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Sponsor: Pfizer Inc

Investigational Product: Lorlatinib

Clinical Study Report Synopsis: Protocol B7461010

Protocol Title: A Phase 1, Single Dose Open-Label Study to Evaluate the Pharmacokinetics of Lorlatinib in Subjects With Impaired Renal Function.

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Centers: The study was conducted in 2 centers in the United States (Appendix 16.1.4.1).

Publications Based on the Study:

Lin S, Gong J, Pithavala Y. P2.14-39. Effects of renal function on lorlatinib safety and pharmacokinetics. J Thorac Oncol 2019; 14(10S):S844-5.

Study Initiation Date: 23 August 2018

Study Completion Date: 20 February 2020

Report Date: 20 July 2020

Previous Report Date(s): Not applicable

Phase of Development: Phase 1

Study Objectives and Endpoints:

The study objectives and endpoints are presented in Table 1.

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Table 1. Study Objectives and Endpoints

Type	Objective	Endpoint
Primary		
PK	To evaluate the effect of renal impairment on the single dose PK of lorlatinib on otherwise healthy participants.	• Plasma AUC_{inf} and C_{max} for lorlatinib.
Secondary		
Safety	To evaluate the safety and tolerability of a single dose of lorlatinib in healthy participants and participants with renal impairment.	• Clinical laboratory tests, physical examination findings, vital sign measurements, ECGs, and AEs.
Tertiary		
PK	To evaluate the PK of lorlatinib metabolite(s) in healthy participants and participants with renal impairment who were otherwise healthy.	• Plasma AUC_{last}, T_{max}, $t_{½}$, CL/F, V_z/F, CL_R, Ae and Ae% for lorlatinib. • Plasma AUC_{inf}, AUC_{last}, C_{max}, T_{max}, $t_{½}$, MRC_{max}, $MRAUC_{inf}$, $MRAUC_{last}$ for lorlatinib metabolite(s).

METHODS

Study Design: This was a Phase 1, open-label, multi-center, single treatment study in participants with normal renal function and varying degrees of renal impairment who were otherwise healthy and met study entry criteria. Each participant received a single oral dose of lorlatinib administered in the fasted state.

This study was planned to enroll approximately 32 evaluable participants (see Table 2 for renal function requirements) who completed the pharmacokinetics (PK) assessments.

Table 2. Renal Function Groups

Group (planned number of participants)	Renal Function	Absolute eGFR
A (n=8)	Normal	≥90 mL/min
B (n=8)	Mild renal impairment	≥60 - <90 mL/min
C (n=8)	Moderate renal impairment	≥30 - <60 mL/min
D (n=8)	Severe renal impairment	<30 mL/min and not requiring dialysis

Participants who did not complete all PK collections could be replaced to ensure 8 evaluable participants in Groups A, B, and C and at least 4 evaluable participants in Group D. The absolute estimated glomerular filtration rate (eGFR) (mL/min) for renal disease classification or participant assignment into different renal disease groups was obtained by multiplying individual participant's normalized body surface area (BSA) (ie, measured BSA/1.73 m^2) with his/her eGFR calculated using the Modification of Diet in Renal Disease (MDRD)

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equation. In addition, creatinine clearance (CL_{cr}) was calculated using the Cockcroft-Gault (C-G) equation.

A single oral dose of lorlatinib 100 mg was administered first to participants with mild renal impairment (Group B). After single oral dose of lorlatinib 100 mg was tolerated in at least 3 participants with mild renal impairment, participants with moderate renal impairment (Group C) were enrolled 1 at a time and administered a single oral dose of lorlatinib. After dosing of 3 participants with moderate renal impairment, the PK, safety, and tolerability were evaluated during an observation period of at least 1 week. Then, the remaining participants in Group C and the participants in Group D (severe renal impairment) were enrolled and dosed. All participants received a single dose of lorlatinib 100 mg. Participants with normal renal function (Group A) were matched to the participants with renal impairment (Groups B, C, and D), therefore, enrollment of Group A began after all participants from Groups B, C, and D had completed the PK collection.

Diagnosis and Main Criteria for Inclusion: Female participants of non-childbearing potential and/or male participants between the ages of 18 and 75 years, inclusive, with body mass index (BMI) of 17.5 to 36 kg/m^2 and a total body weight >50 kg (110 lb), who had normal renal function, and who had varying degrees of renal impairment were eligible to participate in the study.

Study Treatment: Following an overnight fast of at least 10 hours, participants received a 100 mg dose of lorlatinib tablets with approximately 240 mL of ambient temperature water at approximately 0800 hours (±3 hours).

Study drug information is provided in Table 3.

Table 3. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
PF-06463922 25 mg Round White Film Coated Tablet	SW-SDM	16-002268	25 mg	Tablet
PF-06463922 25 mg Round White Film Coated Tablet	SW-SDM	17-001188	25 mg	Tablet

Efficacy Evaluations: Not Applicable

Pharmacokinetic Evaluations:

Plasma

Plasma samples for characterization of PK of lorlatinib and its metabolite were collected prior to lorlatinib dose (time 0) and at 0.5, 1, 1.5, 2, 4, 6, 8, 12, 24 (Day 2), 48 (Day 3), 72 (Day 4), 96 (Day 5), and 120 (Day 6) hours post dosing. An additional blood sample was

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required to be collected from participants experiencing unexpected and/or serious adverse events (SAEs). Plasma samples were assayed using a validated, sensitive, and specific high-performance liquid chromatography tandem mass spectrometric (HPLC-MS/MS) method.

Urine

Urine samples were collected prior to lorlatinib administration. Post-dose urine collection was separated into 0-24, 24-48, 48-72, 72-96, and 96-120 hours intervals. Each participant emptied his or her bladder just prior to dosing. Urine samples were assayed using a validated, sensitive, and specific HPLC-MS/MS method.

The following PK parameters for lorlatinib and its metabolite, PF-06895751, were calculated for each participant, as applicable, using non-compartmental analysis of concentration-time data. Samples below the low limit of quantification (LLOQ) were set to 0 ng/mL for the PK analysis. Actual sample collection time was used for the PK analysis when available, otherwise nominal time post-dose was used.

Lorlatinib and PF-06895751 plasma PK parameters are described in Table 4 and, lorlatinib urine PK parameters are described in Table 5.

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Table 4. Lorlatinib and PF-06895751 (Metabolite) Plasma Pharmacokinetic Parameters Determined, Protocol B7461010

Parameter	Definition	Method of Determination
C_{max}	Maximum observed plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}*/k_{el})$, where $C_{last}*$ was the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis, and k_{el} was the terminal elimination phase rate constant calculated by a linear regression of the log-linear concentration-time curve.
$t_{½}$[a]	Terminal elimination plasma half-life	$\ln(2)/k_{el}$
CL/F [a,b]	Apparent clearance after oral dose	$Dose/AUC_{inf}$
V_Z/F [a,b]	Apparent volume of distribution following oral dose	$Dose/(AUC_{inf} \times k_{el})$
$MRAUC_{inf}$ [a]	Metabolite to Parent Ratio for AUC_{inf}	(Metabolite $AUC_{inf}/MW_{metabolite}$)†/ (Parent AUC_{inf}/MW_{parent})‡
$MRAUC_{last}$	Metabolite to Parent Ratio for AUC_{last}	(Metabolite $AUC_{last}/MW_{metabolite}$)†/ (Parent AUC_{last}/MW_{parent})‡
MRC_{max}	Metabolite to Parent Ratio for C_{max}	(Metabolite $C_{max}/MW_{metabolite}$)†/ (Parent C_{max}/MW_{parent})‡

PK parameter values were calculated using an internally validated software system, electronic non-compartmental analysis (eNCA, version 2.2.4).
† PF-06895751 data corrected for molecular weight (MW) (ng to nmol), [redacted].
‡ Lorlatinib data corrected for MW (ng to nmol), [redacted].
a. If data permitted.
b. Lorlatinib only

Table 5. Lorlatinib Urine Pharmacokinetic Parameters Determined, Protocol B7461010

Parameter	Definition	Method of Determination
Ae	Cumulative amount of drug recovered unchanged in urine	Sum of (urine concentration × sample volume[a]) for each collection interval from 0 to time 120 hours post-dose.
Ae%	Percent of dose recovered unchanged in urine	Ae/Dose × 100% based on urine collections from 0 to time 120 hours.
CL_R	Renal Clearance	Ae/AUC_{last}

PK parameter values were calculated using an internally validated software system, eNCA (version 2.2.4).
a. Sample volume = (Urine weight in g/1.020), where 1.020 g/mL is the approximate specific gravity of urine.

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Safety Evaluations: Safety evaluations included adverse events (AEs) and SAEs monitoring, clinical laboratory assessments, vital signs, single 12-lead electrocardiogram (ECG) monitoring, and physical examinations.

Statistical Methods:

Pharmacokinetics

The PK concentration population was defined as all participants enrolled and treated and who had at least 1 lorlatinib concentration. The PK parameter analysis population was defined as all participants enrolled and treated who had at least 1 of the PK parameters of primary interest. The relationship between PK parameters and renal function (eGFR) was determined by a linear regression model. The effect of the renal impairment on PK parameters was assessed by constructing 90% confidence intervals (CIs) around the estimated difference between each of the Test (renally impaired groups: Groups B, C and D) and the Reference (normal renal function group: Group A) using a one-way analysis of variance (ANOVA) model based on natural log transformed data.

Safety

All participants who received at least 1 dose of study medication were included in the safety analyses and listings. Safety data were presented in tabular and/or graphical format and summarized descriptively, where appropriate. A set of summary tables split by renal function group were produced to evaluate any potential risk associated with the safety and toleration of administering lorlatinib.

RESULTS

Participant Disposition and Demography:

A total of 29 participants (8 with normal renal function, 8 with mild renal impairment, 8 with moderate renal impairment, and 5 with severe renal impairment, including 1 considered as end-stage) were assigned and received a single dose (SD) of lorlatinib 100 mg. All participants completed the study.

Seventeen participants were male and 12 participants were female. The majority of the participants were White (79.3%). The mean (range) age of the participants was 59.7 (43 to 71) years. The mean (range) weight and BMI were 82.4 (61.9 to 101.0) kg and 28.6 (22.4 to 35.0) kg/m^2, respectively.

Efficacy Results: Efficacy evaluations were not done.

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Pharmacokinetic Results:

Lorlatinib Plasma Pharmacokinetics

Following administration of a single oral dose of lorlatinib 100 mg to participants with normal renal function or mild, moderate or severe renal impairment, median lorlatinib plasma concentrations increased marginally for participants in the moderate and severe renal impairment groups compared to the normal and mild impaired renal function groups. Lorlatinib maximum observed plasma concentration (C_{max}) was reached at about the same time in all participants (normal or impaired renal function), with median time for C_{max} (T_{max}) values of 1.0 to 1.5 hours post-dose (Table 6). Terminal lorlatinib elimination plasma half-life ($t_{½}$) was longer in the moderate and severe renal impairment groups, with mean ± standard deviation (SD) values of approximately 39±7.1 and 42±7.6 hours respectively, compared to 26±4.8 and 28±3.5 hours in participants with normal renal function and mild renal impairment, respectively (Table 6). Geometric mean lorlatinib apparent clearance (CL/F) was lower in participants with renal impairment compared to participants with normal renal function, while geometric mean apparent volume of distribution (V_z/F) was generally similar for all renal function groups (Table 6).

The overall lorlatinib plasma exposure based on geometric mean area under the plasma concentration-time profile from time 0 extrapolated to infinite time (AUC_{inf}) values were slightly higher for participants in the moderate and severe renal impairment groups compared to participants with normal renal function and mild renal impairment, while geometric mean C_{max} values were generally similar across all renal function groups (Table 6). Variability in lorlatinib plasma exposure based on geometric percent coefficient of variation (%CV) was similar across renal function groups and ranged from 24% to 52% for C_{max} and 27% to 37% for AUC_{inf}.

The adjusted geometric mean ratios (90% CIs) of lorlatinib plasma AUC_{inf} for the renal impairment groups (Test) versus the normal renal function group (Reference) were 104.25% (79.73%, 136.31%), 118.75% (91.43%, 154.24%), and 141.14% (97.82%, 203.66%) for the mild, moderate and severe renal impairment groups, respectively (Table 7).

The adjusted geometric mean ratios (90% CIs) of lorlatinib plasma C_{max} for the renal impairment groups (Test) versus the normal renal function group (Reference) were 100.53% (66.48%, 152.02%), 88.87% (64.18%, 123.06%), and 92.32% (56.58%, 150.63%) for the mild, moderate and severe renal impairment groups, respectively (Table 7).

The relationship between CL/F and renal function was evaluated utilizing a linear regression model. Results of the linear regression analysis by eGFR suggests a trend in correlation between CL/F and renal function.

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Table 6. Descriptive Summary of Plasma Lorlatinib PK Parameters by Renal Function Group, Protocol B7461010

Parameter (Unit)[a]	Normal Function (N=8)	Mild Impairment (N=8)	Moderate Impairment (N=8)	Severe Impairment (N=5)
N2, N3	8, 8	8, 8	8, 8	5, 5
AUC_{inf} (ng.hr/mL)	8329 (33)	8683 (29)	9890 (27)	11760 (37)
AUC_{last} (ng.hr/mL)	8015 (32)	8307 (28)	8867 (24)	10310 (36)
CL/F (L/hr)	12.02 (33)	11.51 (29)	10.11 (27)	8.507 (37)
C_{max} (ng/mL)	546.8 (48)	549.7 (52)	485.9 (24)	504.8 (50)
$t_{1/2}$ (hr)	25.64±4.7500	28.08±3.5156	39.40±7.1019	41.66±7.6081
T_{max} (hr)	1.50 (1.00-4.00)	1.00 (1.00-1.50)	1.25 (1.00-4.00)	1.00 (1.00-1.50)
V_z/F (L)	436.9 (24)	462.9 (27)	566.2 (21)	503.8 (36)

Source: Table 14.4.5.1.1
N:Total number of participants in the renal function group;
N2:Number of participants contributing to the summary statistics;
N3:Number of participants contributing to the summary statistics for AUC_{inf}, CL/F, $t_{1/2}$ and V_z/F.
a. Geometric mean (geometric % coefficient of variation) for all except median (range) for T_{max} and arithmetic mean±standard deviation for $t_{1/2}$.
[redacted] SDTM Creation: 21MAY2020 (21:23) Source Data: adpp Output File: [redacted] in Date of Generation: 21MAY2020 (21:37)

Table 7. Statistical Summary (ANOVA) of Log Transformed Plasma Lorlatinib PK Parameters - AUC_{inf}, AUC_{last} and C_{max}, Protocol B7461010

Parameter (Unit)	Adjusted Geometric Means		Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) for Ratio[a]
	Test	Reference		
Mild vs Normal				
AUC_{inf} (ng.hr/mL)	8683	8329	104.25	(79.73, 136.31)
AUC_{last} (ng.hr/mL)	8307	8015	103.65	(79.93, 134.41)
C_{max} (ng/mL)	549.7	546.8	100.53	(66.48, 152.02)
Moderate vs Normal				
AUC_{inf} (ng.hr/mL)	9890	8329	118.75	(91.43, 154.24)
AUC_{last} (ng.hr/mL)	8867	8015	110.63	(86.63, 141.28)

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Table 7. Statistical Summary (ANOVA) of Log Transformed Plasma Lorlatinib PK Parameters - AUC_{inf}, AUC_{last} and C_{max}, Protocol B7461010

Parameter (Unit)	Adjusted Geometric Means Test	Reference	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) for Ratio[a]
C_{max} (ng/mL)	485.9	546.8	88.87	(64.18, 123.06)
Severe vs Normal				
AUC_{inf} (ng.hr/mL)	11760	8329	141.14	(97.82, 203.66)
AUC_{last} (ng.hr/mL)	10310	8015	128.67	(90.23, 183.47)
C_{max} (ng/mL)	504.8	546.8	92.32	(56.58, 150.63)

Source: Table 14.4.5.4.1.1
Values had been back-transformed from the log scale.
The model was an ANOVA model with the renal function group as the fixed effect.
a. The ratios (and 90% CIs) were expressed as percentages.
Normal renal function group was the reference group.
[redacted] SDTM Creation: 21MAY2020 (21:23) Source Data: adpp Output File: [redacted] in Date of Generation: 21MAY2020 (21:52)

Lorlatinib Urine Pharmacokinetics

Following administration of a single oral dose of lorlatinib 100 mg to participants with normal renal function or mild, moderate or severe renal impairment, approximately 0.78% to 1.2% of the dose was recovered in urine as unchanged lorlatinib (Ae%) across the renal function groups. Geometric mean renal clearance (CL_R) decreased for participants in the moderate and severe renal impairment groups than observed for the normal and mild impaired renal function groups (Table 8).

Results of the linear regression analysis using eGFR indicates a lack of a correlation between CL_R and renal function.

Table 8. Descriptive Summary of Urine Lorlatinib PK Parameters by Renal Function Group, Protocol B7461010

	Normal Function (N=8)	Mild Impairment (N=8)	Moderate Impairment (N=8)	Severe Impairment (N=5)

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Parameter (Unit)[a]				
N2	8	8	8	5
Ae (mg)	0.9441±0.38542	1.218±0.42974	0.8379±0.54929	0.7836±0.36385
Ae (%)	0.9441±0.38542	1.218±0.42974	0.8379±0.54929	0.7836±0.36385
CL_R (L/hr)	0.1095 (42)	0.1382 (50)	0.08199 (55)	0.06872 (45)

Source: Table 14.4.5.3.1
N:Total number of participants in the renal function group;
N2:Number of participants contributing to the summary statistics.
a. Geometric mean (geometric % coefficient of variation) for all except arithmetic mean±standard deviation for Ae and Ae (%).
CL_R for participant [redacted] was calculated based on Ae_{96} and AUC_{last} since this participant's last quantifiable plasma concentration was at 96 hours.
[redacted] SDTM Creation: 21MAY2020 (21:23) Source Data: adpp Output File: [redacted] in Date of Generation: 21MAY2020 (21:47)

PF-06895751 Plasma Pharmacokinetics

Following administration of a single oral dose of lorlatinib 100 mg in participants with normal renal function or mild, moderate or severe renal impairment, median plasma PF-06895751 concentrations gradually declined for all renal function groups compared to parent lorlatinib. Compared to parent lorlatinib, PF-06895751 C_{max} were reached considerably later with a median T_{max} of 24 hours for the normal renal function and mild renal impairment groups, and a median T_{max} of 72 hours for moderate and severe renal impairment groups (Table 6 [lorlatinib] and Table 9 [PF-06895751]). Mean $t_{½}$ for PF-06895751 was longer in the normal renal function and mild renal impairment groups, with mean values of approximately 41 and 35 hours, respectively, compared to parent lorlatinib in the same renal function groups (Table 6 [lorlatinib] and Table 9 [PF-06895751]).

The molar metabolite ratios (MR: PF-06895751 versus lorlatinib) based on area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (AUC_{last}) and C_{max} were generally similar across all renal function groups (Table 9).

In general, the overall plasma exposures based on geometric mean PF-06895751 AUC_{last} and C_{max} values were similar across the renal function groups (Table 9). Variability in PF-06895751 based on geometric %CV was similar among normal renal function, mild, and moderate renal impairment groups (ranged 26% to 28% for C_{max} and 18% to 28% for AUC_{last}) but was higher in the severe renal impairment group (59% for C_{max} and 58% for AUC_{last}).

The adjusted geometric mean ratios (90% CIs) of PF-06895751 plasma AUC_{last} for the renal impairment groups (Test) versus the normal renal function group (Reference) were

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120.65% (102.91%, 141.45%), 134.59% (109.34%, 165.67%), and 108.79% (65.34%, 181.12%) for the mild, moderate and severe renal impairment groups, respectively (Table 10).

The adjusted geometric mean ratios (90% CIs) of PF-06895751 plasma C_{max} for the renal impairment groups (Test) versus the normal renal function group (Reference) were 117.12% (93.34%, 146.95%), 112.96% (89.32%, 142.86%), and 93.74% (55.51%, 158.30%) for the mild, moderate and severe renal impairment groups, respectively (Table 10).

Table 9. Descriptive Summary of Plasma PF-06895751 PK Parameters by Renal Function Group, Protocol B7461010

Parameter (Unit)[a]	Normal Function (N=8)	Mild Impairment (N=8)	Moderate Impairment (N=8)	Severe Impairment (N=5)
N2, N3	8, 8	8, 7	8, 0	5, 0
AUC_{inf} (ng.hr/mL)	5482 (19)	6462 (17)	NE	NE
AUC_{last} (ng.hr/mL)	4438 (18)	5354 (19)	5973 (28)	4828 (58)
C_{max} (ng/mL)	56.35 (27)	65.99 (26)	63.65 (28)	52.82 (59)
$MRAUC_{inf}$	1.453 (21)	1.701 (36)	NE	NE
MRC_{max}	0.2274 (44)	0.2650 (57)	0.2890 (22)	0.2310 (74)
$t_{1/2}$ (hr)	40.66±11.671	35.46±5.5907	NE	NE
T_{max} (hr)	24.0 (12.0-48.0)	24.0 (12.0-72.0)	72.0 (48.0-120)	72.0 (72.0-96.0)
$MRAUC_{last}$	1.223 (29)	1.421 (39)	1.487 (44)	1.034 (66)

Source: Table 14.4.5.2.1
N:Total number of participants in the renal function group;
N2:Number of participants contributing to the summary statistics;
N3:Number of participants contributing to the summary statistics for AUC_{inf}, $MRAUC_{inf}$ and $t_{1/2}$.
a. Geometric mean (geometric % coefficient of variation) for all except median (range) for T_{max} and arithmetic mean±standard deviation for $t_{1/2}$.
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Table 10. Statistical Summary (ANOVA) of Log Transformed Plasma PF-06895751 PK Parameters - AUC_{inf}, AUC_{last} and C_{max}, Protocol B7461010

Parameter (Unit)	Adjusted Geometric Means Test	Adjusted Geometric Means Reference	Ratio (%) (Test/Reference) of Adjusted Geometric Means[a]	90% CI (%) for Ratio[a]
Mild vs Normal				
AUC_{inf} (ng.hr/mL)	6462	5482	117.87	(100.41, 138.37)
AUC_{last} (ng.hr/mL)	5354	4438	120.65	(102.91, 141.45)
C_{max} (ng/mL)	65.99	56.35	117.12	(93.34, 146.95)
Moderate vs Normal				
AUC_{last} (ng.hr/mL)	5973	4438	134.59	(109.34, 165.67)
C_{max} (ng/mL)	63.65	56.35	112.96	(89.32, 142.86)
Severe vs Normal				
AUC_{last} (ng.hr/mL)	4828	4438	108.79	(65.34, 181.12)
C_{max} (ng/mL)	52.82	56.35	93.74	(55.51, 158.30)

Source: Table 14.4.5.4.2.1
Values had been back-transformed from the log scale.
The model was an ANOVA model with the renal function group as the fixed effect.
a. The ratios (and 90% CIs) were expressed as percentages.
Normal renal function group was the reference group.
AUC_{inf} was not reportable for moderate and severe renal impairment groups.
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Safety Results:

No deaths, SAEs, severe AEs, discontinuations from the study due to AEs, or medication errors were reported during the study.

A total of 18 AEs were reported by 12 participants (5, 2, 4 and 1 participants in the normal renal function, mild, moderate and severe renal impairment groups, respectively). Twelve AEs were mild in severity and 6 AEs were moderate in severity. Most (15) AEs occurred within 5 days following a SD of lorlatinib 100 mg. All AEs resolved by the end of the study and most (14) AEs lasted 4 days or less. Eight AEs in 7 participants (3, 2, 1 and 1 participants in the normal renal function, mild, moderate and severe renal impairment groups, respectively) were considered as treatment-related by the investigator. The participant in the severe renal impairment group who was considered end-stage did not report any AEs during the course of the study.

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Across all groups, the most frequently reported system organ class (SOC) was Nervous System Disorders which was reported by 4 participants. A total of 13 unique preferred terms were reported: 5 were reported by 2 participants, including blood pressure increased, diarrhoea, dizziness, headache, and upper respiratory tract infection; 8 were reported only by 1 participant, including dyspnoea, ecchymosis, hyperglycaemia, myalgia, oropharyngeal pain, skin abrasion, skin laceration, and vessel puncture site pain.

None of the laboratory test abnormalities were considered to be clinically significant or reported as AEs by the investigator.

AEs based on vital signs were reported in 2 participants as PT of blood pressure increased (1 from the mild renal impairment group and the other from the severe renal impairment group). Both AEs were considered as mild in severity and related to the study treatment by the investigator.

No ECG data were considered clinically significant or reported as AEs by the investigator.

Conclusions:

- Comparison of 100 mg single lorlatinib oral dose PK data between healthy participants with normal renal function and participants with impaired renal function who were otherwise considered healthy indicated that lorlatinib exposure (AUC_{inf}) increased approximately 4%, 19% and 41% for the mild, moderate and severe renal impairment groups, respectively. There was no marked difference in lorlatinib C_{max} across the renal function groups.

- Mean $t_{½}$ estimates for lorlatinib were longer in participants with moderate and severe renal impairment (approximately 39-42 hours range for mean values) compared to those with normal renal function and mild renal impairment (approximately 26-28 hours range for mean values).

- Following administration of a single oral dose of lorlatinib 100 mg, exposure (AUC_{last} and C_{max}) for lorlatinib metabolite, PF-06895751, were generally similar across the renal function groups.

- The administration of a single oral dose of lorlatinib 100 mg to participants with normal renal function, mild renal impairment, moderate renal impairment and severe renal impairment was well tolerated.