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To quantify the small-molecule kinase inhibitors ceritinib, dacomitinib, lorlatinib, and nintedanib in human plasma by liquid chromatography/triple-quadrupole mass spectrometry

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ABSTRACT

Multiple small-molecule kinase inhibitors with specific molecular targets have recently been developed for the treatment of cancer. This article reports the development and validation of an ultra-performance liquid chromatography/tandem mass spectrometry (UPLC–MS/MS) method to simultaneously analyse the small-molecule kinase inhibitors dacomitinib, ceritinib, lorlatinib, and nintedanib in human plasma. For chromatographic analyte separation, an Acquity UPLC® BEH C18 column 1.7 μm, 50 mm x 2.1 mm was used with a binary gradient of pure water/formic acid/ammonium formate (100:0.1:0.02, v/v/v) and methanol/formic acid (100:0.1, v/v). Calibration curves for all small-molecule kinase inhibitors were 5.00–500 ng/mL. Validation of this method met all requirements of the Food and Drug administration. Additionally, clinical applicability was demonstrated by quantification of multiple samples from a pharmacokinetic study in patients with lung cancer.

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1. Introduction

Small-molecule kinase inhibitors (SMKIs) are one of the backbones in the treatment of cancer. They are developed to specifically block dysregulated protein tyrosine kinases in tumour cells. [1] Treatment with SMKIs is standard of care for various types of solid and hematologic malignancies. Over the last years, their number has vastly increased. Because of their specificity, most SMKIs are prescribed based on molecular characteristics of a tumour.

In non-small cell lung cancer (NSCLC), the most frequent molecular driver aberrations are epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) translocations. Together, they represent 10–20% of all NSCLC patients, with higher incidences in Asia than in the rest of the world. [2] Dacomitinib is an oral SMKI registered for EGFR mutated NSCLC [3]. Both ceritinib and lorlatinib are SMKIs specifically targeting ALK mutations in NSCLC

[3]. All three SMKIs are administered once daily [3]. Nintedanib is a vascular endothelial growth factor (VEGF) receptor inhibitor approved in combination with docetaxel for second line treatment of patients with NSCLC. This treatment however, is independent of mutational status and is dosed in a twice-daily schedule of 200 mg. [3] Combinations of these four SMKIs have not been reported and based on the specific indications of each drug, combination treatment is not expected.

Also in other fields of medicine, SMKIs are registered for progressive diseases in which cell proliferation is unwanted. Nintedanib for example, has an additional approval for treatment of progressive lung fibrosis. Contrary to its use in medical oncology, nintedanib is registered as monotherapy and administered 150 mg twice daily. [3]

Multiple SMKIs are known to have specific target plasma concentrations and a narrow therapeutic window. [4] Even though oral administration of SMKIs has its benefits, it additionally increases the intra- and interpatient variability. Due to interactions with coadministered drugs [5], food, and beverages [6,7] drug absorption and metabolism could be altered. Subsequent increase in drug concentration above the therapeutic window could lead to (severe)

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toxicity, where effectiveness of treatment is compromised when the target concentration is not reached.

In order to investigate the therapeutic window of SMKIs, compounds that could interact with them, and ultimately performing therapeutic drug monitoring (TDM), a liquid chromatography/tandem mass spectrometric (LC–MS/MS) assay for drug quantification has to be developed and validated. There are multiple LC–MS/MS assays published which separately report the quantification of ceritinib, [8–12] dacomitinib [13], lorlatinib [14], or nintedanib [15–17] in plasma. For dacomitinib and lorlatinib however, these methods were only developed for non-human plasma. We here describe the development and full validation according to U.S. Food & Drug Administration guidelines [18] of an LC–MS/MS method for the simultaneous quantification of the SMKIs ceritinib, dacomitinib, lorlatinib, and nintedanib in human plasma.

2. Material and methods

2.1. Chemicals

Ceritinib ($C_{28}H_{36}ClN_5O_3S$) was acquired from Toronto Research Chemicals (North York, Canada), dacomitinib ($C_{24}H_{25}ClFN_5O_2$) at Sigma-Aldrich (Saint Louis, USA), lorlatinib ($C_{21}H_{19}FN_6O_2$) at MedChemExpress (Monmouth Junction, USA) and nintedanib ($C_{31}H_{33}N_5O_4C_{28}H_{33}N_7O_2$) at LC Laboratories (Woburn, USA). The purity of all SMKIs was 98 % or higher. Labeled internal standard dasatinib-d8 was purchased at Toronto Research Chemicals (Toronto, Canada). Blanc human lithium heparinized plasma was bought at BioIVT (Seralab), (West Sussex, United Kingdom). Dimethylsulfoxide (DMSO) and ammonium formate (1 mol/L) was obtained from Sigma-Aldrich. Acetonitrile, pure water and methanol originated from Biosolve (Valkenswaard, The Netherlands). Formic acid was purchased from JT Baker (Deventer, The Netherlands). These chemicals were of analytical grade or higher. Nitrogen originated from LindeGas (Schiedam, The Netherlands).

2.2. Calibration

Ceritinib, dacomitinib, lorlatinib, and nintedanib were dissolved in DMSO to create three stock solutions of 1.00 mg/mL (inter-stock deviation < 5 %). One was used to prepare Quality Control (QC) samples and one was used to form calibration curve standards. Separately, dasatinib-d6 was dissolved in DMSO to make a solution of 1.0 mg/mL. Acetonitrile was hereafter used to dilute 10,000-fold to create a working solution of 100 ng/mL dasatinib-d6. Calibration standards with the four SMKI concentrations of 5.00, 12.5, 25.0, 50.0, 125, 250, 450 and 500 ng/mL were prepared in human lithium heparinized plasma. QC samples were made to yield final concentrations of 5.00 (lower limit of quantification; LLQ), 15.0 (QC-low), 100 (QC-middle), 400 (QC-high) and 8,000 (QC-diluted) ng/mL. The QC-diluted samples were subsequently diluted prior to processing in human plasma to the level of 400 ng/mL. All stock solutions, internal standard solution, and pools of QC samples were stored at T < -70 °C. Internal standard working solution was kept at T < 6 °C for a maximum of three months.

2.3. Sample pre-treatment

Twenty-five μL plasma of every sample was combined with 100 μL internal standard solution in a 1.5 mL vial. Solutions were 5 s mixed and 10 min centrifuged at 18,000 g. Hereafter, 50 μL of the supernatant was transferred to a 96-deepwell plate, to which 100 μL water/formic acid/ammonium formate (100:0.1:0.02, v/v/v) was added. After 5 min shaking, the plate was positioned in the chilled autosampler. Aliquots of 5 μL were injected onto the LC–MS/MS column.

2.4. LC –MS/MS system

The ultra-performance LC–MS/MS system originated from Waters Chromatography BV (Etten-Leur, the Netherlands) was consisted of a Waters Acquity UPLC I-Class Binary Solvent Manager connecting a Waters XEVO TQ-S Micro Detector.

2.4.1. Data processing

MassLynx version 4.1 SP4 was used for the collecting, processing and displaying of data. TargetLynx software calculated and quantified all samples.

2.4.2. Chromatographic settings

For chromatographic analyte separation, the Acquity UPLC® BEH C18 column 1.7 μm, 50 mm x 2.1 mm (Waters Chromatography BV) was warmed to T =40 °C. Column flow rate was 0.350 mL/min with a binary gradient of mobile phase A which consisted of pure water/formic acid/ammonium formate (100:0.1:0.02, v/v/v) and mobile phase B which consisted of methanol/formic acid (100:0.1, v/v). After injection, separation was yield by linearly increasing phase B from 15 % to 60 % from 1.00 min to 5.00 min. In 30 s, mobile phase B increased to 90 % and after 2.50 min, it linearly decreased to 15 % in 30 s. During the last 1.50 min of the overall processing time of 10.0 min, mobile phase B remained at 15 %. Hereafter, the injection needle was washed with a strong organic mixture containing acetonitrile, methanol, 2-propanol, water and formic acid (25:25:25:25:0.1, v/v/v/v/v) to prevent carry-over.

2.4.3. Tandem mass spectrometry

Tandem mass spectrometry (MS/MS) was performed in the electrospray positive ionization mode. Capillary ion voltage was set at 3.00 kV and the source temperature was set at 150 °C. Desolvation temperature was set at 650 °C while nitrogen was used as desolvation gas at a flow rate of 1,200 l/h. Collision cell Pirani pressure was kept at ~4.5e-3 mbar by argon gas. Mass transitions of ceritinib, dacomitinib, lorlatinib and nintedanib and the internal standard dasatinib-d8 were performed by direct infusion after dissolving all compounds in acetonitrile/water/formic acid (40:60:0.1, v/v/v). The six mass pairs were quantified during multiple reaction monitoring. The MS/MS functions were manually adjusted to obtain the optimal parameters which are presented in Table 1.

2.4.4. Quantification

Peak area ratios per SMKI compared to the internal standard were used in order to from calibration curves; ceritinib (558 > 433), dacomitinib (470 > 124), lorlatinib (407 > 228) and nintedanib (540 > 113) to dasatinib-d8 (496 > 406) with a 1/concentration^2 weight factor.

2.5. Validation

The method has been validated according to the latest U.S. Food & Drug Administration (FDA) guidelines. [18]

2.5.1. Specificity and selectivity

The specificity and selectivity of this assay were tested at the level of the LLQ (5.00 ng/mL) for which 10 sets of single blank human plasma were spiked. All samples were analysed simultaneously.

2.5.2. Accuracy, precision and matrix effect

Five sets of LLQ and QC samples were analysed in three successive runs, which were preceded and finished by a set of calibration

Table 1
Mass spectrometry settings for multiple reaction monitoring.

Compound	Parent (m/z)	Daughter (m/z)	Dwell (msec)	Cone (V)	Collision (V)
Ceritinib	**558**	**433**	**54**	**23**	**29**
Ceritinib	558	516	54	25	24
Dacomitinib	**470**	**124**	**54**	**20**	**34**
Lorlatinib	**407**	**228**	**54**	**35**	**21**
Nintedanib	**540**	**113**	**54**	**10**	**28**
Dasatinib-d8	**496**	**406**	**54**	**30**	**27**

Transitions used for the quantitation are presented in bold.

curve standards. To calculate the assay's accuracy, within-run and between-run precision, a unidirectional analysis of variance (one-way ANOVA analysis) was run, with the cycle as variable. [19] The matrix effect was tested in triplicate with the post-extraction addition method: six blank plasma samples underwent preparation and extraction, where after they were spiked at QC low (15.0 ng/mL) and QC high (400 ng/mL) for all SMKIs (A). A neat solvent standard solution served as reference (B). After analysing all samples, the matrix effect could be quantified by $\frac{B}{A}$ x 100 %.

2.5.3. Stability

Stability of ceritinib, dacomitinib, lorlatinib and nintedanib in plasma was tested at concentration levels of QC-low, QC-high and QC-diluted. QC samples (in triplicate) were stored at ambient temperature for a three-day period as well as following three freeze-thaw cycles at which the samples were thawed in a waterbath at 37 °C for 30 min and refreeze for at least 18 h at < -70 °C. Autosampler stability was tested in triplicate by repeated injection of processed QC-samples stored in a chilled autosampler at 10 °C.

2.6. Clinical applicability

The assay's clinical applicability was demonstrated by analysing plasma samples from patients treated with ceritinib, lorlatinib and nintedanib. These samples were prospectively collected as part of a large pharmacokinetic study in which patients treated with all different SMKIs were included. In order to measure all SMKIs, another LC–MS/MS method has also been developed. [20] The study has been approved by the local ethics committee of the Erasmus MC (MEC 16–643) and patients provided written informed consent prior to study enrolment. Samples were taken after six or twelve weeks of treatment to guarantee steady state plasma concentrations. Patients was asked to wait with SMKI intake until after blood withdrawal, in order to determine plasma trough concentrations. Subsequent after collection, samples were centrifuged for 10 min at 2500 g and 4 °C, after which the plasma was kept at – 70 °C. Unfortunately, no patients were treated yet with dacomitinib in this study.

2.7. Incurred sample reanalysis

In line with the clinical applicability of this assay, incurred sample reanalysis was tested to ensure the preciseness of study sample quantification in a second run. Therefore, all used samples in paragraph 2.6 underwent independent reanalysis. Hereafter, the relative difference between the first sample concentration (C1) and the second -repeated- sample concentration (C2) was calculated by: $\frac{(C1-C2)}{\frac{(C1+C2)}{2}} * 100\%$.

3. Results and discussion

3.1. Method development

Combining the optimal mass-spectrometric parameters and retention times with mobile phase A (pure water/formic acid/ammonium formate; 100:0.1;0.02, v/v/v) and mobile phase B (methanol/formic acid; 100:0.1, v/v) at a gradient 0.350 mL/min flow rate, purest peaks for every SMKI were detected. Selected transitions, proposed fragmentations and ion spectra for these SMKIs are shown in Fig. 1. Primary to secondary ion ratios demonstrated the quality for every observed peak. The selected product ions are presented in Table 1. Dasatinib-d8 was an acceptable internal standard for all compounds, where other authors report using other (isotope-labelled) internal standards. [8–17] Separation of analyts was yielded with a stepped gradient (paragraph 2.4.2). Herewith, representative chromatograms for all SMKIs and internal standard were created, as illustrated in Fig. 2. Retention times for ceritinib, dacomitinib, lorlatinib and nintedanib were 5.72, 3.61, 3.33 and 5.11 min respectively. Acetonitrile deproteinisation proved to be a successful method for quantifying ceritinib, dacomitinib, lorlatinib and nintedanib in human plasma in the range of 5.00–500 ng/mL. To avoid carry-over, a wash period of 3 min of 90 % eluens B was built-in, which led to a total run-time of 10 min.

3.2. Assay performance

3.2.1. Specificity and selectivity

Calibration curve regression coefficients (R^2) were linear from 5.00–500 ng/mL and ranged from 0.9967 to 0.9990. The lower limit of quantitation (5.00 ng/mL) was validated in ten independent pools of human plasma and by five measurements repeated in triplicate (15 samples in total). For every SMKI, all analysed LLQ samples were in the acceptance ranges of accuracy of 80–120%. Blank human plasma did neither interfere with the SMKIs nor the internal standard. Mean ceritinib concentration was 4.85 ng/mL (standard deviation; SD 0.259 ng/mL), mean dacomitinib concentration was 4.61 ng/mL (SD 0.303 ng/mL), mean lorlatinib concentration was 4.59 ng/mL (SD 0.273 ng/mL), and mean nintedanib concentration was 4.65 ng/mL (SD 0.214 ng/mL).

3.2.2. Accuracy, precision and matrix effect

The assay's accuracy, within-run and between-run precision at concentration levels of LLQ and QC low, middle, high and diluted met the requirements of validation of the FDA (LLQ range 80–120 %, QC range 85–115 %). [18] All 15 analysed samples for every SMKI at every concentration fell in these acceptable validation ranges. The post-extraction addition method with six independent samples at QC low and high showed no evidence for significant matrix effect for any SMKI. The matrix effect ranged from 84 to 100 %, showing no interference of the matrix in this method. The results of accuracy, within-run and between-run precision and matrix effect calculations are presented in Table 2.
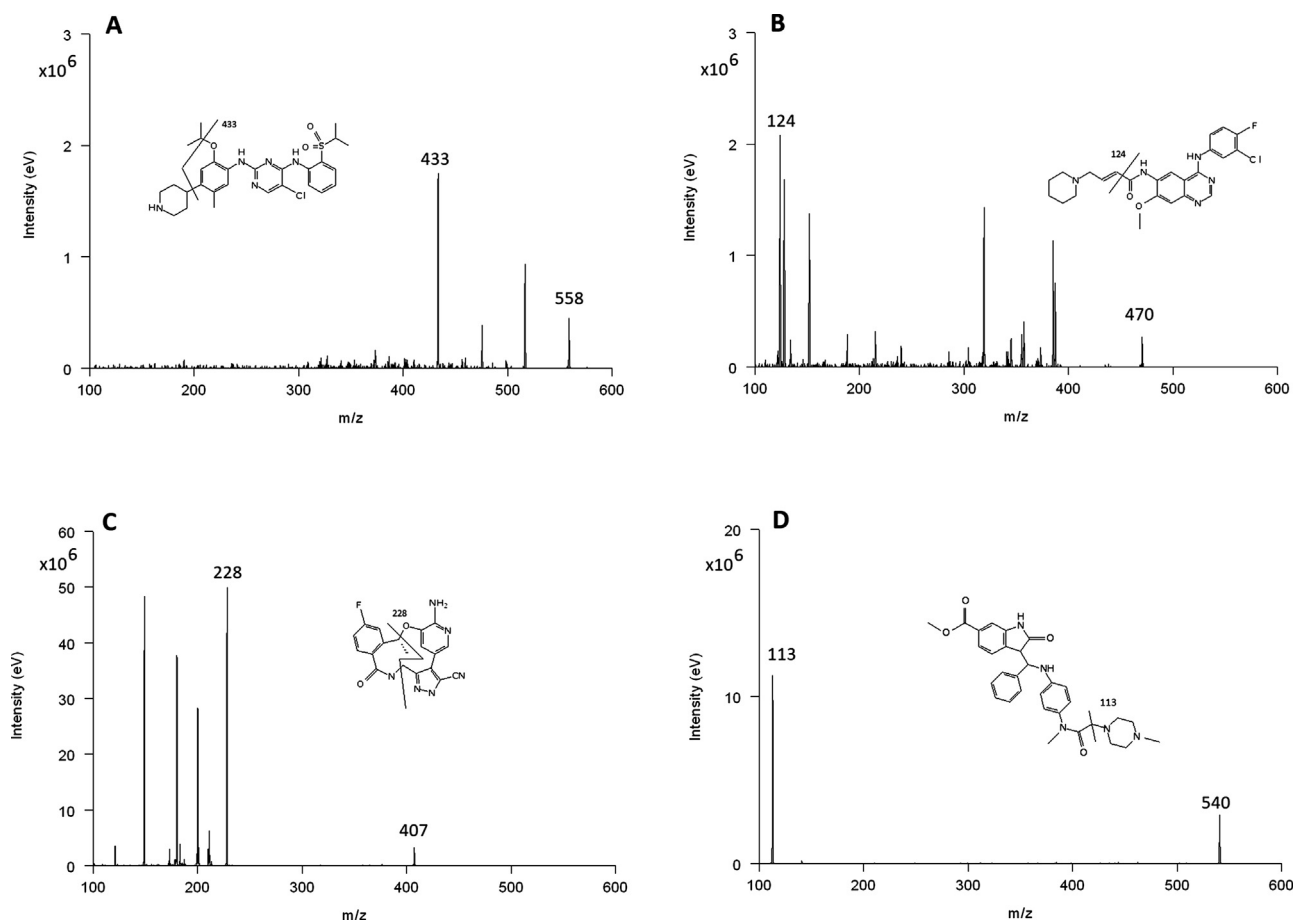
Fig. 1. Selected transitions, proposed fragmentations and ion spectra for ceritinib (A), dacomitinib (B), lorlatinib (C) and nintedanib (D).

Table 2
Accuracy, within-run precision, between-run precision and matrix effect.

Compound	Spiked (ng/mL)	Grand Mean (ng/mL)	Average Accuracy (%)	WRP (%)	BRP (%)	Matrix effect[1] (%)
Ceritinib						
LLQ	5.00	5.44	108.8	12.7	#	–
QC LOW	15.0	15.5	103.3	3.13	5.82	81.9 ± 2.38
QC MIDDLE	100	104	104.0	2.62	5.36	–
QC HIGH	400	408	102.0	2.44	4.29	84.1 ± 3.56
QC DILUTED	8000	7787	97.3	3.01	3.20	–
Dacomitinib						
LLQ	5.00	5.24	104.8	2.49	2.35	–
QC LOW	15.0	14.7	98.0	2.92	1.28	94.7 ± 2.20
QC MIDDLE	100	95.9	95.9	1.17	0.67	–
QC HIGH	400	379	94.8	2.18	1.67	97.9 ± 3.13
QC DILUTED	8000	7308	91.4	3.52	0.94	–
Lorlatinib						
LLQ	5.00	4.80	96.0	2.22	1.20	–
QC LOW	15.0	15.4	102.7	2.16	#	103 ± 1.19
QC MIDDLE	100	103	103.0	1.65	0.47	–
QC HIGH	400	381	95.3	1.80	2.04	100 ± 0.914
QC DILUTED	8000	7509	93.9	3.39	#	–
Nintedanib						
LLQ	5.00	4.89	97.8	2.14	2.30	–
QC LOW	15.0	14.4	96.0	2.02	2.53	99.9 ± 1.08
QC MIDDLE	100	95.7	95.7	1.62	1.06	–
QC HIGH	400	373	93.3	2.44	2.30	98.4 ± 2.40
QC DILUTED	8000	7199	90.0	3.14	2.54	–

Abbreviations: WRP = within-run precision; BRP = between-run precision. # = no additional variation observed by performing the assay in different runs. [1] = data represent mean values ± standard deviation (n=3).

3.2.3. Stability

All SMKIs were stable when the tested human plasma samples where kept for three days at ambient temperature, kept for 23 h in the autosampler and frozen and thawed three subsequent times. Every sample fell within 15 % of nominal concentrations (which is the FDA acceptance range [18]). These results are shown in Table 3.
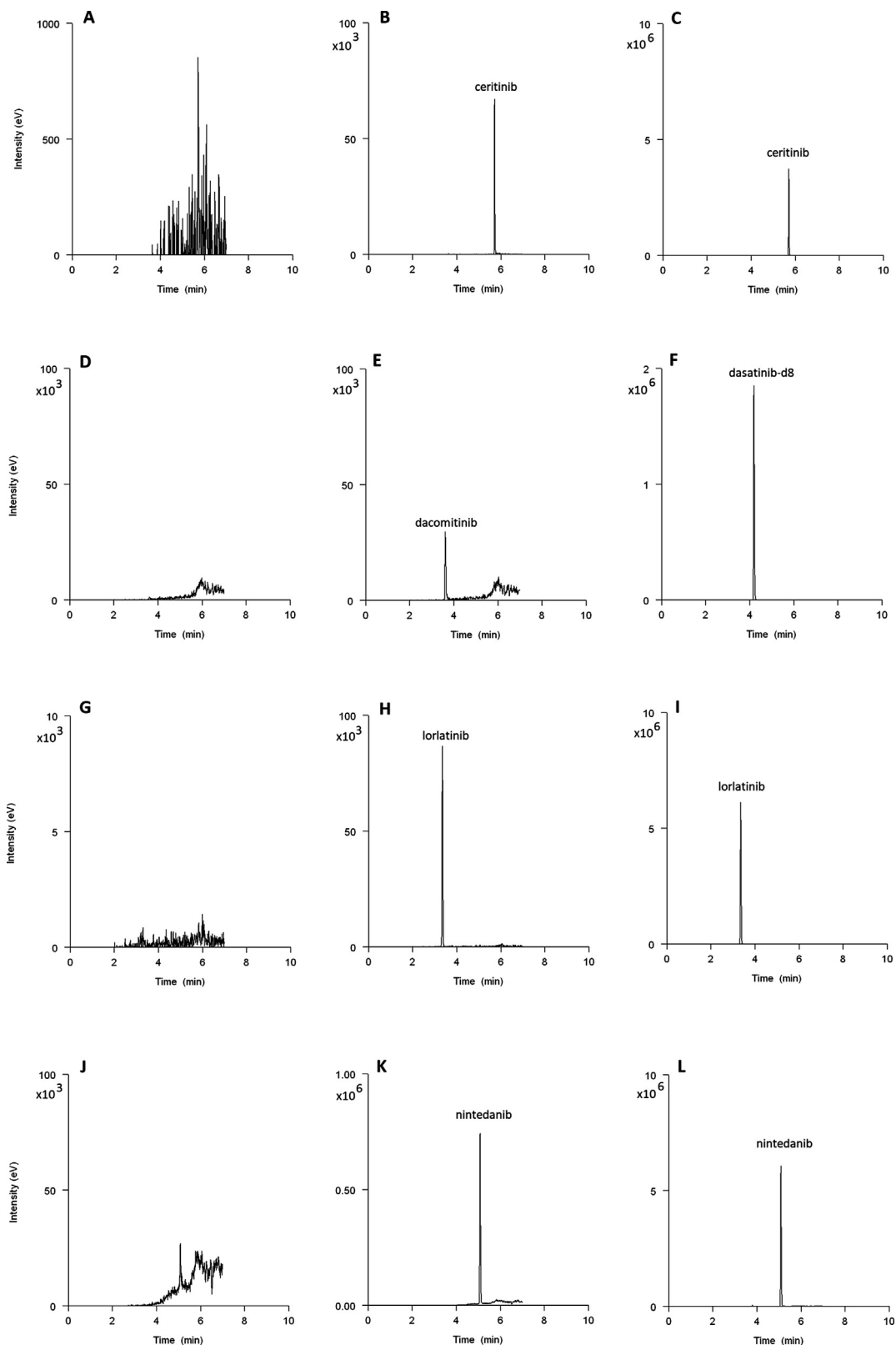
Fig. 2. Representative chromatograms of double blank processed plasma samples (A, D, G and J), plasma samples spiked at the concentration of the LLQ for ceritinib (B), dacomitinib (E), lorlatinib (H), and nintedanib (K), and plasma samples collected in the pharmacokinetic study containing 875 ng/mL ceritinib (C), 305 ng/mL lorlatinib (I), 37.3 ng/mL nintedanib (L) and internal standard dasatinib-d8 (F).

Long-term stability was tested at the time this reported was written. Since the ceritinib stock was stored earlier than the other SMKI stocks, its long-term stability was at least 2 years and 8 months. For dacomitinib, lorlatinib and nintedanib, long-term stability was at least six months and is still ongoing.

Table 3
Stability after different storage conditions.

	Reference	3 days Ambient Temp[1]	3 freeze-thaw-cycles[1]	Autosampler (23 h)[2]
Ceritinib				
QC LOW	16.1 ± 0.529	14.3 ± 0.153 (89.0 %)	16.1 ± 0.458 (100 %)	16.2 (1.3 %)
QC HIGH	434 ± 8.08	403 ± 16.6 (92.8 %)	429 ± 14.7 (98.8 %)	417 (96.3 %)
QC DILUTED	8,214 ± 180	8,436 ± 160 (1.3 %)	9443 ± 279 (115 %)	8575 (98.9 %)
Dacomitinib				
QC LOW	15.0 ± 0.100	12.1 ± 0.058 (80.9 %)	13.6 ± 0.100 (90.7 %)	14.1 (97.9 %)
QC HIGH	392 ± 8.96	343 ± 3.22 (87.3 %)	387 ± 7.94 (98.6 %)	374 (95.7 %)
QC DILUTED	7,429 ± 376	7,112 ± 267 (95.7 %)	7834 ± 898 (106 %)	7482 (95.8 %)
Lorlatinib				
QC LOW	15.9 ± 0.611	15.6 ± 0.173 (98.3 %)	15.7 ± 0.100 (98.9 %)	15.3 (96.2 %)
QC HIGH	396 ± 11.0	396 ± 4.04 (100 %)	396 ± 6.43 (99.8 %)	375 (91.2 %)
QC DILUTED	7,770 ± 405	8,300 ± 266 (107 %)	8521 ± 107 (110 %)	7725 (93.3 %)
Nintedanib				
QC LOW	14.8 ± 0.379	14.1 ± 0.208 (94.8 %)	14.4 ± 0.493 (96.9 %)	15.1 (97.4 %)
QC HIGH	382 ± 12.8	378 ± 13.9 (98.9 %)	387 ± 15.6 (104 %)	392 (94.9 %)
QC DILUTED	7,477 ± 112	8,140 ± 175 (109 %)	8462 ± 286 (1.3 %)	8020 (97.4 %)

Data represent mean ± standard deviation (n = 3). [1] = versus value the reference. [2] = versus value "0h" (n = 1).

Table 4
Incurred samples reanalysis.

Compound	First analysis Conc. (ng/mL)	Second analysis Conc. (ng/mL)	Mean Conc. (ng/mL)	% Difference (%)
Ceritinib				
1	818	875	847	−6.7
2	922	911	917	1.2
3	195	192	194	1.6
4	670	638	654	4.9
5	855	838	847	2.0
Nintedanib				
1	15.0	15.2	15.1	−1.3
2	35.8	37.3	36.6	−4.1
3	11.2	12.1	11.7	−7.7
4	7.41	7.83	7.62	−5.5
Lorlatinib				
1	300	305	303	−1.7
2	631	632	632	−0.2
3	335	361	348	−7.5
4	188	191	190	−1.6
5	36.0	38.7	37.4	−7.2
6	287	395	291	−2.7

% Difference = (first analysis – second analysis)/ (mean of first and second analysis)*100.

3.3. Clinical applicability

Fifteen study samples were successfully used to prove the clinical applicability of this assay. Respectively five, six and four plasma samples of patients treated with ceritinib, lorlatinib and nintedanib were processed and quantified. Table 4 presents the measured concentrations, which were all within this assay's concentration range.

Only ceritinib and nintedanib have exploratory results indicating towards potential target concentrations which could be used for therapeutic drug monitoring (TDM). [4] With TDM, dose optimization and personalization could lead to higher efficacy and lower toxicity of treatment with SMKIs. Further pharmacokinetic research should therefore be focusing on whether or not there exist solid target concentrations for treatment efficacy or toxicity. This is necessary in order to use plasma drug concentrations for optimization of treatment with these SMKIs in the future.

3.4. Incurred sample reanalysis

Reanalysing the patient samples did not result in significant deviation in quantification (last columns of Table 4.). Hence all SMKIs passed the incurred sample reanalysis test, in which the FDA criteria for small-molecules is that at least two-thirds of the samples should have no more than 20 % difference between each other.

[18] Ceritinib had an average 3.3 % difference (-6.7 to 4.9 %), which was for lorlatinib 3.5 % (-7.5 to -0.2 %) and for nintedanib 4.7 % (-7.7 to -1.3 %).

3.5. Performance comparison with other methods

There are multiple LC—MS/MS assays published which report the quantification of ceritinib, [8–12] dacomitinib [13], lorlatinib [14], or nintedanib [15–17] in plasma, with similar quantification concentration ranges. For both ceritinib and nintedanib, methodologies are described to quantify multiple SMKIs simultaneously in human plasma [10,16]. However, only single SMKI LC—MS/MS assays have been described for quantifying dacomitinib (LLQ 1.00 ng/mL) and lorlatinib (LLQ 2.00 ng/mL) in non-human (rodent) plasma. [13,14] In comparison to these latter methodologies, the here reported method is more efficient to quantify essential SMKIs simultaneously and it is the first that is validated for human plasma. It is important to extrapolate animal studies to human studies, since differences in validation and applicability could occur. In the multi-assays for ceritinib and nintedanib, multiple (isotope-labelled) internal standards are used. A compound has potential to serve as an internal standard when is has (almost) equal chemical characteristics (*e.g.* boiling temperature and atomic groups) compared to the compounds that have to be quantified. It is important that compound will not be present in the plasma samples though. Therefore, an isotope-labelled internal standard is often used for every analyte. However, using one internal standard over using all different internal standards is besides financially attractive, also more efficient in preparation and storage, and reduces the influence of repeated random errors in preparation and quantification of the internal standards. In this method, dasatinib-d8 was successfully used as internal standard because of its very similar chemical characteristics.

4. Conclusion

This article reports the development and validation of the first ultra-performance liquid chromatography/tandem mass spectrometry (UPLC–MS/MS) method to simultaneously analyse the SMKIs dacomitinib, ceritinib, lorlatinib, and nintedanib in human plasma, with dasatinib-d8 as sole internal standard. Calibration curves for all SMKIs were linear in the range of 5.00–500 ng/mL. with a lower limit of quantitation of 5.00 ng/mL for all compounds. Validation of this method met all requirements of the FDA. Additionally, clinical applicability was demonstrated by quantification of multiple samples from a pharmacokinetic study in lung cancer

patients. This method can hence be used in the future for TDM in a clinical setting.

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CRediT authorship contribution statement

G.D. Marijn Veerman: Conceptualization, Methodology, Resources, Writing - original draft, Visualization, Funding acquisition. **Peter de Bruijn:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Writing - review & editing, Visualization, Project administration. **Anne-Marie C. Dingemans:** Resources, Writing - review & editing, Funding acquisition. **Ron H.J. Mathijssen:** Resources, Writing - review & editing, Funding acquisition. **Stijn L.W. Koolen:** Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

None.

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