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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SDV is a consultant for GSK and Roche.

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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

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Study Design

Screening
Salivary gland biopsies
Patients stratified based on ESSDAI scores (5–12 vs >12)

Patients randomised 1:2:2:2

Arm 1: Placebo
Belimumab placebo
Belimumab placebo

Arm 2: Combination treatment
Belimumab 200 mg SC (weekly for 24 weeks) + Rituximab 1000 mg IV (at Week 8 and Week 10)
Belimumab
Belimumab

Arm 3: Belimumab monotherapy
Belimumab 200 mg SC monotherapy (weekly for 52 weeks)
Belimumab
Belimumab

Arm 4: Rituximab monotherapy
Rituximab 1000 mg IV monotherapy (at Week 8 and Week 10)
Belimumab placebo
Belimumab placebo

Week 24
Salivary gland biopsies

Week 68
Completer population:
a patient who completed the 52-week treatment and general follow-up periods (including Week 68 visit)

General follow-up period:
Safety assessments
Limited efficacy assessments
For all patients

Individualised follow-up period:
Safety assessments
Limited efficacy assessments
Until CD19+ B-cells return to within normal range of baseline levels (if <LLN)

Safety population:
patients who were randomised and treated with at least one dose of study treatment

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
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)
<table>
<thead>
<tr>
<th>Demographics and Baseline Characteristics (Safety Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Placebo (n=13)</strong></td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
</tr>
<tr>
<td>Female, n (%)</td>
</tr>
<tr>
<td>Time since diagnosis (years), mean (SD)</td>
</tr>
<tr>
<td>ESSDAI, mean (SD)</td>
</tr>
<tr>
<td>ESSDAI activity level, n (%)</td>
</tr>
<tr>
<td>Moderate (≥5 and ≤12)</td>
</tr>
<tr>
<td>Severe (&gt;12)</td>
</tr>
<tr>
<td>ESSPRI, mean (SD)</td>
</tr>
<tr>
<td>Stimulated salivary flow (mL/min), mean (SD)</td>
</tr>
<tr>
<td>Oral dryness (NRS), mean (SD)</td>
</tr>
<tr>
<td>IgG (g/L), mean (SD)</td>
</tr>
<tr>
<td>SG lymphocyte focus score, mean (SD)</td>
</tr>
<tr>
<td>Baseline medication use, n (%)</td>
</tr>
<tr>
<td>Steroids</td>
</tr>
<tr>
<td>Anti-malarials</td>
</tr>
<tr>
<td>Muscarinic agonists</td>
</tr>
</tbody>
</table>

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.

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

SOC, system organ class

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

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

There was no evidence for increased AE rates in the active treatment arms for the most frequent SOCs.
## Safety: Adverse Events of Special Interest (Safety Population)

### AESI

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

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)

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Belimumab/rituximab</th>
<th>Belimumab</th>
<th>Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (IQR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 24</td>
<td>93 (55–518)</td>
<td>0 (0–1)</td>
<td>61 (13–455)</td>
</tr>
<tr>
<td>n=8</td>
<td>n=8</td>
<td>n=15</td>
<td>n=10</td>
</tr>
</tbody>
</table>

Median (IQR) absolute number of CD20+ B cells/mm²

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
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**.

**Efficacy: ESSDAI Total Score Over Time (Completer Population)**

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

Cl, 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.

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**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  
---|---|---|---

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