Development of a primary Sjogren's Syndrome (pSS) quantitative systems pharmacology (QSP) model linking mechanistic pathways to clinical scores.

Vincent Hurez (1)*, Alvaro Ruiz-Martinez (1), Lesley Benyon (1), Krishnakant Dasika (1), Mike Reed (1), Glenn Gauderat (2), Audrey Aussy (2), Laurence Laigle (2), Sylvie Bretin (2), Sylvain Fouliard (2), Emiko Desvaux (2), Perrine Soret (2), Joël van Roon (3), Philippe Moingeon (2)

*1. Rosa & Co., San Carlos, CA, USA; 2. Servier, Suresnes, France; 3. Dept of Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands. *vhurez@rosaandco.com*

Introduction

- Primary Sjogren's syndrome (pSS) is an auto-immune disease characterized by immune infiltrates and impairment of salivary and lachrymal glands (sicca), with 30-50% of patients experiencing inflammation in other organs (joints, skin, …).
- Current pSS treatment options include symptomatic sicca therapies and broad-spectrum immunosuppression for patients with systemic manifestations.
- Evaluating pSS drugs using QSP is particularly challenging due to the complexity of the clinical scores for pSS, which involve multiple "domains".

Objectives

- Establish links between pSS disease pathways represented in the QSP model and components of the clinical pSS domain scores
- Calibrate the change in the pSS domain scores using published responses to biologics and standard of care (SOC) therapies

pSS Model Design

- The QSP Platform was built in MATLAB SimBiology and includes:
  - **Salivary gland, lymph node and blood** compartments
  - **Immune cells:** Lymphocytes and antigen-presenting cells (APC)
  - **Salivary gland epithelial cells (SGECs)**
  - **Cellular activation and recruitment** regulated by pro- and anti-inflammatory mediators, chemokines and cell interactions
- The model also includes the effects of **steroids and hydroxychloroquine (HCQ)** as SOC therapies and **ianalumab** anti-BAFF receptor (BAFFR), an FDA-approved pSS therapy [1]
- The pSS Platform was qualified following Rosa's Model Qualification Method [2]
- The EULAR Sjogren's syndrome disease activity index (**ESSDAI**) score [3] was chosen as the primary pSS clinical endpoint
- Calibration of the ESSDAI domain scores were based on published clinical trial responses to ianalumab [3] and to the leflunomide–hydroxychloroquine combination therapy (RepurpSS-I clinical trial) [4]

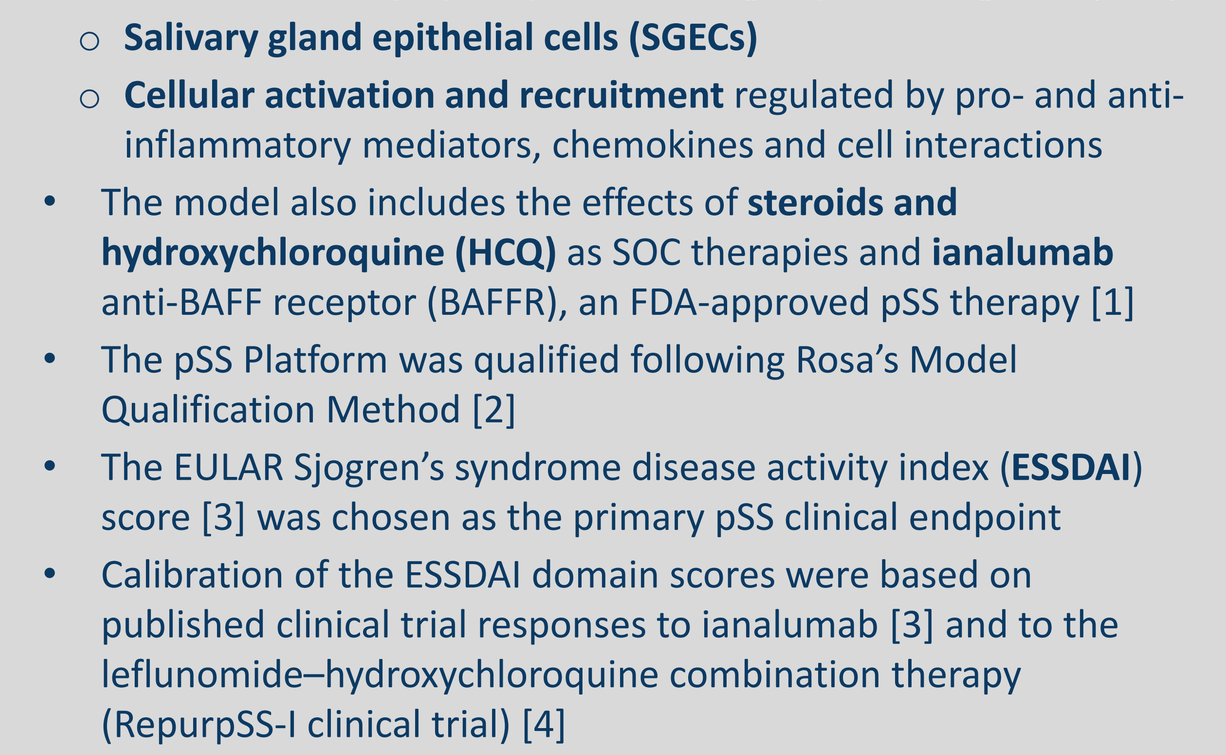

Figure 1. Components of the pSS QSP model and their interactions.

ESSDAI Score

ESSDAI Score Implementation

- Average pSS cell numbers and mediator concentrations in blood, lymph nodes, and salivary glands were identified from the literature to create a representative moderate to severe virtual pSS patient (reference VP) in the Platform
- Changes in tissue biomarkers upon treatment, e.g., lymph node and salivary gland volumes, pro-inflammatory mediators, and immune cell numbers were used to establish correlations between the Platform predicted outcomes and changes in the various ESSDAI domain scores (see **Table 1**)

Table 1. ESSDAI domain scores and their mapping to QSP model species.

ESSDAI domain	Domain Weight	Mapping to QSP model species
Lymphadenopathy	4	Based on lymph node volume
Glandular	2	Based on salivary gland volume
Articular	2	Correlated with APC numbers and pro-inflammatory mediator levels
Cutaneous	3	Correlated with effector T-cell numbers and pro-inflammatory mediator levels
Biological	1	Correlated with blood total IgG concentration
Constitutional	3	Correlated with pro-inflammatory mediator levels
Hematological	2	Based on lymph node volume

Ianalumab simulations match clinical data

- Simulations of ianalumab in the Platform matched published clinical trial ESSDAI responses [1] for both the 300-mg ianalumab-treated and the placebo groups of pSS patients (**Figure 2**)

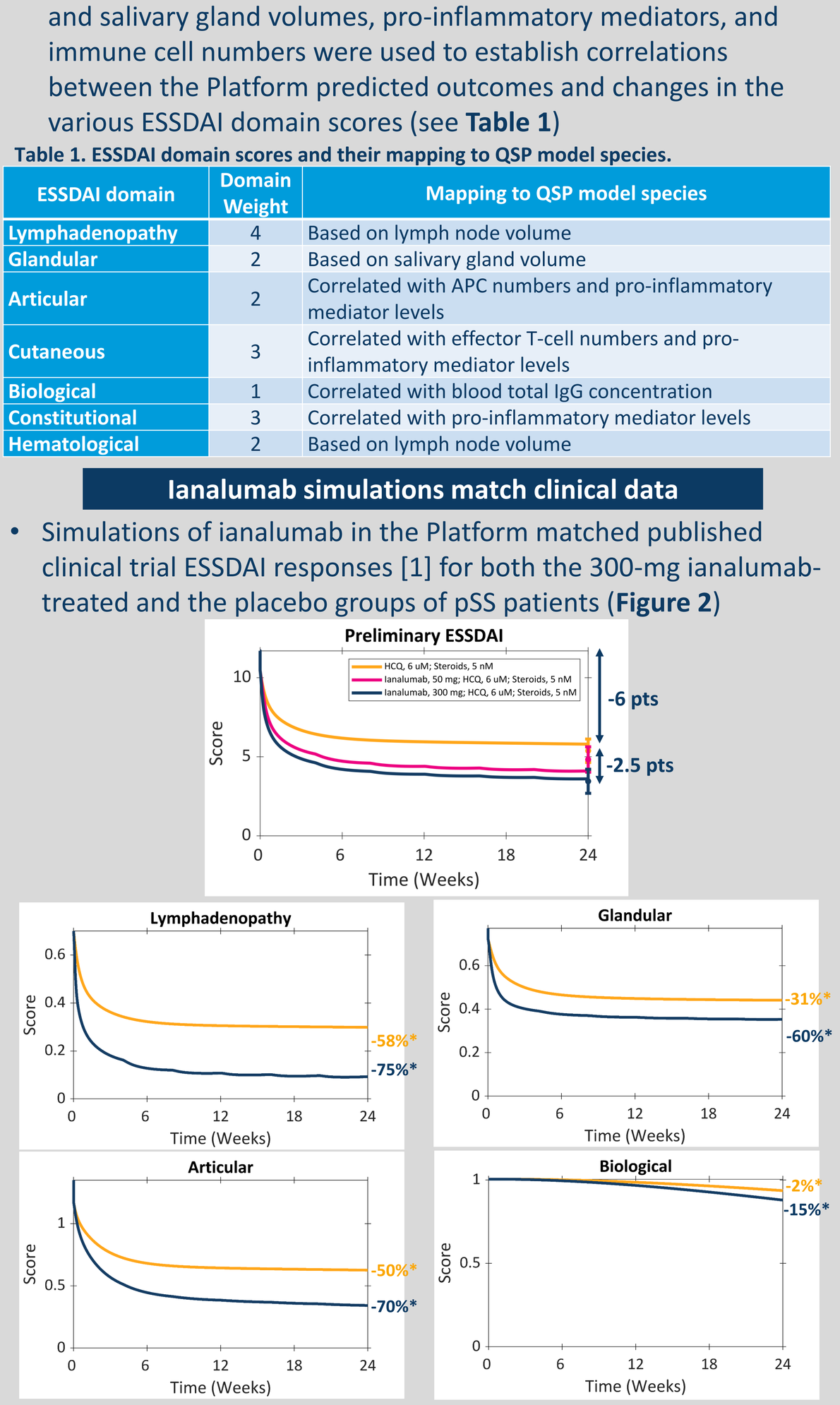

Figure 2. Ianalumab simulations vs data for ESSDAI and domain scores in the reference VP.
Simulations (lines) compared to mean ± SD (top panel ESSDAI) or % decrease from baseline (* bottom panels).

Conclusions

- The pSS Platform was able to predict a complex clinical score from mechanistic outputs
- QSP models able to predict complex clinical endpoints relevant to clinicians facilitate adoption of QSP modeling as an integral part of the drug development process within the organization.

REFERENCES

[1] S. J. Bowman et al. Lancet (2022) 399 ((1)0320) (1)6 (1)- (1)7 (1)

[2] C. M. Friedrich Cpt Pharmacometrics Syst Pharmacol (20 (1)6) 5 (2) 43-53

[3] R. Seror et al. Ann Rheum Dis (20 (1)0) 69 (6) (1) (1)03- (1) (1)09

[4] E. H. M. van der Heijden et al. Lancet Rheumatology (2020) 2 (5) 260-269

For more information about this work, please contact:

Mike Reed
Rosa & Co LLC
(650) 393-3738
mreed@rosaandco.com