Model-based development of the secukinumab dosing regimen in psoriasis

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Ackn.: Secukinumab team, PMX modeling & programming

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Model-based regimen design of secukinumab

- Model-based analysis of phase I / II data allowed design of phase III through prediction of alternative regimens
  → Two predicted regimens which had not be tested previously were chosen for phase III
- 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 ≥ 60 countries

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Secukinumab as treatment in psoriasis

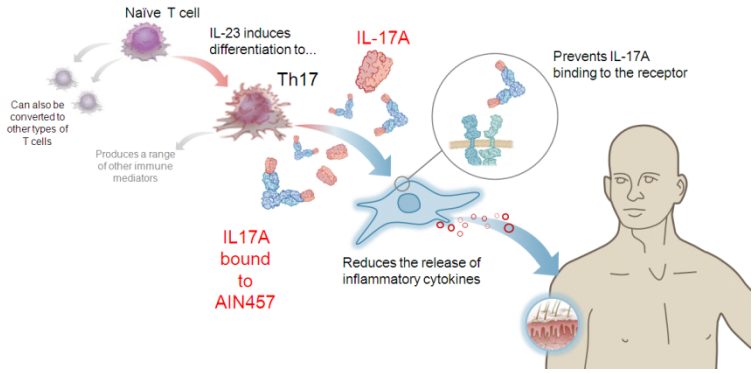
Secukinumab

Human mAb against IL-17A

Neutralizes human IL-17A potently, in vitro and in vivo

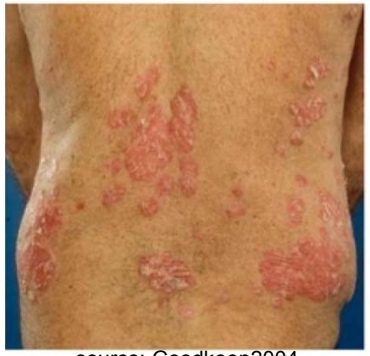
New mode of action to intervene in autoimmune diseases

Terminal half-life ~27 days



Psoriasis

- *Chronic auto-inflammatory skin disease*
- *Affects ~2-3% of population*
- *Impacts quality of life*



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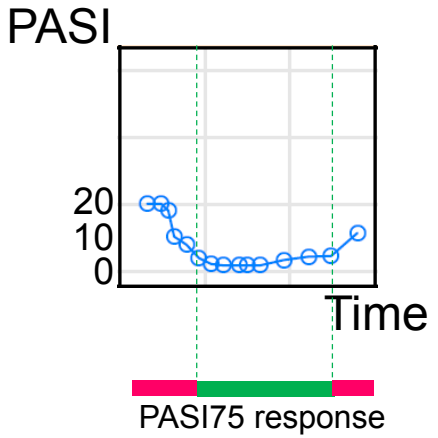

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Comprehensive phase II program

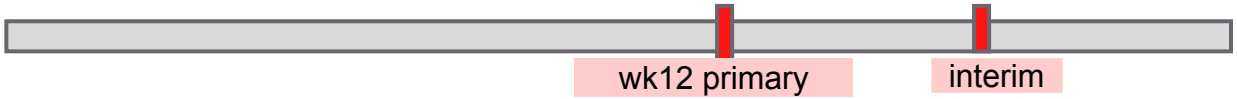
How to select phase III regimens based on comprehensive phase II?

S1; N ≈ 36 ptn — **iv POC study** — 3 mg/kg

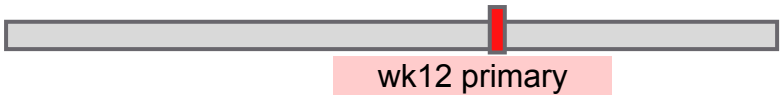
S2; N ≈ 12 ptn — **iv/sc bioavailability** — 1 mg/kg, 150mg

PhIIb/S1; N ≈ 100 ptn; **iv high dose** — 3 mg/kg, 10mg/kg, 3x10mg/kg

PhIIb/S2; N ≈ 396 ptn **sc regimen** — 150mg, 150mg monthly, 4x150mg loading



PhIIb/S3; N ≈ 120 ptn **sc lower doses** — 25mg, 25mg monthly, 75mg monthly, 150mg monthly



Phase III

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Phase II program ↔ modeling

Program benefit from modeling

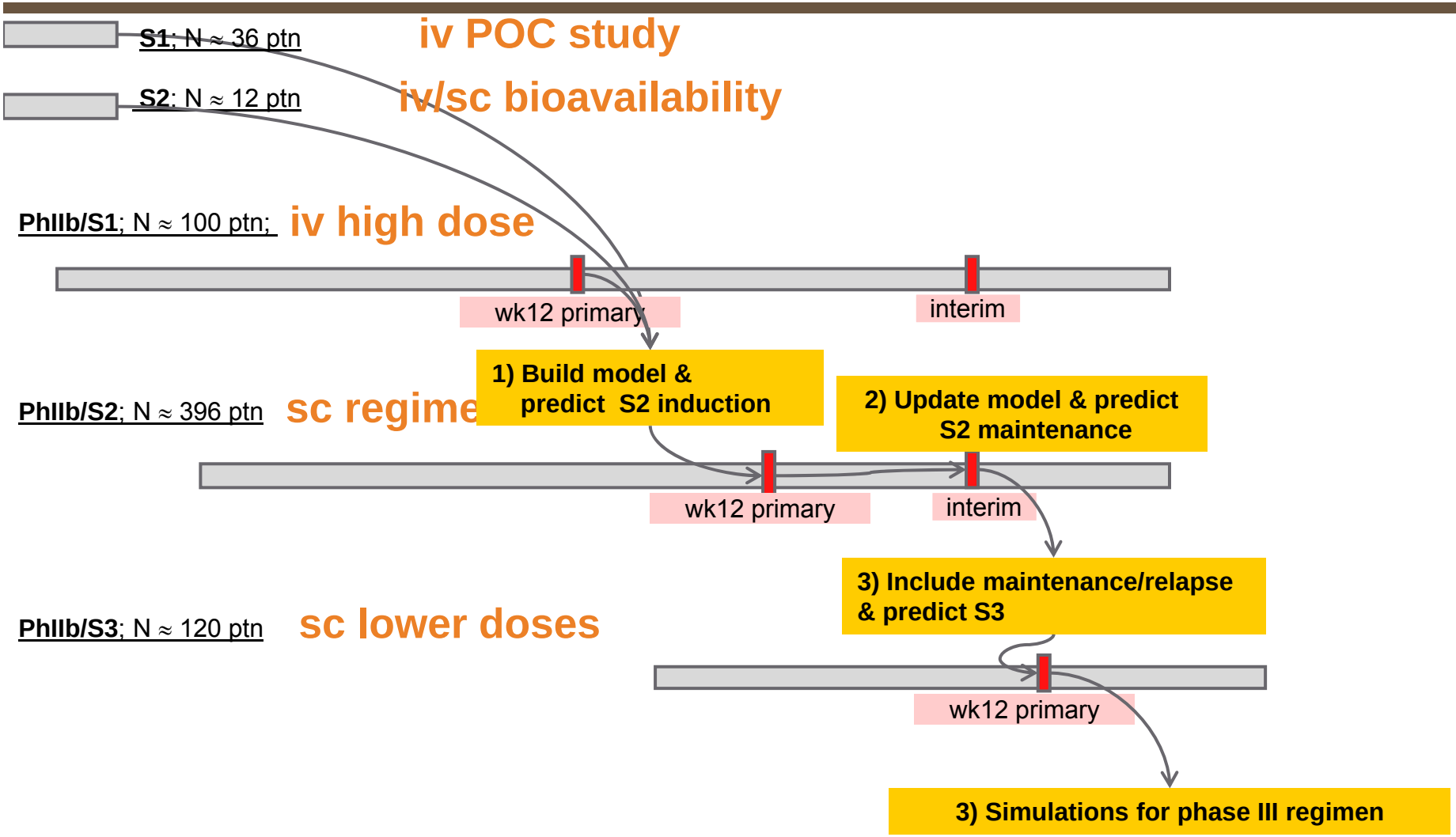
- Bridging across routes, doses, regimens, studies
- Primary endpoint (wk 12) not at steady-state & delay in response
- Optimizing onset, maximum response, maintenance
- Combinatorial optimization of complex regimens not feasible in studies

Modeling benefit from program

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

Comprehensive phase II program

Iterative modeling allowed confident choice of phase III regimens



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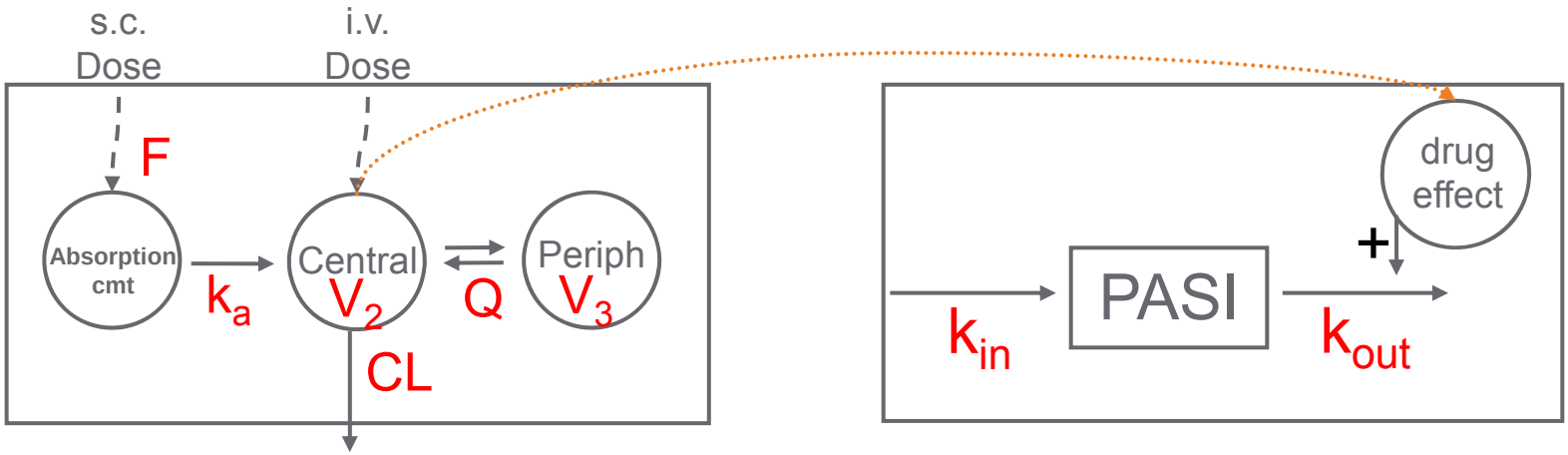
Pharmacometric model

PK model
2-cmt model

PASI model
turnover model



- Model alternatives
- Placebo
- Covariates

- Model validation
  - Goodness-of-fit
  - VPCs
  - Prospective prediction

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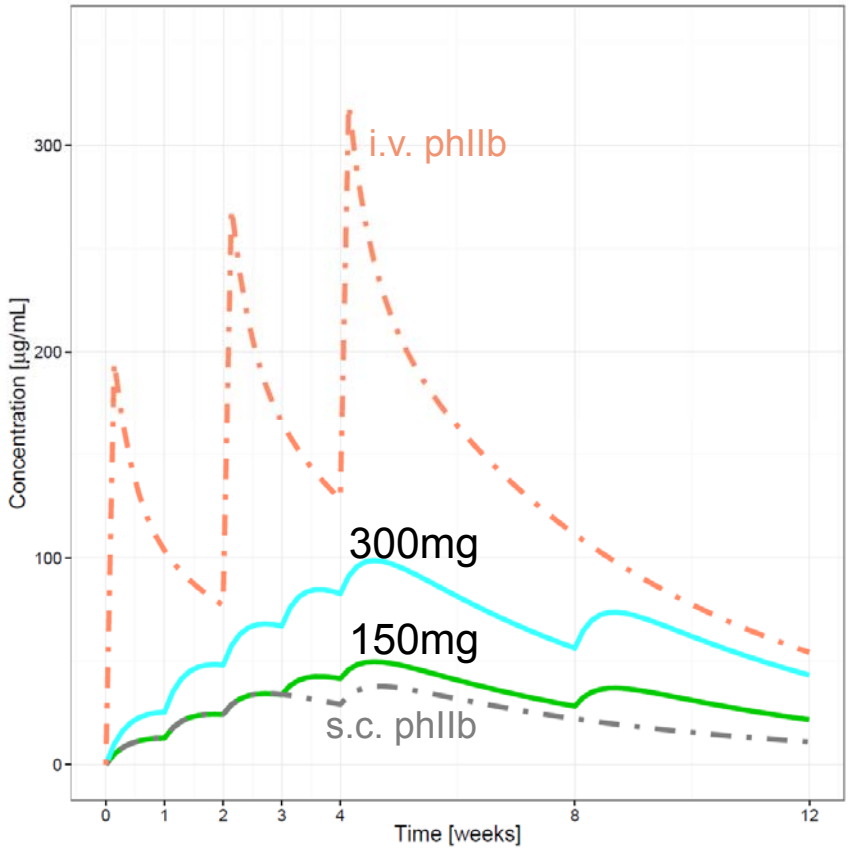
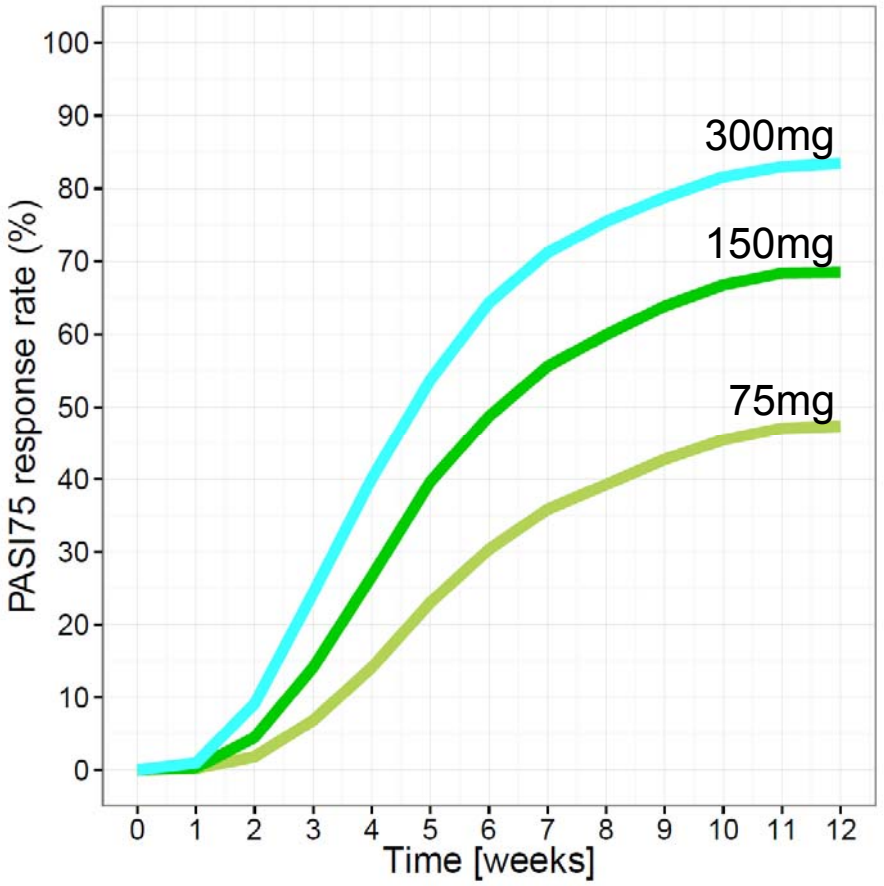
Model-based design of a new regimen

Phase III: 150mg or 300mg given at weeks 0, 1, 2, 3, 4, 8, 12 +q4wk





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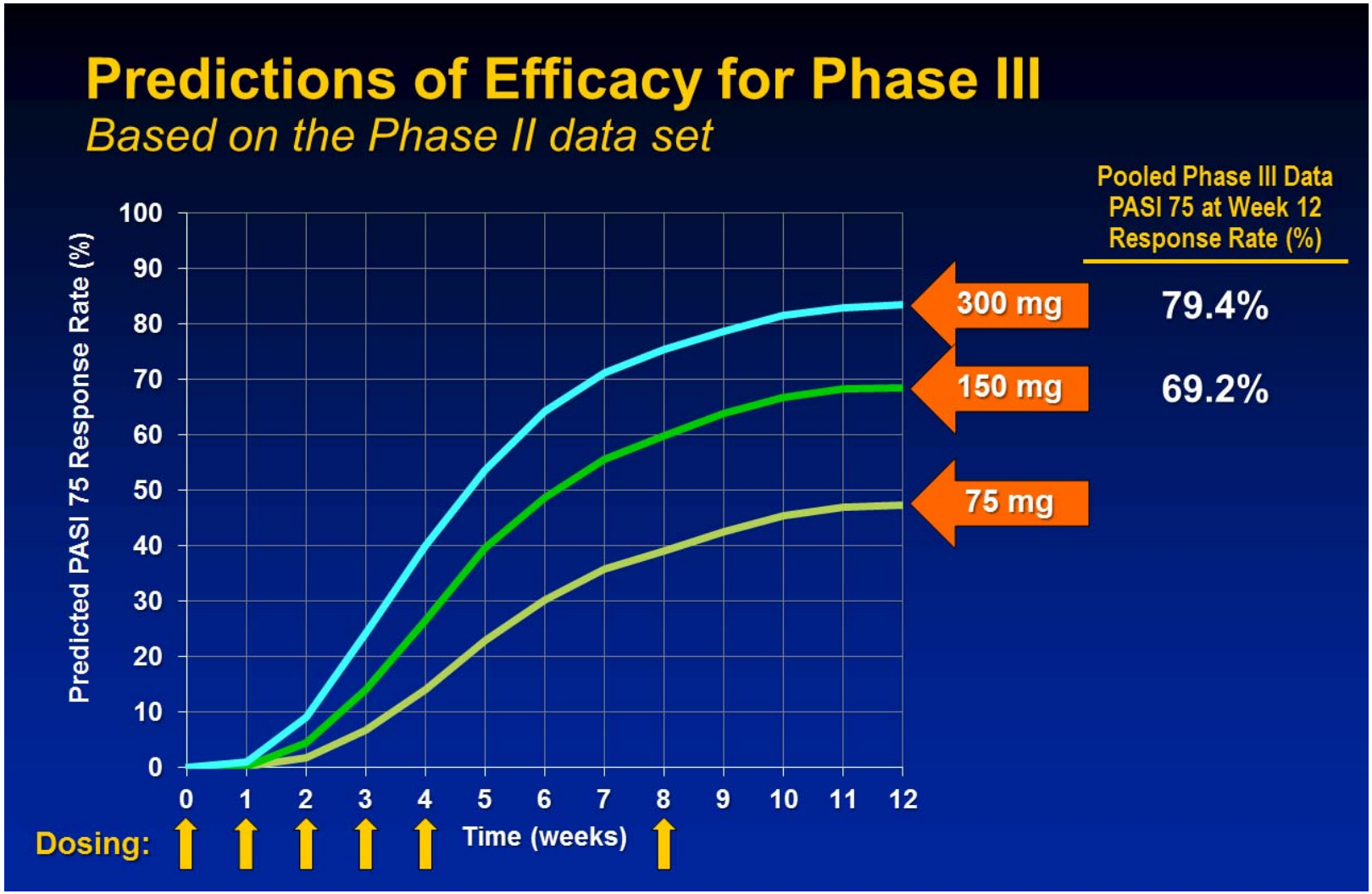
Confirmation of predictions in phase III studies



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Conclusions

- Model-based analysis of phase I/II data allowed design of phase III through prediction of alternative regimens
  → Two predicted regimens which had not be tested previously were chosen for phase III
- 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 ≥ 60 countries
- Model allowed many follow-up questions to be addressed such as a best maintenance therapy