Internal

In-silico clinical trials in virtual asthma patients powered by QSP accelerated the development of lunsekimig

Anastasios Siokis[1], Britta Wagenhuber[1], Lieselot Bontinck[2], Annemie Deiteren[2], Benjamin Suratt[3], Heribert Staudinger[4]

[1]Sanofi R&D, Frankfurt am Main, Germany, [2]Sanofi R&D, Ghent, Belgium, [3]Sanofi R&D, Cambridge, MA, USA, [4]Sanofi R&D, Bridgewater, NJ, USA

Contact details: Anastasios Siokis| **Email:** anastasios.siokis@sanofi.com

Abstract

Asthma is a heterogenous disease affecting millions worldwide. Despite multiple treatment options, many patients fail to respond adequately or experience diminishing therapeutic effects over time, highlighting the need for innovative treatments.

We apply mechanistic quantitative systems pharmacology (QSP) modeling to accelerate the development of lunsekimig, a novel bispecific anti-thymic stromal lymphopoietin (TSLP)/anti-interleukin (IL)-13 NANOBODY® construct.

The QSP virtual patients are calibrated and validated with diverse preclinical and clinical study data from various asthma biologics, including dupilumab, mepolizumab, lebrikizumab and tezepelumab.

The model accurately predicted the outcome of lunsekimig's phase 1b clinical trial and supported the early Proof of Concept. It facilitated lunsekimig's accelerated development by de-risking, supporting dose regimen selection, optimizing study design, and increasing the Probability of Success for the dose-ranging phase 2b study.

Mechanistic Asthma Quantitative Systems Pharmacology (QSP) model

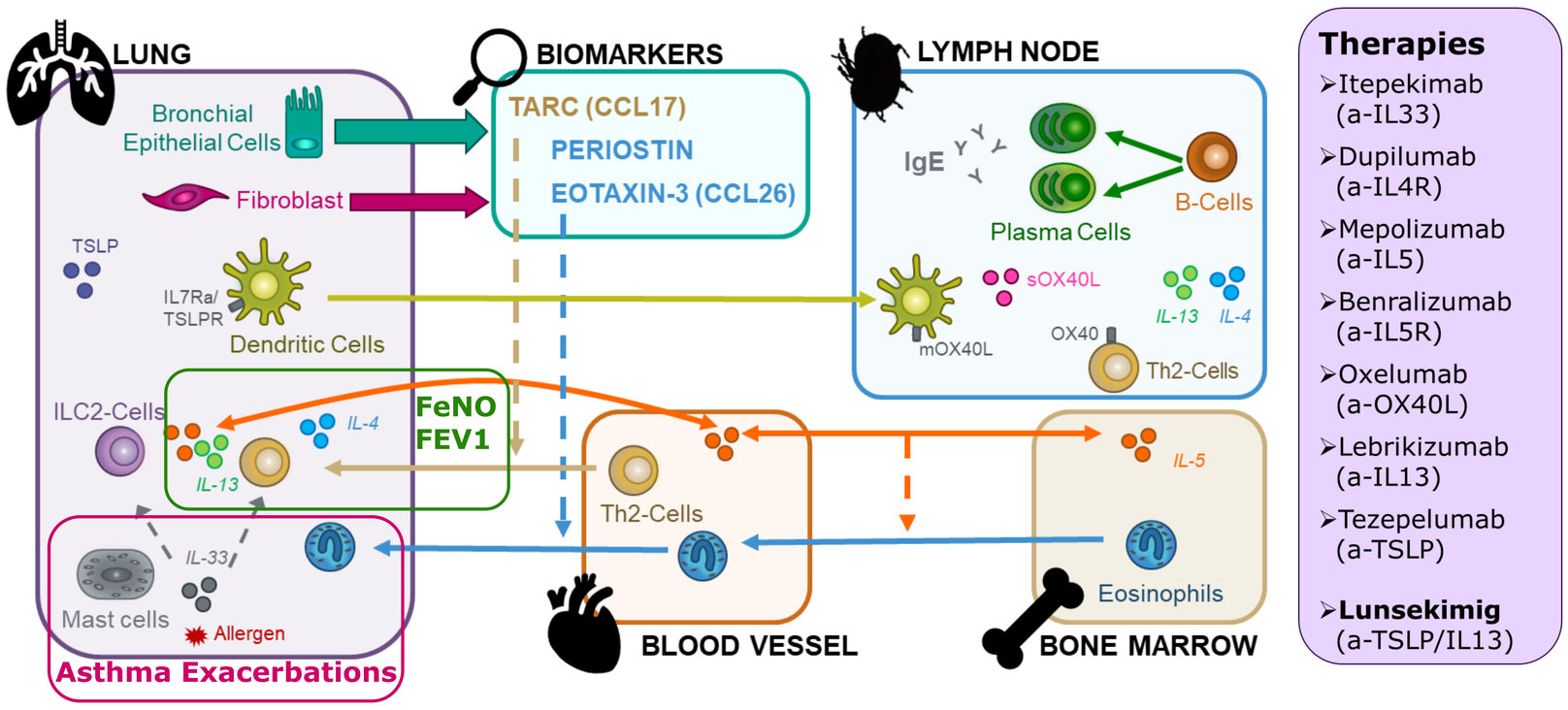

Figure 1: Mechanistic asthma QSP model, describing the type-2 pathophysiology of asthma and the different Mechanisms of Action (MoA), i.e., biologic therapies, it can simulate.

Virtual patient generation

1. **Global & local sensitivity analyses**
   - identify parameters to be perturbed
   - select biologically relevant parameters
2. **Perturb selected parameters**
   - select distribution (normal, lognormal etc.) around "average" patient
3. **Validate virtual patients**
   - Compare biomarker distributions at baseline (specific for each clinical trial to be simulated)
   - Reproduce possible correlations between biomarkers
   - Compare the treatment response of the virtual patients to a clinical trial

Validation of QSP predictions with lunsekimig's phase 1b clinical trial data

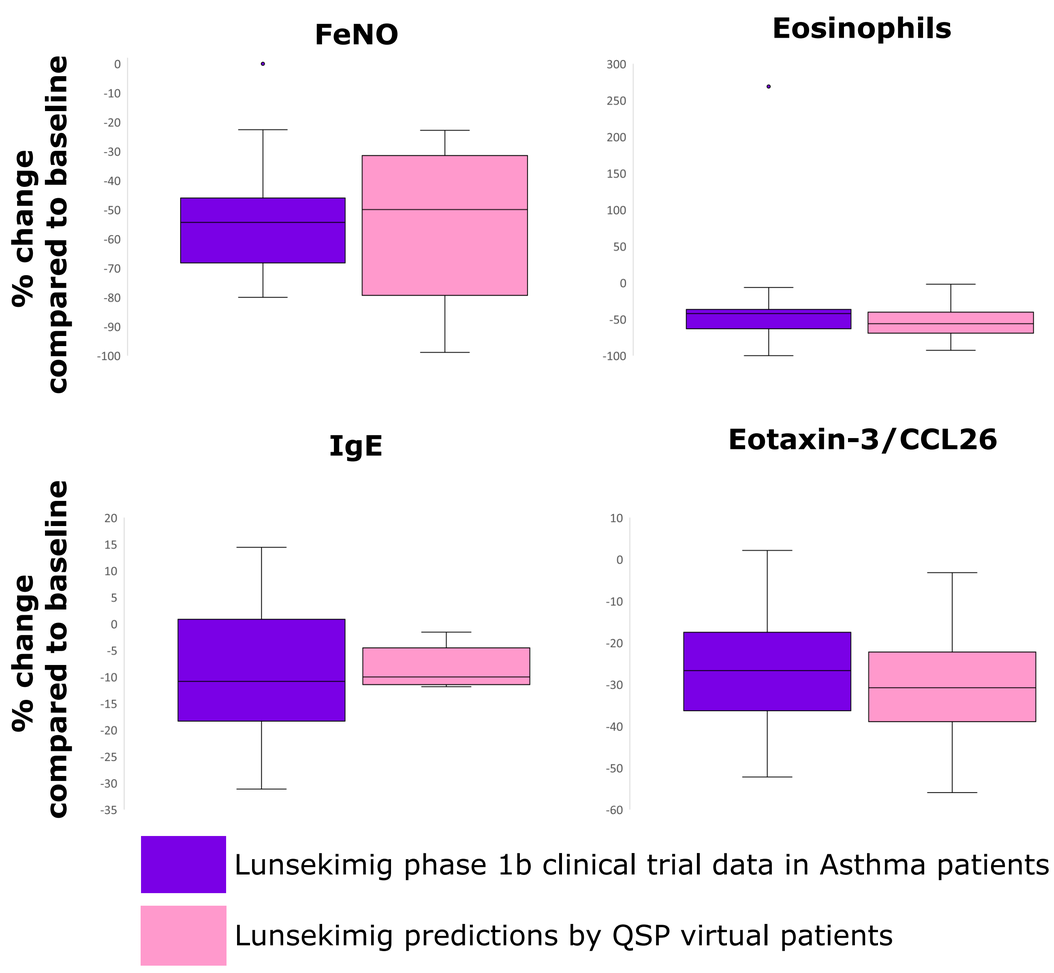

Figure 2: Validation of the QSP asthma model with phase 1b biomarker data from lunsekimig's study in asthma patients (NCT05366764 funded by Sanofi).

Predicted dose-response to de-risk and optimize phase 2b study design

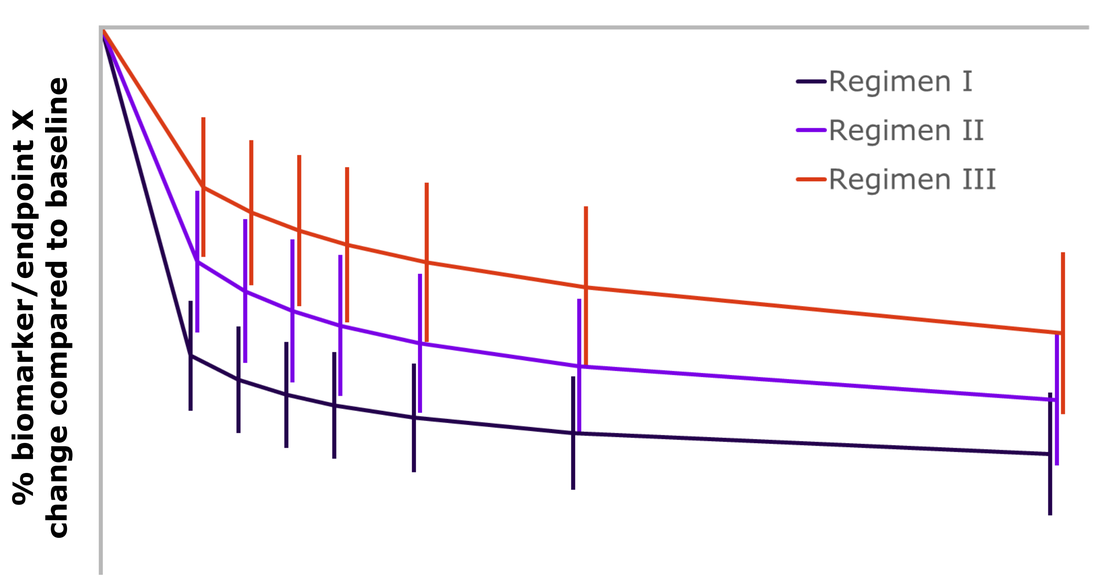

Figure 3: Illustration of predicted dose-response analysis for all biomarkers (blood eosinophils, IgE, CCL17/TARC, Periostin, CCL26/eotaxin-3, IL5, FeNO) and clinical endpoints (FEV1, AAER).

Predicting the potential of lunsekimig in head-to-head in-silico trials

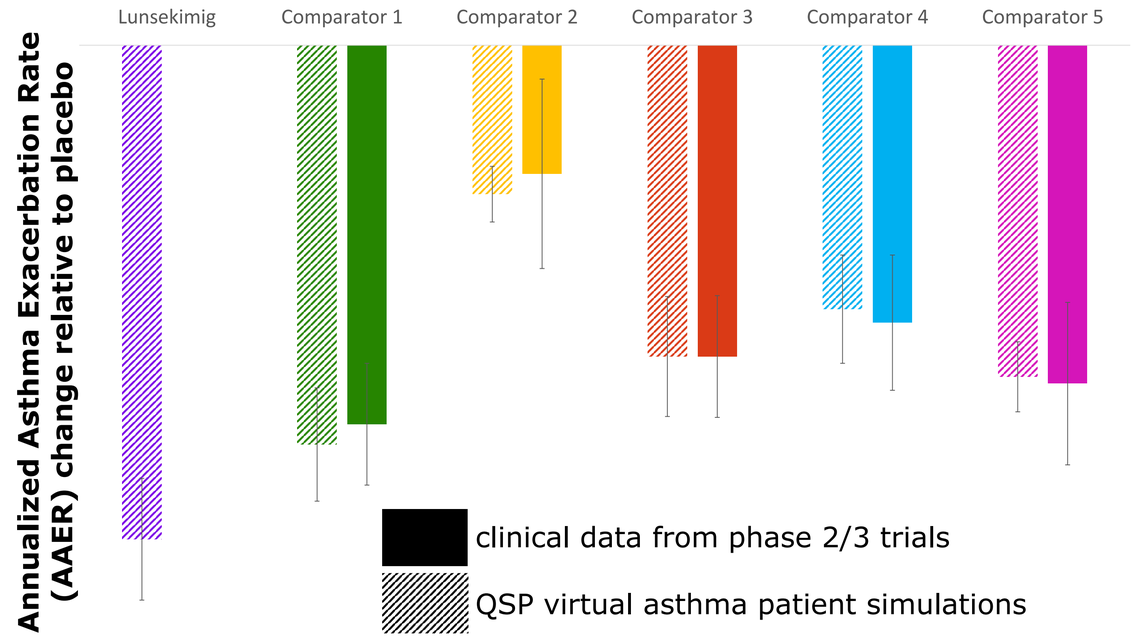

Figure 4: Validation of the QSP-simulated Annualized Asthma Exacerbation Rate (AAER) with competitor data with diverse Mechanisms of Action (MoA) and prediction of lunsekimig potential.

Conclusions

The calibrated and validated mechanistic asthma QSP model accurately predicted the pharmacodynamic response in the FIH lunsekimig study in asthma patients (NCT05366764 funded by Sanofi).

The in-silico head-to-head comparisons using QSP virtual asthma patients complemented the FIH data to support the early Proof of Concept for lunsekimig and were integral in accelerating its transition directly to phase 2b clinical development, by bypassing a phase 2a study. Together with PK and TMDD (target mediated drug disposition) modeling we de-risked, optimized and increased the Probability of Success of the phase 2b study.

[PAGE, 26-28 June 2024, Rome, Italy]

Disclosures: All authors are Sanofi employees and may hold shares and/or stock options in the company