CD&A

Cosentyx in psoriasis

We need(ed) both, exploratory and confirmatory

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2nd EFSPI Workshop on Regulatory Statistics

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→ for disclaimer, see last slide

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Confirmatory & exploratory

We Need Both Exploratory and Confirmatory
Author(s): John W. Tukey
Source: *The American Statistician*, Vol. 34, No. 1, (Feb., 1980), pp. 23-25
Published by: American Statistical Association

Summary

- Development program relied on complementary approaches: exploratory pharmacometric analysis and confirmatory statistics
- Simulations based on pharmacometric model allowed to go into phase III with two dosing regimens that had not been tested previously
- Efficacy and safety (and model-based predictions) for these regimens were confirmed in phase III
- Secukinumab (Cosentyx) has since been approved for moderate to severe psoriasis in US, EU and many other countries

Comprehensive development program

Nine studies in ~4,000 psoriasis patients

Phase	Study*	Description	Secukinumab Dosing Regimen	Number of Psoriasis Patients
Ph II	A2102	Proof of concept (i.v.)	1 x 3 mg/kg	570
	A2220	Low dose-ranging (s.c.)	25, 75, or 150 mg (1x or monthly)	
	A2212	High dose ranging (i.v.)	3 or 10 mg/kg (1x or 3x)	
	A2211	Regimen finding: with/without loading (s.c.)	150 mg (1x, monthly, or "early")	
Ph III	A2302	Placebo controlled	?	3369
	A2303	Placebo and etanercept controlled		
	A2308	Prefilled syringe		
	A2309	Autoinjector		
	A2304	Fixed vs. start-of-relapse		

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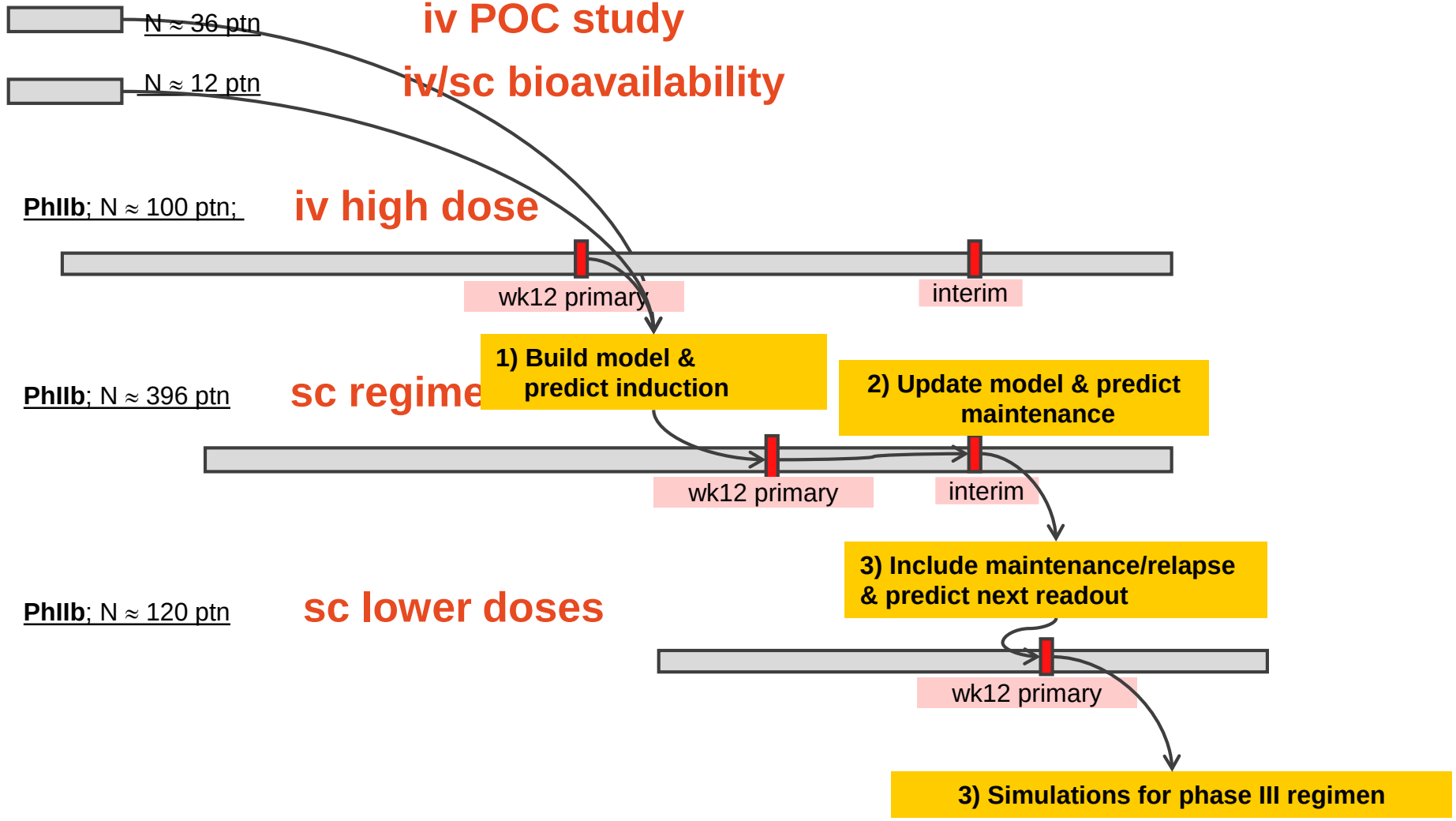
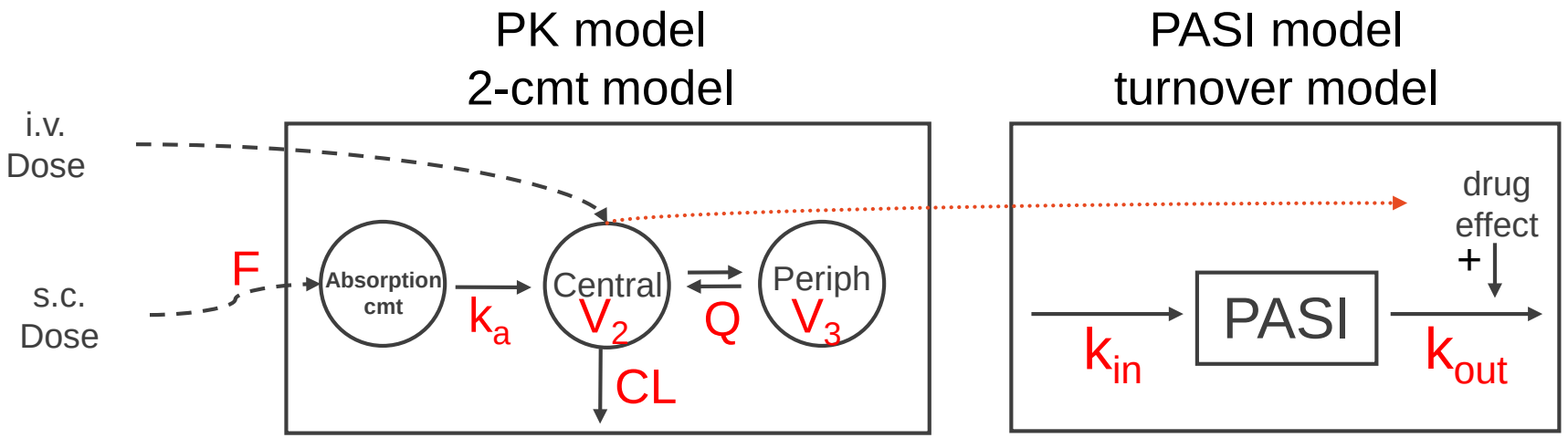
Iterative modeling & predictions to choose phase 3 dosing regimens



D-E-R relation described by pharmacometric PK/PD model

Dose → Exposure → Response



- Model describes dose-exposure-response relationship by compartments (using differential equations) and mixed effects (to characterize variability)
- Model validation by goodness-of-fit, visual predictive checks, and prospective prediction

Phase 2 data made modeling necessary and feasible

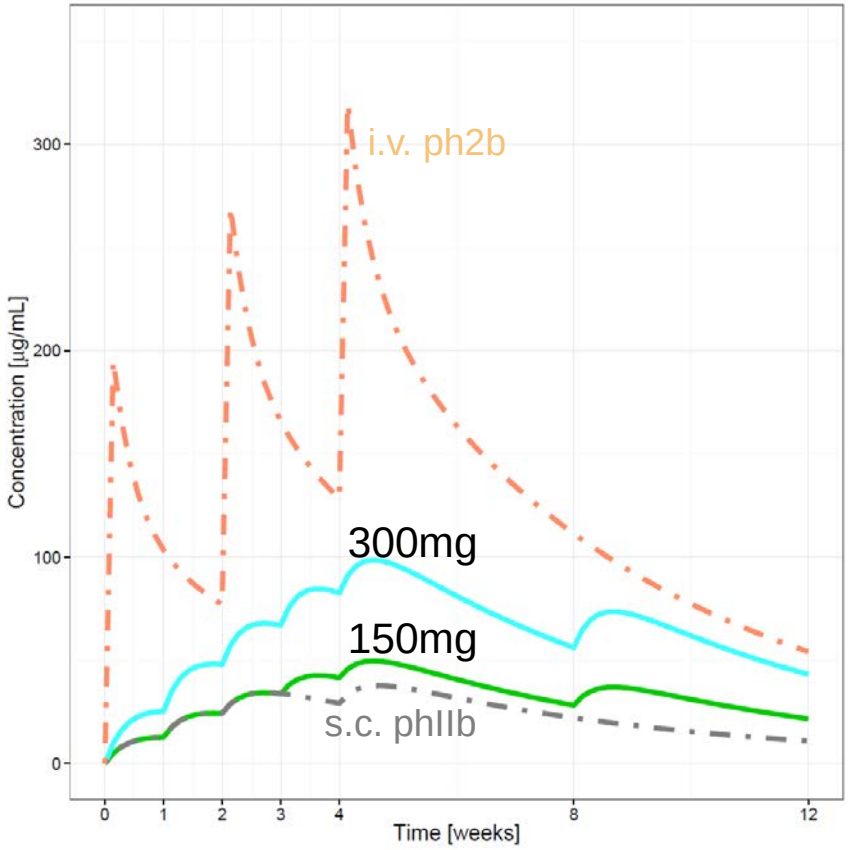
Program benefit from modeling

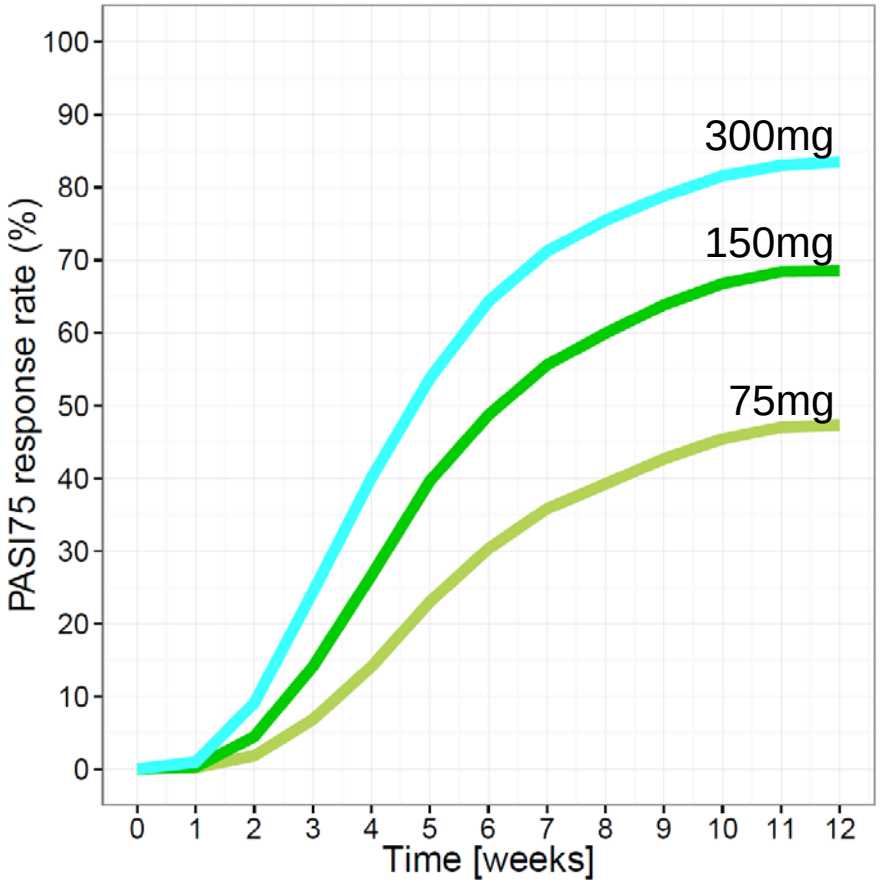
- Bridging across routes, doses, regimens, studies
- Primary endpoint (wk 12) not at steady-state & delay in response
- Optimizing onset, maximum response, maintenance
- Combinatorial optimization of complex regimens not feasible in studies

Modeling benefit from program

- Well-behaved endpoint
- Wide dynamic range of inputs and exposure
- Staggered studies allow iterative modeling building and qualification

Predictions suggested optimized performance for selected regimens

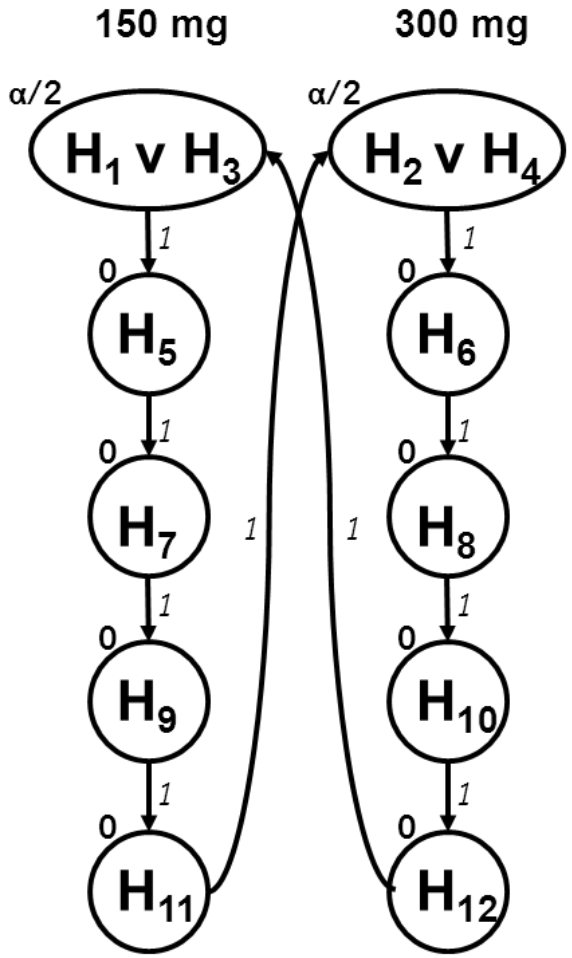




Various endpoints to be included in Phase 3 trials for competitive labeling

Endpoint	Measure
Co-primary Endpoints	**Psoriasis Area and Severity Index (PASI) 75 response** **Investigator Global Assessment: clear or almost clear skin**
Key Secondary Endpoints	**PASI 90 response** **Psoriasis Patient Diary: itch, scaling, pain**
Important Secondary Endpoints	**PASI 100 response** **Dermatology Life Quality Index (DLQI)**

Endpoints ordered by clinical importance in Phase 3 testing strategy



PASI 75 and IGA 0 or 1 response at Week 12 superiority versus placebo

PASI 90 response at Week 12 superiority versus placebo

Psoriasis Diary item pain at Week 12 superiority versus placebo

Psoriasis Diary item itch at Week 12 superiority versus placebo

Psoriasis Diary item scaling at Week 12 superiority versus placebo

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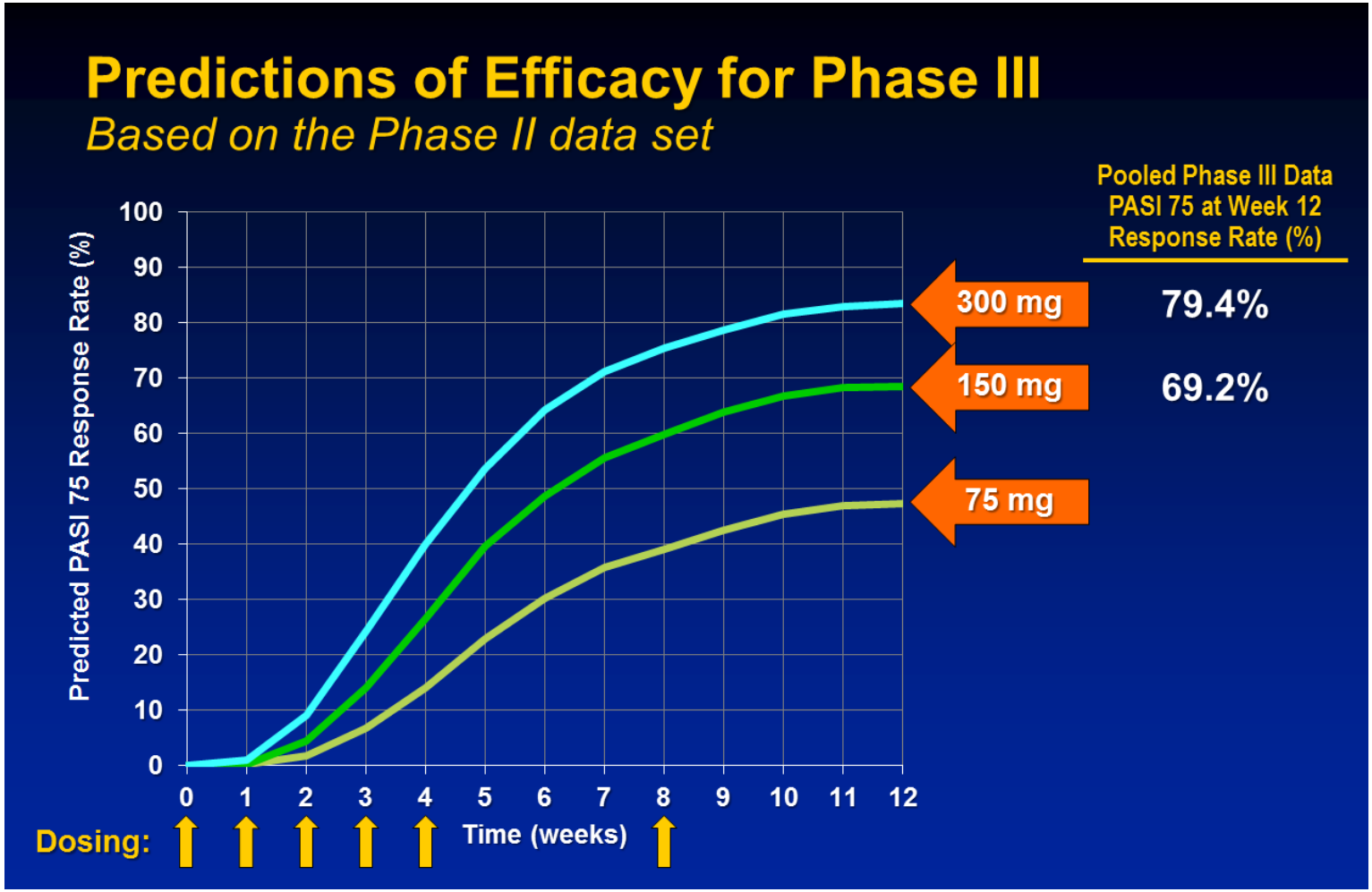
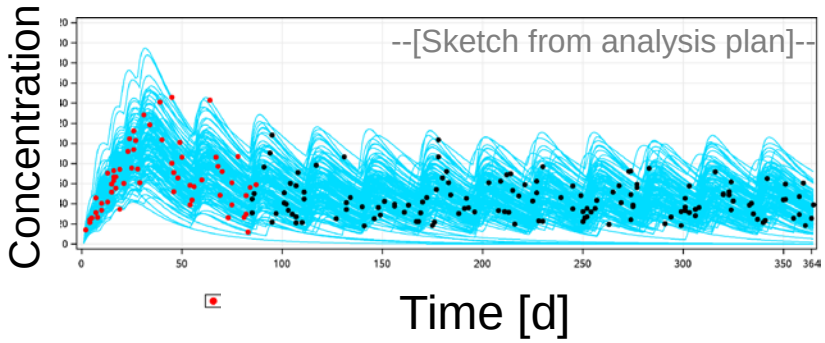
Confirmation of predictions



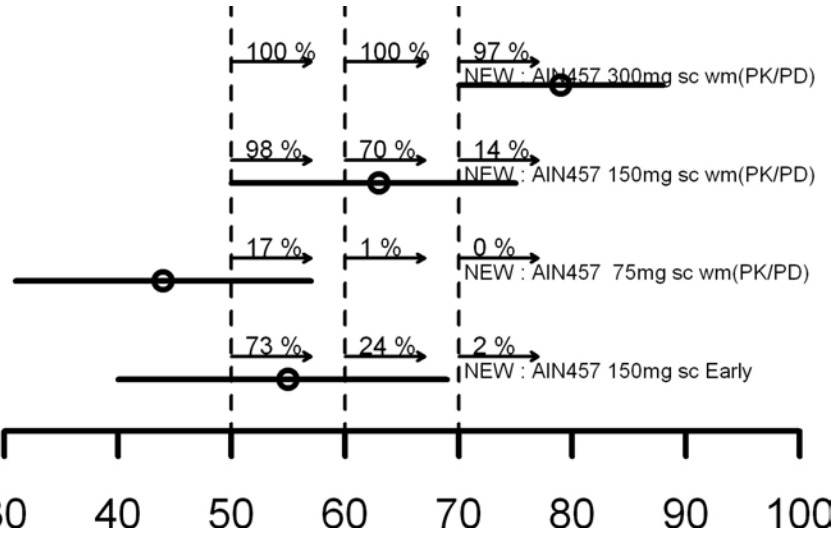
Further applications of PKPD modelling: exposure-AE, PoS calculations

- Exposure-AE



Nasopharyngitis (PT), 300mg group

- Probability of success



Collaboration

How to make it work

- Learn
- Share information / include
- Be open-minded
- Respect

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Aspiring to become more versatile,
quantitative drug developers

Thank you

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