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Abatacept treatment for patients with early active primary Sjögren's syndrome: a single-centre, randomised, double-blind, placebo-controlled, phase 3 trial (ASAP-III study)

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Summary

Background Several small open-label studies have suggested efficacy of abatacept—a co-stimulation inhibitor—in patients with primary Sjögren's syndrome. These promising results warranted further evaluation. We therefore aimed to further assess the safety and efficacy of abatacept compared with placebo in patients with primary Sjögren's syndrome.

Methods We did a single-centre, randomised, double-blind, placebo-controlled, phase 3 trial at the University Medical Center Groningen (Groningen, Netherlands). We included patients with primary Sjögren's syndrome fulfilling the American–European Consensus Group criteria, aged 18 years or older, with positive salivary gland biopsies, time from diagnosis of 7 years or less, and a European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) score of 5 or more. Independent pharmacists randomly allocated patients (1:1) to either the abatacept group or placebo group using a computer-generated sequence stratified by previous use of disease-modifying anti-rheumatic drugs. Patients received at-home subcutaneous injections of abatacept (125 mg) or placebo once a week for 24 weeks. The primary outcome was the between-group difference in ESSDAI score at week 24. Efficacy was analysed in patients who received at least one drug dose and for whom post-baseline data were collected. Safety was analysed in all patients who received at least one drug dose.

Findings Between Aug 14, 2014, and Aug 23, 2018, 580 patients were reviewed for eligibility, of which 80 patients were randomly assigned to receive study treatment. Efficacy was analysed in 40 patients receiving abatacept and 39 patients receiving placebo (one patient in this group was lost to follow-up). The primary outcome did not significantly differ between the treatment groups. The adjusted mean difference in ESSDAI score at week 24 between the abatacept group and placebo group was -1.3 (95% CI -4.1 to 1.6). No deaths or treatment-related serious adverse events occurred. In 38 (95%) of 40 patients in the abatacept group, 103 adverse events occurred, including one serious adverse event and 46 infections. In 38 (95%) of 40 patients in the placebo group, 87 adverse events occurred, including four serious adverse events and 49 infections.

Interpretation On the basis of this trial, we cannot recommend abatacept treatment as standard of care to reduce systemic disease activity in patients with primary Sjögren's syndrome. Further studies should evaluate whether patients with specific clinical manifestations and biological characteristics might benefit from abatacept treatment.

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Introduction

Primary Sjögren's syndrome is a systemic autoimmune disease, characterised by lymphocytic infiltration of the salivary and tear glands, with an estimated prevalence of 0.06%.^{1,2} Patients with primary Sjögren's syndrome experience a wide range of symptoms, including glandular enlargement, sicca symptoms, disabling fatigue, arthritis, skin involvement, renal and lung involvement, and peripheral neuropathy. Despite the major impact of this syndrome on health-related quality of life and socioeconomic status,³ treatment for primary Sjögren's syndrome mostly focuses on symptom relief, and an unmet need exists for systemic treatment options. Efficacy of traditional and biological disease-modifying anti-rheumatic drugs

(DMARDs) in primary Sjögren's syndrome has not been confirmed in large randomised controlled trials.⁴

Abatacept is a fully human soluble fusion protein of cytotoxic T-lymphocyte antigen 4 coupled to the Fc tail of IgG. This biological DMARD prevents T-cell activation by inhibiting co-stimulation. Because T-cell-dependent B-cell hyperactivity has a central role in the pathogenesis of primary Sjögren's syndrome, inhibition of co-stimulation is a promising treatment approach.⁵ In an open-label study of intravenous abatacept in 15 patients with primary Sjögren's syndrome (time since diagnosis ≤ 5 years and active disease), patients showed improvements in the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) and the

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Research in context

Evidence before this study

No systemic treatment options have been approved for patients with primary Sjögren's syndrome. Several studies confirmed the efficacy and safety of abatacept in rheumatoid arthritis. We searched PubMed with the terms "Sjögren's syndrome", "abatacept", and "therapy" to identify trials of abatacept therapy for primary Sjögren's syndrome up to Dec 8, 2019. No randomised, double-blind trials were found. Three small open-label studies were identified. The first study, in which intravenous abatacept was given to 15 patients with primary Sjögren's syndrome, short disease duration, and active disease, reported improvements in the European League Against Rheumatism Sjögren's Syndrome Disease Activity Index (ESSDAI) and Patient-Reported Index (ESSPRI), laboratory parameters, fatigue, and health-related quality of life. The second study reported amelioration of symptoms in some patients, although no validated questionnaires were used. The third study reported improvement of ESSDAI and salivary flow.

Added value of this study

The Abatacept Sjögren Active Patients phase III (ASAP-III) study is, to our knowledge, the first randomised, double-blind trial to compare the efficacy and safety of subcutaneous administration of abatacept with placebo over 24 weeks in patients with primary Sjögren's syndrome that have a short disease duration

and active systemic disease. Abatacept therapy did not result in a significant difference in ESSDAI score compared with placebo treatment at week 24. No significant differences in ESSPRI score were found between abatacept and placebo-treated patients, although abatacept-treated patients showed slightly larger improvements in ESSPRI score, resulting in a higher proportion of ESSPRI responders. Abatacept attenuated B-cell hyperactivity, as shown by a decrease in IgG and rheumatoid factor concentrations. Sexual function in female patients was improved in the abatacept group, but no difference was seen for dryness symptoms, fatigue, and quality of life. Salivary and tear gland function were not significantly improved. In this trial, abatacept treatment showed a good safety profile (no deaths or suspected unexpected serious adverse reaction was reported) in patients with primary Sjögren's syndrome.

Implications of all the available evidence

On the basis of our results, and considering the high cost of abatacept, we cannot recommend the use of abatacept as standard of care to alleviate systemic disease activity in patients with primary Sjögren's syndrome. Further studies could assess whether patients with specific clinical manifestations and biological characteristics might benefit from abatacept treatment and whether longer treatment duration will improve efficacy of abatacept.

European League Against Rheumatism Patient Reported Index (ESSPRI), laboratory parameters, fatigue, and health-related quality of life after 24 weeks.⁶ Another open-label study found that some patients reported amelioration of their symptoms during 28 weeks of abatacept treatment, although no validated questionnaires were used.⁷ In 2019, a third group reported improvement of ESSDAI and salivary flow after 24 months of intravenous abatacept treatment.⁸ Abatacept has also shown efficacy in an open-label study of patients with rheumatoid arthritis and associated Sjögren's syndrome.⁹

These promising results warranted further evaluation of abatacept for the treatment of primary Sjögren's syndrome. We therefore aimed to assess the safety and efficacy of subcutaneous abatacept compared with placebo in patients with primary Sjögren's syndrome.

Methods

Study design and participants

We did a single-centre, randomised, double-blind, placebo-controlled, phase 3 trial (the Abatacept Sjögren Active Patients phase III [ASAP-III] study). This study was done in the multidisciplinary tertiary referral expertise centre for primary Sjögren's syndrome at the University Medical Center Groningen (UMCG; Groningen, Netherlands). We obtained ethical approval from the UMCG institutional review board (METc2014.118). Patients were selected from the UMCG population or referred by other Dutch clinics for trial participation.

Our main inclusion criteria for patients for this study were fulfilment of the American-European Consensus Group criteria for primary Sjögren's syndrome,¹⁰ age 18 years or older, positive gland biopsy, time since diagnosis of 7 years or less, and an ESSDAI score of 5 or more.¹¹ Anti-Sjögren's-syndrome-related antigen A (anti-SSA) positivity was not required. Retrospectively, all patients also fulfilled the American College of Rheumatology (ACR)–European League Against Rheumatism (EULAR) Classification criteria.¹² Patients who had used prednisone (>10 mg/day), non-biological DMARDs including hydroxychloroquine, or pilocarpine for 1 month or less before enrolment were excluded. Previous use of biological DMARDs was not allowed. 6 months after trial commencement, the protocol was amended to allow patients who previously used abatacept (≥6 months before inclusion) or rituximab (≥12 months before inclusion) to participate, as some of these patients showed high disease activity and were eager to join our trial. The appendix (pp 26–28) shows a full list of the inclusion and exclusion criteria. We obtained written informed consent from all participants.

Randomisation and masking

Patients were screened for eligibility (JFvN, EM, GSvZ, RFW, HB). Following enrolment, participants received a study number and were randomly allocated (1:1) to either the abatacept group or placebo group by independent pharmacists according to a computer-generated sequence, which was only known to the pharmacists. Allocation

See Online for appendix

was stratified by previous use of DMARDs (including hydroxychloroquine), using block randomisation with a block size of four. Block size was prespecified in the protocol and therefore could be known to the investigators and outcome assessors. Abatacept and placebo injections were identical in appearance. Participants, investigators, outcome assessors, and care providers were masked to the treatment groups, until the last patient completed week 24 and the database was locked.

Procedures

Patients received instructions to administer subcutaneous injections at home, once a week, for 24 weeks. Injections contained 125 mg of abatacept or placebo. Concomitant use of pilocarpine or DMARDs was not permitted. A stable low dose of prednisone (≤ 10 mg) was permitted. Non-steroidal anti-inflammatory drugs and topical treatments were allowed, but patients were asked to discontinue non-steroidal anti-inflammatory drugs 3 days before each visit, and eye drops 1 h before ocular examinations. Rescue therapy with prednisone or cyclophosphamide was permitted after week 12. Patients visited the UMCG at baseline and weeks 4, 8, 12, and 24. Clinical assessments including laboratory parameters and safety outcomes were done by JFvN, EM, GSvZ, RFW, or HB at each visit. At each visit, patients also completed online questionnaires. Glandular function tests were done by oral medicine specialists and ophthalmologists during the screening visit, week 12, and week 24. Patients from both treatment groups received open-label abatacept for another 24 weeks after the double-blind phase. Safety and efficacy results of the extension phase will be analysed separately.

Outcomes

The primary outcome was the difference in ESSDAI score between the abatacept and placebo groups at week 24.¹¹ Secondary clinical outcomes were ESSDAI score at other timepoints, physician global assessment of disease activity using a numeric rating scale (range 0–10), and Disease Activity Score 28 joint count (DAS-28). Secondary laboratory outcomes were rheumatoid factor, IgG, IgA, IgM, erythrocyte sedimentation rate, and complement C3 and C4. Secondary patient-reported outcomes were the ESSPRI score,¹³ patient global assessment of disease activity, and Patient Acceptable Symptom State at each timepoint; ocular and oral dryness (numeric rating scale [range 0–10]), Multidimensional Fatigue Inventory, Short-Form 36 (SF-36), EuroQoL five dimensions health status questionnaire (EQ-5D-5L), and Work Participation and Activity Impairment Questionnaire (WPAI) at weeks 12 and 24. Physical and mental component scores of the SF-36 were calculated using the QualityMetric Health Outcomes Scoring Software, version 5.1. EQ-5D-5L index values were calculated using syntax provided by EuroQoL, based on a set of weights for the Netherlands. Additionally, EuroQoL five dimensions (EQ-5D) visual analogue scale for general health was used as an outcome. For female

Figure 1: Trial profile

ESSDAI=European League Against Rheumatism Sjögren's Syndrome Disease Activity Index. ITT=intention-to-treat. MALT=mucosa-associated lymphoid tissue. SCLÉ=subacute cutaneous lupus erythematosus. *Numbers of patients fulfilling different exclusion criteria are not available because patients often fulfilled more than one criterion and only the first one that was detected was noted. †One patient in the placebo group was excluded from the efficacy analysis because she was lost to follow-up in week 3 and no post-baseline was collected.

participants, patient-reported outcomes included vaginal dryness (numeric rating scale [range 0–10]) at weeks 12 and 24, and Female Sexual Function Index at week 24. Secondary glandular function outcomes were unstimulated whole salivary flow and citric acid-stimulated whole salivary flow, ocular staining score,¹⁴ tear break-up time, and Schirmer's test without anaesthesia. A full description of the study outcomes is included in the appendix (pp 33–40).

Exploratory outcomes included salivary gland ultrasound, histology, gut microbiome, and additional laboratory outcomes, which will be analysed and reported separately to provide an in-depth translational evaluation of the efficacy of abatacept.

	Abatacept (n=40)	Placebo (n=40)	Total (n=80)
Age (years)	48 (15)	49 (16)	49 (16)
Men	3 (8%)	3 (8%)	6 (8%)
Women	37 (93%)	37 (93%)	74 (93%)
Time since diagnosis (years)	2 (0–4)	2 (1–4)	2 (1–4)
Time since symptoms started (years)	11 (4–14)	8 (4–14)	8 (4–14)
Anti-Ro/SSA	34 (85%)	37 (93%)	71 (89%)
Anti-La/SSB	20 (50%)	23 (58%)	43 (54%)
Baseline stimulated whole salivary flow ≥ 0.05 mL/min	31 (78%)	28 (70%)	59 (74%)
Previous use of disease-modifying anti-rheumatic drugs	18 (45%)	16 (40%)	34 (43%)
Oral corticosteroids	10 (25%)	10 (25%)	20 (25%)
Hydroxychloroquine	15 (38%)	14 (35%)	29 (36%)
Methotrexate	3 (8%)	2 (5%)	5 (6%)
Abatacept*	2 (5%)	3 (8%)	5 (6%)
Rituximab*	1 (3%)	0	1 (1%)
Current medication use			
Corticosteroids	0	1 (3%)	1 (1%)
Non-steroidal anti-inflammatory drugs	16 (40%)	11 (28%)	27 (34%)
Artificial tears	32 (80%)	33 (83%)	65 (81%)
Corticosteroid eye drops	6 (15%)	5 (13%)	11 (14%)
Artificial saliva	7 (18%)	7 (18%)	14 (18%)
ESSDAI subdomain activity†			
Constitutional	20 (50%)	17 (43%)	37 (46%)
Lymphadenopathy	10 (25%)	13 (33%)	23 (29%)
Glandular	36 (90%)	37 (93%)	73 (91%)
Articular	23 (58%)	24 (60%)	47 (59%)
Cutaneous	11 (28%)	7 (18%)	18 (23%)
Pulmonary	3 (8%)	2 (5%)	5 (6%)
Renal	0	0	0
Muscular	1 (3%)	0	1 (1%)
Peripheral nervous system	2 (5%)	5 (13%)	7 (9%)
Central nervous system	0	0	0
Haematological	14 (35%)	20 (50%)	34 (43%)
Biological	32 (80%)	31 (78%)	63 (79%)

Data are mean (SD), median (IQR), or n (%). Some percentages do not add up to 100 because of rounding. ESSDAI=European League Against Rheumatism Sjögren Syndrome Disease Activity Index. SSA=Sjögren's-syndrome-related antigen A. SSB=Sjögren's-syndrome-related antigen B. *Patients with previous abatacept use were participants in the open-label Abatacept Sjögren Active Patients study.⁶ †Time between previous treatment with rituximab or abatacept and inclusion was at least 2 years. ‡Total number of patients with low, moderate, or high activity in ESSDAI subdomains.

Table 1: Baseline characteristics of participants

ESSDAI and ESSPRI response rates were not included in the original protocol, as the minimally clinically important change of ESSDAI and ESSPRI had not yet been published. These were added as secondary outcomes in the statistical analysis plan before unmasking. ESSDAI response was defined as a decrease of three points or more from baseline, and ESSPRI response as a decrease of one point or more or a decrease of 15%.¹⁵ Post-hoc analysis included the evaluation of Sjögren Syndrome Responder Index, which defines response as a 30% improvement or more from baseline in two or more of the five domains (fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, and erythrocyte sedimentation rate).¹⁶

Data for adverse events were collected by clinicians from baseline to week 24, by open-ended questioning and clinical examination, and clinicians specifically inquired about infections. Investigators assessed all adverse events for severity and potential causality.¹⁷ Adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 19.0). Other safety endpoints included laboratory tests and treatment discontinuation.

Statistical analysis

The sample size was based on a difference of two points in the ESSDAI score between the abatacept group and placebo group, as the minimally clinically important change of three points or more had not yet been determined at the time the protocol was written.¹⁵ A sample size of 44 patients per treatment group was needed to detect a two point difference in ESSDAI (estimated SD of three points on the basis of results from previous trials^{6,18,19}) between the abatacept group and placebo group at 24 weeks, with a two-sided 5% significance level and power of 80%, allowing for a 15% dropout rate. However, after enrolment of 61 patients, the dropout rate appeared to be much lower (<5%), after which the predefined sample size was adjusted to 40 patients per group, in consultation with our data and safety monitoring board. An independent data and safety monitoring board reviewed unblinded study data once a year to monitor safety and overall conduct of the clinical trial. There were no predefined stopping rules. No formal interim analysis for efficacy was done.

Before unmasking, a detailed analysis plan was prepared (appendix pp 62–75). According to the modified intention-to-treat principle, all participants who received at least one dose of study medication were included in the efficacy analysis, irrespective of protocol violations, with exception of one patient for whom no post-baseline efficacy data were available (lost to follow-up before week 4). We planned to do a per-protocol analysis of the primary endpoint only if there was a difference of more than 10% between the modified intention-to-treat and per-protocol population. The safety analysis included all participants who received at least one dose of study medication.

Data collected during visits were considered non-valid and coded as missing when three or more injections were skipped within 4 weeks before a visit, when cyclophosphamide was used, or when a dose of 5 mg or more of prednisone or equivalent was used within 2 weeks before the visit, unless corticosteroid dose was stable since baseline.

We considered p values less than 0.05 statistically significant. For the primary endpoint and all secondary efficacy outcomes, except the Patient Acceptable Symptom State and response according to ESSPRI, ESSDAI, and Sjögren's Syndrome Responder Index, the difference between abatacept and placebo groups was evaluated using linear generalised estimating equations. Missing data were not imputed. The generalised estimating equations model included previous DMARD use, baseline

	Baseline		Week 12		Week 24	
	Abatacept	Placebo	Adjusted difference (95% CI)	p value	Adjusted difference (95% CI)	p value
ESSDAI score (primary outcome)	14.0 (9.0 to 16.8)	13.0 (8.0 to 18.0)	-2.4 (-4.7 to -0.1)	0.039	-1.3 (-4.1 to 1.6)	0.385
ESSPRI score*	7.0 (5.4 to 7.7)	7.3 (5.3 to 8.0)	-4.7 (-12.5 to 3.0)	0.232	-5.0 (-12.7 to 2.8)	0.208
Dryness	7.0 (5.3 to 8.0)	7.0 (7.0 to 8.0)	-0.3 (-1.0 to 0.3)	0.311	-0.3 (-0.9 to 0.4)	0.455
Fatigue*	7.5 (7.0 to 8.0)	8.0 (6.0 to 9.0)	-2.0 (-12.5 to 8.6)	0.716	-2.6 (-14.1 to 9.0)	0.664
Pain*	7.0 (5.0 to 8.0)	7.0 (3.0 to 8.0)	-4.5 (-14.7 to 5.7)	0.389	-5.2 (-14.5 to 4.2)	0.279
Ocular dryness (NRS)	6.0 (3.3 to 7.0)	7.0 (6.0 to 8.0)	0.4 (-0.5 to 1.2)	0.388	0.0 (-0.8 to 0.9)	0.972
Oral dryness (NRS)*	7.0 (5.0 to 8.0)	7.0 (6.0 to 8.0)	-3.8 (-11.6 to 4.1)	0.345	-0.6 (-10.1 to 8.9)	0.902
Vaginal dryness (NRS)*	5.0 (3.0 to 8.0)	6.5 (5.0 to 8.8)	-1.4 (-10.2 to 7.3)	0.751	-0.1 (-10.0 to 9.7)	0.981
Patient global disease activity	8.0 (7.0 to 8.0)	7.0 (7.0 to 9.0)	-0.8 (-1.7 to 0.0)	0.063	-0.4 (-1.3 to 0.6)	0.442
Multidimensional Fatigue Index						
General fatigue	16.5 (13.3 to 19.0)	16.0 (13.0 to 20.0)	-0.4 (-2.0 to 1.2)	0.583	-0.8 (-2.8 to 1.2)	0.448
Physical fatigue	15.5 (14.0 to 17.0)	15.0 (13.0 to 18.0)	-0.1 (-1.4 to 1.2)	0.907	-1.3 (-3.0 to 0.4)	0.144
Reduced activity	14.0 (11.0 to 15.0)	13.0 (11.0 to 16.0)	-0.5 (-1.9 to 1.0)	0.509	-0.4 (-2.1 to 1.3)	0.619
Reduced motivation	12.0 (9.0 to 13.0)	11.0 (9.0 to 14.0)	-0.6 (-2.2 to 1.0)	0.487	-1.3 (-2.9 to 0.2)	0.099
Mental fatigue	12.0 (9.3 to 15.0)	13.0 (8.0 to 16.0)	-0.9 (-2.2 to 0.5)	0.216	-0.4 (-1.6 to 0.9)	0.554
Short-Form 36						
Physical component summary	37.1 (7.9)	38.2 (9.8)	2.5 (-0.2 to 5.2)	0.065	2.0 (-0.7 to 4.7)	0.141
Mental component summary	44.0 (38.0 to 52.1)	44.4 (36.5 to 51.6)	-1.9 (-5.5 to 1.8)	0.312	-1.0 (-4.6 to 2.6)	0.594
EQ-5D-5L	0.71 (0.60 to 0.80)	0.71 (0.50 to 0.79)	-0.04 (-0.11 to 0.03)	0.273	-0.03 (-0.10 to 0.04)	0.343
EQ-5D VAS	60.5 (42.3 to 70.0)	60.0 (45.0 to 71.0)	6.2 (-1.5 to 13.9)	0.117	3.1 (-5.0 to 11.3)	0.454
Female Sexual Function Index	11.5 (4.4 to 23.2)	14.7 (5.1 to 23.4)	NA	NA	3.8 (0.1 to 7.4)	0.042
DAS-28 (ESR)	4.82 (1.19)	5.00 (1.48)	-0.37 (-0.80 to 0.06)	0.089	-0.46 (-1.02 to 0.09)	0.101
DAS-28 (CRP)	4.35 (2.63 to 5.08)	4.20 (2.90 to 5.10)	-0.44 (-0.87 to -0.02)	0.041	-0.46 (-1.00 to 0.08)	0.097
Physician global disease activity	5.7 (1.5)	5.7 (1.6)	-0.7 (-1.3 to -0.1)	0.022	-0.6 (-1.4 to 0.2)	0.144
IgG (g/L)*	17.4 (13.4 to 26.7)	18.7 (14.8 to 24.7)	-0.1 (-0.2 to 0.0)	0.215	-0.1 (-0.2 to -0.01)	0.028
Rheumatoid factor (IU/mL)	32.5 (2.1 to 71.0)	24.0 (6.8 to 83.0)	-11.7 (-16.6 to -6.8)	<0.0001	-13.8 (-20.7 to -6.0)	<0.0001
Complement C3 (g/L)	1.2 (1 to 1.3)	1.1 (1.0 to 1.3)	0.0 (-0.1 to 0.1)	0.564	0.0 (-0.1 to 0.1)	0.451
Complement C4 (g/L)	0.19 (0.09)	0.20 (0.07)	0.01 (-0.01 to 0.03)	0.393	0.01 (-0.01 to 0.03)	0.381
ESR (mm/h)*	28.0 (13.3 to 47.0)	33.0 (17.0 to 54.0)	-0.01 (-0.20 to 0.18)	0.881	-0.20 (-0.41 to 0.02)	0.068
Ocular staining score†	4.0 (0.5 to 6.5)	4.5 (2.0 to 7.0)	-0.9 (-1.9 to 0.1)	0.071	0.0 (-1.0 to 1.0)	0.993
Schirmer's test†	3.5 (0.6 to 14.0)	2.5 (0.0 to 8.5)	0.1 (-2.9 to 3.2)	0.927	1.1 (-1.2 to 3.3)	0.367
Tear break-up time (s)†	5.3 (2.5 to 7.5)	4.0 (2.0 to 7.0)	-0.4 (-1.7 to 0.9)	0.548	-0.6 (-2.1 to 0.9)	0.435
Unstimulated whole salivary flow (mL/min)	0.05 (0.01 to 0.12)	0.05 (0.01 to 0.13)	-0.01 (-0.04 to 0.03)	0.744	0.02 (-0.02 to 0.05)	0.375
Stimulated whole salivary flow (mL/min)	0.16 (0.06 to 0.33)	0.10 (0.02 to 0.43)	0.03 (-0.05 to 0.10)	0.481	0.01 (-0.08 to 0.09)	0.861

Baseline data are mean (SD) or median (IQR). Raw outcome data for week 12 and week 24 are in the appendix (p 3). The adjusted difference is the unstandardised regression coefficient from the linear generalised estimating equations models, which represents the difference between the treatment groups (abatacept-placebo), adjusted for baseline values and previous disease-modifying anti-rheumatic drug use. Vaginal dryness and the Female Sexual Function Index include only female patients. CRP=C-reactive protein. DAS-28=disease activity score 28 joint count. ESR=erythrocyte sedimentation rate. ESSDAI=European League Against Rheumatism Sjögren Syndrome Disease Activity Index. ESSPRI=European League Against Rheumatism Sjögren Syndrome Patient Reported Index. EQ-5D=EuroQoL five dimensions. EQ-5D-5L=EuroQoL five dimensions health status questionnaire. NA=not available. NRS=numerical rating scale. VAS=visual analogue scale. *Raw values were transformed before generalised estimating equations analysis. Estimates of the adjusted differences in weeks 12 and 24 therefore represent differences on the transformed scale (square root for IgG, natural logarithm for ESR and second power for ESSPRI total, ESSPRI fatigue, ESSPRI pain, oral dryness, and vaginal dryness). †Average of right and left eye.

Table 2: Baseline values and differences between groups in week 12 and 24

values of the efficacy outcome, treatment (abatacept or placebo), visits, and interactions of treatment by visits. In case of residuals with non-Gaussian distribution, the variable was transformed (second power for ESSPRI total, ESSPRI fatigue, ESSPRI pain, and oral and vaginal dryness; square root for IgG; and natural logarithm for erythrocyte sedimentation rate). Different correlation structures

(exchangeable, M-dependent, unstructured) were tested and the model with the lowest information criterion was used, which was the exchangeable correlation structure for all variables. The comparison of main interest was the difference between groups at 24 weeks (treatment-by-visit interaction). Differences at 4, 8, and 12 weeks were assessed to investigate early treatment efficacy. Differences

in Patient Acceptable Symptom State between treatment groups were similarly evaluated using logistic generalised estimating equations.

Response according to ESSDAI, ESSPRI, and Sjögren's Syndrome Responder Index were evaluated using binary logistic regression with treatment and previous use of disease-modifying anti-rheumatic drugs as factors. For response analyses, missing values were imputed as non-responses. Baseline characteristics, ESSDAI subdomains, and safety endpoints were summarised descriptively.

We did all the statistical analyses using IBM SPSS Statistics (version 23). This study is registered with ClinicalTrials.gov, number NCT02067910.

Role of the funding source

The funder of the study (Bristol-Myers Squibb) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 14, 2014, and Aug 23, 2018, 580 patients were reviewed for eligibility of which 81 patients were enrolled (figure 1). One enrolled patient was excluded before being randomly allocated to a treatment group because their disease activity became too severe to be treated with study

Figure 2: ESSDAI score and secondary efficacy outcomes

The difference between the treatment groups are adjusted for baseline values and previous disease-modifying anti-rheumatic drug use. Error bars are IQR for medians, SD for means, and 95% CI for the ADs. AD=adjusted difference. CRP=C-reactive protein. DAS-28=Disease Activity Score 28 joint count. ESSPRI=European League Against Rheumatism Sjögren's Syndrome Patient-Reported Index. ESSDAI=European League Against Rheumatism Sjögren's Syndrome Disease Activity Index.

medication (abatacept or placebo) between the screening and baseline visits. After randomisation, 40 patients received abatacept and 40 received placebo. The last visit of the double-blind phase was completed on Feb 21, 2019. Table 1 shows the baseline characteristics.

None of the abatacept-treated patients withdrew from treatment or were lost to follow-up (figure 1). Two placebo-treated patients withdrew from treatment because of adverse events, of whom one was excluded from the efficacy analysis, as no post-baseline data were available. The modified intention-to-treat population consisted of 40 patients in the abatacept group and 39 in the placebo group. The per-protocol population consisted of 40 patients in the abatacept group and 37 in the placebo group. As the difference between modified intention-to-treat and per-protocol populations was less than 10%, no per-protocol analysis was done.

Week 12 data for one patient in the placebo group were coded as missing for the efficacy analysis, as this patient skipped three injections between week 8 and week 12. One patient used a maintenance dose of prednisone (5 mg/day) throughout the trial because of autoimmune hepatitis, which was in remission at inclusion. Although rescue therapy was allowed after week 12 according to protocol, two patients received corticosteroids before week 12, intended as bridging therapy while awaiting the effect of study treatment. The first patient received abatacept and used corticosteroids between week 10 and week 17 because of active cutaneous involvement. The second patient received placebo and was treated with corticosteroids between weeks 2–10 and 12–24 for severe arthritis and myositis. Data from week 12 of the first patient and data from weeks 4, 8, and 24 of the second patient were therefore coded as missing for the efficacy analysis. No additional patients received rescue therapy after week 12. After coding non-valid data as missing, all variables had less than 5% missing values per visit, with exception of IgG at week 4, ocular staining score, tear break-up time, Schirmer's test, unstimulated whole salivary flow, and stimulated whole salivary flow at week 12, and stimulated whole salivary flow at week 24, which had 6–10% missing values.

The primary endpoint (the difference in ESSDAI score at week 24) did not significantly differ between treatment groups (table 2, figure 2, appendix p 3). Differences in ESSDAI score between treatment groups, adjusted for baseline values and previous DMARD use, were -2.4 (95% CI -4.7 to -0.1) at week 12 and -1.3 (-4.1 to 1.6) at week 24. ESSDAI score at week 12 was significantly lower in patients receiving abatacept than in those receiving placebo. No significant differences were found in proportions of patients reaching the minimally clinically important change for ESSDAI (figure 3). At week 12, 19 (48%) of 40 patients in the abatacept group and 13 (33%) of 39 in the placebo group were ESSDAI responders (odds ratio [OR] 1.8, 95% CI 0.7–4.5; $p=0.207$). At week 24, 23 (58%) of 40 patients in the

Figure 3: Categorical efficacy outcomes

(A) Response according to the ESSDAI, ESSPRI, and Sjögren's Syndrome Responder Index. (B) ESSDAI subdomain and total activity. ESSDAI response is a decrease of three points or more from baseline.¹⁵ ESSPRI response is a decrease of one point or more, or a decrease of 15% from baseline.¹⁵ Response according to the Sjögren Syndrome Responder Index is an improvement of 30% or more from baseline in two or more of the five domains (fatigue, oral dryness, ocular dryness, unstimulated whole salivary flow, and erythrocyte sedimentation rate).¹⁶ ESSDAI=European League Against Rheumatism Sjögren's Syndrome Disease Activity Index. ESSPRI=European League Against Rheumatism Sjögren's Syndrome Patient-Reported Index.

abatacept group and 20 (51%) of 39 in the placebo group were ESSDAI responders (OR 1.3, 95% CI 0.5–3.1; $p=0.600$). The largest decrease in activity was seen in the articular, glandular, and constitutional ESSDAI subdomains (figure 3, appendix p 4). Improvements in these domains occurred in both treatment groups, although improvement in the articular domain was larger in the abatacept group. ESSDAI scores of individual patients over time are shown in the appendix (p 6).

No significant differences between groups were found for ESSPRI score (table 2, figure 2, appendix p 3), although abatacept did increase the number of patients reaching the minimally clinically important change for ESSPRI (figure 3). At week 12, 21 (53%) of 40 patients in the abatacept group and 11 (28%) of 39 in the placebo group were ESSPRI responders (OR 2.8, 95% CI 1.1–7.1;

	Number of events		Number of patients with events	
	Abatacept	Placebo	Abatacept (n=40)	Placebo (n=40)
Death	0	0	0	0
Suspected unexpected serious adverse reaction	0	0	0	0
Serious adverse event (total)*	1	4	1 (3%)	4 (10%)
Serious adverse event with possible relation to intervention†	0	1	0	1 (3%)
Adverse event (severe)‡	1	3	1 (3%)	3 (8%)
Adverse event (moderate)§	3	7	3 (8%)	7 (18%)
Adverse event (total)	103	87	38 (95%)	38 (95%)
Adverse event with possible relation to intervention†	80	66	36 (90%)	32 (80%)
Infection	46	49	29 (73%)	28 (70%)
Treatment withdrawal due to adverse event	0	2	0	2 (5%)
Temporary treatment discontinuation due to adverse event	6	12	5 (13%)	8 (20%)

Data are n (%), unless otherwise specified. *A definition of serious adverse events is shown in the appendix (p 42). †Possible, probable, or definite relation to treatment, as assessed by the investigators during the trial. ‡Severe adverse events were defined as those that make activities of daily living impossible and usually require treatment or other interventions. §Moderate adverse events were defined as those that limit activities of daily living and for which treatment or another intervention is sometimes necessary.

Table 3: Summary of adverse events by intervention group

$p=0.031$). At week 24, 23 (58%) patients in the abatacept group and eight (21%) in the placebo group were ESSPRI responders (OR 5.7, 95% CI 2.0–15.7; $p=0.001$).

The Female Sexual Function Index at week 24 was significantly better in patients receiving abatacept than in those receiving placebo (adjusted difference 3.8, 95% CI 0.1–7.4; $p=0.042$; table 2, appendix pp 3, 7). No differences were found for oral, ocular, and vaginal dryness, patient global disease activity, fatigue (Multidimensional Fatigue Index domains), or health-related quality of life (SF-36 physical and mental component scores, EQ-5D-5L, EQ-5D visual analogue scale) at any timepoint. No differences were found in proportions of patients with acceptable symptoms at week 12 (OR 0.4, 95% CI 0.1–1.7; $p=0.221$) or week 24 (1.1, 0.2–5.3; $p=0.893$; appendix p 3). As only 20 (50%) of 40 patients in the abatacept group and 21 (54%) of 39 patients in the placebo group had paid employment at baseline, the number of patients with complete WPAIs was small and differences in WPAI outcomes were not statistically tested. At week 24, 21 (53%) of 40 patients in the abatacept group and 19 (53%) of 36 patients in the placebo group had paid employment.

Abatacept significantly decreased physician global disease activity compared with placebo at week 12 (adjusted difference -0.7 , 95% CI -1.3 to -0.1 ; $p=0.022$), but not at week 24 (table 2, figure 2, appendix p 3). Although both DAS-28 (C-reactive protein) and DAS-28 (erythrocyte sedimentation rate) were decreased by abatacept treatment, a significant difference was only seen in DAS-28 (C-reactive protein) at week 12 (adjusted difference -0.44 , 95% CI -0.87 to -0.02 ; $p=0.041$). IgG

was significantly lower in patients receiving abatacept than in those receiving placebo at week 24. IgA and IgM did not significantly differ between groups (data not shown). Rheumatoid factor was significantly lower in patients in the abatacept group than in those in the placebo group at week 4 and all following visits. With the exception of rheumatoid factor, other laboratory efficacy outcomes did not show significant differences at weeks 4 and 8. No differences were seen in erythrocyte sedimentation rate or complement. No significant differences between treatment groups were found in tear or salivary gland function (table 2, figure 2, appendix p 3).

No deaths or unexpected serious adverse reaction occurred (table 3). One serious adverse event occurred in the abatacept group, which was deemed not treatment related, whereas four serious adverse events occurred in the placebo group (appendix p 5). None of the patients receiving abatacept withdrew from treatment because of adverse events. One patient in the placebo group discontinued treatment in week 3 because of the development of autoimmune hepatitis. Another patient in the placebo group discontinued treatment in week 8 because of severe exacerbation of disease activity, with glomerulonephritis, pulmonary involvement, cutaneous vasculitis, and development of high anti-double-stranded DNA concentrations, after which the patient's diagnosis was changed to Sjögren's syndrome combined with systemic lupus erythematosus (SLE). A total of 103 adverse events (including one serious adverse event and 46 infections) occurred in 38 (95%) of 40 patients in the abatacept group compared with 87 adverse events (including four serious adverse events and 49 infections) in 38 (95%) of 40 in the placebo group. Most adverse events were mild. The most common adverse events were infections, occurring in 29 (73%) patients in the abatacept group and 28 (70%) in the placebo group (appendix p 5). General and administration site conditions (including fatigue, malaise, and pyrexia) occurred in 12 (30%) patients in the abatacept group and four (10%) in the placebo group. Gastro-intestinal disorders (including abdominal pain, dyspepsia, nausea, and diarrhoea) occurred in 11 (28%) patients in the abatacept group and five (13%) in the placebo group. Laboratory safety outcomes are shown in the appendix (p 8).

Post-hoc analysis showed significantly more responders according to the Sjögren's Syndrome Responder Index in the abatacept group than in the placebo group at week 12, but not week 24 (figure 3). In week 12, 16 (40%) of 40 patients in the abatacept group and five (13%) of 39 in the placebo group were responders (OR 4.5, 95% CI 1.5–14.1; $p=0.009$). At week 24, 13 (33%) patients in the abatacept group and nine (23%) in the placebo group were responders (OR 1.7, 95% CI 0.6–4.6; $p=0.311$).

Discussion

In the ASAP-III study, we found no significant difference between the abatacept group and placebo group in the

primary endpoint of ESSDAI score after 24 weeks of treatment. Abatacept significantly decreased ESSDAI score compared with placebo at week 12, although no difference between treatment groups was found in the proportion of patients reaching the minimally clinically important change of three points or more in ESSDAI. Physician global disease activity was significantly lower in abatacept-treated patients than in placebo-treated patients only at week 12. These results indicate that while disease activity was lowered in both treatment groups, improvements in ESSDAI and physician global disease activity were seen at earlier timepoints in patients receiving abatacept.

In previous open-label trials, ESSDAI score was significantly decreased during abatacept treatment.^{6,8} In the current trial, improvement of ESSDAI score was found in both treatment groups. The improvements seen over 24 weeks in the placebo and abatacept groups might partly be explained by regression to the mean. A study in which patients were treated with standard of care therapy showed that high baseline ESSDAIs were associated with improvement of ESSDAI after 12 months.²⁰ As only patients with moderate or high ESSDAI scores were included in the ASAP-III study, a natural decrease in ESSDAI scores is expected to occur for some patients, regardless of the treatment group.

Sjögren's syndrome is a highly heterogeneous disease. Therefore, not all patients might respond equally to a particular DMARD, as was shown for rituximab.²¹ Our trial was not powered to show effects on specific systemic manifestations. Further studies should assess whether abatacept is effective in patients with specific characteristics—eg, high articular activity.

Besides ESSDAI, the patient symptom index ESSPRI, which includes questions regarding sicca symptoms, fatigue, and pain, is an important outcome, because both indices are complementary. Abatacept significantly increased the number of ESSPRI responders, based on the minimally clinically important change, compared with placebo at weeks 12 and 24, despite the absence of significant differences in ESSPRI score (which is a continuous variable). This finding shows that although abatacept-treated patients reached minimally clinically important change more often, the difference between groups was small. Female abatacept-treated patients showed improved sexual function at week 24, which might be important, considering the negative effect of primary Sjögren's syndrome on sexual function.²² No differences were found in other patient-reported outcomes including global disease activity, dryness, fatigue, and health-related quality of life.

No significant differences were found in glandular function. During our previous open-label trial,⁶ glandular function also did not improve, but stimulated whole salivary flow remained stable during treatment and deteriorated after treatment discontinuation. Abatacept reduced the number of germinal centres in parotid gland biopsies, but no changes were found in focus score or

size of infiltration.²³ As a recent open-label study found improvement of salivary flow after 24 months of abatacept treatment,⁸ longer treatment might be needed to improve salivary gland function. Evaluation of long-term efficacy of abatacept on glandular function in the ASAP-III open-label extension phase, and the effect on ultrasound and histological findings, will be of interest.

In line with previous results,⁶ abatacept attenuated B-cell hyperactivity, as reflected by the decrease in rheumatoid factor and IgG. This decrease in B-cell hyperactivity might be caused by effects of abatacept on T-follicular helper (Tfh) cells.²⁴ Abatacept decreased the number of circulating Tfh-cells, and expression of inducible T-cell co-stimulator, a marker of T-cell activation.²⁴ Decreased expression of inducible T-cell co-stimulator was associated with ESSDAI improvement.²⁴ Abatacept also decreased Bruton's tyrosine kinase concentrations in naive and memory B cells.²⁵ Unfortunately, this biological effect did not translate into improvement of systemic disease activity, raising the question whether future trials should focus on different treatment targets or on different clinical endpoints, or both. Ongoing in-depth analysis of the biological effects of abatacept might contribute to a better understanding of the molecular pathways involved in primary Sjögren's syndrome.

The choice of endpoints can greatly influence the conclusion of a trial, as previously described in SLE.²⁶ Although development of the ESSDAI, 10 years ago, has been a major step forward in the assessment of primary Sjögren's syndrome, it has certain limitations as a primary endpoint. The ESSDAI does not reflect prominent symptoms experienced by patients (sicca, fatigue, and pain). Furthermore, it is not always possible to separate signs of active disease from irreversible damage, and consequently some of the ESSDAI domains are likely not to improve, such as the pulmonary and peripheral nervous system domains. Finally, the ESSDAI can be insensitive to partial improvements within subdomains, which has also been described for similar outcome measures in SLE.²⁷ For example, a patient with an IgG of more than 20 g/L might show a reduction of IgG, but if IgG does not drop below 20 g/L, the ESSDAI biological subdomain activity does not improve. For these reasons, it is of great importance to develop validated composite endpoints for primary Sjögren's syndrome, which have high sensitivity to change, and adequately reflect disease activity as well as symptoms of primary Sjögren's syndrome. The composite endpoint Sjögren Syndrome Responder Index was created and validated using data from trials with rituximab and infliximab, and includes fatigue, oral and ocular dryness, unstimulated whole salivary flow, and erythrocyte sedimentation rate.¹⁶ At week 12, the number of responders for the Sjögren Syndrome Responder Index was significantly higher in the abatacept group than in the placebo group. The development of a validated response index is the focus of the recently initiated NECESSITY project.²⁸

Abatacept was well tolerated by patients with primary Sjögren's syndrome during the ASAP-III study. No treatment-related serious adverse events or treatment withdrawals occurred in the abatacept group. Prevalence of infections was not increased during abatacept treatment, and most adverse events were mild.

The results of a sponsor-initiated, multicentre trial of abatacept treatment for primary Sjögren's syndrome have recently been presented.²⁹ Similar to our results, despite favourable effects on biological activity, abatacept was no better than placebo for improving ESSDAI, ESSPRI, or stimulated whole salivary flow after 24 weeks of treatment. There are some important differences between the two studies. The sponsor-initiated trial allowed hydroxychloroquine as concomitant treatment and included only patients positive for SSA with no limit to disease duration; by contrast, in our investigator-initiated trial, the use of hydroxychloroquine was not allowed and only patients with positive biopsies and disease duration of 7 years or less were included. The number of patients using concomitant corticosteroid treatment in the ASAP-III study was very low compared with previous trials of primary Sjögren's syndrome.

Our trial has some limitations. Because our sample size was based on the primary endpoint, we cannot rule out that clinically relevant differences in secondary endpoints with large variance, such as salivary flow rate,³⁰ were not detected with the current sample size. Second, because of the large number of secondary outcomes, some statistically significant findings might result from chance. Third, as none of the included patients had renal disease or CNS involvement, the effect of abatacept on these domains could not be assessed. Finally, only a small proportion of our patient population was eligible for participation. Efficacy of abatacept treatment in other patients with primary Sjögren's syndrome—eg, with longer disease duration or low ESSDAI scores—remains unknown.

To conclude, abatacept was well tolerated by patients with primary Sjögren's syndrome. Despite the beneficial biological effects of abatacept, the ASAP-III study does not support the use of abatacept as standard of care to reduce systemic disease activity. As primary Sjögren's syndrome is a highly heterogeneous disease, further studies could evaluate whether patients with specific clinical manifestations and biological characteristics might benefit from abatacept treatment.

Contributors

JFvN, FKLS, FGMK, AV, SA, and HB designed the study. JFvN, EM, GSvZ, RFW, and HB contributed to patient recruitment. JFvN, EM, GSvZ, RFW, KD, AJS, LO, LIL, and HB did the clinical evaluations and data collection. JFvN, KD, and SA did the statistical analysis. JFvN wrote the first draft of the article. All authors interpreted the data, contributed to writing, critically revised the article, and approved the final submitted version.

Declaration of interests

JFvN is a speaker and consultant for Bristol-Myers Squibb. GSvZ is a speaker for Roche. FGMK received an unrestricted grant from

Bristol-Myers Squibb, is a consultant for Bristol-Myers Squibb, and a speaker for Bristol-Myers Squibb, Roche, and Janssen-Cilag. HB received unrestricted grants from Bristol-Myers Squibb and Roche; is a consultant for Bristol-Myers Squibb, Roche, Novartis, Medimmune, and Union Chimique Belge; a speaker for Bristol-Myers Squibb and Novartis; and is a member of the advisory board of Bristol-Myers Squibb, Novartis, and Sanofi. All other authors declare no competing interests.

Data sharing

Currently there are no plans to share additional data beyond what is included in this Article.

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References

- Qin B, Wang J, Yang Z, et al. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. *Ann Rheum Dis* 2014; 74: 1983–89.
- Brito-Zerón P, Baldini C, Bootsma H, et al. Sjögren syndrome. *Nat Rev Dis Prim* 2016; 2: 16047.
- Meijer JM, Meiners PM, Huddleston Slater JJ, et al. Health-related quality of life, employment and disability in patients with Sjögren's syndrome. *Rheumatology* 2009; 48: 1077–82.
- Price EJ, Baer AN. How to treat Sjögren's syndrome. *Rheumatology* 2019; published online Feb 15. DOI:10.1093/rheumatology/key363.
- Verstappen GM, Kroese FGM, Bootsma H. T cells in primary Sjögren's syndrome: targets for early intervention. *Rheumatology* 2019; published online Feb 15. DOI:10.1093/rheumatology/kez004.
- Meiners PM, Vissink A, Kroese FGM, et al. Abatacept treatment reduces disease activity in early primary Sjögren's syndrome (open-label proof of concept ASAP study). *Ann Rheum Dis* 2014; 73: 1–4.
- Adler S, Körner M, Förger F, Huscher D, Caversaccio M-D, Villiger PM. Evaluation of histological, serological and clinical changes in response to abatacept treatment of primary Sjögren's syndrome: a pilot study. *Arthritis Care Res* 2013; 65: 1862–68.
- Machado AC, dos Santos LC, Fidelix T, et al. Effectiveness and safety of abatacept for the treatment of patients with primary Sjögren's syndrome. *Clin Rheumatol* 2020; 39: 243–48.
- Tsuboi H, Matsumoto I, Hagiwara S, et al. Efficacy and safety of abatacept for patients with Sjögren's syndrome associated with rheumatoid arthritis: rheumatoid arthritis with orencia trial toward Sjögren's syndrome Endocrinopathy (ROSE) trial—an open-label, one-year, prospective study-interim analysis of 32 patients for 24 weeks. *Mod Rheumatol* 2015; 25: 187–93.
- Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554–58.
- Seror R, Ravaud P, Bowman SJ, et al. EULAR Sjögren's syndrome disease activity index: development of a consensus systemic disease activity index for primary Sjögren's syndrome. *Ann Rheum Dis* 2010; 69: 1103–09.
- Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism Classification Criteria for Primary Sjögren's Syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Arthritis Rheumatol* 2017; 69: 35–45.
- Seror R, Ravaud P, Mariette X, et al. EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI): development of a consensus patient index for primary Sjögren's syndrome. *Ann Rheum Dis* 2011; 70: 968–72.
- Whitcher JP, Shiboski CH, Shiboski SC, et al. A simplified quantitative method for assessing keratoconjunctivitis sicca from the Sjögren's syndrome international registry. *Am J Ophthalmol* 2010; 149: 405–15.

- 15 Seror R, Bootsma H, Saraux A, et al. Defining disease activity states and clinically meaningful improvement in primary Sjögren's syndrome with EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). *Ann Rheum Dis* 2016; 75: 382–89.
- 16 Cornec D, Devauchelle-Pensec V, Mariette X, et al. Development of the Sjögren's Syndrome Responder Index, a data-driven composite endpoint for assessing treatment efficacy. *Rheumatology* 2015; 54: 1699–708.
- 17 Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981; 30: 239–45.
- 18 Meiners PM, Arends S, Brouwer E, Spijkervet FKL, Vissink A, Bootsma H. Responsiveness of disease activity indices ESSPRI and ESSDAI in patients with primary Sjögren's syndrome treated with rituximab. *Ann Rheum Dis* 2012; 71: 1297–302.
- 19 Meijer JM, Meiners PM, Vissink A, et al. Effectiveness of rituximab treatment in primary Sjögren's syndrome: a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2010; 62: 960–68.
- 20 Baldini C, Ferro F, Luciano N, Elefante E, Tripoli A, Mosca M. Clinically meaningful improvement of ESSDAI and Esspri in patients with primary Sjögren's syndrome in real life: a 12-month longitudinal study. *Arthritis Rheumatol* 2016; 68 (suppl 10): 2679 (abstr).
- 21 Delli K, Haacke EA, Kroese FGM, et al. Towards personalised treatment in primary Sjögren's syndrome: baseline parotid histopathology predicts responsiveness to rituximab treatment. *Ann Rheum Dis* 2016; 75: 1933–38.
- 22 van Nimwegen JF, Arends S, van Zuiden GS, Vissink A, Kroese FGM, Bootsma H. The impact of primary Sjögren's syndrome on female sexual function. *Rheumatology* 2015; 54: 1286–93.
- 23 Haacke EA, van der Vegt B, Meiners PM, et al. Abatacept treatment of patients with primary Sjögren's syndrome results in a decrease of germinal centres in salivary gland tissue. *Clin Exp Rheumatol* 2017; 35: 317–20.
- 24 Verstappen GM, Meiners PM, Corneth OBJ, et al. Attenuation of follicular helper T cell-dependent B cell hyperactivity by abatacept treatment in primary Sjögren's syndrome. *Arthritis Rheumatol* 2017; 69: 1850–61.
- 25 Corneth OBJ, Verstappen GMP, Paulissen SMJ, et al. Enhanced Bruton's tyrosine kinase activity in peripheral blood B lymphocytes from patients with autoimmune disease. *Arthritis Rheumatol* 2017; 69: 1313–24.
- 26 Wofsy D, Hillson JL, Diamond B. Abatacept for lupus nephritis: alternative definitions of complete response support conflicting conclusions. *Arthritis Rheum* 2012; 64: 3660–65.
- 27 Miles A, Pope JE. A comparison of rheumatoid arthritis and systemic lupus erythematosus trial design: a commentary on ways to improve the number of positive trials in SLE. *Clin Exp Rheumatol* 2015; 33: 671–80.
- 28 Innovative Medicines Initiative. New clinical endpoints in primary Sjögren's Syndrome: an interventional trial based on stratifying patients. <https://www.imi.europa.eu/projects-results/project-factsheets/necessity> (accessed Nov 30, 2019).
- 29 Baer A, Gottenberg J-E, St. Clair WE, et al. OP0039 Efficacy and safety of abatacept in active primary Sjögren's syndrome: results of a randomised placebo-controlled phase III trial. *Ann Rheum Dis* 2019; 78 (suppl 2): 89–90 (abstr OP0039).
- 30 Burlage FR, Pijpe J, Coppes RP, et al. Variability of flow rate when collecting stimulated human parotid saliva. *Eur J Oral Sci* 2005; 113: 386–90.