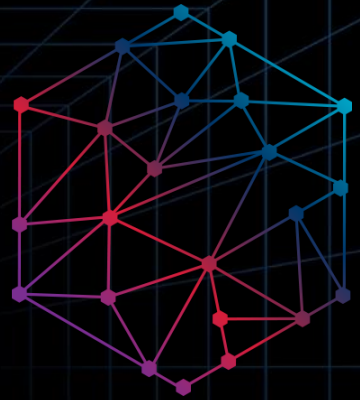
Model-Informed Drug Development

MIDD+

2021 Virtual Conference



Pharmacometrics in Post Approval: Fulfillment of Requirements, Label Extension, and Life-Cycle Management

Aksana Jones, MS

SimulationsPlus

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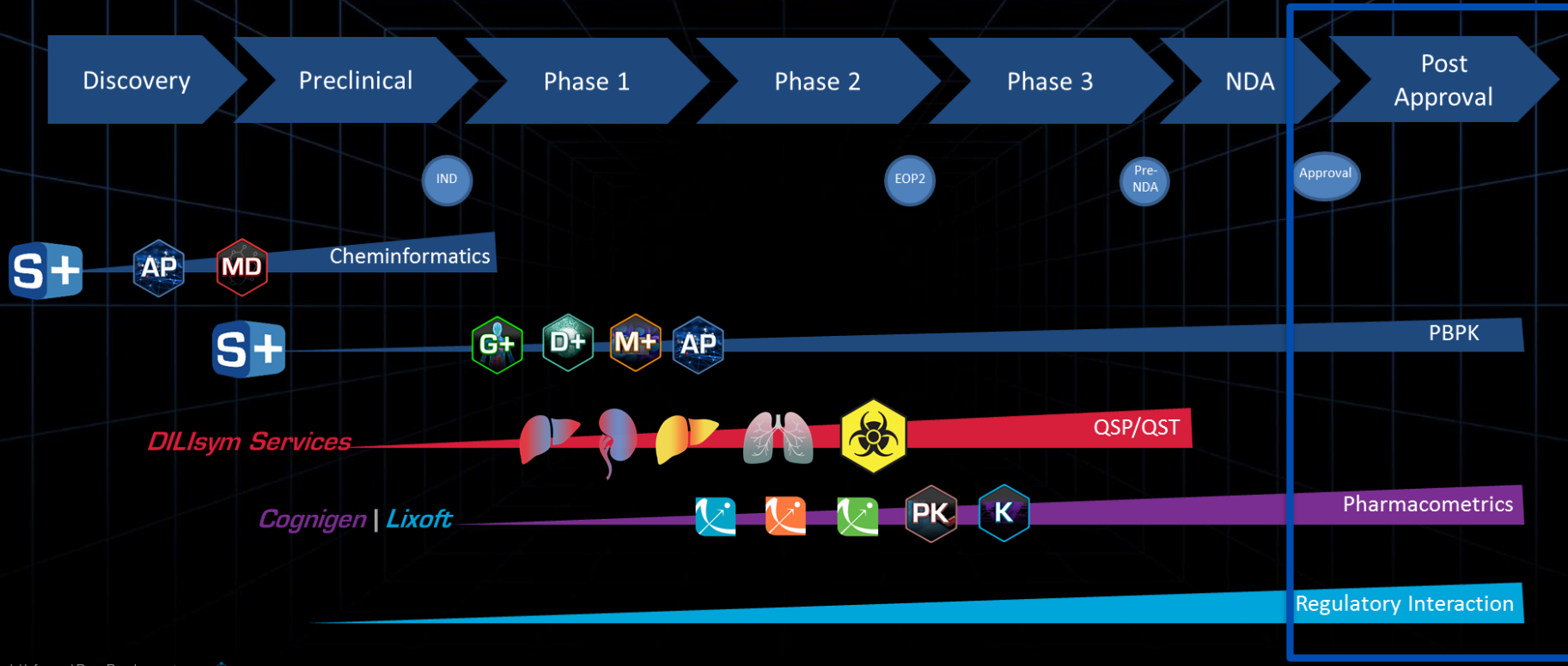
Post Approval



Post Approval

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/YYYY
Section Title, Subsection Title (x.x) M/YYYY

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

Limitations of Use
Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

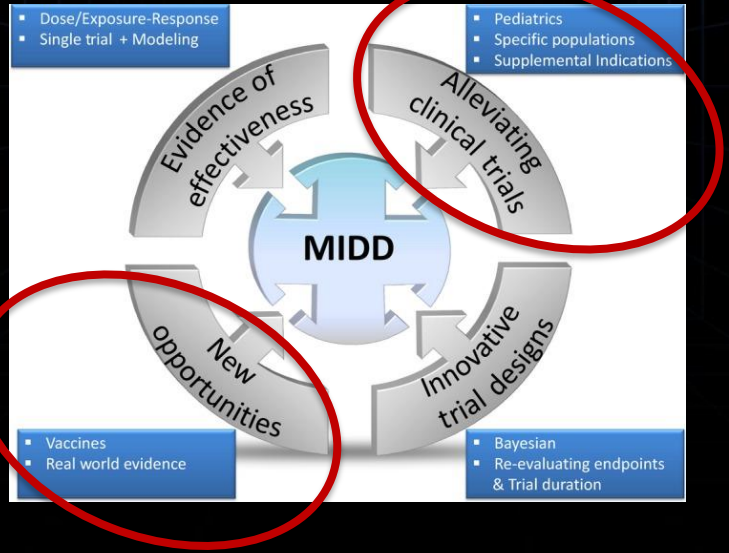
----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide.

Revised: M/YYYY

Unleash the Full Potential of MIDD Post Approval

- MIDD acknowledgment in the PDUFA VI authorization provides an excellent opportunity for industry and regulators to collaborate in further advancing the applications of MIDD and thus potentially changing drug development paradigms[1]



1. Jain L, Mehrotra N, Wenning L, Sinha V. PDUFA VI: It Is Time to Unleash the Full Potential of Model-Informed Drug Development. *CPT Pharmacometrics Syst Pharmacol*. 2019;8(1):5-8. doi:10.1002/psp4.12365

The Pediatric Dose Selection Challenge

- Pediatric patients should have access to safe and effective drugs
  - But what Dose should be used?
- High pediatric trial failure rate (42% of pediatric trials submitted to FDA 2007-2014)[2]
  - 16% due to safety
  - 86% due to lack of efficacy
  - 10 of these cited 'Dosing' as a contributing factor leading to lack of efficacy
- Time from adult labelling to pediatric labelling is approximately 9 years[2]
- Opportunities to bring drugs for use in pediatrics to the market faster:
  - Dose selection
  - Providing supporting evidence to bridge the gap
  - Informing trial design

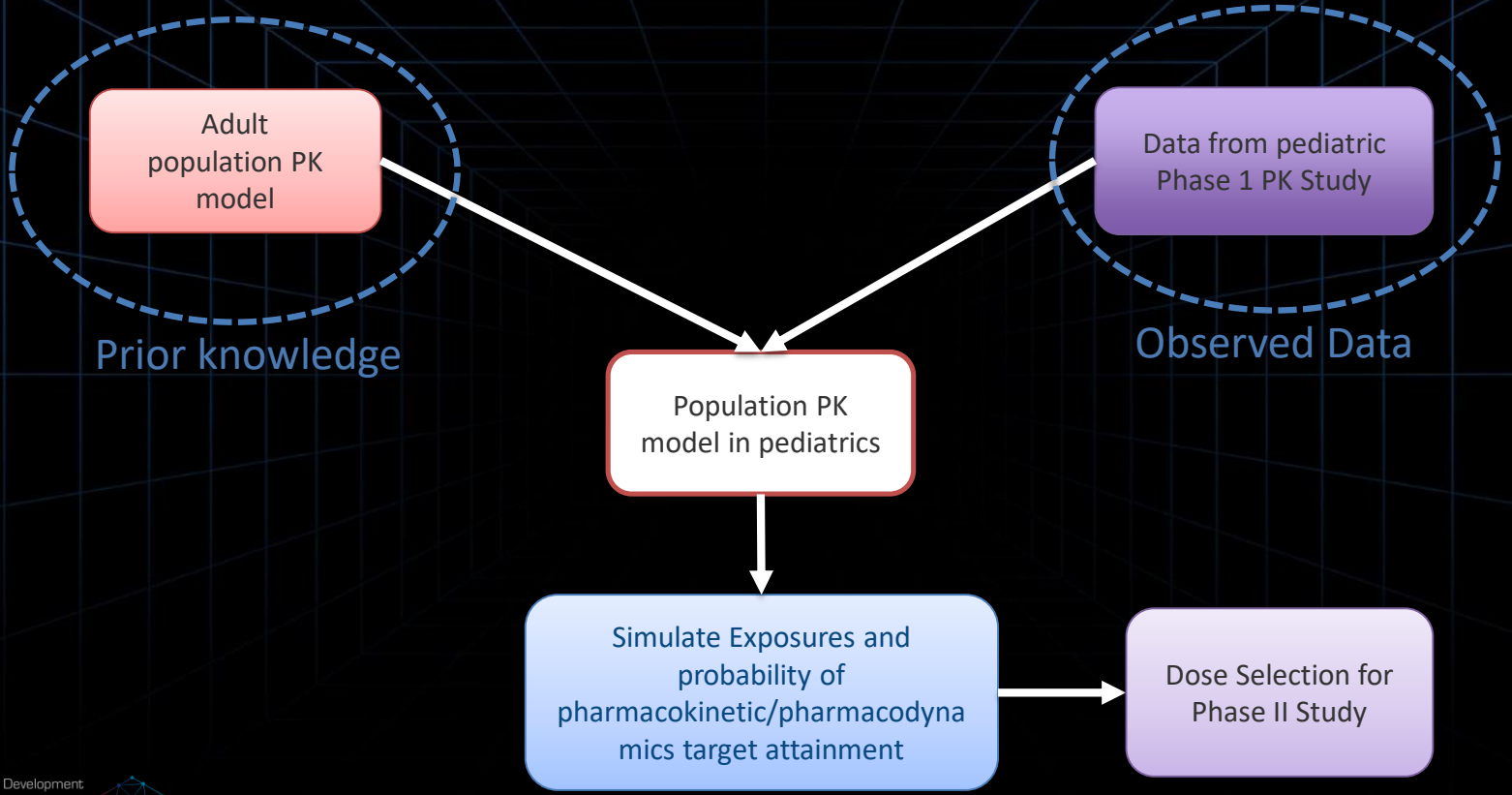
1-Momper et al, Clin Pharmacol & Ther, 2015, vol 98 (3), 245-51.
2-Bi et al, J Clin Pharmacol, 2019, 59(S1), S104-11.

Zerbaxa Dose Selection for Pediatric Patients

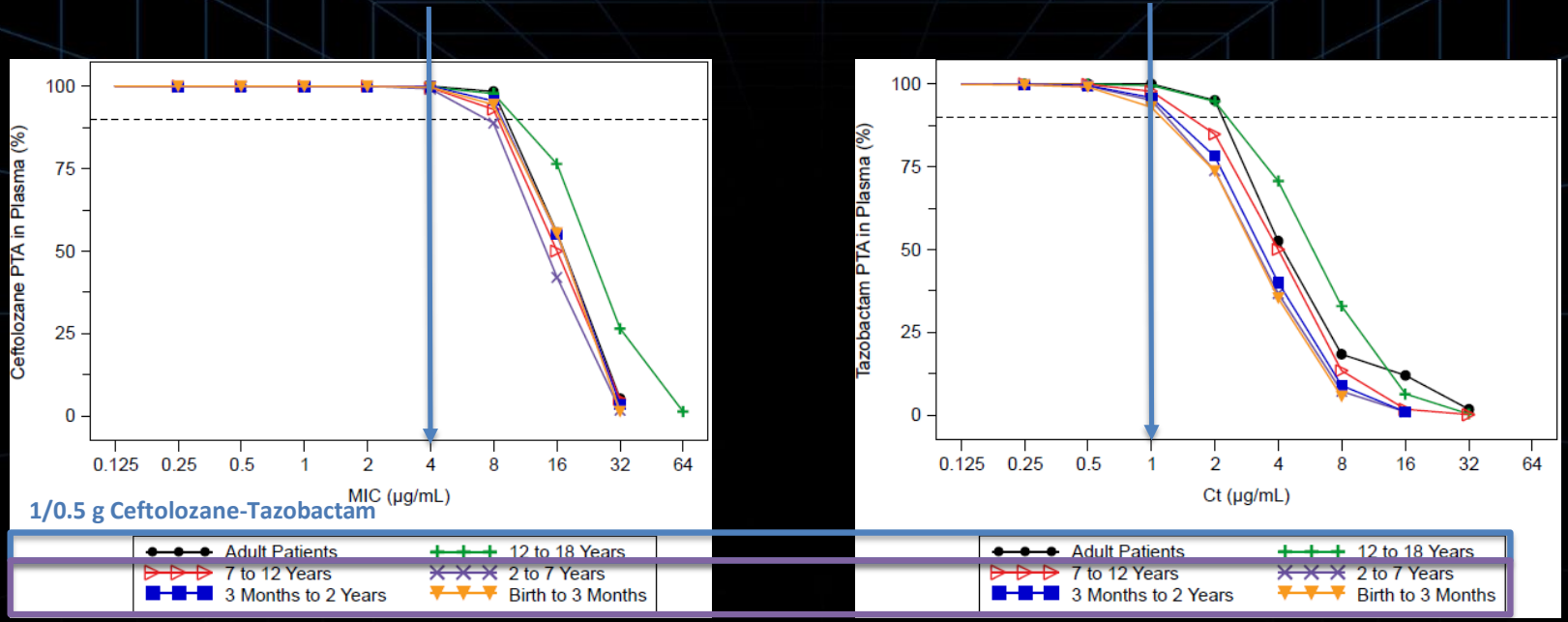
- Zerbaxa (Ceftolozane-tazobactam), is approved for treating complicated urinary tract infections and complicated intra-abdominal infections in adults
- Zerbaxa has not been approved in pediatric patients
- Simulations of various dosing regimens in pediatric patients were conducted to assess each regimen's plasma exposure and the probability of pharmacokinetic/pharmacodynamics target attainment to guide dose selection for further clinical evaluation

Larson KB, Patel YT, Willavize S, Bradley JS, Rhee EG, et al. Ceftolozane-tazobactam population pharmacokinetics and dose selection for further clinical evaluation in pediatric patients with complicated urinary tract or complicated intra-abdominal infections. Antimicrob Agents Chemother. 2019 May 24;63(6):e02578-18.

Zerbaxa Dose Selection for Pediatric Patients



Zerbaxa Dose Selection for Pediatric Patients



1/0.5 g Ceftolozane-Tazobactam

20/10 mg/kg Ceftolozane-Tazobactam

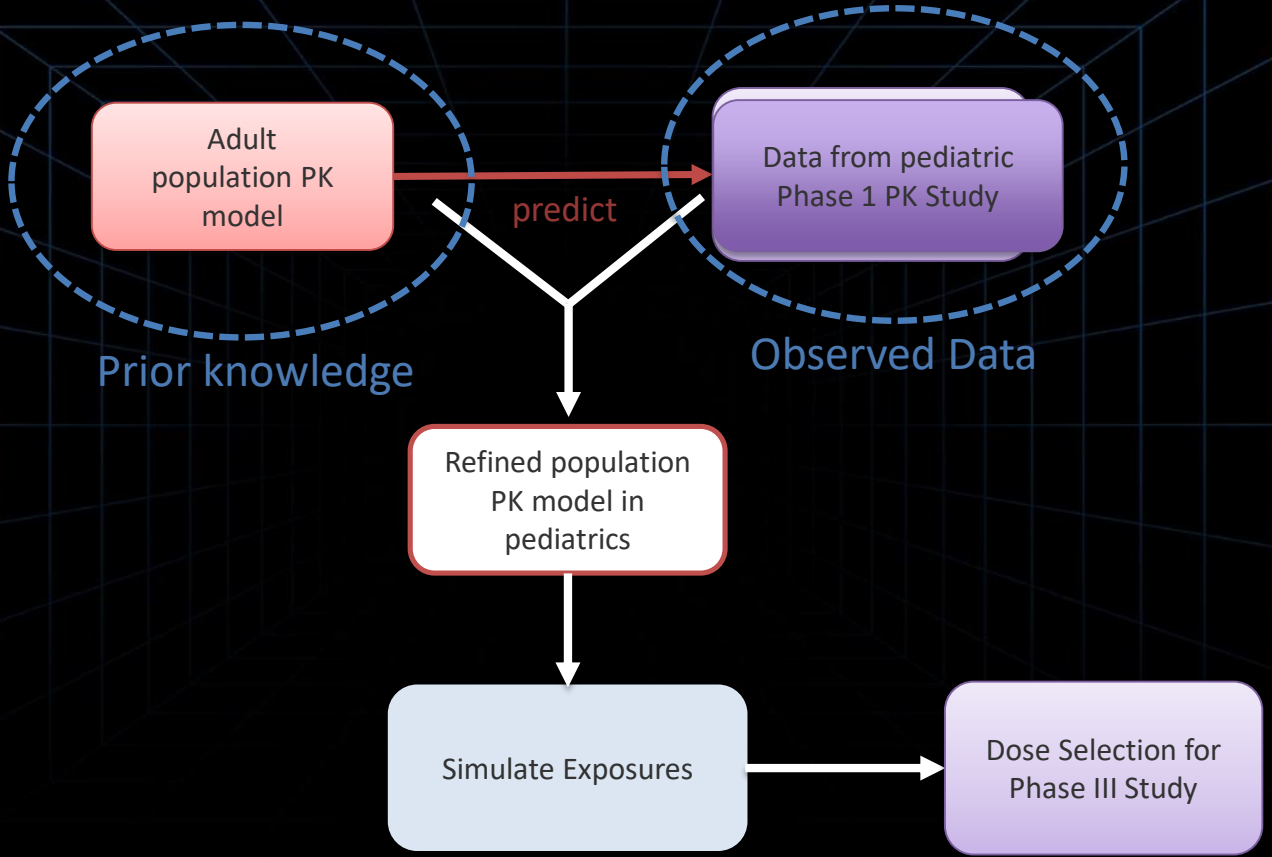
Larson KB, Patel YT, Willavize S, Bradley JS, Rhee EG, et al. Ceftolozane-tazobactam population pharmacokinetics and dose selection for further clinical evaluation in pediatric patients with complicated urinary tract or complicated intra-abdominal infections. Antimicrob Agents Chemother. 2019 May 24;63(6):e02578-18.

Fremanezumab Pediatric Phase III Dose Selection

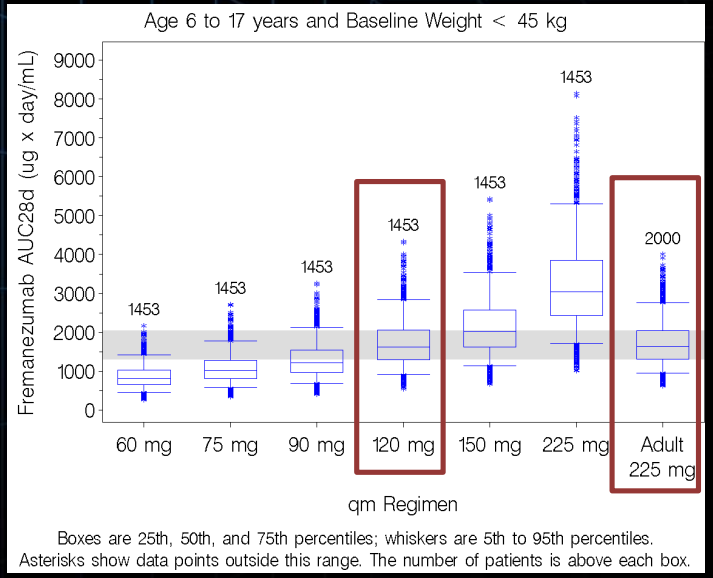
- Potential fremanezumab doses for pediatric patients were evaluated using MIDD, combining prior knowledge from adults[1] with data collected in an open-label phase 1 pharmacokinetic and safety study in pediatric patients with migraine[2]

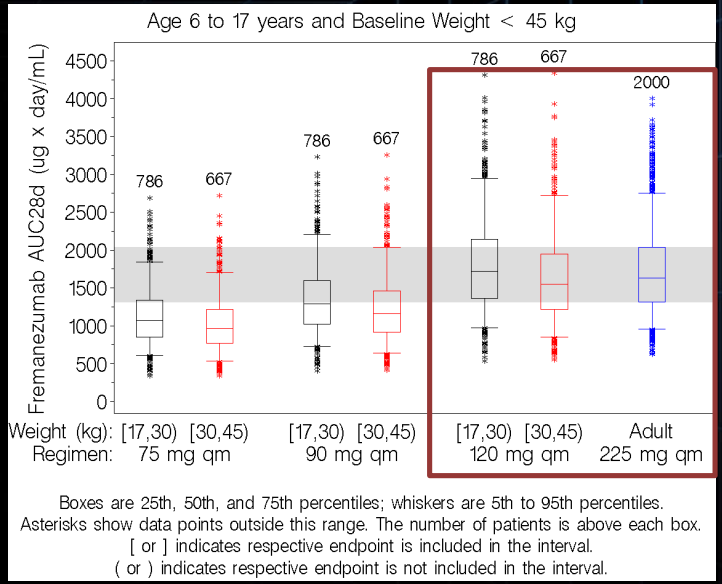
1. Fiedler-Kelly JB, Cohen-Barak O, Morris DN, et al. Population pharmacokinetic modelling and simulation of fremanezumab in healthy subjects and patients with migraine. *Br J Clin Pharmacol* 2019; 85: 2721-2733
2. Cohen-Barak O, Radivojevic A, Jones A, Fiedler-Kelly J, et al. Dose selection for fremanezumab (AJOVY) phase 3 pediatric migraine studies using pharmacokinetic data from a pediatric phase 1 study and a population pharmacokinetic modeling and simulation approach. Cephalalgia. Accepted

Fremanezumab Pediatric Phase III Dose Selection



Fremanezumab Pediatric Phase III Dose Selection





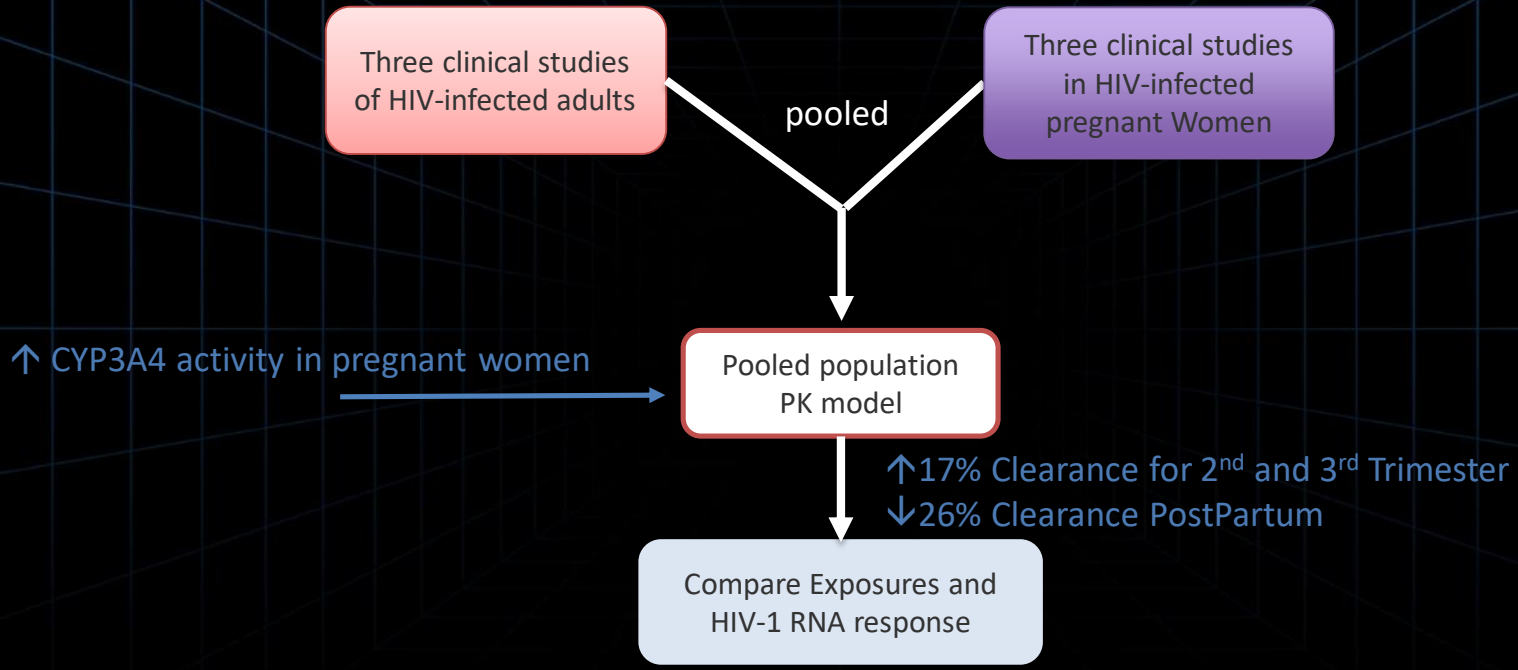
Cohenbarak O, Radivojevic A, Jones A, Fiedler-Kelly J, Gillespie M, Brennan M, Gutman D, Rasamoelisolo M, Loupe P, Rabinovich-Guilatt L, Levi M. Pediatric dose selection for fremanezumab (AJOVY) phase 3 migraine study using pharmacokinetic data from a pediatric phase 1 study and a population pharmacokinetic modeling and simulation approach. Poster presented at the European Headache Federation (EHF) Virtual Congress; June 29 - July 2 2020

The Pregnancy Dose Selection Challenge

- Pregnancy is a complex state where changes in maternal physiology have evolved to favor the development and growth of the placenta and the fetus[1]
- These adaptations may affect preexisting disease or result in pregnancy-specific disorders[1]
- Similarly, variations in physiology may alter the pharmacokinetics or pharmacodynamics that determines drug dosing and effect[1]
  - ↑ CYP3A4 activity in pregnant women
- Model-based approaches have been applied to analyze pharmacokinetics and pharmacodynamics in pregnant and nonpregnant subjects to evaluate dosing recommendations[2]

1. Feghali M, Venkataramanan R, Caritis S. Pharmacokinetics of drugs in pregnancy. Semin Perinatol. 2015;39(7):512-519. doi:10.1053/j.semperi.2015.08.003
2. Salem AH, Jones AK, Santini-Oliveira M, Taylor GP, Patterson KB, Nilius AM, Klein CE. No Need for Lopinavir Dose Adjustment during Pregnancy: a Population Pharmacokinetic and Exposure-Response Analysis in Pregnant and Nonpregnant HIV-Infected Subjects. Antimicrob Agents Chemother. 2015 Nov 2;60(1):400-8. doi: 10.1128/AAC.01197-15. PMID: 26525798; PMCID: PMC4704200.

No Need for Lopinavir Dose Adjustment during Pregnancy



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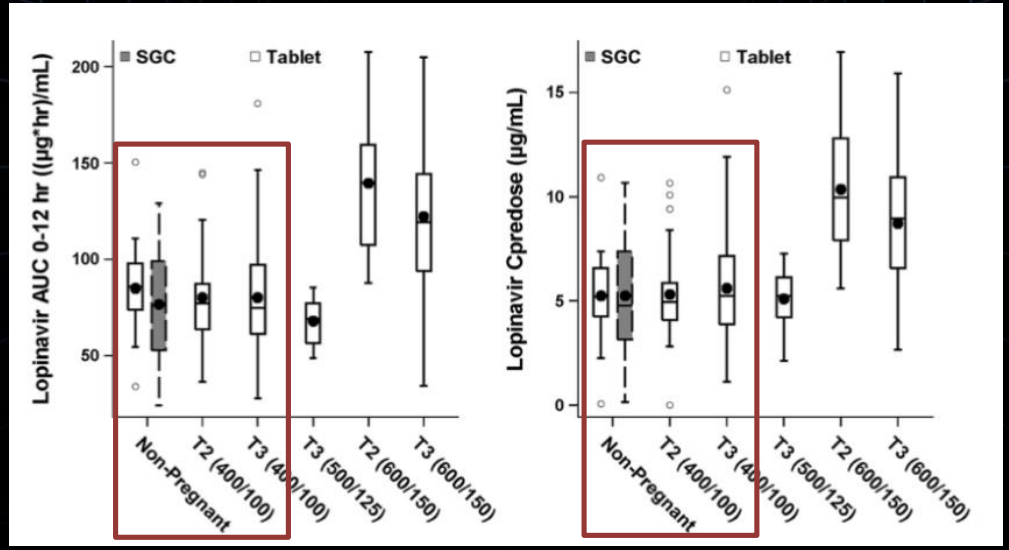
No Need for Lopinavir Dose Adjustment during Pregnancy

- Pregnant women receiving the tablet formulation still maintain Lopinavir exposure that is similar to the efficacious exposure in non-pregnant subjects



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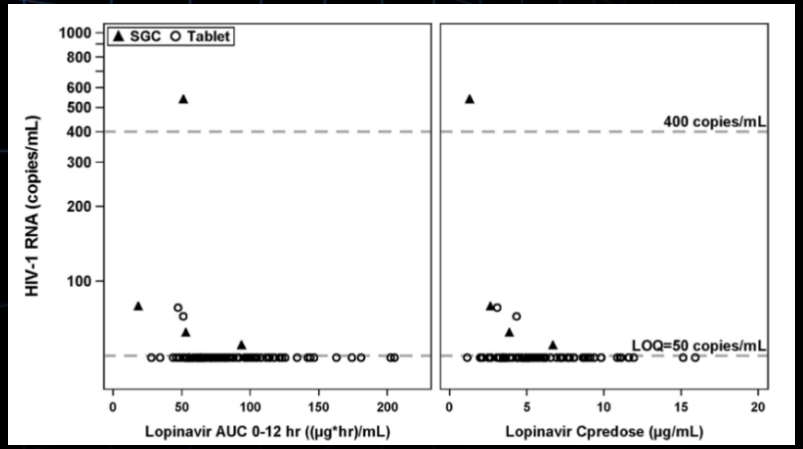
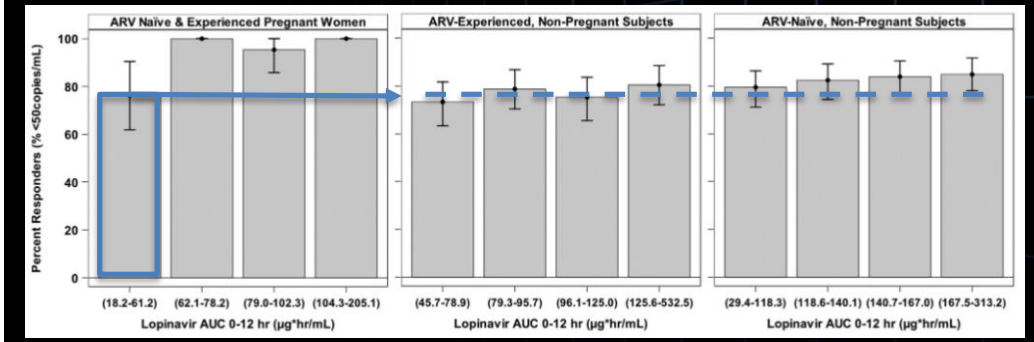
No Need for Lopinavir Dose Adjustment during Pregnancy

- No correlation between the HIV-1 RNA virologic response and LPV exposures achieved in pregnant women or nonpregnant subjects





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No Need for Lopinavir Dose Adjustment during Pregnancy

14 days has been attained (2.3, 5.2)

Pregnancy (2.4):

- 400/100 mg twice daily in pregnant patients with no documented lopinavir-associated resistance substitutions.
- There are insufficient data to recommend a KALETRA dose for pregnant patients with any documented KALETRA-associated resistance substitutions.
- No dose adjustment of KALETRA is required for patients during the postpartum period.

KALETRA [package insert] North Chicago, IL: AbbVie Inc. ; 2016
https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021251s052_021906s046lbl.pdf

Summary: Model-Based Approaches Add Significant Value in Special Population Dose Selection

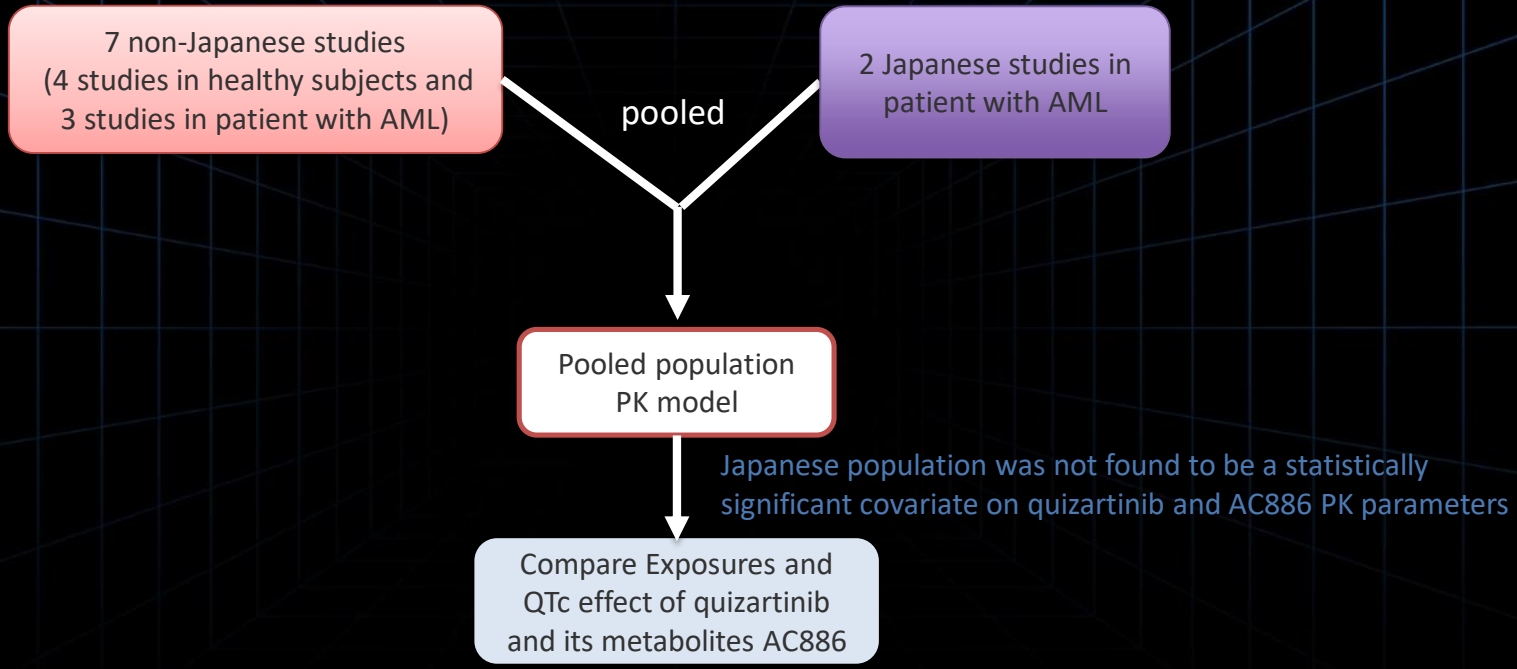
- Model-based approaches can be utilized to select and optimize dose selection and recommendation in:
  - Pediatrics
  - During Pregnancy
  - Elderly
- Model-based approaches have been shown to:
  - Leverage existing knowledge to ultimately bridge knowledge gaps

Life-Cycle Management: Bridging to other Markets

- MIDD can support justification of dose and dosing regimen in different geographic populations
- Quizartinib[1]
  - Goal: To support justification of quizartinib dose and dosing regimen in Japanese AML patients
  - Conclusion: Results support the same dosing regimen for quizartinib in Japanese and non-Japanese AML patients

1. Nakayama S, Tachibana M, Ludwig E, Jaworowicz D, Huang H, Fiedler-Kelly J, et al. Comparison of pharmacokinetics and QTc effect of quizartinib in Japanese and non-Japanese patients with relapsed/refractory (R/R) FLT3/ITD positive acute myeloid leukemia (AML) using population pharmacokinetic (PopPK) analyses. Poster presented at the American Conference on Pharmacometrics (ACoP11); October 4-7, 2020 (Virtual).

Same Dosing Regimen for Quizartinib in Japanese and non-Japanese AML Patients



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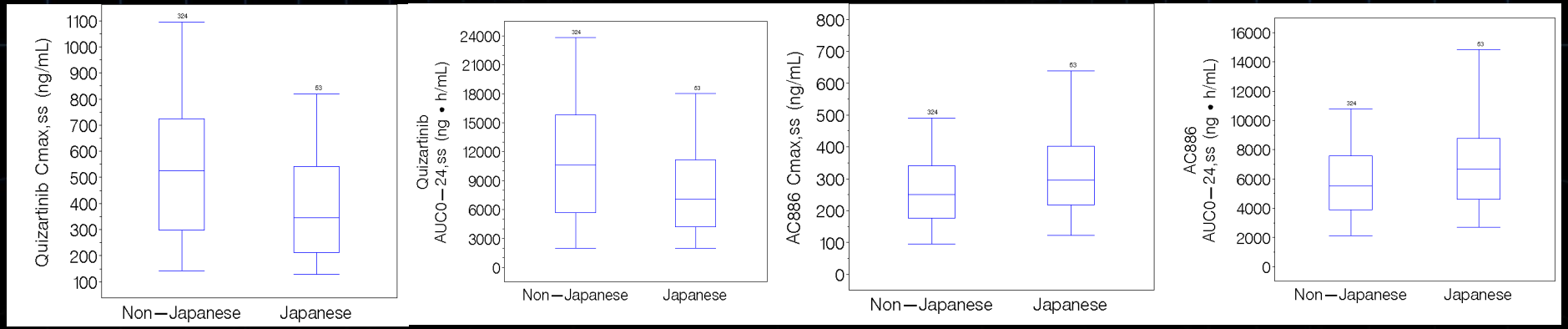
Same Dosing Regimen for Quizartinib in Japanese and non-Japanese AML Patients

- Similar PK profiles of quizartinib and AC886 in Japanese and non-Japanese AML patients
- Results support the same dosing regimen for quizartinib in Japanese and non-Japanese AML patients



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Label Extensions: Drug Drug Interaction Predictions

- The development of PBPK models for use in DDI simulations can support guidance of dose adjustments for coadministered medications
- Efavirenz[1]
  - Developed and validated PBPK model for efavirenz is suitable to be used as a standard perpetrator to evaluate the impact of moderate CYP3A4 induction on CYP3A4-metabolized compounds

Poster presentation 2:05 PM

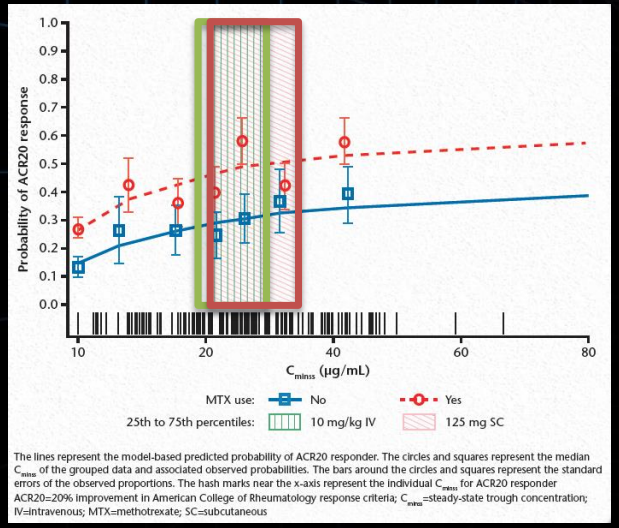
1 Darling I, Owen JS, Lukacova V. Efavirenz physiologically based pharmacokinetic model development and validation as a moderate CYP3A4 inducer for drug-drug interaction predictions. Poster [M1430-13-87] presented at: American Association of Pharmaceutical Scientists (AAPS) PharmSci 360; November 3-6 2019; San Antonio, TX

Life-Cycle Management: New indications

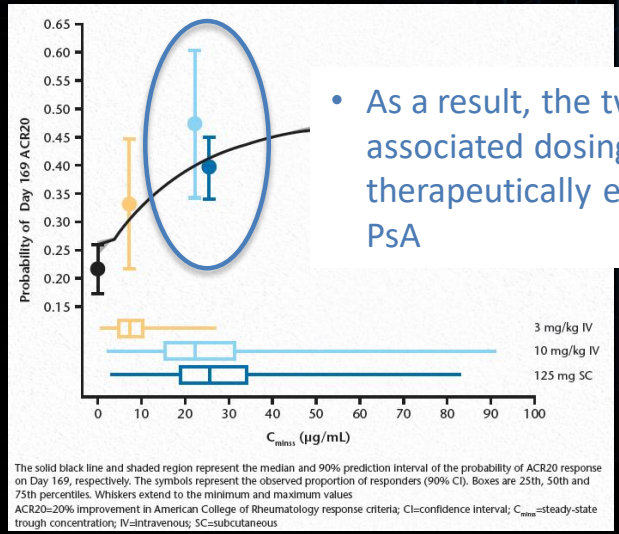
- The development of Exposure-Response models for use in predictions to other indications can support approval in other indications
- Abatacept in psoriatic arthritis (PsA)
  - Both subcutaneous (SC) and intravenous (IV) abatacept, a selective T-cell co-stimulation modulator, are approved for the treatment of adults with moderately to severely active rheumatoid arthritis (RA) and pediatric patients with moderately to severely active polyarticular-course juvenile idiopathic arthritis (pJIA).
- **Goal:** Support the regulatory submission/approval process, to determine whether the proposed IV and SC dosing regimens provided near-maximal efficacy and were therapeutically equivalent in patients with PsA

Life-Cycle Management: New indications

- As in RA, an Emax model (maximum response in logit for Cminss) adequately described the E–R relationship for ACR20 in PsA.



The lines represent the model-based predicted probability of ACR20 responder. The circles and squares represent the median C_{minss} of the grouped data and associated observed probabilities. The bars around the circles and squares represent the standard errors of the observed proportions. The hash marks near the x-axis represent the individual C_{minss} for ACR20 responder
ACR20=20% improvement in American College of Rheumatology response criteria; C_{minss}=steady-state trough concentration; IV=intravenous; MTX=methotrexate; SC=subcutaneous



The solid black line and shaded region represent the median and 90% prediction interval of the probability of ACR20 response on Day 169, respectively. The symbols represent the observed proportion of responders (90% CI). Boxes are 25th, 50th and 75th percentiles. Whiskers extend to the minimum and maximum values
ACR20=20% improvement in American College of Rheumatology response criteria; CI=confidence interval; C_{minss}=steady-state trough concentration; IV=intravenous; SC=subcutaneous

- As a result, the two formulations and their associated dosing regimens are deemed to be therapeutically equivalent for the treatment of PsA

Li X, Passarell J, Morris D, Murthy B, Girgis IG. Abatacept population pharmacokinetics and exposure-response analyses for dose recommendation of SC and IV abatacept in patients with psoriatic arthritis. Poster presented at: Breaking Down Barriers to Effective Patient Care; 119th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics (ASCPT); March 20-24, 2018; Orlando, FL.

Pharmacometrics in Post Approval

- Multiple model-based methods may be considered:
  - Exposure-matching
  - Extrapolation of Efficacy
  - Physiologically based PK model-based: Mechanistic approach
  - Bayesian techniques
    - Population-based modeling frequently invokes Bayesian methods
    - Many modeling approaches include options to inform predictions based on prior knowledge, data, or both

Q&A

Questions & Answers

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