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


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Introduction

- Psoriasis is a chronic, inflammatory, debilitating skin disease characterized by itching, thickened, red scaly plaques
- Lack of 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® (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, guselkumab, secukinumab, methotrexate (MTX))
  - SPASI score

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)

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

Disease phenotype

- Mechanisms
- Average responder
- Anti-IL-17A
- Reduced relative baseline TNF-A
- Average IL-17

Th17 phenotype

- Increased in Th17 cells
- Reduced Th1/Mac/Mac

Th1 phenotype

- Increased Mac/Th1 cells
- Reduced IL-17

Maco/Th1 phenotype

- Reduced relative baseline 6-17 week

Thick plaque

- Increased cellular infiltration, more severe

* All compound responders

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

Conclusions

- Depending on dosing regimens and pharmacokinetics, 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

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