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Long-term abatacept treatment for 48 weeks in patients with primary Sjögren's syndrome: The open-label extension phase of the ASAP-III trial

Liseth de Wolff[a], Jolien F. van Nimwegen[a], Esther Mossel[a], Greetje S. van Zuiden[a], Alja J. Stel[a], Kalle I. Majoor[a], Lisette Olie[b], Leonoor I. Los[b], Arjan Vissink[c], Fred K.L. Spijkervet[c], Gwenny M.P.J. Verstappen[a], Frans G.M. Kroese[a], Suzanne Arends[a], Hendrika Bootsma[a,*]

[a] Department of Rheumatology and Clinical Immunology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands
[b] Department of Ophthalmology, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands
[c] Department of Oral and Maxillofacial Surgery, University of Groningen, University Medical Centre Groningen, Groningen, the Netherlands

A B S T R A C T

Objective: To investigate treatment efficacy of long-term abatacept treatment in pSS patients.
Methods: The single-centre ASAP-III trial consisted of two phases: the randomised, double-blind, placebo-controlled phase (1:1 randomisation) from baseline to week 24, of which results have been published previously, and the open-label extension phase from week 24 to 48, in which all patients received abatacept. Main inclusion criteria were fulfilment of the AECG criteria, positive gland biopsy, disease duration $\leq$ 7 years and ESSDAI $\geq$ 5. Long-term treatment effects of abatacept on clinical, patient-reported, glandular and laboratory outcome measures were assessed in patients treated with abatacept from baseline to week 48. Furthermore, Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) response (response on $\geq$3 of 5 items) was analysed.
Results: In patients on abatacept treatment for 48 weeks (n = 40), median ESSDAI improved from baseline 14.0 (IQR 9.0–16.8) to 4.0 (2.0–8.0) at week 48 ($p < 0.001$), with 50% of patients reaching low disease activity (ESSDAI < 5) at week 48. Median ESSPRI improved from 7.0 (IQR 5.4–7.7) to 5.0 (3.7–6.7) ($p < 0.001$). Significant improvement was also seen in dry eye and laboratory tests. Combining response at multiple clinically relevant items, 73% of patients were CRESS responders at week 48. Additional improvement was seen between week 24 and week 48 of abatacept treatment.
Conclusion: In the open-label extension phase of the ASAP-III trial, improvement was seen up to 48 weeks of abatacept treatment in clinical, patient-reported, dry eye and laboratory outcomes. The majority of patients were CRESS responders at week 48.

Introduction

Primary Sjögren's Syndrome (pSS) is a chronic, systemic autoimmune disease characterised by lymphocytic infiltration of exocrine glands [1,2]. The hallmarks of the disease are sicca complaints of eyes and mouth due to infiltration of the lacrimal and salivary glands. The disease also leads to extraglandular symptoms in approximately 20–40% of patients. Furthermore, a wide variety of laboratory abnormalities can be observed, such as anti-SSA/-SSB positivity, lymphocytopenia, hypergammaglobulinemia, decreased complement or increased rheumatoid factor (RF) levels [1,2].

Currently, treatment mainly consists of symptom relief since no systemic, immunomodulatory treatment has been registered for the treatment of pSS [3]. Although several biological drugs have been tested, most randomised controlled trials (RCTs) failed to show significant efficacy compared to placebo. A drug candidate for pSS, abatacept, has shown promising results in small, open-label trials [4–6]. Abatacept is a fully human CTLA4-Ig fusion protein impairing co-stimulation of T-lymphocytes by blocking CD28-CD80/CD86 interaction. However, the Abatacept Sjögren Active Patients (ASAP-III) RCT in 80 pSS patients and a multinational RCT in 187 pSS patients failed to meet their primary endpoint defined as difference in European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) between treatment groups at week 24 [7,8]. Although a large decrease in ESSDAI was seen in the abatacept groups, an equally large decrease was observed in the placebo groups. The recent failure of multiple RCTs with large (> 50%) placebo

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* Corresponding author.
E-mail address: h.bootsma@umcg.nl (H. Bootsma).

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response rates has led to the development of a new composite endpoint: the Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) [9]. Using CRESS, beneficial treatment effects compared to placebo could be detected in several trials, including the ASAP-III trial.

In both abatacept RCTs, no significant improvement of objective measures for ocular and oral dryness was seen compared to placebo at week 24 [7,8]. However, an open-label trial in 11 pSS patients found significant increase in salivary gland function after 24 months of abatacept treatment, implying that a longer treatment period may be required to improve glandular function [6]. Because pSS is a slowly progressive disease it is plausible that a beneficial treatment effect is only seen after a longer treatment period than 24 weeks since some outcome measures may require a longer time to improve. Therefore, the objective of the open-label extension phase of the ASAP-III trial was to assess efficacy of long-term abatacept treatment on clinical, patient-reported, objective ocular and oral dryness and laboratory outcome measures.

Methods

Study design and participants

The ASAP-III trial was conducted in the multidisciplinary tertiary referral centre for pSS at the University Medical Centre Groningen (UMCG; Groningen, Netherlands) [7]. Ethical approval was obtained from the UMCG institutional review board (METc 2014.118), and all included patients provided a written informed consent. The full trial protocol was published previously [7]. In short, main inclusion criteria were fulfilment of the American-European Consensus Group (AECG) criteria for pSS [10], age $\geq$ 18 years, positive gland biopsy, disease duration of $\leq$ 7 years and an ESSDAI score of $\geq$ 5. All patients also fulfilled the American College of Rheumatology (ACR)/EULAR classification criteria retrospectively [11]. Main exclusion criteria were use of prednisone ($>$ 10 mg/day), non-biological DMARDs including hydroxychloroquine, or pilocarpine for $\leq$ 1 month before enrolment and biological DMARDs within 6 months before inclusion for abatacept and within 12 months for rituximab. Furthermore, one of the exclusion criteria was a flow rate of stimulated whole saliva of $<$ 0.05 ml/min in patients without extraglandular manifestations. However, since all patients had extraglandular manifestations, no patients were excluded based on this exclusion criterion.

The ASAP-III trial consisted of two phases. In the double-blind phase from baseline to week 24, patients were randomised (1:1) and treated with weekly subcutaneous injections of abatacept (125 mg) or placebo. In the open-label extension phase from week 24 to week 48, patients already on abatacept treatment continued abatacept (ABA-ABA group) and patients on placebo switched to abatacept (PLB-ABA group). Abatacept was discontinued in all patients at week 48. Patients visited the UMCG at baseline and weeks 4, 8, 12, 24, 28, 32, 36 and 48.

Outcome assessments

Physicians assessed clinical outcomes which included the ESSDAI [12], physician global disease activity (GDA) and Disease Activity Score 28 joint count including Erythrocyte Sedimentation Rate (DAS-28 ESR) and C-reactive protein (DAS-28 CRP) at all timepoints.

Patient-reported outcomes were the ESSPRI [13] and patient GDA at all timepoints, physical and mental components of the Short-Form 36 (SF-36), calculated using the QualityMetric Health Outcomes Scoring Software, version 5.1, and the Multidimensional Fatigue Inventory (MFI) at weeks 12, 24, 36 and 48. In addition, for female participants, outcomes included vaginal dryness (numeric rating scale, range 0–10) at weeks 12, 24, 36 and 48 and the Female Sexual Function Index (FSFI) at weeks 24 and 48.

Dry eye tests were the Schirmer's test (without anaesthesia), ocular staining score (OSS) [14] and tear break-up time (TBUT). Subgroup analyses were performed in patients with abnormal scores at baseline (Schirmer's test $\leq$ 5 mm and OSS $\geq$ 3 points) [14,15]. Salivary gland function tests were unstimulated (UWS) and stimulated whole salivary flow (SWS) with citric acid. These tests were performed during the screening visit, weeks 12, 24, 36 and 48. Salivary gland ultrasonography (SGUS) was performed at baseline, weeks 24 and 48 and evaluated using the Hocevar score [16].

Laboratory outcomes included RF, immunoglobulin G (IgG), complement (C3 and C4), ESR, CRP and Myxovirus resistant protein A (MxA) serum levels and lymphocyte count.

Minimal clinically important improvement (MCII) response rates for ESSDAI ($\geq$ 3 points decrease) and ESSPRI ($\geq$ 1 point or $\geq$ 15% decrease) [17] and the number of participants with low disease activity (LDA, ESSDAI$<$5) during follow-up were analysed [17]. Additionally, response rates for the CRESS were calculated [9]. A CRESS responder was defined as response on $\geq$ 3 of the following 5 items: systemic disease activity (ClinESSDAI), patient-reported symptoms (ESSPRI), tear gland (Schirmer and OSS), salivary gland (UWS and SGUS) and serology (RF and IgG) [9].

Follow-up visits 6 months after end of ASAP-III trial

After the last ASAP-III trial visit, participants were invited to participate in the REgistry of Sjögren syndrome in Umcg LongiTudinal (RESULT) cohort [18]. RESULT participants were seen at the outpatient clinic approximately 6 months after last study visit (week 48). To evaluate if outcome measures worsened after discontinuation of abatacept, clinical data from these follow-up visits were analysed and compared to the week 48 data. Since the RESULT cohort is an observational cohort, not all outcome measures which are included in the ASAP-III trial were performed at the follow-up visit. Patients were excluded if no follow-up visit was available or their follow-up visit was $<$ 3 or $>$ 12 months from their week 48 ASAP-III visit.

Safety

Serious adverse events (SAEs) and AEs were recorded from baseline to week 48 and were evaluated for severity and potential causality. Other safety endpoints were laboratory tests and treatment withdrawal.

Statistical analysis

All efficacy analyses were performed using the efficacy population for the open-label phase. Patients were included in the efficacy analysis if patients received $\geq$ 1 dose of abatacept after week 24, and if data after week 24 were available. Collected data were considered non-valid and coded as missing if $\geq$ 3 injections were skipped 4 weeks before the visit, if $\geq$ 5 mg of prednisone per day was used 2 weeks before the visit (unless this dose was stable since baseline) or if cyclophosphamide was used as rescue treatment option.

Four different analyses of changes over time were conducted for all outcome parameters. As main analysis, long-term treatment effects of abatacept in the ABA-ABA group were analysed from baseline to week 48. Additionally, change from week 24 to 48 was assessed in the ABA-ABA group to analyse whether improvement continued after week 24. In the PLB-ABA group, change was assessed from baseline to week 24 to assess whether a placebo effect occurred, and from week 24 to week 48 to assess whether an abatacept treatment effect occurred after placebo treatment (Fig. 1).

Linear generalised estimating equations (GEE) was used for analysis of continuous outcome parameters over time. GEE analysis included all available data at the different time points. Missing data were not imputed. If residuals showed a non-Gaussian distribution,

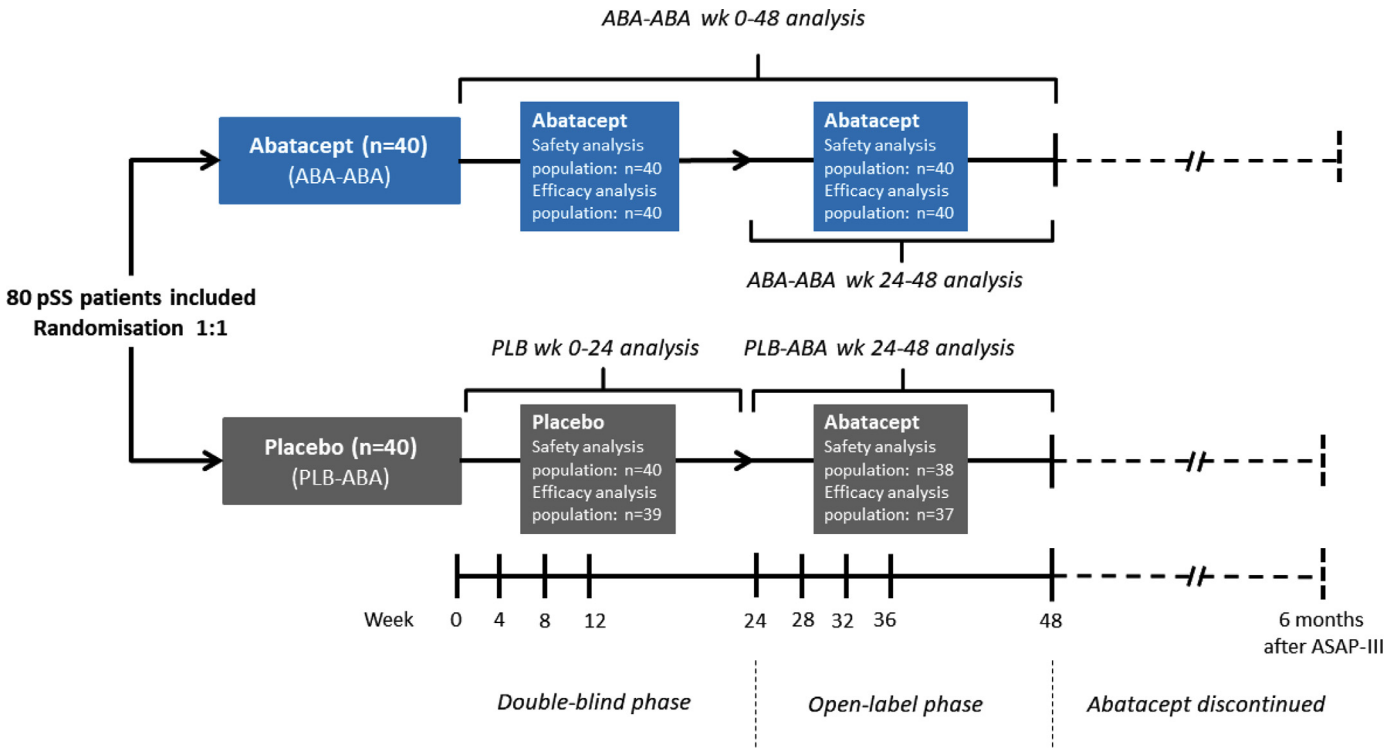

Fig. 1. Study design and flow chart of the ASAP-III trial.

variables were transformed: square root for ESSDAI, MxA, lymphocytes, C4; common logarithm for IgG, C3; natural logarithm for IgG in the abatacept group week 24–48 analysis; second power for ESSPRI. After testing exchangeable, M-dependant and unstructured correlation structures, the model with the lowest information criterion was selected. If non-Gaussian distribution of residuals persisted after transformation, Wilcoxon Signed Ranks test was used. For ESSDAI, ESSPRI and CRESS response analysis, missing values were imputed as non-responders. Statistical significance was set at a p-value of < 0.05. All statistical analyses were performed using IBM SPSS Statistics (version 23).

Results

In total, 80 patients were included in the ASAP-III trial. None of the 40 patients in the ABA-ABA group were lost to follow-up during the double-blind or open-label phase. Two patients on placebo withdrew from treatment during the double-blind phase due to adverse events (auto-immune hepatitis in week 3 and diagnosis of SLE in week 8), and did not participate in the open-label phase. Therefore, the safety analysis population in the open-label phase consisted of 40 patients in the ABA-ABA and 38 in the PLB-ABA group. One patient in the PLB-ABA group was excluded due to administration of high dosage prednisone during the whole open-label phase. Thus the efficacy analysis population consisted of 40 patients in the ABA-ABA and 37 patients in the PLB-ABA group. Patient characteristics and clinical assessments at baseline and week 24 are shown in Table 1.

During follow-up, two patients from the ABA-ABA group used prednisone rescue therapy: one patient at week 28, the other at weeks 28, 32 and 36, and these data were coded as missing. There were no patients in the open-label phase who skipped ≥ 3 injections or who used cyclophosphamide as rescue treatment. Three other patients (two ABA-ABA, one PLB-ABA) discontinued treatment during the open-label phase due to adverse events, of which two had missing data at week 48.

Long-term treatment effects of abatacept (ABA-ABA group week 0–48 and week 24–48)

In the ABA-ABA group, systemic disease activity assessed with ESSDAI improved from median 14.0 (IQR 9.0–16.8) at baseline to 4.0 (2.0–8.0) at week 48 ($p < 0.001$). Significant improvement compared to baseline values was seen at all timepoints from week 8 (Fig. 2A and Supplementary Table S1). ESSDAI MCII was reached by 32/40 (80%) patients at week 48 compared to baseline, and the number of patients reaching LDA was 20/40 (50%) (Fig. 3A, B). Physician GDA and DAS-28 ESR/CRP also improved significantly (Supplementary Table S1).

The patient-reported index ESSPRI improved from median 7.0 (IQR 5.4–7.7) at baseline to 5.0 (3.7–6.7) at week 48 ($p < 0.001$), showing significant improvement at all timepoints from week 4 (Fig. 2B). This improvement was most prominent in the ESSPRI pain and fatigue subscores (Supplementary Table S2). The number of ESSPRI MCII responders was 24/40 (60%) at week 48 (Fig. 3C). Significant improvement was also seen in patient GDA and health-related quality of life assessed with the SF-36 mental component. Fatigue improved for all MFI items. Furthermore, significant improvement in vaginal dryness scores and a trend towards improvement of sexual function assessed with the FSFI were observed (Supplementary Table S2).

No significant changes were seen in the Schirmer's test ($p = 0.975$) (Fig. 4A). When analysing patients with an abnormal Schirmer (≤ 5 mm) at baseline, a slight significant improvement was observed from weeks 12 to 36, but not at week 48 (Supplementary Table S3). OSS showed significant improvement at week 48 ($p = 0.010$) (Fig. 4B). For UWS and SWS a significant improvement was found at week 36 ($p = 0.002$ and $p = 0.002$), but not week 48 (Fig. 4C and Supplementary Table S3). Analyses of a subgroup of patients with some preserved salivary flow (baseline UWS ≥ 0.01 or SWS ≥ 0.1 ml/min) showed similar results as for the whole group (Supplementary Table S3). SGUS Hocevar score showed no significant changes (Fig. 4D and Supplementary Table S3).

Table 1
Patient characteristics at baseline and week 24 of the ASAP-III trial.

	Baseline		Week 24	
	ABA (n = 40)	*PLB (n = 38)*	*ABA (n = 40)*	*PLB (n = 38)*
Age	48 (15)	50 (16)		
Gender (women)	37 (93%)	35 (92%)		
Disease duration (years)	2 (0–4)	2 (1–4)		
Anti-Ro/SSA	34 (85%)	35 (92%)		
Anti-La/SSB	20 (50%)	22 (58%)		
ESSDAI	14.0 (9.0–16.8)	13.0 (8.0–18.3)	8.0 (4.0–14.0)	8.0 (5.0–14.5)
Total ESSPRI score	7.0 (5.4–7.7)	7.3 (5.3–8.0)	6.0 (4.4–7.3)	6.7 (4.6–7.9)
Schirmer's test (mm)*	3.5 (0.6–14.0)	2.5 (0.0–8.8)	5.3 (2.1–10.3)	1.0 (0.0–4.0)
OSS*	4.0 (0.5–6.5)	4.5 (1.9–7.0)	3.0 (1.0–6.4)	3.5 (1.3–7.3)
UWS (ml/min)	0.05 (0.01–0.12)	0.05 (0.01–0.12)	0.06 (0.01–0.15)	0.03 (0.01–0.10)
SWS (ml/min)	0.16 (0.06–0.33)	0.10 (0.02–0.42)	0.19 (0.08–0.44)	0.09 (0.03–0.31)
SGUS (Hocevar score)	23.0 (14.0–28.0)	26.5 (15.3–32.0)	18.0 (13.0–27.0)	23.0 (19.0–32.0)
RF (IU/ml)	32.5 (2.1–71.0)	23.0 (6.8–83.8)	17.5 (1.7–42.0)	29.0 (8.0–90.0)
IgG (g/l)	17.4 (13.4–26.7)	18.5 (14.8–24.5)	17.0 (12.9–26.0)	19.0 (13.7–25.5)

Values are mean ± SD, median (IQR) or n (%). *Abbreviations:* ASAP: Abatacept Sjögren Active Patients, ABA: abatacept, PLB: placebo, ESSDAI: European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index, ESSPRI: EULAR Sjögren's Syndrome Patient Reported Index, OSS: Ocular Staining Score, UWS: unstimulated whole salivary flow, SWS: stimulated whole salivary flow, SGUS: salivary gland ultrasonography, RF: rheumatoid factor, IgG: Immunoglobulin G.

* Mean of right and left eye

.

RF and IgG levels improved significantly from baseline to week 48 ($p < 0.001$ and $p = 0.001$, respectively) (Fig. 2C, D). Results from BSE, CRP, MxA, lymphocyte count and complement (C3, C4) analyses are shown in Supplementary Table S4.

When combining response (≥ 3/5) on systemic disease activity, patient-reported symptoms, tear gland, salivary gland and serology items, 29/40 (73%) patients were CRESS responder at week 48 (Fig. 3D). Response on the individual CRESS items is shown in Table 2.

In the analysis of abatacept treatment effects between week 24 and week 48 in the ABA-ABA group, additional improvement was found in several parameters including ESSDAI, ESSPRI and RF (Fig. 2A–D and Supplementary Tables S1-4).

Placebo treatment effects (PLB-ABA group week 0–24)

To evaluate if a placebo effect occurred, outcome measures were analysed between baseline and week 24 in the PLB-ABA group. A large placebo response was seen in ESSDAI, which improved from median 13.0 (IQR 8.0–16.5) at baseline to 8.0 (5.0–14.5) at week 24 ($p < 0.001$) (Fig. 2A). Also for ESSPRI, significant improvement was

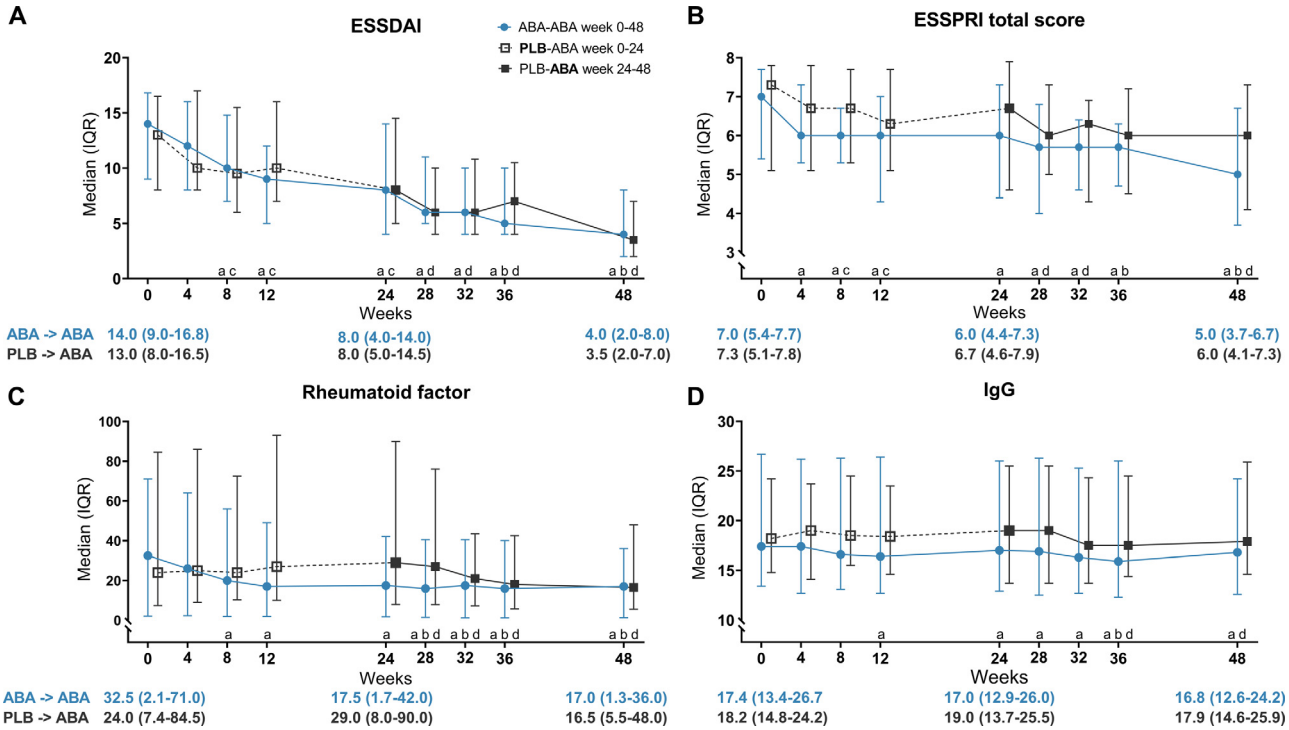

Fig. 2. A. ESSDAI scores week 0–48 B ESSPRI scores week 0–48 C. Rheumatoid factor week 0–48 D. IgG week 0–48. a: significant difference ($p < 0.05$) compared to baseline in ABA->ABA group (patients on abatacept in double-blind and open-label extension phase) b: significant difference ($p < 0.05$) compared to week 24 in ABA-> ABA group c: significant difference ($p < 0.05$) compared to baseline in PLB->ABA group (patients on placebo in double-blind phase and abatacept in open-label extension phase) d: significant difference ($p < 0.05$) compared to week 24 in PLB->ABA group. Abbreviations: see Table 1.

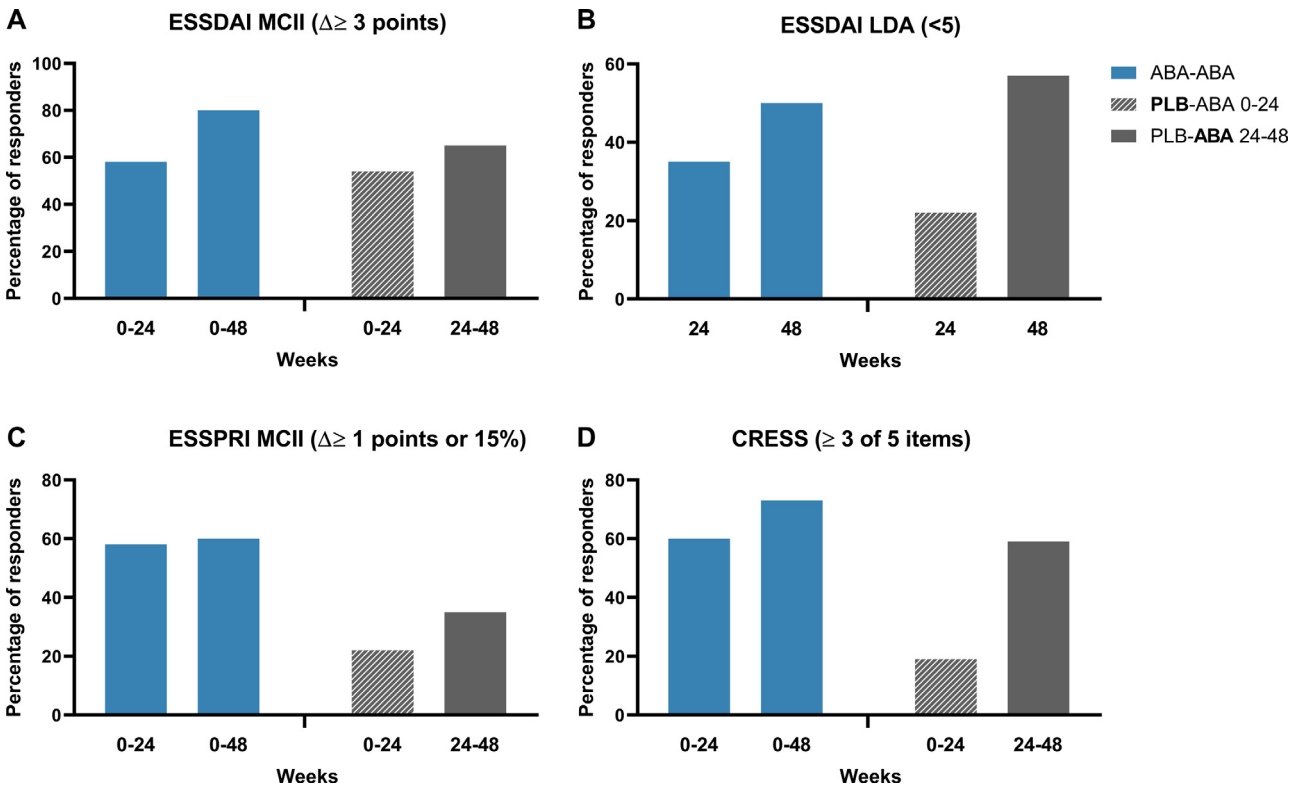

Fig. 3. Response rates of A. ESSDAI minimal clinically important improvement (MCII), decrease of ≥ 3 points B. ESSDAI low disease activity (LDA), score < 5 at week 24 or 48 C. ESSPRI MCII, decrease of ≥ 1 point or 15%. D. Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS), responder on ≥ 3 of 5 items. Response percentages are calculated for the ABA-ABA group for week 24 compared to baseline (week 0–24) and week 48 compared to baseline (week 0–48). For the PLB-ABA group response rates are calculated for week 24 compared to baseline (week 0–24) and week 24 compared to 48 (week 24–48). All analyses were performed using the efficacy population for the open-label phase. Abbreviations: see Table 1.

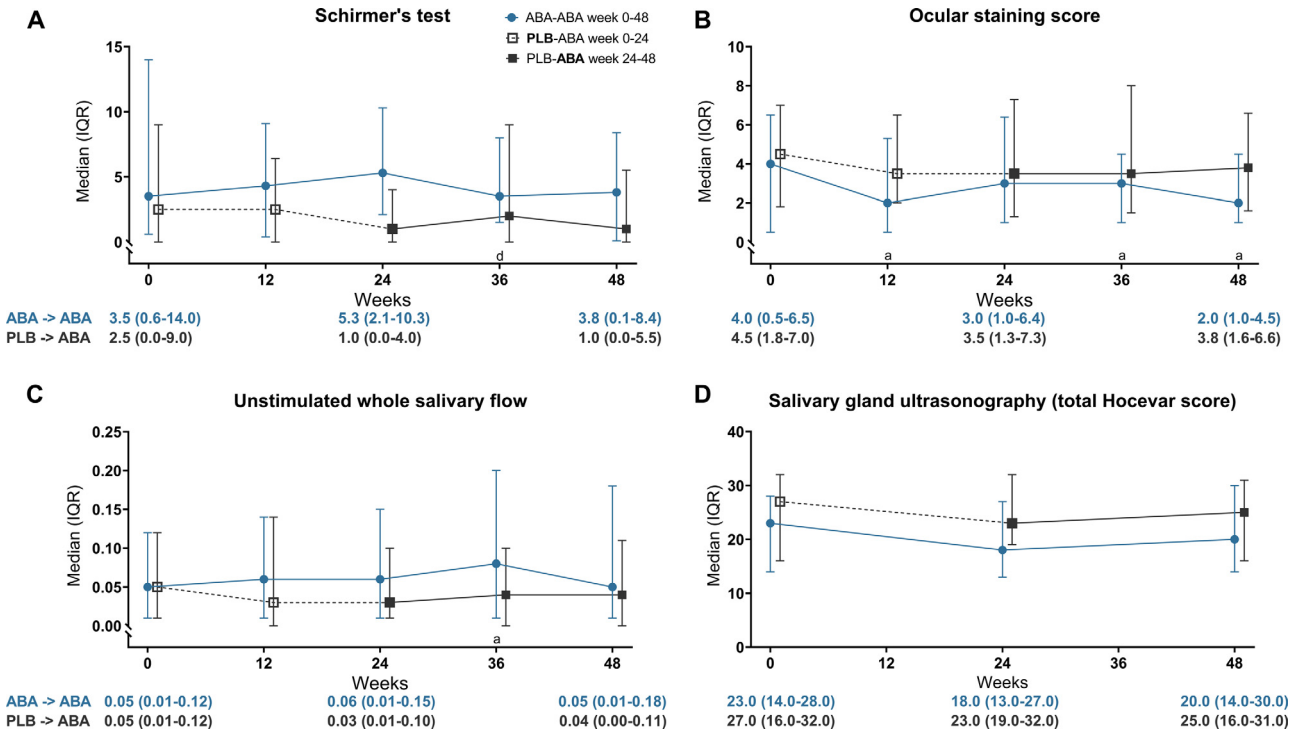

Fig. 4. A. Schirmer's test scores week 0–48 B Ocular staining scores week 0–48 C. Unstimulated whole salivary flow week 0–48 D. Hocevar scores (salivary gland ultrasonography) week 0–48. a: significant difference ($p < 0.05$) compared to baseline in ABA->ABA group (patients on abatacept in double-blind and open-label extension phase) b: significant difference ($p < 0.05$) compared to week 24 in ABA-> ABA group c: significant difference ($p < 0.05$) compared to baseline in PLB->ABA group (patients on placebo in double-blind phase and abatacept in open-label extension phase) d: significant difference ($p < 0.05$) compared to week 24 in PLB->ABA group. Abbreviations: see Table 1.

Table 2
Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) response in ASAP-III open-label extension phase.

Individual CRESS items	ABA-ABA Week 0–24 (%)*	ABA-ABA Week 0–48 (%)	PLB Week 0–24 (%)*	PLB-ABA Week 24–48 (%)
Systemic disease activity	18/40 (45)	24/39 (62)	10/37 (27)	26/36 (72)
Patient-reported symptoms	23/40 (58)	24/38 (63)	8/36 (22)	13/33 (39)
Tear gland	18/40 (45)	21/39 (54)	12/37 (32)	12/36 (33)
Salivary gland	23/40 (58)	19/39 (49)	15/37 (41)	16/36 (44)
Serological	25/40 (63)	28/39 (72)	7/37 (19)	31/36 (86)
Total CRESS response				
Responder on ≥3/5 items	24/40 (60)	29/40 (73)	7/37 (19)	22/37 (59)

Response rates are calculated for the individual CRESS items based on the number of patients with available data, for total CRESS response missing values are included as non-responder. For the ABA-ABA group individual CRESS items and total CRESS response is analysed comparing week 24 to baseline (week 0–24) and comparing week 48 to baseline (week 0–48). For the PLB-ABA group individual CRESS items and total CRESS response is analysed comparing week 24 to baseline (week 0–24) and comparing week 48 to week 24 (week 24–48). Abbreviations: see Table 1.

* Data published previously.

seen at week 8 and 12, but not week 24 (p = 0.055) (Fig. 2B). No improvement was found in objective measures for ocular and oral dryness and laboratory parameters (Fig. 2C, D, 4A–D and Supplementary Table S1–4). The number of CRESS responders after placebo treatment at week 24 was 7/37 (19%) (Fig. 3D and Table 2).

Effects of abatacept treatment after placebo (PLB-ABA group week 24–48)

Despite a large initial placebo effect in ESSDAI in the PLB-ABA group, switching to abatacept resulted in additional improvement from week 24 (median 8.0, IQR 5.0–14.5) to week 48 (3.5, IQR 2.0–7.0, $p < 0.001$). Furthermore, ESSPRI, RF and IgG improved significantly (Figure 2A-D). The objective ocular and oral dryness tests did not show significant improvement during 24 weeks of open-label abatacept treatment (Figure 4A-D and Supplementary Table S1-4). Whereas a low number of CRESS responders was observed in the PLB-ABA group during the double-blind phase, the majority of patients became CRESS responders at week 48 after they switched to abatacept (22/37, 59%) (Figure 3D and Table 2).

Follow-up visits 6 months after ASAP-III trial

70 patients had a follow-up visit after discontinuing abatacept at week 48 (after a median of 6 months, range 3–11 months), of which one patient had missing data at week 48. In the remaining 69 patients, ESSDAI worsened after discontinuation of abatacept from median 4.0 (IQR 2.0–7.5) to 5.0 (3.0–8.0) (p = 0.031). Furthermore, ESSPRI and laboratory parameters worsened significantly. Most objective ocular and oral dryness tests remained the same, although SWS worsened significantly (Table 3).

Safety outcomes

In the extension, open-label phase, three SAEs occurred. One SAE was a diverticulitis (ABA-ABA group), which was deemed possibly related to the treatment. The other two SAEs (PLB-ABA group) were a hypertensive crisis and a stadium IB2 clearcell cervical adenocarcinoma. In total, 173 AEs occurred in the ABA-ABA group, of which 70 during the open-label phase. 166 AEs occurred in the PLB-ABA group, of which 79 during open-label abatacept treatment. The most common AE was infection. The total number of adverse events and treatment withdrawals was comparable between treatment groups (Supplementary Table S5).

Discussion

In the current study, efficacy of long-term (48 weeks) abatacept treatment in pSS patients was evaluated. Significant improvement was found in clinical outcomes, patient-reported symptoms, dry eye and laboratory tests after 48 weeks of abatacept treatment, compared to baseline. In addition, the majority of patients were CRESS responder at week 48. Continuing improvement was seen in clinical and laboratory parameters from week 24 (the end of the double-blind phase) to 48, indicating no plateau was reached 24 weeks after treatment. In patients who were initially treated with placebo, a low number of CRESS responders was observed at week 24, but improvement was seen in clinical, patient-reported symptoms and laboratory parameters when patients switched to abatacept. Because the results at week 48 could not be compared to a placebo group, we could not analyse whether results were influenced by placebo effects or natural variation in disease activity.

In the double-blind phase of the ASAP-III trial and in a multinational abatacept trial in 187 pSS patients, no significant differences were found in ESSDAI improvement between the active treatment and placebo group at week 24, although in both groups a large, significant decrease in ESSDAI was observed compared to baseline, surpassing the MCII of ≥ 3 points decrease [7,8]. Despite the large initial response in the placebo arm, we found additional significant clinical improvement from week 24 to week 48, when these patients switched to abatacept. Continuous significant improvement in ESSDAI after week 24 was also observed in the patients that received

Table 3
Clinical, patient-reported, objective ocular and oral dryness and laboratory outcomes ± 6 months after discontinuation of abatacept.

	Week 48 (ASAP-III)	6 months after end of ASAP-III	p-value
ESSDAI (n = 69)	4.0 (2.0–7.5)	5.0 (3.0–8.0)	0.031
ClinESSDAI (n = 69)	2.0 (0.0–6.5)	4.0 (2.0–7.5)	0.020
Physician GDA (n = 54)	2.0 (1.0–2.0)	3.0 (2.0–3.0	0.000
ESSPRI (n = 59)	5.7 (4.0–6.7)	6.3 (4.7–7.3)	0.002
Patient GDA (n = 53)	6.0 (4.0–7.0)	7.0 (5.5–8.0)	0.001
Schirmer's test (n = 44)	2.5 (0.0–9.0)	3.0 (0.0–7.4)	0.651
OSS (n = 54)	3.0 (1.4–5.6)	2.5 (1.0–5.0)	0.081
UWS (n = 43)	0.07 (0.01–0.18)	0.06 (0.01–0.15)	0.451
SWS (n = 43)	0.19 (0.05–0.37)	0.15 (0.05–0.35)	0.006
Rheumatoid factor (n = 69)	18.0 (2.1–41.0)	20.0 (5.3–54.0)	0.000
IgG (n = 69)	16.8 (13.0–25.2)	18.0 (13.6–26.0)	0.000
Complement C3 (n = 69)	1.11 (0.99–1.28)	1.07 (0.91–1.25)	0.019
Complement C4 (n = 69)	0.20 ± 0.08	0.20 ± 0.07	0.104
Lymphocyte count (n = 65)	1.39 (1.02–1.83)	1.36 (0.92–1.74)	0.103

Values are mean ± SD or median (IQR). Abbreviations: see Table 1.

abatacept for 48 weeks. Moreover, the majority of patients, who all had moderate to high disease activity according to ESSDAI at baseline, reached ESSDAI LDA (< 5) at week 48. When patients discontinued abatacept treatment, ESSDAI worsened significantly. However, a nocebo effect might have contributed to this worsening. Using the recently developed composite endpoint CRESS, only 19% of patients treated with placebo reached CRESS response after 24 weeks, while the majority of patients reached CRESS response at week 48 (ABA-ABA group from baseline: 73%, PLB-ABA group from week 24: 59%).

In the double-blind phase of the ASAP-III trial significantly more ESSPRI MCII responders were seen in the abatacept than the placebo group, although no difference was seen in ESSPRI scores in the multinational RCT [7,8]. In the extension phase analysis, significant improvement of ESSPRI scores was seen in both the ABA-ABA and PLB-ABA group, especially in the pain and fatigue subscores. In addition, improvement in several types of fatigue, measured with the MFI, was seen in patients treated with abatacept for 48 weeks, while no evident improvement occurred during 24 weeks of placebo treatment. Since fatigue is a very common complaint in pSS patients and influences quality of life negatively, this might be a relevant finding [19]. Sexual function and vaginal dryness have also been associated with quality of life [20]. Vaginal dryness improved significantly after 48 weeks of abatacept treatment, and for sexual function a trend towards significant improvement was found.

Considering the lack of improvement in glandular outcome measures after 24 weeks of abatacept treatment in both abatacept RCTs, glandular function might require a longer treatment period to improve [7,8]. Despite some fluctuations in OSS at the separate time points, a significant decrease in OSS was seen after 48 weeks of abatacept treatment in the current study, and some improvement in OSS was also found in the open-label extension phase of the multinational abatacept trial [8]. In our open-label extension phase, no significant improvement was observed in salivary flow rates and no significant improvement was seen in SGUS scores (total Hocevar score). In the ASAP-II open label trial in 15 pSS patients no significant improvement in saliva secretion was found after 24 weeks of abatacept treatment, but after discontinuation of abatacept salivary flow rates worsened [4]. Although data was only available for a subgroup of patients, we observed a significant deterioration of SWS approximately 6 months after discontinuation of abatacept. This could mean that abatacept might help to maintain saliva secretion. Besides a potential stabilization of salivary flow rates, abatacept does not seem to cause major improvements in salivary gland inflammation or morphology. Histopathological analysis of parotid gland tissue of patients in the open-label ASAP-II study showed that abatacept did not lead to a reduction in focus score or areas of lymphocytic infiltrate, nor in the presence and severity of lymphoepithelial lesions [21].

Besides the two abatacept RCTs, several other large, phase III RCTs in pSS patients with other (non-)biological DMARDs did not reveal beneficial treatment effects compared to placebo [7,8,22–24]. Although the biological drugs that were tested may not have been efficacious, the design of these trials may also have influenced results, including the time point and choice of primary endpoint. For example, three recent, large, phase III RCTs found response rates of $> 50\%$ on the ESSDAI MCII in their placebo groups [7,8,22]. With such a high placebo response, it is difficult to demonstrate superiority of the active treatment. However, with the CRESS, in which response on five complementary, clinically relevant items is combined (i.e. systemic disease activity, patient-reported symptoms, tear gland, salivary gland and serology), placebo responses were lowered compared to the ESSDAI MCII [9,25].

Another reason for negative findings in recent RCTs might be that because of the heterogeneity of pSS, targeted biological drugs are only effective in subgroups of pSS patients. Certain extraglandular manifestations might be more likely to respond to certain biological drugs. For example, rituximab treatment may be indicated for symptoms linked to cryoglobulinemic-associated vasculitis [3]. Additionally, the Newcastle Sjögren Stratification Tool (NSST) has been proposed as another way to stratify pSS patients, which identifies four patient clusters based on several patient-reported symptoms: depression, anxiety, pain, fatigue and dryness [26]. With this tool, different treatment responses to hydroxychloroquine or rituximab were identified for the separate clusters [26]. Unfortunately, the sample size of the ASAP-III study was not large enough to analyse efficacy of abatacept in subgroups according to extraglandular manifestations, and the NSST could not be applied, as depression and anxiety were not measured before start of the ASAP-III trial. In future trials, molecular profiling of pSS patients could also be a promising tool to predict treatment response [27].

The findings in our open-label extension phase study indicate efficacy of long-term abatacept treatment. There was evident improvement in clinical disease activity after 48 weeks of treatment, with additional improvement after week 24. Furthermore, significant improvement was seen in patient-reported outcomes, dry eyes measured with OSS and biological parameters. In addition, when combining response at multiple clinically relevant items using the recently developed composite endpoint CRESS, the majority of patients were responders after 48 weeks of abatacept treatment, whereas a low number of responders was seen in patients on placebo at week 24. Based on these findings, it might be worthwhile to extend abatacept for a longer treatment period than 24 weeks.

Statements

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Ethics

Ethical approval was obtained from the UMCG institutional review board (METc 2014.118). All participants provided informed consent according to the declaration of Helsinki.

Data sharing statement

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

Declaration of Competing Interest

L. de Wolff: none to declare; Jolien F. van Nimwegen: speaker and consultant for BMS, Esther Mossel: none to declare, Greetje S. van Zuiden: speaker for Roche, Alja J. Stel: none to declare, Kalle I. Majoor: none to declare, Lisette Olie: none to declare, Leonie I. Los: none to declare, Arjan Vissink: none to declare, Fred K. L. Spijkervet: none to declare, Gwenny M. P. J. Verstappen: none to declare, Frans G. M. Kroese: received an unrestricted grant from BMS, is a consultant and speaker for BMS, and a speaker for Roche and Janssen-Cilag, Suzanne Arends: none to declare, Hendrika Bootsma: received unrestricted grants from BMS and Roche, is a consultant for BMS, Roche, Novartis, Medimmune and Union Chimique Belge, is a speaker for BMS and Novartis.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2022.151955.

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