Abstract PO.5.101 Table 2 PERR, CRR and time to renal-related event or death in the European subgroup

Endpoint	PBO (n=45)	BEL (n=41)	Observed treatment difference vs PBO (%); OR/HR (95% CI)	p-value
PERR at Week 104, n (%)	15 (33.3)	15 (36.6)	3.25 OR 1.22 (0.48, 3.10)	0.683
CRR at Week 104, n (%)	9 (20.0)	12 (29.3)	9.27 OR 1.84 (0.65, 5.18)	0.248
Time to renal-related event* or death†	—	—	— HR 0.52 (0.17, 1.60)	—
Patients with an event, n (%)	11 (24.4)	5 (12.2)	—	—

*Defined as the first event of the following: end-stage renal disease, doubling of serum creatinine from baseline, renal worsening, renal disease–related treatment failure; †*post hoc* analysis
Treatments: BEL, belimumab; PBO, placebo
Endpoints: CRR, complete renal response; PERR, primary efficacy renal response.
Other: CI, confidence interval; HR, hazard ratio; OR, odds ratio

≥60 ml/min/1.73 m2, no rescue therapy) at Week 104; secondary endpoints included complete renal response (CRR: uPCR <0.5, eGFR no more than 10% below the pre-flare value or ≥90 ml/min/1.73 m2, no rescue therapy) at Week 104 and time to renal-related event (end-stage renal disease/doubling of serum creatinine from baseline/renal worsening/renal disease-related treatment failure) or death. The subgroup analyses reported here were pre-specified, except for time to renal-related event or death (post hoc), and are descriptive.

Results Out of the overall population (N=448), the European subgroup comprised 86 patients (19.2%; PBO, n=45; BEL, n=41) from Belgium, the Czech Republic, France, Germany, Hungary, the Netherlands, the Russian Federation, Spain and the United Kingdom. Compared with the PBO group, more patients in the BEL group had nephrotic range proteinuria, and longer disease duration (both LN and systemic lupus erythematosus [SLE]) at baseline (Table 1). Overall, more patients received CYC/AZA than MMF induction therapies (Table 1). Both PERR and CRR had numerical trends in favour of BEL compared with PBO at Week 104 (Table 2), which was consistent with the results of the overall study population.[1] Belimumab reduced the risk of renal-related event or death over time by 48% compared with PBO (Table 2). Consistent with the overall study population, almost all patients reported at least one adverse event, regardless of treatment group (PBO, n=44 [97.8%]; BEL, n=39 [95.1%]).

Conclusions Greater improvements in renal outcomes were seen in favour of BEL compared with PBO; as expected in a small subgroup, these were not statistically different. The higher proportion of patients in the BEL group versus the PBO group with baseline nephrotic range proteinuria and longer disease durations may explain why the PERR and CRR results were less pronounced in the European subgroup than the overall population. These results should be interpreted cautiously due to the inherent limitations of a subgroup analysis and the small sample sizes.

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PO.5.102 PHARMACOKINETIC MODELLING OF BELIMUMAB IN PATIENTS WITH LUPUS NEPHRITIS: INTRAVENOUS AND SUBCUTANEOUS LOADING DOSE REGIMEN JUSTIFICATION

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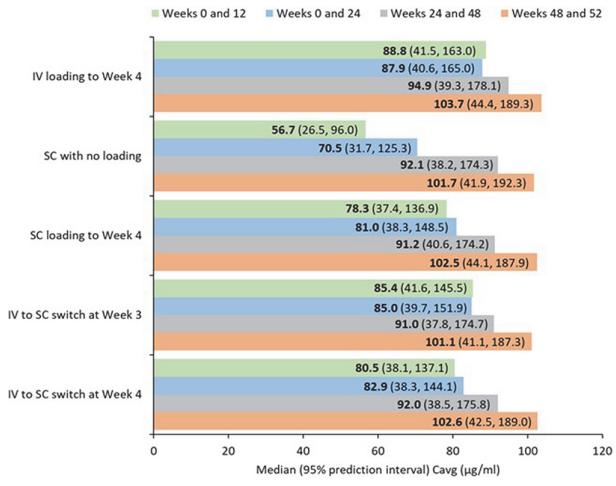
Purpose Intravenous (IV) belimumab (BEL) is approved for lupus nephritis (LN) based on the BLISS-LN study (GSK Study BEL114054, NCT01639339), which showed that BEL 10 mg/kg IV every 4 weeks with loading to Week 4 (administered as an additional 10 mg/kg dose at Week 2) was efficacious.[1,2] Exposure-response analyses showed that proteinuria-based dose adjustment was not required,[3] supporting the approval of this dose for LN. The same dose is approved for extra-renal systemic lupus erythematosus (SLE).2 Unlike the IV dose, the approved subcutaneous (SC) regimen in extra-renal SLE (200 mg once weekly [QW]) does not include loading and takes up to 12 weeks for exposure to reach steady state (SS).[4] SC BEL has not been studied in LN, and although the absence of SC loading does not impact efficacy in SLE, it is unknown whether this also applies to active LN, where proteinuria is higher. Therefore, pharmacokinetic (PK) simulations were used to evaluate SC loading dose regimens in patients (pts) with LN, aiming to match the early exposure observed with BEL IV and to inform the most appropriate time to switch from IV to SC dosing during initial treatment.

Methods A post hoc population PK model for IV dosing in pts with LN was developed from the BLISS-LN dataset. The model was extended to include SC dosing, considering the absorption parameters from the model previously developed for SC dosing in pts with SLE.4 The model was used to simulate BEL exposure for IV and SC dosing in pts with LN. The SC regimen was evaluated with and without loading (Table 1). PK simulations were also used to evaluate BEL

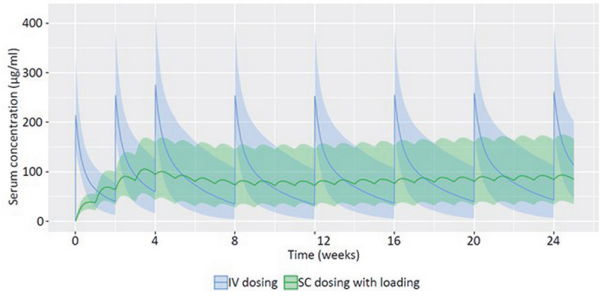
exposure for an IV to SC switch after the Week 2 IV loading dose. Each dosing regimen simulated BEL PK in 1000 virtual pts.
Results Average BEL exposure over the first 12 (Cavg[0–12]) and 24 weeks are shown in Figure 1. SC dosing without loading resulted in lower BEL exposure than IV dosing (Cavg[0–12]: 56.7 µg/ml vs 88.8 µg/ml, respectively). Adding a 4-week loading period (400 mg QW to Day 21) to SC dosing raised BEL exposure for Week 0–12 to average levels similar to those of IV dosing (Cavg[0–12]: 78.3 µg/ml vs 88.8 µg/ml, respectively). Switching from IV to SC at Weeks 3 or 4 (i.e. after the Week 2 IV loading) was shown to yield similar average exposures over the first 12 and 24 weeks compared with remaining on IV. After 24 weeks, when proteinuria levels had decreased in response to treatment and BEL PK was close to SS, the IV and SC regimens predicted similar BEL exposures (Figure 1 and 2).

Abstract PO.5.102 Table 1 Summary of simulated dosing regimens

Dosing regimen	Description
IV loading to Week 4	10 mg/kg IV on Days 0, 14 and 28 then every 4 weeks (the IV dose approved for SLE)
SC with no loading	200 mg SC every week (the SC dose approved for SLE)
SC loading to Week 4	400 mg SC every week to Day 21 then 200 mg every week from Day 28 onwards
IV to SC switch at Week 3	10 mg/kg IV on Days 0 and 14, followed by 200 mg SC every week from Day 21
IV to SC switch at Week 4	10 mg/kg IV on Days 0 and 14, followed by 200 mg SC every week from Day 28



Abstract PO.5.102 Figure 1 Median (95% prediction interval) BEL exposure for IV and SC dosing regimens over 52 weeks



Abstract PO.5.102 Figure 2 Concentration versus time BEL IV and SC loading to week 4

Conclusions PK simulations predicted that the SC dose with 4-week loading (400 mg QW to Day 21) would achieve an average BEL exposure similar to that of the IV regimen. Overall, the results from BLISS-LN and PK simulations support the approval of the IV dose and SC dosing with loading, with no additional dose adjustments required for proteinuria levels.

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PO.5.103 STUDY OF B CELLS IN PATIENTS WITH LUPUS NEPHRITIS: PARAMETERS OF DISEASE ACTIVITY AND REMISSION

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Purpose B cells play a pivotal role in systemic lupus erythematosus (SLE) pathogenesis. The aim of this study was to investigate the relationship between peripheral blood B cell phenotype, disease activity and histological lesions in lupus nephritis (LN-SLE).
Methods One hundred LN-SLE with active renal involvement, 40 at disease diagnosis (Early) and 60 in whom LN occurred after the disease diagnosis (Long) were enrolled, 37 controls were included. Clinical, laboratory and demographic data were collected at baseline and after 6 and 12 months. Disease activity was recorded using SLEDAI-2K. Nephritic class was evaluated according to the ISN/RPS classification. Memory B cells immunophenotyping (IgD/CD27 classification) was analyzed in peripheral blood through flow cytometry. IL-6 and BAFF serum levels were assayed by ELISA.
Results There were no differences in the distribution of the renal classes and in activity and chronicity indices in the Early and Long groups. A direct correlation was observed between chronicity index score and creatinine in the whole cohort ($R=0.342; p<0.01$) and in Early ($R=0.528; p=0.01$) and Long ($R=0.337; p=0.02$). The histological activity index was significantly higher in anti-dsDNA positive than in negative ones (6.6 ± 4.8 vs $2.8\pm3.5; p=0.01$), and in patients with at least one antiphospholipid (APL-ab) positivity (6.8 ± 4.8 vs $5.1\pm4.8; p=0.05$). The presence of histological lesions (glomerulosclerosis and fibrocellular crescents) and the positivity for at least one of the APL-ab were associated to the failure in achieving clinical remission within 12 months, while baseline 24h-UP levels ≤2750mg were associated to remission achievement [OR:2.6(95%CIs:1.1–5.8)]. Regarding B cells subsets, a lower percentage of CD19pos and IgDposCD27pos in LN-SLE compared to controls ($6.8\pm5.5\%$ vs $10.5\pm3.5\%; p<0.01$ and $11.1\pm12.0\%$ vs $15.3\pm8.0\%; p<0.01$, respectively) was observed. In addition, we found higher levels of IgDnegCD27neg and CD27posCD38pos in LN-SLE than in controls [(CD27negIgDneg $10.0\pm8.7\%$ vs $4.1\pm1.9\%; p<0.01$)(CD27posCD38pos $4.4\pm5.3\%$ vs $1.0\pm0.5\%; p<0.01$)]. Furthermore, CD19pos and