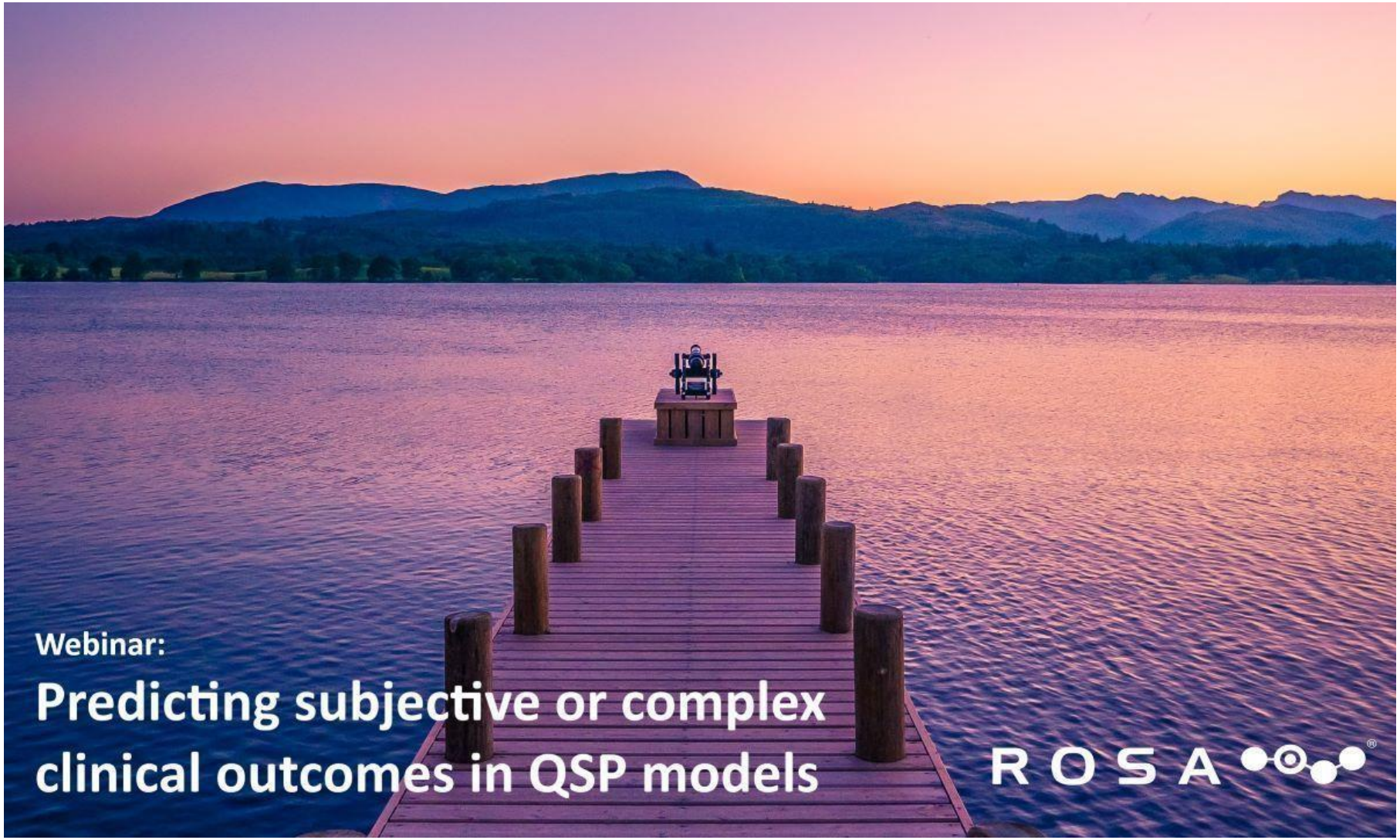

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Senior Scientist
Rosa & Co. LLC

ROSA

May 12th, 2021

The Challenge

Use Quantitative Systems Pharmacology (QSP) models to make critical decisions!

Clinical Trial Optimization

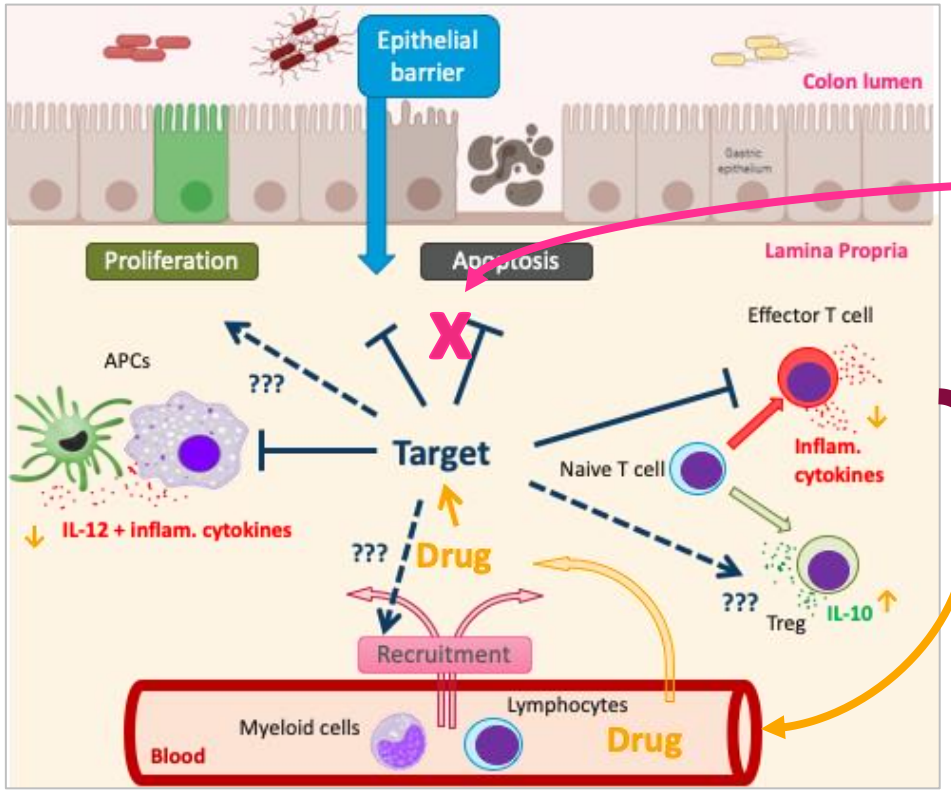
Target Prioritization

Drug MOA for FDA IND Filing

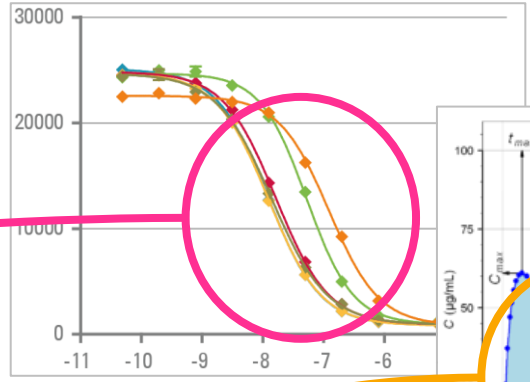
GO/No GO Decision

QSP models are great tools to integrate pre-clinical and PKPD data and predict mechanistic outcomes.

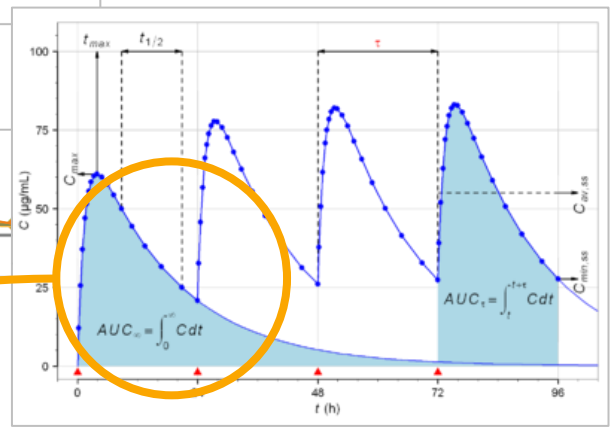
Scientific Understanding



Preclinical Evidence



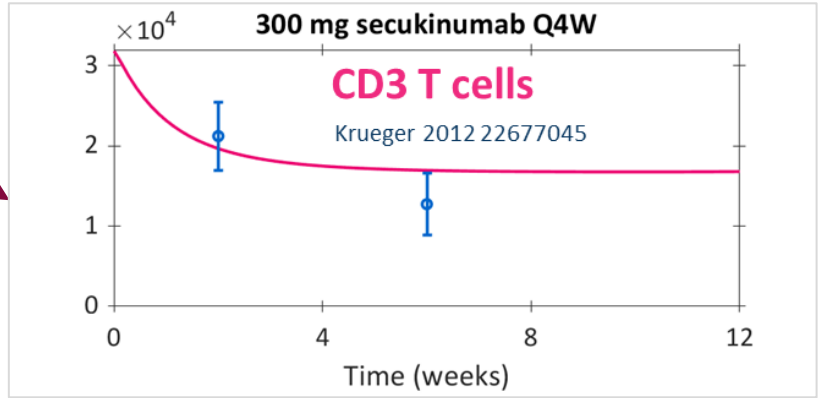
Drug PK



Alfie↑↓© (Helmut Schütz)

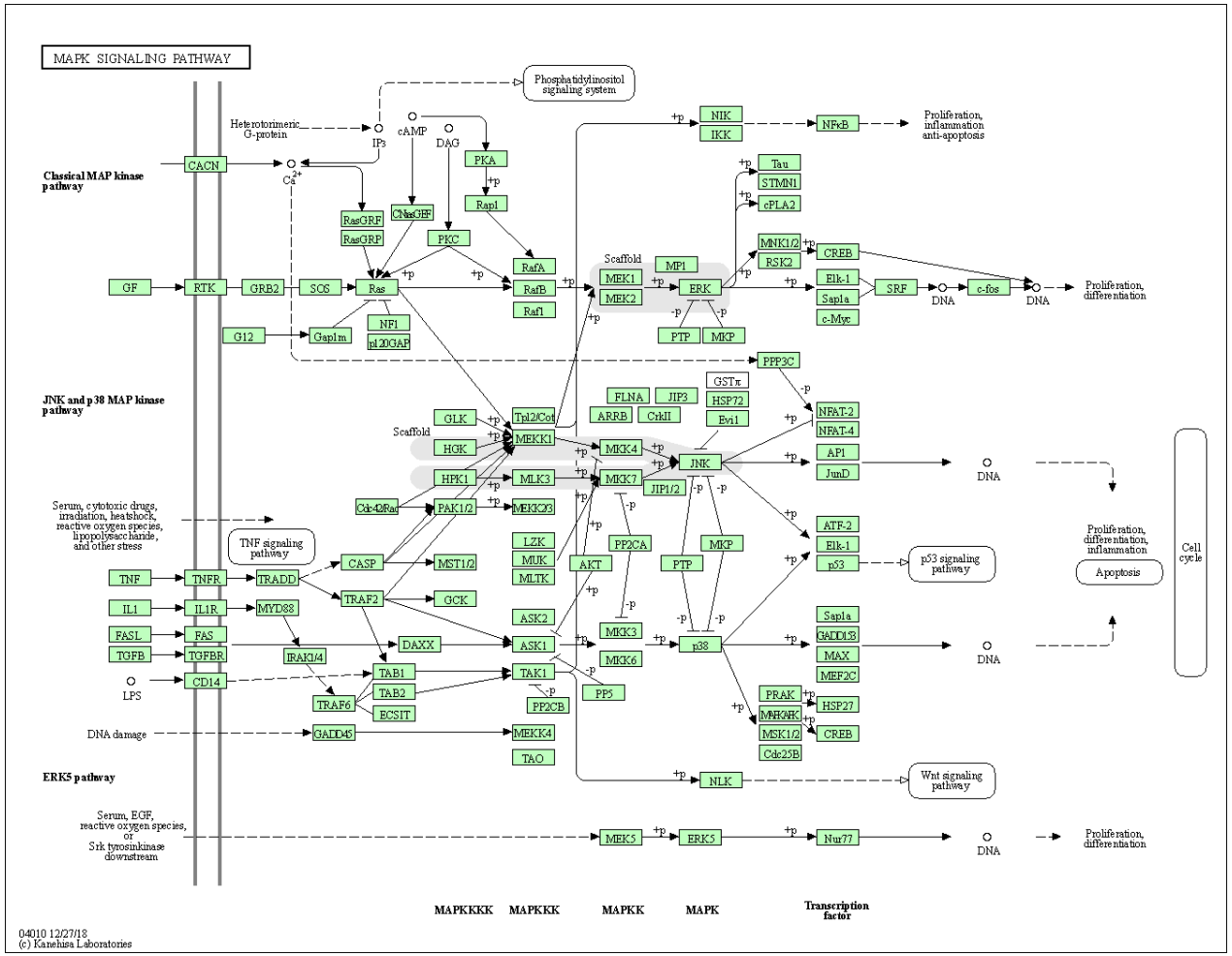
Mechanistic representation informed by in vitro, pre-clinical, and clinical data, all integrated into one modeling platform.

Predictions for cell or mediator specific outcomes



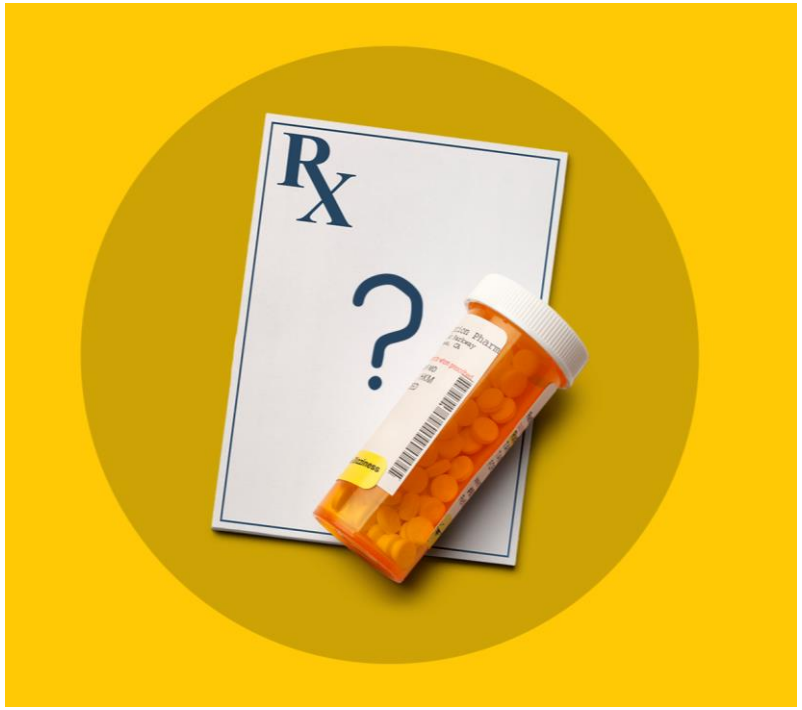
What is the main goal?

Comprehensive quantitative mapping?



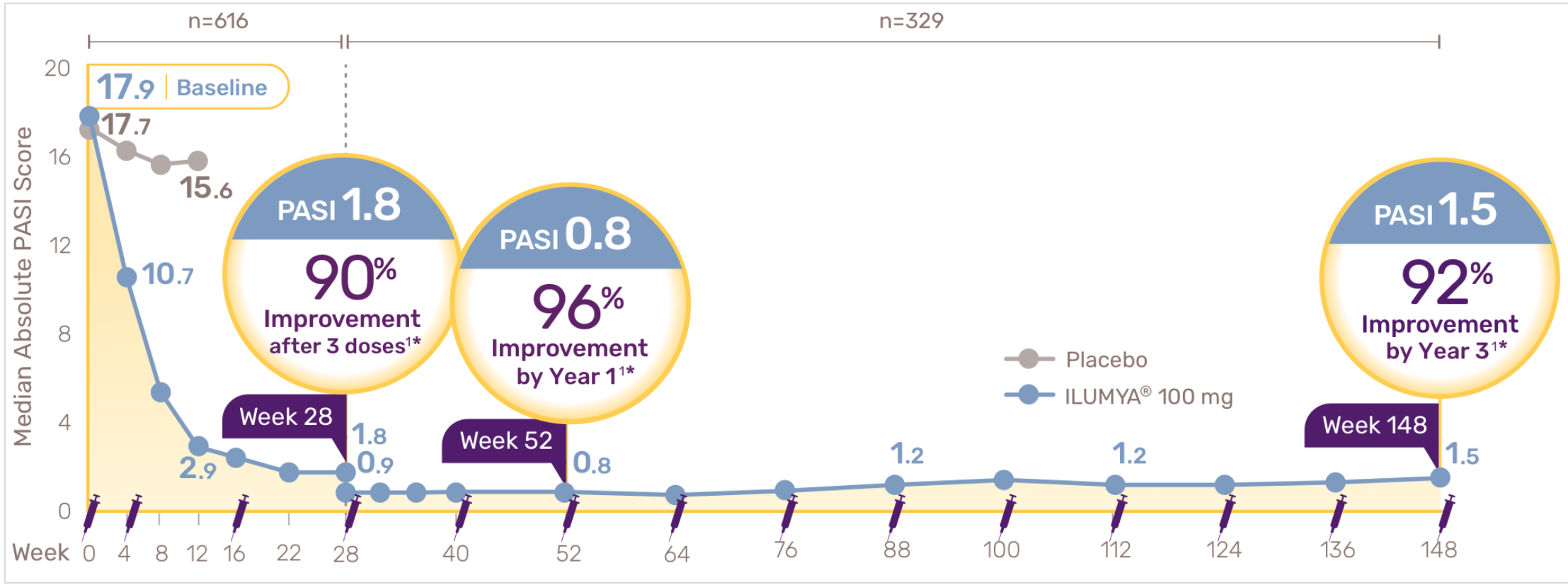
OR

What is the **best drug for me**, Doctor?



Clinicians and regulators rely on various clinical scores to evaluate drug efficacy.

Change in Psoriasis Area & Severity Index (PASI)



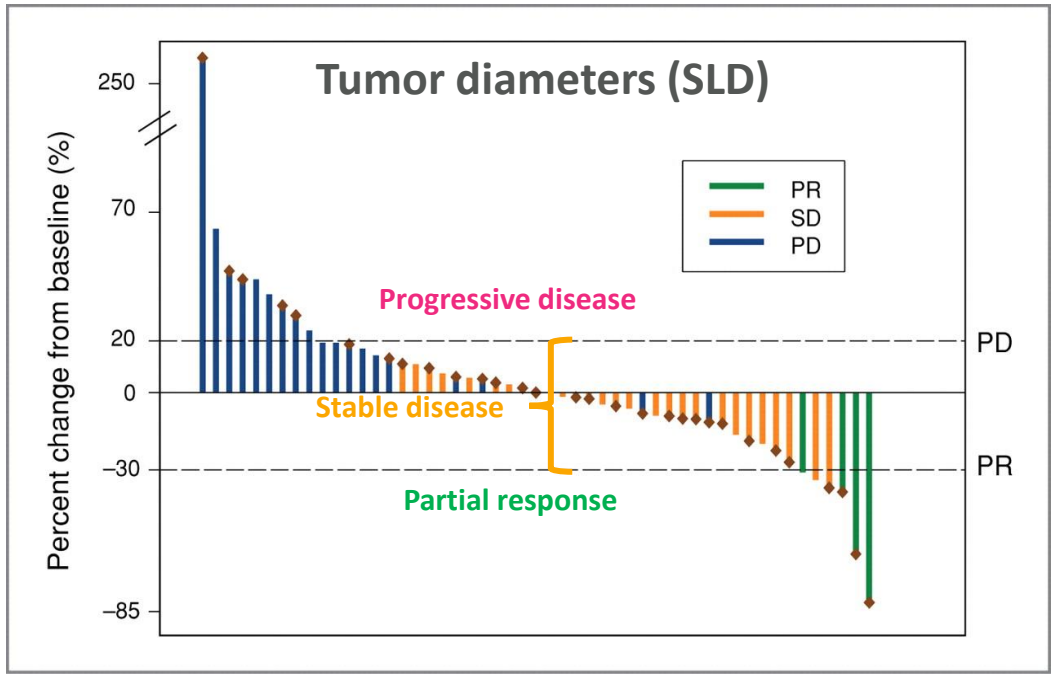
https://www.ilumyapro.com/ilumya-results/

Some clinical endpoints are relatively straightforward to implement with precise, quantitative definitions.

Robarts histology score (colitis)

RHI = 1 × chronic inflammatory infiltrate level (4 levels)
+ 2 × lamina propria neutrophils (4 levels)
+ 3 × neutrophils in epithelium (4 levels)
+ 5 × erosion or ulceration (4 levels after combining Geboes 5.1 and 5.2).

RECIST response criteria (cancer)



DAS28, SDAI score (rheumatoid arthritis)

Formulae to calculate the different DAS and SDAI score

Score	Formula
DAS28	0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.70*ln(ESR) + 0.014*pt global VAS
DAS28-3	[0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.70*ln(ESR)]*1.08 + 0.16
DAS28-CRP	0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.36*ln(CRP+1) + 0.014* pt global VAS + 0.96
DAS28-CRP-3	[0.56*sqrt(28TJC) + 0.28*sqrt(28SJC) + 0.36*ln(CRP+1)] * 1.10 + 1.15
SDAI	28TJC + 28SJC + CRP/10 + pt global VAS/10 + phys global VAS/10
CDAI	28TJC + 28SJC + pt global VAS/10 + phys global VAS/10

Quantitative biomarker (# of affected joints, CRP levels)

Subjective measurement (VAS: visual analog scale)

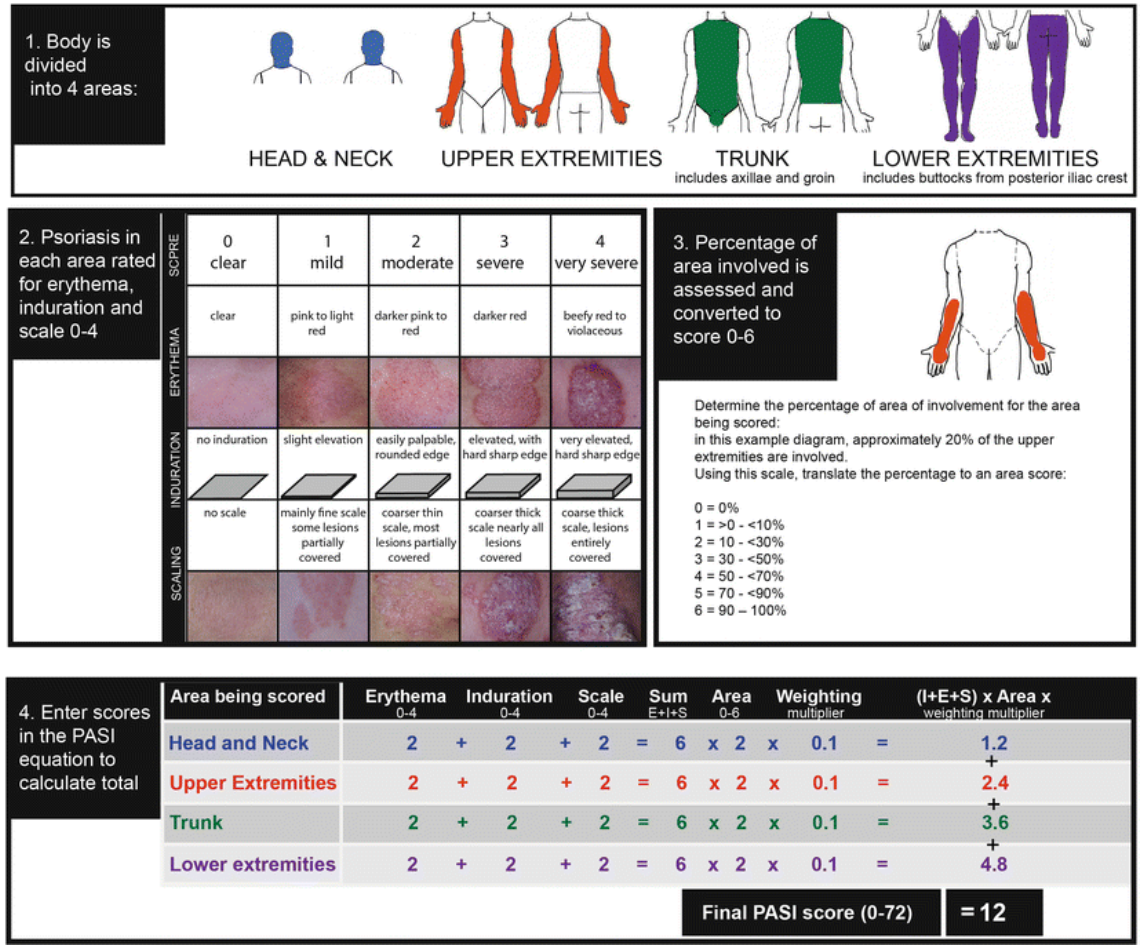
Vander Cruyssen 2005 PMID 16207323

Other disease scores are more complex involving multiple objective and subjective measurements.

PASI (psoriasis)

SCORAD, EASI (atopic dermatitis)

SLEDAI, SJS, BILAG (lupus)



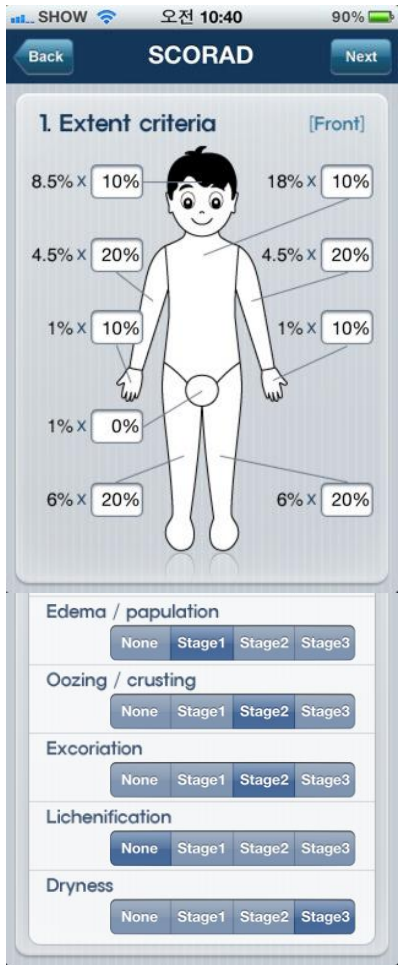


Table 1. Eczema area and severity index: calculation for patients 8 years of age and older[1]

Body region | EASI Score[2,3]

Head
Upp
Trun
Low
EAS

[1]For upp
[2]E=
[3]Wh
2=
6=

SLE ACTIVITY INDEX SCORE (SIS)

Clinical variables		Laboratory variables	
1. Fatique	1	22. ESR 25–50 mm/h	1
2. Temperature >38°C	1	ESR >50 mm/h	2
3. Arthralgia	1	23. DNA binding <50%	1
4. Arthritis (joint effusion)	1	DNA binding ≥50%	2
5. Myalgia	1	24. Mild hypocomplementemia	
6. Muscle weakness	2	(CH50 80–150 U/mL) ∫	1
7. Serositis (pain)	1	Severe hypocomplementemia	
8. Serositis (friction rub/X ray/sonography)	2	(CH50 <80 U/mL) ∫	2
9. Vasculitis (minor*)	1	25. CPK >100, aldolase >10 U/mL	2
10. Vasculitis (major †)	3	26. LE anticoagulant	1
11. Bulluous skin lesions	3	27. Proteinuria <1.5 g/24 h□	1
12. Active SLE rash	1	Proteinuria >1.5 g/24 h□	2
13. Active alopecia	1	28. 5–15 RBC or 1–3 casts/HPF	1
14. Mucosal ulcers	1	>15 RBC or >3 casts/HPF	2
15. CNS (minor ¥)	2	29. Hemolytic anemia (>8 g Hb)	1
16. CNS (major ¶)	3	Hemolytic anemia (<8 g Hb)	2
17. Cranial nerve palsy	2	30. Thrombocytopenia (40–100,000)	1
18. Blood pressure >150/90	1	Thrombocytopenia (<40,000)	2
19. Lymphadenopathy	1	31. Neutropenia (<3,000)	1
20. Noninfectious lung infiltrates	3	32. Lymphopenia (<1,000)	1
21. Active thromboembolic event	1		
Maximum	33	Maximum	19
Total SIS (Maximum: 52)			

Physician's assessment of activity: 0 _____ 100 mm
None Most severe

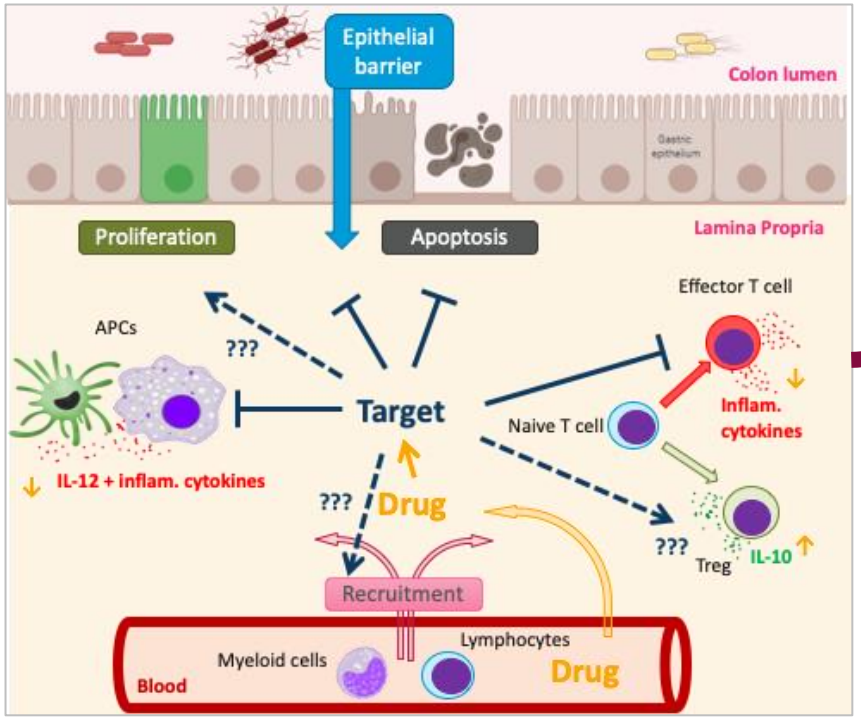
Duffin 2017 doi:10.1007/978-3-319-66884-0_2

Linkwave Inc. App

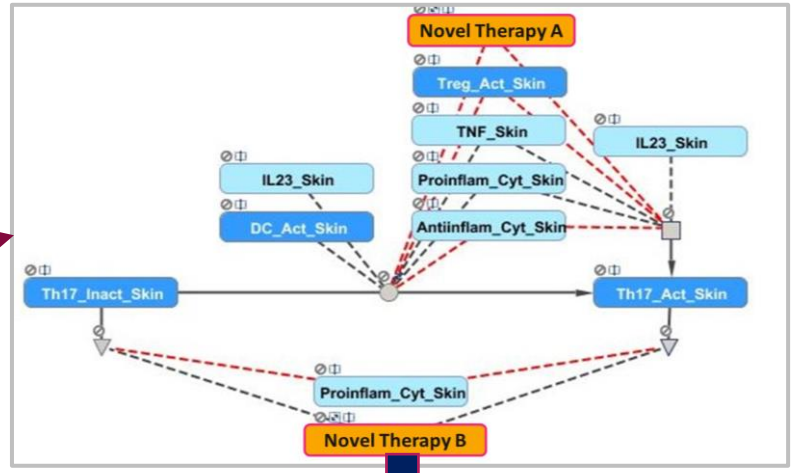
Parker 2019 doi:10.1016/B978-0-323-47927-1.00049-9

How to bridge the gap between QSP model outcomes and relevant clinical trials endpoints?

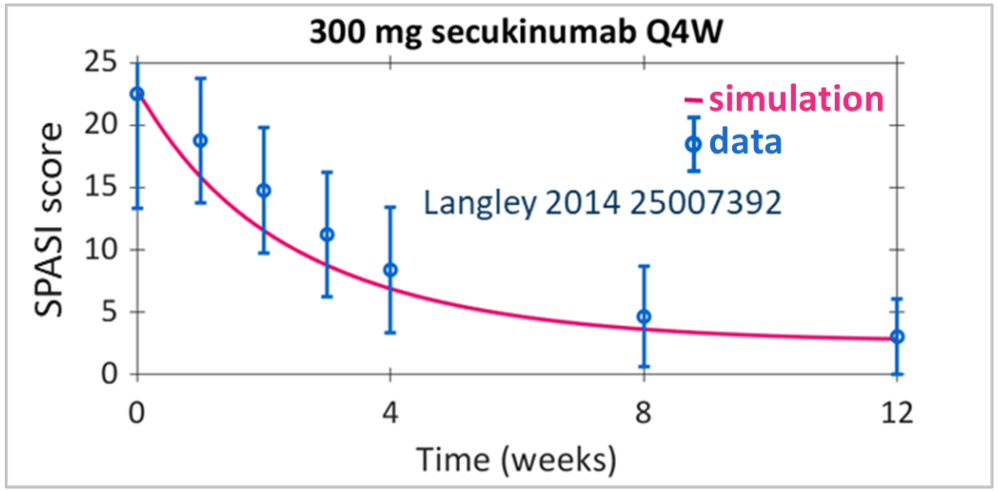
Scientific Understanding



QSP Model



Clinical Outcome Predictions

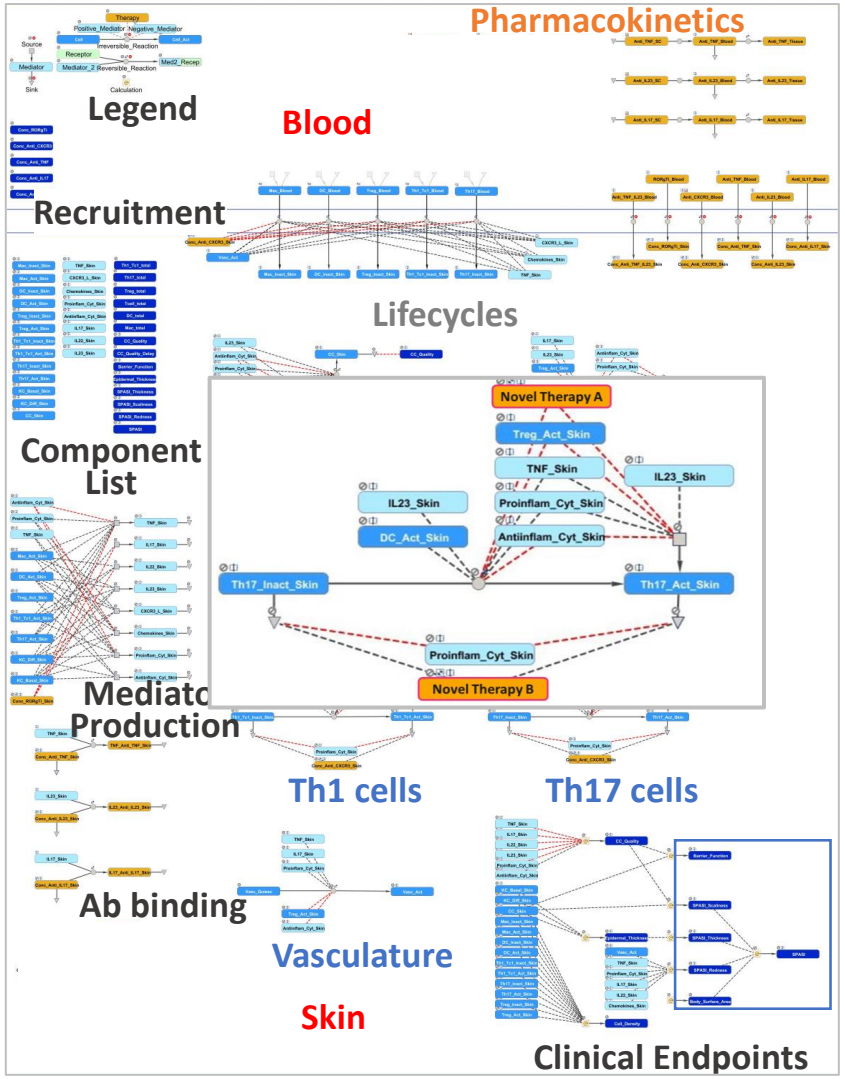


Systematic Process Developed at Rosa

1. Develop QSP model connecting mechanisms to measurable biomarkers

- The goal of the fit-for-purpose QSP model is to address a specific research question
- Model components necessary to represent target MOA and disease pathophysiology are prioritized
- Discussions with the scientific team inform inclusion of relevant biomarkers, therapies and calculations of defined endpoints

Psoriasis Platform



“Focused” clinical endpoints implemented in QSP models can be correlated with complex global outcomes.

Focused Clinical Endpoints (Tissue/pathway-specific)	Link	Global Clinical Endpoints

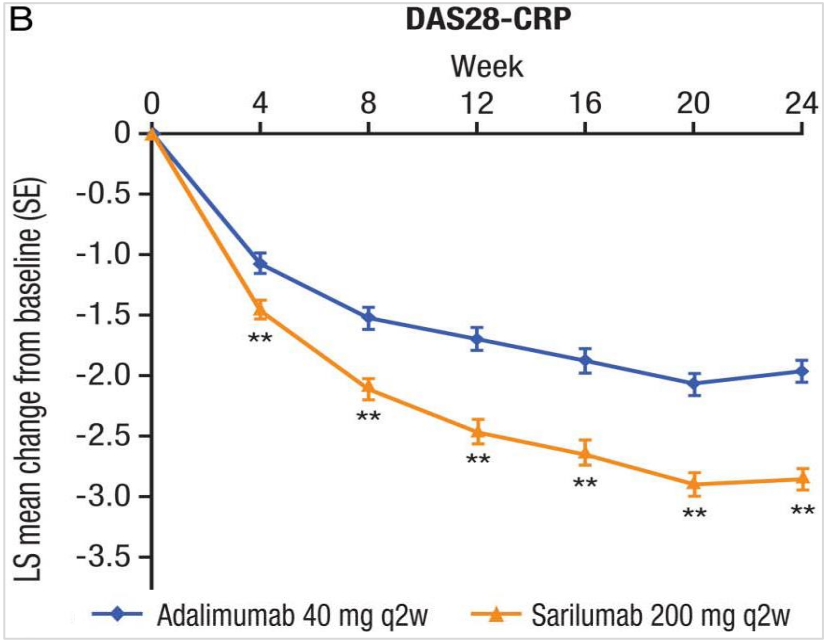
• Skin:
  • Psoriasis: PASI
  • Atopic Dermatitis: EASI
  • Cutaneous Lupus: CLASI
	➔	• Multiple tissue involved
		  • Ex: Lupus SLEDAI (32 measurements), correlation with CLASI, DAS-28 score + other biomarkers reported in literature

• Joint:
  • Rheumatoid Arthritis: DAS-28
  • Lupus Arthritis: DAS-28
	➔	• “Subjective” assessments
		  • Patients or physician visual assessment scores
		  • Fatigue, pain assessment
		  • Correlation with inflamed joints & other biomarkers

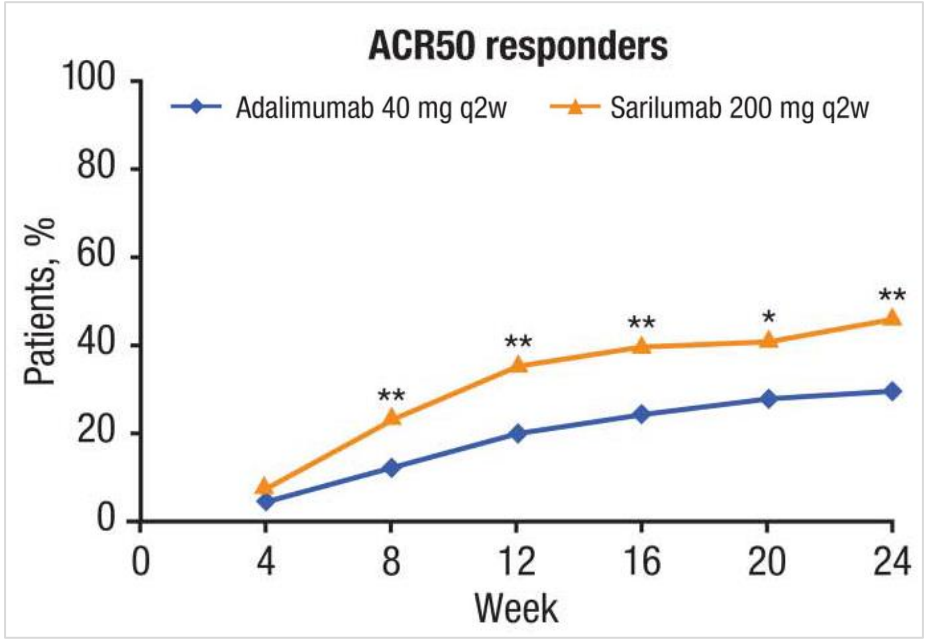
• Cancer: • Sum of longest diameter (SLD)	?	• Life expectancy (cancer survival)

Continuous Clinical Score vs. % of Responder Patients

Absolute change in DAS28-CRP score (RA)



% of patients with ACR50 response (RA)



Burmester 2016 PMID: 27856432

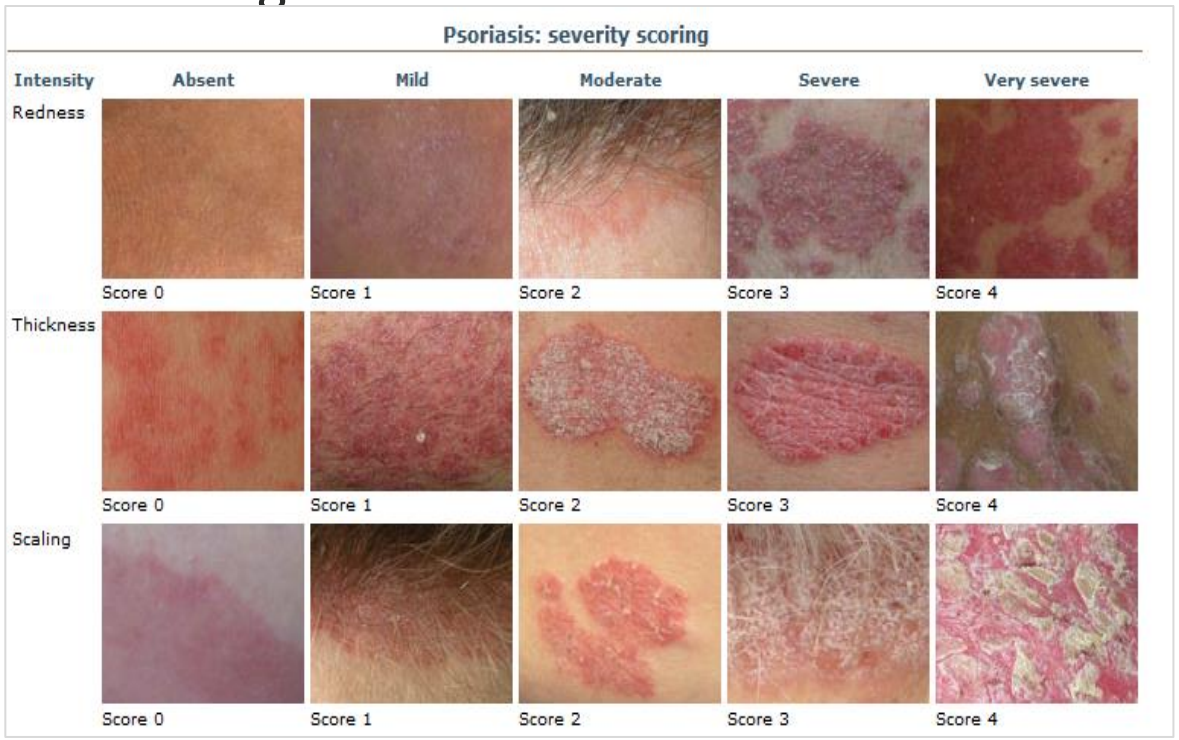
Single virtual patient sufficient

Need prevalence-weighted virtual population

➔ The clinical score of interest can influence the scope of the project

2. Identify relevant data, clinical score definition and subcomponent measurements

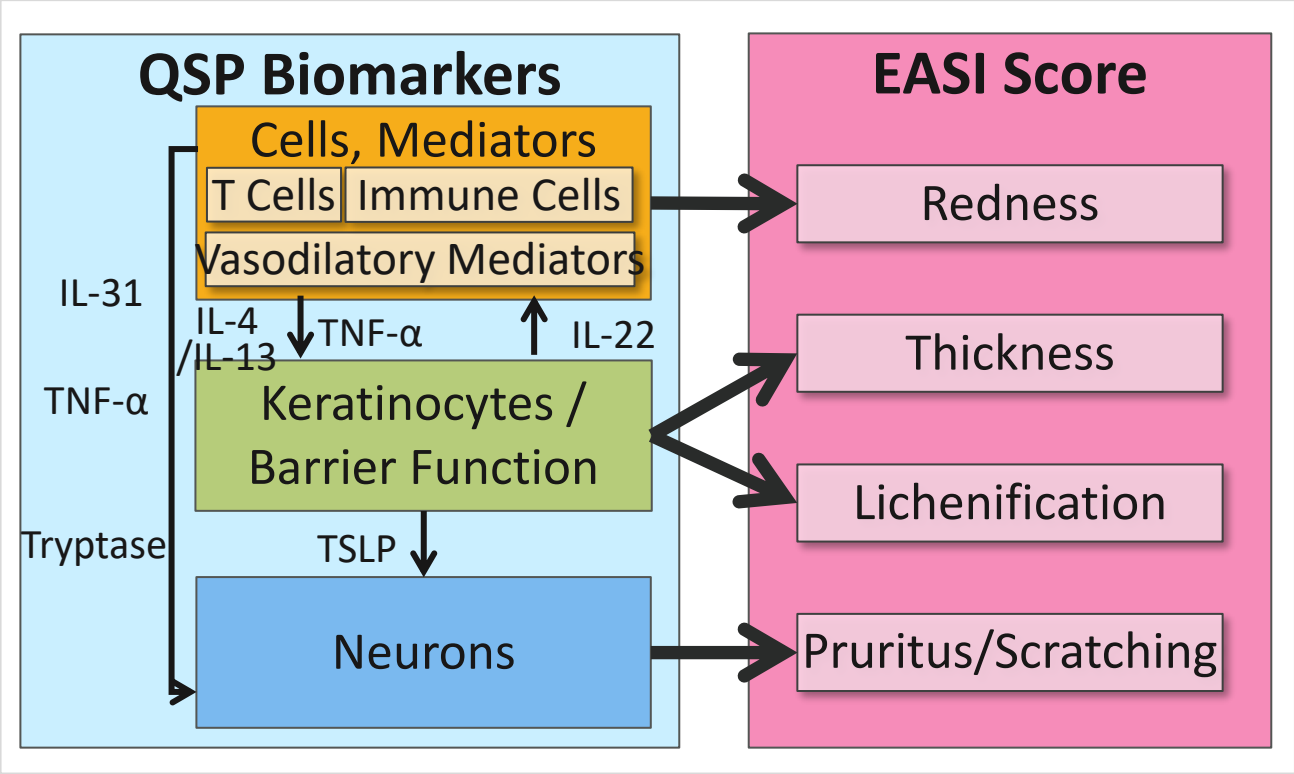
- PASI score $PASI = 0.1 \cdot (E_H + I_H + D_H) \cdot A_H + 0.2 \cdot (E_A + I_A + D_A) \cdot A_A + 0.3 \cdot (E_T + I_T + D_T) \cdot A_T + 0.4 \cdot (E_L + I_L + D_L) \cdot A_L$
  - Body divided into four sections (**H**ead, **A**rms, **T**runk, **L**ower)
    - percent of body surface area (% BSA) involved estimated (A_H, A_A, A_T, A_L)
  - Severity estimated by three clinical signs measured on a scale from 0 to 4
    - **E**rythema (redness)
    - **I**nduration (thickness)
    - **D**esquamation (scaling)



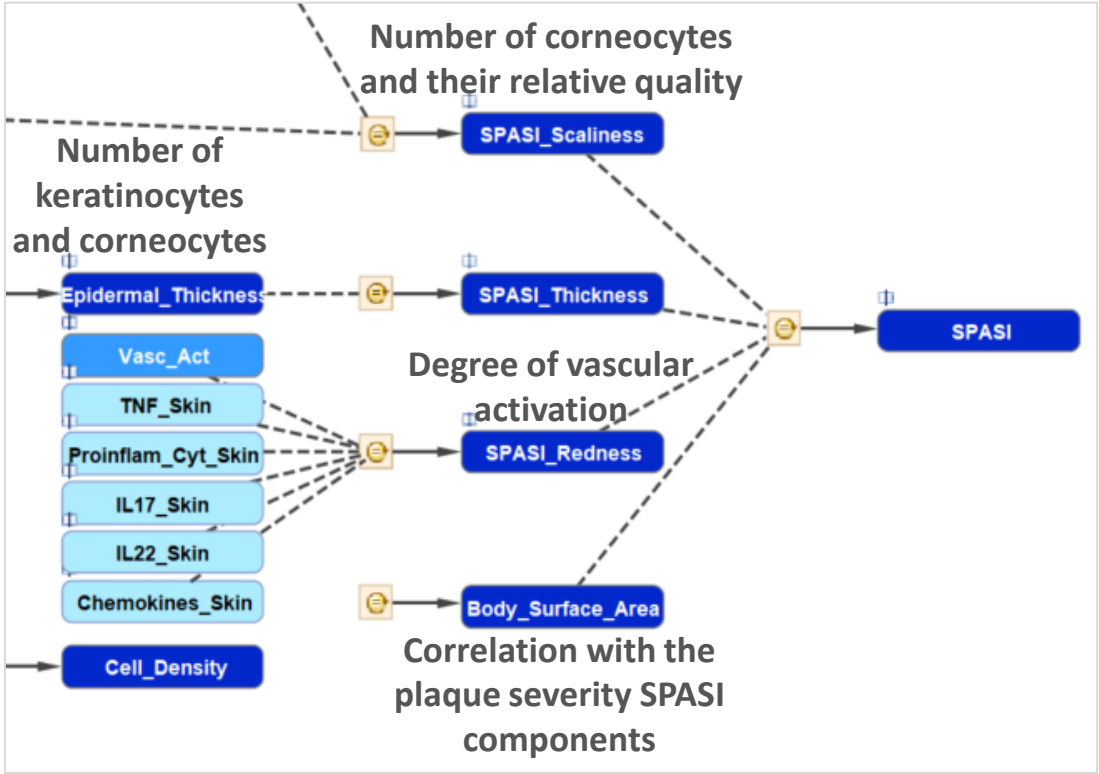
Examples of redness, thickness, and scaling used in a PASI score. (http://www.dermnetnz.org/scaly/pasi.html)

3. Map disease score subcomponents to QSP model species or biomarkers

EASI Score Component Mapping

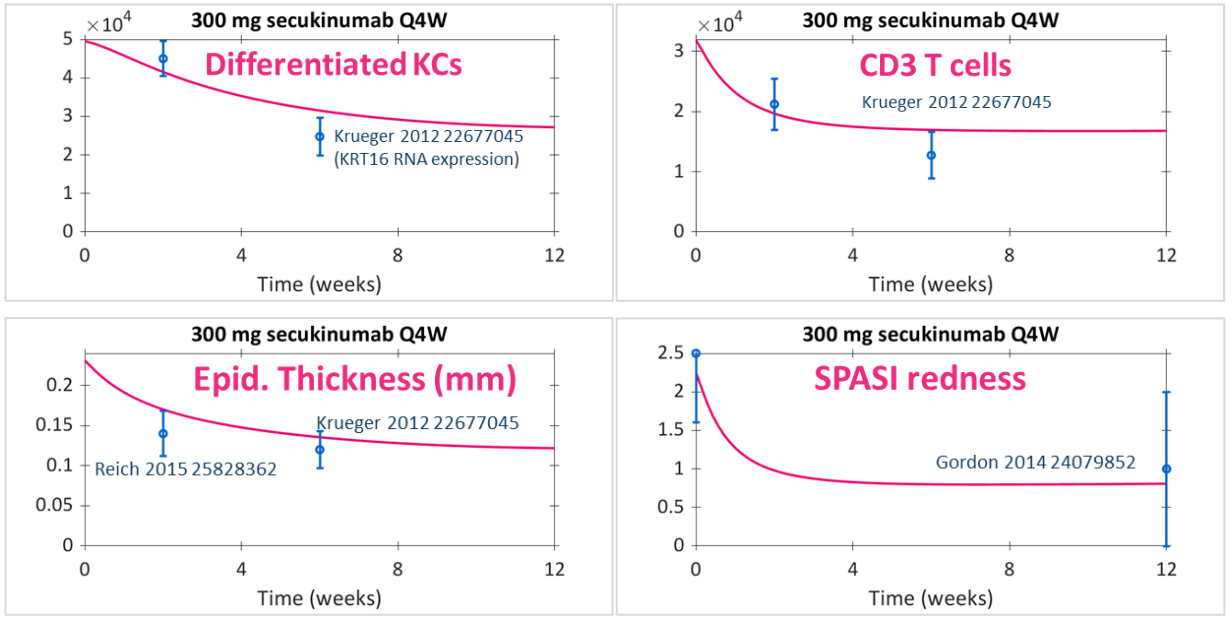


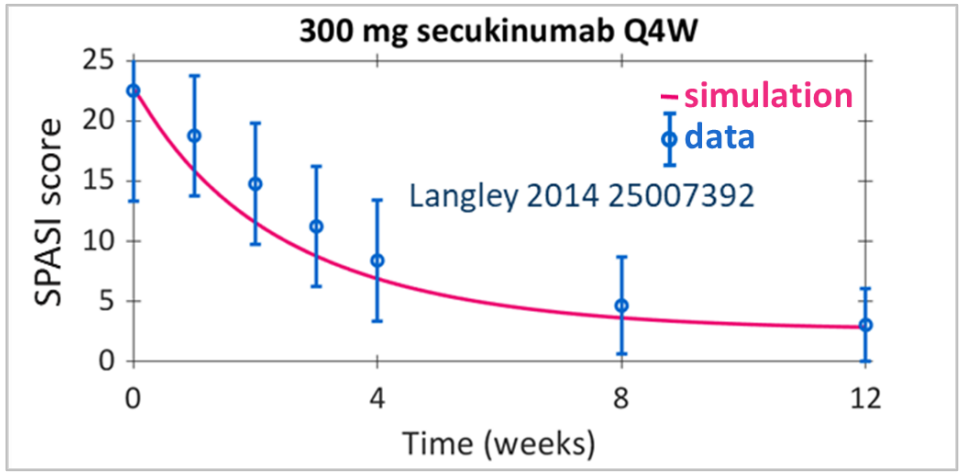
SPASI Score Component Mapping



4 . Fit parameters for outcome calculations to match published/proprietary clinical data

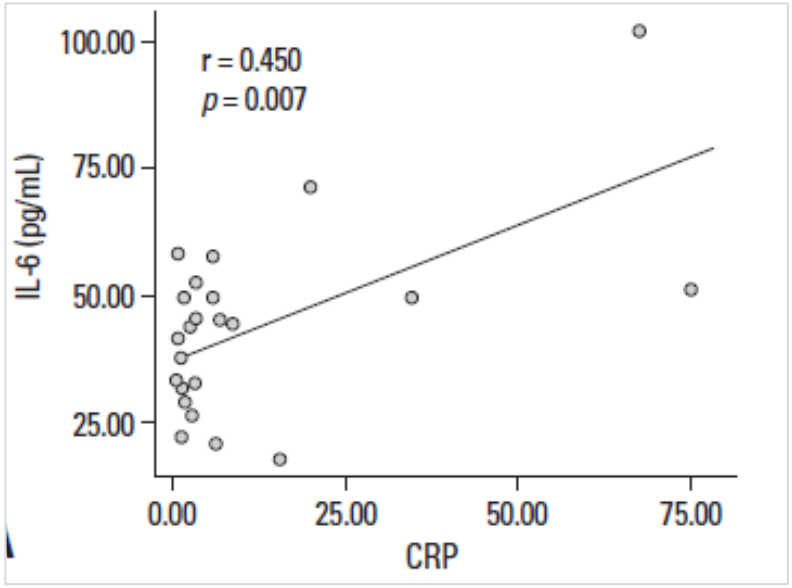
- Calibrate QSP model parameters to match changes in mediators and cell numbers with therapies
- Calculate disease score components parameters to match changes in disease subscores
- Integrate disease subscore components into overall clinical score, adjusting parameters, if necessary, to match clinical data





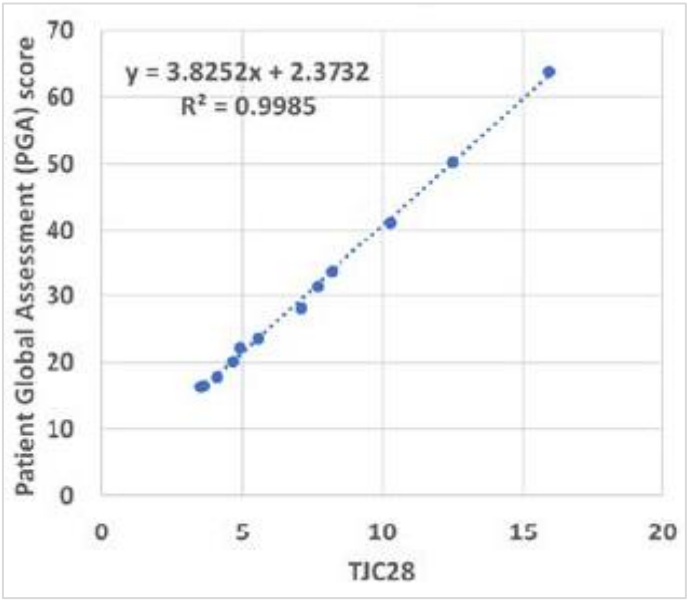
Sometimes, clinical score subcomponents cannot be directly linked to model outcomes.

Correlation between CRP and IL-6



Chung 2011 PMID 21155043 (RA patients)

Correlation between TJC28 and PGA score



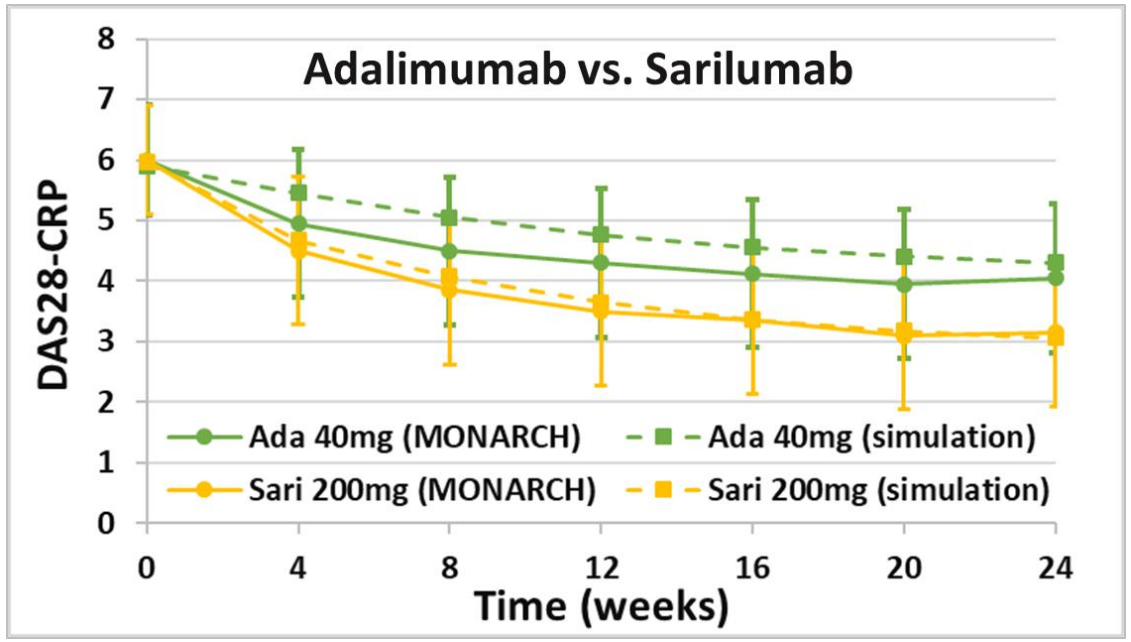
Proprietary Clinical Trial Data

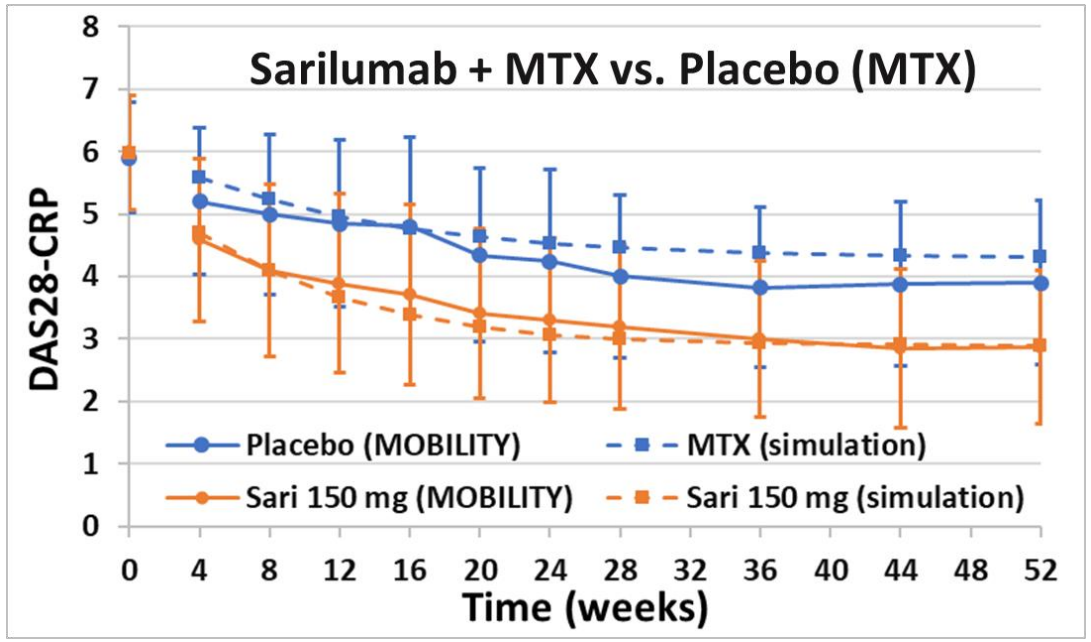
➔ Rely on correlation between QSP model outcomes and clinical score subcomponent not represented

- DAS28-CRP RA Clinical Score:
  - DAS28-CRP = 0.56 × √(TJC28) + 0.28 × √(SJC28) + 0.36 × ln(**CRP** + 1) + 0.014 × **GH** + 0.96
  - From literature and proprietary clinical trial data:
    - **CRP** correlated with IL-6 levels implemented in the QSP model
    - **GH** (patients global health) correlated with TJC28 calculated in the QSP model

5. Use simulated clinical score outcomes to compare efficacy of new drugs to SOC therapies in virtual patients

DAS28-CRP score simulations compared to clinical trial data

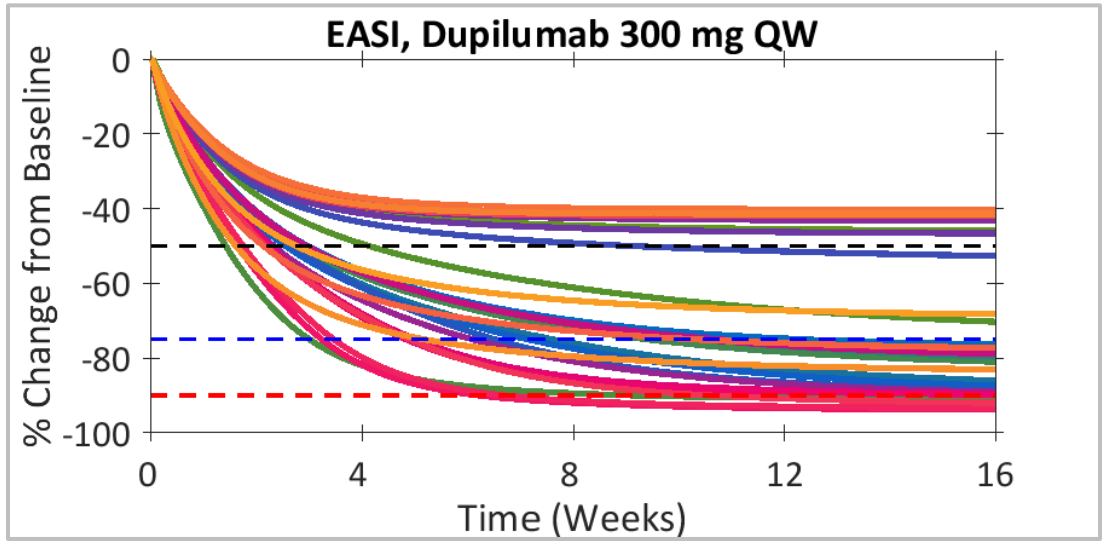




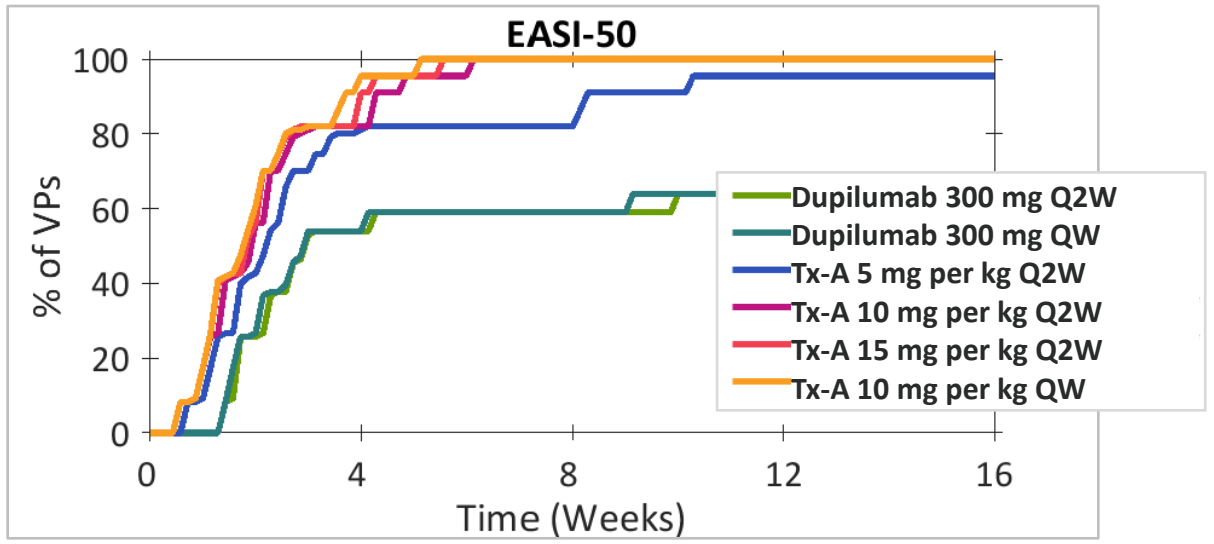
Comparison of predicted reduction in DAS28-CRP (---) with published data (ϕ: mean ± SD)

VPs with different phenotypes can then be created to explore variability in clinical response.

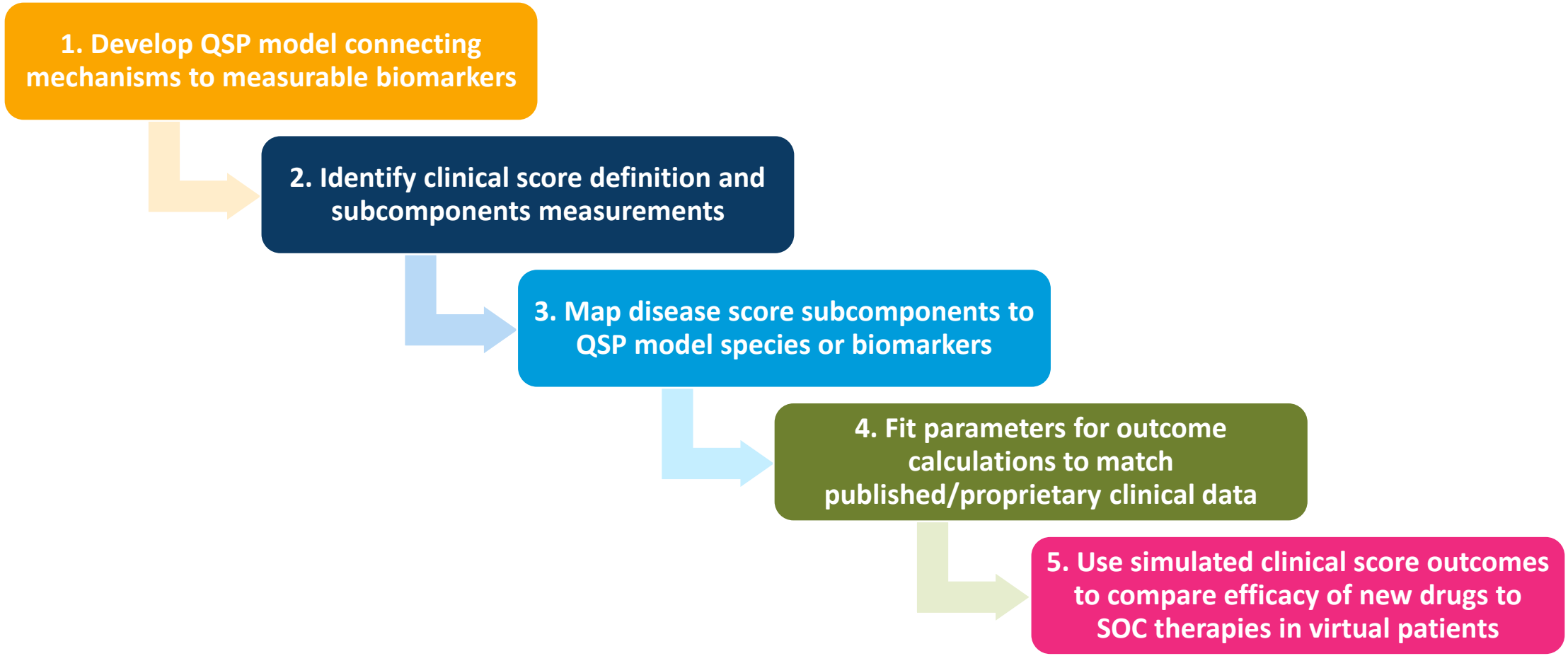
VPs cover the range of EASI response to Dupilumab



% of VPs with EASI-50 response: new therapy (Tx-A) compared to dupilumab



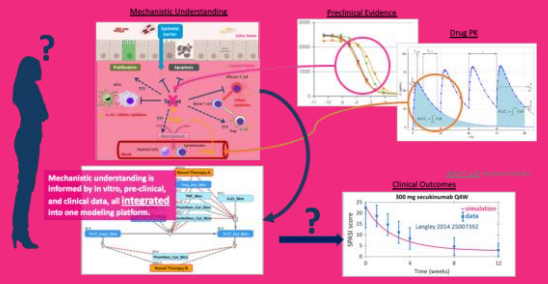
Rosa's Process for Complex Clinical Scores



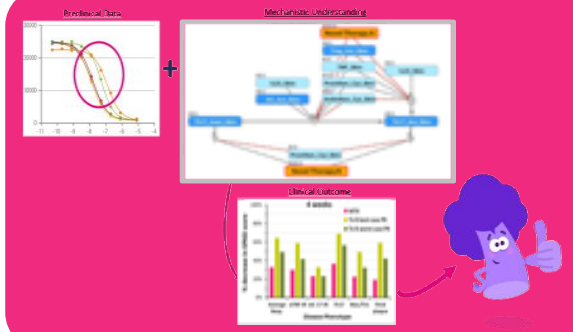
Remaining Challenges and Limitations

Challenging Clinical Endpoints for QSP		Solution Used in QSP Projects
• Trial results expressed as % of patients reaching a specific clinical response criteria (ACR20, EASI-50, RECIST,…)	➔	Build a prevalence weighted virtual patient cohort using detailed individual patient data from existing clinical trial
• Discrete events (flares, nausea, asthma attacks,…)	➔	Use a statistical threshold model based on correlation with a continuous outcome
• Progression-free survival in oncology • Cognitive outcomes in neurological disease	➔	Identify, with clinicians' help, alternate endpoints that can help answering the specific research question

Key Take Home Messages



Complex scores can be simulated in QSP models, if a link between model biomarkers and the disease subscores can be established and calibrated with clinical data.



The capacity of a QSP Platform to report clinically relevant disease scores allows broader adoption of QSP modeling throughout clinical organizations.

ROSA™

Thank you!

QSP models presented developed in collaboration with

SANOFI

Daiichi-Sankyo

SERVIER

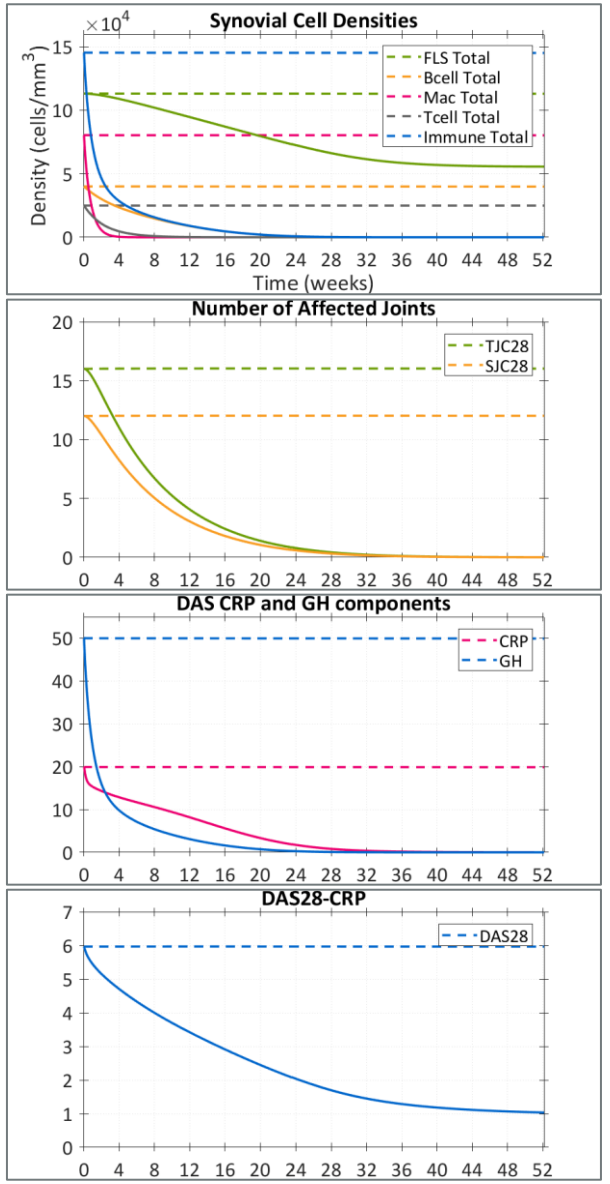
GRÜNENTHAL

Stiefel
a GSK company

DAS28-CRP Calculation in the RA Platform

- DAS28-CRP = DAS28-CRP = 0.56 × √(TJC28) + 0.28 × √(SJC28) + 0.36 × ln(CRP + 1) + 0.014 × GH + 0.96
  - Total immune cell density includes inactive and active immune cells
  - TCJ28 = dynamic calculation function of total immune cell density in joint
  - SCJ28 = 0.75*TJC
  - CRP=4.4*(IL6_Blood)
  - GH = 3.125*TJC28

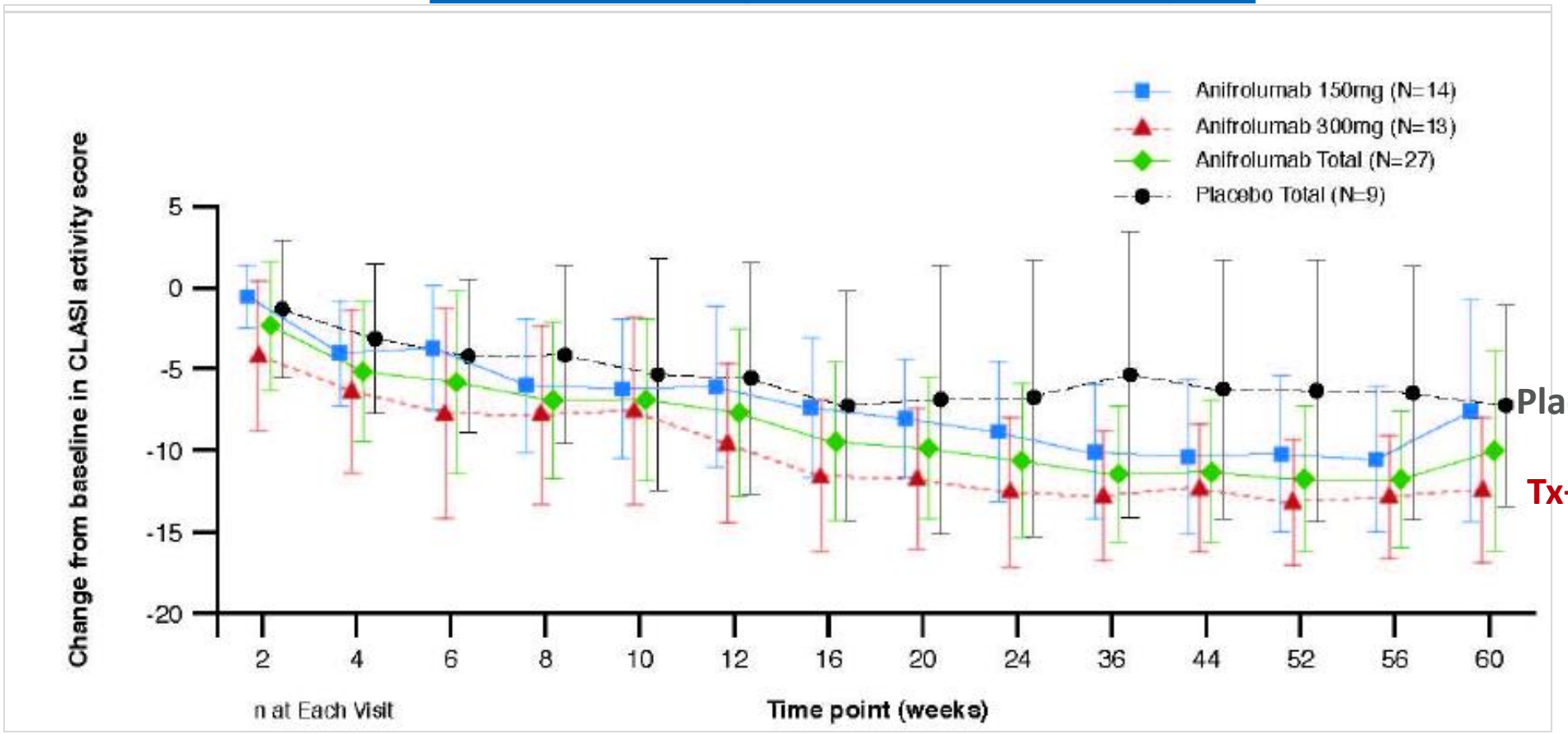
- Example simulation (right) shows hypothetical 100% inhibition of immune cell recruitment



Placebo Representation

Some diseases show strong clinical response in the “Placebo” group.

Absolute change in CLASI score (lupus)



Placebo

Tx+Placebo

QSP models need mechanistic hypothesis to represent the “placebo” effect.

- Identify hypothesis for response in the “placebo” group
  - Background therapy: steroids, topical treatments, palliative interventions
  - Change in disease severity over time
  - Change in diet
  - Better compliance or doctor surveillance
  - …

- Mechanistic components affected by the “placebo” effect must be represented in the QSP model

Implement mechanistic “placebo” hypothesis.

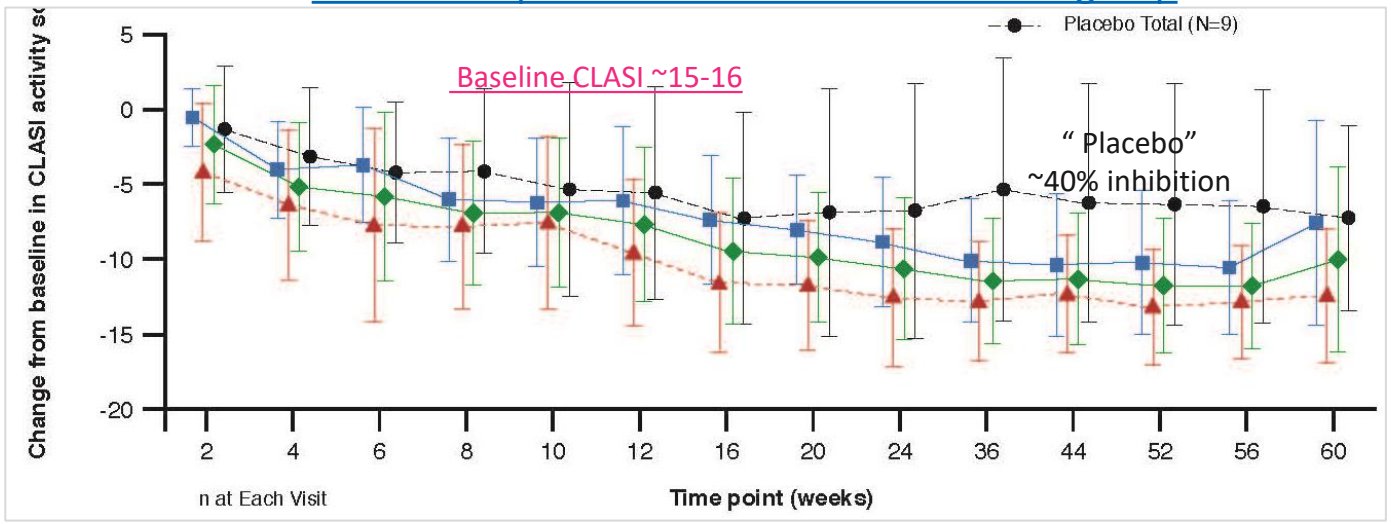
Examples of reported steroids effects on relevant cell types in skin diseases

Cell Type	IC50 (steroids)	Imax	References
Keratinocytes	10-100 nM	- 20-70 %	Stojadinovic 2007 PMID: 17095510; Le 2010 PMID: 20357482
Dendritic Cells	5-50 nM	- 50-80%	de Jong 1999 PMID: 10449154; Piemonti 1999 PMID: 10352262; Weichhart, 2011 PMID 21368289
T cells	1-10 nM	- 60-90%	Migliorati 1994 PMID: 7831194; Braun 1997 PMID: 9314354; Sun, 2011 PMID: 21204899

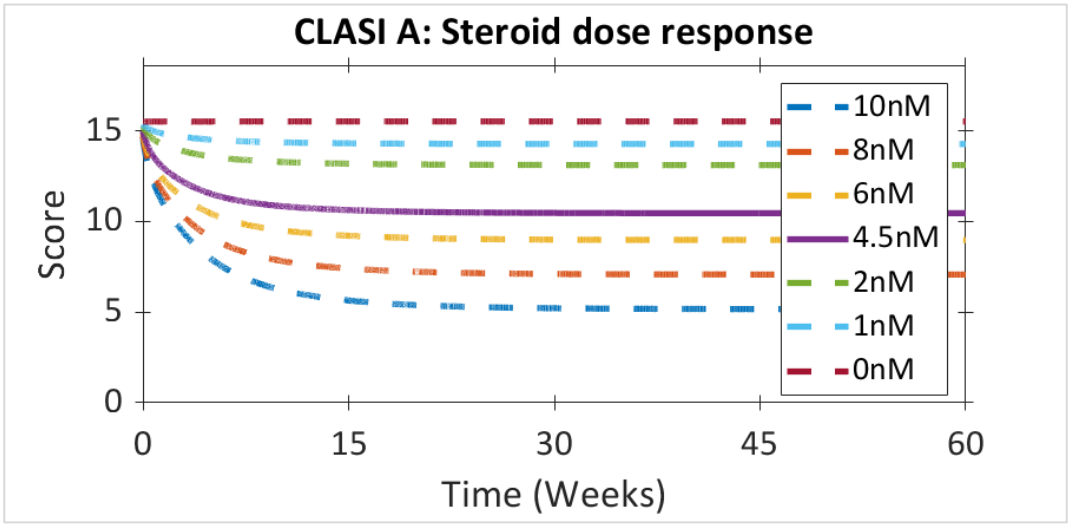
- The “placebo” effect is implemented as a constant effect (no drug PK)
- Hill function inhibition parameters is based on in vitro literature data for the various cell types
- As in vivo drug concentrations in skin are difficult to estimate, the simulations will be calibrated to match clinical trial response by adjusting the [drug]/IC50 ratio

Adjust “placebo” response to match clinical data.

CLASI-A response in anifrolumab “Placebo” group



CLASI-A response to increasing steroid dose in the Platform



Bruce 2019 Arthritis Rheumatol. Abstract Number: 2563

- Protocol
  - Steroid constant effect with doses ranging from 0 to 10nM
- Results:
  - The 4.5nM steroid dose was chosen for the ”Placebo” response in the reference VP