Case Examples: Extrapolation of Efficacy for GERD in Pediatric Patients

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• Throughout the talk, representative examples of commercial products will be used to illustrate a narrative point or analysis. No commercial endorsement is either implied or intended.
Case examples: Proton Pump Inhibitors

• Nexium® (esomeprazole)
• AcipHex® (rabeprazole)

• Similar E-R relationship to support the extrapolation and the dosing in infants
• PK guided dosing
• Adult dose to match
Gastroesophageal Reflux (GER)

- Passage of gastric contents into the esophagus, with or without regurgitation and vomiting

- Normal physiological response to gastric distention

- Common in infants whose lower esophageal sphincter (LES) is immature
  - LES generally matures by the age of 1 year old
Gastroesophageal Reflux Disease (GERD)

- Symptoms or complications of GER
- Caused by exposure to acid
- Due to weak LES muscle

- Symptoms
  - Dry chronic cough, wheezing, nausea, vomiting and pain in the chest or the upper part of the abdomen

- Mucosal injury in the esophagus by the refluxate
  - Erosive Esophagitis (EE)
  - Non-erosive GERD (NERD) without mucosal injury
    - Symptomatic GERD
GERD in children

• Pathophysiology of GERD similar between adults and pediatric patients ≥ 1 year old
  – Suboptimal function of LES
  – Chronic exposure to acidic refluxate to damage esophageal mucosa

• PPIs approved for GERD in pediatric patients
  – To reduce gastric acid production

• Gastric acid secretion in the first day of life
  – Extrapolation of efficacy has been accepted
Extrapolation of efficacy for GERD in infants

- Extrapolation of efficacy has been utilized for GERD in pediatric patients ≥ 1 year-old

- Infants > 1 month old and < 1 year old*
  - Symptomatic GERD
    - Extrapolation is inappropriate
  - Disease not well-defined
  - Likely different pathophysiology e.g. non-acid related
  - Efficacy trials failed to demonstrate clinical benefit of PPIs

- Erosive Esophagitis associated with GERD
  - Caused by exposure to acid
  - Extrapolation is reasonable with supporting PK and PD data

* GIDAC: Gastrointestinal Drugs Advisory Committee meeting on Nov. 5, 2010
Nexium® (esomeprazole) : Studies to support dosing in pediatric patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Oral Esomeprazole</th>
<th>I.V. Esomeprazole</th>
</tr>
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<tbody>
<tr>
<td>Indication</td>
<td>Symptomatic GERD</td>
<td>GERD with EE</td>
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<tr>
<td></td>
<td>Healing of EE</td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>Clinical trials for healing of EE and symptomatic GERD (DB, R, controlled)</td>
<td>Similar PD effects on suppression of acid outputs with oral esomeprazole¹</td>
</tr>
<tr>
<td>12 to 17 years old</td>
<td>PK¹, safety</td>
<td>PK¹</td>
</tr>
<tr>
<td>1 to 11 years old</td>
<td>PK¹, safety</td>
<td>PK¹</td>
</tr>
<tr>
<td></td>
<td>Supportive healing of EE</td>
<td></td>
</tr>
<tr>
<td>Infants</td>
<td>Efficacy trial for symptomatic GERD failed</td>
<td></td>
</tr>
<tr>
<td>(1-11 months old)</td>
<td>PK¹, safety</td>
<td>PK¹</td>
</tr>
<tr>
<td></td>
<td>PK/PD on gastric pH</td>
<td>PK/PD on gastric pH</td>
</tr>
</tbody>
</table>

¹Extrapolation
Esomeprazole (Nexium): Similar Exposure-Response on gastric pH supported the extrapolation and the dosing in infants.
PK Guided Dose Selection: IV Nexium®

• Treatment of GERD with EE
  • Adult dose: 20 mg and 40 mg

• Pediatric Nexium IV
  – Full extrapolation
  – Pop PK & Safety Data: 50 pediatrics (0 – 17 yr)
  – Dosing regimen adjusted so AUC and Cmax values match adult data at 20 mg
Nexium IV: AUCs Values in Pediatrics* ~ Adults

- 20 mg Adult
- 10 mg Pediatric < 55 kg
- 20 mg Pediatric > 55 kg
- 40 mg Adult

* 1-17 years old

NDA 21-689/S-017 Clinical Pharmacology Review by Dr. Earp

Adjustment of the infusion duration for Cmax

For 3 min Infusion

For 30 min Infusion*

10-min infusion: $C_{\text{max}} < 40 \text{ mg}$ in adults ($13.5 \text{ nM/mL}$)  

* Simulated
AcipHex®:
Dose selection for patients 1-11 years old

• Dose for patients 1-11 years old
  – < 15 kg: 5 mg QD with the option to increase to 10 mg QD
  – ≥ 15 kg: 10 mg QD

• Pediatric systemic exposures at 10 mg
  – Lower than those at 20 mg in adults
  – Comparable to those at 10 mg in adults

• Healing of EE was evident in patients 1-11 years old
  – Healing rate was comparable to adult healing rate at 10 mg
Lower exposure in pediatric patients

Predicted median AUCs (pink) and 95% CI (blue)

5 mg for body weight < 15 kg
10 mg for body weight ≥ 15 kg

Mean AUC in adults @ 20 mg
Mean AUC in adults @ 10 mg

Sponsor’s population PK analysis; NDA 204-736 Clinical Pharmacology Review

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204736Orig1s000ClinPharmR.pdf
Effectiveness on healing of EE in patients 1-11 years of age supported the dosing

### 1-11 year-old

<table>
<thead>
<tr>
<th>Endoscopic Classification of GERD At Baseline</th>
<th>Healing Rate at 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Body Weight &lt;15 kg</td>
</tr>
<tr>
<td></td>
<td>5 mg dose</td>
</tr>
<tr>
<td>Erosive&lt;sup&gt;a&lt;/sup&gt;</td>
<td>88% (7/8)</td>
</tr>
<tr>
<td>Non-erosive&lt;sup&gt;b&lt;/sup&gt;</td>
<td>78% (7/9)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Hetzel-Dent score ≥2  
<sup>b</sup>Hetzel-Dent score = 1

### Adults

#### HEALING OF EROSIONAL OR ULCERATIVE GASTROESOPHAGEAL REFLUX DISEASE (GERD) PERCENTAGE OF PATIENTS HEALED

<table>
<thead>
<tr>
<th>Week</th>
<th>10 mg ACIPHEX QD N=27</th>
<th>20 mg ACIPHEX QD N=25</th>
<th>40 mg ACIPHEX QD N=26</th>
<th>Placebo N=25</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>63%*</td>
<td>56%*</td>
<td>54%*</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>93%*</td>
<td>84%*</td>
<td>85%*</td>
<td>12%</td>
</tr>
</tbody>
</table>

*<sup>p<0.001 versus placebo</sup>

No apparent D-R relationship in adults
Case Summary

• Similar E-R relationship on gastric pH supported the extrapolation of efficacy and the dosing for EE in infants, 1-11 months old

• Dose selection based on Cmax and AUC matching to the range of Cmax and AUC observed in adults
  – Dosing based on body-weight cut-off to reduce the PK variability across age groups
  – Modeling and simulation to refine the dosing regimen

• With the exposure-matching approach, the identification of the optimal dose in pediatric patients is dependent on the finding of optimal dose in adults
Acknowledgements

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