Synopsis

Study title	Repetitive levosimendan infusions for patients with advanced chronic heart failure (LeoDOR)
Investigational Product	Levosimendan (Simdax®) versus Placebo
Indication	Advanced chronic heart failure
Design of clinical trial	A randomised, double-blind, placebo-controlled multicentre study with parallel group design. Mortality and rehospitalisation rates are high in the vulnerable phase following heart failure hospitalisation. Previous studies suggest that these events can be reduced by repeat infusions of levosimendan in patients with advanced heart failure.
Number of trial sites	Approximately 24 clinical centres in 9 countries.
Duration of clinical trial / Timetable	Information concerning the clinical trial: • Time of recruitment: 18 months • Planned start (first patient first visit [FPFV]): September 2017 • Planned end of trial (last patient last visit [LPLV]): February / March 2019 Information concerning subjects: • Screening Period: 2 weeks • Active phase: 12 weeks • Follow-up period: 14 weeks • Safety follow-up period: 26 weeks Duration of treatment: Patients with chronic heart failure (CHF) will receive either a 6-hour infusion every 2 weeks or a 24-hour infusion every 3 weeks up to 12 weeks, followed by an efficacy follow-up visit at week 14 and a safety follow-up call at 6 months.
Objectives (Primary/Secondary)	To show that repetitive levosimendan infusions are effective and safe in stabilising patients with advanced chronic heart failure during a vulnerable period following a recent hospitalisation.
Endpoints (Primary/Secondary)	Primary Endpoint: The hypothesis will be tested based on a global rank endpoint in which all participants are ranked across three hierarchical groups: 1. time to death or high-urgent heart transplantation or ventricular assist device (VAD), 2. time to non-fatal HF event requiring i.v. vasoactive therapy (i.v.

	diuretics, i.v. vasodilators or i.v. inotropes – either in-hospital or ambulatory in an emergency department) and 3. time-averaged proportional change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) from baseline to 14 weeks. <u>Secondary Endpoints:</u> 1. Individual components of the primary endpoint at 14 weeks and 26 weeks • time to death / high-urgent heart transplantation / VAD implantation at 14 weeks and 26 weeks • time to non-fatal HF event defined as an episode requiring i.v. vasoactive therapy (i.v. diuretic, i.v. inotropic) at week 14 and 26 • time-averaged proportional change in NT-proBNP from baseline to 14 weeks 2. Change in functional status • 6-minute walk test at baseline and 14 weeks • New York Heart Association (NYHA) class at baseline and 14 weeks 3. Change in symptoms • Kansas City Cardiomyopathy Questionnaire (KCCQ) – clinical summary score - from baseline to 14 weeks • Difference in patient global assessment (PGA) from baseline to 14 weeks 4. Number of combined events • death / heart transplantation / VAD implantation / non-fatal HF event 5. Cumulative number of non-fatal HF events 6. Cumulative number of hospital admissions (AHF vs. cardiovascular admissions vs. non-cardiovascular admissions) 7. Cumulative days alive and out of hospital 8. Cumulative number of death and total (first and recurrent) non-fatal HF events 9. Safety assessment <u>Additional endpoints:</u> 1. Changes in background medication 2. Cost-effectiveness (EQ-5D VAS) 3. Changes in biomarkers

Planned number of subjects	The planned number of patients is 264: • 6-hour infusion group: 88 patients on levosimendan and 44 on placebo • 24-hour infusion group: 88 patients on levosimendan and 44 on placebo
In- and exclusion criteria	<u>Inclusion criteria</u> 1. Written, signed and dated informed consent. 2. Male and female patients over 18 years of age. 3. Women of childbearing potential must have a monthly negative pregnancy test and must refrain from breastfeeding. Women who are postmenopausal (1 year since last menstrual cycle), surgically sterilised or who have undergone a hysterectomy are considered not to be of childbearing potential. 4. CHF diagnosed at least 6 months before screening and treated with individually optimised long-term oral treatment for the last month, unless not tolerated (e.g., ACE-inhibitor or AT II blocker, beta-blocker, mineralocorticoid receptor antagonist, angiotensin II receptor blocker neprilysin inhibitor [ARNI] and with devices [e.g., CRT/ICD], as needed). 5. Left ventricular ejection fraction less than or equal to 30% as assessed using echocardiography, radionuclide ventriculography or contrast angiography within the index hospitalisation. 6. Currently hospitalised for decompensated HF requiring i.v. diuretics, or i.v. vasodilators, or i.v. inotropic therapy, or their combination. 7. Previous hospitalisation or visit to outpatient clinic requiring i.v. diuretics, i.v. vasodilators, or i.v. inotropic therapy, or their combination for acute decompensated HF within 12 months before the current hospitalisation. 8. NT-proBNP level after recompensation of ≥2500 ng/L and/or NYHA class III or IV at study entry <u>Exclusion criteria:</u> 1. Severe obstruction of ventricular outflow tracts such as haemodynamically significant uncorrected primary valve disease or hypertrophic cardiomyopathy or impaired ventricular filling such as restrictive cardiomyopathy. 2. Predominantly right heart failure a/o severe tricuspid regurgitation 3. Cardiac surgery or coronary angioplasty within 30 days before study drug initiation.

	4. Acute coronary syndrome within 30 days before study drug initiation. 5. Patients who are scheduled for cardiac surgery or angioplasty in the next 3 months. 6. History of torsades de pointes. 7. Stroke or transient ischaemic attack (TIA) within 3 months before study drug initiation. 8. Systolic blood pressure less than 90 mmHg at baseline. 9. Heart rate 120 bpm or greater at baseline. 10. Serum potassium less than 3.5 mmol/l before study drug initiation. 11. Severe renal insufficiency (estimated glomerular filtration rate (eGFR) <30 ml/min/1.73m^2). 12. Anaemia (haemoglobin < 10 g/dl). 13. Significant hepatic impairment at discretion of the investigator. 14. Hypersensitivity to levosimendan. 15. Other serious diseases limiting life expectancy considerably (e.g. end-stage cancer, end-stage lung disease). 16. Participation in a clinical trial with any experimental treatment within 30 days prior to screening or previous participation in the present study. 17. Administration of levosimendan within 14 days prior the study drug initiation, the first study drug application has to be postponed for at least 14 days after the end of this premedication 18. Suspected non-compliance, 19. Pregnant women and nursing mothers 20. Failure to use highly-effective (a Pearl Index lower than 1%) contraceptive methods. 21. Persons with any kind of dependency on the investigator 22. Persons held in an institution by legal or official order
Methodology of the study	**<u>Efficacy assessments:</u>** <u>Mortality:</u> date, time, location and cause of death will be recorded. <u>Heart transplantation</u>: date, time, urgency, location will be recorded. <u>Ventricular assist device implantation:</u> date, time, location and urgency will be recorded. <u>Acute decompensated HF (non-fatal HF event):</u> defined as hospitalisation for HF or as any i.v. medication given for heart failure (outside hospital). <u>Hospitalisation:</u> defined as either hospitalisation for any reason or a visit to emergency room for any reason; prescheduled visits to hospital are

	not counted as hospitalisation days. Hospitalisation for cardiovascular and non-cardiovascular reason will be discriminated. Kansas City Cardiomyopathy Questionnaire (KCCQ): completed by the patient at the initiation visit and at 14 weeks. Patient global assessment (PGA): completed by the patient at 14 weeks. NT-proBNP: assessed just before each study drug infusion, and at week 14. 6-minute walk test: at the initiation visit and week 14. NYHA class: at each study drug dosing visit (before the initiation of the drug infusion) and at week 14. Weight: at each study drug dosing visit (before the initiation of the drug infusion) and at week 14. Concomitant medications will be recorded at each visit. **Health-economic assessments:** Cost effectiveness of pulsed infusions of levosimendan will be assessed by utilising the EQ-5D VAS **Safety assessments:** Heart rate and blood pressure: at each study drug dosing visit (just before and at the end of drug infusion) and at week 14. 12-lead electrocardiogram (ECG): at the initiation visit and week 14. **Laboratory tests:** Blood samples for laboratory testing including NT-proBNP will obtained at study entry, at the beginning of each study drug application and at 14-weeks follow-up visit. Adverse events (AEs) and serious adverse events (SAEs) will be followed for 14 weeks following randomisation. The information of deaths and hospitalisations during the study will be collected with specific case report form (CRF) pages. These events will not be reported as SAEs. However, deaths and hospitalisations due to unexpected reasons (not described in current Investigator´s Brochure) must be reported as SAEs.
Statistical methods & analyses	The statistical hypothesis is that levosimendan in patients with advanced CHF will be associated with greater clinical stability as assessed by a global rank endpoint in comparison to placebo. With total of 264 patients, study has approximately 90% power to detect statistically significant difference between treatments. Statistical analysis will be

	performed using Intent-to-treat dataset, including all randomised patients. Primary efficacy variable, global rank test will be analysed using two-sided non-parametric Wilcoxon-Mann-Whitney test. Any time to event analysis for individual and combined components will be performed using log-rank test. Data and Safety Monitoring Board will be established for the study to protect both the ethical rights and safety of the patients participating in the study and to make recommendations about continuation or discontinuation of the study.