# A QUANTITATIVE SYSTEMS PHARMACOLOGY (QSP) MODEL TO PREDICT RECEPTOR OCCUPANCY OF BRUTON'S TYROSINE KINASE (BTK) INHIBITORS IN PERIPHERAL BLOOD MONONUCLEAR CELLS, BONE MARROW, AND LYMPH NODES OF PATIENTS WITH B-CELL MALIGNANCIES

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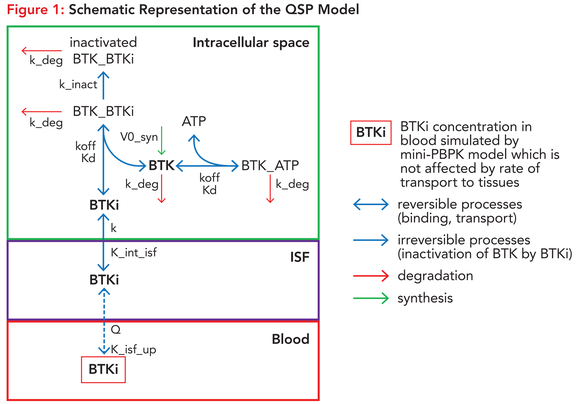
## BACKGROUND

- Bruton's tyrosine kinase (BTK) is a key component of the B-cell receptor signaling pathway
- The BTK inhibitors ibrutinib and acalabrutinib have been approved for the treatment of various B-cell malignancies
- Zanubrutinib is a potent and highly specific next-generation BTK inhibitor that was recently approved for treatment of mantle cell lymphoma and is in phase 3 clinical testing in various indications
- Achieving complete and sustained target engagement with respect to BTK receptor occupancy is thought to be an important factor for attaining deeper and durable clinical responses with the BTK inhibitors
- Testing for BTK occupancy in peripheral blood mononuclear cells (PBMC) can be assessed in clinical studies. However, it is difficult to sample deep target tissues such as bone marrow (BM) and lymph nodes (LN) in patients to assess receptor occupancy
- Quantitative systems pharmacology (QSP) is a mathematical modeling approach to describe dynamic interactions between a drug, biological systems, and disease process at cellular and molecular levels. In this work, QSP was applied to predict target occupancy using pharmacokinetics (PK) of BTK inhibitors and available in vitro data (affinity, physico-chemical properties). Clinical data was used to validate model predictions
- The objectives of this work were:
  1. To develop a QSP model to describe and predict the BTK receptor occupancy in PBMC, BM, and LN after dosing with these BTK inhibitors in patients with B-cell malignancies
  2. To understand the impact of different dosing regimens (once daily [QD] vs twice daily [BID]) on BTK receptor occupancy

## METHODS

- A mathematical model (Figure 1) was developed that describes:
  1. PK of BTK inhibitors
  2. Intracellular concentration of BTK inhibitors in PBMC, BM, and LN
  3. Binding of BTK inhibitors with BTK, including competition with adenosine triphosphate (ATP)
  4. BTK degradation/turnover rate
  5. Degradation of BTK inhibitors bound with BTK, which affects intracellular and interstitial fluid (ISF) concentrations of BTK inhibitors in BM and LN
- This QSP model includes ibrutinib with its metabolite PCI-45227, acalabrutinib with its metabolite ACP-5862, and zanubrutinib
- Previously developed minimal physiologically based pharmacokinetic (PBPK) models were used to reproduce the PK of BTK inhibitors. Distribution of BTK inhibitors was described using the PBPK approach[1-3] and on the basis of physico-chemical properties[3-7]
  - The model takes into account the number of malignant cells in the BM and LN as well as their size and the volume of ISF (Figure 1). This allows for a description of the role that cell number and BTK expression has on BTK inhibitor consumption in tissues (due to BTK inactivation and degradation)
- Variability was introduced in the key model parameters: BTK degradation/turnover, PK parameters, number of malignant cells in BM and LN, ATP intracellular concentration, binding to BTK and its inactivation. Median and 95% confidence bands (CB) for model simulations were calculated on the basis of 1000 simulations

**Figure 1: Schematic Representation of the QSP Model**



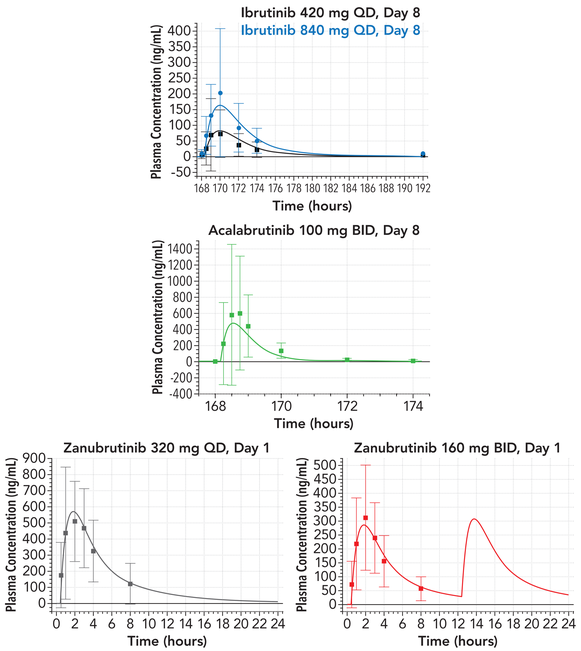

**Abbreviations:** ATP, adenosine triphosphate; BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; ISF, interstitial fluid; PBPK, physiologically based pharmacokinetic; QSP, quantitative systems pharmacology.

## RESULTS

### Model Validation

- PK simulations conducted using the previously developed minimal PBPK model were able to describe the clinical PK data reported for zanubrutinib, ibrutinib, and acalabrutinib (Figure 2)[3,8-11]

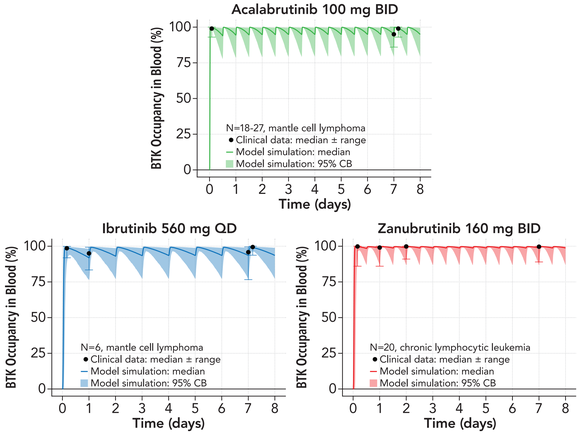
**Figure 2: Comparison of Observed and Predicted PK Profiles in Human Plasma**




**Abbreviations:** BID, twice daily; PK, pharmacokinetic; QD, once daily.

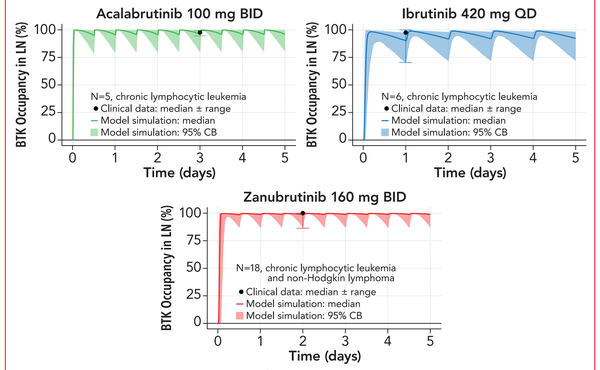
- Model predictions of clinical BTK occupancy in PBMC (Figure 3) and LN (Figure 4) were in agreement with observed clinical data[3,11-15]

**Figure 3: Comparison of Observed and Predicted BTK Occupancy in PBMC**




**Abbreviations:** BID, twice daily; BTK, Bruton's tyrosine kinase; CB, confidence bands; PBMC, peripheral blood mononuclear cells; QD, once daily.

**Figure 4: Comparison of Observed and Predicted BTK Occupancy in LN**

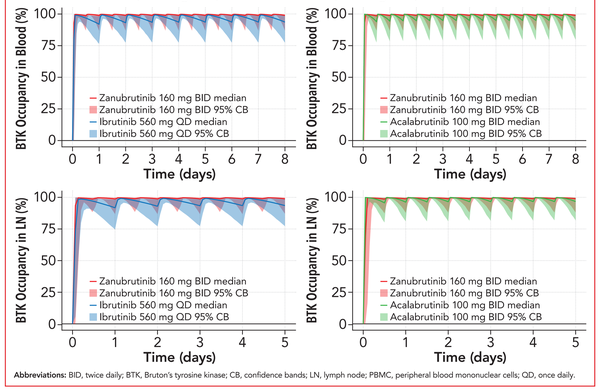



**Abbreviations:** BID, twice daily; BTK, Bruton's tyrosine kinase; CB, confidence bands; LN, lymph node; QD, once daily.

### Model Simulations

- Zanubrutinib (160 mg BID) was predicted to result in higher median BTK occupancy with less variability in both blood (PBMC) and LN compared to ibrutinib (420 mg QD, 560 mg QD) and acalabrutinib (100 mg BID) (Figure 5)

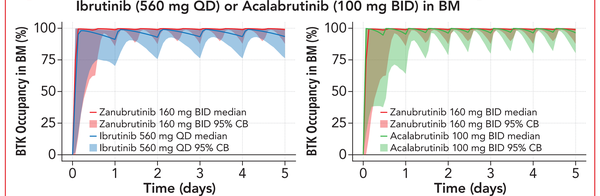
**Figure 5: Comparison of BTK Occupancy Between Zanubrutinib (160 mg BID) and Ibrutinib (560 mg QD) or Acalabrutinib (100 mg BID) in PBMC and LN**




**Abbreviations:** BID, twice daily; BTK, Bruton's tyrosine kinase; CB, confidence bands; LN, lymph node; PBMC, peripheral blood mononuclear cells; QD, once daily.

- In the absence of clinical BTK occupancy data in BM, the model predicted that steady-state trough BTK occupancy in BM was higher after zanubrutinib 160 mg BID administration than those after ibrutinib 560 mg or 420 mg QD administration, and after acalabrutinib 100 mg BID administration (Figure 6)
- BTK occupancy in BM was similar to BTK occupancy in LN, which corresponds to animal studies.[16] In MCL, when the concentration of malignant cells in BM is very high (bone marrow involvement = 95-99%), the concentration of BTK inhibitors in BM and BTK occupancy may decrease 1-2 days after the beginning of treatment. This can be explained by higher BTK inhibitor "consumption" (with BTK inactivation and degradation), because of high BTK expression in MCL cells

**Figure 6: Comparison of BTK Occupancy between Zanubrutinib (160 mg BID) and Ibrutinib (560 mg QD) or Acalabrutinib (100 mg BID) in BM**



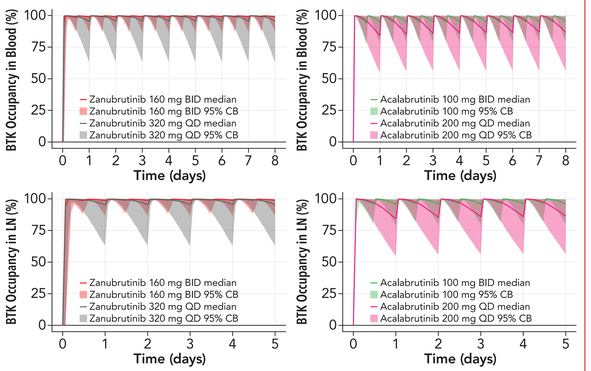

**Abbreviations:** BID, twice daily; BM, bone marrow; BTK, Bruton's tyrosine kinase; CB, confidence bands; PBMC, peripheral blood mononuclear cells; QD, once daily.

## CONCLUSIONS

- A QSP model was successfully developed and validated, which predicted higher median BTK occupancy with less variability for zanubrutinib in PBMC, BM, and LN than ibrutinib and acalabrutinib
- A BID dosing regimen produced higher BTK occupancy than a QD regimen over the dosing interval
- Ongoing clinical trials with zanubrutinib will help determine if improved BTK occupancy in these peripheral and deep target tissues translates to improvements in clinical outcomes

- The model predicted that 160 mg BID of zanubrutinib resulted in higher median trough BTK occupancy than 320 mg QD with less variability, which is consistent with the observed clinical data. The same is predicted for acalabrutinib QD and BID regimens (Figure 7)

**Figure 7: Comparison of BTK Occupancy Between BID and QD Regimens for Zanubrutinib and Acalabrutinib in PBMC and LN**




**Abbreviations:** BID, twice daily; BTK, Bruton's tyrosine kinase; CB, confidence bands; LN, lymph node; PBMC, peripheral blood mononuclear cells; QD, once daily.

- Higher BTK occupancy after the administration of zanubrutinib than after the administration of ibrutinib and acalabrutinib is attributed to the PK properties (higher AUC and fraction unbound in plasma), binding properties to BTK (Kd, inactivation rate constant), and higher lipophilicity for zanubrutinib
- BID regimens showed higher trough BTK occupancy than QD regimens because while both regimens achieve 100% occupancy, BID regimens allow for a more uniform distribution of BTK inhibitor concentrations throughout the day

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### DISCLOSURES

**NB, SS, YO:** BeiGene, Ltd.: employment, equity ownership. **OD, DS, VM:** InSysBio LLC: employment; BeiGene USA, Inc.: consultancy.

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