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Original article

EQ-5D-3L full health state discriminates between drug and placebo in clinical trials of systemic lupus erythematosus

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Abstract

Objectives. The objectives of this study were to investigate the discriminative ability of EQ-5D-3L full health state (FHS) in clinical trials of SLE, and to identify factors associated with FHS after treatment.

Methods. Data from the BLISS-52 (NCT00424476) and BLISS-76 (NCT00410384) trials of belimumab ($N = 1684$) were utilized. FHS was defined as a response of no problems in all five EQ-5D-3L dimensions, yielding an index score of 1. The Pearson's χ^2 or Fisher's exact test was employed for comparisons, and logistic regression for adjustments and assessment of independence.

Results. We demonstrated higher EQ-5D-3L FHS frequencies among patients given standard therapy (ST) plus the licensed belimumab dose *vs* ST alone (26.1% *vs* 19.4%; $P = 0.001$; week 52), and within SRI-4 responders *vs* non-responders (27.0% *vs* 19.8%; $P < 0.001$; week 52) from weeks 36 to 52. In multivariable regression analysis, SLEDAI-2K (OR: 0.90; 95% CI: 0.87, 0.94; $P < 0.001$) and SLICC/ACR Damage Index (OR: 0.79; 95% CI: 0.69, 0.91; $P = 0.001$) scores were independently associated with lower FHS frequencies at week 52, while adding monthly infusions of belimumab 10 mg/kg to ST favoured FHS perception (OR: 1.60; 95% CI: 1.15, 2.24; $P = 0.006$). Add-on belimumab 10 mg/kg yielded higher FHS frequencies in antimalarial users *vs* non-users (29.9% *vs* 20.1%; $P = 0.011$), and in anti-dsDNA- and anti-Sm- positive *vs* negative patients (31.4% *vs* 13.4%; $P < 0.001$ and 33.0% *vs* 22.6%; $P = 0.010$, respectively), whereas no significant differences were observed in patients given ST alone.

Conclusion. EQ-5D-3L FHS distinguished belimumab from placebo and responders from non-responders, and exhibited known-group validity in subgroup analysis. FHS may prove a useful patient-reported outcome in SLE studies.

Key words: systemic lupus erythematosus, health-related quality of life, patient-reported outcomes, patient perspective, outcomes research

CLINICAL SCIENCE

Rheumatology key messages

- EQ-5D-3L full health state discriminated belimumab from placebo and responders from non-responders in SLE randomized clinical trials.
- Add-on belimumab yielded greater EQ-5D-3L FHS frequencies in anti-dsDNA- and anti-Sm- positive versus negative patients.
- Concomitant use of antimalarials enhanced the benefit from belimumab to yield an EQ-5D-3L full health state.

Introduction

SLE is a chronic autoimmune disease with detrimental effects on patients' health-related quality of life (HRQoL) [1]. Patient-reported HRQoL outcomes gain increasing endorsement within the SLE researcher community, as well as in routine care as a complemental part of the clinical evaluation [2]. This marks a paradigm shift towards patient-centred care, from a historical negligence of the patient's perspective.

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During the OMERACT IV consensus conference [3], four important core outcomes for SLE clinical trials were ratified, i.e. disease activity, HRQoL, medication side effects, and organ damage, in that priority order. The known discordance in perceptions of disease activity between physicians and SLE patients [4] further justifies the use of patient-reported outcome measures (PROMs). Indeed, PROMs are increasingly used in SLE clinical trials [2]. The Medical Outcomes Survey Short Form 36 (SF-36) [5] and Functional Assessment of Chronic Illness Therapy Fatigue scale (FACIT-F) [6] were reviewed for their psychometric properties according to guidance by the US Food and Drug Administration (FDA) [7], under the auspices of the OMERACT SLE working group, and are suggested as secondary end points to support labelling claims for novel SLE therapies [8]. Changes in scores in various SF-36 domains and FACIT-F have shown the ability to discriminate between belimumab and placebo in the BLISS-52 and BLISS-76 clinical trials [9]. In the same analysis, changes in index scores of the EuroQol 5-Dimension health questionnaire (EQ-5D) [10] did not exhibit discriminative ability. However, EQ-5D has been shown to have satisfactory psychometric properties for SLE patients in terms of validity and reliability [11], justifying further study on the discriminative ability of EQ-5D in clinical trials applying alternative derivatives to its index score.

EQ-5D is a widely used generic instrument for the assessment of HRQoL, with its short format contributing to its popularity. It consists of a visual analogue scale intended to reflect overall health status, and a descriptive system comprising five questions, each denoting one dimension of health. Responses from no to major problems in these five questions can be presented in a health profile and be summarized in an index score, which is calculated based on population-specific scoring algorithms. This score may range from <0 to 1. A response of "no problems" in all five dimensions, termed full health state (FHS), equals to an EQ-5D index score of 1 and is intended to reflect the desired perception of health status [12].

The aim of this study was to investigate the discriminative ability of EQ-5D FHS in two phase III clinical trials of SLE. More specifically, we investigated the ability of EQ-5D FHS to distinguish belimumab plus standard therapy (ST) from ST alone, and responders from non-responders. Furthermore, we sought to determine factors that were associated with EQ-5D FHS after the trial intervention.

Patients and methods

Study design and population

We performed a *post hoc* analysis of data from BLISS-52 (NCT00424476) [13] and BLISS-76 (NCT00410384) [14], two multicentre phase III clinical trials of belimumab with similar design and end points. BLISS-52 comprised 865 participants from 13 countries in Latin America, Asia Pacific and Eastern Europe, whereas BLISS-76 enrolled 819 participants from 19 countries in Europe and North/Central America (see list of countries in Supplementary Table S1, available at *Rheumatology* online), all fulfilling the ACR revised criteria for SLE [15]. All patients were $\geq$18 years of age, had an ANA titre $\geq$1:80 and/or serum anti-dsDNA antibody level $\geq$30 IU/ml, and a Safety of Estrogens in Lupus National Assessment-SLEDAI (SELENA-SLEDAI) [16] score $\geq$6.

All patients were on stable ST for $\geq$30 days before baseline; this could include glucocorticoids, antimalarial agents, and immunosuppressants. Patients were randomized to receive belimumab 1 mg/kg, belimumab 10 mg/kg, or placebo as i.v. infusions at weeks 0, 2, 4, and thereafter every fourth week until week 48 in BLISS-52 and until week 72 in BLISS-76, in addition to ST, with a final assessment at weeks 52 and 76, respectively.

Longitudinal data from BLISS-52 and BLISS-76, including registrations of the three-level version of EQ-5D (EQ-5D-3L), were made available by GlaxoSmithKline (Uxbridge, UK) through the Clinical Study Data Request (CSDR) consortium. To manage missing values, the last observation was carried forward for all variables except for BMI, for which the mean weight of the previous and next available visits was used in the BMI formula and the last observation was carried forward when values from the last visits were missing. The total number of patients with available EQ-5D-3L data at week 52 was 1665 in the pooled study population.

Ethics

The study complied with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all study participants prior to enrolment in BLISS-52 and BLISS-76. The BLISS study protocols were reviewed and approved by regional ethics review boards for all participating centres, and the study protocol for this *post hoc* analysis was reviewed and approved by the Swedish Ethical Review Authority (2019–05498).

Clinical and laboratory data

SLE disease activity was assessed using the SLEDAI-2K [17], and organ damage using the SLICC/ACR Damage Index (SDI) [18]. The primary end point of the BLISS-52 and BLISS-76 trials, i.e. attainment of SLE Responder Index 4 (SRI-4) [19] at week 52, denoted responders.

Serum levels of anti-dsDNA $\geq$30 IU/ml, anti-Smith (Sm) $\geq$15 U/ml, anti-ribosomal P protein $>$25 EU/ml, aCL IgA $\geq$15 APL U/ml, aCL IgG $\geq$10 GPL U/ml, and aCL IgM $\geq$10 MPL U/ml determined positivity. Levels of complement component 3 (C3) $<$0.9 g/l and complement component 4 (C4) $<$0.16 g/l were considered low.

EQ-5D-3L full health state

The descriptive system of EQ-5D-3L incorporates five HRQoL dimensions, i.e. self-care, mobility, usual activities, pain/discomfort, and anxiety/depression. Respondents may report no problems (level 1), some/moderate (level 2), or extreme/major problems (level 3) in each one of these dimensions. As per the EQ-5D-3L user guide, we defined FHS as a response of no problems in all five dimensions, hence an EQ-5D-3L index score equal to 1 [12], and calculated its frequency in patient subgroups at multiple study visits. We compared EQ-5D-3L FHS frequencies between treatment arms and between SRI-4 responders and non-responders to determine the discriminative ability of this PROM in two a priori known successful trials, both demonstrating superiority of belimumab over placebo to yield an SRI-4 response. While the comparisons between treatment arms mainly served to assess the discriminative ability of EQ-5D-3L FHS to inform future clinical trial design, the comparisons between SRI-4 responders and non-responders mainly served for known-group validity analysis. Apart from responders *vs* non-responders, we compared EQ-5D-3L FHS perception in a priori distinct groups in a subsequent subgroup analysis.

For the purpose of comparison with the general population, we created a US civilian non-institutionalized population-based reference group ($N = 1665$), individually matched for age and sex with the study participants, with distributions of FHS corresponding to the last one of three possible registrations in the Medical Expenditure Panel Survey (MEPS) [20] between 2000 and 2002. MEPS respondents' EQ-5D-3L index score and FHS distributions stratified by age category and sex are presented as Supplementary Data, available at *Rheumatology* online.

Statistics

Data are presented as number (percentage) or mean (S.D.), and in the case of non-normal distributions the median (interquartile range) is indicated. The Mann–Whitney *U* test was used for comparisons of unrelated continuous data, and the Pearson's χ^2 or Fisher's exact test was used for associations between unrelated binomial variables, as appropriate. The McNemar's test was used for comparisons of FHS proportions between SLE patients and individually matched comparators. Logistic regression analysis was employed to adjust for baseline status in comparisons between treatment arms or responders *vs* non-responders. For determination of factors associated with EQ-5D-3L FHS at week 52, univariable logistic regression analysis guided the selection of variables to be used in subsequent multivariable logistic regression analysis.

P values of <0.05 were considered statistically significant. Analyses were performed using the IBM SPSS software version 26 (IBM Corp., NY, USA). The GraphPad Prism 7 (GraphPad Software Inc., CA, USA) was used for the construction of graphs.

Patient involvement

Patient research partners were involved in the study concept and design, interpretation of data, and editing of the manuscript.

Results

Patient characteristics and clinical data for the pooled BLISS population are presented in Table 1, including comparisons between patients reporting EQ-5D-3L FHS and patients not experiencing FHS at the evaluation of week 52. Greater proportions of patients given belimumab 10 mg/kg plus ST (37.6% *vs* 31.8%; $P = 0.035$) and lower proportions of patients who received ST alone (28.2% *vs* 35.1%; $P = 0.012$) were seen among FHS respondents (Table 1). Corresponding data for the BLISS-52 and BLISS-76 trial populations are presented in Supplementary Tables S2 and Table S3, available at *Rheumatology* online, respectively.

Notably, the frequency of FHS at week 52 in the pooled BLISS study population (23.0%; $N = 383$) was 52.8% lower than among age- and sex-matched US population-based EQ-5D-3L respondents (48.7%; $N = 811$; odds ratio, OR: 0.63; 95% CI: 0.58, 0.69; $P < 0.001$).

Discriminative ability

Proportions of patients reporting FHS from baseline through week 52 are delineated in Fig. 1, including stratifications by treatment arm and BLISS study. At week 52, the frequency of FHS was 23.0% in the pooled BLISS study population (Fig. 1A; Supplementary Table S4, available at *Rheumatology* online), 28.1% in BLISS-52 (Fig. 1B; Supplementary Table S5, available at *Rheumatology* online), and 17.7% in BLISS-76 (Fig. 1C; Supplementary Table S6, available at *Rheumatology* online).

In the pooled BLISS study population, higher proportions of patients within the belimumab 10 mg/kg plus ST arm reported EQ-5D-3L FHS compared with patients given ST alone from week 36 through week 52, with a proportion of 26.1% *vs* 19.4% at week 52 (adjusted OR: 1.73; 95% CI: 1.26, 2.37; $P = 0.001$; Fig. 1A). A separation of similar magnitude was observed at week 52 in the BLISS-52 (31.9% *vs* 25.4%; OR: 1.53; 95% CI: 1.01, 2.31; $P = 0.043$; Fig. 1B) and BLISS-76 (20.1% *vs* 13.1%; OR: 2.10; 95% CI: 1.26, 3.50; $P = 0.005$; Fig. 1C) study populations.

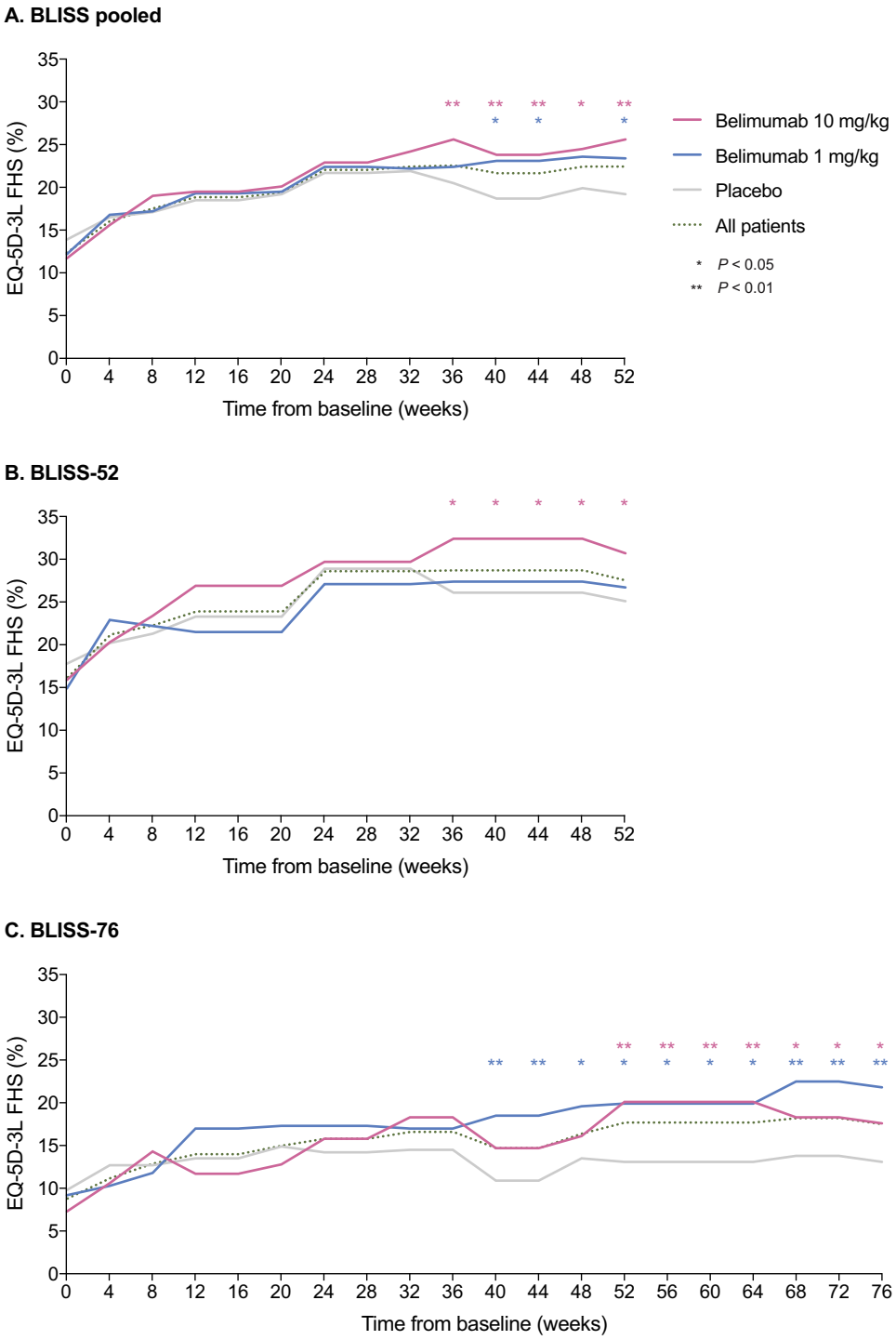
As shown in Fig. 2A and Supplementary Table S7, available at *Rheumatology* online, FHS also discriminated between SRI-4 responders and non-responders from week 36 through week 52 in the pooled BLISS study population, yielding a proportion of 27.0% at week 52 for responders and 19.8% for non-responders (adjusted OR: 1.75; 95% CI: 1.35, 2.26; $P < 0.001$). Similarly, a higher proportion of SRI-4 responders *vs* non-responders reported FHS at week 52 in BLISS-52 (31.1% *vs* 25.2%; OR: 1.63; 95% CI: 1.16, 2.28; $P =$

Table 1 Characteristics of EQ-5D-3L FHS attainers *vs* non-attainers at week 52 in the pooled BLISS study population

	All patients *N* = 1665	FHS *N* = 383	No FHS *N* = 1282	*P* value
Patient characteristics				
Age at baseline (years)	37.8 (11.5)	34.2 (10.8)	38.9 (11.5)	**<0.001**
Female sex	1566 (94.1%)	350 (91.4%)	1216 (94.9%)	**0.012**
Ancestries				
Asian	336 (20.2%)	115 (30.0%)	221 (17.2%)	**<0.001**
Black/African American	148 (8.9%)	22 (5.7%)	126 (9.8%)	**0.014**
Indigenous American[a]	383 (23.0%)	102 (26.6%)	281 (21.9%)	0.054
White/Caucasian	798 (47.9%)	144 (37.6%)	654 (51.0%)	**<0.001**
Hispanic/Latin American ethnicity	593 (35.6%)	148 (38.6%)	445 (34.7%)	0.159
Clinical data				
SLE duration at baseline (years)	4.5 (1.5–9.4)	4.2 (1.3–9.1)	4.5 (1.5–9.6)	0.134
Mean BMI (week 0–52)	25.8 (5.9)	24.2 (4.9)	26.2 (6.1)	**<0.001**
SLEDAI-2K score				
Baseline	9.9 (3.8)	9.7 (4.0)	10.0 (3.8)	**0.019**
Week 52	6.2 (4.4)	5.3 (3.6)	6.4 (4.5)	**<0.001**
SDI score				
Baseline	0.8 (1.2) 0.0 (0.0–1.0); *N* = 1664	0.5 (0.9) 0.0 (0.0–1.0)	0.9 (1.3) 0.0 (0.0–1.0); *N* = 1281	**<0.001**
Week 52	0.8 (1.3) 0.0 (0.0–1.0); *N* = 1664	0.5 (1.0) 0.0 (0.0–1.0)	0.9 (1.3) 0.0 (0.0–1.0); *N* = 1281	**<0.001**
SDI score > 0				
Baseline	705 (42.4%); *N* = 1664	112 (29.2%)	593 (46.3%); *N* = 1281	**<0.001**
Week 52	740 (44.5%); *N* = 1664	116 (30.3%)	624 (48.7%); *N* = 1281	**<0.001**
Serological profile at baseline				
Anti-dsDNA (+)	1154 (69.3%)	310 (80.9%)	844 (65.8%)	**<0.001**
Anti-Sm (+)	523 (31.4%); *N* = 1663	138 (36.1%); *N* = 382	385 (30.1%); *N* = 1281	**0.025**
Anti-ribosomal P protein (+)	273 (16.8%); *N* = 1624	74 (19.7%); *N* = 376	199 (15.9%); *N* = 1248	0.090
aCL IgA (+)	24 (1.4%); *N* = 1657	4 (1.0%); *N* = 382	20 (1.6%); *N* = 1275	0.454
aCL IgG (+)	369 (22.2%); *N* = 1663	80 (20.9%); *N* = 382	289 (22.6%); *N* = 1281	0.504
aCL IgM (+)	112 (6.7%); *N* = 1663	22 (5.8%); *N* = 382	90 (7.0%); *N* = 1281	0.386
Low C3	747 (44.9%)	196 (51.2%)	551 (43.0%)	**0.005**
Low C4	935 (56.2%)	234 (61.1%)	701 (54.7%)	**0.026**
Prednisone eq. dose (mg/day)				
Baseline	10.7 (8.6)	11.2 (8.8)	10.6 (8.6)	0.221
Week 52	8.8 (7.9); *N* = 1324	8.1 (6.3); *N* = 337	9.0 (8.3); *N* = 987	0.086
Antimalarial agents at week 52[b]	1069 (64.2%)	267 (69.7%)	802 (62.6%)	**0.010**
Immunosuppressants at week 52				
AZA	376 (22.6%)	106 (27.7%)	270 (21.1%)	**0.007**
MTX	218 (13.1%)	45 (11.7%)	173 (13.5%)	0.374
Mycophenolic acid	188 (11.3%)	42 (11.0%)	146 (11.4%)	0.819
Other immunosuppressants[c]	33 (2.0%)	6 (1.6%)	27 (2.1%)	0.506
Trial intervention				
Placebo	558 (33.5%)	108 (28.2%)	450 (35.1%)	**0.012**
BLM 1 mg/kg	555 (33.3%)	131 (34.2%)	424 (33.1%)	0.681
BLM 10 mg/kg	552 (33.2%)	144 (37.6%)	408 (31.8%)	**0.035**
SRI-4 at week 52	745 (44.7%)	201 (52.5%)	544 (42.4%)	**0.001**

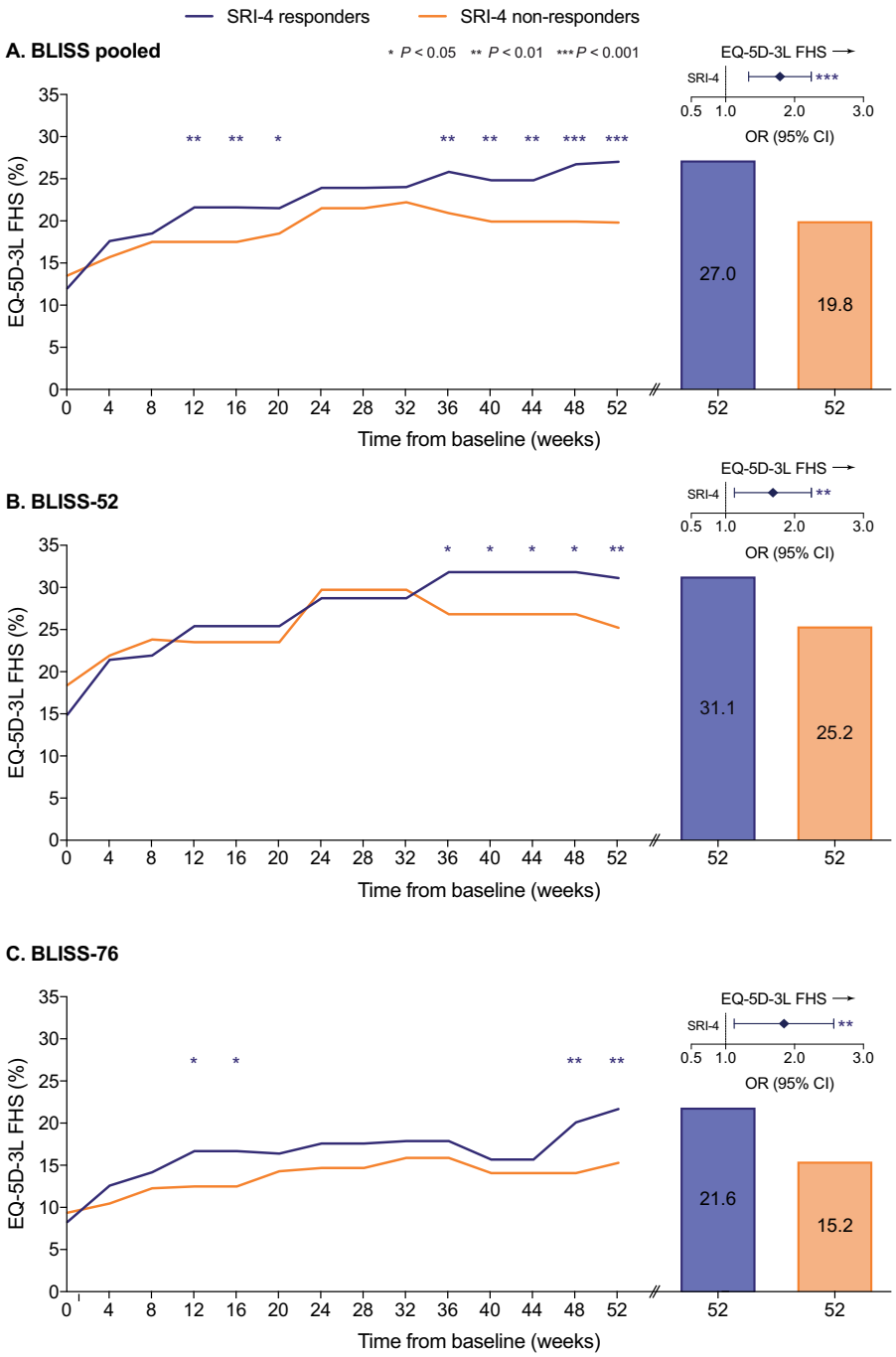
Data are presented as number (percentage) or mean (S.D.). In case of non-normal distributions, the median (interquartile range) is indicated. In case of missing values, the total number of patients with available data is indicated. Statistically significant *P* values are in bold. [a]Alaska Native or American Indian from North, South or Central America. [b]HCQ, chloroquine, mepacrine, mepacrine hydrochloride or quinine sulfate. [c]CSA, oral CYC, LEF, mizoribine or thalidomide. BLM: belimumab; C3: complement component 3; C4: complement component 4; FHS: full health state; SDI: SLICC/ACR Damage Index; Sm: Smith; SRI-4: SLE Responder Index 4.

Fig. 1 Ability of EQ-5D-3L full health state to discriminate between belimumab and placebo



Proportions of patients in EQ-5D-3L FHS at baseline and every fourth week in the pooled BLISS study population (**A**; see Supplementary Table S4, available at *Rheumatology* online for actual data), the BLISS-52 trial (**B**; see Supplementary Table S5, available at *Rheumatology* online for actual data) and the BLISS-76 trial (**C**; see Supplementary Table S6, available at *Rheumatology* online for actual data), including stratification by treatment arm. Longitudinal perception of FHS was adjusted for baseline status using logistic regression analysis. Statistically significant differences are denoted by asterisks. FHS: full health state.

Fig. 2 Ability of EQ-5D-3L full health state to discriminate between SRI-4 responders and non-responders



Proportions of patients in EQ-5D-3L FHS at baseline and every fourth week among SRI-4 responders *vs* non-responders in the pooled BLISS study population (**A**; see Supplementary Table S7, available at *Rheumatology* online for actual data), the BLISS-52 trial (**B**; Supplementary Table S8, available at *Rheumatology* online) and the BLISS-76 trial (**C**; Supplementary Table S9, available at *Rheumatology* online). Bars illustrate EQ-5D-3L FHS proportions at week 52, and the forest plots illustrate the corresponding ORs (diamonds) and 95% CIs (whiskers). Longitudinal perception of FHS was adjusted for baseline status using logistic regression analysis. Statistically significant differences are denoted by asterisks. FHS: full health state; OR: odds ratio; SRI-4: SLE Responder Index 4.

0.005; Fig. 2B; Supplementary Table S8, available at *Rheumatology* online) and in BLISS-76 (21.6% *vs* 15.2%; OR: 1.75; 95% CI: 1.18, 2.62; $P = 0.006$; Fig. 2C; Supplementary Table S9, available at *Rheumatology* online).

Discriminative ability of level 1 response within each EQ-5D dimension

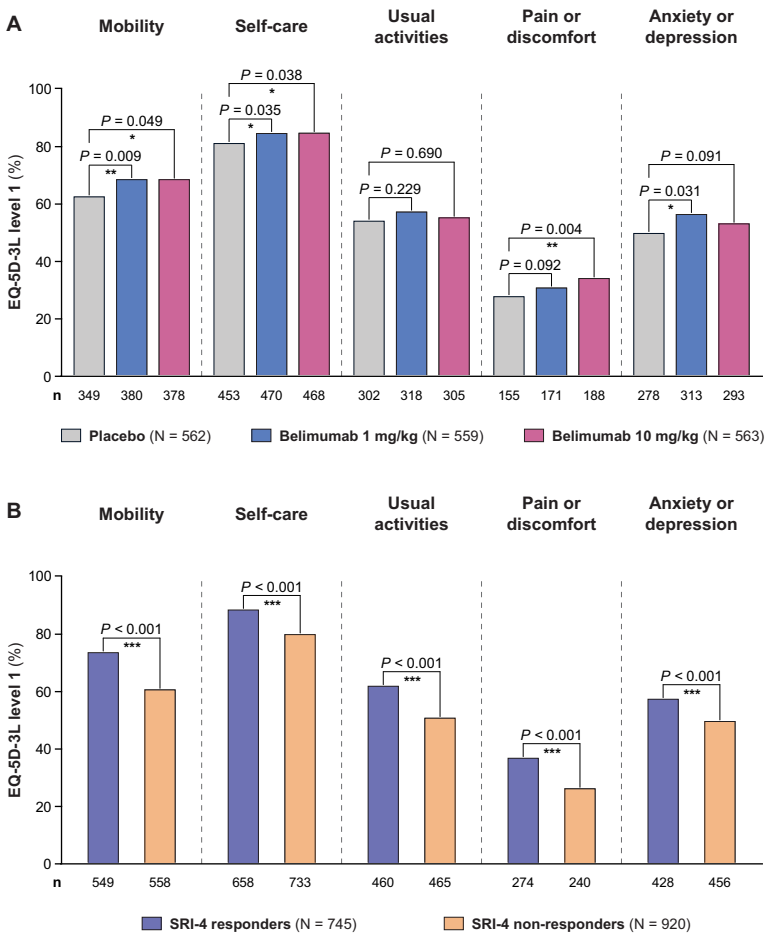
Proportions of patients reporting no problems (level 1) at week 52 within each one of the five EQ-5D dimensions across the three treatment arms are delineated in Fig. 3A (see also online Supplementary Table S10, available at *Rheumatology* online). Higher proportions of patients reported EQ-5D-3L level 1 within the belimumab 10 mg/kg arm than among patients in the placebo arm with regard to mobility (68.5% *vs* 62.5%; OR: 1.32; 95% CI: 1.00, 1.74; $P = 0.049$), self-care (84.8% *vs* 81.2%; OR: 1.46; 95% CI: 1.02, 2.10; $P = 0.038$) and pain/discomfort (34.1% *vs* 27.8%; OR: 1.51; 95% CI: 1.14, 1.99; $P = 0.004$), and within the belimumab 1 mg/kg arm *vs* placebo with regard to mobility (68.5% *vs* 62.5%; OR: 1.45; 95% CI: 1.10, 1.92; $P = 0.009$), self-care (84.7% *vs* 81.2%%; OR: 1.48; 95% CI: 1.03, 2.13; $P = 0.035$) and anxiety/depression (56.4% *vs* 49.8%; OR: 1.34; 95% CI: 1.03, 1.75; $P = 0.031$).

As shown in Fig. 3B (see also online Supplementary Table S11, available at *Rheumatology* online), higher proportions of SRI-4 responders than non-responders reported level 1 in all five EQ-5D dimensions.

Factors associated with EQ-5D-3L FHS after therapeutic intervention

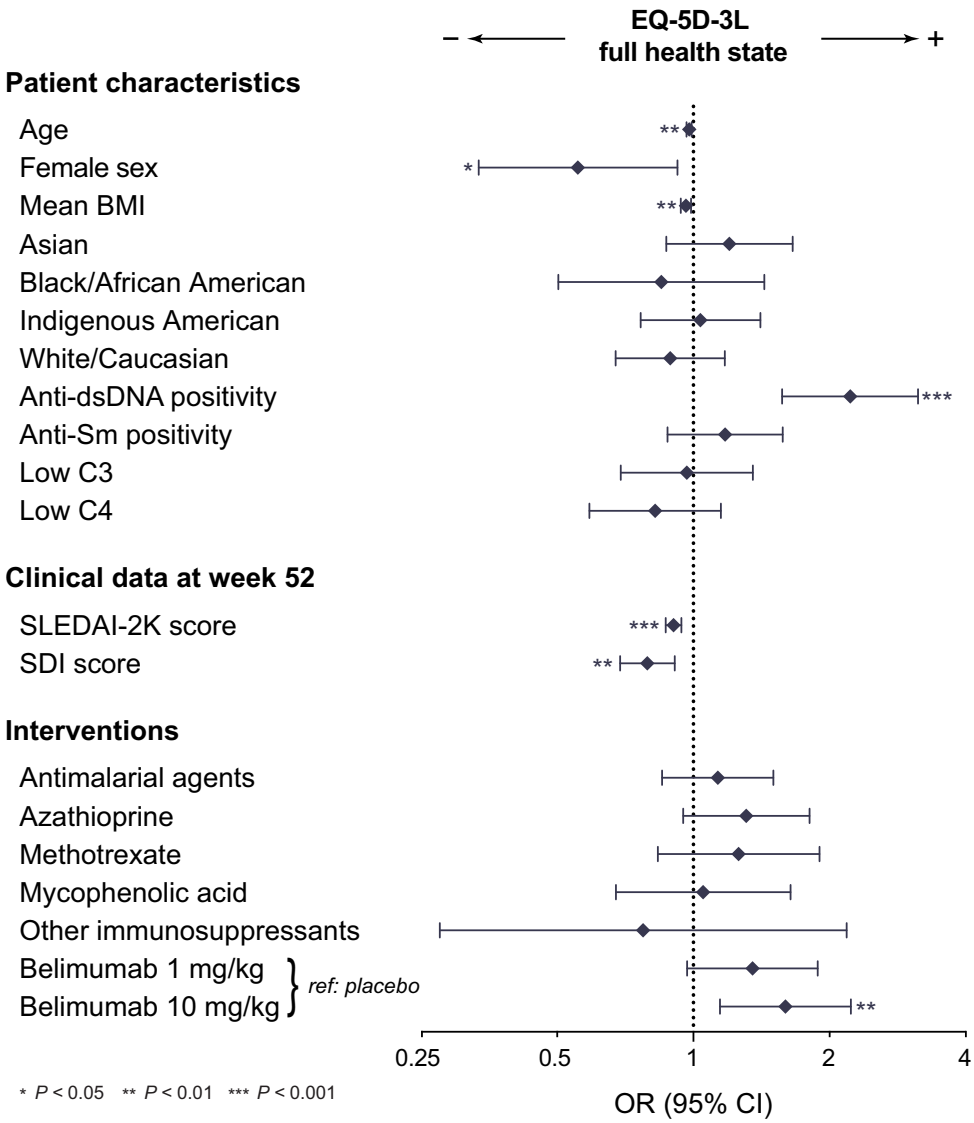
Results from the initial univariable logistic regression analysis are shown in Supplementary Table S12, available at *Rheumatology* online. In the subsequent multivariable logistic regression model (Fig. 4; Supplementary

Fig. 3 Discriminative ability of level 1 response by EQ-5D dimension



Proportions of patients with a level 1 (i.e. "no problems") response at week 52 across treatment arms (**A**; see Supplementary Table S10, available at *Rheumatology* online for actual data) and among SRI-4 responders *vs* non-responders in the pooled BLISS study population (**B**; see Supplementary Table S11, available at *Rheumatology* online for actual data). Comparisons were adjusted for baseline status using logistic regression analysis. Statistically significant differences are denoted by asterisks. SRI-4: SLE Responder Index 4.

Fig. 4 Factors associated with EQ-5D-3L full health state at week 52



Forest plot illustrating ORs (diamonds) and 95% CIs (whiskers) deriving from multivariable logistic regression analysis, with EQ-5D-3L FHS at week 52 as the dependent variable. FHS at baseline was included among covariates in the model (not shown). Statistically significant *P* values are denoted by asterisks. Actual data are presented in Supplementary Table S13, available at *Rheumatology* online. C3: complement component 3; C4 complement component 4; FHS: full health state; OR: odds ratio; SDI: SLICC/ACR Damage Index.

Table S13, available at *Rheumatology* online), FHS at baseline yielded a 10-fold higher probability of FHS perception at week 52 than non-FHS at baseline (OR: 10.01; 95% CI: 7.07, 14.17; $P < 0.001$). Female sex (OR: 0.56; 95% CI: 0.33, 0.92; $P = 0.023$) and increasing BMI (OR: 0.96; 95% CI: 0.94, 0.99; $P = 0.006$) were independently negatively associated with FHS, as were increasing SLEDAI-2K (OR: 0.90; 95% CI: 0.87, 0.94; $P < 0.001$) and SDI (OR: 0.79; 95% CI: 0.69, 0.91; $P = 0.001$) scores at week 52. Notably, anti-dsDNA positivity at baseline (OR: 2.23; 95% CI: 1.58, 3.15; $P < 0.001$) predicted FHS at week 52. Lastly, addition of belimumab 10 mg/kg to ST (OR: 1.60; 95% CI: 1.15, 2.24; $P = 0.006$) independently favoured FHS compared with ST alone.

EQ-5D-3L FHS as a PROM denoting belimumab efficacy in subgroup analysis

Demographics and clinical data of EQ-5D-3L FHS *vs* non-FHS respondents are also presented separately for the patient populations of the placebo (Supplementary

Table S14, available at *Rheumatology* online), belimumab 1 mg/kg (Supplementary Table S15, available at *Rheumatology* online) and belimumab 10 mg/kg (Supplementary Table S16, available at *Rheumatology* online) arms. Based on these results, FHS frequencies at week 52 in the entire BLISS population and the belimumab 10 mg/kg and placebo patient subgroups were next plotted in Fig. 5 to illustrate differences between groups in selected variables. A lower proportion of women (22.3%) *vs* men (33.3%; OR: 0.58; 95% CI: 0.37, 0.89; $P = 0.012$) reported FHS (Fig. 5A) in the entire population, with this difference being more prominent in the placebo group (18.1% *vs* 35.0%; OR: 0.41; 95% CI: 0.21, 0.82; $P = 0.009$). Belimumab 10 mg/kg showed superiority over placebo within the female population, with 26.3% *vs* 18.1% women reporting FHS at week 52 (OR: 1.95; 95% CI: 1.39, 2.73; $P < 0.001$). A similar benefit from belimumab 10 mg/kg was also seen for African Americans (20.0% *vs* 6.0%; OR: 4.50; 95% CI: 1.06, 19.13; $P = 0.042$; Fig. 5B). In the entire population, the frequency of FHS was lower among patients with SDI scores of >0 at week 52 (15.7%) compared with patients with zero SDI scores (28.9%; OR: 0.46; 95% CI: 0.36, 0.58; $P < 0.001$; Fig. 5C). Importantly, while belimumab 10 mg/kg plus ST was superior over ST alone in favouring FHS after the trial intervention both in patients with zero SDI scores (31.7% *vs* 24.2%; OR: 1.29; 95% CI: 1.06, 1.56; $P = 0.010$) and patients with SDI scores >0 (18.5% *vs* 13.5%; OR: 1.35; 95% CI: 1.01, 1.80; $P = 0.045$), a higher frequency of FHS was seen among patients with zero SDI scores treated with belimumab 10 mg/kg (OR: 2.05; 95% CI: 1.36, 3.07; $P < 0.001$).

Within the entire BLISS population, a higher proportion of SLE patients who were anti-dsDNA positive at baseline reported FHS at week 52 (26.9%) than did anti-dsDNA-negative patients (14.3%; OR: 2.20; 95% CI: 1.67, 2.92; $P < 0.001$; Fig. 5D). Similarly, a higher proportion of anti-dsDNA-positive patients within the belimumab 10 mg/kg group reported FHS at week 52 (31.4%) compared with anti-dsDNA-negative patients (13.4%; OR: 2.96; 95% CI: 1.80, 4.87; $P < 0.001$), but no such difference between anti-dsDNA-positive and -negative patients was seen within the placebo group (21.5% *vs* 14.8%; OR: 1.58; 95% CI: 0.98, 2.54; $P = 0.060$). Additionally, a higher proportion of anti-dsDNA-positive patients given belimumab 10 mg/kg plus ST experienced FHS at week 52 (31.4%) than did anti-dsDNA-positive patients who received ST alone (21.5%; OR: 1.95; 95% CI: 1.35, 2.80; $P < 0.001$). Interestingly, a similar pattern was seen for anti-Sm (Fig. 5E).

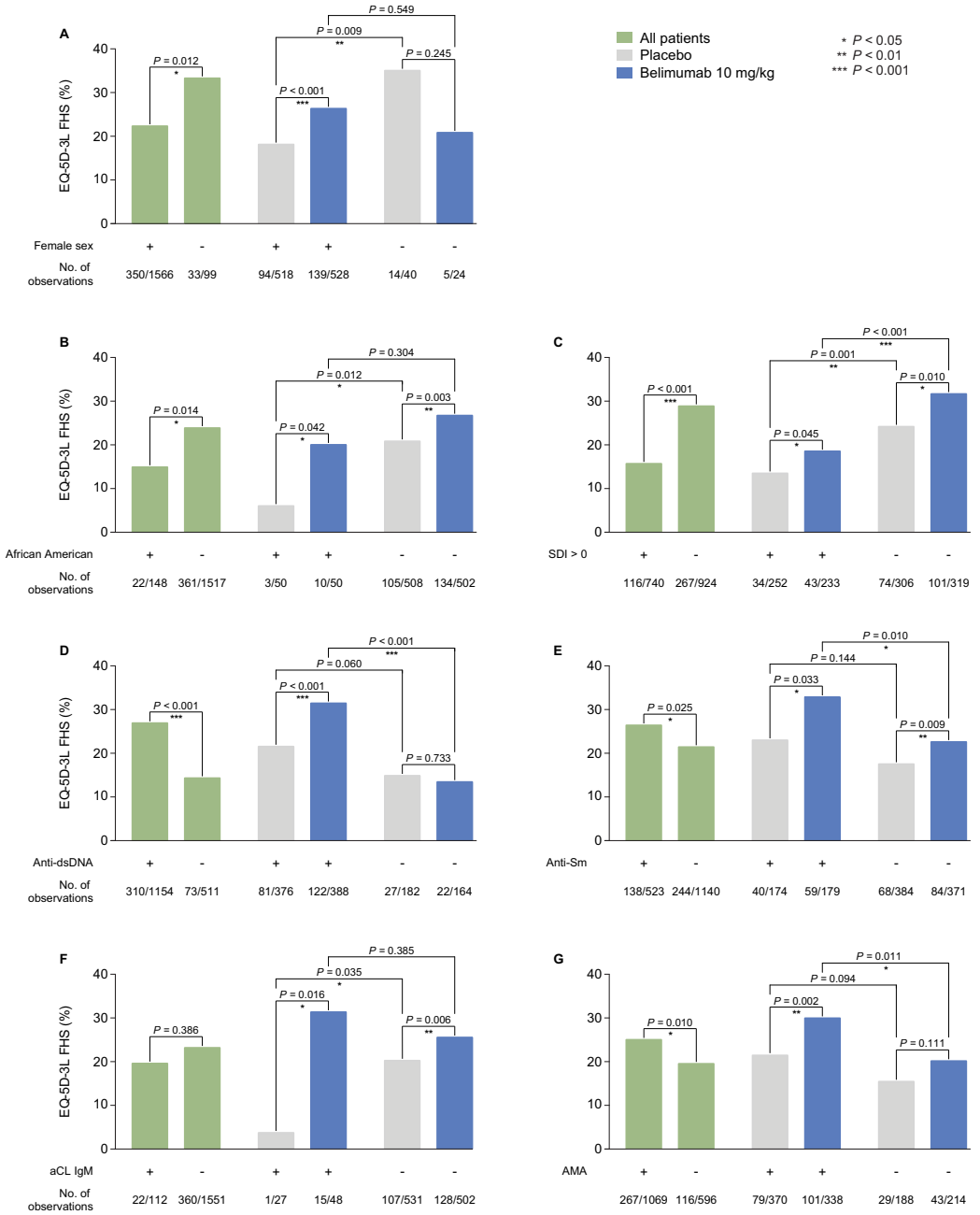
While no difference in EQ-5D-3L FHS frequencies was found in the entire BLISS population or the belimumab 10 mg/kg group between aCL IgM–positive and –negative patients (Fig. 5F), a lower proportion of aCL IgM–positive patients reported FHS within the placebo group (3.7% *vs* 20.2%; OR: 0.15; 95% CI: 0.02, 1.14; $P = 0.035$; $P = 0.063$ after continuity correction). Notably, a higher proportion of antimalarial agents users (25.0%) *vs* non-users (19.5%; OR: 1.38; 95% CI: 1.08, 1.76; $P = 0.010$) reported FHS in the entire population and the belimumab 10 mg/kg group (29.9% *vs* 20.1%; OR: 1.70; 95% CI: 1.13, 2.55; $P = 0.011$), but not in the placebo group (Fig. 5G). Finally, a higher FHS frequency was seen among antimalarial agents users who were also given belimumab 10 mg/kg (29.9%) compared with antimalarial agents users who received placebo (21.4%; OR: 1.84; 95% CI: 1.26, 2.71; $P = 0.002$).

Discussion

Despite a 52-week-long therapeutic intervention, patients with SLE were herein shown to report FHS in EQ-5D-3L 52.8% less frequently than individuals in the general US population, corroborating the known detrimental impact of SLE on HRQoL [1]. EQ-5D-3L FHS displayed the ability to discriminate between belimumab 10 mg/kg plus ST and ST alone in the SLE populations of the BLISS-52 and BLISS-76 trials. Furthermore, FHS also distinguished SRI-4 responders from non-responders. Addition of belimumab 10 mg/kg to ST especially favoured FHS after the trial intervention in anti-dsDNA- and anti-Sm- positive patients, and concomitant antimalarial agents use enhanced the benefit from belimumab to yield FHS perception.

Several findings in the present investigation provide additional support for satisfactory psychometric properties of EQ-5D-3L, FHS (i.e. EQ-5D-3L index score 1) in particular. In the concrete, EQ-5D-3L FHS exhibited discriminative potentiality and clinically relevant properties. First, despite the stringent requirement for a “no problem” response in all five EQ-5D-3L dimensions, FHS was more frequently reported than clinical outcomes intended to reflect low disease activity or remission, such as the Lupus Low Disease Activity State (LLDAS) [21–23] and Definitions of Remission in SLE (DORIS) [24, 25], in the same trials. Second, FHS showed the ability to discriminate between belimumab 10 mg/kg plus ST and ST alone from week 36 onwards in the pooled BLISS study population, and at multiple time points in the BLISS-52 and BLISS-76 trial populations when analysed separately. Third, EQ-5D-3L FHS also showed the ability to separate SRI-4 responders from non-responders, and high disease activity and organ damage scores were both negatively associated with FHS after the trial intervention. In light of conflicting data in the literature regarding the relationship between self-perception of HRQoL and disease activity or damage features, with some studies reporting modest negative associations [26–29] and some other studies demonstrating no interrelationship [30–32], our latter findings support the notion that EQ-5D-3L FHS incorporates patient perceptions of HRQoL that yield good congruence with well-established clinical parameters. Collectively, these findings suggest that EQ-5D-3L FHS may prove a useful PROM in SLE studies, and aspire to inform future clinical trial design.

Fig. 5 EQ-5D-3L full health state frequencies at week 52 in relation to selected variables



Green bars represent EQ-5D-3L FHS frequencies at week 52 within the entire BLISS study population, stratified by selected binomial variables, i.e. sex (**A**), Black/African American ancestry *vs* all other ancestries (**B**), SDI score >0 *vs* 0 (**C**), anti-dsDNA (**D**), anti-Sm (**E**) and aCL IgM positivity *vs* negativity (**F**), antimalarial agents use (**G**). Grey and blue bars represent FHS frequencies within the placebo and the belimumab 10 mg/kg patient subgroup, respectively. *P* values are derived from Pearson's χ^2 test, or logistic regression analysis where adjustment for baseline status was applied (comparisons between belimumab and placebo). Statistically significant differences are denoted by asterisks. FHS: full health state; SDI: SLICC/ACR Damage Index.

PROMs of HRQoL such as SF-36 and FACIT-F have been shown to be sensitive to change along with clinical response, and have also been reported to discriminate between treatment arms in several SLE trials [8]. In fact, belimumab plus ST yielded greater changes than ST alone in several domains of SF-36 and in FACIT-F scores in the BLISS-52 and BLISS-76 trials [9, 33], which however was not the case for EQ-5D-3L index scores. In this respect, it is important to make the distinction between outcomes that represent change, e.g. improvement, and outcomes that represent a state that is independent of a preceding or baseline evaluation. While both concepts provide important indications regarding the efficacy of a trial intervention on HRQoL, definitions of improvement may be met when the outcome still is unsatisfactory. By contrast, when PROMs denote current states, such as FHS rather than index scores in the case of EQ-5D-3L, such states may be met even when no actual change has occurred, yet still representing desirable conditions and therefore constituting pertinent outcomes. However, it is worth noting that change also captures improvement and worsening from the baseline health profile, which is omitted in the report of a current state. To account for this, we herein present longitudinal FHS perception during the study period before and after adjustment for baseline status.

A finding worth noting was that add-on belimumab 1 mg/kg was associated with a response of "no problems" in the anxiety/depression EQ-5D dimension, whereas no such association was seen for belimumab 10 mg/kg. This observation becomes interesting in light of previous reports of depression, suicidal attempts and self-injury in an open label extension of BLISS-52 and BLISS-76, mainly during the first year of follow-up [34]. Although no firm conclusions can be drawn from these observations, further investigation of potential belimumab-related psychiatric adverse events is warranted, especially in the subset of patients with neuropsychiatric SLE for which data on belimumab use are scarce [35].

In conformity with early reports from the BLISS-52 and BLISS-76 trials demonstrating a beneficial impact of belimumab in various HRQoL aspects [9], we found that belimumab 10 mg/kg favoured EQ-5D-3L FHS perception, also after adjustment for factors with confounding potentiality and within patient subgroups of particular interest; the benefit from belimumab remained evident after adjustment for baseline status. While female sex and increasing BMI were independently negatively associated with FHS after the trial intervention, in line with their known negative impact on HRQoL in SLE patients [36–38], we herein demonstrated that women benefited from belimumab 10 mg/kg towards FHS perception. Asian ethnicity was associated with FHS after the trial intervention, which contrasts with the generally heavier SLE disease burden in Asians compared with Caucasians [39]; however, this association did not hold true after adjustment for baseline status. In subgroup analysis, African Americans showed a disbenefit in attaining FHS compared with other ancestries, which nevertheless was effaced by the addition of belimumab 10 mg/kg to ST. In agreement with previous findings from observational [40, 41] and clinical trial settings [42, 43] showing a greater benefit from belimumab in patients with minimal or no organ damage, belimumab 10 mg/kg resulted in a higher percentage of FHS respondents at week 52 in patients with no organ damage than among patients with SDI scores >0.

Interestingly, higher proportions of FHS at week 52 were seen in anti-dsDNA-positive *vs* -negative patients who received belimumab 10 mg/kg plus ST, but no such difference was observed in patients who received ST alone, in conformity with the previously reported clinical and HRQoL benefit of belimumab in anti-dsDNA-positive individuals [44]. The same pattern was seen for anti-Sm-positive *vs* -negative patients, which aligns with previous reports of anti-Sm positivity predicting clinical benefit from B cell therapy with belimumab [45] or rituximab [46]. The apparent resemblance between the clinical benefit and the increased probability of experiencing FHS exerted by belimumab in anti-dsDNA- and anti-Sm-positive individuals consolidates the known-group validity of EQ-5D-3L FHS and further supports the notion that clinically relevant properties are incorporated in this PROM.

Recently, we reported an association between antimalarial agent use and EQ-5D-3L FHS in the same SLE population; however, this was before the trial intervention [47]. We herein demonstrated a similar association following 52 weeks of treatment, which held true in patients given belimumab 10 mg/kg, but not among patients who received placebo. Additionally, we demonstrated a greater benefit from belimumab 10 mg/kg towards FHS when given along with antimalarial agents *vs* without. Collectively, our findings imply that belimumab and antimalarial agents both contribute to full health perception, which is enhanced by their concomitant use. Supportive of this synergy at a mechanistic level were recent reports of decreasing aPL levels following belimumab and antimalarial agents treatment combined, but not belimumab alone [48], especially in SLE patients on long-standing antimalarial agents treatment [49]. Antimalarial agents have been shown to be associated with diminutions of serum levels of B cell activating factor (BAFF) [50, 51], which is, at least partly, explained by downregulation of type I IFN-mediated BAFF production [52]. Along with the direct binding of belimumab to circulating BAFF, this may contribute to additive BAFF neutralization. As evidence accumulates within molecular and herein HRQoL facets, exploration of mechanisms underlying the synergy between belimumab and antimalarial agents is warranted.

The *post hoc* nature of our analysis constituted a limitation. Moreover, data on comorbidities with confounding potentiality, e.g. FM, as well as socio-economic status, were unfortunately unavailable. Finally, patients with severe active LN or neuropsychiatric lupus were excluded from the trials, and our findings may not apply

to these SLE subgroups. Strengths included the large SLE population and extensive longitudinal data, allowing for essential adjustments in statistical analyses. While this study focused on EQ-5D-3L FHS, further investigation of the psychometric properties of EQ-5D in SLE populations has merit. For instance, sensitivity analysis of different index score thresholds could determine less stringent EQ-5D-based definitions with equal or greater discriminative ability in SLE clinical trials. Importantly, since different response patterns may result in similar index scores, such sensitivity analysis should be conducted along with separate analysis for each one of the five EQ-5D dimensions to ensure the clinical relevance of the findings. Finally, acknowledging the clinical heterogeneity of SLE, stratification by disease manifestations is merited in future studies.

Conclusions

In this investigation, EQ-5D-3L FHS displayed the ability to discriminate between belimumab and placebo, as well as between responders and non-responders, in two large phase III clinical trials of SLE that both had met their primary end points. Using this outcome in subsequent analyses, we corroborated a benefit from belimumab in anti-dsDNA- and anti-Sm- positive SLE patients, as well as a synergistic effect of antimalarial agents when combined with belimumab. Our data consolidate important psychometric properties for EQ-5D-3L FHS, and call for future studies to provide credence for its usefulness in SLE study design.

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Data availability statement

The datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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