Pharmacokinetic-target engagement modelling of an anti-CCL17 monoclonal antibody in healthy volunteers and osteoarthritis patients

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Introduction

- GSK3858279 is a human monoclonal antibody that binds to CCL17 chemokine with high affinity, thereby preventing CCL17 downstream signalling via its G-protein coupled C-C chemokine receptor, CCR4 [1, 2]. CCL17 has been implicated in OA-associated chronic pain due to its role in inflammatory processes [1].
- PK-TE modelling is a pivotal approach in understanding the in vivo interaction between therapeutic agents and their targets [3].
- The evaluation of PK-TE relationship in early phase studies not only aids in identification of effective dose ranges, but also supports the design of robust late phase studies that maximises therapeutic outcomes while minimising adverse effects [4, 5].

Methods

Data

- 877 total GSK3858279 and 1712 total CCL17 concentrations in serum were available from 118 healthy volunteers and OA patients [1, 2].

Table 1: **Key characteristics of analysis dataset**

Characteristic	Value
Age [yrs], median (range)	53 (18, 75)
Weight [kg], median (range)	81.9 (51.5, 107)
Sex [male/ female], count (%)	77/ 23
Population Type [healthy/ OA], count (%)	59/ 41
Treatment Range	0.1-10 mg/kg single IV doses; 3 mg/kg (up to 240 mg maximum) single SC dose; 240 mg weekly SC dosing
Administration Route	1-hr IV infusion; SC injection

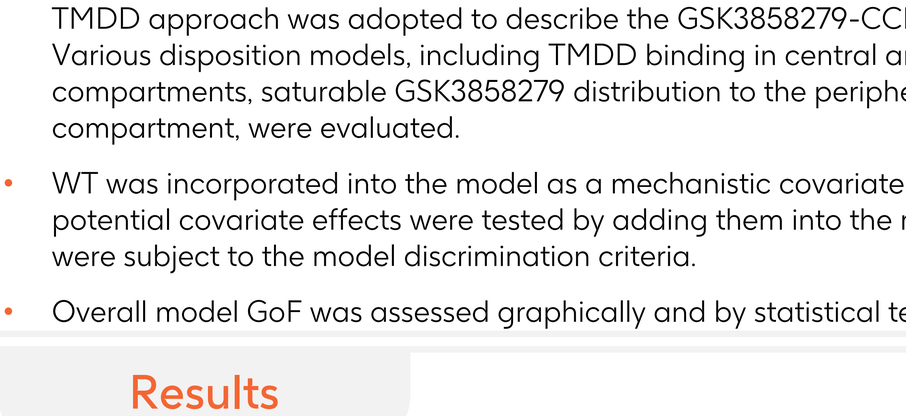
Modelling

- The analysis was conducted using NONMEM (version 7.4) and facilitated by Perl-speaks-NONMEM (version 5.2.6).
- A two-stage approach was employed. In the first step, a PK model to describe the time course of GSK3858279 PK was developed. In the second step, a TMDD approach was adopted to describe the GSK3858279-CCL17 binding. Various disposition models, including TMDD binding in central and peripheral compartments, saturable GSK3858279 distribution to the peripheral compartment, were evaluated.
- WT was incorporated into the model as a mechanistic covariate. Any other potential covariate effects were tested by adding them into the model and were subject to the model discrimination criteria.
- Overall model GoF was assessed graphically and by statistical tests.

Results

- A two-compartment model with first-order absorption and first-order elimination from the central compartment, saturable free GSK3858279 distribution to the peripheral compartment and drug-target binding occurring in the central compartment was found to best describe the PK of GSK3858279 and its binding to CCL17 (Figure 1, Table 2).
- The Quasi Steady-State approximation was adopted to describe the drug-target binding [6].

Figure 1: **Schematic representation of the PK-TE model**



- IIV was characterised by an exponential distribution. RUV was explained by a proportional error model and was estimated for each route of administration.
- The following covariate-parameter relationships were included in the model: baseline WT on CL, Vc, and Krd terms (which were allometrically scaled to 0.75, 1 and -0.25, respectively) and study on BASE.

Conclusions

- The PK-TE model could adequately describe the PK profile of total GSK3858279 and disposition of total CCL17 in healthy adults and OA patients.
- WT was included as a mechanistic covariate on CL, Vc, and Krd, with fixed allometric exponents. A study-specific BASE was estimated which significantly improved model performance.
- The developed PK-TE model will be used for simulations to support design characteristics and dose predictions in late phase studies.

Objectives

A population PK-TE modelling analysis was performed with the following objectives:

- to characterise the time course of GSK3858279 PK as well as its binding to its soluble target, CCL17, in healthy volunteers and OA patients
- to evaluate the PK-TE relationship in early phase studies to support design and dose predictions in late phase studies.

Results (cont'd)

- Shrinkage on the Kint parameter was high (59.8%).
- Model diagnostics indicated satisfactory predictive performance for total GSK3858279 and total CCL17 concentrations, supporting model utility for individual exposure predictions in healthy adults and OA patients.

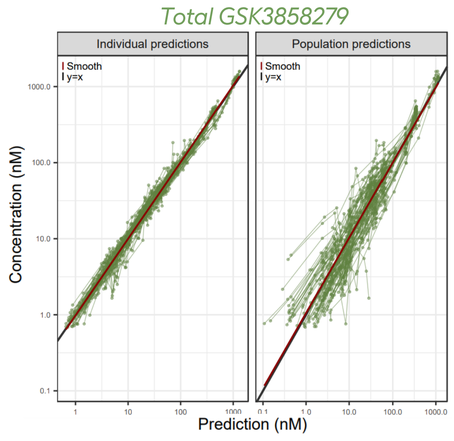
Table 2: **Summary of PK-TE model parameter estimates**

Parameter [Unit]	Value	RSE (%)
CL [L/day]	2.47	8.42
Vc [L]	4.61	13.4
Krd [1/day]	0.110	9.96
ka [1/day]	0.327	8.72
F [-]	0.470	0.410 - 0.522*
BASE [nM]	0.0737	4.44
BASE [nM] for study 209973 [2]	0.115	11.4
kdeg [1/day]	28.3	3.94
Kint [1/day]	0.0531	15.8
Kss [pM]	57.0	4.00
Vmax [nmol/day]	55.3	7.52
KM [nM]	13.6	16.1
RUV PK (IV) [CV]	0.199	3.33
RUV total CCL17 (IV) [CV]	0.366	2.02
RUV PK (SC) [CV]	0.262	2.79
RUV total CCL17 (SC) [CV]	0.270	1.24
IIV CL [CV]	0.400	9.91
IIV Vc [CV]	0.533	7.97
IIV Krd [CV]	0.229	28.1
IIV BASE [CV]	0.383	7.96
IIV Kint [CV]	0.313	64.5
IIV Vmax [CV]	0.264	18.7

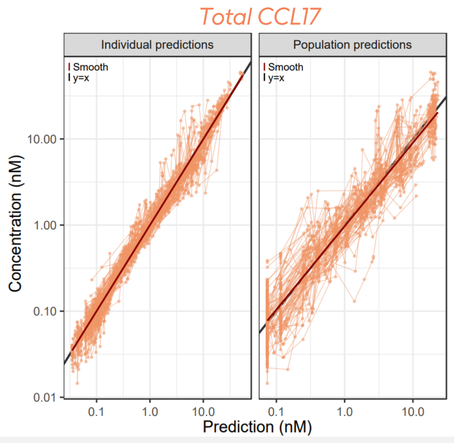
Notes:
CV, Coefficient of Variation; F, bioavailability; ka, first-order absorption rate constant; kdeg, first-order degradation rate constant; KM, concentration at half maximum velocity; Kss, quasi-steady-state equilibrium constant; RSE, Relative Standard Error; Vmax, maximum velocity of enzymatic reaction.
The RSE for IIV and RUV parameters are reported on the approximate standard deviation scale.
*90% confidence interval for F instead of RSE is presented in the table.

Figure 2: **PK-TE model diagnostic plots**

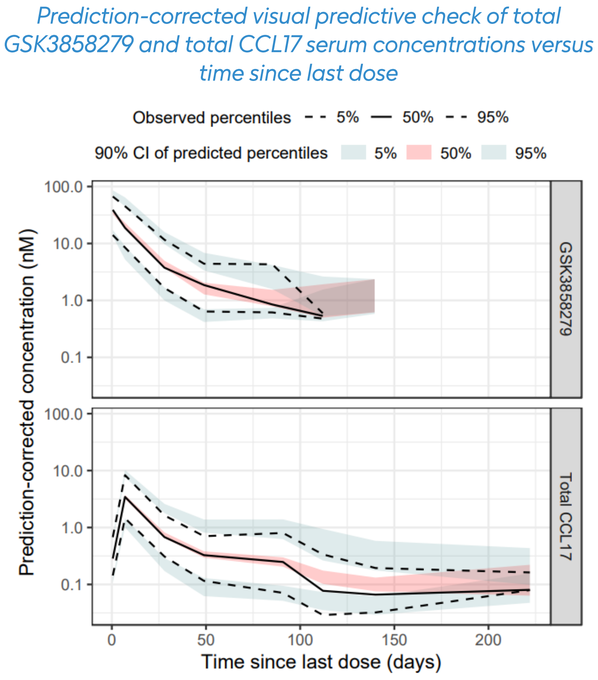
Total GSK3858279



Total CCL17



Prediction-corrected visual predictive check of total GSK3858279 and total CCL17 serum concentrations versus time since last dose



Notes:
CI, Confidence Interval.
Prediction-corrected visual predictive check was based on 200 simulations.

Abbreviations

BASE, total CCL17 baseline; CCL17, C-C motif Ligand 17; CL, Clearance; GoF, Goodness of Fit; IIV, Inter-Individual Variability; IV, Intravenous; K, first-order elimination rate constant; Kint, internalisation rate constant; Krd, distribution rate constant of GSK3858279 from peripheral to central compartment; ksyn, synthesis rate of free target; OA, Osteoarthritis; PK, Pharmacokinetics; RUV, Residual Unexplained Variability; SC, Subcutaneous; TE, Target Engagement; TMDD, Target-Mediated Drug Disposition; Vc, central volume of distribution; Vp, peripheral volume of distribution; WT, Weight

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Disclosures

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