Quantitative Clinical Pharmacology in Drug Development and Drug Approval

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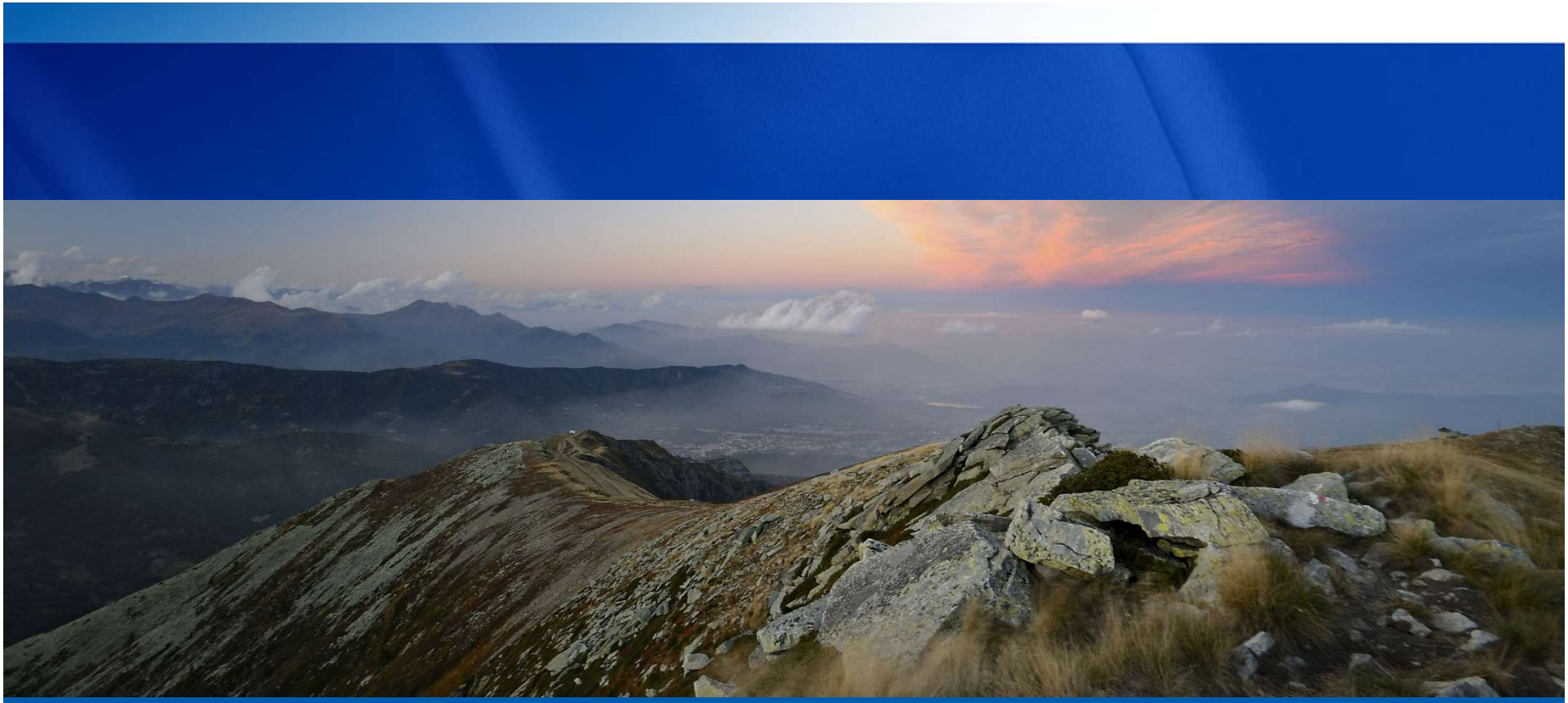
Overview

- Case 1: : QCP in DDI Assessment for Drug A
- Case 2: Application of QCP in Plegridy Approval
- Model Based Drug Development

QCP: quantitative clinical pharmacology



Case Study 1: QCP in DDI Assessment for Drug A

CYP Inhibition by Drug A

Ruled out clinical DDI for CYP inhibition

CYP450	Assay	AUCR (600 mg)
CYP1A2	Phenacetin *O*-deethylase	1.02
CYP2B6	Bupropion hydroxylase	1.02
CYP2C8	Amodiaquine *N*-deethylase	1.17
CYP2C9	Diclofenac 4′-hydroxylase	1.05*
CYP2C19	S-Mephenytoin 4′-hydroxylase	1.01
CYP2D6	Bufuralol 1′-hydroxylase	1.01
CYP3A4/5	Testosterone 6β-hydroxylase	ND
CYP3A4/5	Midazolam 1′-hydroxylase	1.10

All AUCR below 1.25 per guidance, no further action needed

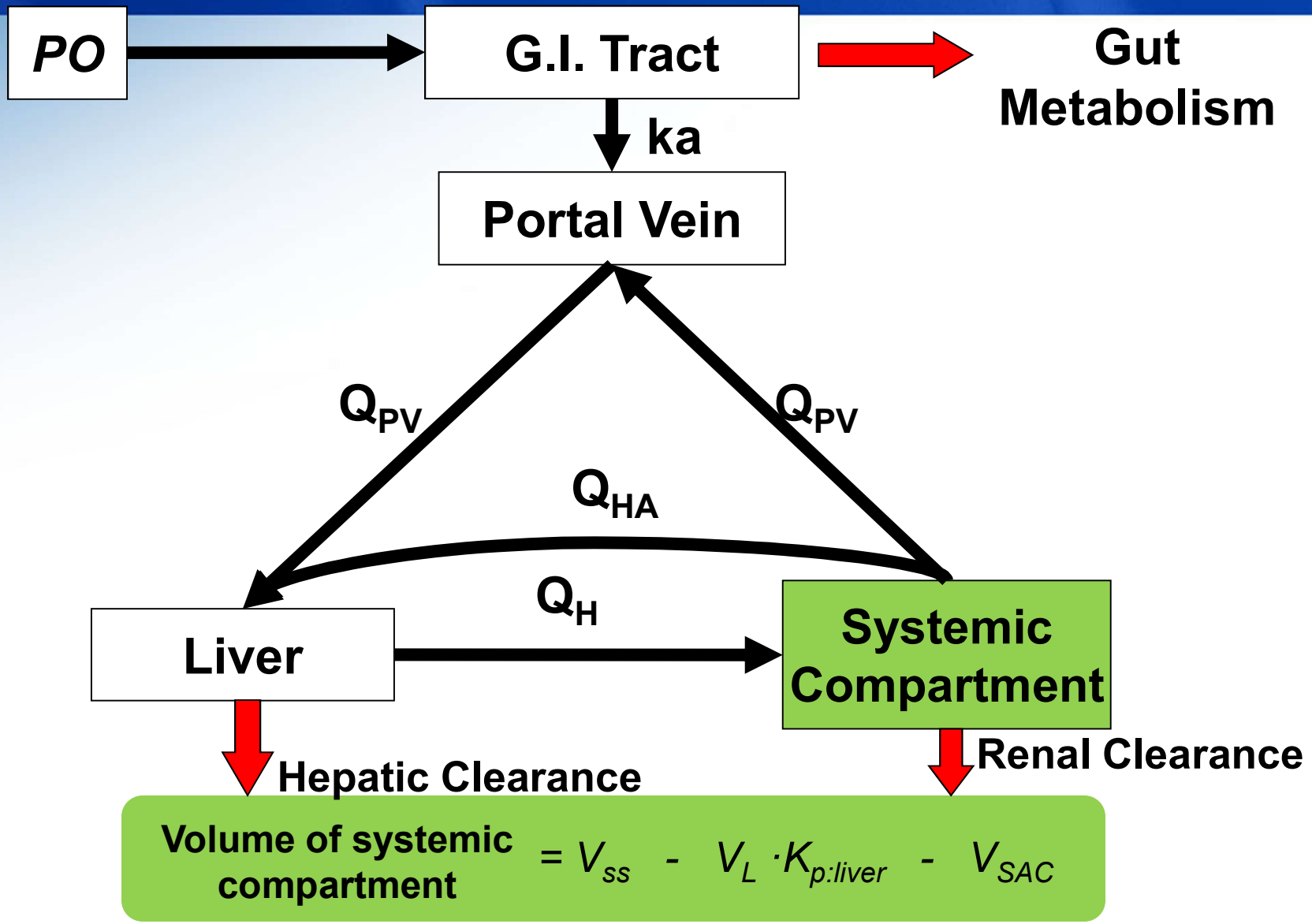
Drug A as an Inhibitor of Transporters

Transporter	Substrate
P-gp	Digoxin (10 μM)
BCRP	Prazosin
OATP1B1	^{3}H-Estradiol-17β-glucuronide (50 nM)
OATP1B3	^{3}H-Estradiol-17β-glucuronide (50 nM)
OCT2	^{14}C-Metformin (10 μM)
OAT1	^{3}H-Aminohippurate (1 μM)
OAT3	^{3}H- Estrone-3-sulfate
MATE-1	^{14}C-Metformin (10 μM)
MATE-2K	^{14}C-Metformin (10 μM)

Probe Substrates of Transporters

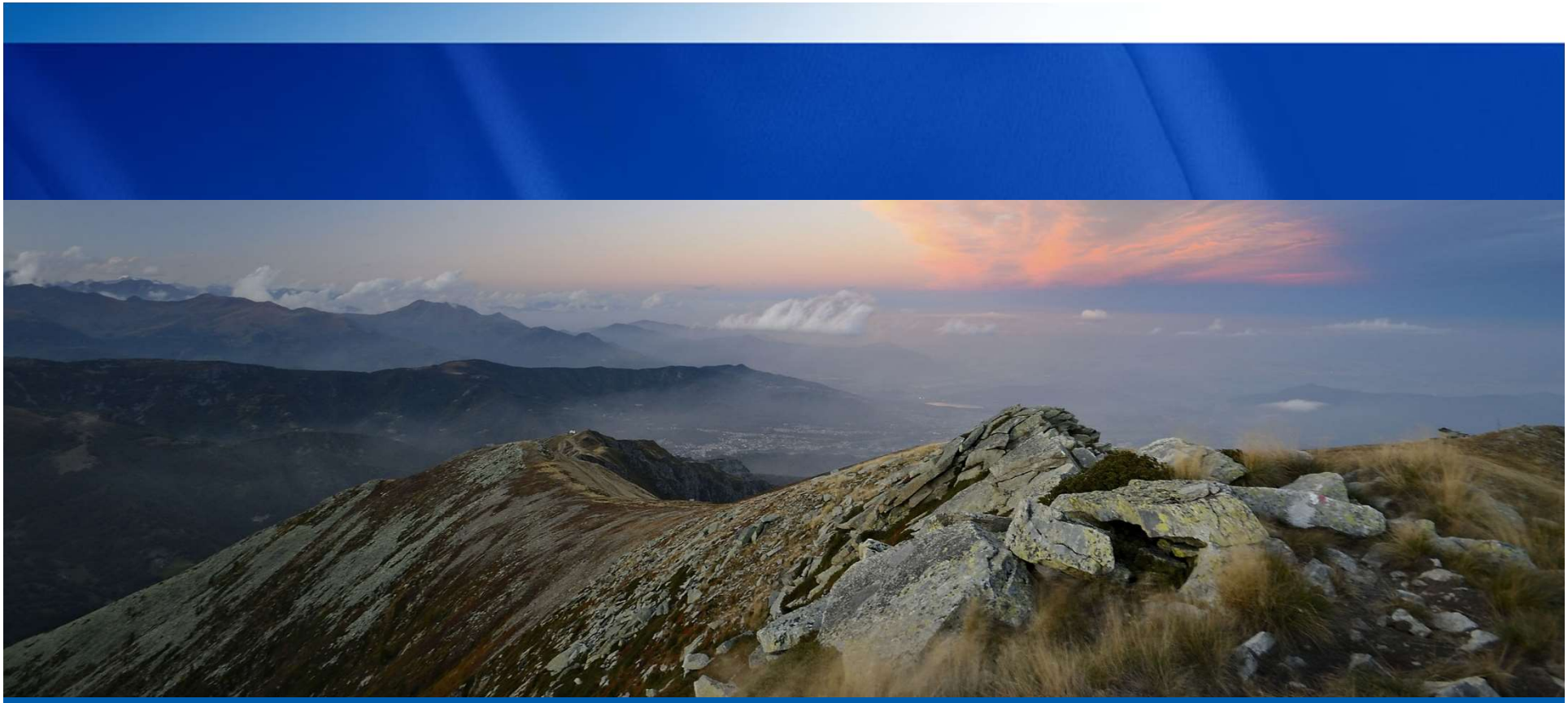
Substrate	Transporters	Dose	Route
Digoxin	pgp	0.5 mg	Oral
Rosuvastatin	OATP1B1 and BCRP	20 mg	Oral
Methotrexate	OAT1/OAT3	200 mg/m^2	IV

Illustration of the minimal PBPK model



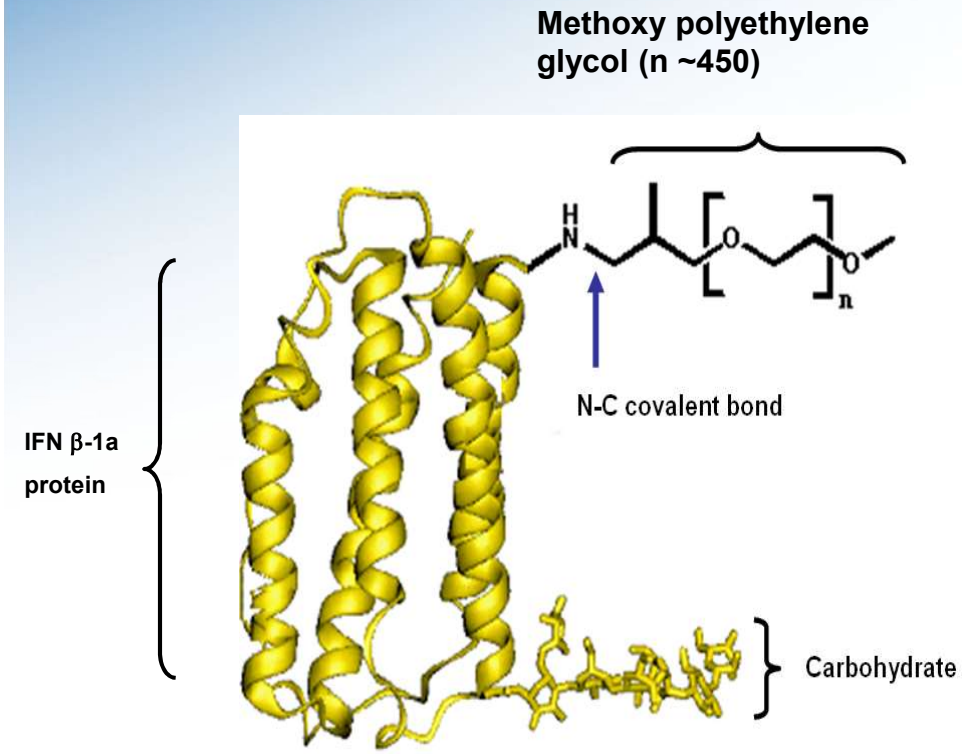
SUMMARY

- Clinical studies: pgp, OATP1B1 and BCRP inhibition by Drug A
- Test staggering strategy for OATP1B1
- Waiver application: OAT1 and OAT3 inhibition by Drug A



Case Study 2: QCP in Plegridy Approval

Plegridy Overview



- Interferon β -1a: approved to treat multiple sclerosis (MS) in 1996 (30 µg IM once weekly);
- Plegrigy: attacheing 20K to the α-amino group of the N-terminal amino acid residue.
- Longer half-life and greater exposure
- Plegridy was approved in 2014 by FDA and EMA to treat MS (125 µg, SC, every two week)

Application of QCP

- Dose rationale in pediatric subjects
- Support of the optimal dosing regimen in the label

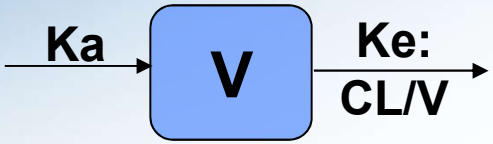
Dose Selection Rationale for Plegridy PIP

- Question
  - What dose should be given to pediatric patients?
- Knowledge available
  - Two Phase 1 HV studies
  - One PK model

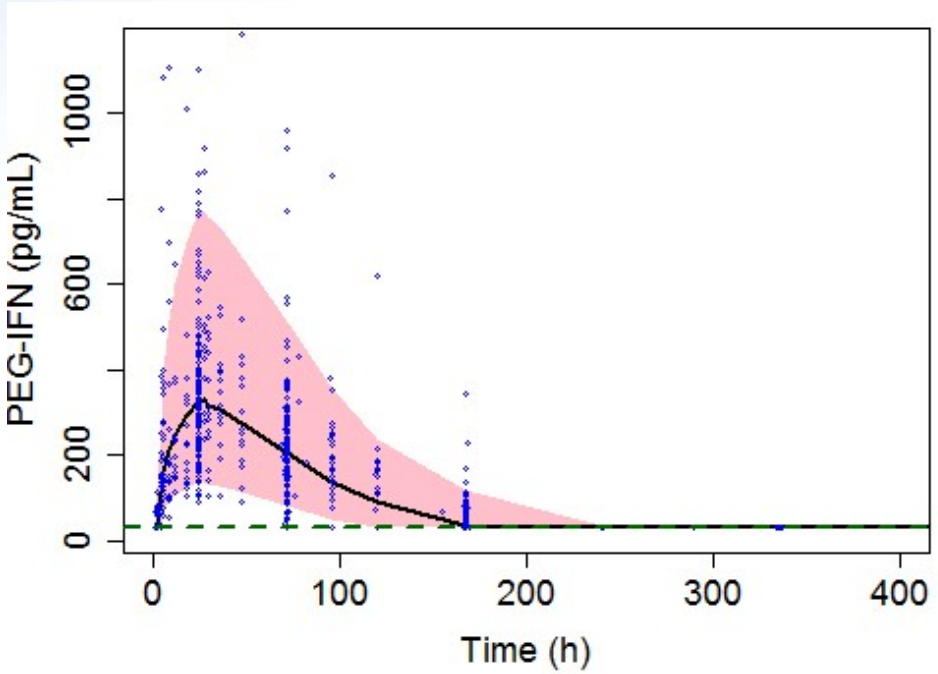
PIP: **P**aediatric **I**nvestigation **P**lan;
HV: healthy volunteer

Population PK Model from Phase 1

- Model:



CL: total body clearance
Ka: absorption rate
Ke: elimination rate
V: volume of distribution



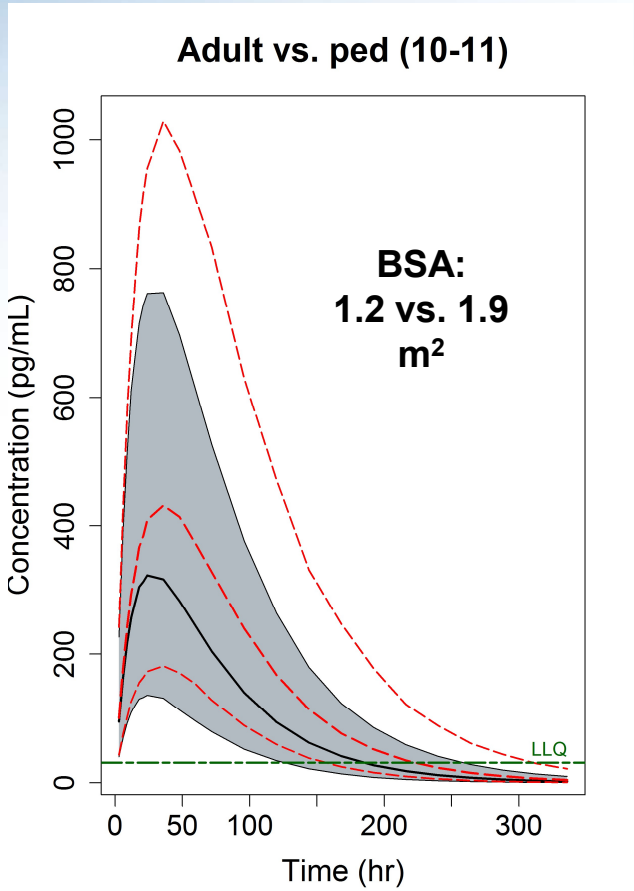
- Covariates:
  - No impact by age, body weight, body mass index, or body surface area
  - Full dose (125 μg) was proposed

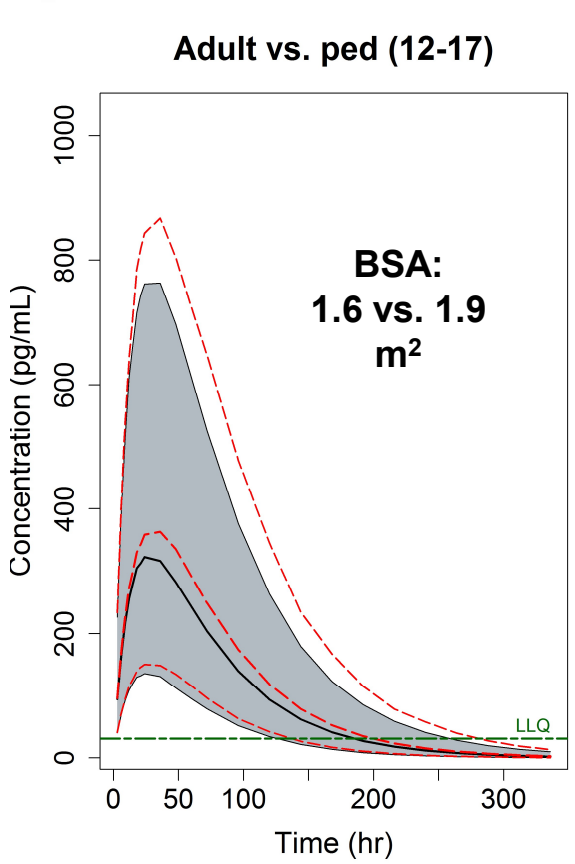
Feedback from PDCO

- Request from PDCO to provide further rationale
  - Reference PEGASYS and PEGINTRON pediatric dosing regimen

Dose Rationale in Pediatric Trial

- **Simulation in peds based on BSA extrapolation**

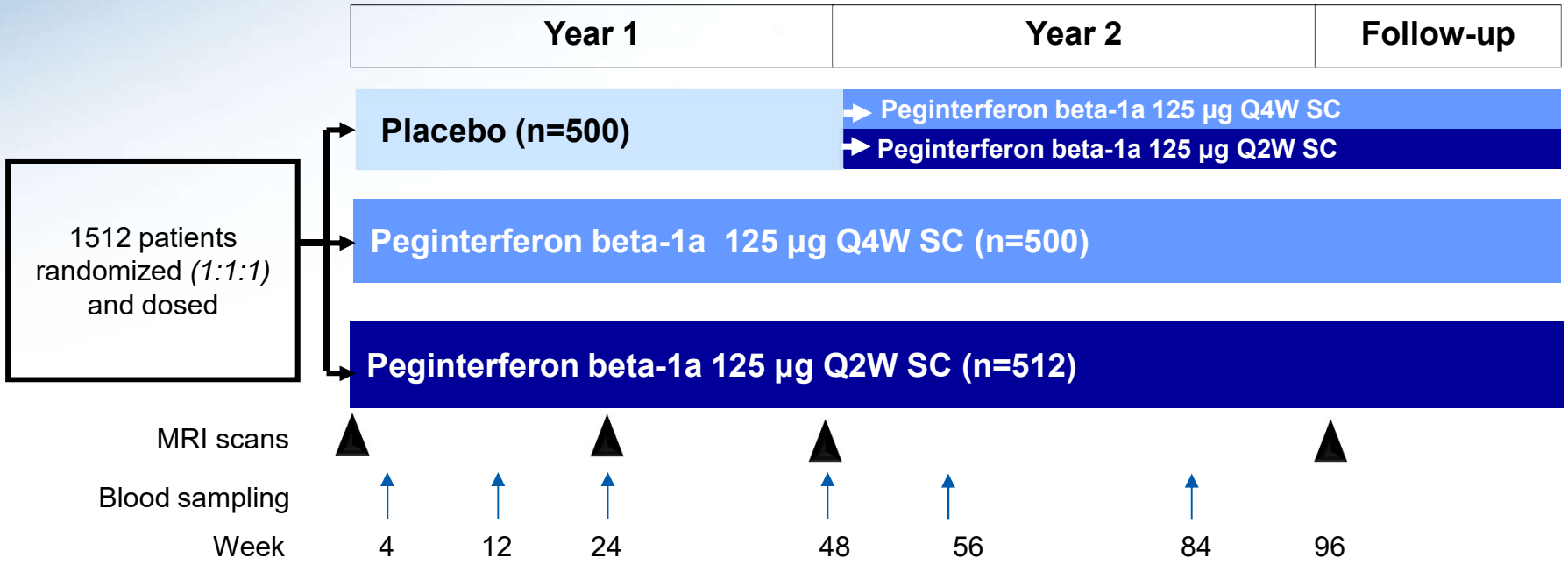




Adult median and [5th, 95th] percentile

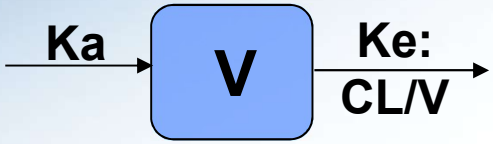
Pediatric median and [5th, 95th] percentile

Pivotal Phase 3 Study Design



Q2W = every 2 weeks; Q4W = every 4 weeks

Final Population PK Model

- Model: 

CL: total body clearance
Ka: absorption rate
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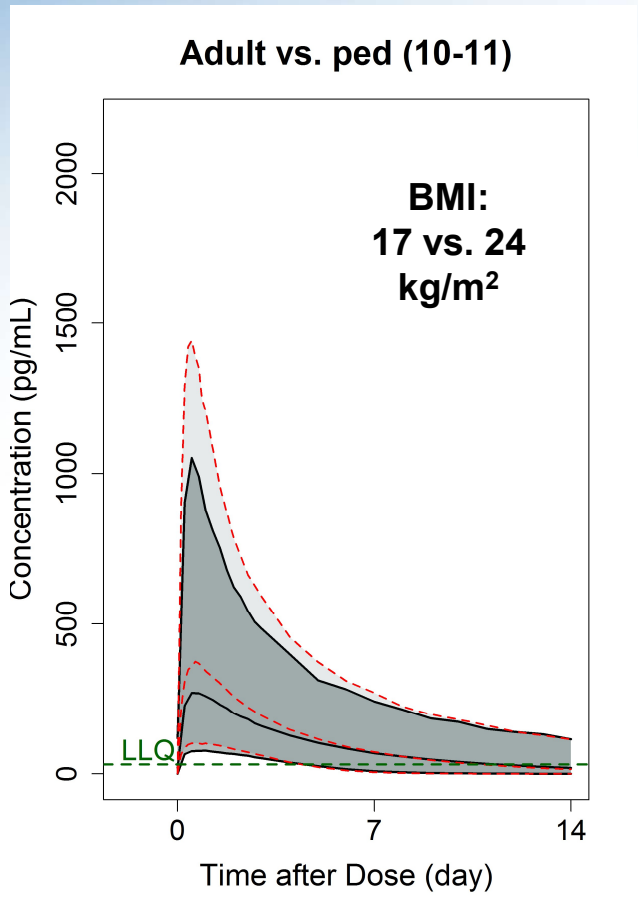
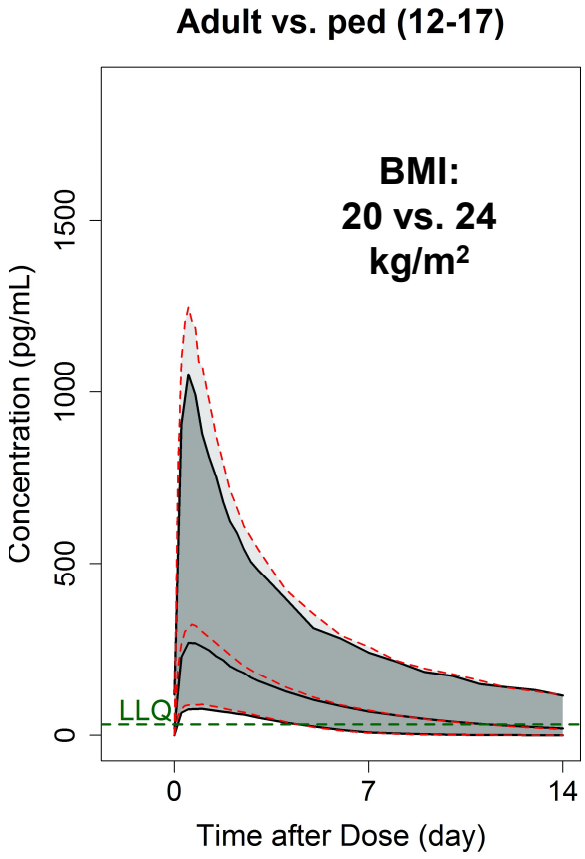
V: volume of distribution

- Covariates:
  - BMI affected both AUC and C_{max}

Final PK Model Simulation for Pediatric Study





Adult median and [5th, 95th] percentile

Pediatric median and [5th, 95th] percentile

Simulation Conclusion

- Model based simulations support full dose of 125 μg in the ongoing pediatric study

Phase 3 Efficacy and Regulatory Request

- 1° Endpoint: annualized relapse rate
  - Placebo: 0.397
  - Every 2 weeks: 0.256 (p=0.0007)
  - Every 4 weeks: 0.288 (p=0.0114)

- Request from EMA on Day 80 and 120 questions to build an exposure-response model
  - **Is there a relationship between exposure and efficacy?**

Model 1: AUC-ARR

- Mathematical Model (negative binomial model/Poisson-Gamma mixture)

$$Relapse_i \sim Poisson(\lambda_i * Duration_i)$$

$$\lambda_i \sim gamma(\alpha, \alpha/\lambda hat_i)$$

$$Log(\lambda hat_i) = log(\lambda 0) + b * AUC_i$$

Relapse$_i$ = *relapse number of subject i*
λ_i = ARR of subject I
λ*hat* = mean of the gamma distribution
Duration$_i$ = study duration in years
α = shape factor of gamma distribution

α/λ*hat* = rate parameter;
λ*0* = baseline ARR
AUC$_i$ = cumulative AUC over 4 weeks for subject i
b = slope for AUC

Hu X, et. al., 2017, JCP

Model 1: AUC-ARR Model

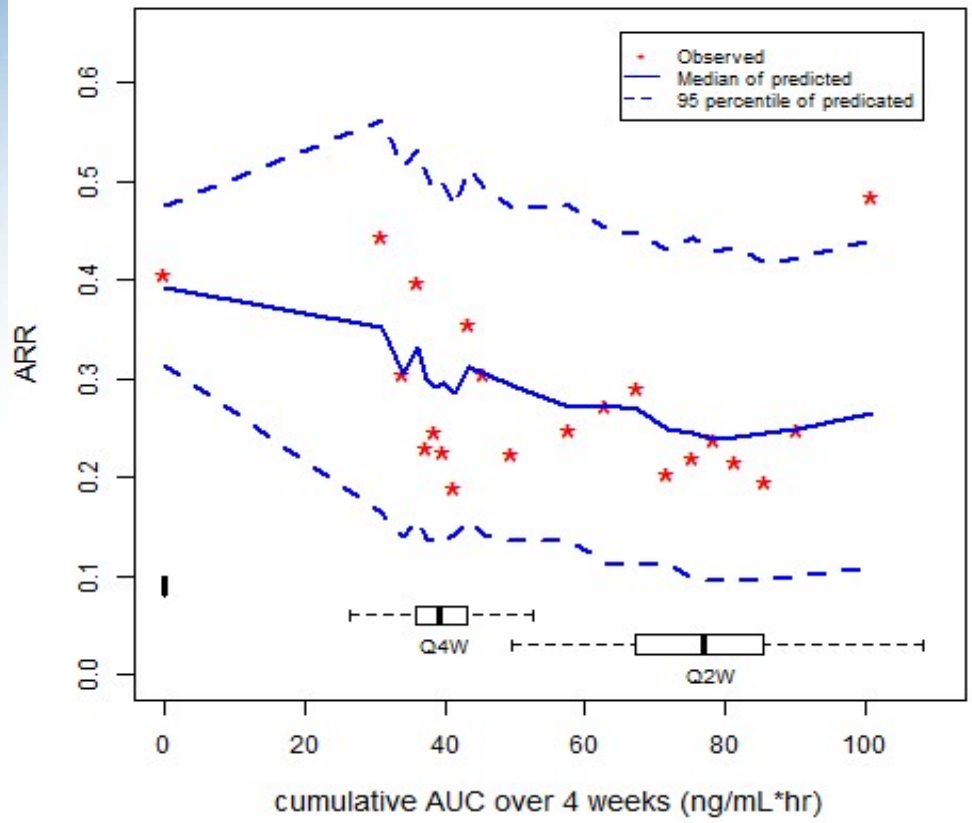
- Final Model

$$\mathbf{Log(\lambda hat_i) = log(0.391) - 0.00518 * AUC_i}$$

- **Greater plegridy exposure of q2W is associated with greater ARR reduction**

Hu X, et. al., 2017, JCP

Relationship between AUC and ARR

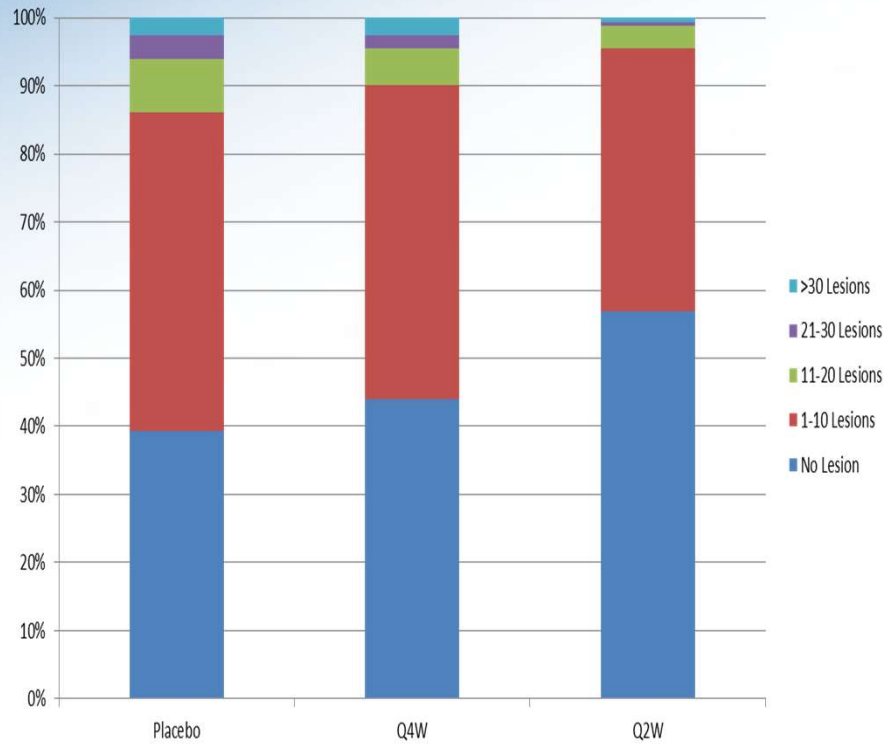


- Observed data aligned with model predicted data
- Correlation between cumulative monthly AUC and ARR
- Steep ARR decline in the AUC range of Q2W, vs a more flat curve in the AUC range of Q2W

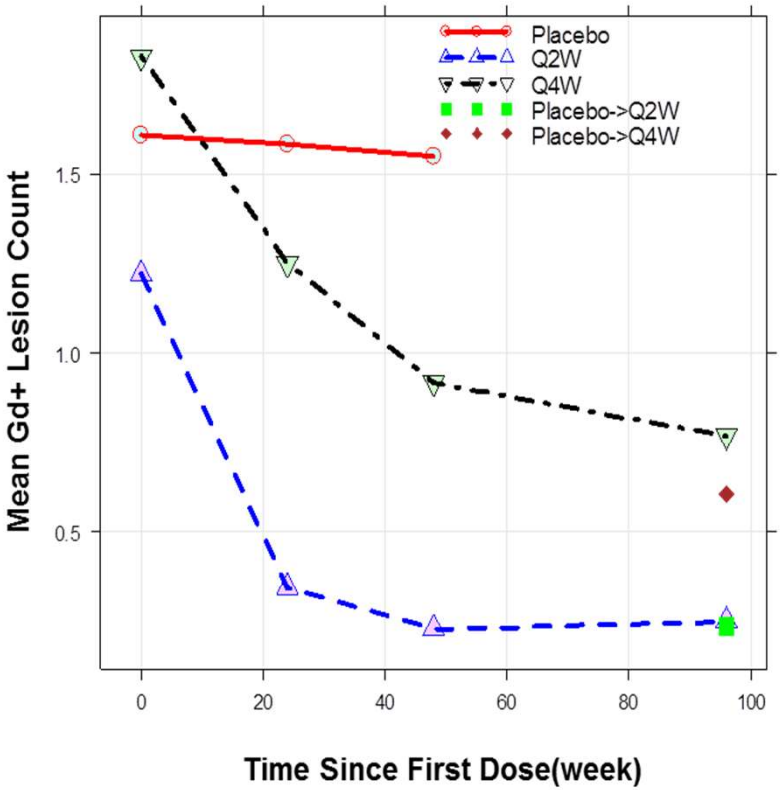
Hu X, et. al., 2017, JCP

Gd+ Lesion Data Examination

Distribution of Total Gd+ Lesion Count on the Trial



Gd+ Lesion Count over Time



Gd+ = gadolinium-enhancing; Q2W = every 2 weeks; Q4W = every 4 weeks

Hang Y., et. al.,2016, JPKPD

Model 2: AUC-Gd+ Lesion Model

- Mathematical Model (A mixture model with negative binomial distribution)

$$\lambda_{i0} = \lambda_{i0,1} * I\{Y = 1\} + \lambda_{i0,2} * I\{Y = 0\}$$

$$Y \sim Bernoulli(1, p)$$

$$\lambda_{i0,1} \sim LN(\mu_1, \omega_1^2),\ \lambda_{i0,2} \sim LN(\mu_2, \omega_2^2),$$

$$\mathrm{P}(Lesion_{ij} = \mathrm{k}) = \frac{\Gamma(\mathrm{k}+\frac{1}{r})}{\Gamma(\mathrm{k}+1)*\Gamma(\frac{1}{r})} * \left(\frac{1}{1+r*\lambda_{ij}}\right)^{\frac{1}{r}} * \left(\frac{\lambda_{ij}}{\lambda_{ij}+\frac{1}{r}}\right)^{\mathrm{k}}$$

Final Model:

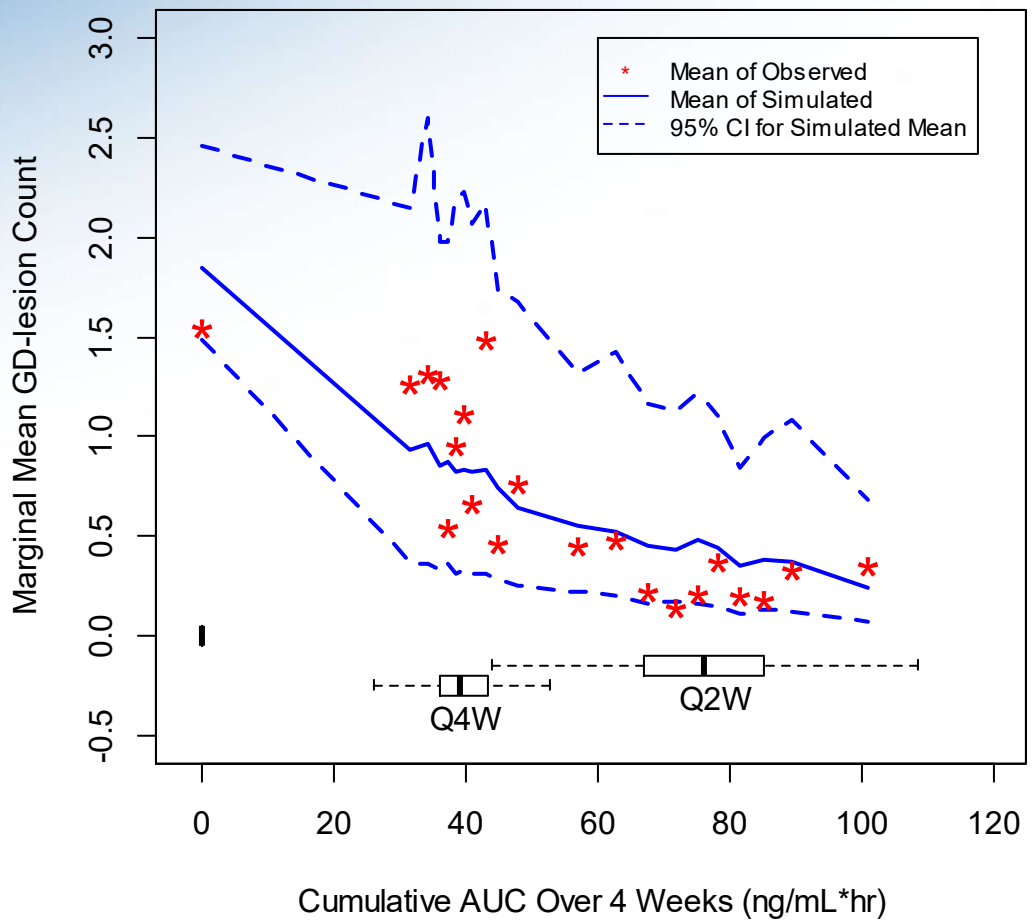
$$\log(\lambda_{ij}) = \log(\lambda_{i0}) - \mathbf{0.0256} * AUC_{ij} * \left(1 - exp\left(-\frac{0.69}{t_{1/2}} * t_{ij}\right)\right)$$

λ_{i0} = Lesion count at baseline for subject i
$\lambda_{i0,1}$ = Baseline lesion count for low activity population;
$\lambda_{i0,2}$ = Baseline lesion count for high activity population;
p = Proportion of subjects with lower baseline lesion activity
Y = low or high activity indicator n
μ_1= Mean lesion count for the low activity population
μ_2= Mean lesion count for the high activity population

$Lesion_{ij}$ = *Gd+ lesion count for subject i at measurement j*;
r = over dispersion factor and can take one of the two values;
b = slope for AUC
AUC_{ii} = cumulative AUC over 4 weeks for subject i
$t_{1/2}$ = half-life of Gd+ lesion count decline

Hang Y., et. al., JPKPD, 2016

Relationship between AUC and ARR



- Observed data aligned with model predicted data
- Correlation between cumulative monthly AUC and Gd+ lesion data
- Steep Gd+ decline in the AUC range of Q4W, vs a more flat curve in the AUC range of Q2W

Hang Y., et. al., JPKPD, 2016

Plegridy dosing regimen in the label

Conclusion from exposure-response analyses

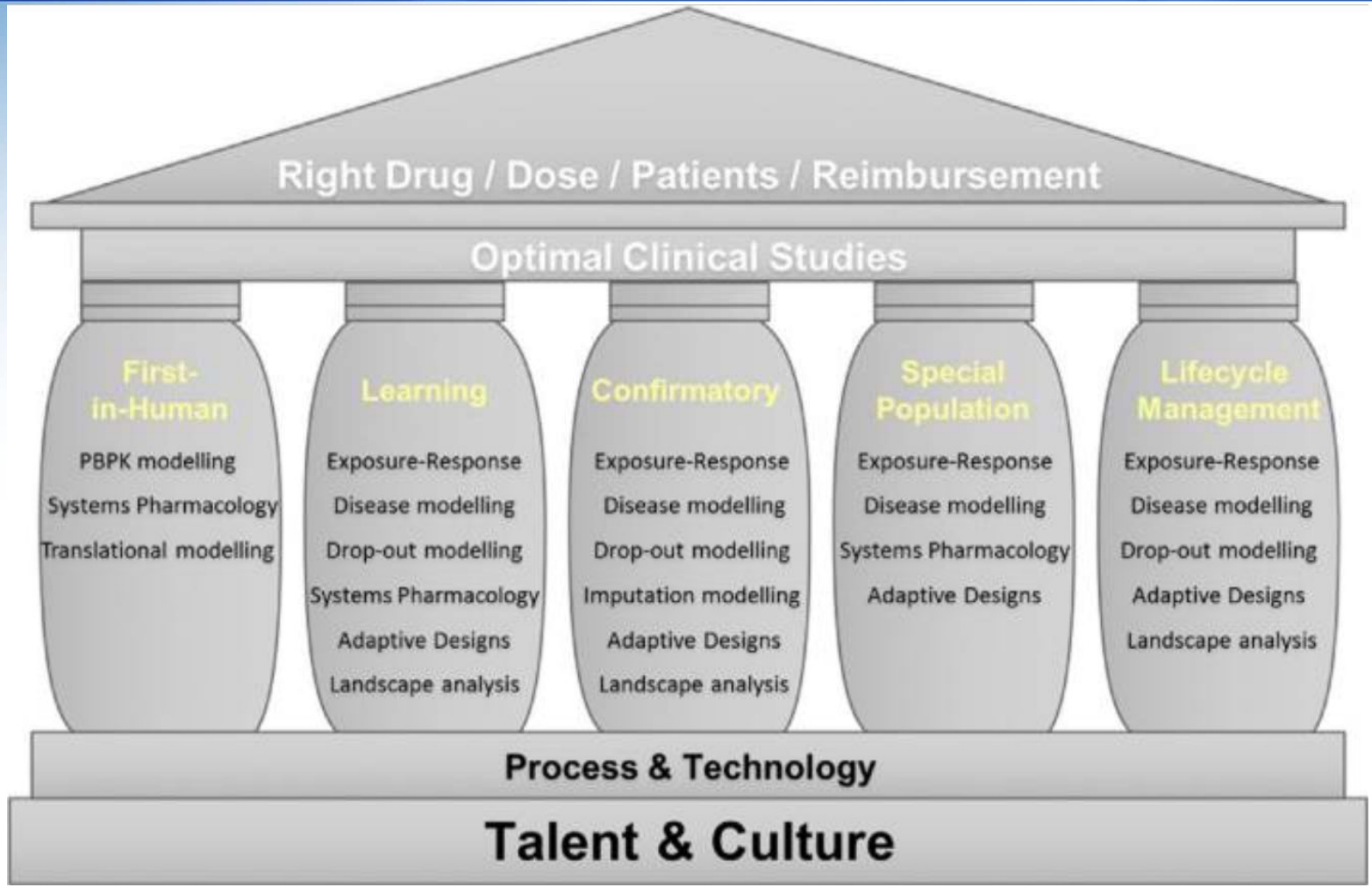
- Greater plegridy exposure in the Q2W group explained the enhanced efficacy as compared to the Q4W group.
- Q2W was the only recommended dosing regimen

Overall Summary

- Quantitative Clinical Pharmacology has been applied to
  - In silico DDI assessment for Drug A provided rationales of DDI study waivers
  - Application of QCP to support Plegridy label and pediatric studies

- Quantitative clinical pharmacology plays a key role in drug development.

Structure of Model Based Drug Development



Kimko H and Pinheiro J. *British Journal of Clinical Pharmacology*. 2015

General Consideration in Reality

Long term plans — Immediate needs

Priority

Significance of Impact

When there's data, there's a best model to describe it

- Weather forecast (with probability)
- Predictive model for successful marriage (≥6 years)*

$$W_{t+1} = a + r_1 W_t + I_{HW}(H_t)$$

$$H_{t+1} = b + r_2 H_t + I_{WH}(W_t)$$

- Hormone surge*

Women's Hormone Equations

$$\frac{dx_i}{dt} = x_i\{K - D(X - M_1 x_i)(X - M_2 x_i)\}, \quad i = 1, \ldots, N, \quad \frac{1}{M_1} + \frac{1}{M_2} < 1, \quad X = \sum_{j=1}^{N} x_j.$$

Men's Hormone Equations

$$\lambda(t) = H_{1,2}\left(\int_{(t-l_{1,1})\vee 0}^{t} X_{Te}(r)\,dr, \int_{(t-l_{2,1})\vee 0}^{t} X_G(r)\,dr\right), \quad \int_{s-l_2}^{s-l_1} X_A(r)\,dr \stackrel{\text{def}}{=} \begin{cases} \frac{1}{l_2-l_1}\int_{s-l_2}^{s-l_1} X_A(r)\,dr, & \text{if } l_2 > l_1 \\ X_A(s-l_1), & \text{if } l_2 = l_1 \end{cases},$$

$$p(s \mid T_G^{k-1}, \lambda(\cdot)) = \gamma \times \lambda(s)\left(\int_{T_G^{k-1}}^{s} \lambda(r)\,dr\right)^{\gamma-1} \exp^{-\left(\int_{T_G^{k-1}}^{s} \lambda(r)\,dr\right)^{\gamma}}, \quad T_L^k = \left[\min_j \left\{T_G^j \mid T_G^j \geq T_L^{k-1} + r_L\right\}\right] + r_L,$$

$$N_G(t) = \sum_{j=1}^{\infty} 1_{\{T_G^j \leq t\}}, \quad N_L(t) = \sum_{j=1}^{\infty} 1_{\{T_L^j \leq t\}}, \quad S_G(t) = H_3\left(\int_{(t-l_{3,1})\vee 0}^{t} X_{Te}(s)\,ds\right) + \xi_G(t), \quad S_{Te}(t) = H_4\left(\mu(t) \times \int_{(t-l_{4,2})\vee 0}^{(t-l_{4,1})\vee 0} X_L(s)\,ds\right) + \xi_{Te}(t),$$

$$S_L(t) = H_{5,6}\left(\sum_{j=0}^{N_L(t)} \int_{(T_L^j - l_{5,2})\vee 0}^{T_L^j - l_{5,1})\vee 0} X_G(s)\,ds \times \Gamma(t - T_L^j), \int_{(t-l_{6,2})\vee 0}^{(t-l_{6,1})\vee 0} X_{Te}(s)\,ds\right) + \xi_L(t),$$

$$d\xi_i(t) = -\delta_i \xi_i(t) + \tau_i(S_i(t))\,dB_i(t), \quad \xi_i(0) = 0, \quad \delta_i > 0, \quad i = Te, G, L,$$

$$A_G^j = \int_{T_G^{j-1}}^{T_G^j} S_G(t)\,dt, \quad A_L^j = \int_{T_L^{j-1}}^{T_L^j} (1 - e^{-\eta(t - T_L^{j-1})}) S_L(t)\,dt, \quad M_i^j = \Psi_i(T_i^{j-1}, T_i^j) \times M_i^{j-1} + A_i^j, \quad i = G, L,$$

$$Z_G(t)\,dt = [\beta_G + M_G^{N_G(t)} \psi_G(t - T_G^{N_G(t)})]\,dt, \quad dX_G(t) = \{-\alpha_G(X_G(t))X_G(t) + Z_G(t)\}\,dt + \sigma_G(X_G(t))\,dW_G(t),$$

$$Z_L(t)\,dt = [\beta_L + M_L^{N_L(t)} \psi_L(t - T_L^{N_L(t)}) + e^{-\eta(t - T_L^{N_L(t)})} + S_L(t)]\,dt, \quad dX_L(t) = \{-\alpha_L(X_L(t))X_L(t) + Z_L(t)\}\,dt + \sigma_L(X_L(t))\,dW_L(t),$$

$$Z_{Te}\,dt = [\beta_{Te} + S_{Te}(t)]\,dt, \quad dX_{Te}(t) = \{-\alpha_{Te}(X_{Te}(t))X_{Te}(t) + Z_{Te}(t)\}\,dt + \sigma_{Te}(X_{Te}(t))\,dW_{Te}(t).$$

*Clio Cresswell, TEDx Sydney Talk 2014

Thank you!