Quantitative modelling to assess target engagement and pharmacology in early clinical development of an anti-OSM humanised mAb

Chiara Zecchin[1] and Stefano Zamuner[1]

[1]Clinical Pharmacology Modelling and Simulation, GlaxoSmithKline, London, UK

Introduction

- Oncostatin M (OSM) is a pleiotropic member of the gp130/IL-6 cytokine family and is involved in pathological processes of fibrosis, inflammation and vasculopathy.
- GSK2330811 is a humanized IgG1κ monoclonal antibody (mAb) that functionally blocks human OSM from binding to the gp130 receptor. Inhibition of OSM signalling is expected to reduce inflammation, vascular dysregulation and fibrosis.
- GSK2330811 possible indications include systemic sclerosis (SSc) and other immune-mediated diseases.

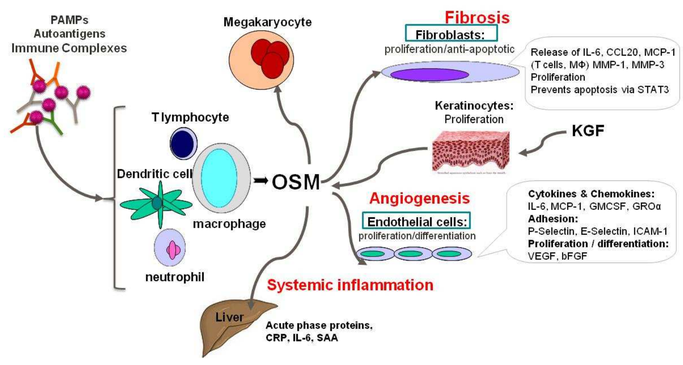

Figure 1. Schematic representation of OSM involvement in physiological processes.

Objectives

1. To develop a PKPD model to describe target engagement (TE) with GSK2330811.
2. To simulate TE for repeat dosing at several dosing levels.
3. To optimise the design of the Proof-of-Mechanism (PoM) study.

Data

Data collected during the Phase I single ascending dose study 201246 in healthy volunteers:

- doses of 0.1, 0.3, 1, 3 and 6 mg/kg were injected subcutaneously to 30 subjects (6 per cohorts)
- longitudinal PK and OSM samples in **plasma** were collected for all cohorts
- longitudinal PK and OSM samples in **blister fluid** were collected for cohorts 1, 3 and 6 mg/kg
- a total of 428 plasma and 54 blister-fluid PK observations and 394 plasma and 51 blister fluid OSM observations were available for modelling.

Methods

The mPBPK model [1] with target mediated drug disposition (TMDD) in plasma and in leaky tissues best described drug and OSM concentration in plasma and blister fluid.

The quasi-steady-state (QSS) [2] approximation was used to describe TE. The QSS model assumes that the binding rate is balanced by the sum of the dissociation and internalization rates.

GSK2330811 and OSM affinity were assumed to be identical in plasma and blister fluid.
The elimination rate of GSK2330811+OSM was allowed to assume different values in plasma and blister fluid.
The bioavailability was fixed to 0.8 (based on preclinical data).
Physiological parameters were fixed to their physiological value [1].

Inter-individual variability (IIV) in the PKPD model parameters was identified and included in a step wise manner, assuming log-normal distribution of the parameter values.
Residual unknown variability was modelled using a proportional error model.
Model selection was based on general goodness of fit criteria, which include, but are not limited to, diagnostic Goodness-of-Fit plots, reduction in minimum value of objective function, precision of parameter estimates, convergence of the minimisation algorithm and visual predictive check for the final PKPD model.

The PKPD model parameters were estimated simultaneously with the IMP estimation method in NONMEM 7.3 [3]

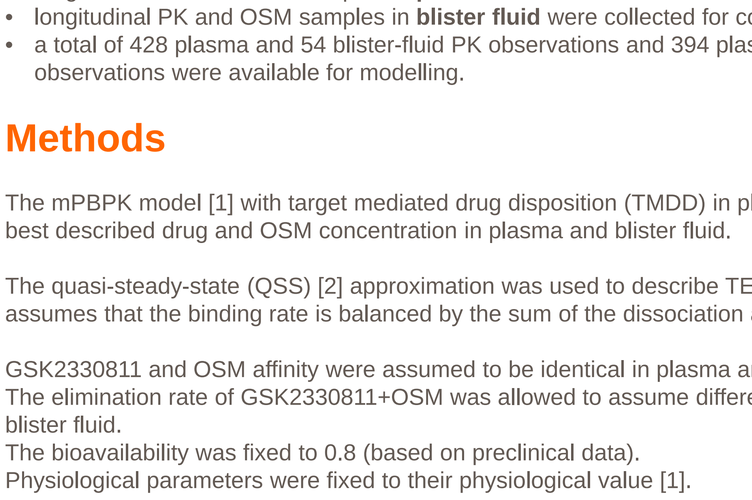

Figure 2. Schematic representation of the mPBPK model with TMDD in plasma and in blister fluid. Estimated parameters are highlighted with colours.

Virtual trials were simulated in R [4] using both uncertainty on mean estimates of population parameter values and IIV to guide the design of the PoM on the basis of TE criteria.
Different study designs (sample size, dose and dosing frequency) were tested.
Success was defined as the lower bound of the 95% CI of TE above 85% at steady state (day 56).

100 experiments were simulated for each scenario.

Results

- All parameters were estimated with good precision (%RSE≤40%) and IIV was estimated for KA, CL and KD.
- The median estimated in vivo mAb/OSM affinity equilibrium constant was 630 pM (95% CI: 494-802).
- The estimated degradation (target turnover) rate of free OSM was 1.90 hr-1 (1.45-2.50).
- The estimated degradation rate of mAb+OSM complex was 0.0477 hr-1 (0.0388-0.0587) in plasma and 0.0864 hr-1 (0.0660-0.113) in blister fluid.

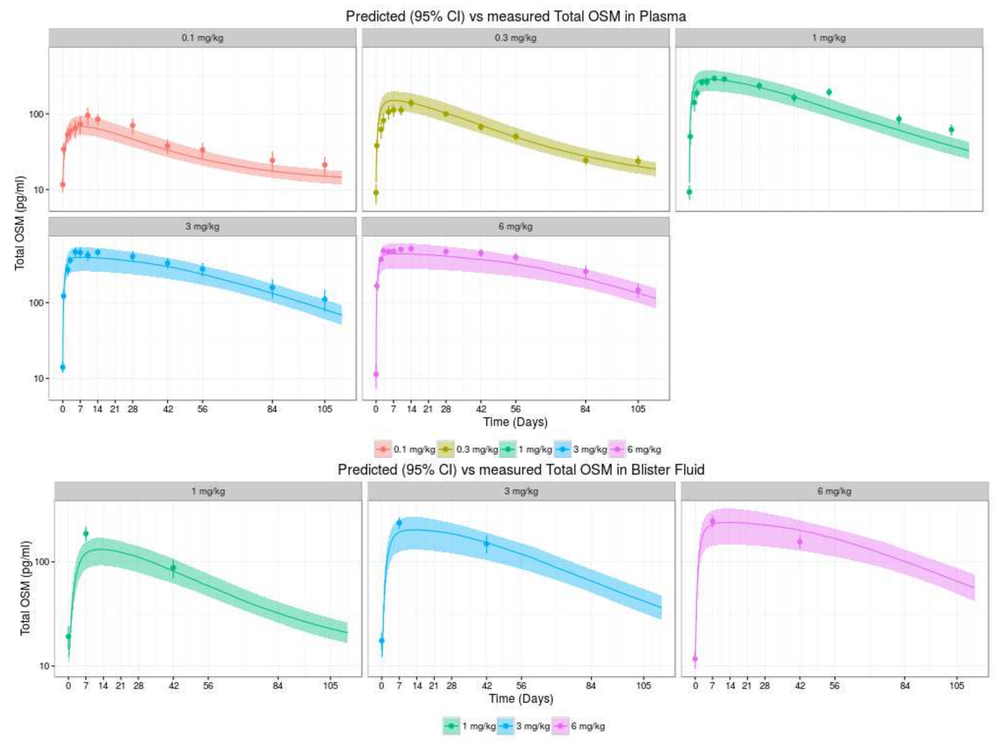

Figure 3. Model predicted (95% CI) vs measured (mean and errorbar) total OSM concentration in plasma and in blister fluid.

Target Engagement simulation

- TE was derived as 100*(1-free_OSM/free_OSM$_{baseline}$). Predicted values for free_OSM were used.
- Simulations of TE during repeat dosing were performed to aid dose selection in the PoM clinical trial in patients. TE confidence intervals are based on parameters uncertainty.
- The optimal dose for the PoM study was predicted to be 300 mg every 2 weeks.

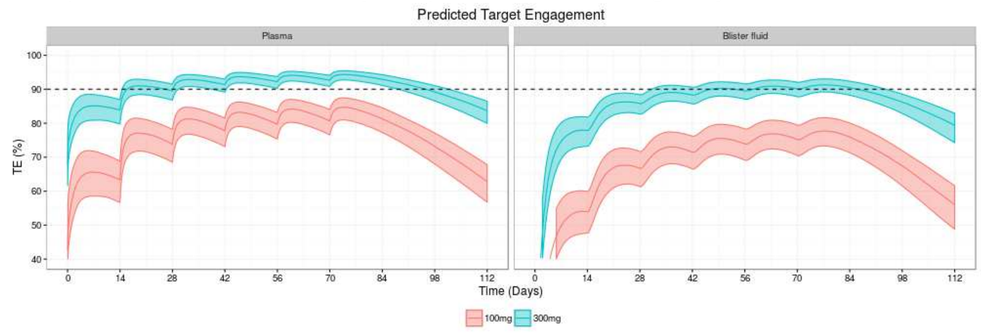

Figure 4. Model predicted (95% CI) target engagement in plasma and in blister fluid at dose levels of interest for the PoM study.

Simulation of probability of success

- Success was defined as the lower bound of the 95% CI of TE above 85% at steady state (day 56).
- For each sample size N, 100 experiments of N subjects were generated using both uncertainty on mean estimates of population parameter values and IIV. TE was predicted based on the PKPD model assuming a dose of 300 mg every 2 weeks. The lower bound of the 95% CI of TE at steady state was computed, for each experiment, assuming a t-statistic.
- A sample size of 15 - 20 subjects with a dose of 300 mg every 2 weeks was suggested to maximise the probability of success of the PoM study.

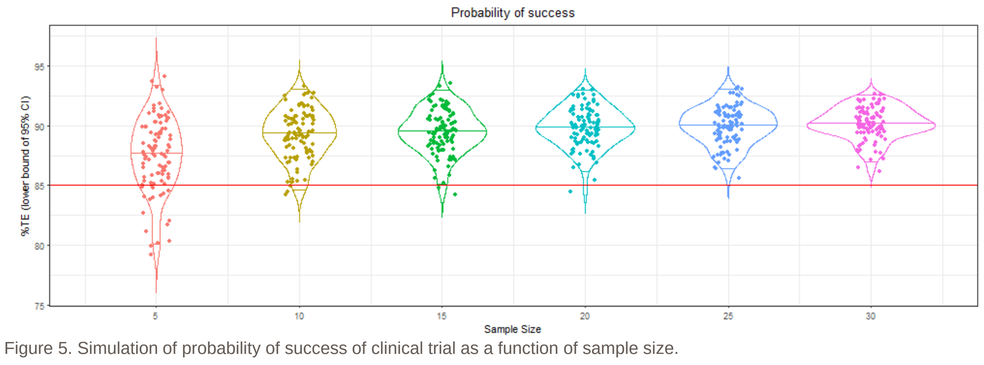

Figure 5. Simulation of probability of success of clinical trial as a function of sample size.

Conclusions

Mechanistic PKPD modelling and simulation was used to predict TE in human for repeat dosing of GSK2330811 based on data observed in a FTIH study.

These predictions helped to select optimal doses, dosing interval and sample size in the PoM study.

Acknowledgements

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References

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** C Zecchin and S Zamuner are employees and share holders of GlaxoSmithKline

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