Journal of Chromatography B 1083 (2018) 204–208

Contents lists available at ScienceDirect

Journal of Chromatography B

journal homepage: www.elsevier.com/locate/jchromb

Bioanalytical assay for the quantification of the ALK inhibitor lorlatinib in mouse plasma using liquid chromatography-tandem mass spectrometry

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ARTICLE INFO

Keywords:
Lorlatinib
LC-MS/MS
Mouse plasma
ALK inhibitor

ABSTRACT

A bio-analytical assay for the first third generation ALK inhibitor lorlatinib in mouse plasma was developed and validated. Ten-µl plasma samples were prepared by adding rucaparib as the internal standard and precipitation of the plasma proteins. For LC-MS/MS analysis, compounds were eluted at 0.5 mL/min and separated on a 3-µm particle-size, polar embedded octadecyl silica column by gradient elution using 0.1% of formic acid (in water) and methanol. Compounds were monitored with positive electrospray ionization using a triple quadrupole mass spectrometer in selected reaction monitoring mode. The assay was fully validated in the 2–2000 ng/mL calibration range. Within−day (8.0–11.6%) and between−day (10.0–15.0%) precisions and accuracies (99.0–113.3%) were within acceptable range. Plasma samples were deemed stable for 6 h at ambient temperature, during three freeze-thaw cycles and for 2 months at −30 °C. Finally, the new assay was applied successfully to pilot pharmacokinetic studies in male and female wild-type mice.

1. Introduction

Lorlatinib (PF-06463922; Fig. 1) is an orally available ATP-competitive selective inhibitor of receptor tyrosine kinases, the anaplastic lymphoma kinase (ALK) and the related C-ros oncogene 1 (ROS1) and it is the first drug belonging to the third generation of ALK inhibitors [1]. ALK performs a key role in nervous system development and its dysregulation is associated with several tumors; ROS1 plays a prominent role in cell growth and survival of cancer cells. ALK inhibitors are now considered effective agents against ALK positive non-small cell lung cancer (NSCLC) [2]. However, their effectiveness over time tends to decrease due to the emergence of mutations resistant to therapy with crizotinib (first generation) and second generation ALK inhibitors as well [1,2]. The ALK protein, encoded by the *ALK* gene, represents a clinical target in adult cancers in which the ALK domain is fused to an array of amino-terminal partners, such as the echinoderm microtubule-associated protein-like 4 (EML4) in NSCLC or nucleophosmin (NPM) in anaplastic large cell lymphoma (ALCL) [3]. Since EML4-ALK was recognized as an attractive drug target, the development of ALK inhibitors resulted in approval of crizotinib, ceritinib, alectinib, brigatinib, entrectinib and lorlatinib to treat NSCLC patients harboring ALK fusions [3]. Currently, lorlatinib is in phase 1/2 clinical trials for treatment of ALK-driven cancers [4], specifically in patients after failing crizotinib and ceritinib [1]. It was reported that it is highly potent against known clinically acquired *ALK* mutations with superior brain penetration compared to previous generations of ALK inhibitors [1].

In order to support (pre)clinical studies with lorlatinib, it is necessary to develop bio-analytical assays that are able to monitor the

Abbreviations: ALK, anaplastic lymphoma kinase; EMA, European Medicines Agency; EML4, echinoderm microtubule-associated protein-like 4; ESI, electro spray ionization; FDA, Food and Drug Administration; IS, internal standard; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantification; NPM, nucleophosmin; NSCLC, non-small lung cancer; QC, quality control; ROS1, proto-oncogene tyrosine kinase; SRM, selected reaction monitoring

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https://doi.org/10.1016/j.jchromb.2018.03.014
Received 6 December 2017; Received in revised form 9 February 2018; Accepted 9 March 2018
Available online 09 March 2018

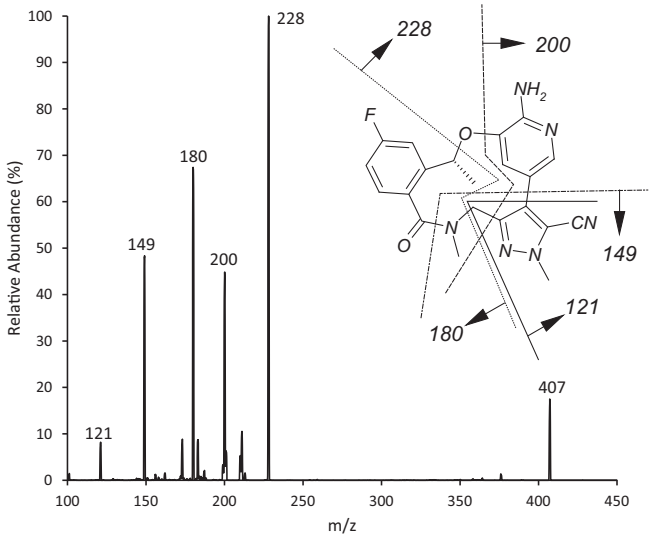

Fig. 1. Chemical structure and product spectrum formed by collision induced dissociation of the protonated molecule of lorlatinib, *m/z* 407.1@ − 25 V.

concentration of this drug in different biological matrices. Plasma concentrations of lorlatinib were previously determined by LC-MS/MS [5,6], using protein precipitation to pretreat the plasma samples. Analytical and validation details given for this assay were, however, very limited. Therefore, in the present study a straightforward bioanalytical assay for lorlatinib in mouse plasma was set up using LC-MS/MS, providing complete analytical details and a full bioanalytical validation for small mouse plasma samples. The present assay also uses a simple protein precipitation step followed by LC-MS/MS quantification and it could be successfully applied for these samples.

2. Materials and methods

2.1. Chemicals and reagents

Lorlatinib (> 99.9%) was obtained from TargetMol (Boston, USA) and rucaparib (phosphate salt, > 98.5%) from Sequoia Research Products (Pangbourne, UK). LC–MS grade water, acetonitrile of HPLC-S gradient grade quality and methanol of HPLC quality and were acquired from Biosolve (Valkenswaard, The Netherlands). Water purified by reversed osmosis on a multi-laboratory scale was applied for all other purposes than preparing chromatographic eluents. Formic acid (analytical grade) was obtained from Merck (Darmstadt, Germany). Lithium-heparinized plasma (pooled from humans and mice) and plasma of six single mice was obtained from Sera Laboratories (Haywards Heath, West Sussex, UK).

2.2. Chromatography and MS/MS method

The Shimadzu (Kyoto, Japan) chromatographic system was build up from a DGU-14A degasser, two LC10-ADvp-μ pumps, a Sil-HTc autosampler and a CTO-10Avp column oven. Prepared samples were injected (5 μL) on a Varian Polaris C18-A (50 × 2.0 mm, 3 μm, Varian, Middelburg, The Netherlands), protected by an Agilent Polaris C18-A Chromsep guard cartridge (10 × 2.0 mm, 3 μm, Agilent, Santa Clara, USA). The auto injector rack was maintained at 4 °C and the column oven at 40 °C. For the binary gradient, 0.1% (v/v) formic acid in water (A) and methanol (B) were mixed to obtain a total flow rate of 0.5 mL/min. After injection, 20% B was increased linearly to 45% in 1.2 min followed by flushing with 100% B for 0.3 min and equilibration of the column at the initial 20% B for 1.5 min until starting the following injection. The eluate was transferred to the electrospray nebulizer from 0.6 until 2.5 min after injection by switching the MS inlet valve. A TSQ Quantum Discovery Max quadrupole mass spectrometer (Thermo Fisher Scientific, San Jose, CA, USA) was used for ionization, ion separation and detection. The Thermo Fisher Xcalibur software (Version 2.0.7 SP1) was used for data collection and control of the mass spectrometer. Positive electrospray ionization was optimized by introducing 0.5 mL/min of a mixture of methanol and 0.1% v/v formic acid in water (50/50, v/v) and mixing the solvent mixture with 5 μg/mL lorlatinib at 5 μL/min. Settings with the highest response were used for monitoring both compounds: 4000 V spray voltage; 400 °C capillary temperature; nitrogen gas settings (arbitrary units) were 60 for sheath, 8 for ion sweep and 10 for the auxiliary gas; the skimmer voltage was set off (0 V); the argon collision gas pressure in SRM mode was 1.5 mTorr. The tube lens off-set was 113 V for lorlatinib and 92 V for rucaparib. Lorlatinib was monitored at *m/z* 407.1 → 121, 180.1, 200.1 and 228.1 at respectively − 41, − 23, − 26 and − 23 V collision energies and rucaparib at *m/z* 324 → 293 at − 17 V collision energy, all with 0.1 s dwell times. Both separating quadrupoles were set at *m/z* 0.7 mass resolution.

2.3. Calibration standards and quality control samples

Stock solutions were prepared in methanol at 250,000 ng/mL for calibration and at 500,000 ng/mL lorlatinib solution for quality control (QCs) samples. The highest calibration solution at 2000 ng/mL was made by diluting the 250,000 ng/mL stock solution in blank mouse plasma; it was stored in polypropylene tubes at − 30 °C until further use. Additional calibration solutions were produced by diluting the highest calibration solution to 1000; 200; 100; 20; 10 and 2 ng/mL with blank mouse plasma. The 500,000 ng/mL lorlatinib stock solution was used to produce QC samples at 1500 (high), 75 (medium), 5 (low) and 2 (lower limit of quantitation, LLOQ) ng/ml by serial dilution with blank mouse plasma. QCs were also stored at − 30 °C until further use.

2.4. Sample preparation

10 μL of plasma was pipetted into a 1.5-ml polypropylene (PP) reaction tube. After addition of 20 μL of 200 ng/mL IS solution, 200 ng/ml rucaparib in acetonitrile, proteins were precipitated by vortex mixing vigorously for approximately 5 s. Centrifugation at 12000 × *g* for 5 min at 10 °C resulted in a clear supernatant of which 20 μL was transferred to a 1.5 mL vial with a 250 μL glass micro-insert. The vial was closed after addition of 100 μL water and placed in the autosampler for injection of 5 μL of the final mixture.

2.5. Bioanalytical method validation

International guidelines (EMA [7] and FDA [8]) were used to obtain validation procedures for this bioanalytical assay.

2.5.1. Calibration

All calibration samples were pretreated in duplicate for each daily calibration. The calibration curve was constructed using weighted ($1/x^2$; x is the concentration of analyte) linear regression and data were calculated from the peak area of the analyte relative to the IS.

2.5.2. Precision and accuracy

Analytical performance (within- and between-day) was calculated after six-fold analysis of each QC in three analytical runs on separate days for all four QC samples (total: $n = 18$ per QC). In addition, dilution integrity was tested on one day ($n = 6$) at 4000 ng/ml lorlatinib after 5-fold dilution of 10 μL of mouse plasma with human plasma.

2.5.3. Selectivity

Individual mouse plasma samples ($n = 6$) were investigated for the selectivity of the assay. Each sample was analyzed as double blank (no lorlatinib, no IS), blank (no lorlatinib, with IS) and LLOQ spiked (2 ng/

mL lorlatinib, with IS).

2.5.4. Recovery and matrix effect

The extraction recovery of the protein precipitation was determined at each QC level (high, medium, low) by comparing processed samples ($n = 4$) with equivalent solutions of lorlatinib in blank plasma extracts. For assessment of the (absolute) matrix effect, an experiment was conducted in which lorlatinib and IS were both infused (5 µg/mL, 5 µL/min) post-column and mixed with the eluate during chromatographic runs, in which diluted blank extracts ($n = 6$) of individual plasma samples were injected on the column, without using the divert valve. Further, the relative matrix effect for lorlatinib and rucaparib was determined by comparing the responses in an extracted plasma sample of six individual donors to reference solutions at high and low QC levels.

2.5.5. Drug stability

The plasma stability of lorlatinib was investigated for QC-high and -low samples stored in separate portions (10 µL; $n = 4$). These portions in polypropylene tubes were exposed to three different conditions in three separate experiments: room temperature for 6 h, three freeze-thaw cycles (thawing at room temperature and freezing again at −30 °C for at least 12 h) and − 30 °C for two months. For autosampler stability, an analytical run was re-injected after additional storage of the diluted extracts at 4 °C for 24 h. Finally, stability in methanolic stock solutions was investigated after 6 h exposure to ambient temperature and after 30 weeks storage at −30 °C ($n = 3$) by comparison to freshly prepared stocks. LC–MS/MS analysis was used after sufficient dilution of the stock solutions with 25% (v/v) methanol and adding IS.

2.6. Pharmacokinetics in mice

A pharmacokinetic pilot study in wild type female mice (FVB/NRj genetic background) receiving 10 mg/kg lorlatinib orally ($n = 7$) was conducted. Lorlatinib was dissolved in dimethyl sulfoxide (50 mg/mL), followed by 2.5-fold dilution with polysorbate 80/ethanol (1:1, v/v), and then 20-fold with 5% glucose in water to yield a drug working solution of 1 mg/mL, prepared freshly on each day of experiment. Mice were housed and handled according to institutional guidelines complying with Dutch legislation and treated similar to earlier reported protocols [9]. Shortly, mice were 10 to 14 weeks of age and housed in a temperature-controlled environment with a 12-h light/12-h dark cycle. Animals received a standard diet and acidified water *ad libitum* and were fasted for 3 h before lorlatinib was administered by gavage into the stomach, using a blunt-ended needle. At 0.5, 1, 2, 4, and 8 h after administration, blood was collected from the tail vein in heparinized capillary tubes (Sarstedt, Germany). Mice were anesthetized with isoflurane after 24 h and a final blood sample was acquired by cardiac puncture. The pilot study was followed by similar studies in male mice for 8 h ($n = 5$, sampling at 0.25, 0.5, 1, 2, 4, and 8 h) and 2 h ($n = 6$, sampling at 0.125, 0.25, 0.25, 1, and 2 h). Plasma was obtained by centrifugation at 9000 × g for 6 min at 4 °C and stored at −30 °C until analysis. The mouse plasma samples from $t = 0.5$–8 h were diluted 5 times with human lithium heparin plasma. The further analytical procedure has been described above. Incurred samples reanalysis was conducted for 20 of the diluted female mouse samples.

The following pharmacokinetic parameters were assessed in female mice: maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), terminal half-life ($t_{1/2}$) calculated from C_8 and C_{24}, area under the plasma concentration-time curve until 2 h, 8 h, 24 h, and until infinity ($AUC_{0\rightarrow2}$, $AUC_{0\rightarrow8}$,$AUC_{0\rightarrow24}$ and $AUC_{0\rightarrow\infty}$) calculated using the trapezoidal rule and extrapolation from 24 h to infinity. Finally, apparent clearance (Cl/F), apparent volume of distribution (V_d/F) and absorption rate (k_a) were computed using the first order one-compartment model. For male mice, C_{max}, t_{max}, $AUC_{0\rightarrow2}$, and $AUC_{0\rightarrow8}$ were calculated. These parameters were compared to female results by a two-sided unpaired heteroscedastic Student's t-test after dose correction using the measured drug concentration in the administered working solutions for the three different studies.

3. Results and discussion

3.1. Method development

Protein precipitation followed by LC-MS/MS has been applied in development of bio-analytical assays for many kinase inhibitors [10]. This procedure is simpler than methods using liquid-liquid extraction or solid-phase extraction. Acetonitrile is considered the most efficient organic precipitation agent for plasma, the volume was kept small (2:1, v/v) to limit sample dilution of the small samples (10 µL). Because stable isotopically labeled lorlatinib was not commercially available, three different drugs eluting at similar retention times were investigated as potential internal standards during bio-analytical development. Rucaparib showed slightly better precisions and accuracies compared to dabrafenib and AT7519 during the first pilot experiments (data not shown) and was therefore chosen as IS for the complete analytical method validation. No metabolites of lorlatinib were known during the study and were therefore not considered to be included in the assay.

Chromatographic conditions initially were based on an existing method for rucaparib [11]. After chromatographic optimization, based on retention time and peak shape, and MS response optimization by varying organic modifier (methanol or acetonitrile), gradient profile and amount of formic acid, positive mode for ESI–MS/MS was selected at m/z 407.1 for lorlatinib and m/z 324.1 for rucaparib. In order to optimize the sensitivity, the sum of the four most abundant dissociation products were measured for lorlatinib (m/z 121; 180.1; 200.1; 228.1). A product spectrum of lorlatinib is shown in Fig. 1.

3.2. Validation

According to pharmacokinetic and pharmacodynamic (PKPD) parameters of lorlatinib estimated in mouse studies by Yamazaki et al. [5,6], a 2–2000 ng/mL range was investigated during validation according to accepted guidelines [7,8]. Representative chromatograms of analyte and IS in mouse plasma are shown in Fig. 2.

3.2.1. Calibration

Linear calibration curves were observed ($n = 8$), with an average coefficient of determination (R^2) of 0.993 ± 0.002 (n = 8). The linear function was $Y = 0.0111(\pm 0.0025) \times X + 0.0016(\pm 0.0017)$ for lorlatinib (mean ± SD) where Y is the ratio of the analyte and IS response and X the concentration in ng/mL.

3.2.2. Precision and accuracy

Assay performance data of the assay in mouse plasma are listed in Table 1. Precisions and accuracies of three analytical runs were within ± 15% for high, medium and low QCs and within ± 20% for LLOQ as required [7,8]. For dilution integrity at 4000 ng/mL ($n = 6$) precision was 4.3% and accuracy 96.8%, meeting the same ± 15% requirements.

3.2.3. Selectivity

Double blank and blank mouse plasma samples ($n = 6$) showed no peaks potentially interfering with lorlatinib or IS. Blank lorlatinib responses were all < 20% of the LLOQ as dictated by guidelines [7] and blank IS responses were all < 1% of the regular response. Concentrations calculated at the LLOQ spiked samples (2 ng/mL; $n = 6$) were 1.80 ± 0.19 ng/mL showing the allowance of the tested LLOQ level [8].

3.2.4. Recovery and matrix effect

Recoveries ($n = 4$) were 115.8 ± 9.2%, 118.9 ± 4.9% and 117.9 ± 3.1% at the QC-high, -medium and -low levels. Values are

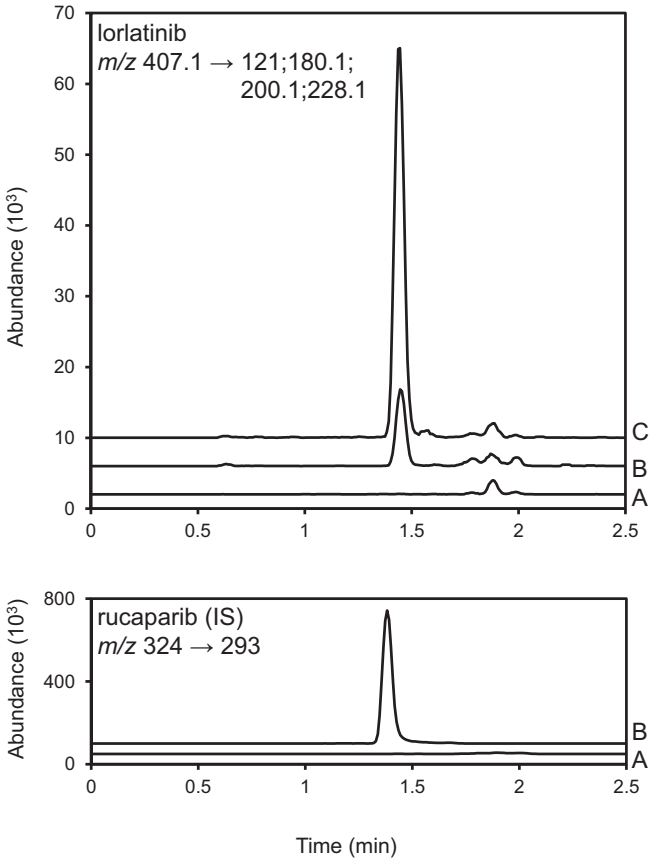

Fig. 2. SRM chromatograms of lorlatinib and rucaparib in mouse plasma. (A) blank sample; (B) LLOQ sample; (C) plasma sample 24 h after administration of 10 mg/kg lorlatinib to wild type mouse (9.9 ng/ml).

Table 1
Assay performance data of lorlatinib resulting from four validation (QC, $n = 18$ each) samples in 3 analytical runs ($n = 6$).

Level (ng/ml)	Within-day precision [%]	Between-day precision [%]	Accuracy [%]
1500	10.4	12.2	99.0
75	8.0	12.0	109.5
5	9.0	10.0	113.3
2	11.6	15.0	108.8

high, which can partly be explained by the volume reduction due to protein precipitation, but consistent. The infusion experiments to assess absolute matrix effect showed no relevant matrix effect in each individual mouse plasma analyzed in time range from 1 to 1.5 min. The relative matrix effect (IS normalized matrix factor, n = 6) resulted in the factors 92.2 ± 9.9% and 88.4 ± 6.4% at the high and low QC levels. The standard variations of these IS-normalized MF calculated from the 6 lots of matrix were within ± 15% as required [7].

3.2.5. Stability

The stability of lorlatinib in lithium heparin mouse plasma is presented in Table 2 for three investigated conditions, recoveries and precisions were all within ± 15%. *Re*-injection of one set of calibration and QC samples after storage at 4 °C for 24 h demonstrated only 2 QC samples out of 24 exceeding 115% [7,8]. Based on recovery from stock solutions ($n = 3$) after 6 h at ambient temperature (96.3% ± 7.1%) and after 30 weeks at −30 °C (101.5% ± 6.5%) lorlatinib was considered stable in methanolic stocks too.

Table 2
Stability data (recovery (%); ± SD; $n = 4$) of lorlatinib in mouse lithium heparin plasma.

Storage conditions	QC-high	QC-low
3 freeze-thaw cycles	106.2 ± 8.8	98.9 ± 10.2
6 h at ambient temperature	99.0 ± 4.9	87.1 ± 7.9
2 months at −30 °C	90.0 ± 4.5	98.2 ± 11.1

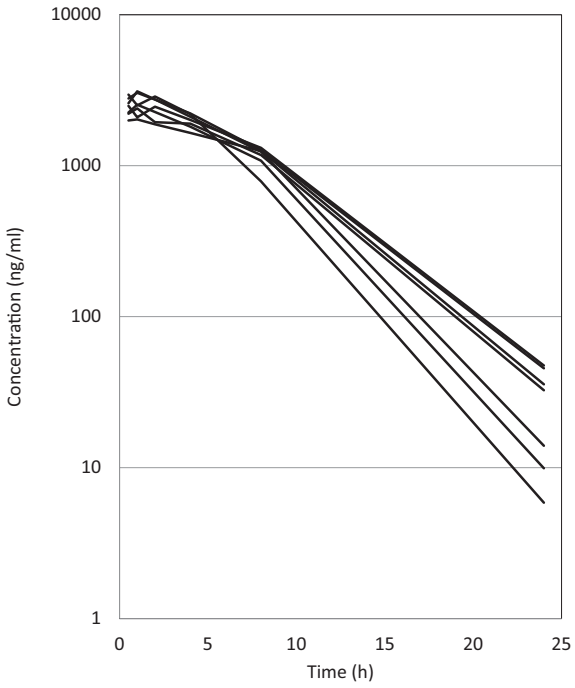

Fig. 3. Pharmacokinetic plots of lorlatinib in plasma after administration of 10 mg/kg orally to female FVB/NRj mice ($n = 7$).

3.3. Pharmacokinetics in mice

As a final validation parameter, incurred samples reanalysis resulted in 3 samples out of 20 exceeding a ± 20% difference, meeting the 33% EMA criterion [7].

The pharmacokinetic plots for 7 female mice are shown in Fig. 3 with small variations at $t = 0.5$–8 h. Calculated parameters are: $t_{max} = 0.86 \pm 0.24$ h, $C_{max} = 2651 \pm 398$ ng/ml, $t_{1/2} = 2.9 \pm 0.5$ h, $AUC_{0\rightarrow 24} = 24{,}534 \pm 2123$ ng·h·ml^{-1}, $AUC_{0\rightarrow\infty} = 24{,}656 \pm 2173$ ng·h·ml^{-1}, $Cl/F = 408 \pm 35$ ml·h^{-1}·kg^{-1}, $V_d/F = 1670 \pm 233$ ml/kg and $k_a = 0.44 \pm 0.11$ h^{-1}. Compared to a previous oral study in implanted female athymic nu/nu mice [5] Cl/F is 3–4 times lower, V_d/F 3–6 times smaller and k_a 3–9 times slower in the present study. Differences in mouse strain, drug formulation, fasting state, lab-specific microflora, and commercial chew, either alone or in combination, might underlie these differing pharmacokinetic parameters. Results in male mice showed only a small significant difference ($P < 0.05$) compared to female mice for $AUC_{0\rightarrow 8}$ and not for C_{max}, t_{max}, and

Table 3
Comparison of pharmacokinetic data of male and female mice after dose correction using the measured drug concentration in the administered working solutions.

	Male	Female ($n = 7$)	P
C_{max}	2272 ± 351 ($n = 11$)	2637 ± 396	0.07
t_{max}	0.91 ± 0.58 ($n = 11$)	0.86 ± 0.24	0.8
$AUC_{0\rightarrow 2}$	3922 ± 685 ($n = 11$)	4320 ± 612	0.22
$AUC_{0\rightarrow 8}$	12,948 ± 5423 ($n = 5$)	14,965 ± 1531	0.038

$AUC_{0\rightarrow 2}$ as shown in Table 3. It thus appears that there is no substantial gender difference in lorlatinib oral pharmacokinetics.

4. Conclusions

A simple and appropriate bioanalytical assay has been developed and successfully validated for lorlatinib, the first third-generation ALK inhibitor, in only 10 μL mouse plasma. It is the first completely reported validated assay for lorlatinib. Pharmacokinetic properties in female and male FVB/NRj mice seem similar but different from those in female athymic nu/nu mice. The new LC-MS/MS method can be used for further pharmacokinetic studies of lorlatinib in mice.

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