Protocol Registration Receipt
10/21/2014

Grantor: CDER IND/IDE Number: 66,448 Serial Number: 20080611 037

Safety and Efficacy Study of Istaroxime in Acute Decompensated Heart Failure Patients

This study was withdrawn prior to enrollment.
(The study was not started due to a re-evaluation of the istaroxime development program)

Sponsor:	Debiopharm International SA
Collaborators:	
Information provided by:	Debiopharm International SA
ClinicalTrials.gov Identifier:	NCT00838253

Purpose

The purpose of this study is to assess the safety and efficacy of istaroxime in patients hospitalized for Acute Decompensated Heart Failure (ADHF) not requiring inotropic therapy.This will be done by comparing the hemodynamic effect of a 24-hour infusion of three different doses of the drug versus placebo. Efficacy will be measured as a change in Pulmonary Capillary Wedge Pressure from pre-infusion to 6 hours after infusion start. Secondary objectives will include the evaluation of clinical efficacy and safety through assessment of cardiovascular and renal tolerability as well as changes in biological markers such as brain natriuretic peptide (BNP) and troponin I (TNI), and the neurohormones renin and aldosterone and also to assess the pharmacokinetics of istaroxime and its metabolites.

Condition	Intervention	Phase
Heart Failure	Drug: Istaroxime Drug: Placebo	Phase 2

Study Type: Interventional
Study Design: Treatment, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Randomized,

Safety/Efficacy Study

Official Title: A Multicenter, Randomized, Double-blind, Placebo-controlled Staggered Dose-escalating Phase IIb Study of the Safety and Efficacy of Istaroxime Over 24 Hours at Three Doses in Acute Decompensated Heart Failure Patients (The IGNITE Trial)

Further study details as provided by Debiopharm International SA :

Primary Outcome Measure:

- PCWP change from baseline [Time Frame: 6 hours after infusion start] [Designated as safety issue: No]

Secondary Outcome Measures:

- PCWP, MRAP, SVR, PVR, Cardiac Index and SBP [Time Frame: 1, 3, 6, 12 and 24 hours after infusion start and 1 and 3 hours after infusion end.] [Designated as safety issue: No]
- Safety parameters and drug pharmacokinetics [Time Frame: 1, 3, 6, 12 and 24 hours after infusion start and 1 and 3 hours after infusion end] [Designated as safety issue: No]

Enrollment: 0

Study Start Date: June 2009

Arms	Assigned Interventions
Experimental: 1	Drug: Istaroxime Istaroxime 0.5 µg/kg/min (30 µg/kg/h) continuous i.v. infusion for 24 hours
Experimental: 2	Drug: Istaroxime Istaroxime 1.0 µg/kg/min (60 µg/kg/h) continuous i.v. infusion for 24 hours
Experimental: 3	Drug: Istaroxime Istaroxime 1.5 µg/kg/min (90 µg/kg/h) continuous i.v. infusion for 24 hours
Placebo Comparator: 4	Drug: Placebo Placebo continuous i.v. infusion for 24 hours

The 32-day study includes a 48–hour screening period, a 30-minute to 2-hour pre treatment period, a maximum 2-hour period for randomization and measurement of baseline values, a 24-hour treatment period, and a 96-hour post-treatment period. A 25-day follow-up period including a visit on Day 30 will take place after the active phase of the study When considered to be eligible, a first cohort of 88 patients will be randomized in a 3:1 ratio to receive 24-hrs treatment with istaroxime 0.5 µg/kg/min or placebo. If after the continuous safety monitoring and interim analyses the DMC determines that there are no safety issues with this dose, a second cohort of 88 patients will be randomized in a 3:1 ratio to receive 24-hrs treatment with istaroxime 1.0 µg/kg/min or placebo. If after the continuous safety monitoring and interim analyses of the second cohort the DMC determines that there are no safety issues with this dose, a third cohort of 88 patients will be randomized in a 3:1 ratio to receive 24-hrs

treatment with istaroxime 1.5 µg/kg/min or placebo. In all cohorts, patients will receive standard of care therapy.

Eligibility

Ages Eligible for Study: 18 Years and older
Genders Eligible for Study: Both

Inclusion Criteria:

- Male or female patients ≥18 years;
- Admission for ADHF
- Systolic blood pressure ≤ 120 mmHg;
- Ejection fraction (EF) ≤ 35 %
- Signed informed consent.

Randomization inclusion criteria:

- Persistence of ADHF signs despite initial treatment with i.v. diuretics and/or vasodilators;
- Cardiac index ≤ 2.5 L/min/m²;
- Pulmonary capillary wedge pressure ≥ 20 mmHg
- Systolic BP between 85 and 120 mmHg (limits included) without signs or symptoms of hypoperfusion

Exclusion Criteria:

- Main screening exclusion criteria:
- Positive pregnancy test in females of childbearing potential;
- Systolic blood pressure < 85 mmHg or > 120 mmHg;
- Oral treatment with digoxin within one week before current hospitalization;
- Any inotrope administered during the current hospitalization
- Presence of cardiogenic shock or its occurrence within the past month;
- Acute coronary syndrome within the past 3 months;
- Coronary artery bypass graft or percutaneous coronary intervention within the past month;
- Stroke within the past 6 months;
- Atrial fibrillation with uncontrolled HR (HR > 100 beats per minute (bpm);
- Life threatening ventricular arrhythmia or ICD (implantable cardioverter defibrillator) shock within the past month;
- Presence of a CRT (cardiac resynchronization therapy), ICD or pacemaker devices implanted within the past month;
- Second or third degree atrio-ventricular block without pacemaker;
- Abnormal safety lab values obtained within the last 24 hours of the screening period prior to pulmonary arterial catheter (PAC) insertion

Randomization exclusion criteria:

- Any inotrope administered during the current hospitalization period
- Heart rate > 120 bpm or < 50 bpm;
- cTnI > 0.5 ng/mL or cTnI > ULN and > 1.25x the first screening assessment

Contacts and Locations

Locations

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Medical Center of General Management Department of the President of the Russian Federation City Hospital #51

Moscow, Russian Federation, 121039

Federal State Institution "Federal center of heart, blood and endocrinology n.a. Almazov of Rosmedtechnologoie"

St-Petersburg, Russian Federation, 194156

City Hospital #26

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Investigators

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More Information

http://www.debiopharm.com

Publications:

Gheorghiade M, Blair JE, Filippatos GS, Macarie C, Ruzyllo W, Korewicki J, Bubenek-Turconi SI, Ceracchi M, Bianchetti M, Carminati P, Kremastinos D, Valentini G, Sabbah HN; HORIZON-HF Investigators. Hemodynamic, echocardiographic, and neurohormonal effects of istaroxime, a novel intravenous inotropic and lusitropic agent: a randomized controlled trial in patients hospitalized with heart failure. J Am Coll Cardiol. 2008 Jun 10;51(23):2276-85. Epub 2008 Apr 9.

Responsible Party:	Debiopharm S.A. (Dr Hein Van Ingen, M.D.)
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Health Authority:	United States: Food and Drug Administration France: Afssaps - Agence française de sécurité sanitaire des produits de santé (Saint-Denis) Italy: The Italian Medicines Agency Lithuania: State Medicine Control Agency - Ministry of Health Poland: Office for Registration of Medicinal Products, Medical Devices and Biocidal Products Romania: National Medicines Agency