SYNOPSIS

Name of Sponsor:
Solvay

Individual Study Table:

(For National Authority Use only)

Name of Finished Product:
SLV320

Name of Active Ingredient:
SLV320

Study Title:
A Double-Blind, Placebo-Controlled, Randomized, Multi-Center, Dose-Finding Study of SLV320, a Selective A1 Adenosine Receptor Antagonist, to Evaluate the Effect on Renal Function and Safety in Subjects Hospitalized with Acute Decompensated Heart Failure and Renal Dysfunction. (Reno-Defend 1)

Investigators:
26 Investigators

Study Center(s):
Planned: 150 study centers in 17 countries.

Only 26 study centers in 3 countries (Poland, Russia, and United States of America) actively recruited subjects before the premature termination of the study.

Publication (Reference):
Not applicable.

Study Period:
02 FEB 2009 (first subject first visit) to
04 JAN 2010 (last subject last visit)

Phase of Development:
II

Objectives:

Primary Objective

The primary objective was to compare the effect of four intravenous SLV320 doses with placebo on the change in serum creatinine from Baseline to Day 14.

Secondary Objectives

1. To compare the effect of four SLV320 doses with placebo on the change in the following variables from Baseline to various time points:
   - Dyspnea (Likert Scale, provocative dyspnea assessment [PDA]).
   - Serum creatinine.
   - Plasma cystatin C.
   - Estimated glomerular filtration rate (eGFR) (Modification of Diet in Renal Disease [MDRD] formula).
   - Subject Global Clinical Assessment Score.
   - Body weight.

- Urine volume (as no Baseline value would be available for urine volume, the urine volume obtained for each dosing group at Day 1, Day 2, and Day 3 were to be compared to that of placebo).
- Urine osmolality.
- Serum osmolality.
- Blood urea nitrogen (BUN).
- Urea.
- Sodium and potassium in urine.
- Sodium and potassium in serum.
- Troponin I.
- Brain natriuretic peptide (BNP).

2. To compare the effect of four intravenous doses of SLV320 with placebo using the Trichotomous Endpoint of Treatment success, Treatment failure, or No change, where:
   - Treatment success was dyspnea reported by the subjects as Moderately or Markedly better at both Day 2 and Day 3 compared to start of treatment, and the absence of treatment failure.
   - Treatment failure was any one of the following:
     - Death from heart failure, re-admission to the hospital for heart failure, or unexpected post-discharge visits for heart failure, for example, emergency department visit through Day 14.
     - Worsening of heart failure requiring the use of intravenous rescue therapy more than 24 hours following the start of the first infusion of SLV320 or placebo to discharge from hospital or Day 7 (whichever was earliest). Rescue therapy is defined as the unexpected or unplanned need for intravenous intervention secondary to signs and symptoms of heart failure without which the subject will decline and included intravenous vasodilators, intravenous inotropes, emergent use of intravenous diuretics, need for mechanical ventilation, hemodialysis, or ultrafiltration. Minor dosing adjustments of ongoing/established subject therapy were not to be considered as rescue therapy.
     - Persistent renal impairment (the worsening of renal function defined by an increase of >0.3 mg/dL in serum creatinine from Baseline to Day 7, confirmed at Day 14).
   - No change was neither treatment success nor treatment failure.

3. To compare the effect of four intravenous doses of SLV320 with placebo on total loop diuretic dose (dosage of diuretics was to be measured using furosemide equivalent doses [1 mg bumetanide = 10 mg torsemide = 40 mg furosemide]).
4. To compare the effect of four intravenous doses of SLV320 with placebo using a Composite Endpoint of all-cause mortality, cardiovascular hospitalization, or hospitalization for worsening renal function, in time to event and frequency, during the Post-treatment Period.
5. To determine the pharmacokinetic (PK) profile of intravenous SLV320 and its active metabolites.

Exploratory Objectives

1. To explore the relationship between SLV320 exposure and response using serum creatinine and selected adverse events (AEs).
2. To explore potential protein biomarkers using proteomics that are predictive to optimize the treatment regimen of SLV320.
3. To explore the effects of four SLV320 doses compared with placebo on the change from Baseline in dyspnea, measured using the PDA.

Safety Objective

To compare the safety and tolerability of four SLV320 doses with placebo up to Day 180 (±7 days) by assessing the following: AEs, vital signs, 12-lead electrocardiogram (ECG), laboratory data, and use of concomitant medication.

Methodology:

This study was a randomized, double-blind, placebo-controlled, parallel group, multi-center study in subjects hospitalized with acute decompensated heart failure (ADHF) and renal dysfunction. A planned 450 subjects were to be randomized to receive SLV320 2.5 mg daily, 7.5 mg daily, 15 mg daily, or 30 mg daily administered as 1-hour intravenous infusions of 1.25 mg twice daily, 3.75 mg twice daily, 7.5 mg twice daily, or 15 mg twice daily every 12 hours for 3 days (a total of six doses) or placebo, on top of standard treatment (including loop diuretics).

The study consisted of a Screening/Baseline Period (Screening [Day -1 to Day 1]), a Treatment Period (Day 1 to Day 3) and a Post-treatment Period (Day 4 to Day 180 [±7 days]).

The recruitment for the S320.2.011 study was stopped on 06 JUL 2009 pending the review of the safety data. On 29 OCT 2009 the study was prematurely terminated by Solvay based on strategic drug development considerations. The decision to prematurely terminate the S320.2.011 study was not related to any safety concerns with the use of SLV320.

At the time of premature termination of the study, 49 subjects had been enrolled in the study and 46 subjects had been randomized.

Number of Subjects (Planned, Consented, Randomized and Analyzed):
Planned: 450 subjects (90 subjects in each treatment group).

All Subjects Consented subject sample: 49 subjects.

All Subjects Randomized subject sample: 46 subjects.

Safety subject sample: 45 subjects.

Full Analysis (FA) subject sample: 45 subjects.

PK subject sample: 33 subjects.

Diagnosis and Main Criteria for Inclusion:
Male and female subjects older than 18 years who gave written informed consent.

Subjects had to have renal dysfunction (defined as estimated eGFR of 20 mL/min to 80mL/min).

Female subjects had to be surgically sterile (bilateral oophorectormy and/or hysterectomy) or be

at least one year post-menopausal, as judged by the investigator.

Subjects with BNP ≥400 pg/mL or N-terminal fragment of probrain natriuretic peptide >2000 pg/mL.

Subjects who had a history of systolic or diastolic chronic heart failure of at least 14 days duration for which loop diuretic therapy was prescribed.

Subjects who had clinical evidence of volume overload manifested by at least two of the following features: dyspnea, rales, peripheral edema and/or pre-sacral edema, increased jugular venous distension, chest X-ray consistent with congestive heart failure.

Subjects who required hospitalization for treatment of the current episode of ADHF with intravenous diuretics as well as; received at least 40 mg intravenous furosemide (or equivalent) for the treatment of the current episode of ADHF before the start of the initial study medication infusion, unless a rationale for a lower dose was provided by the investigator and; received the first study medication infusion within 24 hours (± 4 hours) following the presentation to the hospital (including the emergency department) for this episode of ADHF.

Subjects who had low output syndrome (defined as having the need for treatment with intravenous inotropes or vasopressors), systolic blood pressure (SBP) of <95 mmHg at the time of randomization, body temperature of >38°C at the time of randomization, significant stenotic valvular disease (severe aortic or mitral stenosis), or needed mechanical ventilation, were to be excluded from the study.

Subjects who had clinical evidence of acute coronary syndromes in the two weeks before Screening or had myocardial infarction or hemodynamically destabilizing significant arrhythmias, or ECG evidence of a second degree heart block or third degree AV-block in the absence of a pacemaker, within 30 days of Screening, were to be excluded from the study.

Subjects who had acute myocarditis or hypertrophic obstructive, restrictive, or constrictive cardiomyophathy as well as subjects who had implantation of a cardiac defibrillator or cardiac resynchronization device (pacemaker) or temporary pacing wire within seven days of Screening were to be excluded from the study.

Subjects who had serum potassium of <3.5 mEq/L and/or serum sodium of <130 mEq/L, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 times the upper normal limit of normal, and/or total bilirubin >3 mg/dL.

Test Product, Dose and Mode of Administration, Batch Number:

Subjects received SLV320 2.5 mg daily, 7.5 mg daily, 15 mg daily, or 30 mg daily administered as 1-hour intravenous infusions of 1.25 mg twice daily, 3.75 mg twice daily, 7.5 mg twice daily, or 15 mg twice daily every 12 hours for 3 days (a total of six doses).

Batch Numbers:

SLV320 4 mL ampoules, 1.25 mg/mL: 1059987-610177 and 1059987-610285.

SLV320 4 mL ampoules, 2.50 mg/mL: 1060517-610176 and 1060517-610286.

Duration of Treatment:

Treatment Period: 3 days.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Placebo administered as 1-hour intravenous infusions twice daily for 3 days.

Batch Numbers:

Placebo ampoules, 4 mL: 1059989-70517 and 1059989-70338.

Criteria for Evaluation

Not applicable for an abbreviated Clinical Study Report (CSR).

Statistical Methods:

In this abbreviated report only for a very few variables inferential statistics were to be presented. For the primary efficacy variable (serum creatinine) and supporting laboratory variables (cystatin C and eGFR), an analysis of covariance (ANCOVA) to compare the effect of the four intravenous doses of SLV320 with placebo on the change from Baseline at all relevant post-baseline visits and Endpoint was performed with treatment as factor and geographical region and the Baseline laboratory variable value as covariate. For PK dose-proportionality was assessed based on a regression model. For all other data only descriptive statistics are presented.

Summary - Conclusions

Efficacy Results:

Due to the small sample size, as a result of the premature termination of the study, no definite conclusions can be made, however the following observations were made:

No statistically significant difference between each of the four SLV320 doses and placebo for the change in serum creatinine from Baseline was observed at Day 14 (±3 days)/Endpoint (LOCF).

A class effect with respect to dose-response efficacy was shown with adenosine A1 receptor antagonists. At sub maximal doses of these agents, dose-response curves were shown to be plateaued while higher doses were shown to be less effective similar to the effect seen with SLV320 on serum creatinine in this study. This response trend was also seen in studies with other adenosine A1 antagonists, BG9719 and rolofylline on GFR. The reason for this is unclear. The possibility of nonselective adenosine receptor interaction at higher doses has been proposed, although this was not demonstrated.

No statistically significant difference between each of the four SLV320 doses and placebo were noted for the change from Baseline at Day 14 (±3 days)/Endpoint (LOCF) in cystatin C or eGFR.

For the secondary efficacy variables (BUN, serum urea, serum osmolality, serum sodium, serum potassium, troponin I, BNP, cumulative urine volume, urine osmolality, urine sodium, urine potassium, body weight) no definite conclusion can be drawn.

At all relevant post-baseline visits in the Treatment Period the majority of subjects in all the treatment groups assessed their dyspnea as Improved, based on the collapsed categories of the 7-point Likert Scale.

For the PDA final dyspnea severity score (DSS) a mean increase was observed at all relevant post-baseline assessments. A trend was noted for the mean increase to become larger over time in all the treatment groups.

The majority of subjects in all treatment groups showed a Significant improvement, Moderate improvement, or Minimal improvement from Baseline in their Global Assessment Score at Endpoint.

Composite Endpoint events of death and/or cardiovascular/renal hospitalization were reported in all the treatment groups.

Pharmacokinetic Results:

SLV320 area under the concentration-time curve from zero to infinity (AUC) and maximum observed concentration (C_{max}) on Day 1 as well as area under the concentration-curve over a dosing interval τ ($AUC_{0-\tau}$) and C_{max} on Day 3 showed a less than proportional increase over the 1.25 mg to 15 mg SLV320 dose range.

M6 AUC and C_{max} on Day 1 as well as $AUC_{0-\tau}$ and C_{max} on Day 3 showed a less than proportional increase over the selected SLV320 dosing range.

Safety Results:

One subject in the 15 mg twice daily treatment group was reported as a treatment-emergent death. Post-treatment deaths were reported in all the treatment groups except for the 15 mg twice daily treatment group (1 subject in the 1.25 mg twice daily, 1 subject in the 3.75 mg twice daily, 2 subjects in the 7.5 mg twice daily, and 3 subjects in the placebo treatment groups).

Treatment-emergent serious adverse events (SAEs) were reported by 1 subject in the 3.75 mg twice daily treatment group, 2 subjects in the 7.5 mg twice daily treatment group, and 1 subject in the 15 mg twice daily treatment group. Post-treatment SAEs were reported by subjects in all the treatment groups (6 subjects in the 1.25 mg twice daily, 3 subjects in the 3.75 mg twice daily, 6 subjects in the 7.5 mg twice daily, 3 subjects in the 15 mg twice daily, and 6 subjects in the placebo treatment groups).

One subject in the 7.5 mg twice daily treatment group and 1 subject in the 15 mg twice daily treatment group prematurely discontinued from the study due to treatment-emergent adverse events (TEAEs). During the Post-treatment Period 1 subject in the 1.25 mg twice daily treatment group, 1 subject in the 3.75 mg twice daily treatment group, 2 subjects in the 7.5 mg twice daily treatment group, and 3 subjects in the placebo treatment group prematurely discontinued from the study due to AEs.

The majority of subjects reported TEAEs and post-treatment AEs considered not having a reasonable possibility for a causal relationship to the study medication and the majority of subjects reported TEAEs considered to be mild in severity.

The number of subjects who reported at least one TEAE increased as the dose level increased, however, the majority of subjects in the placebo treatment group also reported at least one TEAE.

Clinically significant abnormal laboratory values, as judged by the investigator, were noted for subjects in all the treatment groups. No notable trends were observed over time or across treatment groups for any of the laboratory variables.

No notable trends were observed over time or across treatment groups for the vital signs measurements.

Most subjects had abnormal not clinically significant overall ECG assessments at all the relevant time points, but abnormal clinically significant overall ECG assessments were also noted in all the treatment groups at all the relevant time points. No notable trends were observed over time or across treatment groups for the overall ECG assessments.

Conclusion:

- The S320.2.011 study was prematurely terminated by Solvay based on the strategic drug development considerations. The decision to prematurely terminate the S320.2.011 study was not related to any safety concerns with the use of SLV320.
- Although an improvement was indicated according to the subjects' own assessments, the efficacy variables did not show a statistically significant difference across the treatment groups. Most subjects had a modified Trichotomous Endpoint category of Not treatment success. The 1.25 mg twice daily treatment group had the largest proportion of subjects with a modified Trichotomous Endpoint category of Treatment Success (4 subjects [50.0%]).
- A class effect with respect to dose-response efficacy was shown with adenosine A1 receptor antagonists. At sub maximal doses of these agents, dose-response curves were shown to be plateaued while higher doses were shown to be less effective similar to the effect seen with SLV320 on serum creatinine in this study. This response trend was also seen in studies with other adenosine A1 antagonists, BG9719 and rolofylline on GFR. The reason for this is unclear. The possibility of nonselective adenosine receptor interaction at higher doses has been proposed, although this was not demonstrated.
- SLV320 and M6 exposure parameters AUC and C_{max} on Day 1 as well as $AUC_{0-\tau}$ and C_{max} on Day 3 appeared to increase in a less than dose-proportional manner across the dose range of 1.25 mg to 15 mg of SLV320.
- For the safety variables no real difference across all the treatment groups including placebo were observed.