Safety and Efficacy of Belimumab in Patients with Lupus Nephritis: Open-label Extension of BLISS-LN Study

Running head: Open-label study of belimumab in lupus nephritis

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*At the time of the study

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Supplemental material

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Withdrawal criteria

Patients were withdrawn from the study if any of the following criteria were met:

- Missed 3 or more consecutive doses of study treatment
- Prohibited concurrent medication (live vaccine, biologics, and other investigational drugs)
- Prohibited therapy (anti-tumor necrosis factor therapy, intravenous immunoglobulin G [IgG], plasmapheresis)
- Unacceptable toxicity
- Pregnancy
- Withdrew consent
- Patients positive for anti-hepatitis B core antigen at screening who developed elevated liver function tests >2.5 × upper limit of normal during the study, followed by a hepatitis B virus DNA test that showed detectable viral load

Patients who entered the open-label phase and withdrew early returned for an exit visit approximately 4 weeks after their last dose of study treatment, as well as a follow-up visit approximately 8 weeks after the last dose of study treatment.

Supplemental Table 1. Double-blind phase baseline characteristics for patients enrolled in the open-label phase and the overall population of the double-blind phase (modified intention-to-treat populations)

	Open-label phase population (N=254)		**Double-blind phase overall population (N=446)**	
	Placebo-to-belimumab Intravenous 10 mg/kg (N=122)	**Belimumab-to-belimumab Intravenous 10 mg/kg (N=132)**	**Placebo (N=223)**	**Belimumab Intravenous 10 mg/kg (N=223)**
Race, n (%)				
American Indian or Alaska Native	3 (3)	1 (0.8)	6 (3)	4 (2)
Asian	67 (55)	71 (54)	109 (49)	114 (51)
Black African/American Ancestry	13 (11)	12 (9)	31 (14)	30 (13)
White/Caucasian	38 (31)	47 (36)	75 (34)	73 (33)
Mixed race	1 (0.8)	1 (0.8)	2 (0.9)	2 (0.9)
Age (years), mean (SD)	34 (10)	34 (10)	33 (11)	34 (11)
Female, n (%)	110 (90)	118 (89)	196 (88)	197 (88)
Lupus nephritis class, n (%)				
Class III or IV	70 (57)	78 (59)	132 (59)	126 (56)
Class III + V or Class IV + V	31 (25)	36 (27)	55 (25)	61 (27)

Class V	21 (17)	18 (14)	36 (16)	36 (16)
UPCR (g/g), median (IQR)	2.8 (1.4, 4.7)	2.0 (0.9, 4.0)	2.5 (1.4, 4.8)	2.6 (1.1, 4.4)
UPCR category (g/g), n (%)				
<0.5	5 (4)	7 (5)	8 (4)	9 (4)
≤0.7	9 (7)	19 (14)	15 (7)	22 (10)
0.5−<3	62 (51)	77 (58)	123 (55)	123 (55)
≥3	55 (45)	48 (36)	92 (41)	91 (41)
eGFR (ml/min/1.73 m^2), median (IQR)	98 (67, 122)	99 (74, 120)	98 (67, 127)	99 (72, 124)
SLEDAI-S2K score, median (IQR)	12 (8, 16)*	12 (8, 15)	12 (8, 16)	12 (8, 16)
SLEDAI-S2K category, n (%)				
<8	22 (18)	26 (20)	36 (16)	37 (17)
8−<12	29 (24)	33 (25)	60 (27)	55 (25)
12−<16	37 (30)	40 (30)	59 (27)	63 (28)
≥16	33 (27)	33 (25)	67 (30)	68 (31)
Missing	1 (0.8)	0 (0)	1 (0.4)	0 (0)

*N=121.

eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation; SLE, systemic lupus erythematosus; SLEDAI-S2K, SLE Disease Activity Index-2000; UPCR, urine protein:creatinine ratio

Treatment failures and discontinuations among non-responders for primary efficacy renal response and complete renal response (based on the double-blind phase criteria; *post hoc* analyses)

The observed decrease in primary efficacy renal response and complete renal response rates at open-label Week 28 in the belimumab-to-belimumab group was mainly due to discontinuations (n=8) or intake of concomitant medications (n=9) that were allowed during the open-label phase but were counted as treatment failures for the statistical analysis. Of the 9 patients who were treatment failures due to prohibited medications, 1 patient took prednisone for non-SLE reason of excemal dermatitis as well as for a kidney-related reason, 3 patients took prednisone >10 mg after the open-label baseline for non-kidney SLE reasons of arthritis and rash flare, and 5 patients took prednisone, IgG, hydroxychloroquine or switched to subcutaneous belimumab due to non-SLE reasons of upper respiratory infections, allergy prevention, immuno-enhancement for a serious AE, and maintenance medication. In the placebo-to-belimumab group, one patient took concomitant medication of prednisone for non-kidney reasons of bronchitis and swelling of hands, which was counted as treatment failure for the statistical analysis.

Of the 8 patients who discontinued from the study in the belimumab-to-belimumab group, 4 were due to AEs (peripheral edema, sinusitis, cellulitis, skin ulcer, myringitis, pharyngitis, disseminated tuberculosis) and 4 were due to other reasons (lost to follow-up, protocol deviation, consent withdrawal). In the placebo-to-belimumab group, there was one patient who discontinued from the study; the patient died due to multiple organ dysfunction syndrome, sepsis secondary to nosocomial pneumonia, and chronic kidney disease.