Sponsor

Novartis

Generic Drug Name

Serelaxin

Trial Indication(s)

Patients with severe renal impairment or End Stage Renal Disease (ESRD) on hemodialysis compared to matched healthy control subjects

Protocol Number

CRLX030A2102

Protocol Title

A single dose, open-label, parallel-group study to assess the pharmacokinetics of serelaxin in patients with severe renal impairment or End-Stage Renal Disease on hemodialysis compared to matched healthy control subjects

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

26 Aug 2013 to 18 Dec 2013

Reason for Termination (If applicable)

Not applicable.

Study Design/Methodology

This was a single dose, open-label, parallel-group study to assess the pharmacokinetics of serelaxin in patients with severe renal impairment or End-Stage Renal Disease on hemodialysis compared to matched healthy control subjects. Each subject underwent a Screening visit of up to 21 days prior to dosing, during which a clinical examination was performed and each of the eligibility criteria was assessed. Eligible subjects were admitted to the study site at Baseline, where eligibility for enrollment into the study was confirmed. The duration of the treatment period was three days. All subjects received a single 4-hour infusion (10 µg/kg) of serelaxin. From baseline as well as during and following the treatment period, subjects were required to remain domiciled at site for approximately 3 days (until the morning of Day 3 [48h]) for collection of blood for PK, immunogenicity and safety assessments. Between the treatment period and the End of Study (EOS) visit the subjects were released from the study site provided there were no safety or tolerability concerns as judged by the Investigator. Each subject was instructed to return to the study site for an end of study evaluation on Day 15 (±2 days). Total duration of the trial for one subject was maximally 38 days (including screening).

Centers

1 center in 1 country: Germany (1)

Publication

Not applicable.

Objectives:

Primary objective

- To investigate the pharmacokinetics of serelaxin after a single dose of 10 µg/kg as iv infusion administered for 4 hours in patients with severe renal impairment and ESRD on hemodialysis (with PK on the day of dialysis and during the dialysis-free interval) in comparison to healthy control subjects.

Secondary objectives

- To assess safety and tolerability of serelaxin after a single dose of 10 µg/kg as iv infusion administered for 4 hours in patients with severe renal impairment and ESRD on hemodialysis (with PK on the day of dialysis and during the dialysis-free interval) and healthy control subjects
- To assess immunogenicity of serelaxin after a single dose of 10 µg/kg as iv infusion administered for 4 hours in patients with severe renal impairment and ESRD on hemodialysis (with PK on the day of dialysis and during the dialysis-free interval) and healthy control subjects.

Test Product (s), Dose(s), and Mode(s) of Administration

Serelaxin (RLX030) 3.5 mg/3.5 mL per vial (1.0 mg/mL), was prepared by Novartis and supplied to the Investigator as open labeled bulk medication. Serelaxin was administered intravenously. Single 10 µg/kg dose of serelaxin was administered as 4 hour infusion in all groups (Group 1, 2, 3 and 4).

Statistical Methods

The primary aim of this study was to assess the PK in renally impaired patients. To this end a statistical analysis was done on PK parameters of serelaxin. The ratios of PK parameters (renal impaired patients vs. matched healthy subjects) along with the 90% confidence intervals were calculated.

For characterizing the PK of serelaxin in renal impaired group vs. respective matched healthy subjects, PK parameters (Cmax, AUClast, AUC0-28hr and AUCinf) of serelaxin were compared between each renal impaired group (severe, ESRD on hemodialysis with PK on day of dialysis and ESRD on hemodialysis with PK during the dialysis-free interval) vs. respective matched healthy subjects group. Log-transformed PK parameters were analyzed using a linear mixed effect model with subject group as fixed effect and matching pair as random effect. Least square means for each group as well as estimated difference between renal impaired patients and respective matched healthy subjects with corresponding 90% confidence intervals on the log-scale were calculated. These estimates were back-transformed to obtain ratio of geometric means, and the associated 90% CI for the comparison of renal impaired group vs. matched healthy subjects.

In addition, PK parameters (Cmax, AUClast, AUC0-28hr and AUCinf) obtained on the day of hemodialysis versus during the dialysis-free interval were compared between the two groups of patients with ESRD, in order to evaluate the impact of hemodialysis on the PK of serelaxin with subject group as fixed effect.

Safety and tolerability variables including vital signs, AEs, ECG and laboratory variables, as well as demographic information, were analyzed.

Results of the anti-RLX030 antibody assay were listed by subject group, subject and sampling time. Incidence of positive anti-RLX030 antibodies were summarized by subject group and sampling time.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

All subjects

- Male and female subjects 18 to 75 years of age (inclusive) and had to have a body mass index (BMI) within the range of 18 - 35 kg/m^2 with at least 50 kg of body weight

Patients with severe renal impairment / ESRD

- Severe renal impairment as evidenced by clinically significantly abnormal creatinine and creatinine clearance (15mL/min/1.73m^2 ≤ eGFR < 30mL/min/1.73m^2) or ESRD on hemodialysis.
- Sitting vital signs should have been within the following ranges:
    - oral body temperature between 35.0-37.5°C
    - systolic blood pressure, 110 to 170 mmHg
    - diastolic blood pressure, 60 to 105 mmHg
    - pulse rate, 45 - 100 bpm

Healthy subjects

- eGFR > 90mL/min/1.73m^2; matching in race, age (±10 years), gender, BMI (±15%) to an individual subject with renal impairment in Group 1, 2 or 3.
- Subject had to be in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening.
- Sitting vital signs should have been within the following ranges:
    - oral body temperature between 35.0-37.5°C
    - systolic blood pressure, 100 to 150 mmHg
    - diastolic blood pressure, 60 to 95 mmHg
    - pulse rate, 50 to 100 bpm

Exclusion criteria

All subjects

- History of clinically significant ECG abnormalities at Screening or Baseline, according to the opinion of the investigator.

- Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
- Women of child-bearing potential unless they were using highly effective methods of contraception during dosing of study treatment.
- Sexually active males (incl. vasectomized men) were to use a condom during intercourse while taking drug and for 2 weeks after stopping study medication.
- Recent (within the last three years) and/or recurrent history of autonomic dysfunction (e.g., recurrent episodes of fainting, palpitations, etc.).

Patients with severe renal impairment / ESRD

- Presence of any non-controlled and clinically significant disease, surgical or medical condition that could have affected the study outcome or that would have placed the patient at undue risk as judged by the investigator.
- Hemoglobin levels below 9.0 g/dL at screening and baseline, other laboratory parameters at screening and baseline outside acceptable limits as judged by the investigator (considering the underlying disease(s) of the patients).
- Treatment with any cytostatic drug or autonomic alpha blocker.

Healthy subjects

- Use of any prescription drugs (other than hormonal contraception, herbal supplements, within four (4) weeks prior to initial dosing, and/or over-the-counter (OTC) medication, dietary supplements (vitamins included) within two (2) weeks prior to initial dosing.
- History or presence of any disease, surgical or medical condition of any major system organ class considered clinically significant by the investigator.
- Laboratory parameter at screening and baseline outside of normal limits. For small deviations which could have been attributed to the characteristics of the subjects (e.g. age) it was at the discretion of the investigator to consider them as exclusive or not.
- A positive Hepatitis B surface antigen or Hepatitis C test result.

Participant Flow Table

Subject disposition – n (percent) of subjects (Safety analysis set)

	Group 1 N=6 n (%)	Group 2 N=6 n (%)	Group 3 N=6 n (%)	All impaired subjects N=18 n (%)	All healthy subjects (Group 4) N=18 n (%)	All subjects N=36 n (%)
Subjects						
Completed	6 (100%)	6 (100%)	6 (100%)	18 (100%)	18 (100%)	36 (100%)

Group 1: Patients with severe renal impairment

Group 2: Patients with ESRD (on hemodialysis), with PK on a day of dialysis

Group 3: Patients with ESRD (on hemodialysis), with PK during dialysis-free interval

Group 4: Matched healthy volunteers

Baseline Characteristics

Demographic summary by treatment group (Safety analysis set)

		Group 1 N=6	Group 2 N=6	Group 3 N=6	All impaired subjects N=18	All healthy subjects (Group 4) N=18	All subjects N=36
Age (years)	Mean (SD)	58.7 (10.13)	46.5 (11.95)	52.3 (15.78)	52.5 (13.10)	52.0 (12.01)	52.3 (12.39)
	Median	59.0	44.0	50.5	52.5	53.0	52.5
	Min; Max	44; 73	31; 66	35; 74	31; 74	31; 70	31; 74
Sex - n (%)	Male	5 (83.3 %)	4 (66.7 %)	5 (83.3 %)	14 (77.8 %)	14 (77.8 %)	28 (77.8 %)
	Female	1 (16.7 %)	2 (33.3 %)	1 (16.7 %)	4 (22.2 %)	4 (22.2 %)	8 (22.2 %)
Race - n (%)	Caucasian	6 (100 %)	6 (100 %)	6 (100 %)	18 (100 %)	18 (100 %)	36 (100 %)
Ethnicity - n (%)	Other	6 (100 %)	6 (100 %)	6 (100 %)	18 (100 %)	18 (100 %)	36 (100 %)
Height (cm)	Mean (SD)	174.5 (5.50)	172.3 (12.56)	177.0 (9.23)	174.6 (9.18)	171.6 (6.78)	173.1 (8.10)
	Median	172.5	167.5	177.5	172.5	171.5	172.0
	Min; Max	170; 184	160; 193	165; 190	160; 193	160; 182	160; 193
Weight (kg)	Mean (SD)	84.9 (12.17)	75.6 (6.86)	83.1 (24.62)	81.2 (15.91)	76.7 (10.25)	79.0 (13.38)
	Median	80.8	76.1	77.4	77.3	76.2	77.3
	Min; Max	75.7; 108.0	65.0; 85.1	57.8; 120.0	57.8; 120.0	62.0; 99.3	57.8; 120.0
Body Mass Index (kg/m^2)	Mean (SD)	27.91 (3.99)	25.53 (1.98)	26.24 (6.08)	26.56 (4.22)	26.02 (2.78)	26.29 (3.53)
	Median	27.39	25.40	25.32	25.65	25.53	25.62
	Min; Max	22.89; 34.08	22.84; 27.88	19.91; 33.40	19.91; 34.08	22.23; 31.52	19.91; 34.08

Group 1: Patients with severe renal impairment

Group 2: Patients with ESRD (on hemodialysis), with PK on a day of dialysis

Group 3: Patients with ESRD (on hemodialysis), with PK during dialysis-free interval

Group 4: Matched healthy volunteers

Summary of Efficacy

Primary Outcome Result(s)

Summary statistics for serum serelaxin PK parameters of primary interest per group

Group	Statistic	AUCinf (hr*ng/mL)	AUClast (hr*ng/mL)	AUC0-28hr (hr*ng/mL)	Cmax (ng/mL)
Group 1	n	6	6	6	6
	Mean (SD)	145 (20.3)	143 (19.9)	139 (18.5)	21.9 (2.90)
	Geo-mean (CV%)	144 (13.0)	142 (12.9)	138 (12.5)	21.7 (13.4)
	Median [Min; Max]	139 [129;184]	138 [128;182]	134 [123;174]	21.9 [18.0;26.0]
Group 2	n	6	6	6	6
	Mean (SD)	132 (16.1)	130 (15.4)	125 (14.1)	20.6 (1.92)
	Geo-mean (CV%)	131 (12.5)	130 (12.1)	125 (11.4)	20.5 (9.4)
	Median [Min; Max]	129 [108;152]	128 [107;151]	122 [105;146]	20.1 [17.8;23.2]
Group 3	n	6	6	6	6
	Mean (SD)	174 (18.7)	171 (18.9)	163 (19.2)	21.5 (4.09)
	Geo-mean (CV%)	173 (10.5)	170 (10.7)	162 (11.4)	21.2 (18.1)
	Median [Min; Max]	172 [150;207]	169 [148;205]	160 [141;197]	20.6 [17.5;28.8]
Group 4	n	18	18	18	18
	Mean (SD)	82.9 (11.2)	82.6 (11.2)	81.8 (10.9)	15.6 (2.17)
	Geo-mean (CV%)	82.2 (13.3)	81.9 (13.3)	81.2 (13.0)	15.4 (13.5)
	Median [Min; Max]	80.9 [67.2;104]	80.6 [67.0;103]	80.4 [66.8;103]	15.2 [12.5;20.0]

Group 1: Patients with severe renal impairment

Group 2: Patients with ESRD (on hemodialysis), with PK on a day of dialysis

Group 3: Patients with ESRD (on hemodialysis), with PK during dialysis-free interval

Group 4: Matched healthy volunteers

Secondary Outcome Result(s)

Refer to Safety Result section for secondary outcome result.

Frequency and percentage of subjects with or without positive anti-serelaxin antibodies (Safety analysis set)

Visit	Immunogenicity	Group 1 N=6 n/N (%)	Group 2 N=6 n/N (%)	Group 3 N=6 n/N (%)	All impaired subjects N=18 n/N (%)	All healthy subjects (Group 4) N=18 n/N (%)	All subjects N=36 n/N (%)
Day1 (Pre-dose)	No immunogenicity	6/ 6 (100%)	6/ 6 (100%)	6/ 6 (100%)	18/18 (100%)	18/18 (100%)	36/36 (100%)
	Positive immunogenicity	0	0	0	0	0	0
EOS	No immunogenicity	6/ 6 (100%)	6/ 6 (100%)	6/ 6 (100%)	18/18 (100%)	18/18 (100%)	36/36 (100%)
	Positive immunogenicity	0	0	0	0	0	0

EOS: End of study visit

Group 1: Patients with severe renal impairment

Group 2: Patients with ESRD (on hemodialysis), with PK on a day of dialysis

Group 3: Patients with ESRD (on hemodialysis), with PK during dialysis-free interval

Group 4: Matched healthy volunteers

Summary of Safety

Safety Results

Incidence of treatment emergent AEs by primary system organ class - n (percent) of subjects (Safety analysis set)

	Group 1 N=6 n (%)	Group 2 N=6 n (%)	Group 3 N=6 n (%)	All impaired subjects N=18 n (%)	All healthy subjects (Group 4) N=18 n (%)	All subjects N=36 n (%)
Subjects with AE(s)	1 (16.7)	0	0	1 (5.6)	1 (5.6)	2 (5.6)
System organ class						
Investigations	1 (16.7)	0	0	1 (5.6)	0	1 (2.8)
Nervous system disorders	0	0	0	0	1 (5.6)	1 (2.8)

Arranged in descending order of frequency (in total group) and alphabetically by system organ class.

Under one treatment, a subject with multiple occurrences of an AE is counted only once in the AE category; a subject with multiple AEs within a body system is 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 AEs occurring at or after study drug administration are included.

Group 1: Patients with severe renal impairment; Group 2: Patients with ESRD, with PK on a day of dialysis

Group 3: Patients with ESRD, with PK during dialysis-free interval; Group 4: Matched healthy volunteers

Incidence of treatment emergent AEs by preferred term - n (percent) of subjects (Safety analysis set)

	Group 1 N=6 n (%)	Group 2 N=6 n (%)	Group 3 N=6 n (%)	All impaired subjects N=18 n (%)	All healthy subjects (Group 4) N=18 n (%)	All subjects N=36 n (%)
Subjects with AE(s)	1 (16.7)	0	0	1 (5.6)	1 (5.6)	2 (5.6)
Preferred term						
Blood creatine phosphokinase increased	1 (16.7)	0	0	1 (5.6)	0	1 (2.8)
Headache	0	0	0	0	1 (5.6)	1 (2.8)

Arranged in descending order of frequency (in total group) and alphabetically by preferred term.
Under one treatment, a subject with multiple occurrences of an AE is counted only once in the AE category;
A subject with multiple AEs within a body system is 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 AEs occurring at or after study drug administration are included.
Group 1: Patients with severe renal impairment; Group 2: Patients with ESRD, with PK on a day of dialysis
Group 3: Patients with ESRD, with PK during dialysis-free interval; Group 4: Matched healthy volunteers

All four AEs were of mild intensity.

There were no deaths, SAEs or AEs leading to discontinuations in this study.

Other Relevant Findings

Not applicable.

Conclusion:

- Typical iv infusion serum PK profiles in all subjects were observed following a 4-hr iv infusion of serelaxin at a dose of 10 µg/kg, with a rapid increase soon after the start of infusion, a peak concentration reached at the end of the infusion, and a fast declining phase upon the end of the infusion. Compared to the matched healthy subjects, patients with severe renal impairment or ESRD had a higher Cmax (geometric mean ratio of impaired vs. healthy subjects =1.30-1.42) and a higher AUCinf (geometric mean ratio of impaired vs. healthy subjects =1.61-2.15). Differences in serelaxin PK were much smaller when compared between the groups of patients with renal impairment.
- No anti-serelaxin antibodies were detected in any subjects following the 4-hr iv infusion of serelaxin.
- Serelaxin was well tolerated by patients with severe renal impairment/ESRD requiring hemodialysis and healthy subjects in this study.
- No deaths, serious adverse events (SAEs) or adverse events (AEs) leading to discontinuations were reported during the study.
- There were four AEs (of which two were treatment emergent) reported, and all were of mild severity. Only headache was suspected to be related to the study drug. No AE of hypotension was reported.

Date of Clinical Trial Report

19 June 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

17 November 2014

Date of Latest Update

Not applicable.

Reason for Update

Not applicable.