FDA-UNIVERSITY OF MARYLAND

Workshop on Quantitative Assessment of Assumptions to Support Extrapolation of Efficacy in pediatrics

Quantitative Assessment of Exposure/Response Similarity in Rheumatoid Arthritis (RA) and Juvenile Idiopathic Arthritis (JIA)

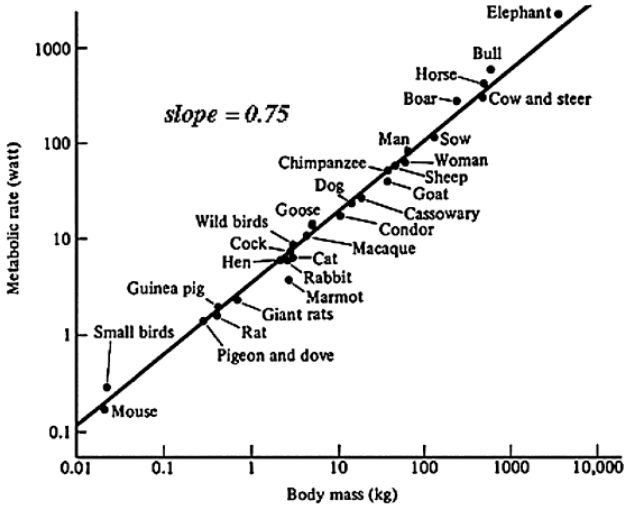
MEGAN GIBBS, BscPharm, Ph.D., FCP
Clinical Pharmacology, Modeling and Simulation, Amgen
JUNE 1, 2016

AMGEN®
Pioneering science delivers vital medicines™

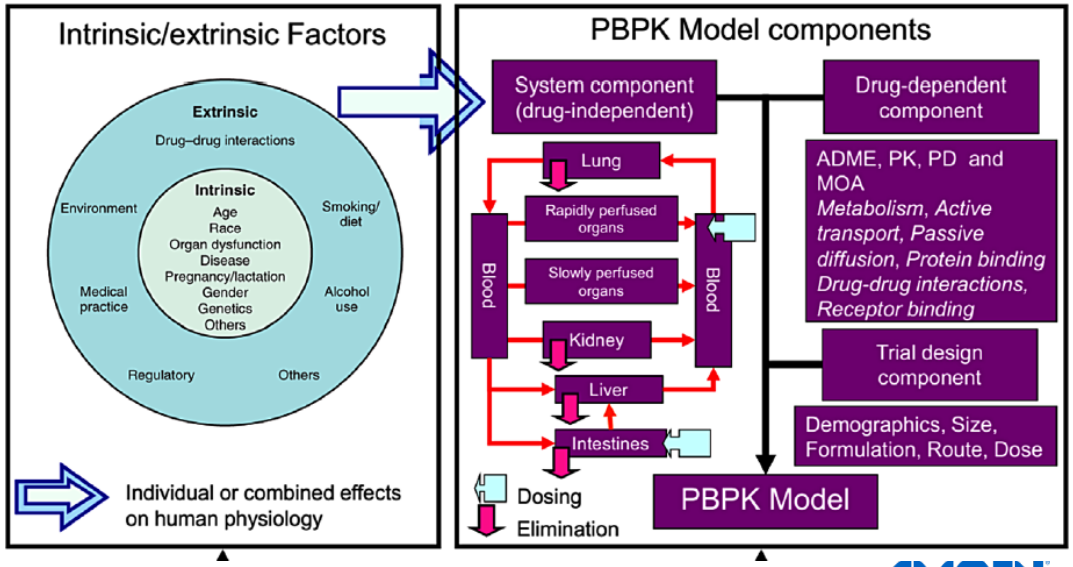
INTRODUCTION

- **Conducting studies in the pediatric population is challenging.**
- **Appropriate pharmacokinetic and pharmacodynamic studies may facilitate pediatric drug development by supporting partial extrapolation, dose optimization, and product labeling.**
- **Frequently, extrapolation of adult PK is required to inform pediatric dosing and study design.**

Allometry

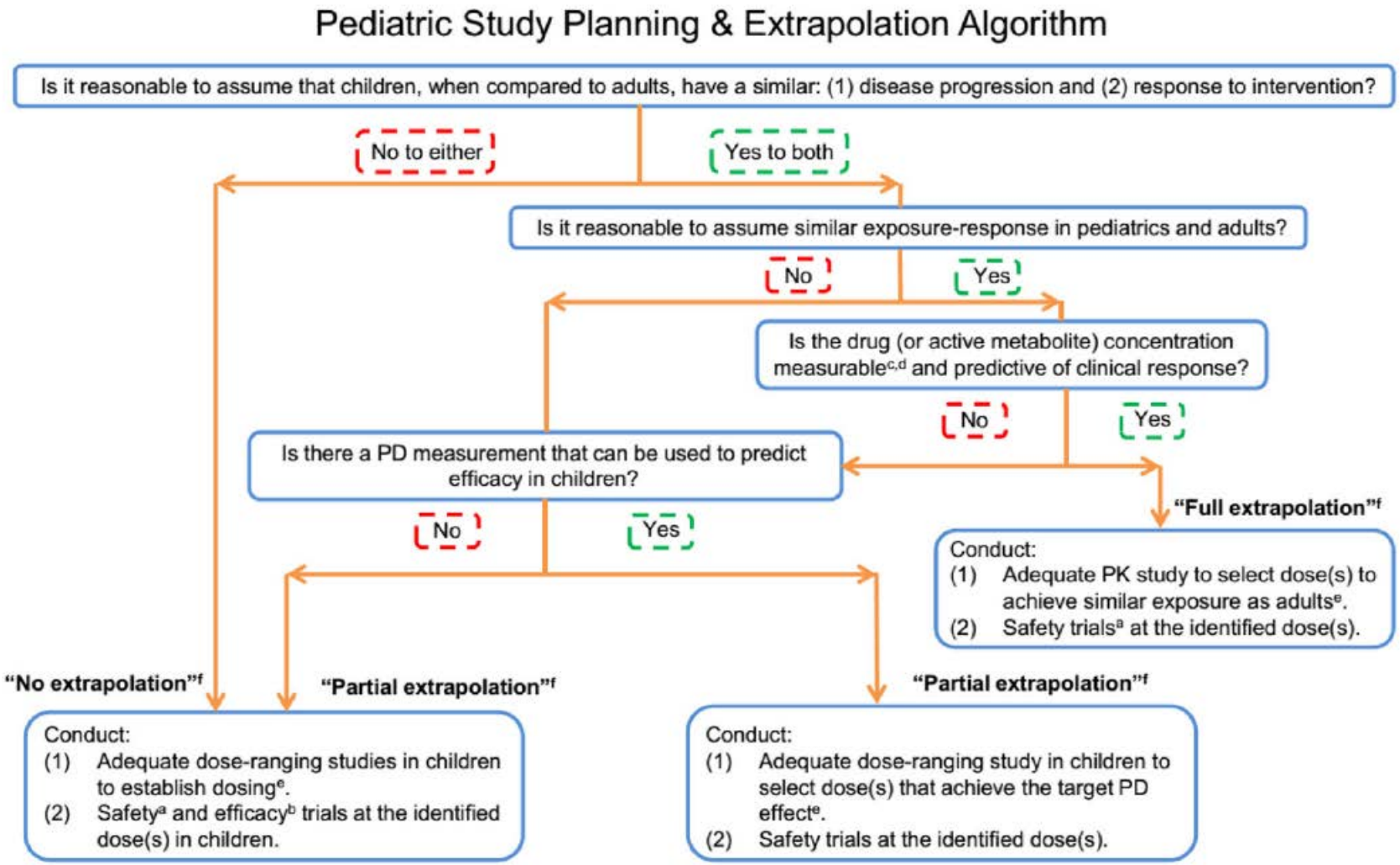


Physiologically Based PK



Samant, et al, JCP 55(11), 1207-1217, 2015

FDA PEDIATRIC DECISION TREE



SUMMARY OF APPROACHES TO EXTRAPOLATION

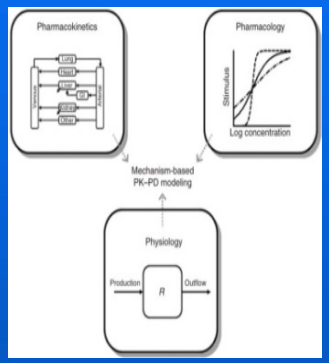
TABLE 1 Summary of Approaches to Use of Extrapolation of Efficacy From Adult Population to Pediatric Population

Extrapolation of Efficacy From Adult Data	Assumptions Made to Extrapolate Efficacy	Purposes of Pediatric Studies	Supportive Evidence Requested From Pediatric Studies	Products for Which WRs Issued, *n*/*N* (%)	New or Expanded Pediatric Indication Achieved, *n*/*N* (%)
No extrapolation	Disease/condition and/or response to intervention are not similar.	Demonstration of efficacy and assessment of safety.	Two adequate, well-controlled, efficacy and safety trials plus pharmacokinetic data.	19/166 (11)	7/19 (37)
		For oncology products only, demonstration of response and assessment of safety.	For oncology products only, sequential approach starting with phase 1/2. Do not proceed if no evidence of response.	10/166 (6)	3/10 (30)
Partial extrapolation	Disease/condition and/or response to intervention are similar but there is some uncertainty about the strength of assumptions.	Confirmation of efficacy and assessment of safety.	Single, adequate, well-controlled, efficacy and safety trial plus pharmacokinetic data.	67/166 (40)	35/67 (52)
	Disease/condition and/or response to intervention are similar but there is less uncertainty about the strength of assumptions (or patient numbers are such that it would not be feasible to conduct a controlled or adequately powered study).	Confirmation of response and assessment of safety.	Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus pharmacokinetic data.	20/166 (12)	15/20 (75)
			Single exposure-response trial (not powered for efficacy determination) plus pharmacokinetic and safety data, pharmacokinetic/pharmacodynamic and uncontrolled efficacy data plus safety data, or pharmacokinetic/pharmacodynamic data plus safety data.	26/166 (16)	19/26 (73)
Complete extrapolation	Disease/condition and/or response to intervention are similar and there is a high degree of certainty about the strength of assumptions.	Exposure data to confirm age- appropriate dose and assessment of safety.	Pharmacokinetic and safety data.	10/166 (6)	9/10 (90)
	Disease/condition and/or response to intervention are similar and there is a high degree of certainty about the strength of assumptions. Dose assumed to be the same (eg, topical application).	Assessment of safety.	Safety data only.	14/166 (8)	6/14 (43)

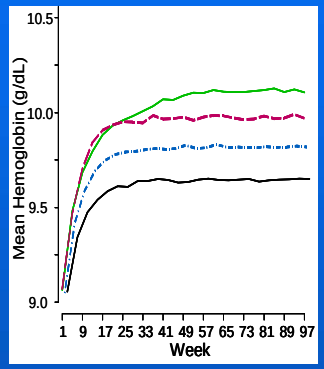
Dunne et al, Pediatrics, Vol 128:5, 2011

AMGEN

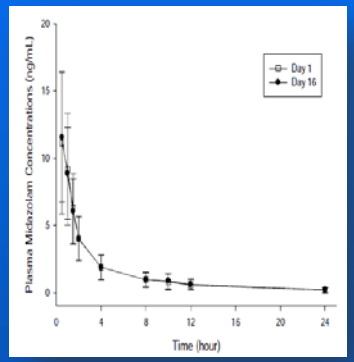
CLINICAL PHARMACOLOGY MODELING & SIMULATION KEY APPLICATIONS FOR PEDIATRIC EXTRAPOLATION



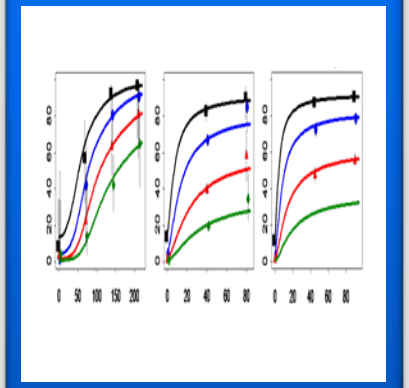
Optimize Dose And Regimen



Optimize Trial Design



Evaluate Intrinsic Factors



Understanding of Disease in Pediatrics

Dose Selection

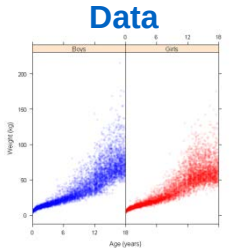
Trial Simulation

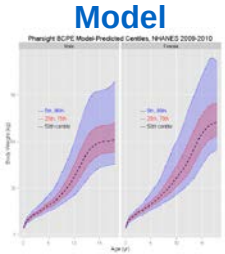
Covariate Analysis

Systems Biology

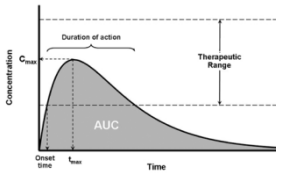
Application to Optimize Regulatory Decision Making for Pediatric Plans

PLATFORM APPROACH TO IMPACT REGULATORY STRATEGY: STANDARDIZED APPROACH FOR PEDIATRIC STUDY PLANS





Demographic Model



PK
(drug attributes)

- Regulatory feedback
- Sub-populations
- Additional demographic data

Refinement

Computational Tool

S-PLUS code integrates demographic model and PK to provide best practice for pediatric simulations based on a large database

S-PLUS Code

Application: Pediatric dose selection discussions

- Guided age group and dose selection of Ph 1 bridging PK study
- Adult SKUs (70 to 140 mg) predicted to cover potential pediatric dose range

Study & Protocol Design

S-PLUS Code

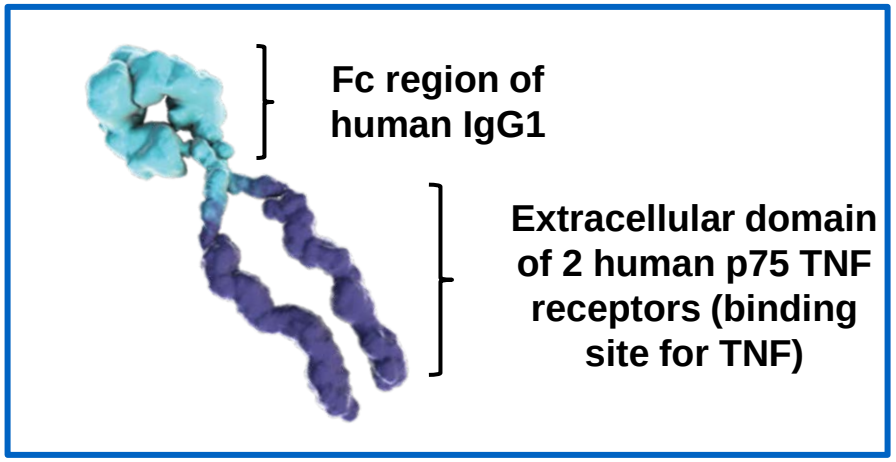
PIP/PSP Strategy

Application: Exploratory analysis to support PIP/PSP discussions

- Established Ph 1 adult and Japanese PK covered older adolescents
- Guided team to apply for adolescent waiver

CASE STUDY:
ENBREL® (ETANERCEPT)

- A dimeric fusion protein consisting of the extracellular ligand-binding portion of the human p75 TNF receptor linked to the Fc portion of human IgG1
- It consists of 934 amino acids and has an apparent molecular weight of approximately 150 kD
- Etanercept is produced by recombinant DNA technology

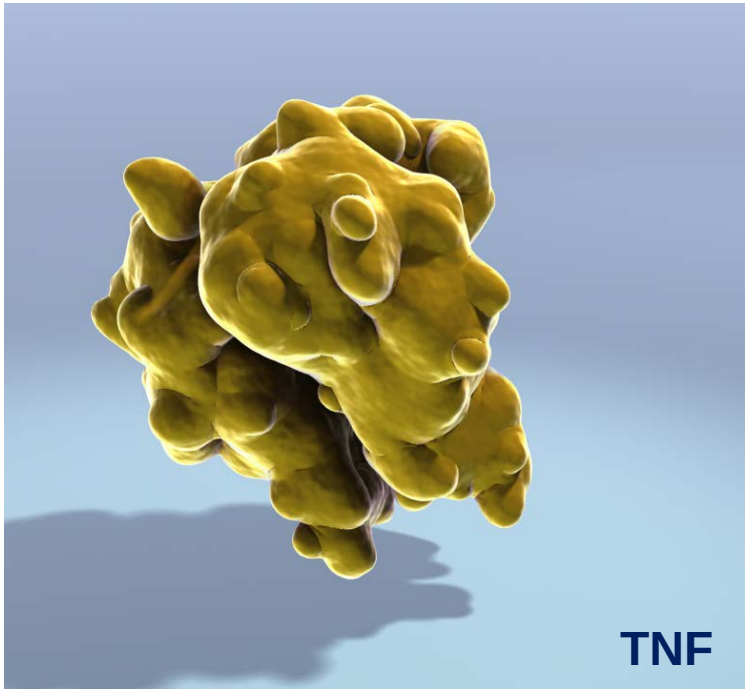


Ig = immunoglobulin; TNF = tumor necrosis factor.

Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif.

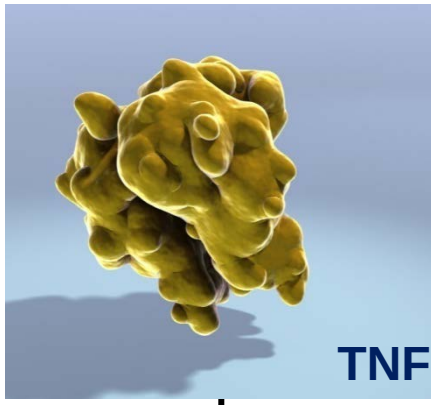
ROLE OF TNF IN THE PATHOGENESIS OF ARTHROPATHIES

- **Plays a role in the inflammatory processes, resulting in joint pathology of**
  - **Rheumatoid arthritis (RA)**
  - **Polyarticular juvenile idiopathic arthritis**
  - **Psoriatic arthritis**

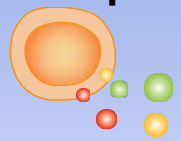


1. Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif. 2. Goffe B, et al. J Am Acad Dermatol. 2003;49:S105-S111. 3. Scott DL, et al. N Engl J Med. 2006;355:704-712.

TNF-ALPHA PLAYS A ROLE IN RA

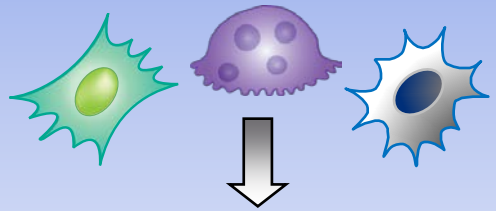


Induction of inflammatory cytokines. Adhesion molecule expression



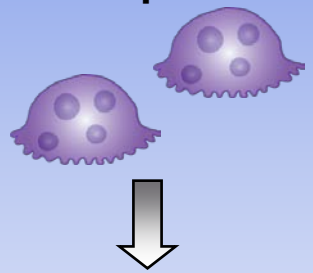
Inflammation

Stimulates synovial fibroblasts, osteoclasts, and chondrocytes



Release of tissue-destroying matrix metalloproteinases

Stimulates osteoclast development



Bone degradation

1. Choy EHS, et al. N Engl J Med. 2001;344:907-916. 2. Scott DL, et al. N Engl J Med. 2006;355:704-712.

ENBREL®(ETANERCEPT): PHARMACOKINETICS

- **Rheumatoid Arthritis 50 mg Weekly**
  - **Cmax 2.4 mcg/mL, half life 102 +/-30 hours**
  - **PK parameters were not different between men and women and did not vary with age in adult patients**
  - **Pharmacokinetics were not altered by concomitant MTA in RA patients**
  - **No formal renal or hepatic studies conducted**

Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif

COMPARISON OF ADULT RA AND JIA
A CASE FOR EXTRAPOLATION?

	JIA	RA
Clinical Profile	Significant heterogeneity • 7 disease subtypes • Significant variation in developmental stage across age range	Heterogeneous, clinically similar
PK/PD relationship	Association of age and response not well characterized Not established across a dose range	Established, concentration dependent across a dose range
Trial Design	Withdrawal/Flare Design	Traditional Induction Trial
Outcome Measure	JIA 30,50,70 score	ACR 20, 50,70 score
Prevalence	Rare Disease 70-100,000 active and inactive (CDC)	~ 4.7 million

Leverage Enbrel PK/PD from Adults with RA to Inform Treatment in JIA

SUMMARY OF APPROACHES TO EXTRAPOLATION

TABLE 1 Summary of Approaches to Use of Extrapolation of Efficacy From Adult Population to Pediatric Population

Extrapolation of Efficacy From Adult Data	Assumptions Made to Extrapolate Efficacy	Purposes of Pediatric Studies	Supportive Evidence Requested From Pediatric Studies	Products for Which WRs Issued, *n*/*N* (%)	New or Expanded Pediatric Indication Achieved, *n*/*N* (%)
No extrapolation	Disease/condition and/or response to intervention are not similar.	Demonstration of efficacy and assessment of safety.	Two adequate, well-controlled, efficacy and safety trials plus pharmacokinetic data.	19/166 (11)	7/19 (37)
		For oncology products only, demonstration of response and assessment of safety.	For oncology products only, sequential approach starting with phase 1/2. Do not proceed if no evidence of response.	10/166 (6)	3/10 (30)
Partial extrapolation	Disease/condition and/or response to intervention are similar but there is some uncertainty about the strength of assumptions.	Confirmation of efficacy and assessment of safety.	Single, adequate, well-controlled, efficacy and safety trial plus pharmacokinetic data.	67/166 (40)	35/67 (52)
	Disease/condition and/or response to intervention are similar but there is less uncertainty about the strength of assumptions (or patient numbers are such that it would not be feasible to conduct a controlled or adequately powered study).	Confirmation of response and assessment of safety.	Single, controlled or uncontrolled, efficacy and safety trial (qualitative data) plus pharmacokinetic data.	20/166 (12)	15/20 (75)
			Single exposure-response trial (not powered for efficacy determination) plus pharmacokinetic and safety data, pharmacokinetic/pharmacodynamic and uncontrolled efficacy data plus safety data, or pharmacokinetic/pharmacodynamic data plus safety data.	26/166 (16)	19/26 (73)
Complete extrapolation	Disease/condition and/or response to intervention are similar and there is a high degree of certainty about the strength of assumptions.	Exposure data to confirm age-appropriate dose and assessment of safety.	Pharmacokinetic and safety data.	10/166 (6)	9/10 (90)
	Disease/condition and/or response to intervention are similar and	Assessment of safety.	Safety data only.	14/166 (8)	6/14 (43)

Clinical Strategy for Enbrel® (etanercept) JIA
Partial Extrapolation

Dunne et al, Pediatrics, Vol 128:5, 2011

ENBREL®(ETANERCEPT) CASE STUDY: STEPS IN EXTRAPOLATION IN JIA POPULATION

Integrate

- **Integrate prior clinical data on etanercept using a population PK model**
- **Understand assumptions of the model such as similar disease progression across populations**

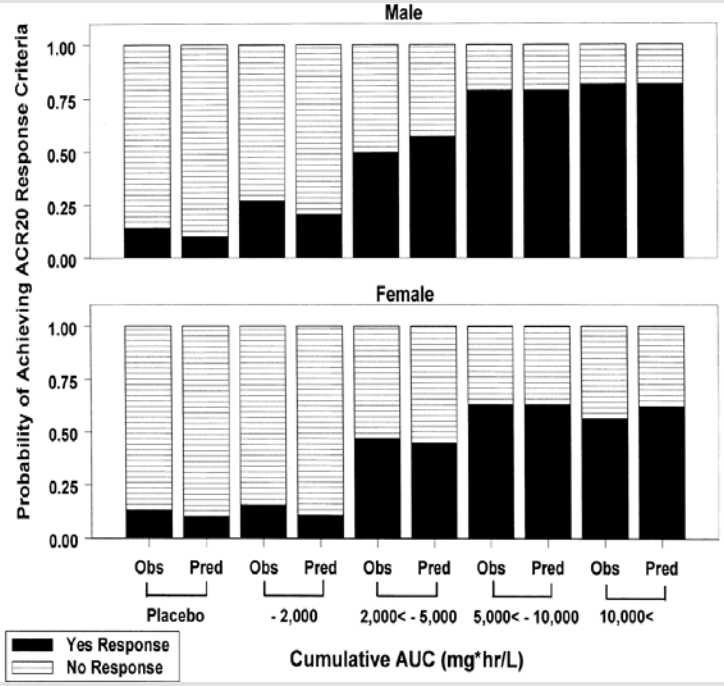
Extrapolate

- Make adjustments to model to account for potential differences in pediatric subjects
- Extrapolate PK and conduct clinical trial simulations
- Optimize design of pediatric trial

Validate

- Conduct clinical trial to validate predictions
- Confirm dosing in pediatrics
- Propose interchangeability across regimen based on trial simulations

ENBREL®(ETANERCEPT) CASE STUDY
ADULT POPULATION PKPD ANALYSIS



- **Population PK Model**
  - 1 Compartment with 1st order abs.
  - Covariates of sex and race on CL/F and standardized body weight on CL/F and V/F
- **Population PKPD Model**
  - Cumulative AUC as exposure variable related with binary ACR clinical outcome variable

Adult Model Based PKPD Analyses are the 1st step to Support the Pediatric Extrapolation Strategy

Lee et al, CPT, 73, 2003

ENBREL®(ETANERCEPT) CASE STUDY: STEPS IN EXTRAPOLATION IN JIA POPULATION

Integrate

- Integrate prior clinical data on etanercept using a population PK model
- Understand assumptions of the model such as similar disease progression across populations

Extrapolate

- **Make adjustments to model to account for potential differences in pediatric subjects**
- **Extrapolate PK and conduct clinical trial simulations**
- **Optimize design of pediatric trial**
  - **Propose mg/kg dosing in pediatrics**

Validate

- Conduct clinical trial to validate predictions
- Confirm dosing in pediatrics
- Propose interchangeability across regimen based on trial simulations

ENBREL® (ETANERCEPT) IN MODERATELY TO SEVERELY ACTIVE POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS (JIA)

ENBREL is indicated for reducing signs and symptoms of moderately to severely active polyarticular JIA in patients ages 2 and older.

Study Name (Patient Type)	Etanercept (ETN) Therapy	Journal Citation
Pivotal JIA Study (Polyarticular JIA [methotrexate (MTX)-refractory or intolerant])	Monotherapy	Lovell DJ, et al. *N Engl J Med.* 2000;342:763-769.*

***Above referenced study is included in the Enbrel® (etanercept) Prescribing Information. It is not listed with a study number.**

Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif.

STUDY DESIGN

- **Objective**
  - **To evaluate the efficacy and safety profile of ETN in children (4–17 years) with polyarticular JIA who did not tolerate or had an inadequate response to MTX**
- **Endpoints**
  - **Primary: The number of patients developing disease flare in the double-blind phase**
  - **Others: Changes of individual measures of disease activity**

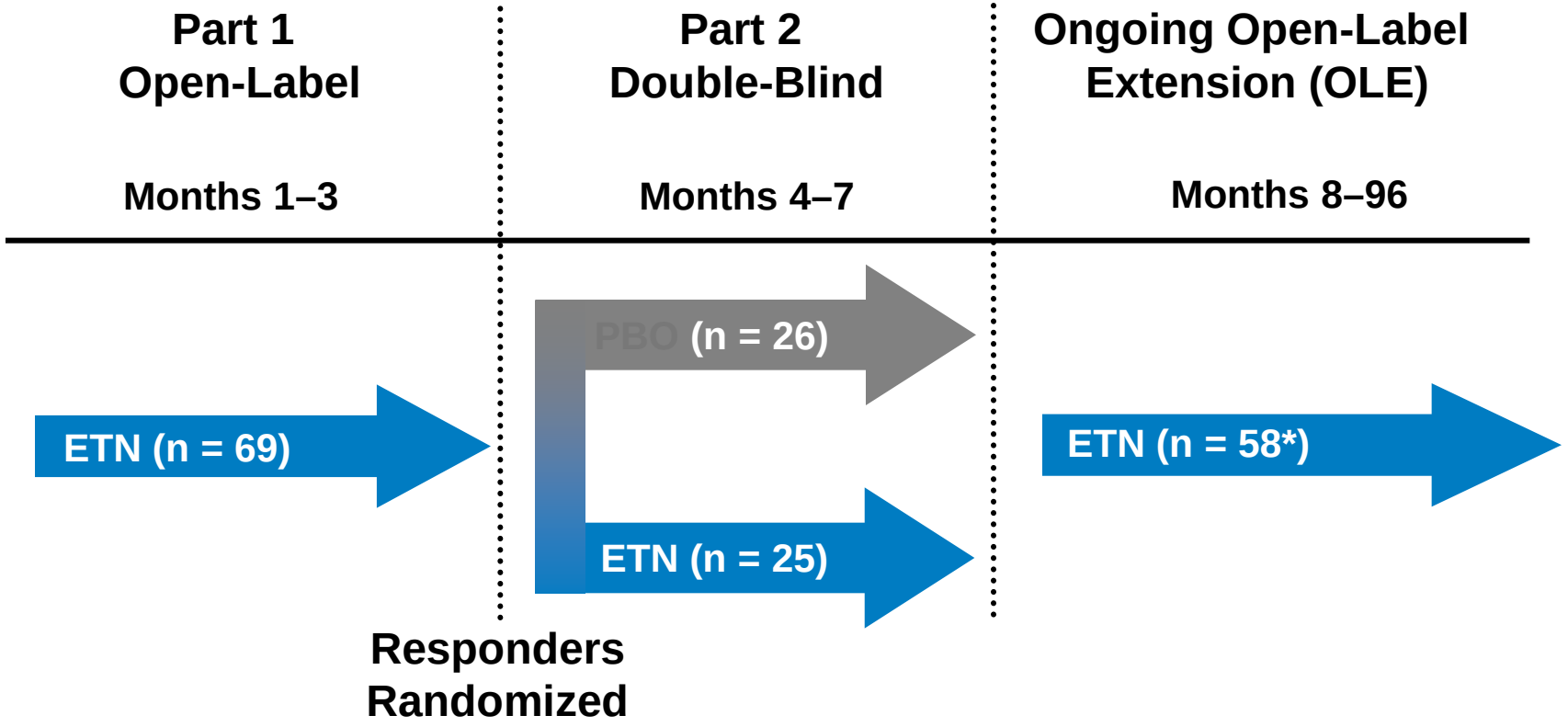
1. Lovell DJ, et al. N Engl J Med. 2000;342:763-769. 2. Data on file, Amgen.

STUDY DESIGN (CONT'D)

- **69 children with moderately to severely active polyarticular JIA with a variety of onset types were evaluated**
- **Patients were refractory to or intolerant to MTX**
- **Stable dose of a single nonsteroidal anti-inflammatory drug (NSAID) and/or prednisone (≤ 0.2 mg/kg/day or 10 mg maximum) were allowed**
- **Two-part trial**
  - **Part 1: All patients received ETN 0.4 mg/kg (maximum 25 mg per dose) subcutaneously (SC) twice weekly**
  - **Part 2: At day 90, the 51 responders were randomized to continue ETN or receive placebo (PBO) for 4 months and assessed for disease flare**

1. Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif. 2. Lovell DJ, et al. N Engl J Med. 2000;342:763-769. 3. Data on file, Amgen.

STUDY DESIGN (CONT'D)



Dose: ETN 0.4 mg/kg SC twice weekly (maximum 25 mg/dose)

*Includes 8 nonresponders from part 1 and 25 patients from each arm in part 2.
After 1 year of the extension, the use and doses of corticosteroids, NSAIDs, and pain medications could be adjusted and MTX could be added.

1. Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif. 2. Lovell DJ, et al. Arthritis Rheum. 2006;54:1987-1994. 3. Lovell DJ, et al. Arthritis Rheum. 2008;58:1496-1504.

ENDPOINTS

- **Primary**
  - **Patients with disease flare in part 2 (double-blind portion) of the study defined as**
    - **≥ 30% worsening in 3 of 6 JIA core set criteria* and a minimum of 2 active joints**
    - **≥ 30% improvement in no more than 1 of 6 JIA core set criteria***
- **Other**
  - **Definition of response (part 1)**
    - **JIA definition of improvement (JIA 30 response)**
      - **≥ 30% improvement in at least 3 of 6 JIA core set criteria,* and**
      - **≥ 30% worsening in no more than 1 of the 6 JIA core set criteria***
    - **JIA 50 and 70 responses†**
    - **Improvement in the individual components of the JIA core set criteria**
    - **Safety**

***Active joint count, number of joints with limitation of motion, patient/parent global assessment, physician global assessment, functional assessment (Childhood Health Assessment Questionnaire), and erythrocyte sedimentation rate. Number of joints with limitation of motion was accompanied by pain and/or tenderness.**

†JIA 50 and 70 responses were defined by a 50% or 70% improvement, respectively, in at least 3 of the 6 response criteria with no more than 1 criterion worsening by more than 30%.

1. Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif. 2. Lovell DJ, et al. N Engl J Med. 2000;342:763-769. 3. Data on file, Amgen.

JIA STUDY: BASELINE PATIENT DEMOGRAPHICS

Subject Disposition (n = 69)	
Female (%)	62
Caucasian (%)	75
Mean age in years (range)	10.5 (4–17)
Mean JIA disease duration in years	5.9
MTX at washout (%)	72
Concomitant therapy (%) at start of washout period*	
• NSAIDs	96
• Corticosteroids	36

- **From study onset through year 1 of the extension, prednisone dose had to remain stable (0.2 mg/kg/d or 10 mg/d maximum). After year 1 of the extension, doses of corticosteroids, NSAIDs, and pain medications could be adjusted and MTX could be added (10–20 mg/m^2/wk)**

- **ENBREL is not approved for use in patients with pediatric plaque psoriasis**

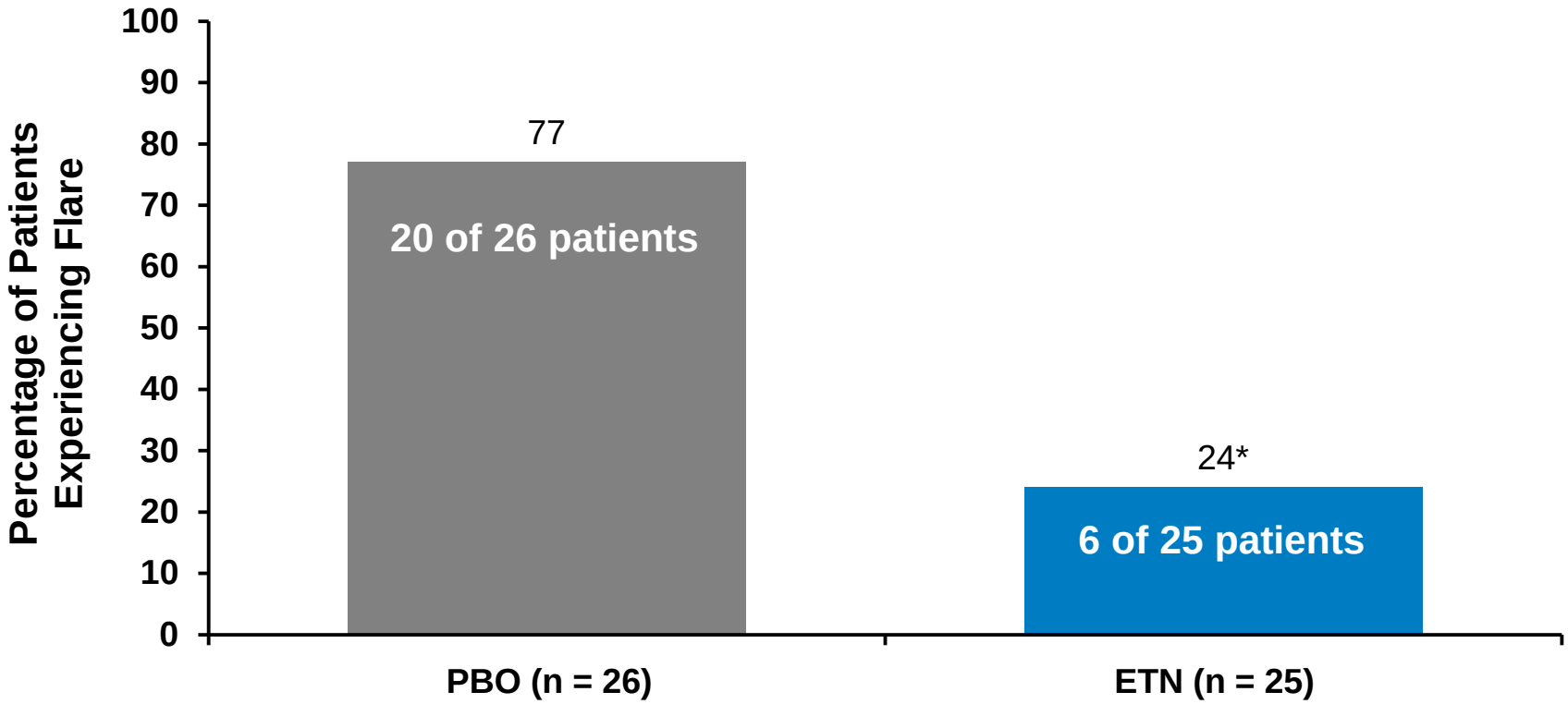
1. Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif. 2. Lovell DJ, et al. N Engl J Med. 2000;342:763-769. 3. Lovell DJ, et al. Arthritis Rheum. 2006;54:1987-1994. 4. Data on file, Amgen.

OPEN-LABEL: CLINICAL RESPONSE

- **51 of 69 (74%) patients demonstrated a clinical response in part 1 (open-label phase) and entered part 2 (double-blind phase)**

1. Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif. 2. Lovell DJ, et al. N Engl J Med. 2000;342:763-769. 3. Data on file, Amgen.

DOUBLE-BLIND: DISEASE FLARE

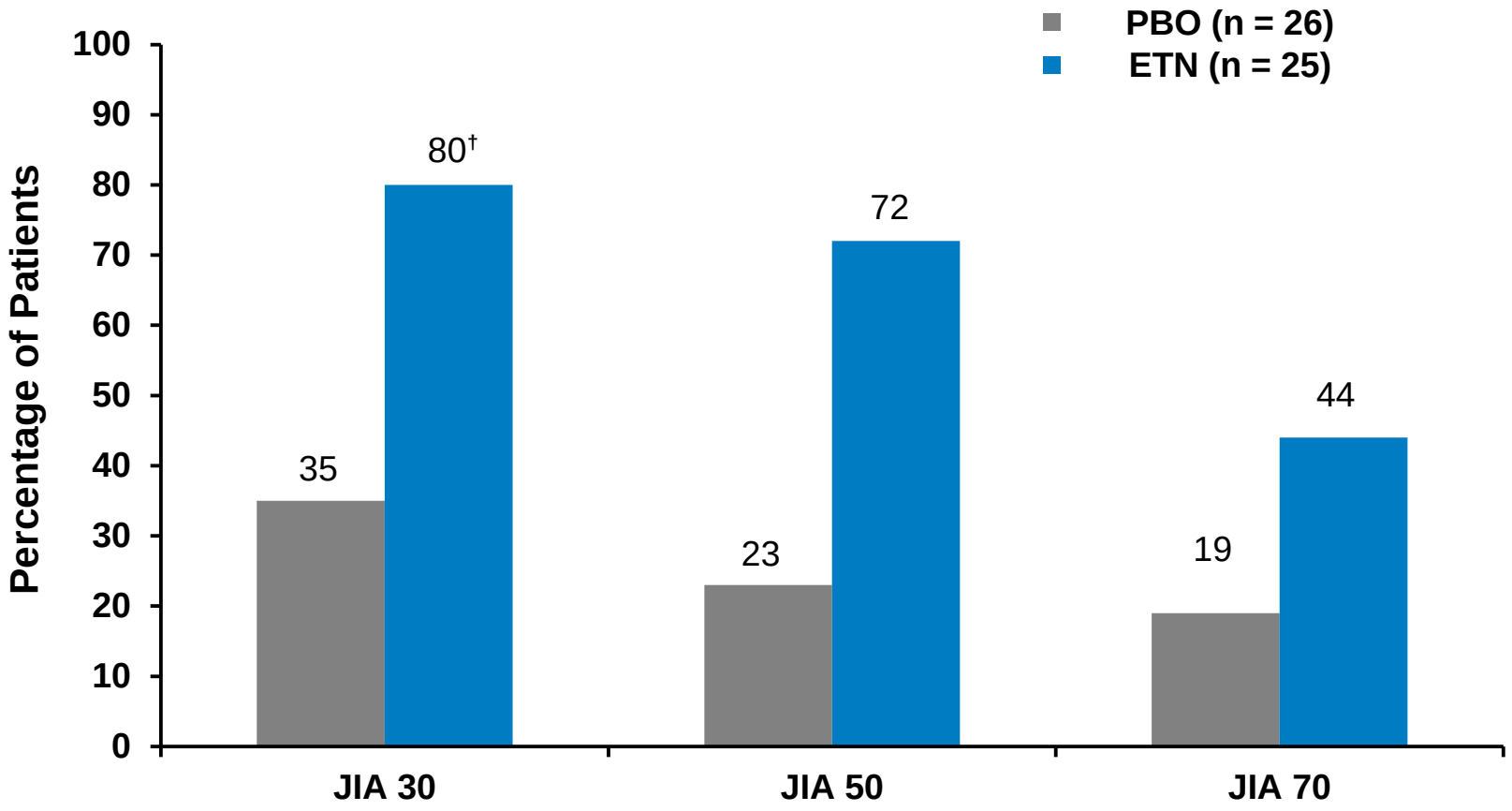


Median Time to Flare: **28 days** **≥ 116 days**

*P = 0.007

Enbrel® (etanercept) Prescribing Information, Immunex Corporation, Thousand Oaks, Calif.

DOUBLE-BLIND: CLINICAL RESPONSE*



*At the end of the 7-month study (3-month open-label and 4-month double-blind).
†P < 0.01 ETN vs PBO.

Lovell DJ, et al. N Engl J Med. 2000;342:763-769.

ENBREL®(ETANERCEPT) CASE STUDY: STEPS IN EXTRAPOLATION IN JIA POPULATION

Integrate

- Integrate prior clinical data on etanercept using a population PK model
- Understand assumptions of the model such as similar disease progression across populations

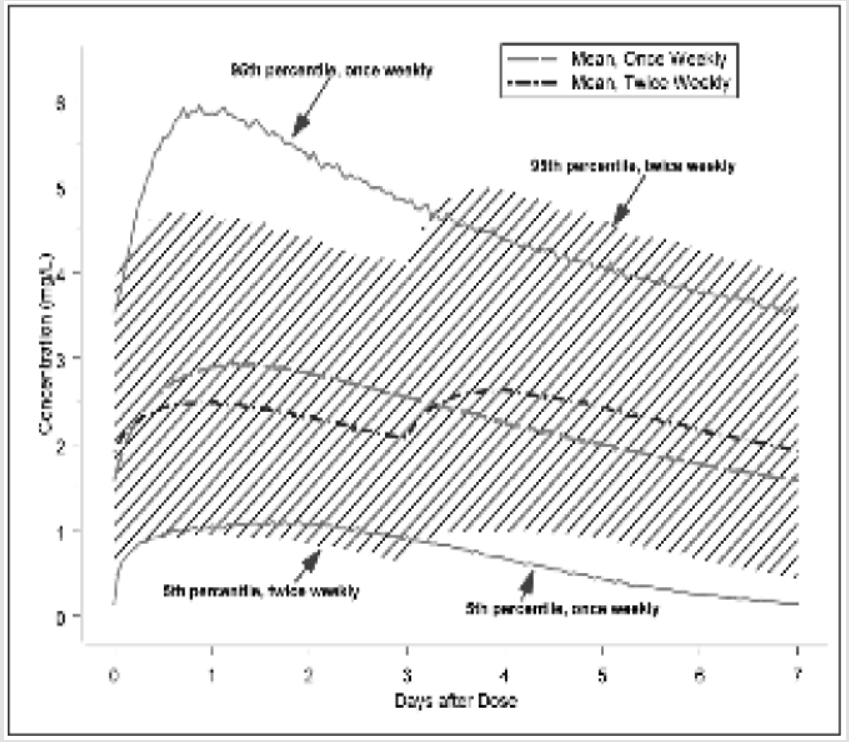
Extrapolate

- Make adjustments to model to account for potential differences in pediatric subjects
- Extrapolate PK and conduct clinical trial simulations
- Optimize design of pediatric trial

Validate

- **Conduct clinical trial to validate predictions**
- **Confirm dosing in pediatrics**
- **Propose interchangeability across regimen based on trial simulations**

POPULATION PHARMACOKINETIC ANALYSIS AND SIMULATION OF THE TIME-CONCENTRATION PROFILE OF ENBREL®(ETANERCEPT) IN PEDIATRIC PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS



- **Initial efficacy study dose was at 0.4 mg/kg twice weekly**
- **Simulation study at 0.8 mg/kg once weekly**
  - **Widely overlapping concentration profiles at steady-state**

Approval of Enbrel®(Etanercept) Dose and Regimen Change in Pediatrics Based on Simulation

Yim, et al, JCP 45, 2005

CLINICAL PHARMACOLOGY, MODELING AND SIMULATION APPLYING DIVERSE TECHNOLOGIES TO SERVE A UNIFIED PURPOSE

Integrate

- Integrate prior clinical data on etanercept using a population PK model
- Understand assumptions of the model such as similar disease progression across populations

Extrapolate

- Make adjustments to model to account for potential differences in pediatric subjects
- Extrapolate PK and conduct clinical trial simulations
- Optimize design of pediatric trial

Validate

- Conduct clinical trial to validate predictions
- Confirm dosing in pediatrics
- Propose interchangeability across regimen based on trial simulations

"Advancing our Understanding of Biology to Advance Clinical Medicine"

AMGEN

ACKNOWLEDGEMENTS

- James Chung, MD
- Jane Parnes, MD
- David Reese, MD
- Elliott, Levy, MD
- Lisa Bollinger, MD
- Mark Taisey, Ph.D.
- Sree Kaishchayanuula, Ph.D.
- John Gibbs, Ph.D.
- Andrew Chow, Ph.D.
- Desmond Padhi, PharmD.
- Deborah Wenkert, MD