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**Title:** Population pharmacokinetics of imatinib in patients with pulmonary arterial hypertension

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**Body:** Introduction: Pulmonary arterial hypertension (PAH) results in increased pulmonary vascular resistance, right ventricular failure and eventually death. Imatinib is a tyrosine kinase inhibitor which may have efficacy in the treatment of PAH. This study evaluated biochemical and physiological covariates affecting pharmacokinetics of imatinib in patients with PAH Methods: Pharmacokinetic data were analyzed from 98 PAH patients receiving 200 mg imatinib (2 weeks), followed with 400 mg imatinib, if tolerated well, until 24 weeks in a phase III randomized study (IMPRES). Imatinib population pharmacokinetics were described by a one-compartment disposition model with zero order input and inter-individual variability (IIV) on apparent clearance (CL/F) and volume of distribution (V/F). Covariates included age, gender, race, hemoglobin, white blood cell count, and co-medications (CYP3A4 inhibitors such as sildenafil and bosentan) Results: Parameter estimates of the final population pharmacokinetic model for imatinib in PAH patients are presented below

| Parameter | Estimate (Standard Error) |
|---|---|
| CL/F (L/h) | 10.8 (0.83); IIV: CV=43% |
| V/F (L) | 267 (30.0); IIV: CV=64% |
| Fractional increase of CL/F and V/F due to bosentan | 0.46 (0.15) |
| Effect (power coefficient) of hemoglobin on V/F and CL/F | 0.49 (0.25) |
| Duration of first-order input | 1.52 (0.15) |

CL/F in absence of bosentan was similar in PAH, chronic myeloid leukemia (CML) and gastrointestinal stromal tumor (GIST) patients. V/F was almost identical to that in CML patients, approximately 40% larger in GIST patients. Hemoglobin levels correlated with both CL/F and V/F Conclusion: Comparable population

pharmacokinetic parameters are reported with imatinib in PAH, CML and GIST patients.