A single center, randomized, open-label, cross-over exploratory study to evaluate the pharmacodynamic and pharmacokinetic response to a subcutaneous administration or oral administration of furosemide in subjects presenting with chronic fluid overload

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Primary Objective • To assess the effects of 80mg of furosemide delivered by subcutaneous delivery in the abdominal area over 5 hours when compared to oral administration in patients with heart failure with chronic fluid overload. Secondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON41092

Source
ToetsingOnline

Brief title
Furosemide Pharmacodynamics after SC or Oral Administration (scFUROPHARM)

Condition

- Heart failures

Synonym
heart failure

Research involving
Human

Sponsors and support

Primary sponsor: scPharmaceuticals Inc.
Source(s) of monetary or material Support: scPharmaceuticals (sponsor)

Intervention

Keyword: diuresis, furosemide

Outcome measures

Primary outcome

Efficacy/Pharmacodynamic Assessments: • Diuresis - Time to first void, volume of first void, diuresis measured for each of the following intervals: 0-60 min; 60-120 min; 120-240 min; 240-360 min, and 360-480 min. • Natriuresis and renal clearance - Creatinine, sodium, potassium, and chloride will be determined for each of the collection intervals: 0-60 min; 60-120 min; 120-240 min; 240-360 min and 360-480 min.*

Secondary outcome

Dyspnea score (Likert scale) • Scoring of HF symptoms • Scoring of thirst questionnaire and thirst distress scale • Bioimpedance measurements Safety Assessments to be performed at screening, prior start and following completion.

Study description

Background summary

The term heart failure (HF) is used both for acute decompensated heart failure (ADHF) and its chronic/stable form, also referred to as congestive heart failure (CHF). We will study HF patients with chronic fluid overload despite maintenance doses of furosemide. These patients have signs and symptoms of HF,

typically dyspnea, edema, and fatigue, and some of these patients may periodically require parenteral administration of furosemide to relief signs and symptoms. The novel scFurosemide subcutaneous therapy may be used as an alternative to periodic iv treatment in patients with chronic fluid overload, in patients with worsening heart failure/early decompensation to prevent progression to the more serious acutely decompensated heart failure (ADHF), and to continue a course of parenteral loop diuretics started in the hospital to achieve the desired reduction in fluid overload. Furosemide is a potent, rapid-onset, loop diuretic commonly used in the treatment of HF and edema. Furosemide is currently approved for oral, intravenous (i.v.) and intramuscular (i.m.) administration. Oral furosemide is the standard of care for chronic administration in patients with congestive heart failure. Intravenous furosemide therapy is the standard of care in the treatment of edema associated with congestive heart failure in patients who temporarily require greater diuretic potential than what can be achieved with oral furosemide alone. Many patients require from time to time parenteral administration of furosemide to effectively treat fluid overload and its associated signs and symptoms. Consequently iv furosemide has become the cornerstone of the treatment of CHF patients with chronic fluid overload. Furosemide was first introduced in the 1960s and at that time obtained approval for i.m. administration. Furosemide is poorly soluble and a clinical dose would require administration of 5 mL or more. Administration of a clinical dose of furosemide in this way may be suitable in emergency situations, but would not be suitable in a clinical setting due to the extreme pain. Both i.v. and i.m. administration are unsuitable for self-administration or administration by a care giver in an alternative setting (e.g., home). Subcutaneous administration of furosemide offers an alternative method to overcome these limitations. In general, sc delivery of medicinal agents offers multiple theoretical advantages, including: • Bioavailability generally equal to that of i.v. administration • Reduced costs of administration when compared to i.v. • Potential for delivery in alternative settings, reducing personal and economic burden of heart failure. • Reduced risk of complications when compared to i.v. • Reduced pain and higher clinical acceptance than i.m. The pharmacologic characteristics of furosemide make it well-suited for sc administration: low viscosity, non-cytotoxic, non-irritating, and well-absorbed from adipose and connective tissues. However its relatively poor solubility would require administration of 5mL or more in most circumstances making this unsuitable for a regular s.c. injection by syringe. Commercial furosemide products for injection have an alkaline pH (range 8.3-9.0) and are unsuitable for subcutaneous injection. scPharmaceuticals developed new furosemide formulation for injection which is isotonic and buffered to physiologic pH (7.4). The proposed pilot study will investigate this new formulation. The solution is buffered with a low concentration of tromethamine - a widely used inactive ingredient in injectable pharmaceutical products. scFurosemide will be delivered using a biphasic delivery profile with 30mg of furosemide delivered over the first hour followed by 12.5mg/hour for four hours. This delivery profile was optimized to improve diuretic efficacy and reduce potential for renal toxicity. The available

clinical evidence regarding subcutaneous administration of furosemide is limited but compelling. In a randomized, double-blind, cross-over study of 12 healthy volunteers, 20 mg of furosemide administered s.c. induced a rapid and marked diuresis and natriuresis (Verma et al, 2004). The current study is designed to provide information on response to subcutaneous administration of scFurosemide when compared to oral administration of the same dose. This information is of importance for the design and power calculations of pivotal studies in support of regulatory filings and claims of clinical utility for scFurosemide. A cross-over design was chosen to facilitate the interpretation of results. Fluid overload and associated symptoms are inherently variable and differences in fluid overload between the two treatment periods may exist. However the use of bioimpedance measurements provides a measure for fluid overload (total body water) allowing diuretic response to be interpreted as a function of fluid overload. Further, we will measure the B-type natriuretic peptide, which is a marker of myocardial stretch and a very well established surrogate marker of loading status of the heart. Although bioimpedance and B-type natriuretic peptide (BNP) can be used to compare the degree of fluid overload within an individual over time, measurements between individuals are difficult to interpret. Additionally, the within subject variability between two periods is inherently smaller than the inter subject variability. So by using a randomized cross over design, the interpretation of diuretic response is markedly enhanced by allowing the diuretic response to be interpreted in the context of differences in bioimpedance and BNP measurements. No or minimal carry-over effect is expected following the single treatment and resumption of baseline oral therapy. .

Study objective

Primary Objective • To assess the effects of 80mg of furosemide delivered by subcutaneous delivery in the abdominal area over 5 hours when compared to oral administration in patients with heart failure with chronic fluid overload. Secondary Objective(s) • To assess the effects of the furosemide regimen on natriuresis • To assess the effects on signs and symptoms of heart failure (e.g. dyspnea) • To investigate if furosemide induced diuresis correlates with changes in bioimpedance parameters • To investigate if pretreatment bioimpedance measurements predict diuretic response to furosemide • To investigate injection site reactions and discomfort during sc administration • To obtain plasma samples for pharmacokinetic analyses.

Study design

This is a single center, randomized, open-label, cross-over, exploratory study in subjects with heart failure with chronic fluid overload. The study will enroll participants after presenting with signs or symptoms of chronic fluid overload to the heart failure outpatient clinic. Participants must be on oral furosemide (40 mg oid or bid) or therapeutic equivalent (e.g. bumetianide 1 mg

oid or bid) for a period 90 days, Subjects visiting the heart failure outpatient clinic will be assessed for eligibility criteria for the study as part of their routine care. If the eligibility criteria are met, the subject will be informed of the study, invited to participate, and provided with study information to review at home. Approximately 7 days later, the subjects will contact the site and if they agree to participate, they will be scheduled for a screening visit. . The informed consent will be reviewed and signed at the screening visit and a number of assessments will be done to evaluate eligibility. Eligible patients will be invited for the first study period if they agree to participateParticipants will be planned for 2 visits, and on the day of the first treatment period, they will be randomized to subcutaneous or oral therapy for the first treatment period with the other treatment being administered at the second treatment period which is to take place 14 + 3 days later. One each treatment day, participants will be subject to an observation period of 8 hours from the start of the treatment. Urine will be collected during the observation period for assessment of diuresis, natriuresis, albumin, creatinine clearance and pharmacokinetics (PK). Blood samples will be taken at specified intervals for PK analyses and for assessment of routine biochemical parameters and selected routine cardiac markers including NT Pro-BNP (ng/l), hs-Trop T (ng/l), and Galectin-3 (ng/mL). Safety assessments will include physical examinations, vital signs, investigator assessments of signs and symptoms, inspection of injection site (sc therapy only) standard clinical laboratory evaluations (hematology, blood chemistry, and urinalysis), adverse event and serious adverse event monitoring. Bioimpendance measurements will be performed at selected time points during the study.

Intervention

In this cross-over study, each of the study subjects will be randomly assigned to one of two treatment groups. Group 1 will first receive 80 mg scFurosemide (8mg/mL) administered abdominally via standard sc infusion set with the use of a commercial infusion pump, over 5 hours (30mg in first hour followed by 12.5mg/hour over 4 hours) followed by oral furosemide (80 mg tablet) in the second period. Group 2 will receive the same treatments in the reverse order, starting with oral furosemide followed by scFurosemide treatment in the second period. All treatments are open label. Participants will be supine or in a reclined sitting position with the legs elevated during the 8-hour observation period with the legs elevated. Patients are allowed to stand and walk as needed.

Study burden and risks

Although clinical reports have described the successful subcutaneous administration and clinical use of the unbuffered alkaline commercial furosemide scPharmaceuticals developed a buffered isotonic formulation at neutral pH. Use of isotonic formulations at neutral pH for injection is

consistent with current pharmaceutical standards and reduce the risk of pain or discomfort upon administration. The scFurosemide product uses a standard buffering agent in the form of tromethamine (TRIS or THAM). Tromethamine is widely used as an excipient in approved solutions for injection and in topical formulations. Additionally tromethamine is approved as a standalone pharmaceutical product known as THAM SOLUTION (Tromethamine Injection manufactured by Hospira, Lake Forrest, IL). THAM SOLUTION is indicated to be administered intravenously for the prevention and correction of metabolic acidosis. Each 100 mL THAM SOLUTION contains 3.6 g (30 mEq) tromethamine in water for injection. The solution is hypertonic 389 mOsmol/L (calc.) with a pH 8.6 (8.4-8.7). (FDA Application No. (NDA) 013025; Company HOSPIRA; Approval Date December 16, 1965). There are no known risks associated with the use of tromethamine as a buffering agent and tromethamine is listed as an approved inactive ingredient list, which exempt companies from having to perform additional preclinical or clinical safety studies upon adding the ingredient to a pharmaceutical product. Risks of the study may include pain and discomfort from study-related procedures including vena puncture and sc drug administration of the drug product. Additional risk may also include the risk of orthostatic hypotension following the administration of the drug as a result of ensuing diuresis. During each of the two study phases 14 samples of blood (5mL each) will be obtained for pharmacokinetic analysis. This volume is required for analysis of samples in duplicate. The total volume of blood samples is less than 200mL during the study or approximately 40% of what is normally donated for a blood transfusion.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Written informed consent must be obtained before any assessment is performed;Male and female subjects >=18 years of age, with body weight < 120 kg and body mass index (BMI) < 30 kg/m2;Participant must have been on oral furosemide 40 mg qd or bid for a period 90 days;History of chronic heart failure with presence of moderate symptoms of decompensation. DHF is defined as presence of signs and symptoms of heart failure, like dyspnea at rest or minimal exertion, pulmonary congestion and/or peripheral edema at the time of presentation in combination with elevated levels on natriuretic peptides (NT-proBNP < 300 pg/mL);In the opinion of the investigator, able to participate in the study

Exclusion criteria

Contraindication to furosemide ;Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant;Systolic BP (SBP) < 90 mm Hg ;Temperature > 38°C (oral or equivalent) or sepsis or active infection requiring i.v. anti-microbial treatment;Serum sodium < 130 mEq/L and Serum potassium < 3.0 mEq/L;Current or planned (throughout the completion of study drug infusion) treatment with any i.v. therapies, including inotropic agents, vasopressors, levosimendan, nesiritide or analogues; or mechanical support (intra-aortic balloon pump, endotracheal intubation, mechanical ventilation, or any ventricular assist device);History of gastric or intestinal surgery that may affect absorption of oral medication;Diagnosed with diabetes mellitus requiring pharmacotherapy;Presence or need for urinary catheterization ;Current or planned ultrafiltration, hemofiltration, or dialysis;Impaired renal function defined as an estimated glomerular filtration rate (eGFR) on admission < 15mL/min/1.73 m2, calculated using the simplified Modification of Diet in Renal Disease (sMDRD) equation;Administration of intravenous radiographic contrast agent within 72 hours prior to screening or acute contrast-induced nephropathy at the time of screening;Major surgery within 30 days prior to screening;Administration of an investigational drug or implantation of investigational device, or participation in another trial, within 30 days before screening;Inability to follow instructions or comply with procedures;Any surgical or medical condition which in the opinion of the investigator may interfere with participation in the study or which may affect the outcome of the study

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-12-2014
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lasix
Generic name:	furosemide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	TBD
Generic name:	furosemide for subcutaneous injection

Ethics review

Approved WMO

Date:	22-07-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	03-10-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-12-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-01-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2014-002546-49-NL
CCMO	NL49817.042.14