Population Pharmacokinetics of Brigatinib in Healthy Volunteers and Patients With Cancer
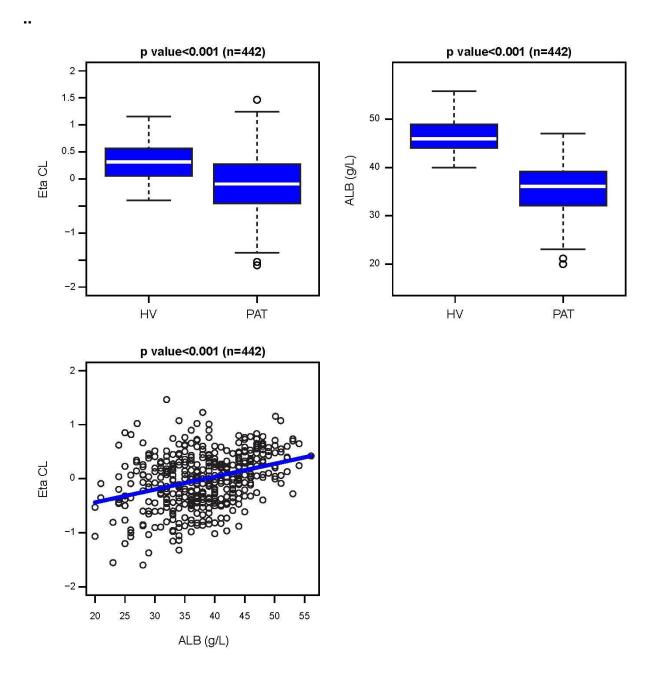
Clinical Pharmacokinetics

Neeraj Gupta[1]; Xiaohui Wang[2]; Elliot Offman[2]; Marita Prohn[3]; Narayana Narasimhan[4*]; David Kerstein[4*]; Michael J. Hanley[1]; Karthik Venkatakrishnan[1†]

[1]Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA; [2]Certara, Princeton, NJ, USA; [3]qPharmetra, Nijmegen, the Netherlands [4]ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA

Corresponding Author:

Neeraj Gupta

Senior Director, Quantitative Clinical Pharmacology

Millennium Pharmaceuticals, Inc.

40 Landsdowne Street

Cambridge, MA, USA 02139

Phone: 617-444-2119

E-mail: Neeraj.Gupta@takeda.com

Online Resource 1. Serum albumin concentration by patient status (patients with cancer vs healthy volunteers). The blue line in the third panel is a linear regression line. *ALB* albumin, *Eta CL* individual random effect on clearance, *HV* healthy volunteer, *PAT* patient with cancer

..

Online Resource 2. Diagnostic plots for the final population PK model for brigatinib. **a** Goodness-of-fit plots showing individual predicted plasma brigatinib concentrations versus observed brigatinib concentrations (*left*) and population predicted plasma brigatinib concentrations versus observed plasma brigatinib concentrations (*right*) on a logarithmic scale. *Points* are individual data, *red solid lines* represent the unity diagonal, and *blue dashed lines* represent the locally weighted scatterplot smoothing (loess) fitting. **b** Conditional weighted residuals (CWRES) versus time after the first dose (*left*), versus time after the previous dose (*middle*), and versus the predicted concentration (*right*). *Points* are individual data. *Red solid lines* represent the unit line at zero. *Blue dashed lines* represent absolute value of CWRES of 4. **c** Prediction-corrected visual predictive check comparing model simulated values to the observed data for the overall population over the first 24 hours after the previous dose. *Circles* are observed brigatinib plasma concentrations, *solid red line* represents the simulated median value, and *red shaded areas* represent the spread of the median predicted values (5th to 95th percentile). Blue lines represent the simulated 5th and 95th percentile, and *blue shaded areas* represent the spread (5th to 95th percentile) of the simulated 5th and 95th percentile concentrations. *CWRES* conditional weighted residuals, *PK* pharmacokinetics, *PRED* predicted concentration

a

b

c