Evaluation of competitive differentiation of novel therapies and the impact of patient variability on efficacy in a psoriasis QSP platform

V. Hurez[1], M. Weis[1], R. Baillie[1], M. Reed[1]*, M. Rehberg[2], K. Beuke[2], A. Dietrich[2], B. Göbel[2], N. Biesemann[2], C. Asbrand[2], A. Subramaniam[2], W. Seiz[2], M. Herrmann[2], T. Klabunde[2], F. Nestle[2]

*[1]Rosa and Co. LLC, USA, [2]Sanofi, Germany/USA, *mreed@rosaandco.com*

Introduction

- **Psoriasis is a chronic inflammatory, debilitating skin disease** characterized by itching, thickened, red scaly plaques
- **Lack or loss of response, safety concerns, and tolerability** can limit the benefit of current therapeutic options
- Novel drugs (such as small molecules or new biologics) with **fewer side-effects or more convenient dosing** are being developed to help overcome these obstacles

Objectives

- Assess the potential of novel oral drugs and anti-cytokine antibodies in psoriasis.
- Compare efficacy to standard of care therapies, i.e., methotrexate, adalimumab, guselkumab, and secukinumab.
- Identify mechanistic drivers and impact of patient variability on treatment response.

Methods

The Psoriasis PhysioPD™ Research Platform is a mechanistic, QSP model of chronic psoriasis

- PhysioPD Platforms are graphical, mathematical, **fit-to-purpose QSP biological models** developed in SimBiology®
- Rosa and Sanofi developed **the Psoriasis PhysioPD Platform**, using **engineering approaches** and **scientific data analysis** to evaluate the potential of novel psoriatic drugs
- PhysioPD Platforms are qualified in accordance with **Rosa's Model Qualification Method[1] (MQM)** (Figure 1)
- The Psoriasis Platform represents the **physiology of a single chronic psoriasis plaque** (Figure 2) including:
  - Keratinocytes (KCs), immune cells, cytokines, chemokines, and their regulation
  - Standard therapy classes (adalimumab, gusel-kumab, secukinumab, methotrexate [MTX])
  - SPASI clinical score

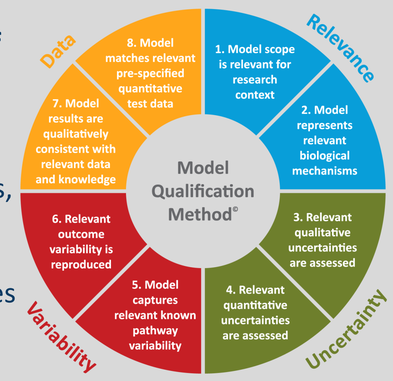


Figure 1. Rosa's Model Qualification Method[1] (MQM)

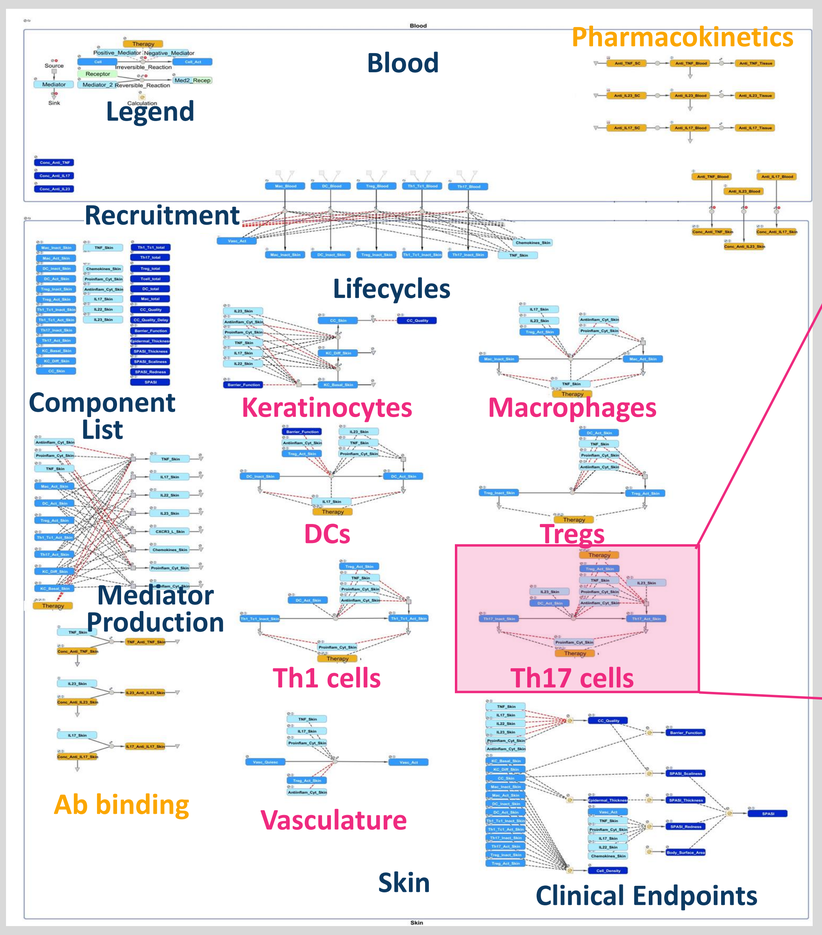


Figure 2. SimBiology[2] Overview of the Psoriasis PhysioPD Platform .

Platform Qualification

The reference virtual patient (VP) is representative of an average moderate/severe psoriasis patient

- Cell numbers in blood and skin were calibrated to match the average from several studies in moderate/severe psoriasis and are stable in untreated conditions (Figure 3)
- Dermal mediator levels, determined by clearance rates, cell numbers, and cell-type specific production rates also matched reported literature averages (not shown)

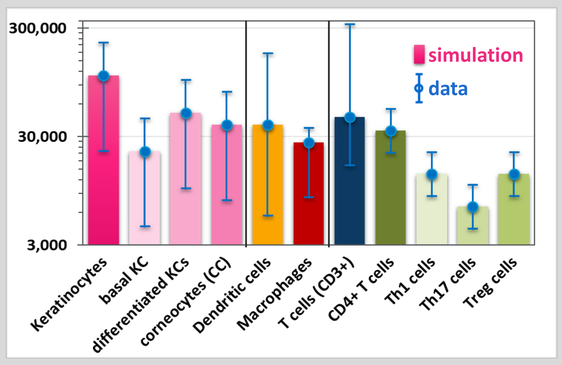
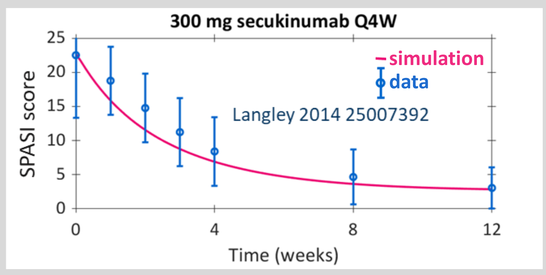


Figure 3. Mean psoriasis keratinocyte and immune cell densities are implemented. Average ± range (ϕ) from literature data overlaid.

Standard therapies dosing and outcomes were used to qualify the Psoriasis Platform

Outcomes	Therapy	Dosing schedule	References
• **Reduction in cellular infiltration** • **PASI score & subscores**	Adalimumab (anti-TNFα)	80 mg SC once, then, after 1 week, 40 mg SC Q2W	[3-8]
	Guselkumab (anti-IL-23)	100 mg SC at week 0, week 4, and Q8W thereafter	[4, 9-13]
	Secukinumab (anti-IL-17)	300 mg SC: QW for 4 weeks and Q4W thereafter	[14-18]
	Methotrexate	15 mg oral weekly dose	[3, 19-23]



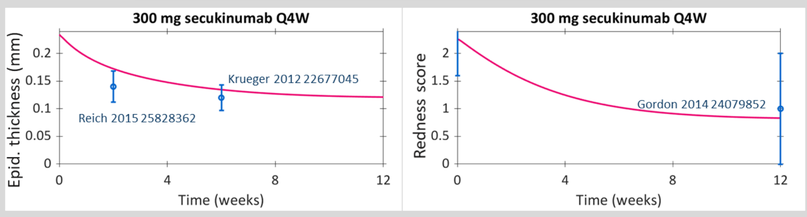
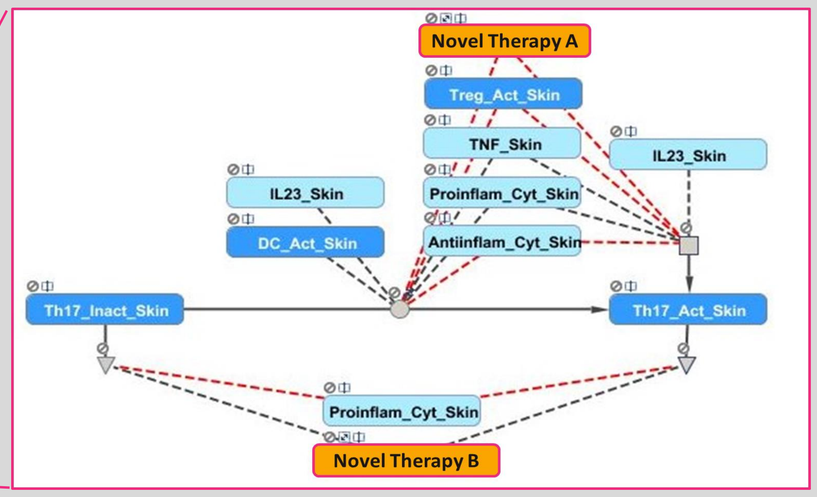


Figure 4. Decrease in PASI score, epidermal thickness and redness score with secukinumab treatment in the reference VP. Literature data from secukinumab, ixekizumab and brodalumab (ϕ) expressed as mean ± SD

Novel Therapy Evaluation



Novel therapy efficacy predicted to be slightly better than current biologics in average virtual patient

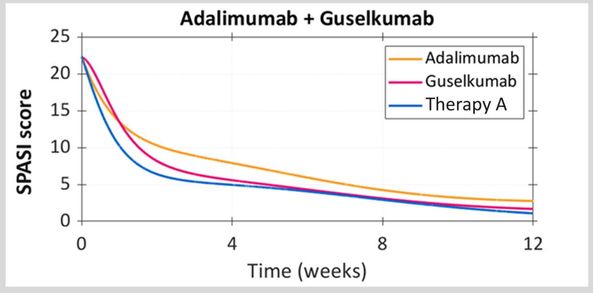


Figure 5. Decrease in SPASI score in reference VP treated with adalimumab (40 mg Q2W), guselkumab (100 mg Q8W) or novel therapy A (100 mg Q8W)

Alternative Virtual Patients

Alternative disease phenotypes were created by varying baseline cytokine levels or cell numbers

Disease phenotype0	Mechanisms	Mac/ Th1	Th17	Tregs	KCs	DCs	TNF EC50/ [skin]	IL-17 EC50/ [skin]
Average responder	▪ Average response to standard therapies	1x	1x	1x	1x	1x	1x	1x
Anti-TNF-IR*	▪ Reduced relative baseline TNFα levels	1x	1x	1x	1x	1x	0.2x	1x
Anti-IL-17-IR	▪ Reduced relative baseline IL-17 levels	1x	1x	1x	1x	1x	1x	0.1x
Th17 phenotype	▪ Increased in Th17 cells ▪ Reduced Th1/Mac/Tregs	0.5x	3-4x	0.5x	1x	1x	1x	1x
Mac/Th1 phenotype	▪ Increased Mac/Th1 cells ▪ Reduced Th17 effects	3-4x	0.5x	1x	1x	1x	1x	1x
Thick plaque[24]	▪ Increased cellular infiltration, more severe	1.25x	1.25x	0.75x	1.25x	1.5x	1x	1x

*** IR: inadequate responder**

The alternate VPs covered a range of response to standard therapies

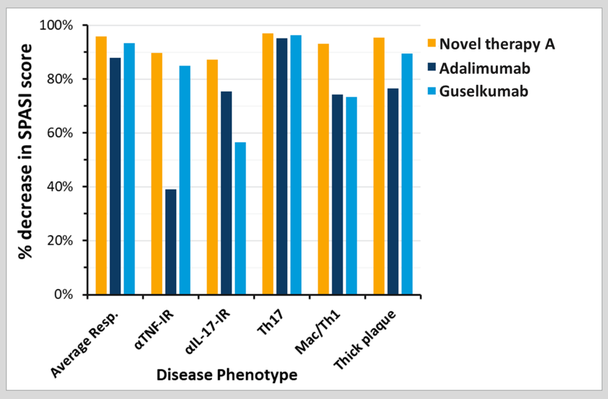
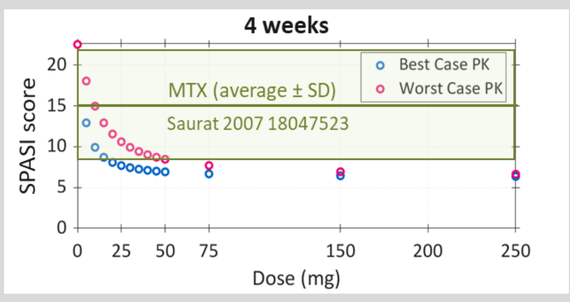


Figure 6. Decrease in SPASI score with adalimumab, guselkumab or therapy A. Simulations of 16-week treatment in all disease phenotypes.

Simulation of a 4-week trial predicts better efficacy for the novel oral drug compared to methotrexate



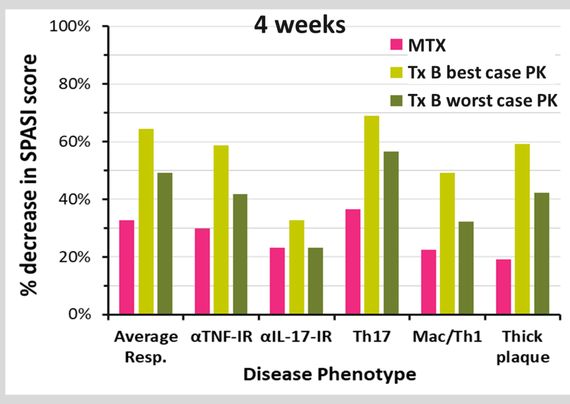


Figure 7. Decrease in SPASI with novel therapy B in comparison to MTX at 4 weeks. Top: SASI with increasing doses of Tx B with 2 different PK scenarios compared to published average ± SD MTX response. Bottom: SPASI response to MTX and Tx B in all VPs.

Conclusions

- Depending on dosing regimens and pharmacokinetics estimates, novel experimental drugs can be superior to standard of care therapies
- Targeting IL-17 pathways with a novel oral compound is predicted to be as efficacious as SOC therapies in most disease phenotypes
- Key uncertainties related to target expression and drug biodistribution in the skin were identified
- A shorter trial should be sufficient to demonstrate efficacy with significantly reduced patient burden and study costs

References

1. Friedrich, C.M. CPT Pharmacometrics Syst Pharmacol 5, 43-53 (2016).
2. Schmidt, H. & Jirstrand, M. Bioinformatics 22, 514-515 (2006).
3. Saurat, J.H., et al. Br J Dermatol 158, 558-566 (2008).
4. Micali, G., et al. Skin Res Technol 22, 341-348 (2016).
5. Balato, A., et al. J Eur Acad Dermatol Venereol 28, 1016-1024 (2014).
6. Rios-Navarro, C., et al. European journal of pharmacology 765, 355-365 (2015).
7. Marble, D.J., Gordon, K.B. & Nickoloff, B.J. J Dermatol Sci 48, 87-101 (2007).
8. Hendriks, A.G., et al. Br J Dermatol 170, 571-580 (2014).
9. Hu, C., Wasfi, Y., Zhuang, Y. & Zhou, HJ Pharmacokinet Pharmacodyn 41, 239-250 (2014).
10. Reddy, M., et al. J Dermatol 37, 413-425 (2010).
11. Sofen, H., et al. J Allergy Clin Immunol 133, 1032-1040 (2014).
12. Pierard-Franchimont, C. & Pierard, G.E J Biomed Biotechnol, 870194 (2012).
13. Toichi, E., et al.. J Immunol 177, 4917-4926 (2006).
14. Langley, R.G., et al. N Engl J Med 371, 326-338 (2014).
15. Krueger, J.G., et al. J Allergy Clin Immunol 130, 145-154 e149 (2012).
16. Reich, K., et al. Exp Dermatol 24, 529-535 (2015).
17. Russell, C.B., et al.. J Immunol 192, 3828-3836 (2014).
18. Hueber, W., et al. Sci Transl Med 2, 52ra72 (2010).
19. Sigmundsdottir, H., et al. Exp Dermatol 13, 426-434 (2004).
20. Yazici, A.C., et al. Arch Dermatol Res 297, 249-255 (2005).
21. Ozkanli, S., et al. Cutan Ocul Toxicol 34, 276-281 (2015).
22. Elango, T., Thirupathi, A., Subramanian, S., Dayalan
23. Warren, R.B., et al. Lancet 389, 528-537 (2017).
24. Kim, J., et al. PLoS One 10, e0132454 (2015).

www.rosaandco.com

For more information about this work, please contact:
Mike Reed
Rosa & Co LLC
(650) 784-0771
mreed@rosaandco.com