Target engagement analysis of belimumab in patients with systemic lupus erythematosus and primary Sjögren's syndrome

Poster No. IV-69

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Introduction

- The B-lymphocyte stimulator (BLyS) binds to B-cell receptors, stimulating B-cell survival and proliferation[1]
- Elevated BLyS levels are found in B-cell–mediated autoimmune diseases such as systemic lupus erythematosus (SLE) and primary Sjögren's syndrome (pSS)[1,2]
- Belimumab (BEL), an immunoglobulin (Ig)G1λ monoclonal antibody, specifically inhibits BLyS, and is approved in SLE at an intravenous (IV) dose of 10 mg/kg every 4 weeks (Q4W; ≥5 years old), and at a subcutaneous (SC) dose of 200 mg weekly (adults only)[3]
- BEL has also been tested in patients with pSS but with less clear clinical efficacy[4]

Objective

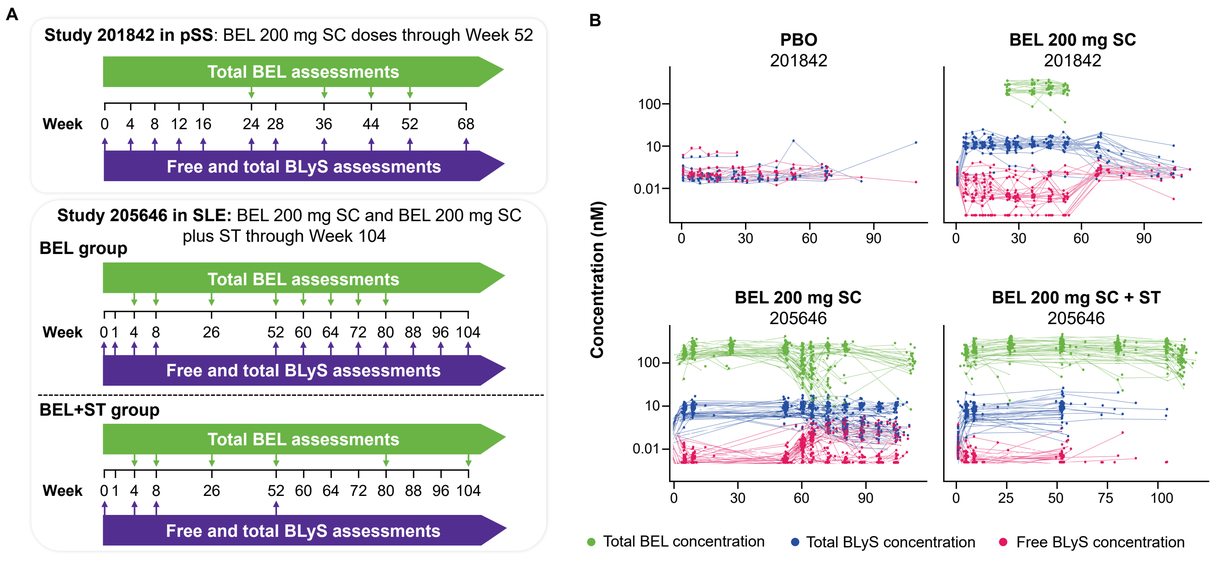
To develop a target-mediated drug disposition (TMDD) model for BEL based on total BEL pharmacokinetic (PK) and total BLyS data from two studies (201842 study in pSS [NCT02631538][2] and 205646 study in SLE [NCT03312907][5]), and to predict and characterise BEL target engagement (TE) in patients with SLE for the approved dosing regimens

Methods

Model development

- TMDD model development was based on data from the two clinical studies (**Figure 1A**)
- Total BEL, as well as free and total BLyS concentrations, were measured frequently throughout the two studies (**Figure 1B**)
- Free BLyS measurements may be overestimated due to complex dissociation in the assay, so the final model was fitted to total drug and total BLyS concentration data only

Figure 1. (A) Overview of studies used in the TMDD model development. (B) Overlay of individual observed total BEL, free BLyS and total BLyS concentrations versus time after the first dose for the patients in the source data set, stratified by study*

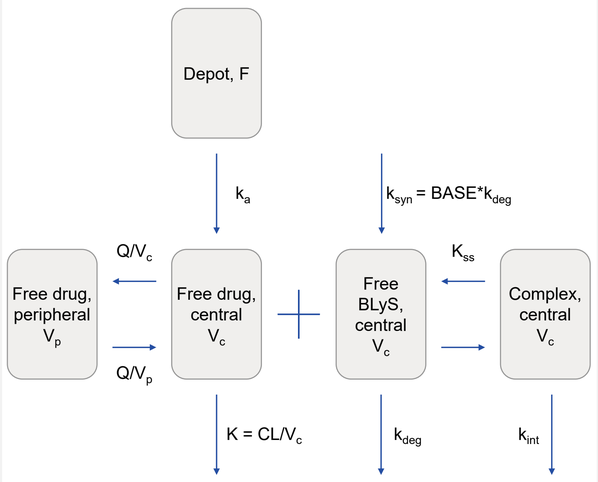


*Data are presented on a semi-logarithmic scale.
PBO, placebo; ST, standard therapy.

Final model

- A two-compartment PK model with a TMDD model component to describe BEL binding to BLyS in the central compartment was developed (**Figure 2, Table 1**) based on a previous population PK model for SC BEL[6]
- Bioavailability was fixed at the value from the previous PK model, and the clearance (CL) and volume of distribution (V) parameters were used as priors to ensure the 2-compartment PK kinetics were preserved, when fitting to a SC data set
- BASE is the baseline BLyS concentration, equal for both SLE and pSS consistent with the observed data, and k_{deg} is the first-order degradation rate constant of free BLyS (**Figure 2**)
- The degradation rate of the BEL-BLyS complex (k_{int}) was assumed to be equal between SLE and pSS

Figure 2. Illustration of the final BEL TMDD model



BASE, baseline concentration; CL, clearance; F, bioavailability; k_a, first-order absorption rate constant; k_{deg}, first-order degradation rate constant; k_{int}, degradation rate of BEL-BLyS complex; k_{ss}, quasi steady-state affinity constant; k_{syn}, synthesis rate; Q, inter-compartmental clearance; V_c, central volume of distribution; V_p, peripheral volume of distribution.

Table 1. Parameter estimates of the final BEL TMDD model

	Unit	Value	RSE (%)
CL (×WT/69)$^{0.75}$	(L/day)	0.193	2.93
V_c (×WT/69)	(L)	2.68	6.06
Q (×WT/69)$^{0.75}$	(L/day)	0.729	8.80
V_p (×WT/69)	(L)	2.86	4.80
k_a	(/day)	0.225	5.34
F		0.742	(FIX)
t_{lag}	(day)	0.179	1.98
BASE	(nM)	0.0513	4.59
k_{deg}	(/day)	1.14	7.95
k_{int}	(/day)	0.0544	8.08
K_{ss}	(pM)	541	14.1
IIV CL	(CV)	0.349	4.23
IIV V_c	(CV)	0.713	4.83
Corr CL-V_c		0.280	10.3
IIV Q	(CV)	1.01	10.4
IIV V_p	(CV)	0.329	7.45
IIV BASE		0.526	7.55
IIV k_{int}		0.549	9.73

The RSE for IIV parameters are reported on the approximate standard deviation scale. IIV, inter-individual variability; RSE, relative standard error; t_{lag}, absorption lag time; WT, body weight.

BEL TE simulations

BEL TE was defined as the degree of free BLyS depletion from baseline:

$$TE(t) = 100 \times \left(1 - \frac{\text{Free BLyS}(t)}{\text{BASE}}\right)$$

- The model was used to simulate BEL TE in SLE and pSS in a virtual population of 1000 patients, for the following dosing regimens:
  - **IV**: 1 mg/kg, 4 mg/kg, and 10 mg/kg on Days 0, 14, 28, then every 28 days thereafter
  - **SC**: 200 mg weekly

Assessment criteria

- For each dosing regimen, the simulated TE across a dosing interval at steady state was characterised by the percentage of the population having minimum and average TE above 80%, 85%, 90%, and 95% in a dosing interval

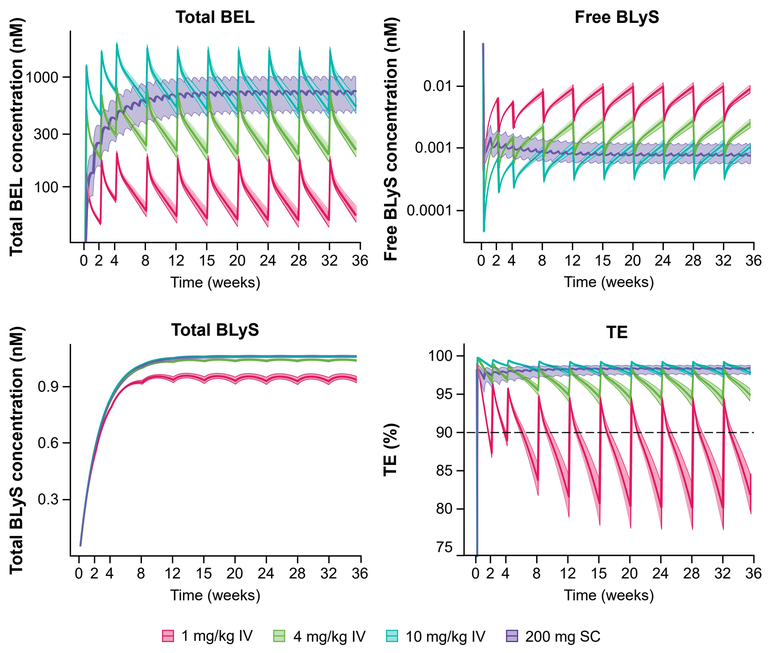
Post hoc analysis

- In a post hoc analysis, the model was used to explore TE in the two pivotal Phase 3 studies of IV BEL in patients with SLE, BLISS-52 (BEL110752)[7] and BLISS-76 (BEL110751),[1] which measured efficacy achieved for 1 mg/kg and 10 mg/kg IV Q4W

Results

- The BEL TMDD model, using the quasi steady-state approximation, was successfully fitted to the data without free BLyS observations (**Table 1**)
- Simulated profiles, considering IIV variability due to WT only for clarity, showed high TE for the 10 mg/kg IV and 200 mg SC doses approved for SLE, which clearly separated from the lower simulated dose levels 1 mg/kg and 4 mg/kg IV (**Figure 3**)

Figure 3. Simulated median and 95% prediction intervals of total BEL, free and total BLyS concentrations and the corresponding TE versus time since the first dose, including IIV due to WT only



BEL concentration data are presented on a semi-logarithmic scale. The y-axis on the TE plot starts from 75%, and the horizontal dashed line indicates 90% TE.

- Across the dosing interval at steady state, only the 10 mg/kg IV and 200 mg SC dosing regimens, approved for SLE, achieved a minimum TE of >90% in at least 95% of the population (**Table 2A**)
  - In comparison, 1 mg/kg and 4 mg/kg IV dosing regimens were expected to achieve a minimum TE >90% in only 15.6% and 80.2% of the population, respectively (**Table 2A**)
- Similarly, an average TE at steady state of >95% in at least 95% of the population was expected for the 10 mg/kg IV and 200 mg SC dosing regimens, whereas only 5.3% and 67.7% of the population met this condition for the 1 mg/kg and 4 mg/kg IV doses (**Table 2B**)

Table 2. Percentage of the population having minimum TE (A) and average TE (B) in a dosing interval at steady state above 80%, 85%, 90%, and 95%

A (Minimum TE at steady state)

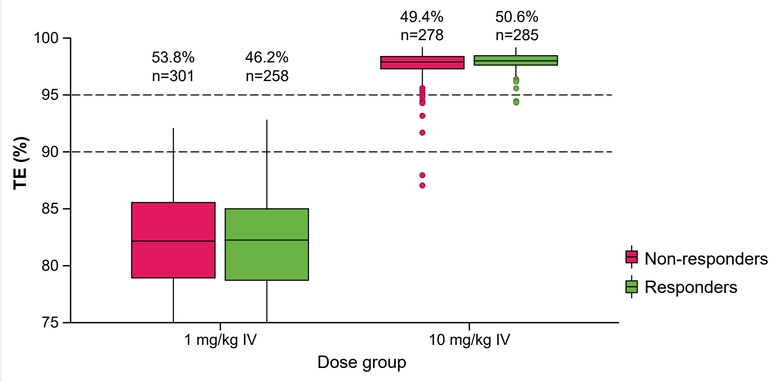
Dose regimen	>80% TE	>85% TE	>90% TE	>95% TE
1 mg/kg IV	51.5	34.4	15.6	2.0
4 mg/kg IV	96.6	91.2	80.2	46.4
10 mg/kg IV	99.5	99.4	97.8	85.8
200 mg SC	100.0	100.0	99.7	95.9

B (Average TE at steady state)

Dose regimen	>80% TE	>85% TE	>90% TE	>95% TE
1 mg/kg IV	75.5	59.5	31.3	5.3
4 mg/kg IV	99.5	98.8	93.7	67.7
10 mg/kg IV	100.0	99.8	99.6	97.0
200 mg SC	100.0	100.0	99.9	96.9

- These findings were supported by the post hoc analysis of the PK and BLyS levels from the BLISS-52 and BLISS-76 studies
- The predicted average TE at steady state was generally >95% for the 10 mg/kg IV dose group but <90% for the 1 mg/kg IV dose group (**Figure 4**)

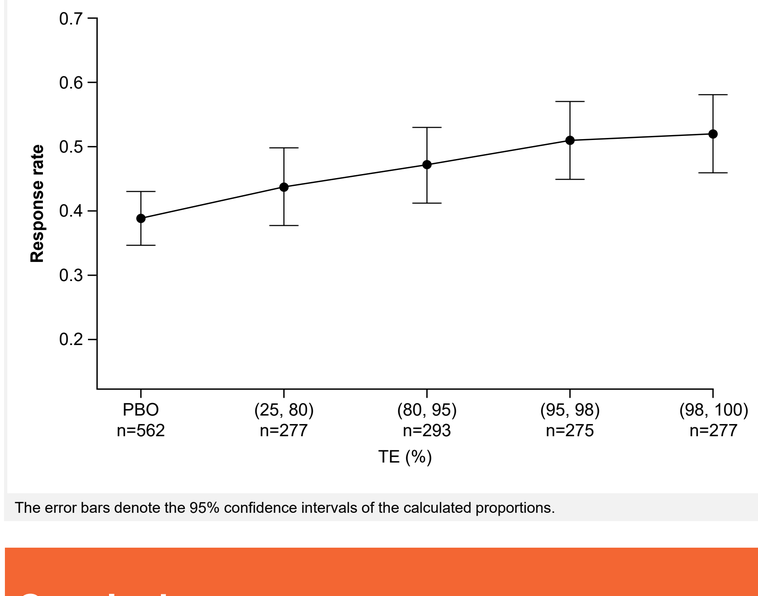
Figure 4. Boxplots of average TE at steady state versus dose group, stratified by non-responders and responders



Responder is defined as a patient with an SRI response (4-point reduction in SELENA-SLEDAI score, no new BILAG A organ domain score and no more than 1 new BILAG B score, and no worsening (increase <0.3) in PGA score versus baseline) at Week 52. The proportions of patients and patient counts per stratified dose group are shown above each boxplot. For comparison, PBO response rate was below 40.0%. BILAG, British Isles Lupus Assessment Group; PGA, Physician's Global Assessment; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment–SLE Disease Activity Index; SRI, SLE Responder Index.

- Across all patients from both 1 mg/kg and 10 mg/kg IV dose levels, there was a positive correlation between efficacy and average TE at steady state, with maximum efficacy achieved for average TE of 95% (**Figure 5**)
- These pivotal Phase 3 studies demonstrated that average TE at steady state >95% is associated with maximum efficacy for BEL treatment and that this is achieved for 10 mg/kg IV

Figure 5. Response rate after 52 weeks treatment versus binned average TE intervals at steady state or PBO



The error bars denote the 95% confidence intervals of the calculated proportions.

Conclusions

- In this analysis, the observed PK and total BLyS levels from 201842 pSS and 205646 SLE studies were combined in a TMDD model to characterise TE in response to BEL therapy
- A high degree of TE was predicted for the 10 mg/kg IV and 200 mg SC dosing regimens, approved for SLE, compared with the lower 1 mg/kg and 4 mg/kg IV regimens
- Maximum efficacy was associated with an average TE at steady state >95%, and minimum TE at steady state >90%, and was achieved in at least 95% of patients for the approved SLE dosing regimens

Disclosures

RD and **JWTY** are employees of GSK and hold stocks and shares in the company. **ES** and **EM** are employees of Pharmetheus AB and have worked as paid consultants for GSK.

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