Model-informed analysis during NDA/BLA review

*Insights from two FDA case reviews*

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Disclaimer: My remarks today do not necessarily reflect the official views of the FDA
Take Home Message

• Analysis on PK and exposure-response relationship facilitates FDA’s assessment on efficacy and safety.

• Modeling informed analysis can be used to inform trial design in the post-marketing setting.
Outline

• Relevance of model-informed analysis for NDA/BLA review
  – Case Study
    • Analysis
      – Rociletinib
    • Design
      – Lenvatinib + Everolimus in renal cell carcinoma

• Summary
Case Study 1: Rociletinib

Proposed Indication
• Treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, who have progressed on or after EGFR TKI therapy.

Applicant Proposed dose
• 625 mg PO BID

Primary Efficacy
• Rociletinib efficacy were primarily assessed under three dose levels from two clinical studies

<table>
<thead>
<tr>
<th>Analysis Value</th>
<th>500 mg (N=79)</th>
<th>625 mg (N=170)</th>
<th>750 mg (N=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>22.8% (14.1, 33.6)</td>
<td>32.4% (25.4, 39.9)</td>
<td>32.9% (22.5, 44.6)</td>
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</table>

Adverse Reactions of Special Interest
• *QTc Prolongation, Hyperglycemia, etc.*

*Patients were NOT randomized into different dose cohorts*
Rociletinib PK

- Highly variable
- No accumulation (3.7 hours half-life)
- Practically insoluble (<0.1 mg/mL) when pH >2
- Food effect: high-fat meal increases AUC by 54% (Taken with food)
- Metabolism
  - Mainly by amide hydrolysis and N-acetylation

Rociletinib PK Highlights & Biotransformation Pathway

\[ T_{1/2} \text{(M502)}: \text{20 hours} \]
\[ T_{1/2} \text{(M460)}: \text{51 hours} \]
Similar Rociletinib Exposure from 500 to 1000 mg BID

Dose-Exposure Relationship is flat
Flat Exposure-Response Relationship for Efficacy

From 500 to 750 mg BID
- Rociletinib exposure was comparable
- No E-R relationship for ORR was identified

No meaningful difference in efficacy would be expected from 500 mg BID to 750 mg BID
Steep Exposure-Safety Relationships

Hyperglycemia

- Grade 3/4 hyperglycemia (%)
- Metabolite M502 AUCss (ng*h/mL)
  - 1000 mg N=4
  - 750 mg N=63
  - 625 mg N=122
  - 500 mg N=39

QTc Prolongation

- ΔQTcF (ms)
- Metabolite M460 Concentrations (ng/mL)
Summary of Case 1

• Dose-exposure relationship is flat from 500 to 1000 mg BID

FDA Approach: Pooling of the efficacy and safety data across several dose groups may provide a reasonable estimate of the true effect of rociletinib on tumor response, and of the drug toxicity.

• Exposure-efficacy relationship is flat, while exposure-safety relationship is steep

625 mg BID not adequately supported

• FDA’s analysis was discussed and accepted at the advisory committee meeting

ODAC vote: 12:1 against approval based on available data

FDA issued a complete response letter on this submission.
The applicant terminated the development program.
**Case Study 2: Lenvatinib for RCC**

Tyrosine kinase inhibitor (TKI) for

- Differentiated Thyroid Cancer (DTC)
- Advanced Renal Cell Carcinoma (RCC)

  - Approved Dose: 18-mg Lenvatinib + 5-mg Everolimus QD
  - 89% patients required dose reduction/interruption

**PMR To Conduct a Dose Optimization Study**

*Which Dosing Regimen to Study?*

*PMR: Post-marketing Requirement*
Dose Adjustment: Challenges for E-R Modeling

- Shorter survival → Higher Exposure
- Longer survival → Lower Exposure

- Exposure not constant over time
- Biased ER relationship

E-R: Exposure-Response; AE: Adverse Event
E-R Analysis incorporating Dose Adjustment

- Time – vary exposure
  - Exposure at each time interval
- Longitudinal tumor size used
  - Capture the varying drug effect over time
- Adverse event (AE) was associated with the concurrent exposure

- Dynamically generate dose/exposure profile in the simulation
E-R Relationship Estimation

• E-R for Efficacy:
  – An exposure - tumor dynamics model:
    \[
    \text{Tumor Growth Rate} = \text{Natural Growth Rate} - (\text{Suppression by lenvatinib} + \text{Suppression by everolimus})
    \]

• E-R for Safety:
  – An exposure – dosing altering AE model:
    o AE leading to dose adjustment was treated as one repeated event
    o A longitudinal logit mixed effect model for dose-altering AE was developed by sponsor
    o Basis for dosing history generation in the simulation step
Clinical Trial Simulation: 
Evaluate different dosing regimens

I. Various candidate dosing regimens
   • Rules of dose adjustment were pre-defined

II. Dosing history generated
    • E-R model for safety utilized

III. Tumor dynamics generated
     • Exposure-tumor model utilized
Efficacy Profile Prediction

• Tumor dynamics was simulated based on the simulated dosing record
• Lower Starting Doses + Uptitration could provide comparable efficacy
Regulatory Decisions on Lenvatinib

- Post-marketing requirement (PMR) issued for dose optimization
  - Lower starting doses with the option of dose escalation
    - 14 mg Lenvatinib with up-titration + 5 mg everolimus

Summary of Case 2

- Dynamics dose adjustment should be appropriately integrated.
- Modeling and simulation can be used to inform the trial design for optimizing the dosing regimen
Take Home Message

• Analysis on PK and exposure-response relationship facilitates FDA’s assessment on efficacy and safety.

• Modeling informed analysis can be used to inform trial design in the post-marketing setting.
  – Frequent dose modification should be appropriately incorporated in exposure-response analysis for dose evaluation.
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THANK YOU