Safety and Efficacy of Subcutaneous Belimumab and Intravenous Rituximab Combination in Patients With Primary Sjögren's Syndrome: A Phase 2, Randomised, Placebo-Controlled 68-Week Study

OP0135

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FB is a consultant for and has received financial grants from GSK, UCB, Roche and Actelion. **FB** is an employee of Candel Therapeutics.

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SDV is a consultant for GSK and Roche.

KLC, PM, RP, AV, NW and **DAR** are employees of and own shares in GSK.

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Background and Objectives

- Currently, there are no approved disease-modifying treatments for primary pSS[1,2]
- Activation of B cells is a major contributor to the pathogenesis of pSS[3]
- BLyS (BAFF) is a potent cytokine that promotes B-cell hyperactivity and patients with pSS have elevated serum levels of BLyS[4]
- Belimumab (anti-BLyS) and rituximab (anti-CD20) are B-cell targeting agents[5,6]
- Rituximab, a B-cell depleting agent, has limited efficacy in pSS[7,8]
  - In part, this may reflect resistance of B cells present in tissue (salivary gland) to complete depletion by rituximab[9]
  - Increases in circulating BLyS are observed post-rituximab which could contribute to repopulation of autoreactive B cells after administration of rituximab[10]
- Treatment with both anti-BLyS and B-cell depleting agents may be more efficacious at reducing levels of B cells compared with the use of either agent alone[11]

This is the first study to explore the immunological effects of combining belimumab with rituximab in patients with pSS

Primary objective:

To evaluate the safety and tolerability of belimumab with a cycle of rituximab (belimumab/rituximab), belimumab monotherapy and rituximab monotherapy in adult patients with active pSS

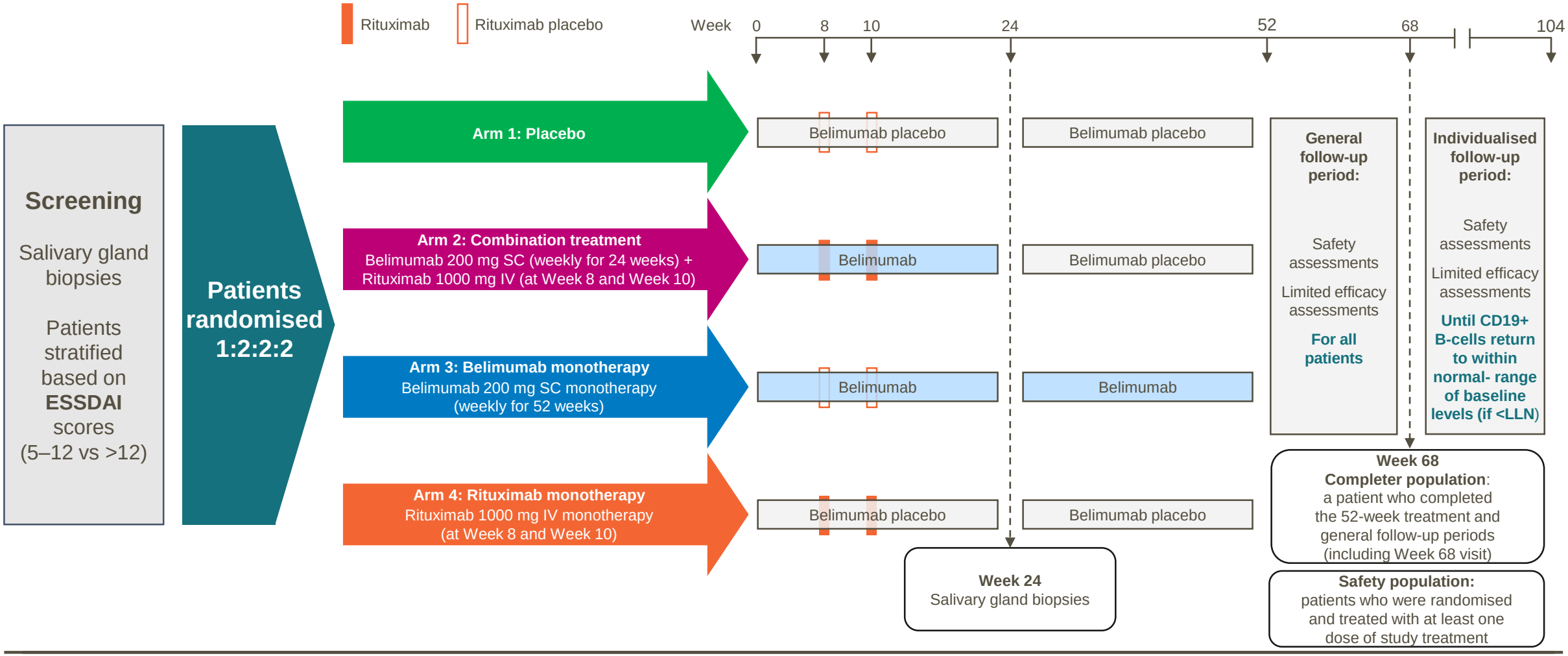
Secondary objective:

To assess the efficacy and impact upon salivary gland B cells of belimumab/rituximab, belimumab monotherapy, and rituximab monotherapy in adults with active pSS

BAFF, B-cell activiating factor; BLyS, B-lymphocyte stimulator; pSS, primary Sjögren's Syndrome

[1]Del Papa N and Vitali C. *Ther Adv Musculoskelet Des* 2018;10(2):39-54; [2]Ramos-Casals M, *et al. Net Rev Rheumatol* 2012;8(7):399-411; [3]Ittah M, *et al. Arthritis Res Ther* 2006;8:R51; [4]Quartuccio L, *et al*. *Rheumatology* 2013;52:276-81; [5]Gandolfo S and De Vita S. *Clin Exp Rheumatol* 2019;37 Suppl 118(3):199-208; [6]Mariette X, *et al*. *Ann Rheum Dis* 2015;74(3):526-31; [7]Devauchelle-Pensec V, *et al*. *Ann Intern Med* 2014;160(4):233-42; [8]Bowman SJ, et al. *Arthritis Rheumatol* 2017;69(7):1440-50; [9]Pijpe J, *et al. Arthritis Rheum* 2009;60(11):3251-6; [10]Pers J-O, *et al. Arthritis Rheum* 2007;56(5):1464-77; [11]Lin WY, *et al. Arthritis Rheumatol* 2015;67(1):215-24

Study Design



ESSDAI, EULAR Sjögren's Syndrome Disease Activity Index; EULAR, European League Against Rheumatism; IV, intravenous; LLN, lower limit of normal; SC, subcutaneous

Key Study Selection Criteria and Endpoints

Key Inclusion Criteria

- Aged ≥18 years
- Diagnosis of pSS per AECG
- ESSDAI score of ≥5 points
- Symptomatic oral dryness (≥5/10 on patient completed NRS)
- Baseline unstimulated salivary flow >0 or stimulated baseline salivary flow >0.05 ml/min

Key Exclusion Criteria

- Diagnosis of secondary pSS
- Active life-threatening or organ-threatening complications of SS
- Severely immunocompromised state
- History of acute or chronic infections requiring management, and progressive multifocal leukoencephalopathy

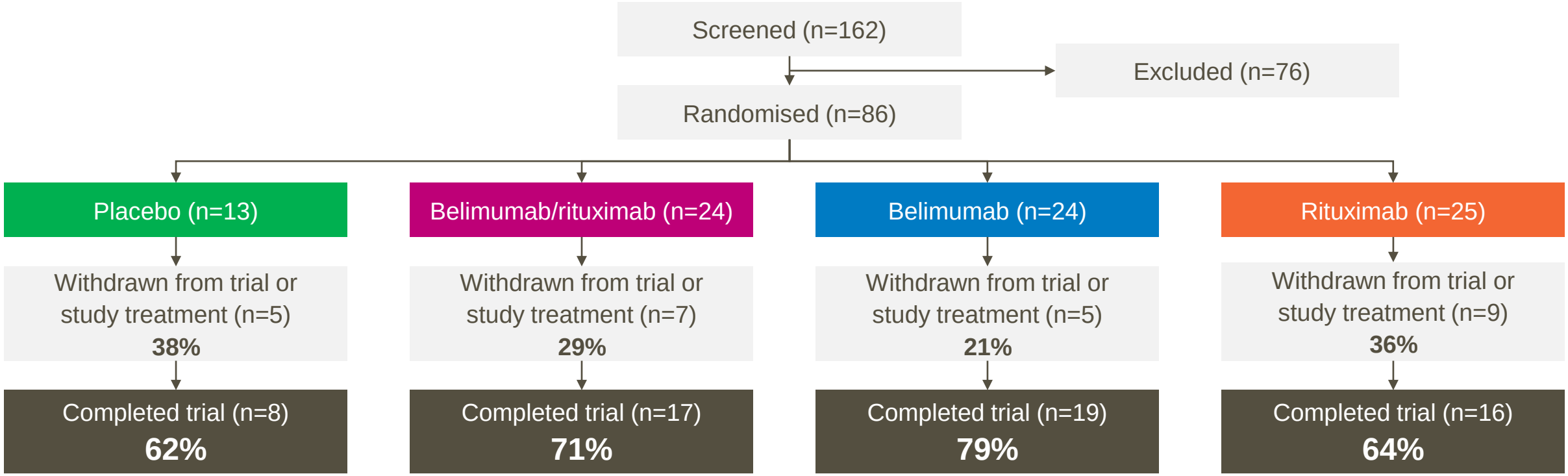
Primary Endpoint: AEs, SAEs and AESI (Safety population)

Secondary Endpoints (Completer population)	• ESSDAI score* over time • Stimulated salivary flow over time	• Oral dryness (NRS) over time • Quantification of B cells in salivary gland biopsy at Week 24
Other Endpoints (Completer population)	Responder analysis over time for ESSDAI	ESSPRI score over time

AE, adverse event; AESI, adverse event of special interest; AECG, American-European Consensus Group; ESSPRI, EULAR Sjogren's Syndrome Patient Reported Index; NRS, Numeric Response/Rating Scale; SAE, serious adverse event

*ESSDAI is an assessment of disease activity across 12 different clinically relevant domains for patients with Sjögren's Syndrome. ESSDAI is assessed by the treating physician

Patient Disposition



A total of 60 patients were included in the completer population (70% overall)

The most common reason for withdrawal from treatment was AEs (n=10 [12%] overall)

Demographics and Baseline Characteristics (Safety Population)

	Placebo (n=13)	Belimumab/rituximab (n=24)	Belimumab (n=24)	Rituximab (n=25)
Age (years), mean (SD)	52.7 (12.67)	45.1 (10.93)	52.0 (11.49)	55.2 (15.07)
Female, n (%)	13 (100.0)	22 (91.7)	22 (91.7)	23 (92.0)
Time since diagnosis (years), mean (SD)	8.8 (8.61)	7.4 (6.96)	6.8 (7.70)	6.1 (4.32)
ESSDAI, mean (SD)	12.2 (5.23)	11.5 (5.37)	10.3 (5.98)	11.2 (5.20)
ESSDAI activity level, n (%)				
Moderate (≥5 and ≤12)	8 (61.5)	15 (62.5)	18 (75.0)	18 (72.0)
Severe (>12)	5 (38.5)	9 (37.5)	6 (25.0)	7 (28.0)
ESSPRI, mean (SD)	6.3 (1.99)	5.8 (1.97)	6.5 (1.80)	6.3 (2.02)
Stimulated salivary flow (mL/min), mean (SD)	0.4 (0.25)	0.7 (0.67)	0.4 (0.35)	0.6 (0.57)
Oral dryness (NRS), mean (SD)	7.8 (1.41)	7.0 (1.84)	7.5 (2.06)	7.3 (1.82)
IgG (g/L), mean (SD)	20.5 (6.46)	17.2 (5.37)	16.5 (7.04)	17.9 (6.99)
SG lymphocyte focus score, mean (SD)	3.1 (1.74)	2.1 (1.85)	3.0 (2.02)	2.7 (2.19)
Baseline medication use, n (%)				
Steroids	4 (30.8)	9 (37.5)	8 (33.3)	8 (32.0)
Anti-malarials	7 (53.8)	11 (45.8)	16 (66.7)	14 (56.0)
Muscarinic agonists	5 (38.5)	1 (4.2)	0 (0.0)	1 (4.0)

Ig, immunoglobulin; SD, standard deviation; SG, salivary gland.

Safety: Adverse Events (Safety Population)

The proportions of patients experiencing at least one AE were similar across the 4 treatment groups

There was no evidence for increased AE rates in the active treatment arms for the most frequent SOCs

While SAEs were observed in the active treatment arms, none were observed for the placebo group. No unexpected events were detected

	Placebo (n=13)	Belimumab/rituximab (n=24)	Belimumab (n=24)	Rituximab (n=25)
AEs*, n (%)	**13 (100)**	**24 (100)**	**23 (96)**	**24 (96)**
Infections and infestations	**11 (85)**	**19 (79)**	**21 (88)**	**18 (72)**
Musculoskeletal and connective tissue disorders	5 (38)	14 (58)	13 (54)	11 (44)
General disorders and administration site conditions	9 (69)	14 (58)	12 (50)	5 (20)
Gastrointestinal disorders	6 (46)	12 (50)	11 (46)	8 (32)
Nervous system disorders	6 (46)	11 (46)	10 (42)	9 (36)
Skin and subcutaneous tissue disorders	6 (46)	8 (33)	8 (33)	9 (36)
Respiratory, thoracic and mediastinal disorders	4 (31)	5 (21)	7 (29)	6 (24)
Drug-related AEs, n (%)	**10 (77)**	**17 (71)**	**16 (67)**	**14 (56)**
AEs leading to discontinuation/withdrawal, n (%)	**1 (8)**	**5 (21)**	**3 (13)**	**5 (20)**
SAEs, n (%)	**0**	**3 (13)**	**2 (8)**	**4 (16)**
Number of SAEs	0	4	2	7
Number of drug-related SAEs	0	2	1	2
Deaths, n (%)	**0**	**1 (4)†**	**0**	**0**

SOC, system organ class

*Only AEs occurring in >30% of patients in any treatment group were included
†Food aspiration, not considered related to treatment

Safety: Adverse Events of Special Interest (Safety Population)

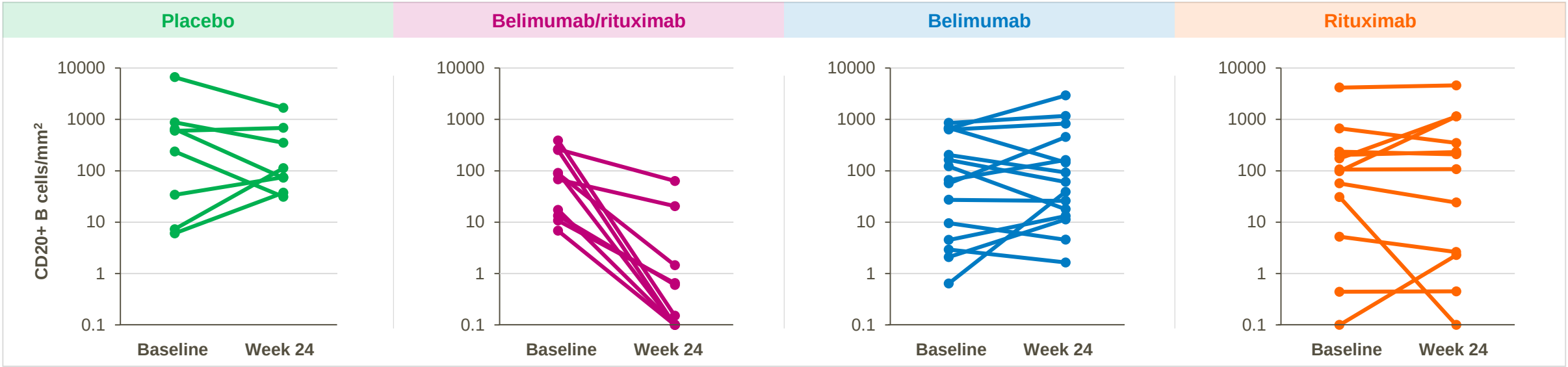
AESI	Placebo (n=13)		Belimumab/rituximab (n=24)		Belimumab (n=24)		Rituximab* (n=25)	
	Number of events	n (%)	Number of events	n (%)	Number of events	n (%)	Number of events	n (%)
Post-administration systemic reactions	**7**	**4 (30.8)**	**2**	**2 (8.3)**	**6**	**3 (12.5)**	**6**	**5 (20.0)**
Serious delayed acute reactions	0	0	0	0	0	0	**1**	**1 (4.0)**
All infections of special interest (OI, HZ, TB, sepsis)	**2**	**2 (15.4)**	**2**	**1 (4.2)**	**4**	**3 (12.5)**	**2**	**2 (8.0)**
Serious infections of special interest (OI, HZ, TB, sepsis)	0	0	0	0	0	0	0	0
Depression (including mood disorders and anxiety)/ suicide/self-injury	0	0	**3**	**3 (12.5)**	**5**	**5 (20.8)**	**2**	**1 (4.0)**
Suicide/self-injury	0	0	0	0	0	0	**1**	**1 (4.0)†**

HZ, herpes zoster; NMSC, non-melanoma skin cancer; OI, opportunistic infection; TB, tuberculosis

*There were two events of malignancies including NMSC in the rituximab group in 1 (4.0%) patient and no other malignancy events
†One case of suicidal ideation; there were no completed suicides in the study

Mechanistic Biomarker: CD20+ B-cell Depletion in Salivary Gland Biopsies (Completer Population)

In contrast with placebo, belimumab and rituximab monotherapies, salivary gland biopsies from **belimumab/rituximab** showed **near complete CD20+ B-cell depletion** (at Week 24)



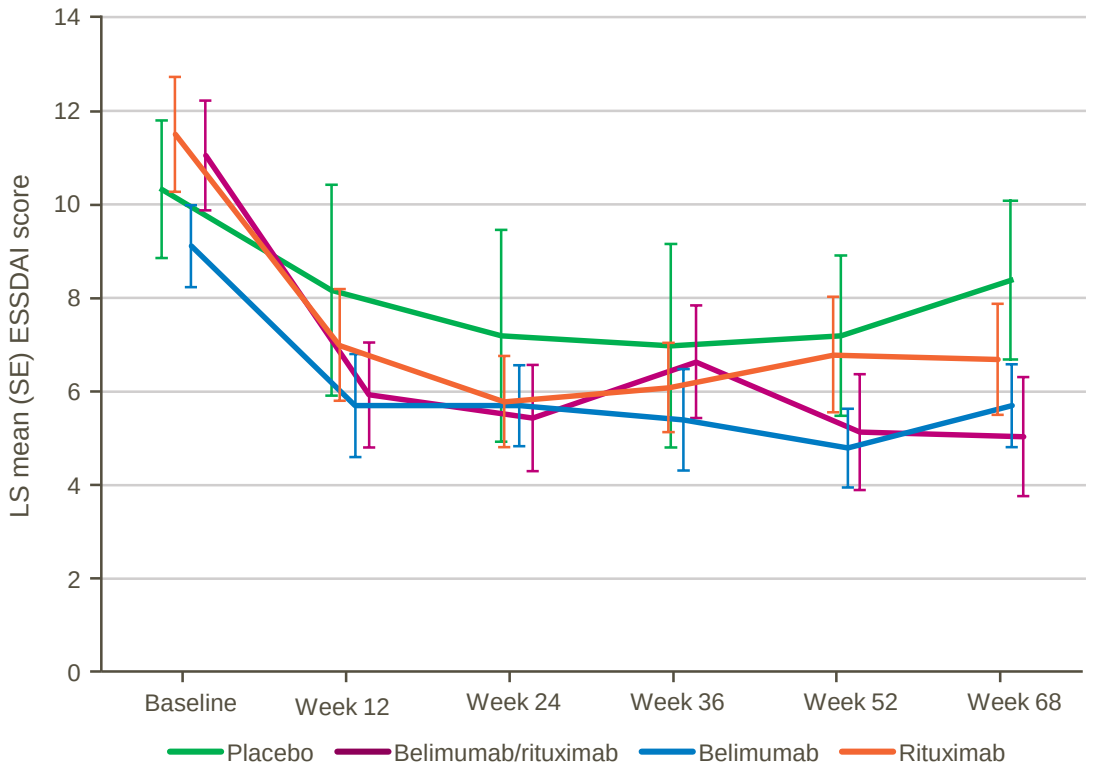
	Placebo		Belimumab/rituximab		Belimumab		Rituximab	
Median (IQR) absolute number of CD20+ B cells/mm²	**418** (21–763) n=8	**93** (55–518) n=8	**88** (13–252) n=15	**0** (0–1) n=10	**66** (5–636) n=19	**61** (13–455) n=15	**106** (31–235) n=13	**158** (2–745) n=12

IQR, interquartile range

Figure: Post-hoc analysis; displays data only for patients with paired baseline and Week 24 biopsies. Minimum values are constrained to 0.1
Table: Displays all baseline and Week 24 data for completer population

Efficacy: ESSDAI Total Score Over Time (Completer Population)

The overall improvement from baseline in mean ESSDAI total scores at Week 68 was numerically greater in the active treatment arms vs placebo with the **largest difference** observed in the **belimumab/rituximab group**



Statistical analysis (MMRM)
Change from baseline:

Belimumab/rituximab vs placebo difference (95% CI):

Week 12: −2.86 (−6.38, 0.67)

Week 24: −2.45 (−5.67, 0.77)

Week 52: −2.80 (−5.95, 0.34)

Week 68: −3.99 (−7.39, −0.58)

MCII* vs placebo achieved at Week 68

CI, confidence interval; LS, least squares; MCII, minimal clinically important improvement; MMRM, mixed model repeated measures; SE, standard error.

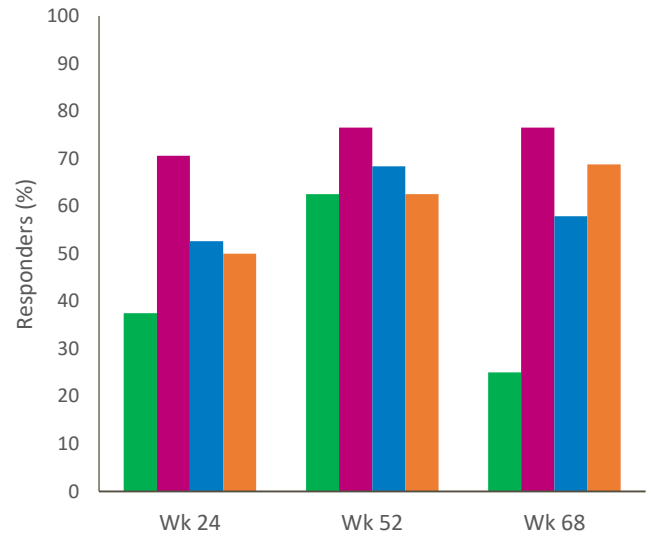
*MCII = 3-point reduction relative to placebo

Efficacy: ESSDAI Responder Analysis (Completer Population)

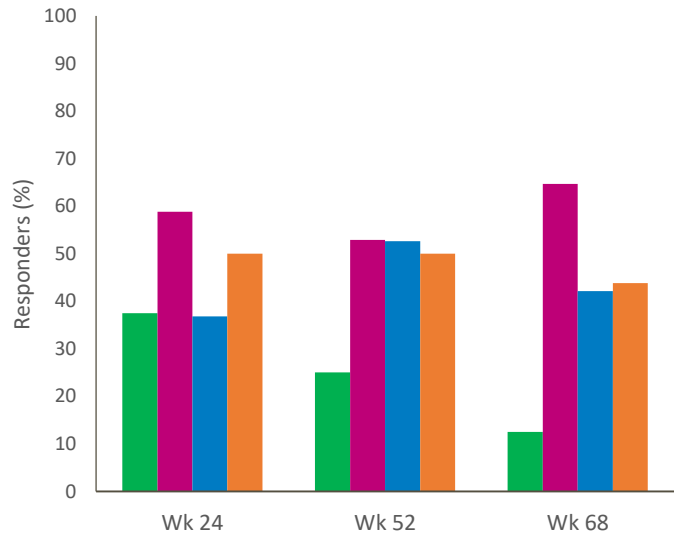
At Week 52, there was a **numerically higher proportion** of responders in the **belimumab/rituximab** group than in the placebo group; this trend was sustained to Week 68

This trend was also observed for the belimumab and rituximab groups versus the placebo group

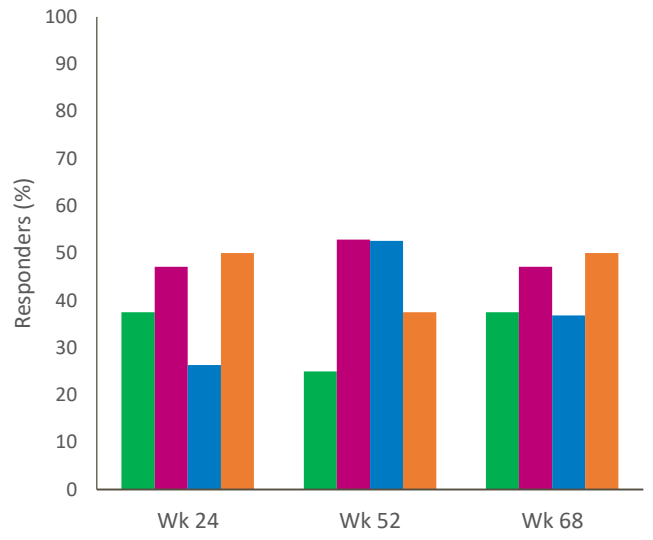
Percentage of ESSDAI responders (≥3-point improvement vs. baseline)



Percentage of ESSDAI responders (≥5-point improvement vs. baseline)



Percentage of ESSDAI responders (total score <5)

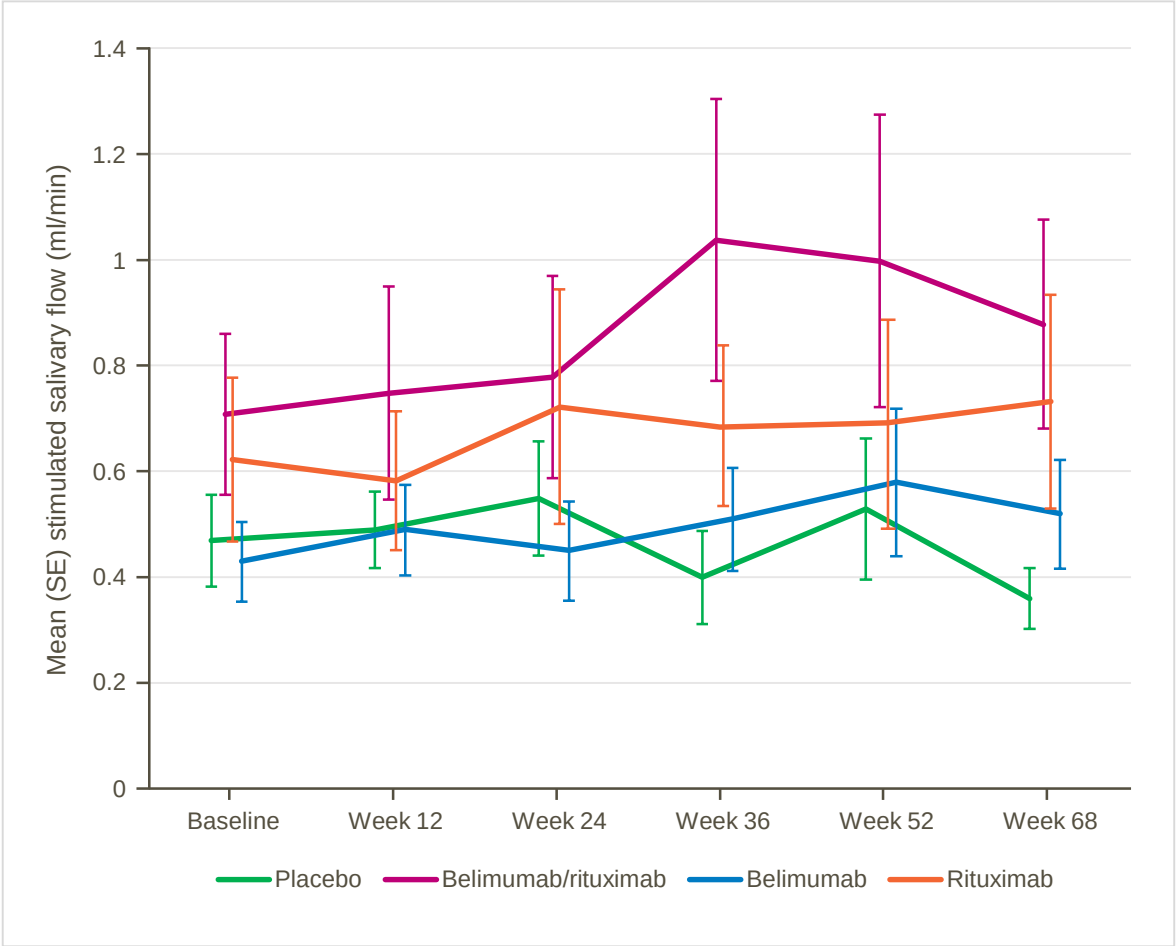


Placebo | Belimumab/rituximab | Belimumab | Rituximab

Efficacy: Stimulated Salivary Flow (Completer Population)

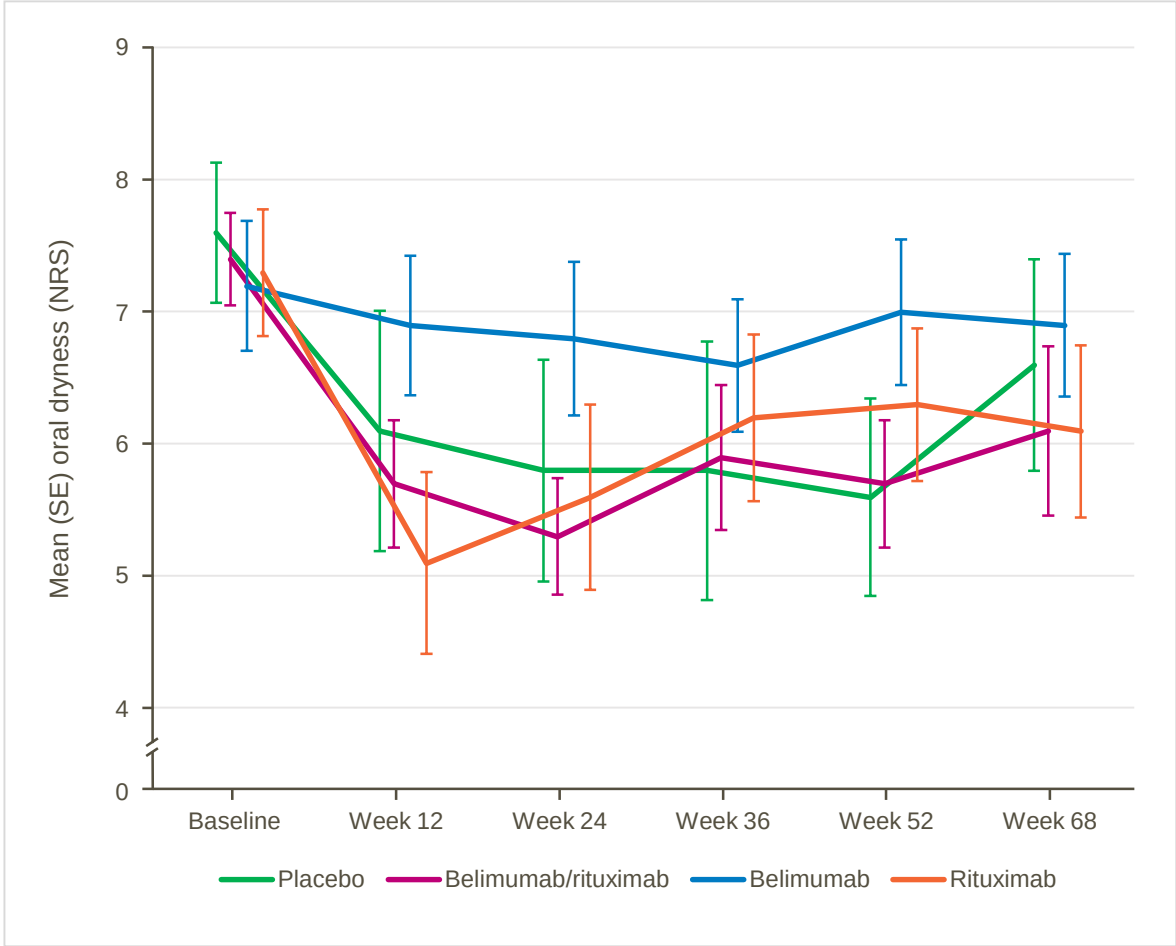
At Weeks 36, 52 and 68, the **stimulated salivary flow rate** showed a trend for numerically **greater increases** in the **belimumab/rituximab group** compared with the placebo group

Changes in stimulated salivary flow rate throughout the study were similar between the placebo and monotherapy groups



Efficacy: Patient Reported Oral Dryness (Completer Population)

Relative to placebo, there was no notable improvement in oral dryness observed in any of the active treatment groups



NRS, Numeric Response/Rating Scale

Conclusions

Safety and tolerability data were in line with the known safety profiles of belimumab and rituximab. **No new safety issues** were observed with **belimumab/rituximab** compared with monotherapy

Near complete depletion of **salivary gland CD20+ B-cells** was observed (Week 24) in the **belimumab/rituximab** group, which was not observed in other treatment groups

Compared with placebo, all active treatments showed a **trend towards improvement** in **ESSDAI total score over time**. The **belimumab/rituximab** group showed the **greatest response** which also appeared to be sustained post treatment

Belimumab/rituximab treatment also showed a trend at later time points for **stimulated salivary flow improvement** relative to placebo

There were no notable improvements in ESSPRI score or patient-reported symptoms of oral dryness over this study period

This study comprised a relatively small sample size, which limits the conclusions that can be drawn from the mechanistic and efficacy endpoints

Overall, the results of this Phase 2 study merit further investigation of belimumab/rituximab combination or belimumab monotherapy in patients with pSS

Thank you

We thank the patients who took part in this study, the investigators, sub-investigators and site staff, GSK central and country teams, including clinical study monitors, experts who participated in the safety review committee, and the central laboratories and medical writing teams.

Back-up slides

Efficacy: ESSPRI Score (Completer Population)

Total ESSPRI score improved (reduced) over time in the **placebo group**

Relative to placebo, there was no noticeable improvement in ESSPRI score for any of the active treatment groups