Leveraging multiple R tools to make effective pediatric dosing decisions

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Biomedical Decision Informatics

Bringing a quantitative approach to drug development

Quantitative Systems Pharmacology, Biomarker Exposure-Response
PK, PK-PD, Probability of Technical Success
Model Based POC, Population PK-PD, Trial Design, Dose Selection
Trial Simulation, Filing Pop PKPD for Safety & Efficacy
Comparative Effectiveness, Real World Evidence

Translational
Phase I
Phase II
Phase III
Post Marketing

Off-The-Shelf Disease Area Platform Content: Disease Progression, Quantitative Systems Pharmacology, Competitor Model-Based Meta-Analysis, Trial Simulation Tools
Pediatric Drug Development Questions

- What dose?
- What formulation?
- What endpoints?
- What age?
- How many?
- When?
- Other considerations?
A Typical Scenario - All Open Source

- **Cosentyx® (Secukinumab)**
- human IgG1 monoclonal antibody
- interleukin-17A antagonist
- 150 or 300 mg injection approved in adults
  - moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy
  - psoriatic arthritis
  - ankylosing spondylitis

- Potential treatment in pediatric population
secukinumab (COSENTYX®)
- Anti IL-17A human mAb
- Adult patients with:
  - Plaque psoriasis
  - Psoriatic arthritis
  - Ankylosing spondylitis
- Induction dose (adults):
  - 150/300 mg qw x5, then q4w

Questions
- What dose is appropriate in pediatric population?
- Should different weight groups get different doses?
  - How to compose weight groups?
  - What dose to give each group?
- How might we conduct therapeutic drug monitoring?

Model
- Published in FDA Clin Pharm Review
  - 125504Orig1s000
- Two-compartment PK
  - Weight is only covariate on clearances and volumes
- Endpoint is PASI75
- Turnover-type PD model for PASI
Simulation: Exposure
Simulation: Outcome

Model Inputs

Pediatric dose (mg)
50

Weight groups (kg)

Model Results Up to Date

[Graph showing the outcome over time with Weight Group >= 10]
Simulation: Exposure
Simulation: Outcome

Model Inputs

Pediatric dose (mg)
25 75 150

Weight groups (kg)
25 50

Model Results Up to Date

PROBLEM PLAN EXPOSURE OUTCOME

Weight Group < 25 (25-50) ≥ 50

PASI 75

Time (weeks)
• Integration of tools
• Interactive simulation for decision makers
• Support for regulatory interactions
• Exploration of pediatric dosing rules

R/Pharma, Boston 2019
References

• Pediatric Study Plan (FDA)

• Pediatric Investigation Plan (EMA)

• Shiny app
  ○ https://metrumrg.shinyapps.io/mrgsolve-demo-acop7/

• mrgsolve
  ○ https://mrgsolve.github.io/

• Lee et.al., Effect of Body Weight on Risk-Benefit and Dosing Regimen Recommendation of Secukinumab for the Treatment of Moderate to Severe Plaque Psoriasis, Clin. Pharm & Ther (2019)
THANK YOU!