MIDD by Phase

### Regulatory Decision Support
- Target Authorization and Mechanistic Understanding
- Candidate Comparison, Selection, Human PK and Dose Prediction
- Study Design Optimization
- Predicting and Characterizing ADME Including Intrinsic and Extrinsic Factors Impacting PK Variability
- Risk/Benefit Characterization, and Outcome Prediction from Early Clinical Responses
- Dose and Schedule Selection and Label Recommendations (Including Drug Combinations)
- Comparator/Standard-of-Care Differentiation and Commercialization Strategies
- Patient Population Selection and Bridging between Populations (Pediatrics, Elderly, Obese)
Post Marketing Activities

- Bridging Populations
  - Ethnic / Regional Differences
  - Pediatric population
- Bridging Indications
  - Other disease(s)
- Labeling Support
  - Completion of Clin Pharm Package
    - DDI, organ impairment
  - Dosage Administration
    - New formulations

*Capitalize on quantitative understanding of efficacy/toxicity exposure response*

Venkatakrishnan K et al. CPT 2015; 97: 37-54.
Ibrutinib – Covalent BTK Inhibitor

• Bruton’s tyrosine kinase (Btk) is an enzyme in the B-cell receptor (BCR) signal transduction pathway involved in B cell proliferation.
• Ibrutinib (PCI-32765) is a covalent inhibitor of Bruton’s tyrosine kinase with IC50 of 0.46 nM (bind to cysteine residue Cys 481 of BTK).
• BTK inhibition targeted for B-cell malignancies and other diseases that involves abnormal activation of B-cell pathway.
Indications (FDA)
Monotherapy or In Combination

- Approved for various B cell malignancies (monotherapy and/or combination) and cGVHD

- MCL 2nd line (AA)
- CLL 2nd line
- SLL with 17p deletion
- MZL in patients who require systemic therapy and after anti-CD20 (AA)
- CLL/SLL front line
- SLL with 17p deletion
- cGVHD after failure of 1 or more lines of systemic therapy

MCL = Mantle Cell Lymphoma; CLL = Chronic Lymphocytic Leukemia; SLL = Small Lymphocytic Lymphoma; WM = Waldenström’s macroglobulinemia; cGVHD = Chronic Graft versus Host Disease; MZL = Marginal Zone Lymphoma
MIDD Activities to Support Ibrutinib

• Development of ibrutinib in various combinations, different indications & populations

• Continued assessment of drug-drug interactions
  • Use of PBPK model for predictions of the effects of different doses of inhibitors on ibrutinib, and other scenarios
  • Predictions of ibrutinib exposure with different dose adjustment based on understanding of target engagement & exposure response
  • Fulfillment of PMRs/PAMs including study with omeprazole (PAM)

• Support pediatric development
  • Predictions of starting dose
  • Bayesian evaluation of pediatric exposure and recommendations of clinical dose in different age cohorts

• Support development of different formulations

PBPK=Physiologically Based Pharmacokinetic Modelling;
PMR=Post-Marketing Requirements; PAM=Post Authorization Measure
PAM: DDI Study with PPI

• Rationale
  • Ibrutinib is a weak base with pH dependent solubility (practically insoluble at pH ≥ 3)
  • BCS Class 2 (high permeability/low solubility) with rapid absorption (Tmax 1-2 hrs)
  • Food increases Cmax (2- to 4-fold) and AUC (2-fold); ibrutinib can be taken with or without food

• Study Objective
  • Evaluate effect of repeat dose omeprazole, a proton pump inhibitor (PPI), on the single dose PK of ibrutinib

• Study Design
  • Single center, open-label, sequential design drug interaction study in 20 healthy subjects. Ibrutinib 560 mg administered alone on Day 1 and with omeprazole on Day 7. Omeprazole 40 mg administered on Days 3 to 7.
Plasma Concentration Ibrutinib Alone and With Omeprazole
Comparison of PK parameters of ibrutinib alone and with omeprazole

<table>
<thead>
<tr>
<th></th>
<th>Geometric Mean</th>
<th>Geometric Mean Ratio (90% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ibrutinib Alone</td>
<td>Ibrutinib + omeprazole</td>
</tr>
<tr>
<td>N</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>C_{max}, ng/mL</td>
<td>39.5</td>
<td>14.8</td>
</tr>
<tr>
<td>AUC_{24h}, ng.h/mL</td>
<td>176</td>
<td>147</td>
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<tr>
<td>AUC_{48h}, ng.h/mL</td>
<td>217</td>
<td>213</td>
</tr>
<tr>
<td>AUC_{last}, ng.h/mL</td>
<td>210</td>
<td>195</td>
</tr>
<tr>
<td>Tmax, hr</td>
<td>1.0 (0.5–4.0)</td>
<td>2.0 (0.5–24.2)</td>
</tr>
<tr>
<td>Half-life, hr</td>
<td>11.4 ± 5.1</td>
<td>15.0 ± 10.6</td>
</tr>
</tbody>
</table>

Results Study CLL1005
Effect of Omeprazole on Individual Cmax and AUC

Results Study CLL1005
How to quantitatively evaluate impact of lower Cmax?

- Based on MoA with covalent binding, lower Cmax unlikely to affect inhibition of target
  - Evaluate in quantitative manner using mechanistic model
  - Predict BTK target inhibition of ibrutinib based on PK profiles with/without omeprazole and binding kinetics
  - Sensitivity analysis for different parameters
  - Compare outcome to clinical BTK occupancy data
- Exposure-response for clinical efficacy based on AUC and Cmax

Results to be presented at ASCPT March 2018
By Nahor Haddish-Berhane et al.
Mechanistic model of BTK inhibition by Ibrutinib

E = BTK  I = Ibrutinib

**Protein synthesis**

\[
\begin{align*}
V_{synth} & \quad E & \quad + & \quad I & \quad \xrightarrow{k_{on}} & \quad E \cdot I & \xrightarrow{k_{inact}} & \quad E - I \\
& \quad k_{deg} & \quad & \quad k_{out} & \quad & \quad k_{off} & \quad & \quad k_{deg}
\end{align*}
\]

**Protein degradation**

**Drug elimination**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>(k_{on})</td>
<td>2.4 \times 10^5</td>
<td>1/M \cdot s</td>
<td>Association rate (ref 1)</td>
</tr>
<tr>
<td>(k_{off})</td>
<td>5.7 \times 10^{-5}</td>
<td>1/s</td>
<td>Dissociation rate (ref 1)</td>
</tr>
<tr>
<td>KD</td>
<td>0.24</td>
<td>nM</td>
<td>Affinity (k_{off}/k_{on}) (ref 1)</td>
</tr>
<tr>
<td>(k_{inact})</td>
<td>0.0084</td>
<td>1/s</td>
<td>Covalent binding rate (exp data)</td>
</tr>
<tr>
<td>BTK half-life</td>
<td>24</td>
<td>h</td>
<td>BTK protein half-life (ref 2)</td>
</tr>
</tbody>
</table>

Predicted Receptor Occupancy (RO) for Steady-State Ibrutinib Alone and with Omeprazole

No relevant difference in average RO (94% and 96% for ibrutinib alone and with omeprazole, respectively)
Sensitivity Analysis for Different Parameter Assumptions

BTK Half-Life: Nominal 24 h

- 3x up
- 3x Down

%Change in ROavg,ss

kon: Nominal 2.4×10^5 1/M/s

- 10x Down
- 10x up

%Change in ROavg,ss

kinact: Nominal 0.0084 1/s

- 10x Down
- 10x up

%Change in ROavg,ss
BTK Receptor Occupancy and Ibrutinib PK After SD Administration

Results from PCYC-1102

SD=Single Dose
Efficacy is ORR and shown in Subjects with CLL; Similar profiles in Subjects with MCL
Conclusions

• Mechanistic model developed to support outcome of the drug interaction study with omeprazole and provide clinical recommendations with no dose adjustments and no restrictions

• Data support lack of clinical relevance for the difference in Cmax given that AUC was similar with and without omeprazole

• Small example to illustrate how MIDD is used to support post-marketing activities for ibrutinib

DDI=Drug Drug Interaction
Acknowledgments

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  • **Juthamas Sukbunthreng**, Pharmacyclics, GCP leader

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