NOVARTIS

**Clinical Trial Result Database**

| |
|---|
| **Sponsor**<br>Novartis |
| **Generic Drug Name**<br>RLX030 - serelaxin |
| **Therapeutic Area of Trial**<br>Hepatic impairment |
| **Approved Indication**<br>Investigational – in development for acute heart failure (AHF) |
| **Protocol Number**<br>CRLX030A2101 |
| **Title**<br>A single-dose, open-label parallel study to assess the pharmacokinetics of RLX030 in subjects with mild, moderate and severe hepatic impairment compared to healthy control subjects |
| **Phase of Development**<br>Phase I |
| **Study Start/End Dates**<br>29-Jun-2011 to 16-Dec-2011 |
| **Study Design/Methodology**<br>This was a two-center, multinational, open labeled, parallel-group design in patients with mild, moderate and severe hepatic impairment along with demographically matched healthy control subjects with normal hepatic function to assess the pharmacokinetics of RLX030. The duration of constant infusion with RLX030 was planned to be 24 hours at a dose of 30 µg/kg/day. Subjects were matched by race, sex, age (±5 years) and weight (±15%). The groups, i.e. patients with mild (Group 1; 8 subjects), moderate (Group 2; 8 subjects) and severe (Group 3; 8 subjects) hepatic impairment and healthy volunteers (Group 4, 24 subjects), were enrolled in parallel into the study. |
| **Centres**<br>2 centers in 2 countries: Germany and Russia. |
| **Publication**<br>Not applicable. |

**Outcome measures**

Primary outcome measures(s)

- Area under the serum concentration-time curve from time zero to infinity (AUCinf)
- Area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast)
- Serum concentration at 24 hour (C24h) after administration

Timeframe: Screening, Day 1, 2, 3, 4 and Day 15

Outcome Measure Description: Blood samples will be collected during screening, days 1 through 4 and then on Day 15 for the determination of serum concentrations of RLX030

Secondary outcome measures(s)

- Number of patients with adverse events, serious adverse events and death

Timeframe: Day 15

Outcome Measure Description: Adverse events will be based on evaluation of physical signs, electrocardiograms and clinical laboratory assessments

- Mean residence time [MRT] of RLX030
- Terminal elimination half life (T ½) of RLX030
- Systemic clearance of RLX030 from serum (CL)
- Volume of distribution at steady state (Vss)

Timeframe: screening, days 1, 2, 3, 4 and 15

Outcome Measure Description: Blood samples will be collected during screening, days 1 through 4 and then on Day 15 for the determination of serum concentrations of RLX030

- Determination of the presence and quantification of anti-RLX030 antibodies

Timeframe: Baseline and end of study (Day 15)

Outcome Measure Description: Blood will be collected and serum analyzed for the presence of antiRLX030 antibodies. Anti-RLX030 antibodies will be evaluated in serum in a validated four-tiered assay approach

**Test Product, Dose, and Mode of Administration**

Vials: 3.5 mg/3.5 mL per vial (1.0 mg/mL)
Serelaxin, 30 µg/kg/day administered as a single IV 24 hour infusion

**Statistical Methods**

The pharmacokinetic parameters were determined from serum RLX030 concentration–time data using non-compartmental method(s). Listings and descriptive statistical summaries by groups were provided for all PK parameters. Graphical presentation was employed to show mean and individual concentration-time profiles.
PK parameters AUC0-48h, AUCinf, and C24h of RLX030 were compared between each

hepatically impaired group (mild, moderate and severe) vs. the matched control group. Log-transformed PK parameters were analyzed separately using a linear mixed effects model with group as fixed effect and matched pair as random effect. Least square means for each group as well as contrasts between control and each hepatically impaired group with corresponding 90% confidence intervals on the log-scale were calculated. Back-transformed ratios and 90% confidence interval were also provided.
In addition, regression analyses of the primary PK parameters versus the Child-Pugh score were done for impaired subjects, and were illustrated by scatter plots.
Safety and tolerability variables including vital signs, AEs, ECG and laboratory variables, as well as demographic information, were analyzed in a descriptive manner (by frequency tables or descriptive summary statistics as appropriate). The safety population, consisting of all enrolled subjects who took at least one dose of study drug, was used for safety analyses.
Immunogenicity results were also analyzed.

**Study Population: Inclusion/Exclusion Criteria and Demographics**

**Inclusion criteria**

Groups 1, 2, 3 and 4 (all subjects):

Male and female subjects 18 to 70 years of age (inclusive) and had to have a body mass index (BMI) within the range of 18 - 35 kg/m2.

Groups 1, 2 and 3 (subjects with hepatic impairment)

Subjects had to satisfy the criteria for hepatic impairment as evidenced by a Child-Pugh score of A, B or C at screening

- Mild hepatic impairment (=Group 1): Child-Pugh Class A (5-6 points)
- Moderate hepatic impairment (=Group 2): Child-Pugh Class B (7-9 points)
- Severe hepatic impairment (=Group 3): Child-Pugh Class C (10-15 points)

Group 4 (healthy subjects)

Each healthy subject was to match in race, age (±5 years), gender, weight (±15%) to an individual subject with hepatic impairment in Group 1, 2 or 3

**Exclusion criteria**

Groups 1, 2, 3 and 4 (all subjects)

- Hepatic impairment due to non-liver disease
- History of hypersensitivity to RLX030 or to drugs of similar classes

Groups 1, 2 and 3 (subjects with hepatic impairment)

- Presence of any non-controlled and clinically significant disease that could have affected the study outcome or that would have placed the subject at undue risk
- Treatment with any cytostatic drug, vasodilator, autonomic alpha blocker or B2 agonist.
- Encephalopathy Stage III or IV; Primary biliary liver cirrhosis
- History of gastro-intestinal bleeding within the past 6 months prior to screening

Other protocol defined inclusion/exclusion criteria applied.

## Participant Flow (Safety Analysis Set)

| | Group 1 N=9 | Group 2 N=8 | Group 3 N=8 | All patients with hepatic impairment N=25 | Group 4 N=24 | All Subjects N=49 |
|---|---|---|---|---|---|---|
| Subjects n (%) | | | | | | |
| Completed | 8 (88.9%) | 8 (100.0%) | 8 (100.0%) | 24 (96.0%) | 24 (100.0%) | 48 (98.0%) |
| Discontinued | 1 (11.1%) | 0 (0.0%) | 0 (0.0%) | 1 (4.0%) | 0 (0.0%) | 1 (2.0%) |
| Main cause of discontinuation | | | | | | |
| Subject withdrew consent | 1 (11.1%) | 0 (0.0%) | 0 (0.0%) | 1 (4.0%) | 0 (0.0%) | 1 (2.0%) |

Group 1: Child-Pugh A, subjects with mild hepatic impairment
Group 2: Child-Pugh B, subjects with moderate hepatic impairment
Group 3: Child-Pugh C, subjects with severe hepatic impairment
Group 4: Matched healthy subjects

## Baseline Characteristics (Safety Analysis Set)

| | | Group 1 N=9 | Group 2 N=8 | Group 3 N=8 | All Impaired Subjects N=25 | Group 4 N=24 | All Subjects N=49 |
|---|---|---|---|---|---|---|---|
| Age (years) | Mean (SD) | 53.8 (5.61) | 51.4 (6.41) | 50.3 (12.23) | 51.9 (8.27) | 52.2 (9.48) | 52.0 (8.79) |
| | Median | 52.0 | 51.0 | 54.5 | 53.0 | 53.0 | 53.0 |
| | Range | 44 - 61 | 40 - 60 | 30 - 65 | 30 - 65 | 28 - 65 | 28 - 65 |
| Sex - n (%) | Male | 6 (66.7) | 5 (62.5) | 5 (62.5) | 16 (64.0) | 15 (62.5) | 31 (63.3) |
| | Female | 3 (33.3) | 3 (37.5) | 3 (37.5) | 9 (36.0) | 9 (37.5) | 18 (36.7) |
| Race - n (%) | Caucasian | 9 (100.0) | 8 (100.0) | 8 (100.0) | 25 (100.0) | 24 (100.0) | 49 (100.0) |
| Ethnicity - n (%) | Other | 9 (100.0) | 8 (100.0) | 8 (100.0) | 25 (100.0) | 24 (100.0) | 49 (100.0) |
| Weight (kg) | Mean (SD) | 82.56 (14.082) | 82.09 (15.572) | 82.85 (15.000) | 82.50 (14.232) | 81.81 (12.873) | 82.16 (13.446) |
| | Median | 76.70 | 82.05 | 77.40 | 77.90 | 78.00 | 77.90 |
| | Range | 65.0 - 103.0 | 58.0 - 101.5 | 67.8 - 109.1 | 58.0 - 109.1 | 63.6 - 110.5 | 58.0 - 110.5 |
| Height (cm) | Mean (SD) | 170.8 (10.39) | 171.5 (8.30) | 169.0 (12.64) | 170.4 (10.19) | 173.8 (10.34) | 172.1 (10.30) |
| | Median | 171.0 | 170.5 | 173.0 | 171.0 | 173.0 | 171.0 |
| | Range | 156 - 190 | 160 - 187 | 151 - 186 | 151 - 190 | 152 - 195 | 151 - 195 |
| Body Mass Index ($kg/m^2$) | Mean (SD) | 28.31 (4.101) | 27.89 (5.053) | 29.05 (4.392) | 28.41 (4.348) | 27.14 (4.116) | 27.79 (4.240) |
| | Median | 26.73 | 26.47 | 28.69 | 27.51 | 26.37 | 26.60 |
| | Range | 23.0 - 34.9 | 22.6 - 34.7 | 23.7 - 34.7 | 22.6 - 34.9 | 21.3 - 34.8 | 21.3 - 34.9 |

## Outcome measures

### Primary Outcome Results (Pharmacokinetic Analysis Set)

| PK Parameters Geometric Mean (CV% Geo-Mean); Range | Group 1_Mild (n=8) | Group 2_Moderate (n=8) | Group 3_Severe (n=8) | Group 4_Healthy Matched (n=24) |
|---|---|---|---|---|
| Dose-normalized C24h (kg*ng/mL/µg) | 0.3826 (21.77); 0.252-0.494 | 0.3465 (70.12); 0.083-0.800 | 0.4103 (26.95); 0.296-0.709 | 0.3943 (25.21); 0.253-0.726 |
| Dose-normalized AUCinf (hr*kg*ng/mL/µg) | 10.19 (15.71); 8.48-11.9 | 10.60 (33.90); 5.92-18.4 | 10.04 (28.17); 7.77-17.1 | 10.26 (23.38); 6.43-16.1 |
| Dose-normalized AUC0-48h* (hr*kg*ng/mL/µg) | 10.8 (15.72); 8.37-11.8 | 10.45 (34.25); 5.77-18.2 | 9.920 (27.85); 7.73-16.9 | 10.15 (23.14); 6.35-15.8 |

CV% geo mean = sqrt(exp(variance for log transformed data)-1)) * 100.

*For the non-compartmental PK parameters, the AUC0-48h was reported instead of AUClast, which was the intended primary outcome measure specified in the protocol. This was because not all subjects had the same time point when the last detectable serum RLX030 was observed (Tlast=48h or 72h).

### Secondary Outcome Results

For objective "safety and tolerability" see below: Safety results.

### Pharmacokinetic parameters: (Pharmacokinetic Analysis Set)

| PK Parameters Geometric Mean (CV% Geo-Mean); Range | Group 1_Mild (n=8) | Group 2_Moderate (n=8) | Group 3_Severe (n=8) | Group 4_Healthy Matched (n=24) |
|---|---|---|---|---|
| MRT (hr) | 3.551 (12.28); 2.88-4.08 | 3.771 (29.53); 2.52-5.27 | 4.246 (24.28); 2.80-5.77 | 3.287 (38-19); 1.93-12.7 |
| T1/2 (hr) | 7.644 (8.48); 6.86-8.53 | 7.736 (12.54); 6.33-9.04 | 6.865 (24.05); 4.08-8.84 | 7.815 (22.03); 4.81-10.9 |
| CL (mL/hr/kg) | 98.12 (15.71); 83.9-118 | 94.36 (33.90); 54.2-169 | 99.56 (28.17); 58.5-129 | 97.45 (23.38); 62.2-156 |
| Vss (mL/kg) | 348.4 (20.73); 256-473 | 355.8 (49.15); 229-890 | 422.7 (29.51); 243-691 | 320.3 (41.07); 179-1080 |

### Immunogenicity: (Safety Analysis Set)

| Visit | Immunogenicity | Group 1 N=9 (n,%) | Group 2 N=8 (n,%) | Group 3 N=8 (n,%) | Group 4 N=24 (n,%) |
|---|---|---|---|---|---|
| Day 1 pre-dose | Yes | 0 ( 0.0) | 0 ( 0.0) | 1 (12.5) | 0 ( 0.0) |
| | No | 9 ( 100) | 8 ( 100) | 7 (87.5) | 24 ( 100) |

| | | | | | | |
|---|---|---|---|---|---|---|
| EOS | Yes | 0 ( 0.0) | 0 ( 0.0) | 1 (12.5) | 0 ( 0.0) | |
| | No | 9 ( 100) | 8 ( 100) | 7 (87.5) | 24 ( 100) | |

## Safety Results

### Adverse Events by System Organ Class

| | | | | All Impaired | | All |
|---|---|---|---|---|---|---|
| | **Group 1** | **Group 2** | **Group 3** | **Subjects** | **Group 4** | **Subjects** |
| | **N=9** | **N=8** | **N=8** | **N=25** | **N=24** | **N=49** |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Subjects with AE(s) | 0 (0.0) | 2 (25.0) | 0 (0.0) | 2 (8.0) | 3 (12.5) | 5 (10.2) |
| **System organ class** | | | | | | |
| Gastrointestinal disorders | 0 (0.0) | 1 (12.5) | 0 (0.0) | 1 (4.0) | 0 (0.0) | 1 (2.0) |
| Hepatobiliary disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.2) | 1 (2.0) |
| Investigations | 0 (0.0) | 1 (12.5) | 0 (0.0) | 1 (4.0) | 0 (0.0) | 1 (2.0) |
| Musculoskeletal and connective tissue disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.2) | 1 (2.0) |
| Nervous system disorders | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.2) | 1 (2.0) |

Group 1: Child-Pugh A, subjects with mild hepatic impairment

Group 2: Child-Pugh B, subjects with moderate hepatic impairment

Group 3: Child-Pugh C, subjects with severe hepatic impairment

Group 4: Matched healthy subjects

Under one group: A subject with multiple occurrences of an adverse event was counted only once in the AE category. A subject with multiple adverse events within a body system was counted only once in the total row. N = number of subjects studied. n = number of subjects with at least one AE in the category. Only adverse events occurring at or after first drug intake were included.

**10 Most Frequently Reported AEs Overall by Preferred Term n (%)**

| | | | | All Impaired | | All |
|---|---|---|---|---|---|---|
| | Group 1 | Group 2 | Group 3 | Subjects | Group 4 | Subjects |
| | N=9 | N=8 | N=8 | N=25 | N=24 | N=49 |
| | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Subjects with AE(s) | 0 (0.0) | 2 (25.0) | 0 (0.0) | 2 ( 8.0) | 3 (12.5) | 5 (10.2) |
| Preferred term | | | | | | |
| Dyspepsia | 0 (0.0) | 1 (12.5) | 0 (0.0) | 1 (4.0) | 0 (0.0) | 1 (2.0) |
| Haemoglobin decreased | 0 (0.0) | 1 (12.5) | 0 (0.0) | 1 (4.0) | 0 (0.0) | 1 (2.0) |
| Headache | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.2) | 1 (2.0) |
| Hyperbilirubinaemia | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.2) | 1 (2.0) |
| Pain in extremity | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1 (4.2) | 1 (2.0) |

Under one group: A subject with multiple occurrences of an adverse event was counted only once in the AE category. A subject with multiple adverse events within a body system was counted only once in the total row. N = number of subjects studied. n = number of subjects with at least one AE in the category. Only adverse events occurring at or after first drug intake were included.

**Serious Adverse Events and Deaths**

No serious adverse event or death or another significant adverse event occurred in the study.

**Other Relevant Findings**

Not applicable.

**Date of Clinical Trial Report**

30 NOV 2012

**Date Inclusion on Novartis Clinical Trial Results Database**

06 DEC 2012

**Date of Latest Update**

26 NOV 2012