Financial Disclosure

There were 80 investigators in the clinical development program of Furoscix. FDA Form 3454, "Certification: Financial interests and arrangements of clinical investigators" was submitted. It certifies that the sponsor has no financial arrangements with the listed clinical investigators whereby the value of compensation could be affected by the outcome of the study. It also certifies that the listed clinical investigators were required to disclose to the sponsor whether they had a proprietary interest in the product or a significant equity in the sponsor and that none disclosed such interests. It also certifies that the no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). All investigators who participated were included on the list. The form was signed by the sponsor.

Patient Disposition

Study CP-00001 had the following three subject populations:

- Intent-to-Treat (ITT): All enrolled subjects
- Safety Population: All enrolled subjects who initiated treatment.
- Modified Intent-to-Treat (mITT): All subjects who completed the full 5-hour test treatment.

Efficacy analyses were performed on the mITT population. All subjects who were enrolled completed the study.

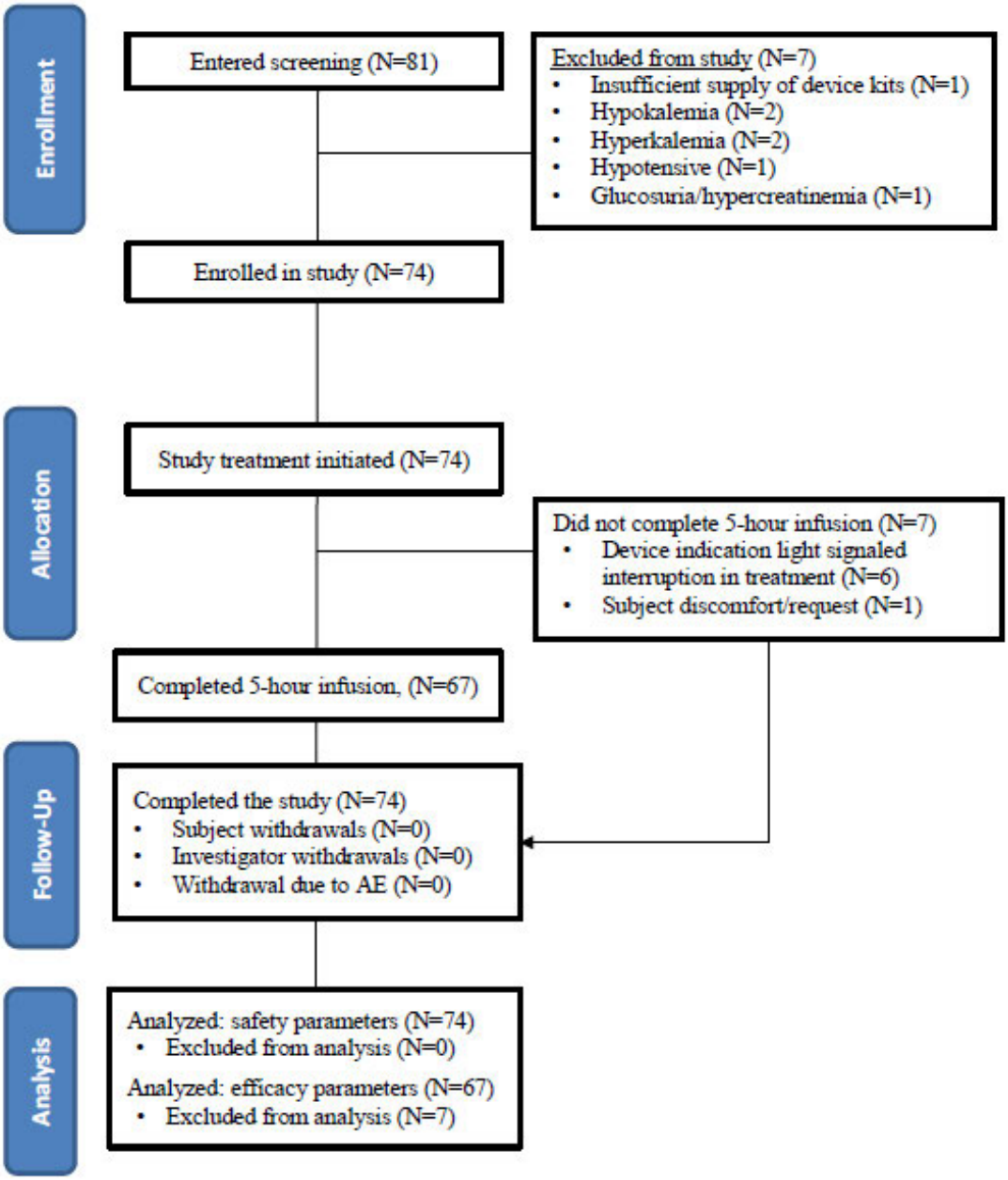
Of the 81 patients who were screened, 7 were excluded at screening. There were 7 subjects who did not complete the full 5-hour infusion because of a known software defect and were excluded from the primary efficacy analysis as prespecified in the protocol; 6 subjects did not complete the 5-hour infusion because the device indication light signaled interruption in treatment (known software defect in five subjects and cartridge/ activator disconnection in one subject), and 1 subject requested to stop treatment because of discomfort a few minutes prior to completion. Sixty-seven subjects completed the study and were included in the mITT population and in the primary and secondary analyses. No subjects discontinued. See Table 3. A pictorial representation of the reasons for exclusion from the study and exclusion from the mITT population is provided in Figure 1.

Table 3: Disposition

Disposition	N
Screened	81
ITT	74
MITT	67
Completed Study	74
Discontinued	0

[Source: CSR Table 10.1]

Figure 1: Disposition



Source: CSR (Study CP-00001) p. 32.

Protocol Violations/Deviations

A tabular listing of protocol deviations is provided in Table 4. Most of the protocol deviations pertain to premature stoppage of infusion. The sponsor states that the alarm defect was anticipated prior to trial initiation and was expected to occur in (b) (4) of the infusions because of

known software defects. The size of the trial was based on this understanding and subjects could be replaced for these types of failures as needed. A total of 6 (of 74 total devices) delivery interruptions due to self-reporting alarms were observed corresponding to 8.1%; 5 alarms were due to known software defects (6.8%) and 1 alarm was due to disconnection of the Cartridge from the Activator (1.4%). As prespecified in the protocol, failures due to known software defects were excluded from the mITT and the primary endpoint analysis. And any hardware malfunction (such as the disconnection between the Cartiridge from the Activator) was also excluded from the mITT if it occurred within the 5-hour delivery window.

Table 4: Protocol Deviations

Deviation Details	Numbers of Subjects Affected	Comments
Mislabeled photographs	6	Most of these errors were corrected.
Missed photographs	3	
Missed follow-up visit (or delayed)	4	
Infusion stopped prior to 5 hr for pain	1	Subject not treated per protocol
Infusion stopped prior to 5 hr because of either device alarm and light blinking or another malfunction	6	Two of these considered not treated per protocol (b) (6) (b) (6)
Lab sample not acquired	2	
PK assessment not completed	2	
Discovered that subject should not have met eligibility criteria	1	Had hepatitis C
Portion of the tape became dislodged	1	Subject began to sweat because abdominal band was placed so that subject could go to work. Device remained attached.

Reviewer's Comments:

The large number of protocol deviations due to device alarms and known software defects cause concern regarding how the device would function in the real-world setting. The CDRH review states the following regarding the post CP-00001 study device modifications: "Due to the deficient reports, the evidence does not support that acceptable mitigations have been implemented and verified to support the top-level

goal of safety".
If the trial had succeeded on its primary endpoint, the one subject (b) (6) ***whose infusion was stopped prior to the 5-hr mark for "pain" thus excluding him from the mITT, would have raised a red flag regarding study conduct. After having an active day and completing 4.75 hours of the infusion subject*** (b) (6) ***complained of pain like someone was pulling a hair under the device. With only a few minutes left of the infusion, the subject insisted on device removal. It is unknown if subject*** (b) (6) ***would have met criteria for study failure had he completed because information on volume remaining in this subject's cartridge at end of study was not included in the study report or datasets (presumably because he was not included in the mITT). Similarly, the subject*** (b) (6) ***who had the cartridge-activator disconnection could reasonably be considered to have had a device failure. Some might argue this subject should have been included in the mITT.***

Table of Demographic Characteristics

The demographics of study CP-00001 are provided in Table 5. The study subjects were entirely NYHA class II and III, despite the inclusion criteria that aimed to enroll patients with NYHA class II-IV. There was acceptable age and gender distribution. Regarding race, there were equal numbers of African Americans or Blacks and Whites but underrepresentation of other races and Hispanics. Most subjects were obese. Unfortunately, obesity is a common condition in the US population (> 30% of adults) and it is a risk factor for heart failure.

Table 5: Demographic and Clinical Characteristics

Demographic Parameters	Treatment	
	ITT (N= 74) n (%)	mITT (N=67) n (%)
Sex		
Male	**47(63.5)**	**42(62.7)**
Female	**27 (36.5)**	**25 (37.3)**
Age		
Mean years (SD)	**61.8 (12.2)**	**61.3 (12.3)**
Median years (min, max)	**61 (32, 85)**	**61 (32, 85)**
Age Group		
< 17 years	**0**	**0**
≥ 17 - < 65 years	**43 (58.1)**	**39 (58.2)**
≥ 65 years	**31 (41.9)**	**28 (41.8)**
> 65 - < 75 years	**17 (23.0)**	**16 (23.9)**
≥ 75 years	**14 (18.9)**	**12 (17.9)**
Body Mass Index (kg/m2)		
Mean (SD)	**35.7 (8.5)**	**35.6 (8.4)**
Median (Min, Max)	**33.7 (19.1, 56.6)**	**33.8 (19.1, 55.9)**
Category ≤ 30	**17 (23)**	**16 (23.9)**
Category > 30	**57 (77)**	**51 (76.1)**
NYHA Association		
NYHA Class I	**0**	**0**
NYHA Class II	**59 (79.7)**	**54 (80.6)**
NYHA Class III	**14 (20.3)**	**13 (19.4)**
NYHA Class IV	**0**	**0**
Race		
White	**37 (50)**	**33 (49.3)**
Black or African American	**35 (47.3)**	**32 (47.8)**
Asian	**1 (1.4)**	**1 (1.5)**
American Indian or Alaska Native	**0**	**0**
Native Hawaiian or other Pacific Islander	**1 (1.4)**	**1 (1.5)**
Other[1]	**0**	**0**
Ethnicity		
Hispanic or Latino	**2 (2.7)**	**2 (3.0)**
Not Hispanic or Latino	**72 (97.3)**	**65 (97)**
Region		
United States	**74 (100)**	**67 (100)**

Reviewer's Comments: ***The few Hispanics, Native Americans and Asians enrolled created little cause for concern because the LD, furosemide, has been used successfully in these populations for decades and there is no reasonable concern that they would have unique efficacy or safety issues with the new formulation or device.***

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The comorbid medical conditions and the concomitant medications, listed in Table 6 and Table 7 are congruent with the to-be-marketed US population. Common cardiovascular conditions for the enrolled subjects were as expected; hypertension (~90%), hyperlipidemia (~74%), valvular conditions (73%) and arrhythmia (~70%).

Table 6: Comorbid Medical Conditions

Condition	n/N (%)
Hypertension	67/74 (90.5)
Hyperlipidemia	55/74 (74.3)
Valvular Dysfunction	54/74 (73.0)
Arrhythmia	52/74 (70.3)
Previous PCI	21/72 (29.2)
Previous MI	27/73 (37.0)
Previous Stroke	11/72 (15.3)
Diabetes mellitus	43/74 (58.1)

Note: where characteristic is "unknown", subject is excluded from denominator

Source: CP-00001 study report, p. 34.

Table 7: Concomitant Medications

Medication	n/N (%)
ACE Inhibitors or ARBs	62/74 (83.8)
Mineralocorticoid Receptor Antagonists	36/74 (48.6)
Beta-Blockers	68/74 (91.9)
Calcium Channel Blockers	10/74 (13.5)
Digoxin	10/74 (13.5)
Loop Diuretic	73/74 (98.6)
Thiazide or thiazide like Diuretic	10/74 (13.5)
Lipid Lowering Agent	48/74 (64.9)
Aspirin	43/74 (58.1)
Warfarin	17/74 (23.0)
Novel Anti-Thrombotic Therapy (Anti-Platelet etc.)	26/74 (35.1)

Source: CP-00001 study report, p. 34.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Preparation, fill and placement of the drug-device combination was done in accordance with the study specific instructions which are based on the sc2Wear Furosemide Pump Instructions for Use as they existed at the time of the study.

All device handling, including activation and device removal, was done by study personnel.

Information regarding preparation, fill, placement, activation, and removal were recorded. This was a single dose study. All subjects were followed for full length of study and completed all study assessments.

> ***Reviewer's Comment:*** ***Because this was a single dose study where the device-drug combination product was administered by study staff with little requirement from the subjects except to return for the follow-up visit, compliance was not an issue.***

Efficacy Results – Primary Endpoint

According to the Sponsor, 63 of 67, or 94 (b) (4)% (95% CI: 85 (b) (4)%, 98 (b) (4)%) of sc2Wear Furosemide Combination Products were free from major system-related failure. There were 4 cases in which drug delivery fell below the predefined criterion of 80 mg ± 10% furosemide. Because the H_0 and H_1 are one-sided hypotheses, the 95% confidence interval is also presented in Table 8 as a one-sided interval with the upper limit of (b) (4). Also, because one subject's cartridge was disconnected from the adaptor during the study and one subject required the infuser to be removed near completion of infusion, the clinical and statistical reviewers decided to treat either one or both as failures in "exploratory results" 1 or 2. Per protocol, these two subjects were eliminated from the mITT. Including them as failures (which would have required a redefinition of device failure to include non-completion of infusion because of a non-software mediated failure or because of reasons of intolerability) requires that the denominator be increased accordingly.

Table 8: Efficacy Analysis and Exploratory analyses – Primary endpoint (mITT)

Absence of Failures	n/N (%)	95% CI	P-value	Comment
CSR results	63/67 (94.03%)	(b) (4)		Sponsor's Results
Reviewer's results	63/67 (94.03%)			One-sided 95% CI
Exploratory result 1	62/68 (92.6%)			One additional failure
Exploratory result 2	61/69 (91.3%)			Two additional failures

Source: Statistical Reviewer's Results

Of the 4 devices with reported drug delivery less than 80 mg (10 mL) ± 10% furosemide, 3 were due to filling errors and 1 was due to dispensing failure. In an exploratory analysis conducted by the sponsor looking at success only in devices that were filled adequately, 63/64 (95% CI: (b) (4) (b) (4)) of the devices delivered the pre-specified dose. This result still falls disappointingly below the prespecified criteria for success.

The sponsor acknowledged that the average plateau furosemide level in the 4 subjects with delivery errors was less than the average achieved in the PK/PD study, scP-01-002, but emphasized that the levels were well above what was prespecified as a device failure if there had also been concomitant leakage (250 ng/mL). The clinical reviewer believes that the absence of subtherapeutic drug levels is not particularly reassuring because it is likely that in practice, more serious filling errors could occur resulting in lower furosemide levels. Furthermore, the plateaus in study CP-00001 were assessed with only one PK measurement. Because AUCs were not calculable, and the PD effects were not collected, it is not clear that the 4 subjects who had major device failures received therapeutic doses of furosemide.

See table below for subject level data for the subjects who had device failures and summary data on subjects in the mITT populations of CP-00001 and the pivotal PK Study (scP-01-002). This was a post-hoc analysis.

Table 9: Subject Level Data: Inadequate Volume Dispensed [mITT Population]

Subject	Plasma Furosemide Concentration (ng/dl)	Fill Volume (ml)	Residual Volume (ml)	Volume Dispensed (ml)*	Reason Inadequate Volume Dispensed
(b) (6)	1027[1]			(b) (4)	Fill Error (under-filled)
	763[2]				Fill Error (under-filled)
	1495				Dispense Failure
	1993				Fill Error (use-error)
Inadequate Volume Dispensed Mean (N=4)	**1319**				
PDCV (CP-00001) mITT Population Mean	**2160** (N=66)	(N=67)	(N=67)	(N=67)	
Pivotal PK Study (scP-01-002) Mean	**1780** (N=16)				

(b) (4)

(b) (4)

Source: p. 37 of the CP-00001 study report

During execution of study CP-00001 it is notable that 6/80 (7.5%) Cartridge components (4 users) and 1/75 Activator (1.3%) components failed to complete appropriate filling and were detected by the user prior to proceeding with the procedure. Because users could identify the filling error prior to initiation of infusion, the devices were replaced (following the study protocol) with new components. (b) (4)

(b) (4)

(b) (4) This means that 5/67 (7%) completers had to have their device preparation restarted by trained study staff because of detected errors. Again, these events provide further evidence that the design of the Furoscix Infusor is flawed.

Data Quality and Integrity

There are no data quality and integrity issues.

Efficacy Results – Secondary and other relevant endpoints

Prespecified secondary endpoints that pertain to comfort of wear, pain, skin irritation and device dislodgement and tolerability are presented in the Safety section 8.5.1.

Dose/Dose Response

Furoscix has inflexible dosing. There is only one dose choice: 80 mg. This 80 mg dose is customary for IV furosemide making it an appropriate choice. While there is relatively low intra-patient variability in dose response, there is wide inter-patient variability depending on renal function and other factors. Patients requiring higher doses could be prescribed more than one dose to be taken in one day. Dose and dose response is addressed in greater detail in the Clinical Pharmacology review.

Durability of Response

N/A.

Persistence of Effect

N/A.

Additional Analyses Conducted on the Individual Trial

N/A.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

N/A.

7.1.2. Secondary and Other Endpoints

N/A.

7.1.3. Subpopulations

N/A.

7.1.4. Dose and Dose-Response

N/A.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

N/A.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The CP-00001 study did not test the device fairly. Patients were not responsible for self-administration in the study and so it is not clear how high the failure rate would be in patients with heart failure in the post-marketing setting.

7.2.2. Other Relevant Benefits

A simpler to use, reliable device with alarms to alert patients when device filling and drug delivery was inadequate would be a benefit to edematous patients who are unresponsive to oral diuretics because if might allow them to avoid hospitalization.

7.3. Integrated Assessment of Effectiveness

A Clinical Pharmacology Study (scP-01-002) performed in stable heart failure patients was conducted to demonstrate biosimilarity between the pH neutral furosemide formulation, SCP-101 and the LD, IV furosemide (Hospira, NDA 18667). In study scP-01-002, SCP-101, using a different device than the to-be-marketed device (the B. Braun Perfusor® Pump, CDRH cleared for subcutaneous infusion) produced equivalent areas under the curve (AUCs) and pharmacodynamic (PD) effects (sodium excretion and urine volume) to the RLD administered intravenously. The study indicated that the extent of systemic furosemide exposure is comparable between SCP-101 administered as subcutaneous infusion to the LD administered as an IV injection. However, the Cmax was lower and took longer to achieve for subcutaneous SCP-101 compared to IV furosemide. Compared to IV furosemide, the time to onset of diuresis was longer for the subcutaneous SCP-101. However, the pharmacodynamic effect on urinary volume and sodium excretion was the same when measured at the end of the 24-hour study period. This study showed that if the sc2Wear Furoscix Infusor could deliver SCP-101 reliably, it would produce similar PD effects to IV furosemide, except for rapidity of effect which would lag by ~1-2 hours. Therefore, in nonemergency clinical situations where patients require IV diuretics, an 80-mg subcutaneous infusion of SCP-101 would produce a diuresis equivalent to an equivalent IV dose of the RLD after 24 hours.

The Product Design Clinical Validation Study (CP-00001) was the pivotal clinical trial designed to demonstrate the reliability of the sc2Wear Furoscix Infusor and was the

bridging study for the drug/device product. According to prespecified performance criteria, the sc2Wear Furoscix Infusor did not reliably deliver SCP-101. There were 4/67 major system-related failures leading to under-infusion of SCP-101. Because of these failures, the primary endpoint of the study was not met (meeting predefined performance acceptance criteria in ≥ 95% of completed infusions with the lower bound of the 95% confidence interval for the actual success > 95%). A major system-related failure was defined as failure to dispense 80 mg ± 10% furosemide (calculated from fill volume and residual volume measurements despite completing the full 5-hour infusion or a combination of obvious leakage AND failure to achieve furosemide plasma levels > 250 ng/mL during the plateau phase of delivery). Three of the 4 failures occurred because of dispensing failures related to inadequate preparation of the device and device design flaws (b) (4) (b) (4). The other dispensing failure resulted from (b) (4) (b) (4) (b) (4). The devices were prepared, applied and removed at end of the 5 -hour treatment by trained study staff. Because heart failure patients and lay caregivers will be responsible for the preparation, attachment and removal of the device in the post-marketing setting, the results from study CP-00001 should be considered a best-case scenario. Analyzing the results from a positive perspective, the success rate was 94% (b) (4) (b) (4). Therefore, under ideal conditions, the device probably would work reliably on average ~94% of the time. (b) (4) (b) (4)

To fairly analyze the efficacy results of study CP-00001, one must consider that the failure rate seen in the study is most likely lower than what it would be in the post-marketing setting. Because patients with edema from heart failure, (b) (4) are often elderly and infirm and may suffer from decreased eyesight, coordination and/or intellectual function, they may not be able to effectively follow the IFU and the device failure rate would be expected to be considerably higher than in an ideal clinical study setting where trained study staff members are administering the treatment. Furthermore, there will be lag times between the time when patients first receive instruction on use of the Infusor, possibly by a nurse in the doctor's office and the time when they need to self-administer, making risk for failure even higher. It is not possible to know what the failure rate would be if patients had self-administered the Furoscix Infusor in study CP-00001, thus leading to uncertainty about the true major system-related device failure rate.

Validation studies of the revised IFU and reengineered device following failed study CP-00001 have not been satisfactorily conducted according to the CDRH review, thus failing to ensure that the Furoscix infusor would deliver acceptable doses of drug to patients for whom it would be prescribed. Furthermore, the device flaws (b) (4) (b) (4) were not addressed by the sponsor.

8. Review of Safety

8.1. Safety Review Approach

The safety profile of IV furosemide is well documented and characterized. Systemic side effects would be expected to be the same for SCP-101 (furosemide) or less as for furosemide because of similar AUCs (because of the similar AUC and lower Cmax). For instance, ototoxicity of IV loop diurectics is thought to be related to the high Cmax.

Common adverse effects of parenteral diuresis are electrolyte imbalances, metabolic alkalosis, worsening renal function, hyperuricemia, gout, arrhythmia, volume depletion, dry mouth, tachycardia, alterations in blood glucose and glucose tolerance tests, and dizziness.

The delayed and lower Cmax observed for Furoscix is not a safety concern. The only safety concerns relate to skin irritation and that was the focus of this safety review. All studies were reviewed for safety.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Overall Extent of Exposure
Across all of the Sponsor-conducted studies [the pivotal Product Design Clinical Validation Study (CP-00001), the pilot clinical validation study (CP-00002), the pilot sc2Wear study with saline infusion (CP-00003), skin adhesive study (scP-00-002), the pilot PKPD study (scP-01-001), and the pivotal PK/PD study (scP-01-002)], 166 subjects were exposed to the Infusor, 26 subjects were exposed to a commercial pump, and 127 subjects were exposed to the SCP-101 furosemide formulation (all with stable heart failure). A total of 101 subjects were exposed to SCP-101 administered subcutaneously via the Furoscix Infusor (in the pilot and pivotal Clinical Validation studies). All studies used only single infusions of SCP-101. Only in the pivotal PK/PD

study (scP-01-002) did subjects get crossed over between two parenteral furosemide formulations (the LD given IV and the Furoscix Infusor). See table below for a tabular listing of exposure.

Table 10: Exposure to Device and Drug by Study

Study Number	Subjects who used the Infusor	Subjects who received SCP-101 via a Commercial Pump	Subjects who used SCP-101 furosemide formulation
CP-00001[a]	74	0	74
CP-00002 [a]	27	0	27
CP-00003	21	0	0
scP-00-002[b]	44	0	0
scP-01-001 [a]	0	10	10
scP-01-002 [a]	0	16	16
Total	**166**	**26**	**127**

[a]Study included patients with heart failure.
[b]Subjects in Study scP-00-002 were only exposed to a mock replica of the Infusor for the purposes of investigating various skin adhesives. No needle insertions were made, and the device was not used for infusion.

8.2.2. Relevant characteristics of the safety population:

The safety population was mostly heart failure patients NYHA II-III. The difference between the safety population in this development program and the intended use population is that the intended use population will be less well compensated from a congestive heart failure perspective because they will be unresponsive to their usual oral furosemide dose. The skin-related safety profile of the intended use population can reasonably be extrapolated from the better compensated heart failure population.

8.2.3. Adequacy of the safety database:

The safety database was adequate to assess skin adverse effects.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The submission quality, data quality and integrity were adequate for review.

8.3.2. Categorization of Adverse Events

The sponsor's approach to collecting, categorizing and documenting AEs was appropriate. MedDRA version and definition of TEAE are provided in the appropriate sections below.

The only AEs that could reasonably be linked to the combination product were skin related.

The sc2Wear Furosemide Combination Product was not associated with any overt safety issues as evidenced by there being no severe AEs, and only one unrelated SAE.

8.4. Safety Results

8.4.1. Deaths

There were no deaths in any of the studies.

8.4.2. Serious Adverse Events

There was one SAE – (ventricular tachycardia). The subject was a 67-year-old female with history of ischemic cardiomyopathy, chronic kidney disease and COPD. 4 days after administration of investigational product, the subject felt a sudden onset of lightheadedness followed by approximately 2 seconds of loss of consciousness before her AICD fired and she awoke. She was brought to the hospital by EMS. Her device was interrogated, and it showed true ventricular tachycardia (VT) that was not eliminated by device pacing. Of note, the subject had prior incidents of VT (b) (6). A right and left heart catheterization was performed following this event which showed stable non-obstructive coronary artery disease with patent stents. The subject had no further episodes of VT throughout her hospital stay. She was discharged to home in stable condition with recommendations to schedule an outpatient ablation procedure.

The investigator assessed the event as unrelated to investigational product or procedures and "definitely related" to the subject's underlying disease. The sponsor agreed with this assessment. The clinical reviewer thinks the assessment is reasonable but thinks that a systemic furosemide effect may have been a contributory factor (volume loss, electrolyte abnormality).

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no dropouts or discontinuations.

8.4.4. Significant Adverse Events

There were no significant adverse events that could reasonably be linked to the Furoscix Infusor.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

MedDRA version 19 was used for adverse event reporting. All AEs that occurred in the safety population, defined as having received at least a partial dose of drug, were recorded in the CRF. Any AE was considered a TEAE which is appropriate for the short follow-up duration of the trials. See section 8.5.1 for the skin safety findings. No AEs aside from skin AEs occurred in more than one patient. For this reason, non-skin-related non-serious AEs will not be discussed further in this review.

8.4.6. Laboratory Findings

Laboratory abnormalities were expected given the patients' underlying cardiac condition.

In the randomized, crossover PK/PD bridging study (Study scP-01-002), during subcutaneous administration of Furosemide Injection (SCP-101), there were no safety signals detected in laboratory tests. However, there were 3 laboratory AEs occurring in two subjects during the washout or follow-up period (i.e., BNP, CK and troponin). Only one of the three lab tests (CK) was unresolved at the end of the trial. Despite multiple attempts to contact the patient to return, the patient was lost to follow-up.

In the PDCV pivotal study (CP-00001) and PDCV pilot study (CP-00002), laboratory assessments were only performed at screening.

8.4.7. Vital Signs

There were no pertinent vital sign aberrations.

8.4.8. Electrocardiograms (ECGs)

There were no pertinent ECG changes during the studies.

8.4.9. QT

N/A.

8.4.10. Immunogenicity

N/A.

8.5. Analysis of Submission-Specific Safety Issues

The only submission specific safety concern was skin toxicity because of the subcutaneous route of delivery. See section 8.5.1.

8.5.1. Tolerability and Adverse Skin Reactions

Secondary safety endpoints that pertain to comfort, pain, skin irritation and device dislodgement are presented in this section, followed by a review of the reported adverse events that pertain to skin reactions. It is notable that the results of the instruments that were used to assess comfort, pain, skin irritation and device dislodgement may have been susceptible to bias because of the unblinded nature of the study. The photographs which were included in the submission for review corroborated the findings, making the results of these symptom/ sign inventories believable.

As shown in Table 11, most subjects experienced little to no pain (0-3). A few subjects had moderate pain (4-7) and no subjects experienced severe to "worst pain imaginable" (8-10). In Table 12, skin irritation scores are presented. All subjects had either no evidence of irritation or minimal erythema. The Comfort-of-Wear questionnaire results (obtained within one hour of removal of device) are presented in Figure 2. Most subjects experienced no difficulties performing ADLs but some subjects had great difficulties. If the device were to be approved, there would be some subjects who would find the limitations to activity unacceptable, but this would be a small minority. There were 3 cases of device dislodgement (shown in Table 13), but these partial dislodgements did not interfere with drug delivery. The adhesive seems adequate for the proposed use.

Table 11: Pain Assessments (mITT population)

	Needle Insertion	Upon Removal	Maximum Pain during Wearing
0 (no pain)	29/67 (43.3%)	55/67 (82.1%)	43/67 (64.2%)
1	21/67 (31.3%)	8/67 (11.9%)	11/67 (16.4%)
2	11/67 (16.4%)*	3/67 (4.5%))*	4/67 (6.0%)*
3	3/67 (4.5%)	1/67 (1.5%)	6/67 (9.0%)
4	1/67 (1.5%)	0	2/67 (3.0%)
5	1/67 (1.5%)	0	1/67 (1.5%)
6	0	0	0
7	1/67 (1.5%)	0	0
8	0	0	0
9	0	0	0
10 (Worst pain imaginable)	0	0	0
Mean (Min, Max)	1.0 (0,7)	0.3 (0,3)	0.7 (0,5)

* Subject (b) (6) who asked for device to be removed stated that maximum pain was 2 at each phase

Source: CP-00001 study report, p. 47.

Table 12: Skin Irritation Scores (mITT population)

	Pre-placement	Upon Removal	1-hour post-removal	5-7 days post-removal
0-no evidence of irritation	65/67 (97%)	45/67 (67.2%)	54/67 (80.6%)	63/67 (94%)
1-minimal erythema	2/67 (3%)	16/67 (23.9%)	9/67 (13.4%)	3/67 (4.5%)
2- erythema or minimal edema or minimal papules	0	0	0	0
3-erythema and papules	0	0	0	0
4- def. edema	0	0	0	0
5- edema, erythema and papules	0	0	0	0
6- vesicles/ulcers	0	0	0	0
7- spreading reaction	0	0	0	0
Mean scores (min/max)	0.03 (0, 1)	0.42 (0, 2)	0.25 (0, 2)	0.07 (0, 2)

Source: CP-00001 study report, p. 47-48.

Figure 2: Comfort-of-Wear Questionnaire (mITT population)

A. OVERALL COMFORT WEARING DEVICE

	Very Comfortable	Moderately Comfortable	Slightly Comfortable	Neither Comfortable/ Uncomfortable	Slightly Uncomfortable	Moderately Uncomfortable	Very Uncomfortable
Comfort wearing the device	48%	34%	6%	3%	5%	2%	3%

B. COMFORT UPON DEVICE REMOVAL

	No Discomfort	Mild Discomfort	Moderate Discomfort	Severe Discomfort
Comfort upon device removal	91%	9%	0%	0%

C. RESTRICTIVENESS DURING ACTIVITES

	Did Not Interfere	2	3	4	5	6	7	8	9	Completely Interfered	*N/A Did Not Do or Try*
Walking	93%	5%	0%	0%	0%	0%	0%	0%	0%	2%	*2%*
Standing	93%	2%	3%	0%	0%	0%	0%	0%	0%	2%	*2%*
Sitting while reading/watching TV	88%	8%	2%	0%	0%	0%	0%	0%	0%	2%	*2%*
Lying down/napping	48%	3%	0%	0%	3%	0%	0%	0%	0%	2%	*45%*
Using the bathroom	90%	6%	3%	0%	0%	0%	0%	0%	0%	2%	*0%*
Driving or riding in a car	36%	0%	0%	0%	0%	0%	0%	2%	0%	2%	*61%*

A. Responses based on question: "Please rate how comfortable or uncomfortable you felt wearing the device today. Select the appropriate number." (N=67).
B. Responses based on question "Please rate any discomfort you may have felt when the device was removed today. Select the appropriate number." (N=67).
C. Responses based on question: Please indicate if wearing the device interfered with your activities of daily living. For each activity listed below, please enter NA if you did not do/try the activity; or enter a number on a scale of 1 to 10 (with 1 = Not at All and 10 = Completely), to indicate if wearing the device interfered with the activity." (N=67).

Source: P. 53 of the CP-00001 study report.

Table 13: Device Dislodgement (mITT population)

Time Point	Extent of Device Dislodgment	Treatment (N=67)
Placement (Hour 0)	0 - Essentially no lift off the skin	67/67 (100.0%)
	1 - Some edges only lifting off the skin	0
	2 - Less than half of the patch lifting off the skin	0
	3 - More than half of patch lifting off the skin without falling off	0
	4 - Patch completely off the skin	0
Post-Delivery (Hour 5-8)	0 - Essentially no lift off the skin	64/67 (95.5%)
	1 - Some edges only lifting off the skin	2/67 (3.0%)
	2 - Less than half of the patch lifting off the skin	1/67 (1.5%)
	3 - More than half of patch lifting off the skin without falling off	0
	4 - Patch completely off the skin	0

Source: Table 14.3.7.1 Device Dislodgement

Source: p. 55-56 of the CP-00001 study report.

There were two other trials that had relevant prespecified clinical assessments of the tolerability of SCP-101 (with or without the Furoscix Infusor). Study CP-00002, was the pilot study for the pivotal clinical PDCV study. It was not an efficacy study but evaluated the suitability of methods and procedures for the tolerability assessments that would be used in the pivotal clinical study. It was conducted in 24 heart failure patients (NYHA Class II-IV) using the Furoscix Infusor with SCP-101. The results of the pain and skin irritation assessments and the Comfort-of-Wear questionnaire were similar to the results shown in the PDCV Study (Study CP-00001). The scP-01-002 PK study (using the B. Braun infusor) also showed similar results on the skin irritation assessment.

Pain, skin irritation, erythema and edema were absent or minimal problems for most patients in all clinical studies. Comfort-of-Wear questionnaire results showed acceptable results or most subject fin Study CP-00001, pilot study CP-00002, and Study scP-01-002.

The skin assessments included photographs. The clinical reviewer's assessment of the photographs done at baseline, immediately after placement, one hour post-removal and one week later was that all skin reactions were minimal to mild and most were absent by follow-up. There were no incongruities between the skin AE description and the photographs. The safety assessments were also congruent with the secondary analyses (described in section 6.1.2) which showed no significant skin irritation or pain in the large majority of subjects. Because of the variability among studies in skin AEs, instead of combining the results, study safety results

are presented individually below. The most common skin AEs were stinging/ burning (12.1 - 40%; probably not captured in PK studies), application site erythema (25-50%), application site bruising (0-14.9%) and edema (4-43.8%).

The skin reactions were related to the use and removal of the adhesive and the physical effects of infusion. The sponsor states that they are unrelated to pharmacological or possible toxicological effects of the drug formulation. The clinical reviewer maintains that the clinical skin effects may have been secondary to toxicity from subcutaneously administered furosemide – but the toxicity if it is responsible for some the pain, erythema and bruising is mostly mild and therefore of limited concern.

Most notably, bruising was minor and was unrelated to the use of anti-platelet or anticoagulant medications. AEs that were probably unrelated to the combination product were back pain, cardioverter implant infection, skin laceration (at a remote site from the device), non-cardiac chest pain, ventricular tachycardia and vomiting.

In the paragraphs below, the rate of skin reactions is captured from my own analyses of the AE data sets for each of the individual studies in which SCP-101 was administered subcutaneously.

Study CP-00001 (PDCV study) N=74
21 (28.4%) application site erythema
11 (14.9%) application site bruising
3 (4.2%) had edema at site of the device (2 without erythema or bruising, 1 with bruising).
9 (12.1%) had pain or burning at the site of injection;
1 (1.4%) had application site scab at the follow-up visit.

Study CP-00002 (PDCV pilot study) N=24
1 (4.2%) erythema and papules upon removal
6 (25%) minimal erythema
3 (12.5%) minimal erythema with minimal edema or minimal papules.
2 (12.5%) bruising

By 5-7 days post-removal, all skin irritation was resolved.

Study SCP-01001 (PK pilot study) N=10
1 (10) bruise at injection site
4 (40) stinging at injection site
1 (10) red discharge at injection site

Study scP-01002 (PK- bridging study, N=16)

	Furosemide (SCP-101) SQ n/N (%) N=16	Furosemide (RLD) IV
Application site erythema	8/16 (50)	1/16 (6.3)
Application site edema	7/16 (43.8)*	0/16 (0)

*All edema was "very slight edema" on the Draize edema scale.

8.6. Safety Analyses by Demographic Subgroups

With such small studies and few AEs, it was not appropriate to do demographic subgroup analyses. Of note, a subgroup analysis of subjects who had bruising showed that concomitant treatment with anticoagulants had no effect on risk of bruising.

8.7. Specific Safety Studies/Clinical Trials

N/A.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

N/A.

8.8.2. Human Reproduction and Pregnancy

N/A.

8.8.3. Pediatrics and Assessment of Effects on Growth

Similar PK/PD relationships in children provide evidence of extrapolatable efficacy for children who are large enough to accommodate the device on their abdomens and weigh enough so that the dose of 80 mg is appropriate (42.5 kg and above).[5] (b) (4)

(b) (4)

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

[5] van der Vorst MM, den Hartigh J, Wildschut E, Tibboel D, Burggraaf J. An exploratory study with an adaptive continuous intravenous furosemide regimen in neonates treated with extracorporeal membrane oxygenation. Crit Care. 2007;11(5):R111.

The device design (single use cartridge/ vial adapter), IFU and package warnings make it unlikely that the device would be used for other drug use (the only concern vis-à-vis drug abuse potential). Overdose, withdrawal and rebound are not concerns with furosemide.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

N/A.

8.9.2. Expectations on Safety in the Postmarket Setting

The safety and tolerability of the Furoscix Infusor is adequate. The concern about the product is about its efficacy. Without an efficacious product, there is concern that patients who require parenteral diuretics might not receive them and this could result in poor health outcomes.

8.9.3. Additional Safety Issues From Other Disciplines

See CDRH review for a more complete assessment of device safety.

8.10. Integrated Assessment of Safety

The 2 looming safety concerns are described in section 8.9.2; namely, there is uncertainty about whether patients and their caregivers can safely and effectively administer Furoscix with the currently labeled instructions and there is concern that patients may think they have received the full dose when they haven't ((b) (4) thus leading to delay in treatment and the potential for developing an acute exacerbation of their underlying condition. (b) (4) . The clinical reviewer thinks that it is quite possible that most patients will not be able to readily determine if they are having an appropriate diuresis. One can imagine a scenario where a heart failure patient is prescribed 3-5 days of the Furoscix Infusor for worsening edema with instructions to return to the office after the course of treatment. If this patient is unaware of device failure, he/she could worsen and develop acute decompensated heart failure. Heart failure patients are a particularly vulnerable population and have an increased risk of death for months after each hospitalization. A reliable device that could signal major system failures would be necessary to feel confident about safety. Furthermore, a repeat of study CP-00001 in which patients self-administer using the "to be marketed" IFU would be necessary to ensure that patients can self-administer this product safely and effectively.

Aside from these large safety concerns which can only be resolved with device reengineering and another clinical study, the only other significant safety findings were mild skin irritation,

bruising, erythema and edema.

9. Advisory Committee Meeting and Other External Consultations

N/A.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

N/A.

10.2. Nonprescription Drug Labeling

N/A.

11. Risk Evaluation and Mitigation Strategies (REMS)

The Sponsor has not proposed a REMS. Were this combination product approved after a determination that it was safe and effective; institution of a REMS would not enhance safety and would be unnecessarily burdensome. Labeling of limitations of use and instructions for use would be sufficient to ensure safe use.

12. Postmarketing Requirements and Commitments

N/A.

13. Appendices

13.1. References

See footnotes.

13.2. Financial Disclosure

APPEARS THIS WAY ON ORIGINAL

Covered Clinical Studies: All clinical studies included in this NDA are included in the financial disclosure table.

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 80		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3 APPENDIX A: Study Assessments

Time and Events Table	Screening Phase Day - 3 to 1	Treatment Phase Day 1					Follow-Up Phase
		Pre-Placement	Placement (Hour 0)	Delivery (Hour (0-5)	Post-Delivery Prior Removal (Hour (> 5-8)	Post-Delivery After Removal (Hour > 5-8)	5-7 Days Post Treatment
Informed Consent	X						
Confirmation of Eligibility	X						
Med History & Demographics	X						
Limited Physical Examination[1]	X						
Weight and Height Measurements	X						
Vital Signs[2]	X	X					
Clinical Laboratory/ Urinalysis	X						
Plasma for Furosemide[3]		X		X			
Urine Pregnancy test[4]	X						
NYHA Classification Assessment	X						
Medication Taken	X	X			X		
Schedule Next Study Visit	X					X	
Weight measurements of Vial and attached Adapter (before and after filing the Cartridge)		X					
Adhesive Site Skin Assessment[5]		X				X	X
Documentation of other local skin reactions[6]		X				X	X
Proper Device Filling Photography[7]		X					
Treatment Emergent Adverse Events			X	X	X	X	X
Needle Insertion Reporting[8]				X			
Leakage Check[9]				X	X		
Malfunction Observation[10]				X	X		
Subject Recording of Activities[11]						X	
Comfort of Wear Questionnaire[12]						X	
Device Placement /Dislodgement & Photography[13]			X		X		
Pain Assessment[14]						X	
Device Inspection for sharps and residual volume Photography[15]		X				X	

1. A limited physical examination was performed at Screening consisting of the following: skin of abdominal area, lungs/chest, heart, and abdomen.
2. Vital signs included respiration rate (breaths per minute), oral temperature, and blood pressure (mmHg) and heart rate (beats per minute [bpm]). Blood pressure and heart rate was obtained after the Subject had been resting in sitting position for 5 minutes. For subjects not treated on day of screening, vitals were taken and Investigator confirmed that no medically significant changes have occurred since screening visit
3. Drug delivery was assessed by measurement of plasma furosemide levels at Pre-placement and once during the plateau phase (1-5 hours) post start of drug administration.
4. Pregnancy testing for females of childbearing potential was performed at screening.
5. Adhesive site skin reaction was scored on an 8-point scale, at pre-placement, upon removal and 1 hour after removal of device and at follow up. The following scoring was used: 0=No evidence of irritation, 1=Minimal erythema, barely perceptible, 2=Definite erythema, readily visible; or minimal edema; or minimal papular response, 3= Erythema and papules, 4=Definite edema, 5=Erythema, edema, and papules, 6=Vesicular eruption; skin ulceration, 7=Strong reaction spreading beyond test (i.e. application) site.
6. Documentation of other local skin reactions such as petechiae, hematomas, necrosis, sclerosis, etc. was also done.
7. Proper device filling and photography was performed pre-placement of device.
8. Needle insertion as reported by the subject upon starting the device.
9. Incidence of obvious leakage as observed by study staff or subject during delivery and prior to removal of device.
10. Interruption of Delivery during operation (red "X" and/or light bar blinking and error melody) and low battery alert during delivery and prior to removal of device.
11. Study staff recorded activity during wear of combination product within 1 hour after removal of device.
12. Subjects completed a comfort of wear questionnaire within 1 hour after removal of device.
13. Dislodgement was scored on a 5-point scale upon placement and immediately prior to removal. The following scoring was used: 0 = ≥ 90% adhered (essentially no lift off the skin) 1 = ≥75% to < 90% adhered (some edges only lifting off the skin) 2 =≥50% to < 75% adhered (less than half of the patch lifting off the skin) 3 = > 0% to < 50% adhered but not detached (more than half of the patch lifting off the skin without falling off) 4 = 0% adhered - patch detached (patch completely off the skin).
14. Pain assessment was performed within 1 hour after removal using an 11-point numeric rating scale of 0 to 10 with zero equivalent to no pain and 10 equivalent to the worst pain imaginable.
15. Device Inspection for: (1) Exposed needle sharp pre-placement and immediately after device removal and (2) Residual volume photography performed post-delivery after device removal.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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05/17/2018

STEVE G BAI
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HSIEN MING J HUNG
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