VALIDATED BIOANALYTICAL METHOD

Bioanalytics, Metabolomics and Pharmacokinetics Shared Resource (BMPK)

Director: Dr. James Mohler

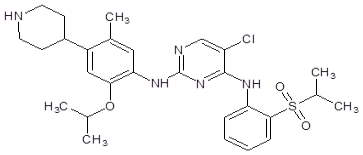
Ceritinib in Heparinized Human Plasma

(Sensitivity: 1.00 ng/mL)

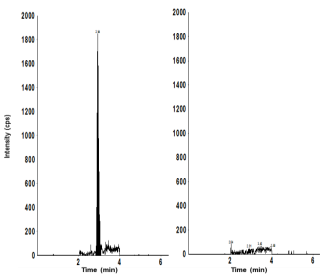
BMPK validated a highly sensitive liquid chromatographic tandem mass spectrometric assay (LC-MS/MS) for the analysis of ceritinib in heparinized human plasma. Ceritinib (ZYKADIA™) has been approved by the FDA for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive metastatic non-small cell lung cancer (NSCLC) who have previously been treated with crizotinib. Compared to crizotinib, ceritinib is approximately 20-fold more potent and is more selective for ALK. Clinical studies of ceritinib co-administered with CYP3A inhibitors (e.g., ketoconazole) or inducers (e.g., rifampin) have resulted in changes in the overall exposure of ceritinib and should be avoided whenever possible. The validated method has been used to support a clinical trial conducted at Roswell Park Comprehensive Cancer Center entitled "*Phase I Study of Ceritinib (LDK378), a Novel ALK Inhibitor, in Combination with Gemcitabine-Based Chemotherapy in Patients with Advanced Solid Tumors*".

Specifications and Validation Performance

Matrix (Anticoagulant):	Human Plasma (Lithium Heparin)
Required Volume:	100 µL
Preparation Procedure:	Protein Precipitation
HPLC Column:	C18
Mobile Phase:	Acetonitrile with Acetic Acid
Flow Rate:	300 µL/min
Detection Type:	Tandem Mass Spectral (MS/MS)
Calibration Ranges:	1.00 - 500 ng/mL
Calibrator Accuracy:	100% (97.8 - 102%; n=5)
Calibrator Precision:	1.79% CV (0.688 - 5.20%; n=5)
QC Concentrations:	3.00, 15.0 and 375 ng/mL
QC Accuracy:	97.9% (95.6 - 101%; n=18)
QC Precision:	4.91% CV (3.01 - 7.44%; n=18)



Ceritinib
Formula: $C_{28}H_{36}ClN_5O_3S$
MW: 558.1433 g/mol



LLOQ S/N = 16.5 **Matrix Blank**

Human Pharmacokinetic Parameters of Ceritinib[1,2]

Recommended Dosing	450 mg single oral daily administration without food; steady-state is achieved after ~15 days of daily dosing
Maximum Tolerated Dose (MTD)	750 mg single oral daily administration
Bioavailability	Absolute bioavailability unknown; systemic exposure increased when taken with food, which may increase adverse events
Active Metabolites	None
Metabolism	~82% of the drug circulates in plasma unchanged (~92% is eliminated in feces with ~68% as unchanged parent compound)
Plasma Protein Binding	97.2% in humans; independent of drug concentration
Maximum Plasma Concentration (C_{max})	Occurs 4-6 hours after dosing; increases dose proportionally over a 50 to 750 mg oral dose range
Plasma Terminal Half-Life ($t_{1/2}$)	41 hours with nonlinear PK over time

[1]Ceritinib (LDK378) Investigator's Brochure, Novartis, Edition 8, and [2]ZYKADIA Prescribing/Patient Information, Novartis, Revised 12/2017

BMPK offers a wide range of bioanalytical and PK/PD modeling services to assist investigators in their basic research, preclinical, and clinical study objectives. For information on services and pricing, contact Wenjuan Zha, Ph.D., Associate Director at (716) 845-3258 or Wenjuan.Zha@RoswellPark.org.

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