Model informed weight-tiered fixed dosing in clinical development

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I Background

- Model Informed Drug Development
- Weight Based Dose vs Weight-tiered Fixed Dose

Model informed drug development

Decision 1b:
- Acceptable variation in PK profile

Decision 6:
- Special population
- Ethnicity bridging

Pre-Clinical › Phase 1 › Phase 2a › Phase 2b › Phase 3 › Approval

Dose and dosing regimen, optimal study design, formulation, drug delivery

Decision 1:
- Safety
- Tolerability
- Safe starting dose

Decision 2 & 3:
- Dose/Schedule
- PK/PD
- Tolerability
- Single agent activity

Decision 4 & 5:
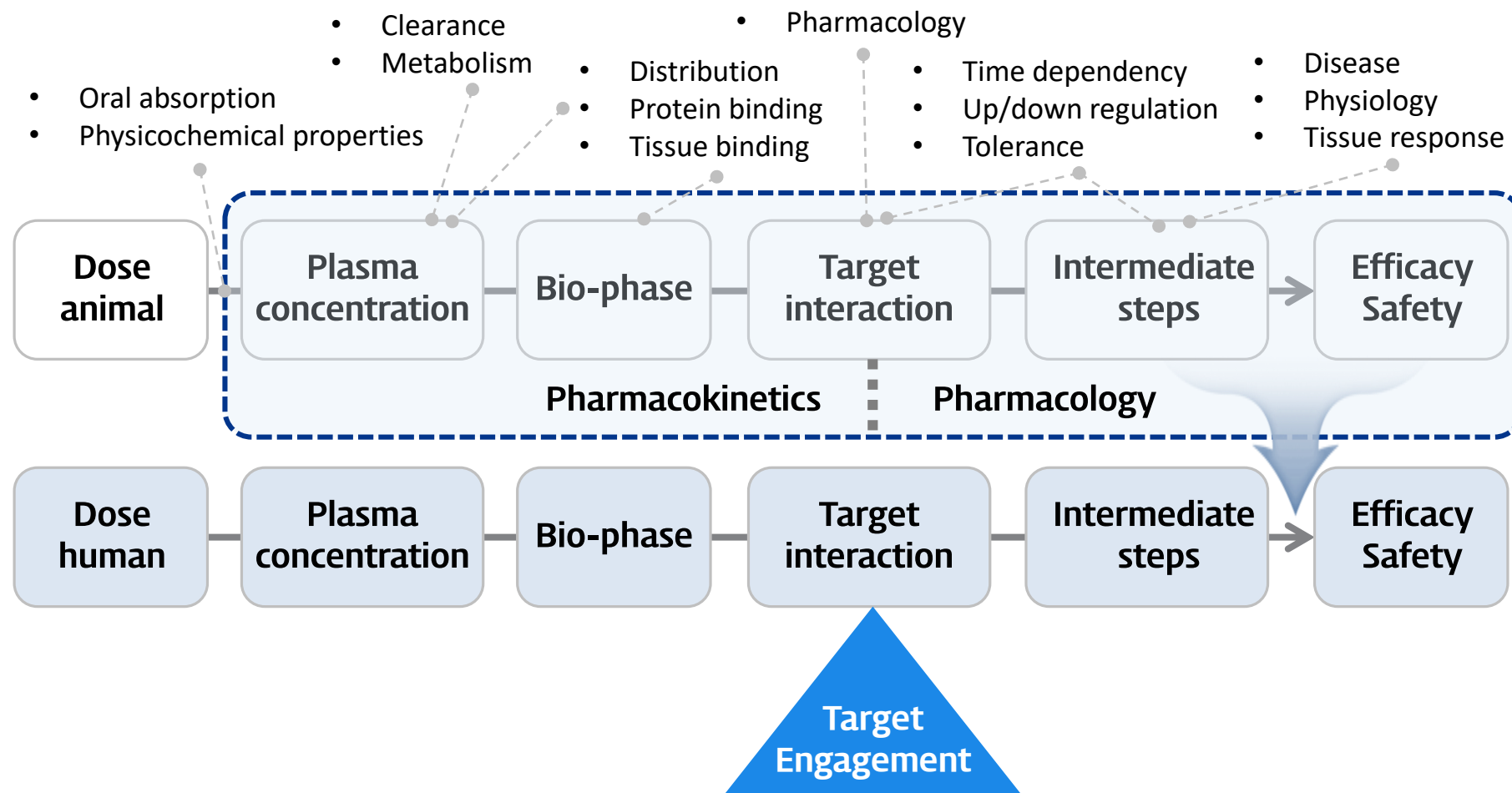- Efficacy (POC)
- Product decision

Mechanism-based models

Evidence-based models

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Model informed drug development

- Translate pharmacodynamic elements to human

Weight Based Dose vs Weight-tiered Fixed Dose

- Definition, advantage, and disadvantage

Category	Weight-Based Dose (mg/kg)	Weight-Tiered Fixed Dose
Definition	Dose adjusted proportionally to body weight	Fixed doses assigned to predefined weight ranges
Advantages	• Precision in dose based on individual weight • Useful for narrow therapeutic index drugs	• Simplicity in administration • Reduces risk of dose calculation errors • Easier for clinical use in pediatrics
Disadvantages	• Complex calculations • Higher variability due to weight fluctuations • Potential for overdosing or underdosing	• Less individualized compared to mg/kg dosing • May not be optimal for all patients within the same weight range

Ⅱ Case Study 1: AST-001

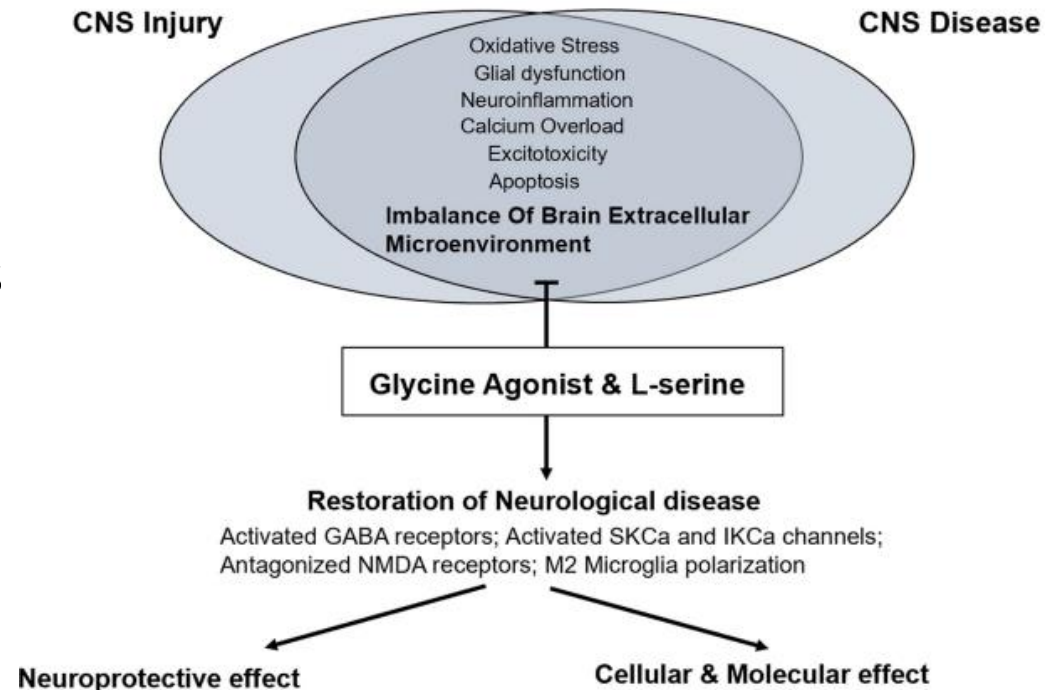- Modeling and Simulation for Phase 2 and Phase 3 Dose Selection

AST-001

- Autism spectrum disorder (ASD)
  - Neurodevelopmental disorders
  - Impaired social interaction and communication, restricted interests, repetitive behaviors
  - Genetic and nongenetic, or environmental, components that impact brain development
    → dopamine dysfunction

- L-serine
 - Neuroprotective effect against oxidative-stress
  - Increased the spontaneous firing of
    dopamine neurons

CNS Injury

CNS Disease

Oxidative Stress
Glial dysfunction
Neuroinflammation
Calcium Overload
Excitotoxicity
Apoptosis

Imbalance Of Brain Extracellular Microenvironment

Glycine Agonist & L-serine

Restoration of Neurological disease
Activated GABA receptors; Activated SKCa and IKCa channels;
Antagonized NMDA receptors; M2 Microglia polarization

Neuroprotective effect

Cellular & Molecular effect

Ye, L. et al (2021). *Frontiers in Molecular Neuroscience, 14.*

Phase I clinical trial

- Randomized, open-label, single and multiple ascending dose study
  - 24 healthy subjects, assessed baseline endogenous level during 24 h
  - Single dose PK after10, 20, 30 g of AST-001 & multiple dose PK after 15 g BID
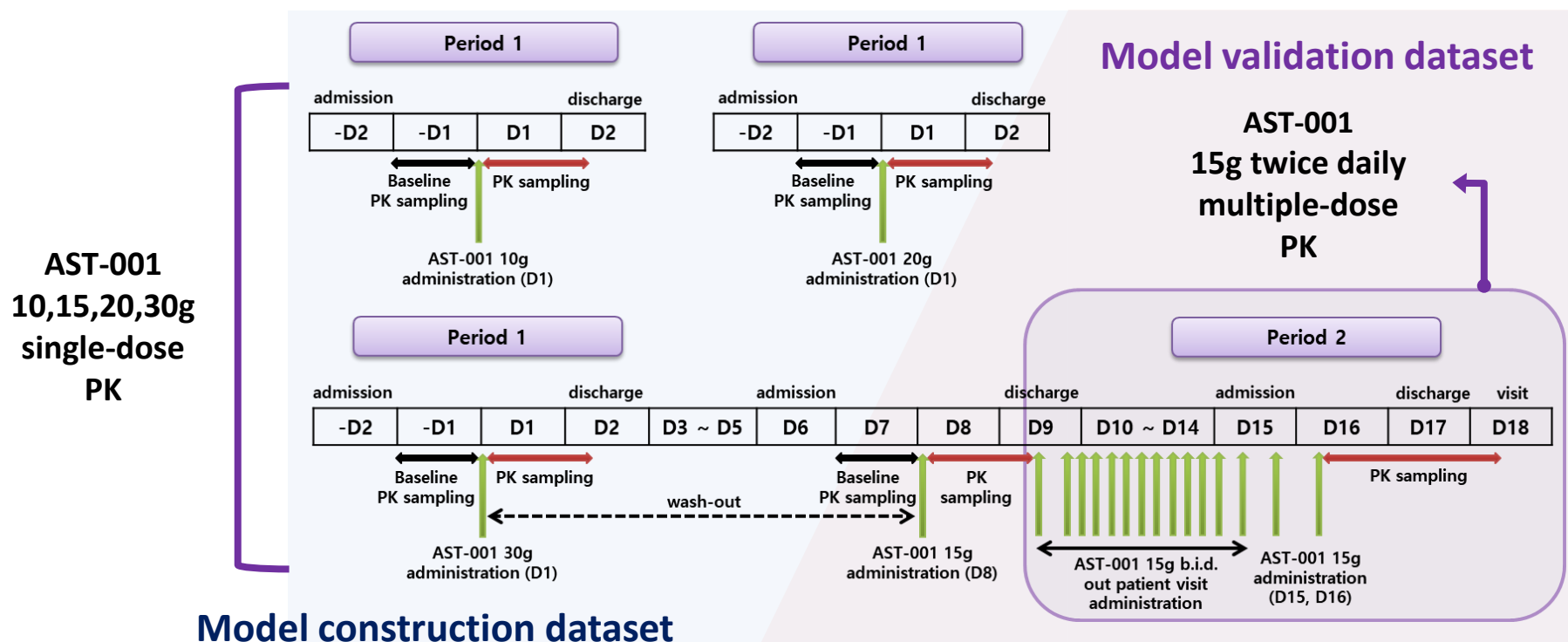
PK model

- Population PK model

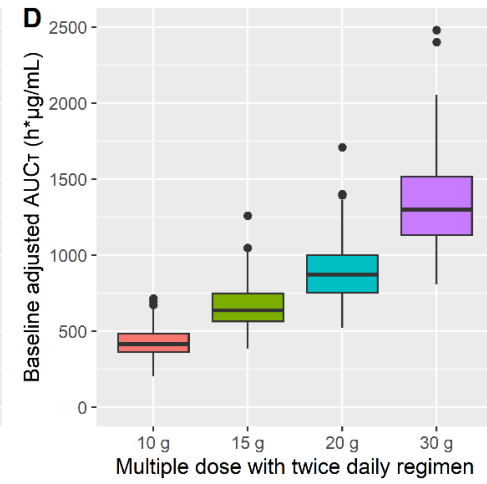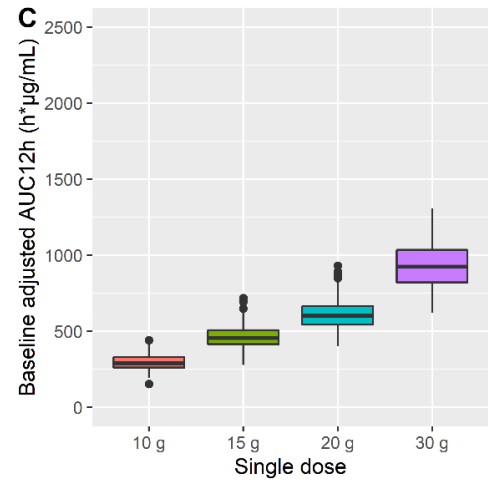 - Estimated endogenous L-serine production rate: 287 mg/h

AST-001

D1

Endogenous
production

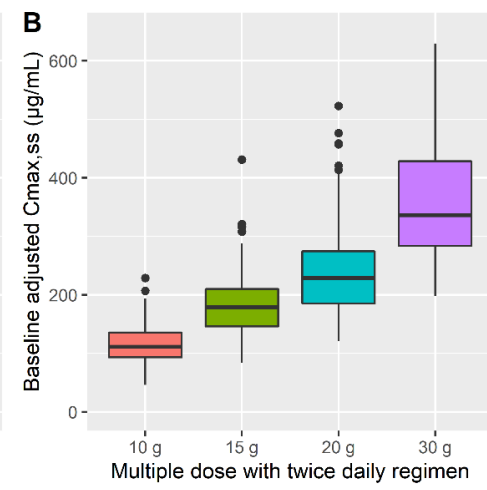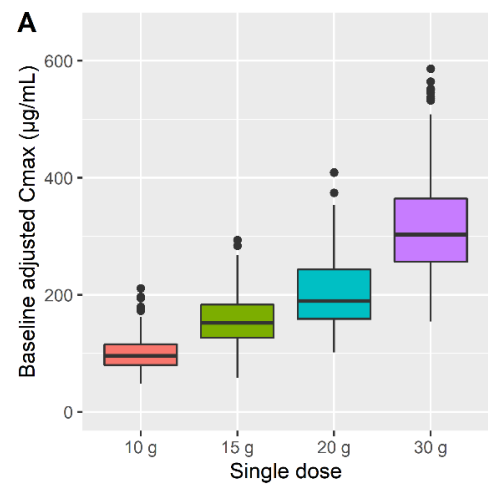R1
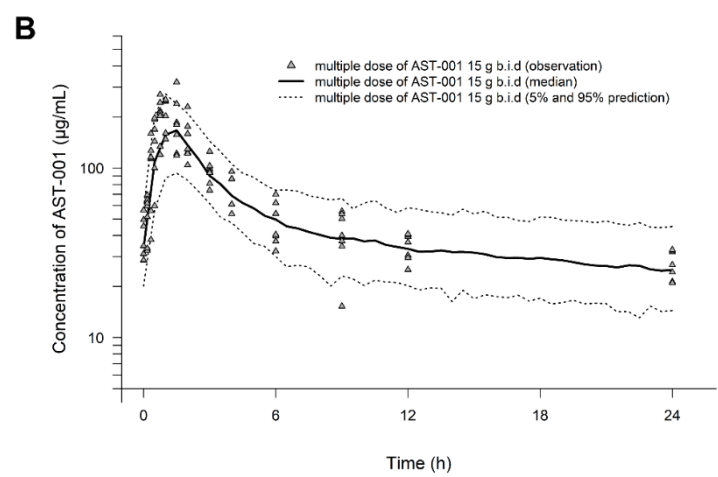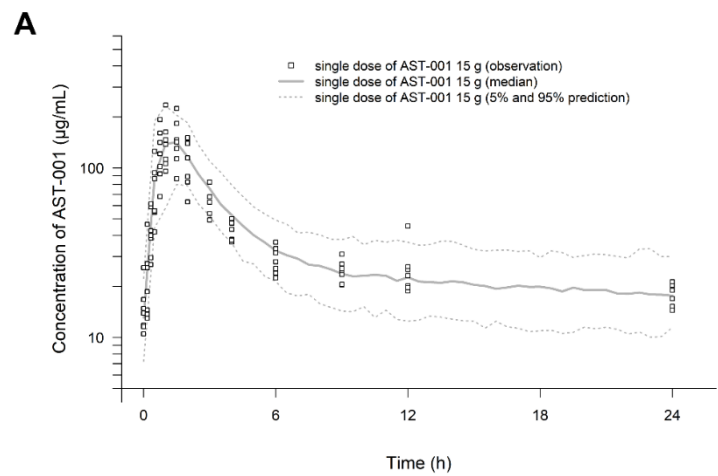
Central
compartment

Q/F

Peripheral
compartment

CL/F
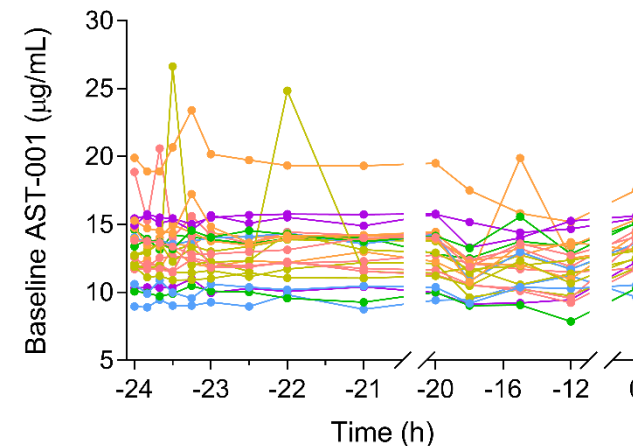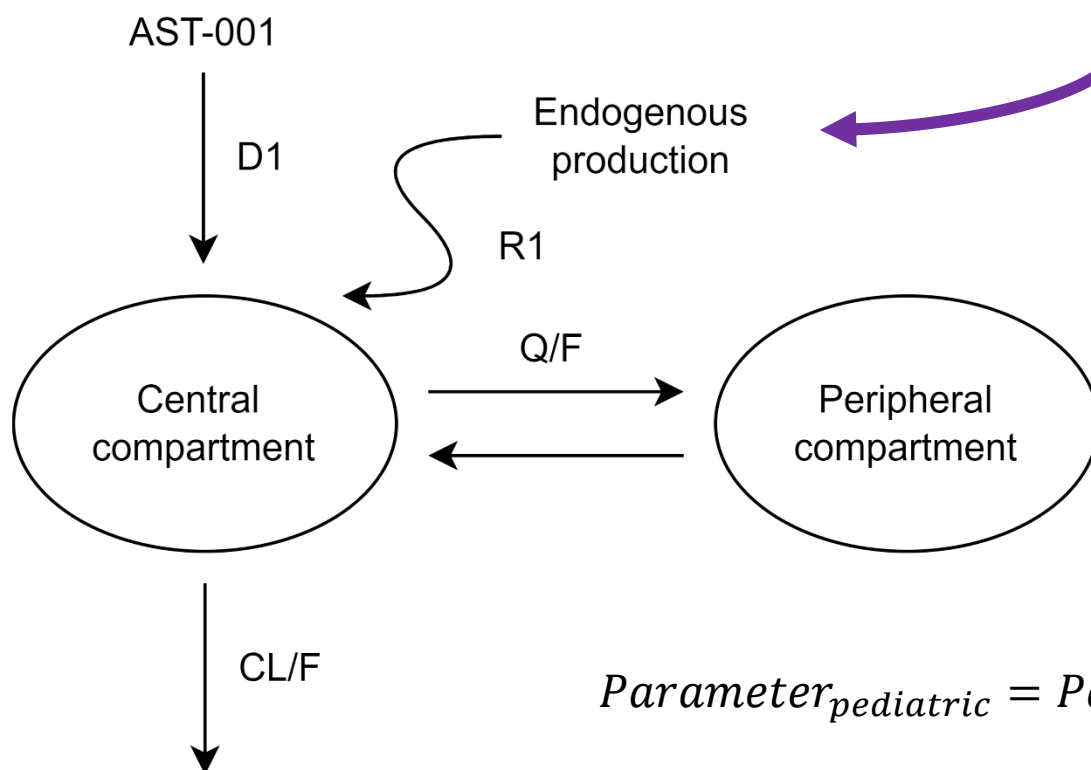
Applying allometric scaling
- $\theta = 0.75$: CL/F, Q/F
- $\theta = 1$: V1/F, V2/F

$$Parameter_{pediatric} = Parameter_{adult} \times (\frac{WT_{pediatric}}{70})^{\theta}$$
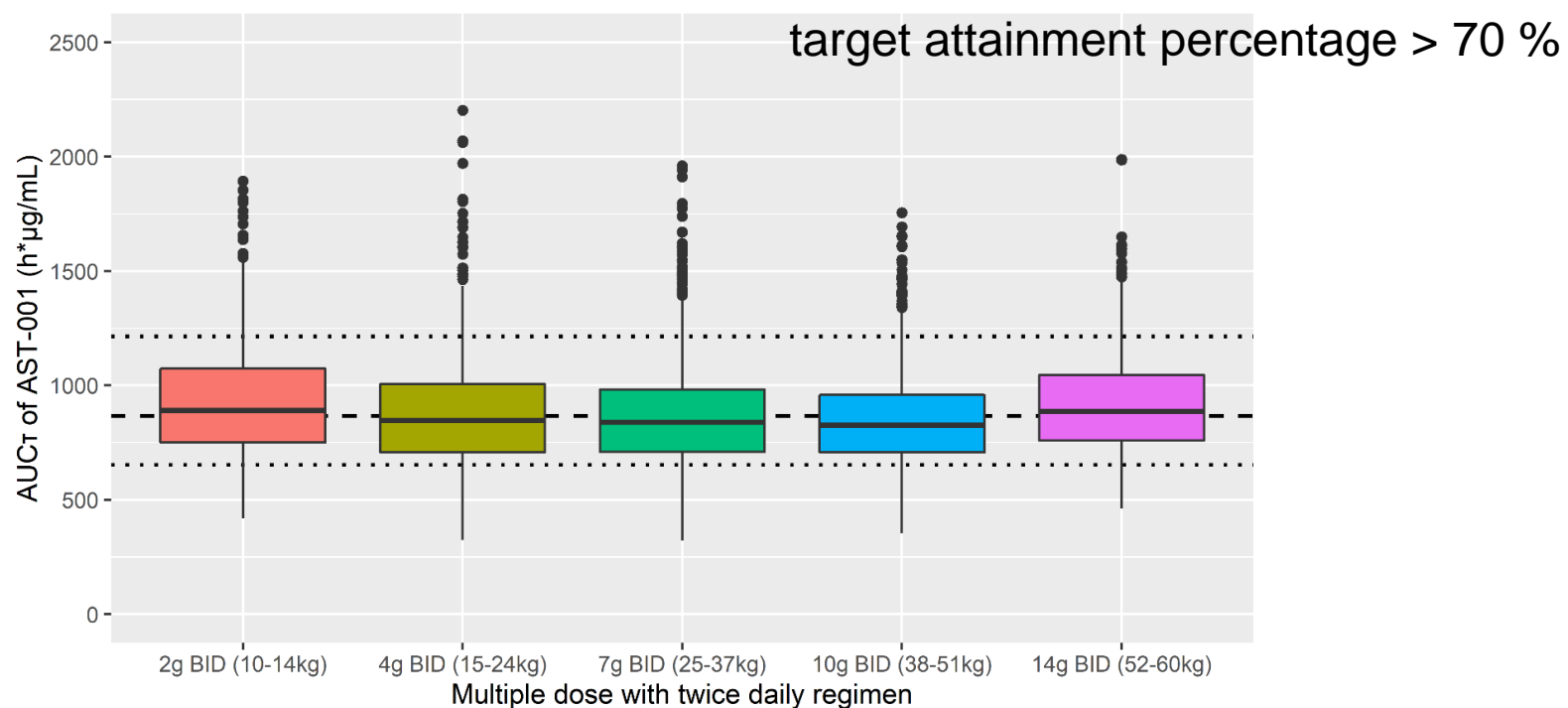
PK model

- Population PK model well predicted observed concentration and exposures
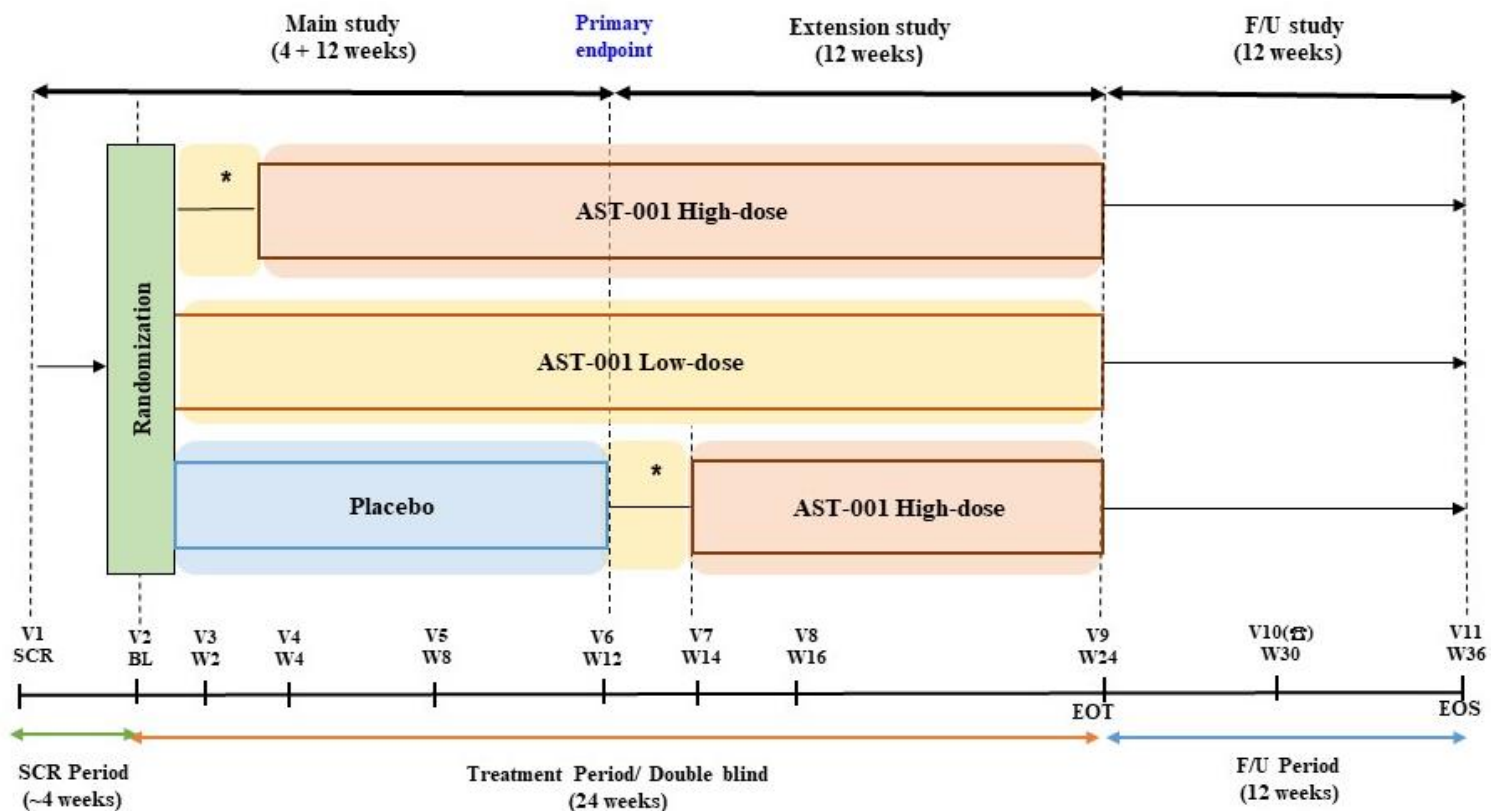
Phase II trial dose selection

- AST-001 after 7-days twice-daily doses of 1–15 g was simulated with a weight range of 10–60 kg.
  - Efficacy target: AUC range of 653–1214 h*μg/mL

target attainment percentage > 70 %

Phase II clinical trial

- Children ages 2 to 11 years old with ASD consists of a 12-week, placebo-controlled, phase 2 trial

Phase II clinical trial
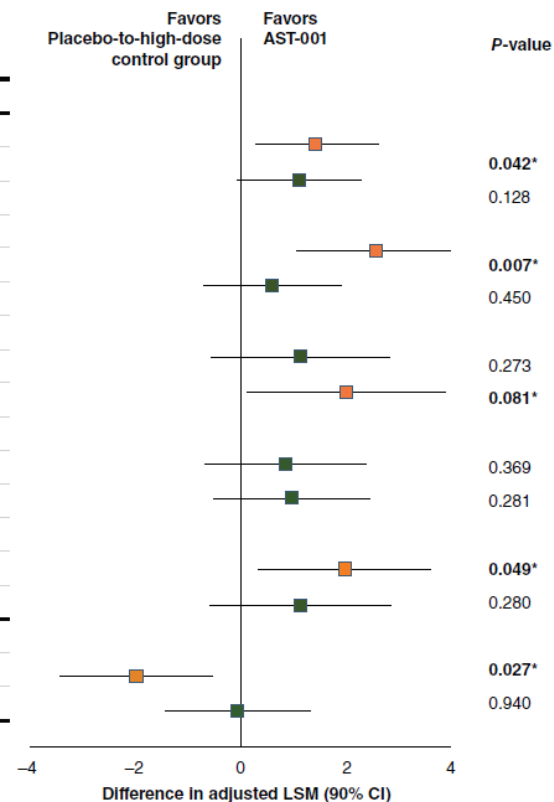
- Result of Phase II clinical trial
  - Mean change on the Adaptive Behavior Composite (ABC) score of the Korean Vineland Adaptive Behavior Scales, Second Edition (K-VABS-II) from baseline to week 12.

Change at 12 weeks	AST-001 CfB-LSM (SE)	Placebo-to-high-dose control group CfB-LSM (SE)	Difference in adjusted LSM (90% CI)		P-value
K-VABS-II					
Adaptive Behavior Composite					
High-dose	3.08 (0.49)	1.66 (0.48)	1.43 (0.28 to 2.58)		**0.042***
Low-dose	2.82 (0.50)	1.73 (0.51)	1.10 (−0.09 to 2.28)		0.128
Communication					
High-dose	3.85 (0.65)	1.30 (0.63)	2.56 (1.03 to 4.08)		**0.007***
Low-dose	1.92 (0.56)	1.32 (0.56)	0.60 (−0.72 to 1.92)		0.450
Daily living skills					
High-dose	2.79 (0.73)	1.65 (0.71)	1.14 (−0.58 to 2.85)		0.273
Low-dose	3.76 (0.79)	1.76 (0.80)	2.00 (0.12 to 3.88)		**0.081***
Socialization					
High-dose	2.82 (0.66)	1.98 (0.64)	0.84 (−0.70 to 2.38)		0.369
Low-dose	2.94 (0.63)	1.96 (0.64)	0.97 (−0.52 to 2.46)		0.281
Motor Skills					
High-dose	3.30 (0.68)	1.31 (0.72)	1.98 (0.33 to 3.63)		**0.049***
Low-dose	2.37 (0.71)	1.24 (0.75)	1.13 (−0.60 to 2.85)		0.280
K-PSI-4-SF Parental Distress					
High-dose	−1.85 (0.63)	0.14 (0.61)	−1.99 (−3.45 to −0.52)		**0.027***
Low-dose	0.15 (0.58)	0.21 (0.59)	−0.06 (−1.44 to 1.32)		0.940

Forest plot: Favors Placebo-to-high-dose control group / Favors AST-001. Difference in adjusted LSM (90% CI), x-axis from −4 to 4.

Kim, Hyo-Won, et al. *Psychiatry and Clinical Neurosciences* (2024).

Phase II clinical trial to Phase III clinical trial

임상 2상 → 임상 3상

- Phase II clinical trial dose (high-dose group)

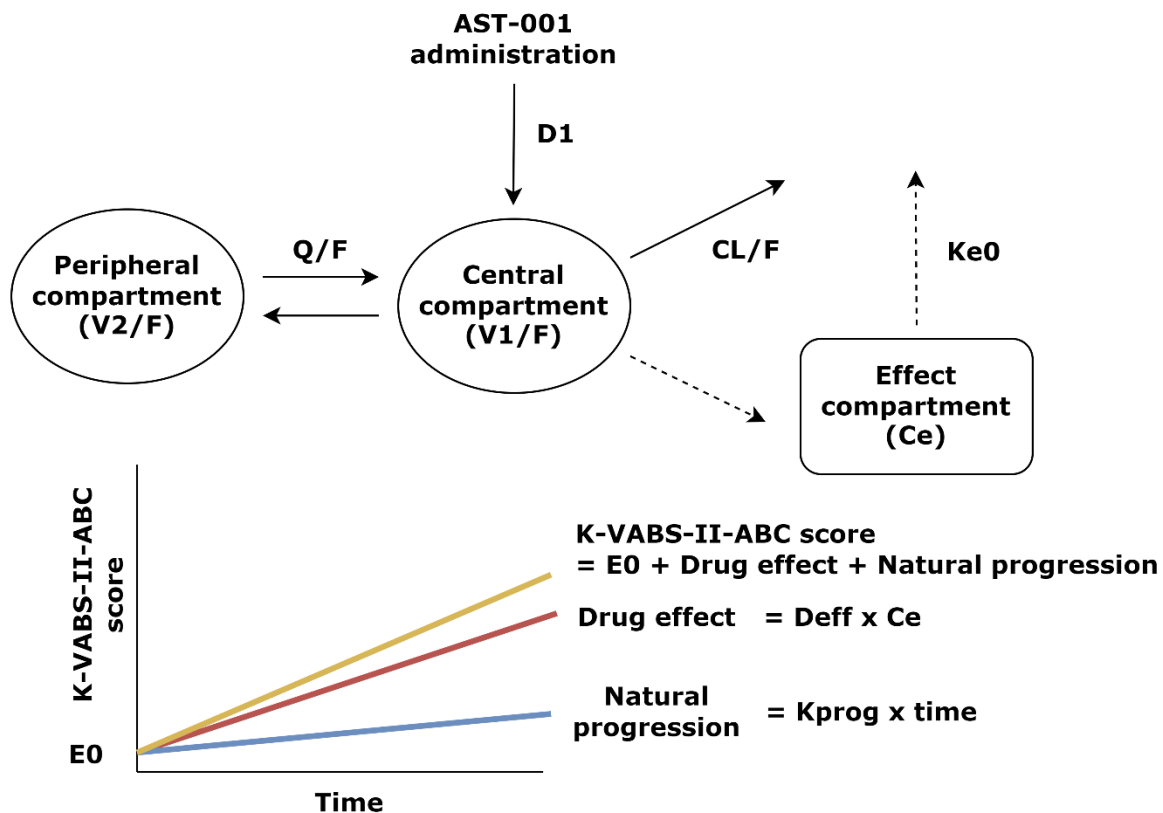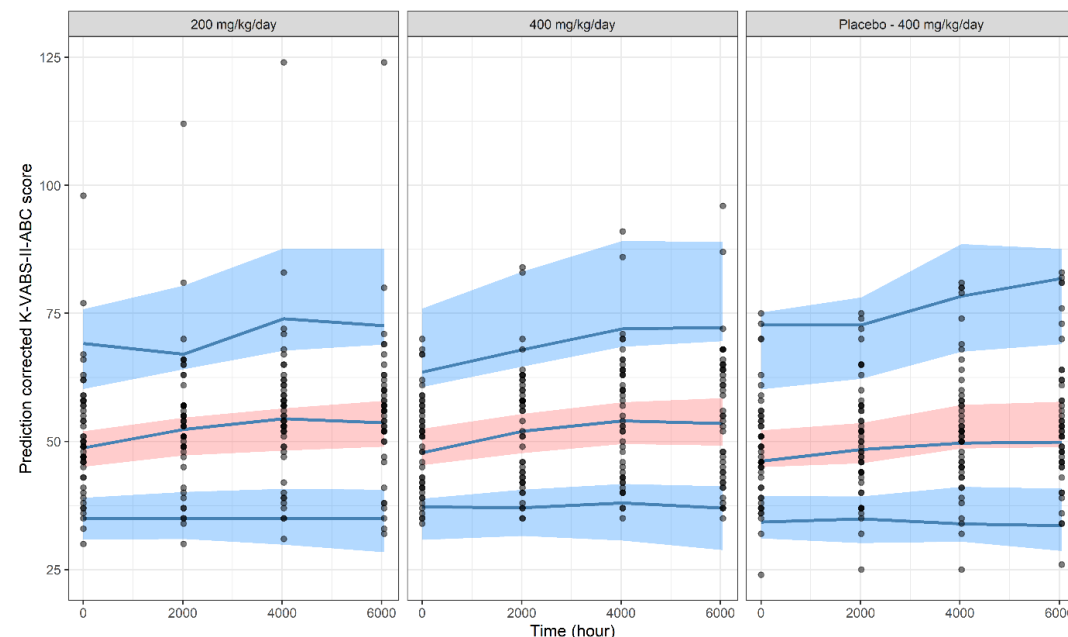| 2 g BID	4 g BID	7 g BID	10 g BID	14 g BID
10-14 kg	15-24 kg	25-37 kg	38-51 kg	52-60 kg
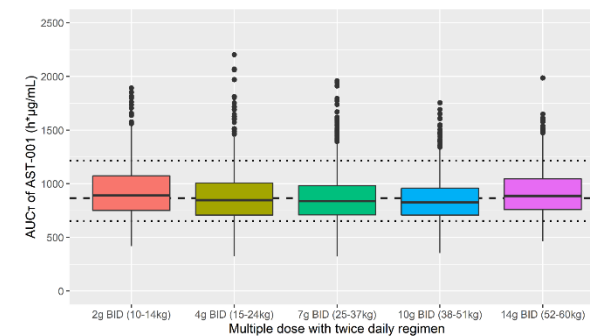
- Formulation: 2g (20mL)/ pouch ➡ Drug compliance issue

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Dose optimization for phase III clinical trial

- Combining healthy adult PK data with pediatric patient PD data
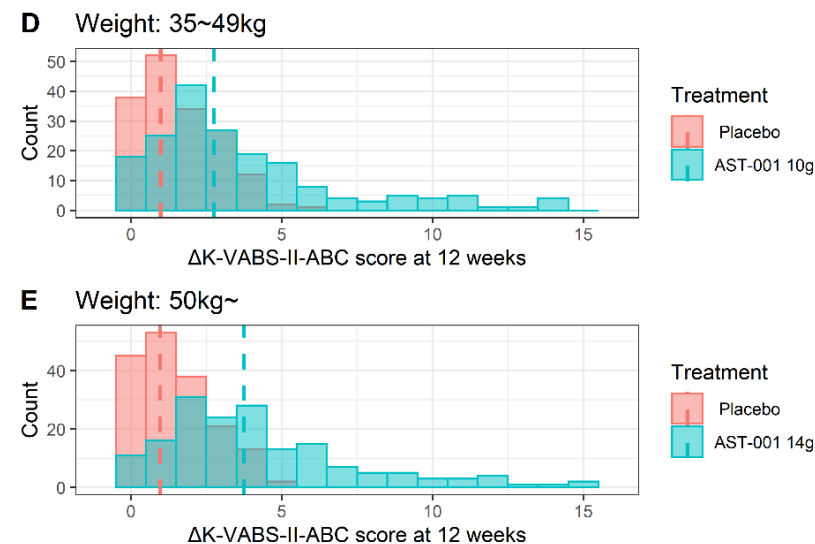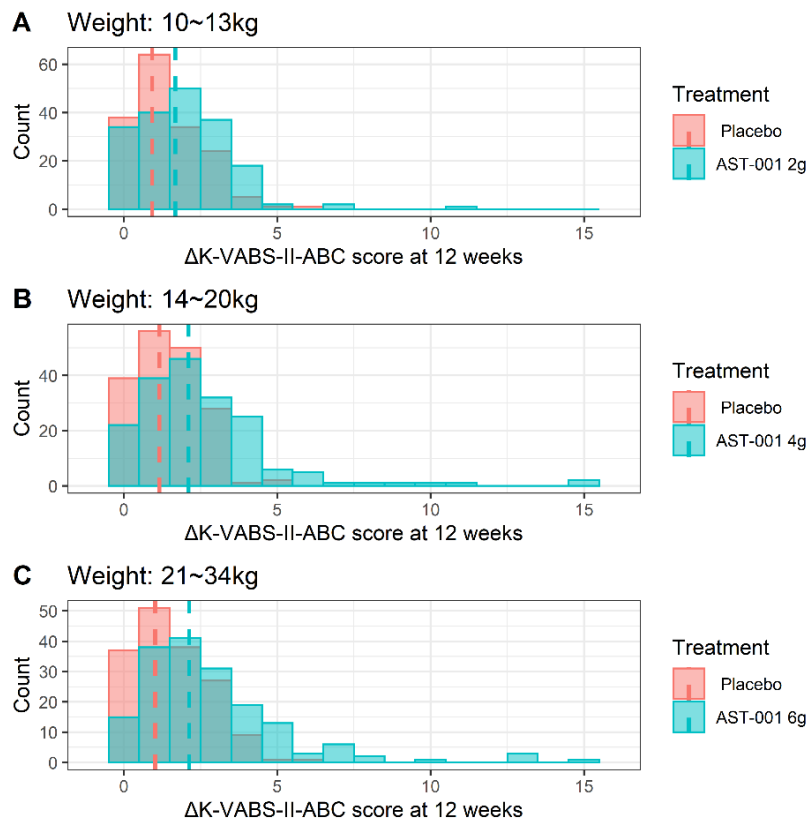 - Population PK/PD model of AST-001 and K-VABS-II-ABC score.

Soyoung Lee, et al. (2024) *Accepted in Frontiers in pharmacology*

Dose optimization for phase III clinical trial

- Histogram plots for changes in K-VABS-II-ABC score at 12 weeks from baseline in 200 virtual pediatric patients (Placebo vs weight tiered fixed dose)

Dose optimization for phase III clinical trial

- Weight-based dose vs weight tiered fixed dose
  - Box plots for changes in K-VABS-II-ABC score at 12 weeks from baseline (ΔK-VABS-II-ABC) in 200 virtual pediatric patients after AST-001 treatment
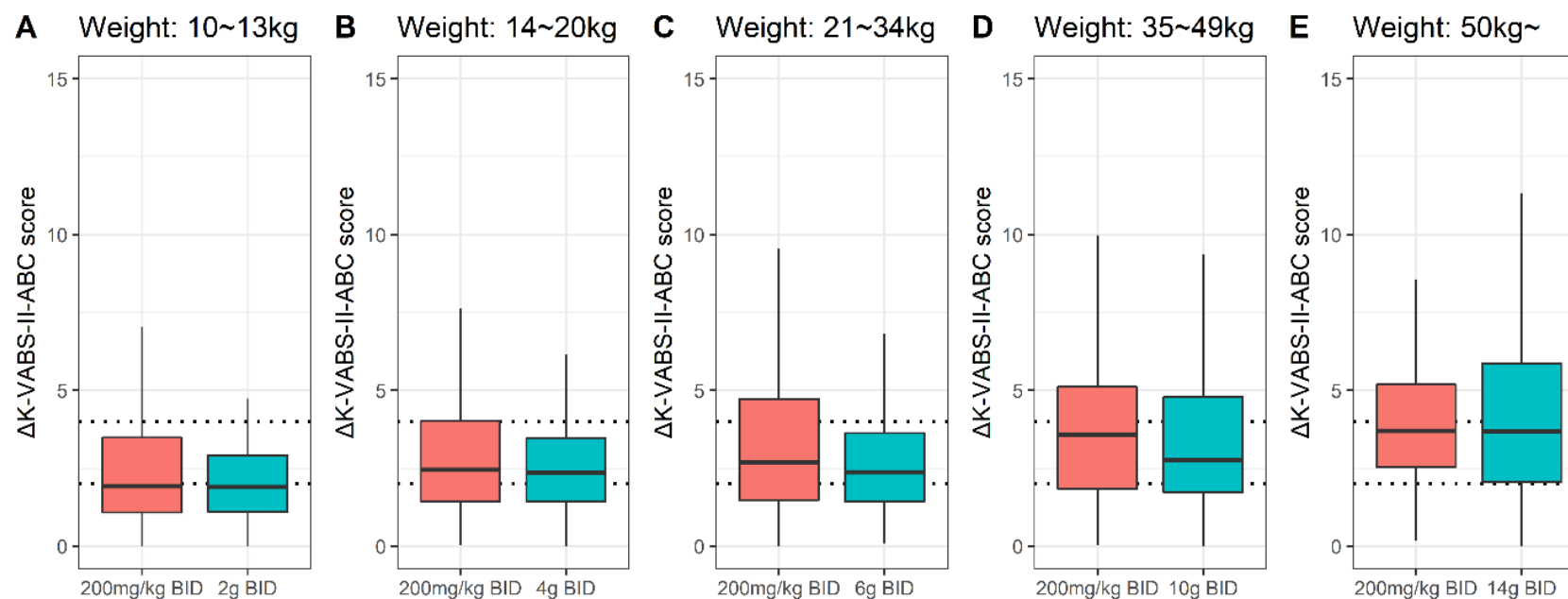
Dose optimization for phase III clinical trial

- We suggest weight tiered fixed dose regimen for ongoing phase III trial, which are expected to improve autism symptoms similar to weight based dose
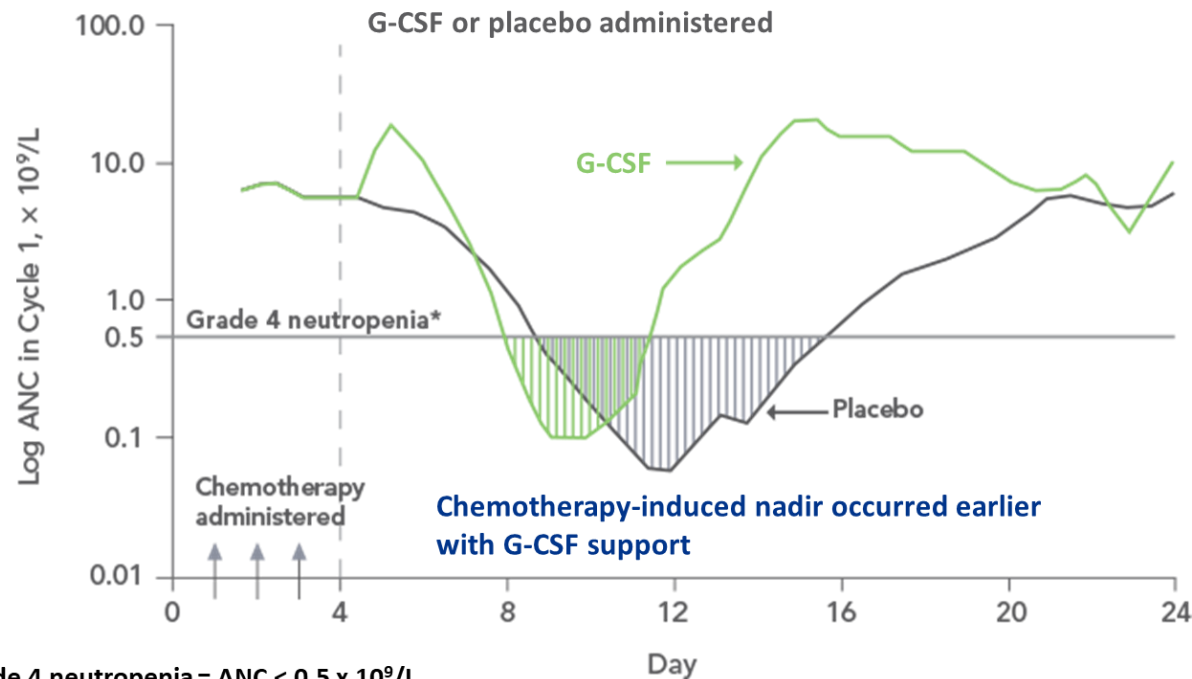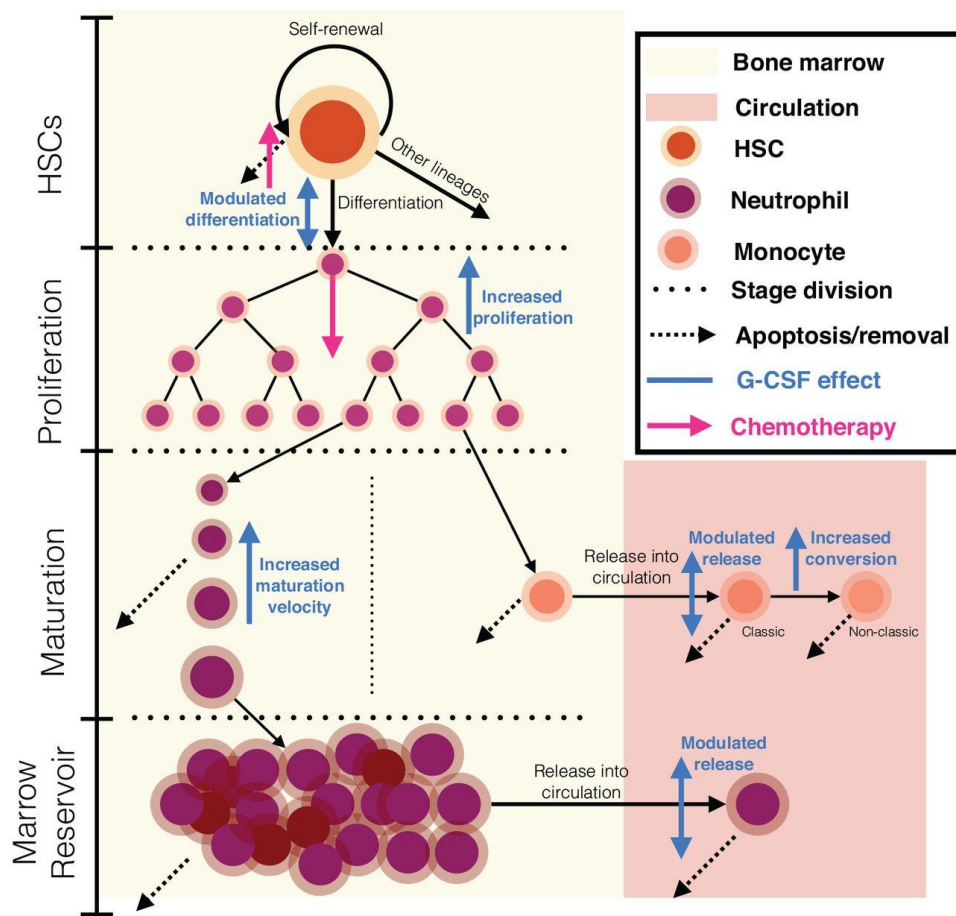
Ⅲ Case Study 2: Tripegfilgrastim

- Modeling and Simulation for Weight-tiered Fixed Dose Regimen in Pediatrics

Granulocyte colony stimulating factor

- Use to prevent chemotherapy-induced neutropenia

HSC,
hematopoietic stem cell

Cassidy, Tyler, et al. *Bulletin of Mathematical Biology*, 2020

* Grade 4 neutropenia = ANC < 0.5 x 10^9/L

Granulocyte colony stimulating factor

- Short acting G-CSF (ex. filgrastim)

  - **50 μg/m² once daily** subcutaneous injection (10 days)

가. filgrastim(품명: 그라신주 등), lenograstim(품명: 뉴트로진주)

2) 만 19세 미만의 소아암환자에게 나.의 1)항의 요법(발열성 호중구감소증 위험성 20% 초과 요법)을 시행하는 경우 호중구수 수치와 관계없이 요양급여를 인정하며, 나.의 2)항의 요법(발열성 호중구감소증 위험성 10-20%인 요법)을 시행하는 경우 G-CSF 예방적 투여를 하지 않았던 이전 주기에서 발열성 호중구 감소증이 있었거나 용량제한을 초래한 호중구감소증(ANC 500미만)이 있었던 경우 호중구수 수치와 관계없이 요양급여를 인정함

* '5mcg/kg/일'도 투여할 수 있음

Allowance of medical care for short-acting G-CSF in pediatric patients

- Long acting G-CSF (ex. pegfilgrastim, tripegfilgrastim)

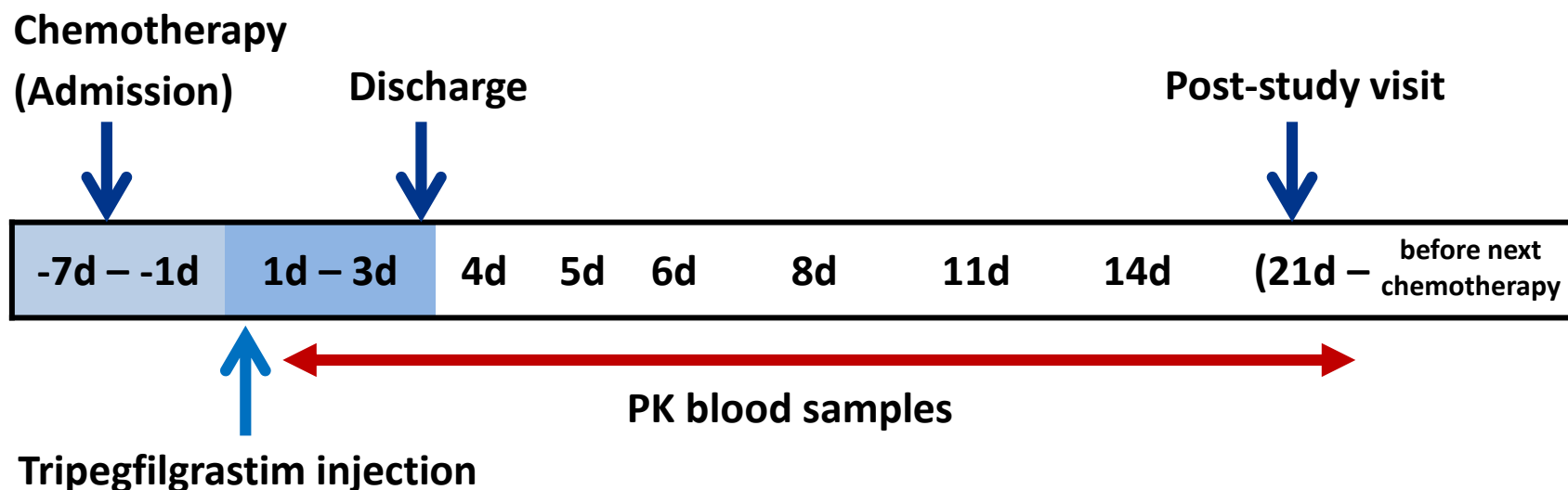 - **Single 6 mg** subcutaneous injection per chemotherapy cycle

9. 소아에 대한 투여 ⊖

소아 환자에 있어 이 약의 안전성 및 유효성은 확립되어 있지 않다.

Tripegfilgrastim label

Clinical research in pediatrics

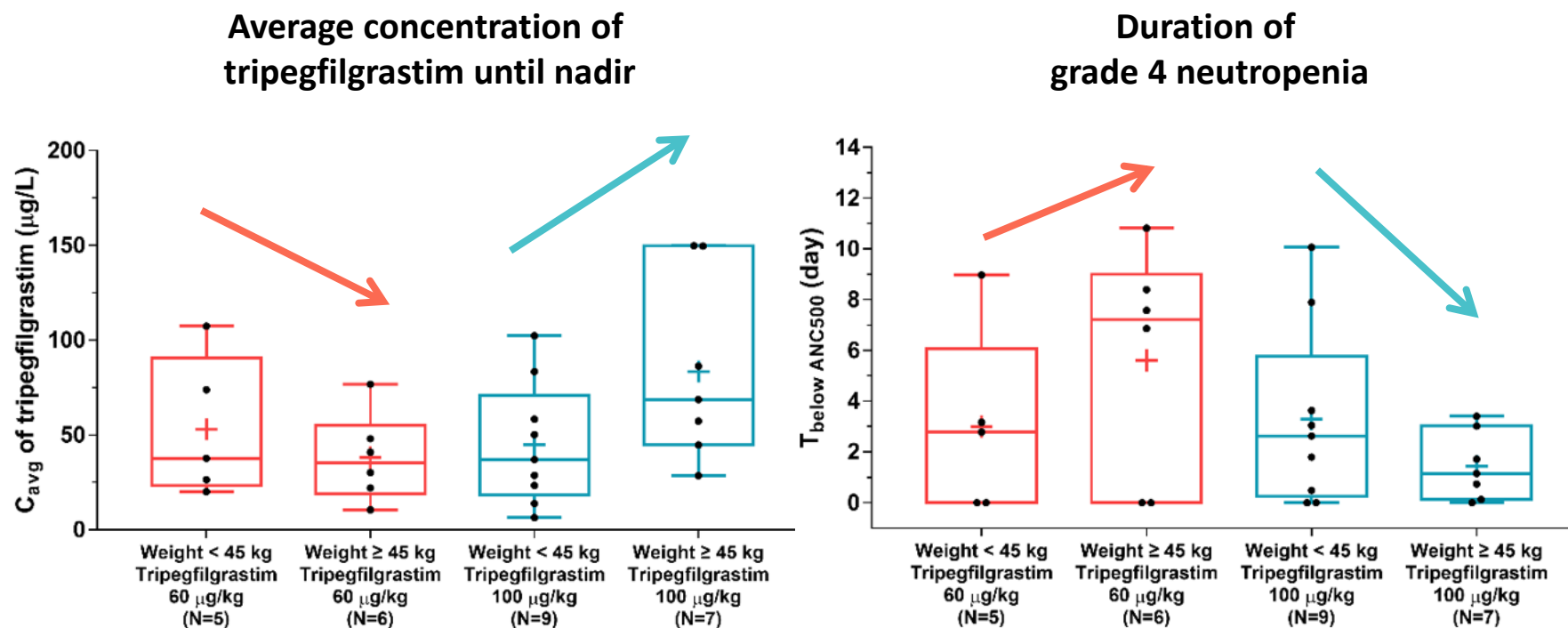- Conducted clinical research collaborating with pediatricians

Chemotherapy (Admission) **Discharge** **Post-study visit**

| -7d – -1d | 1d – 3d | 4d | 5d | 6d | 8d | 11d | 14d | (21d – before next chemotherapy |

Tripegfilgrastim injection

PK blood samples

	Dose group	Age group	Completed Patients
3.6 mg group in adult	60 µg/kg	6 years ≤ age < 12 years	4
	60 µg/kg	12 years ≤ age < 19 years	7
6 mg group in adult	100 µg/kg	6 years ≤ age < 12 years	8
	100 µg/kg	12 years ≤ age < 19 years	8

Clinical research in pediatrics

- Exposure and efficacy relationship
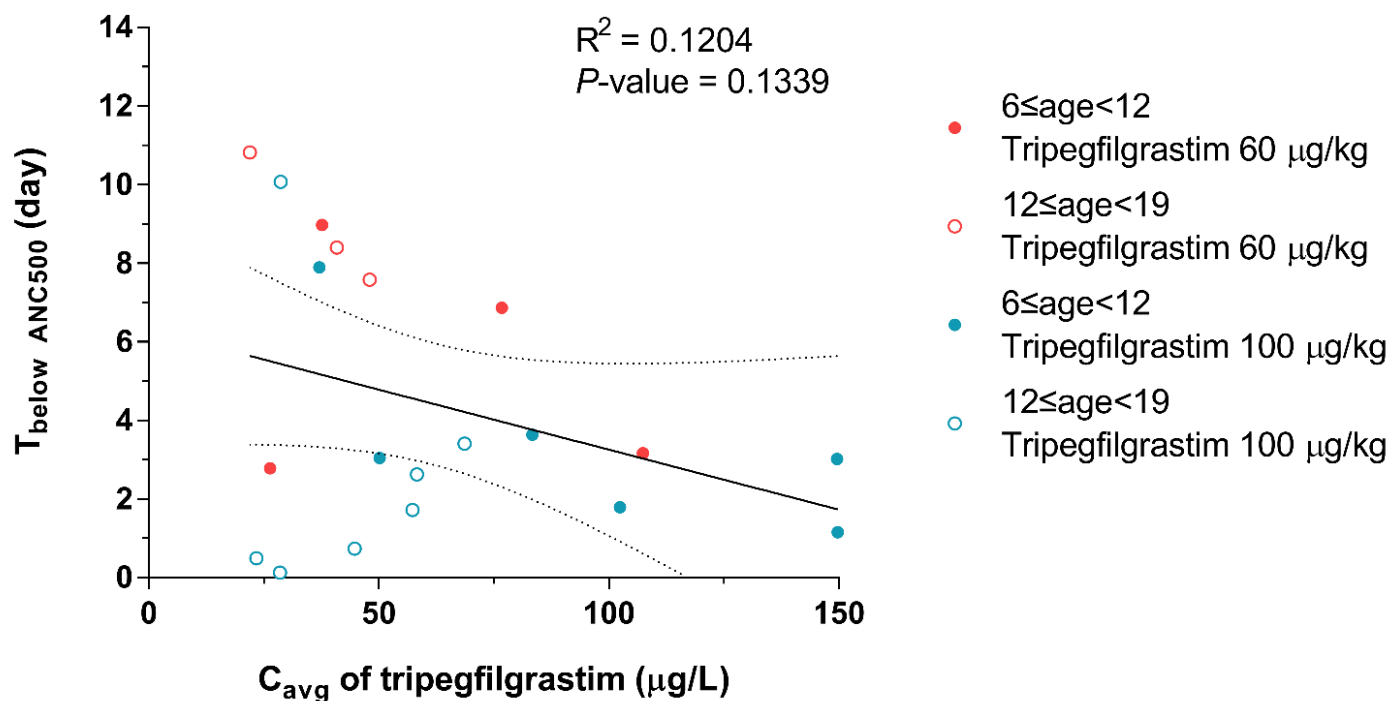 - Average drug concentration during the initial neutrophil recovery process is important for efficacy

Average concentration of tripegfilgrastim until nadir

Duration of grade 4 neutropenia

Soyoung Lee, et al. (2022) *Clinical Pharmacology & Therapeutics*

Clinical research in pediatrics

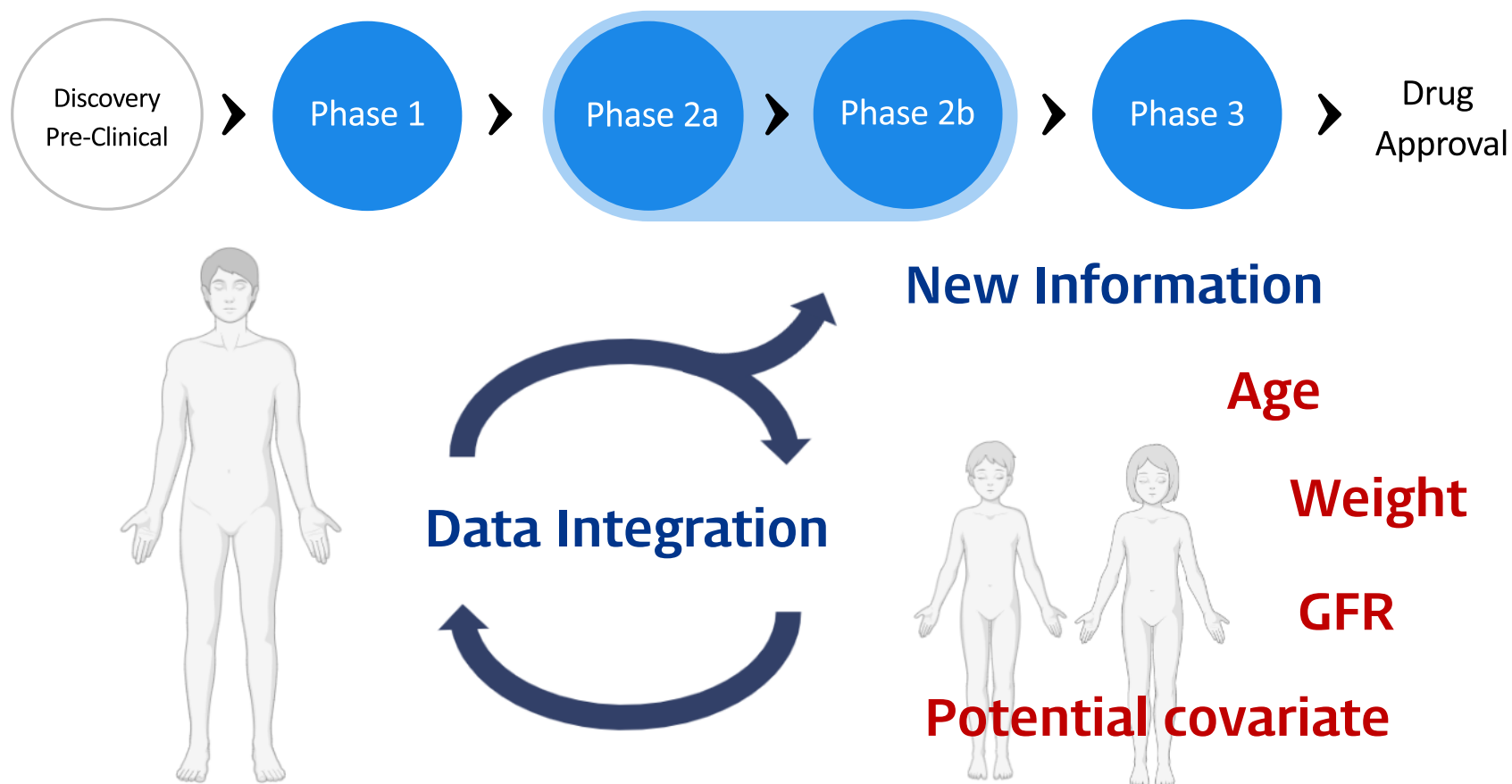**Exposure and efficacy relationship**

- Pharmacotherapeutic evidence for using tripegfilgrastim 100 μg/kg in pediatric patients

$R^2 = 0.1204$
P-value = 0.1339

- (filled red) 6≤age<12 Tripegfilgrastim 60 μg/kg
- (open red) 12≤age<19 Tripegfilgrastim 60 μg/kg
- (filled teal) 6≤age<12 Tripegfilgrastim 100 μg/kg
- (open teal) 12≤age<19 Tripegfilgrastim 100 μg/kg

X-axis: C_{avg} of tripegfilgrastim (μg/L)
Y-axis: $T_{below\ ANC500}$ (day)

Soyoung Lee, et al. (2022) *Clinical Pharmacology & Therapeutics*

Integrated model analysis

- Healthy adults and pediatric patients

Discovery Pre-Clinical ❯ Phase 1 ❯ Phase 2a ❯ Phase 2b ❯ Phase 3 ❯ Drug Approval

New Information

Data Integration

Age

Weight

GFR

Potential covariate

Tripegfilgrastim model

- ## Tripegfilgrastim model
  - ### PK model
    - ✓ Target mediated drug disposition

Parameter	Healthy adult	Pediatric patients
Kd (μg/L)	42.2	16.2

  - ### PD model
    - ✓ Neutrophil physiology

Parameter	Value
Proliferation effect	14.4
Maturation effect	13.8

  - ### K-PD model
    - ✓ Chemotherapy effect
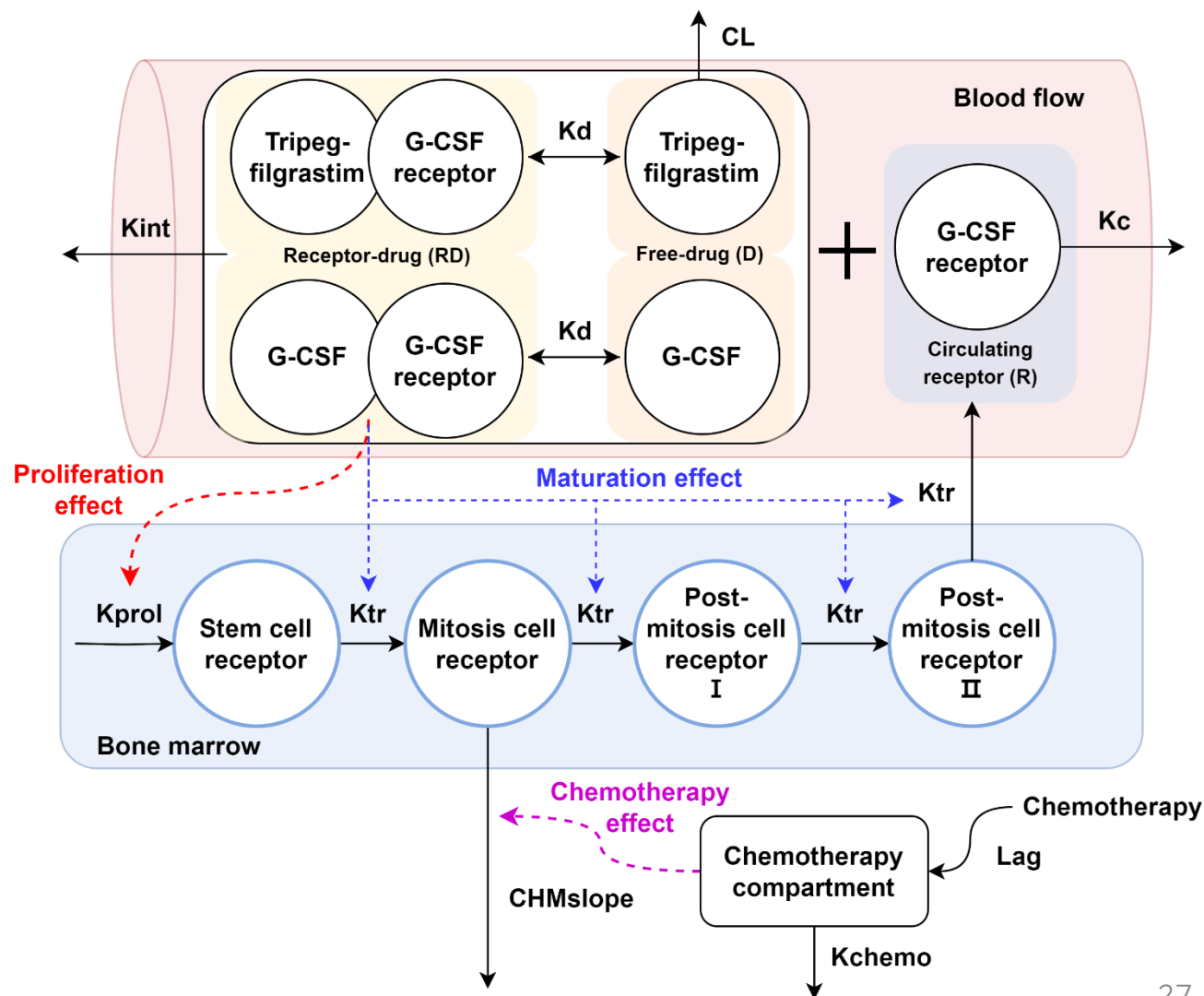
Fractional occupancy
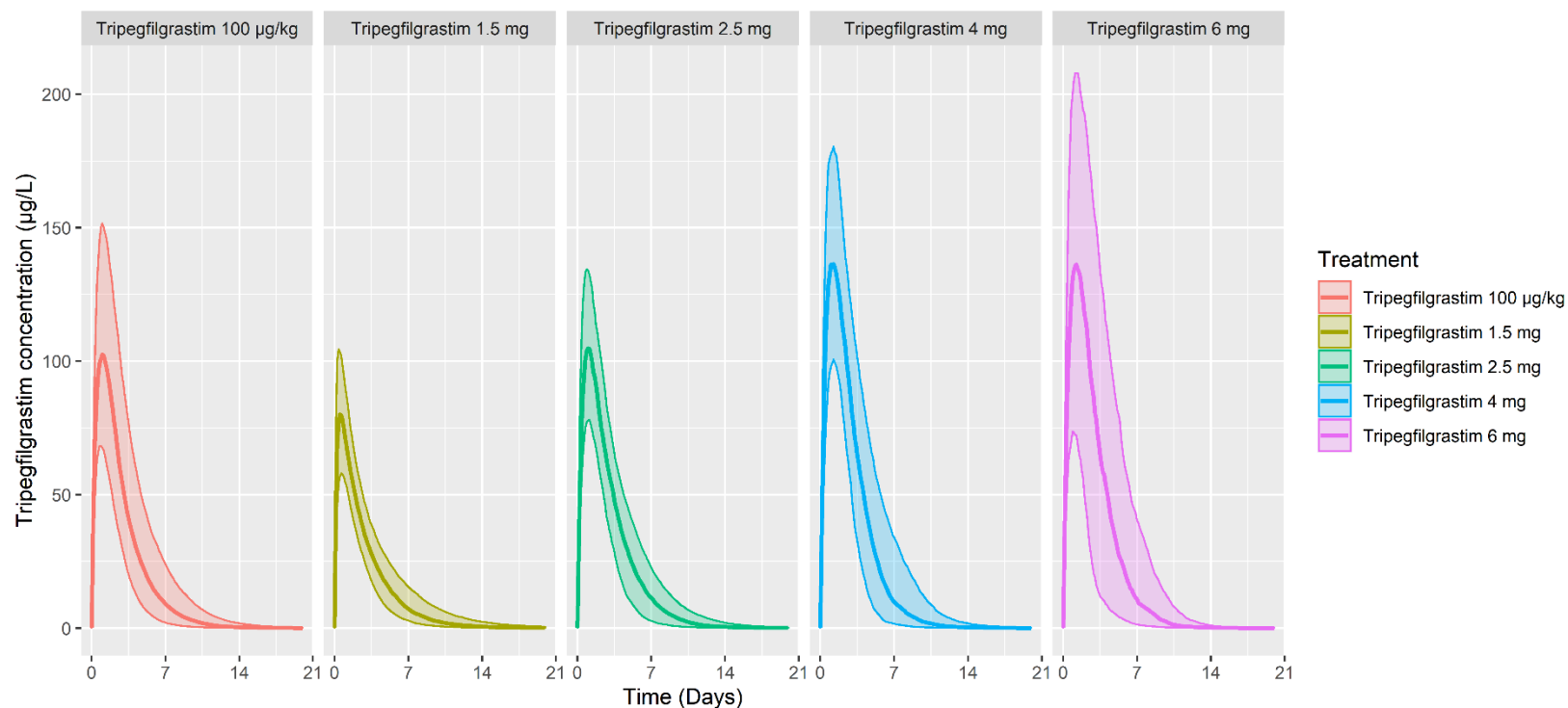
Fractional occupancy of
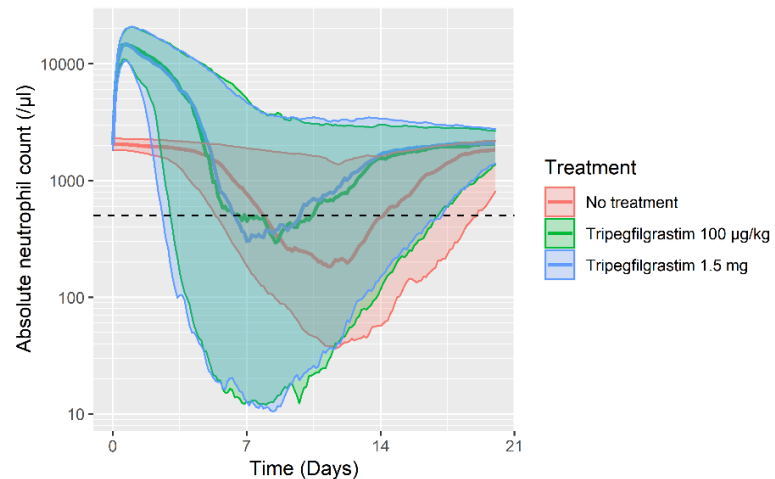G-CSF receptor with drug $= \dfrac{\text{Free drug concentration}}{\text{Free drug concentration} + Kd}$

Soyoung Lee, et al. (2023) *CPT: PSP* 12:1319-1334
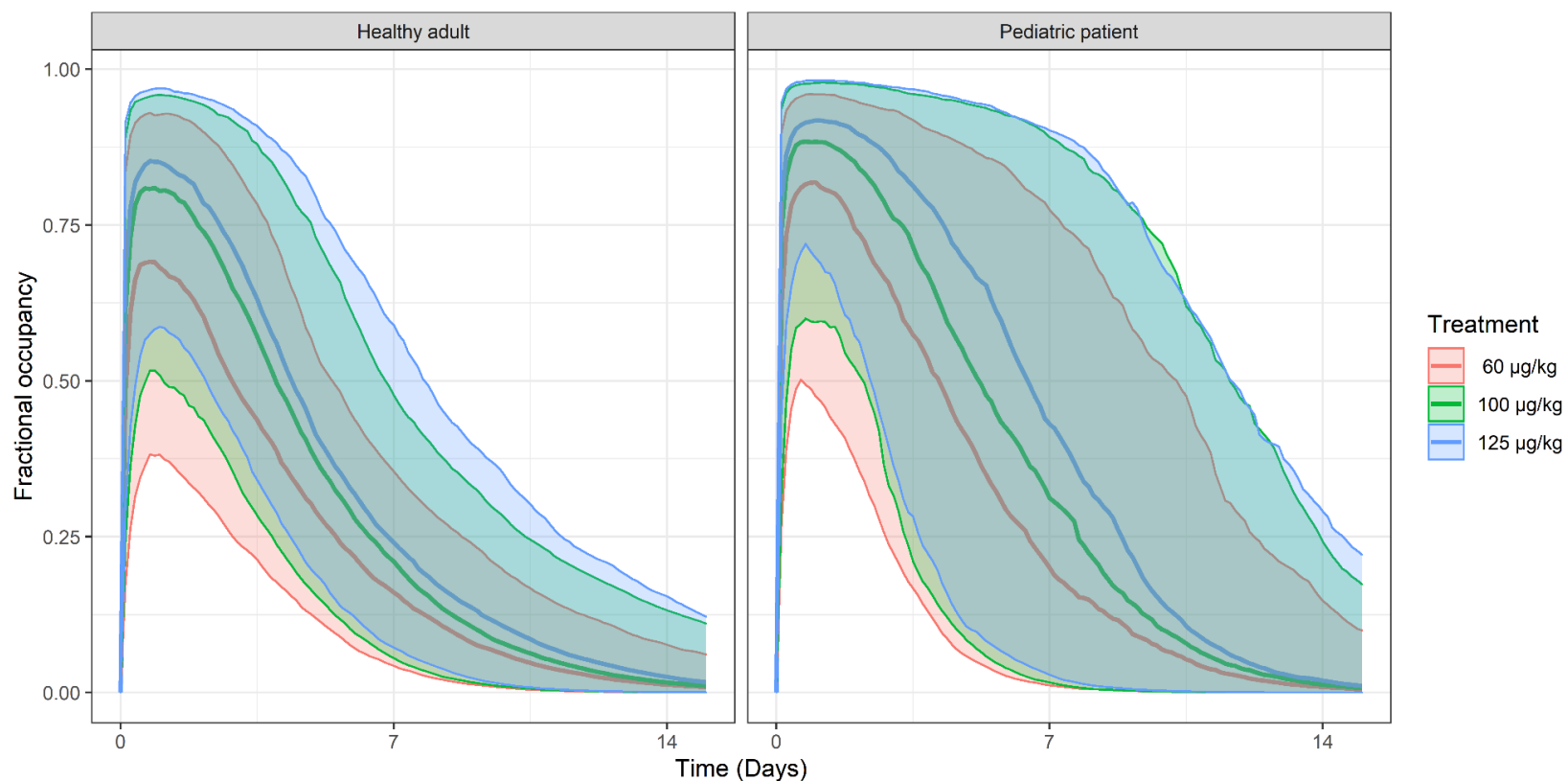
Simulation: Tripegfilgrastim PK

- Weight-based dose vs weight-tiered fixed dose

100 µg/kg	1.5mg	2.5mg	4mg	6mg
10-70 kg	10-20 kg	21-30 kg	31-44 kg	45-70 kg

Soyoung Lee, et al. (2023) *CPT: PSP* 12:1319-1334

Simulation: Absolute Neutrophil Count (ANC)

Soyoung Lee, et al. (2023) *CPT: PSP* 12:1319-1334
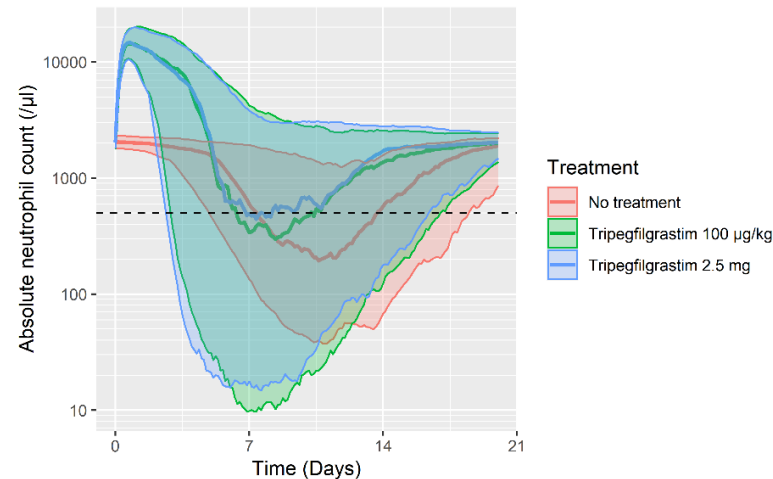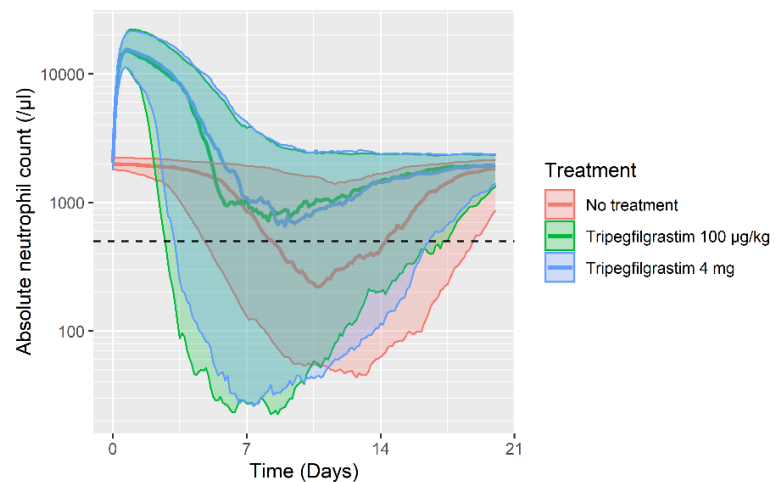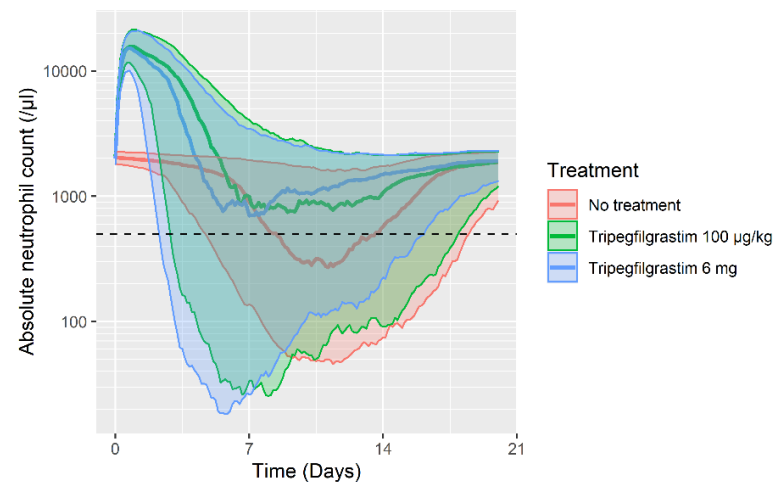
Simulation: Grade 4 neutropenia duration

- Similar efficacy compared to weight-based dose

100 µg/kg	1.5mg	2.5mg	4mg	6mg
10-70 kg	10-20 kg	21-30 kg	31-44 kg	45-70 kg

Soyoung Lee, et al. (2023) *CPT: PSP* 12:1319-1334
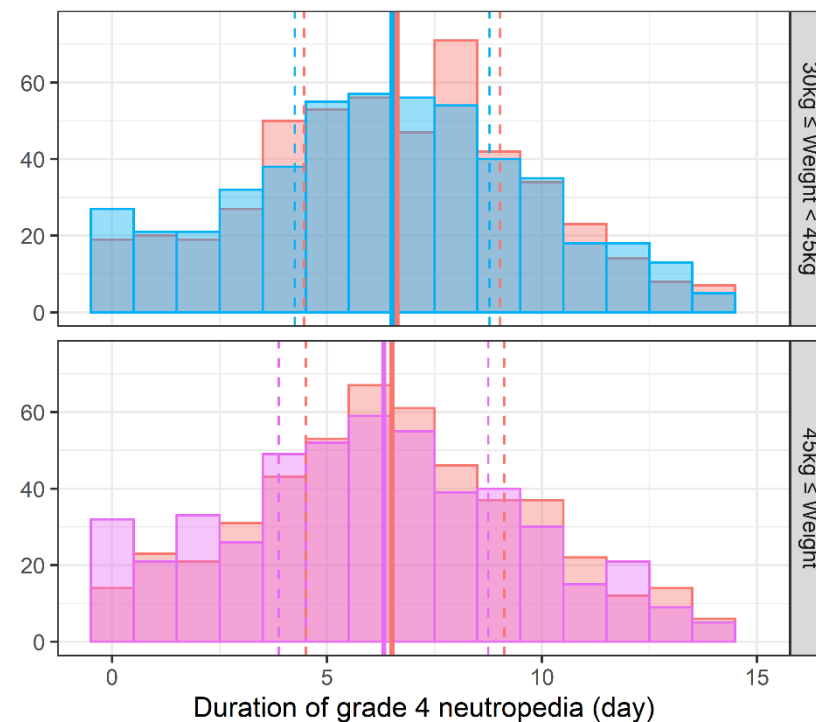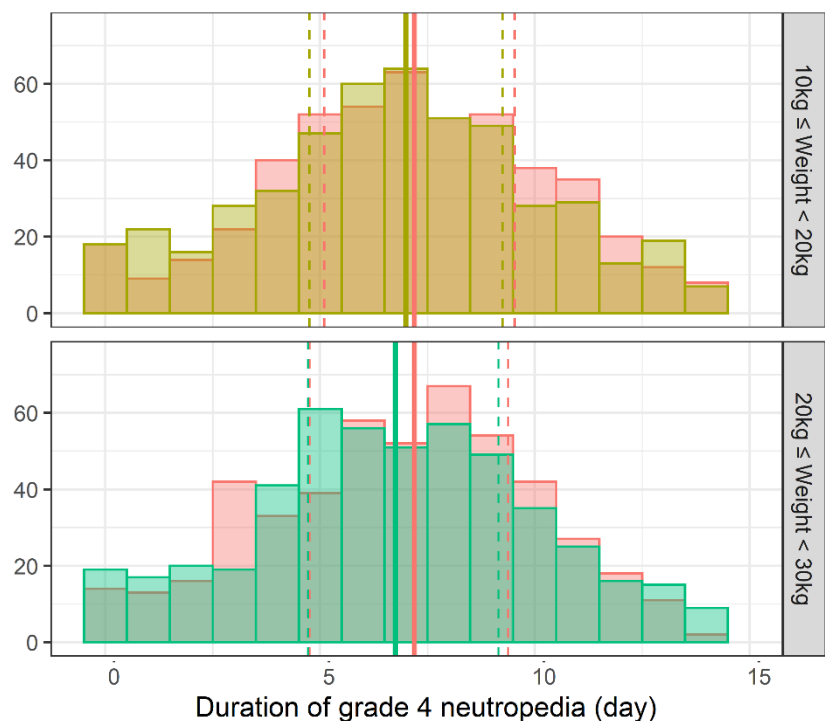
Translational research

◉ Convenient dose regimen for long acting G-CSF treatment for pediatrics

- Modeling and simulation can inform optimal weight-tiered fixed-dose regimens in pediatric patients to reduce the duration of grade 4 neutropenia with similar effects in weight-based dose regimens.

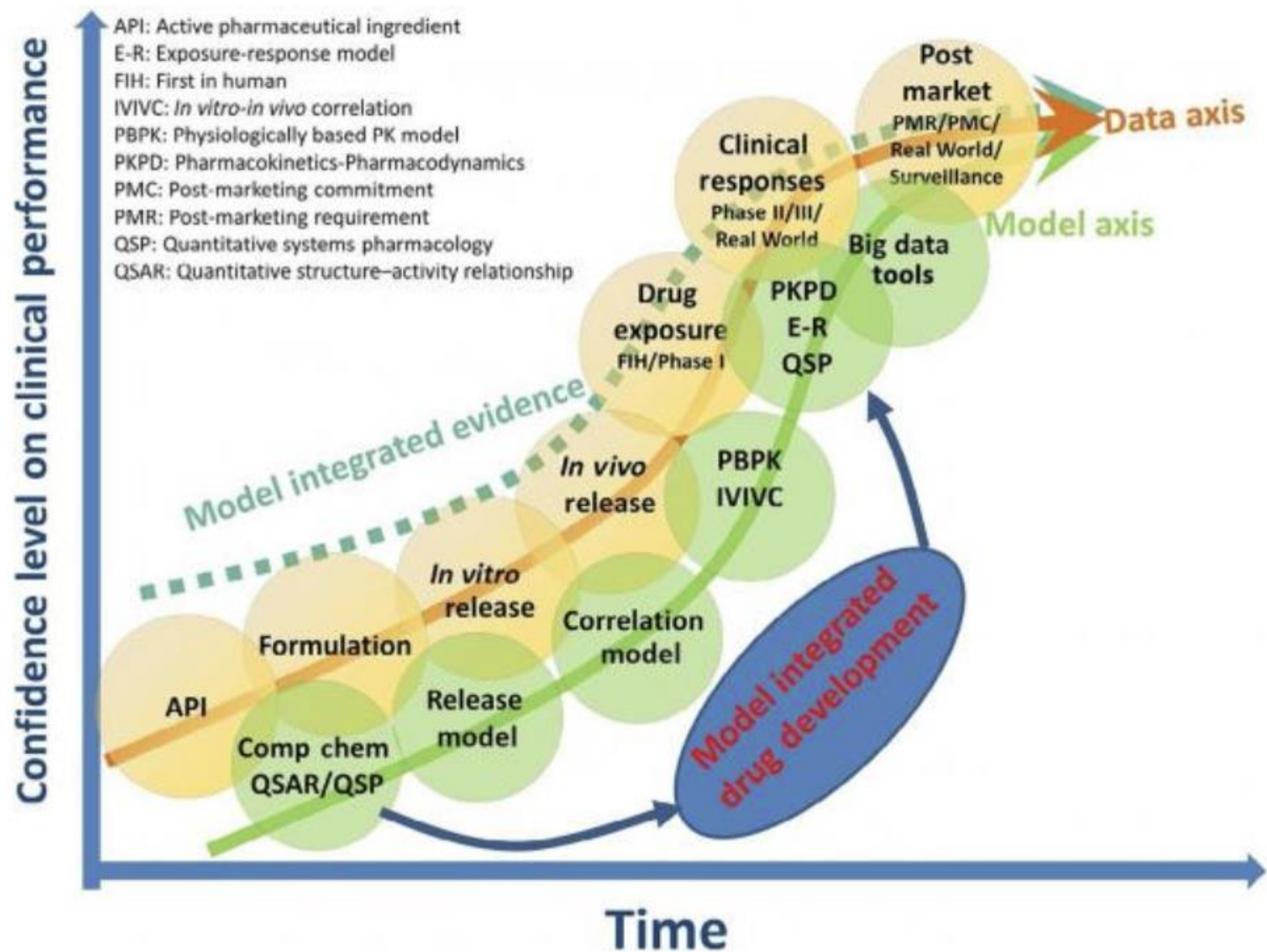**Modeling and simulation based pharmacotherapy for pediatric patients**
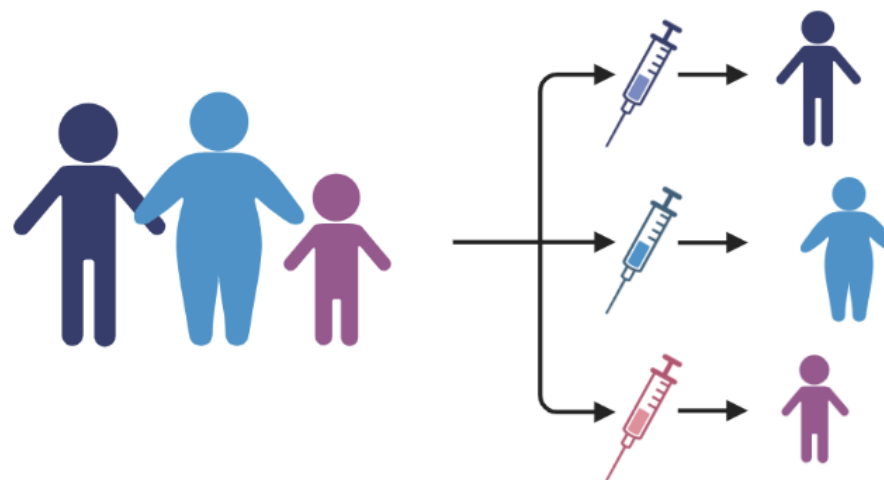
Ⅳ Take Home Message

- Application of Pharmacometrics in
  New Drug Development

Model-Informed Drug Development

Acknowledgement

- Seoul National University Clinical Pharmacology and Therapeutics (SNUCPT) & Seoul National University Bundang Hospital
  - Prof. In-Jin Jang, Prof. Kyung-Sang Yu
  - Prof. Jae-Yong Chung

- Seoul National University Children's Hospital
  - Prof. Hyoung Jin Kang, Prof. Kyung Taek Hong

- Jeju National University
  - Prof. Jaeseong Oh

- Sponsor
  - Astrogen, inc. (AST-001)
  - DONG-A ST Co.,Ltd. (Tripegfilgrastim)

Thank you

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