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Published in:
The Lancet Rheumatology

DOI:
[10.1016/S2665-9913\(21\)00122-3](https://doi.org/10.1016/S2665-9913(21)00122-3)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Arends, S., de Wolff, L., van Nimwegen, J., Verstappen, G., Vehof, J., Bombardieri, M., Bowman, S. J., Pontarini, E., Baer, A. N., Nys, M., Gottenberg, J.-E., Felten, R., Ray, N., Vissink, A., Kroese, F. G. M., & Bootsma, H. (2021). Composite of Relevant Endpoints for Sjogren's Syndrome (CRESS): development and validation of a novel outcome measure. *The Lancet Rheumatology*, 3(8), E553-E562.
[https://doi.org/10.1016/S2665-9913\(21\)00122-3](https://doi.org/10.1016/S2665-9913(21)00122-3)

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Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS): development and validation of a novel outcome measure

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Summary

Background Recent randomised controlled trials (RCTs) in primary Sjögren's syndrome used the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) as their primary endpoint. Given the heterogeneous and complex nature of primary Sjögren's syndrome, it might be more appropriate to also assess other clinically relevant disease features. We aimed to develop a novel composite endpoint for assessing treatment efficacy in patients with primary Sjögren's syndrome: the Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS).

Methods A multidisciplinary expert team selected clinically relevant items and candidate measurements for inclusion in the composite score. For each measurement, cutoff points for response to treatment were chosen based on expert opinion, previously published data on minimal clinically important improvements, and trial data, primarily the week-24 data of the single-centre ASAP-III trial of abatacept versus placebo. CRESS was validated using data from three independent RCTs: one trial of rituximab (TRACTISS), one of abatacept (multinational trial), and one of tocilizumab (ETAP). We calculated the number and percentage of patients who were responders in the separate CRESS items, and the percentage of responders based on the total CRESS at the primary endpoint visits (week 48 for TRACTISS, week 24 for the other two trials). Patients with fewer than three items available for evaluating CRESS response were imputed as non-responders.

Findings Based on expert opinion, five complementary items were selected to assess response: (1) systemic disease activity by Clinical ESSDAI (less than 5 points); (2) patient-reported symptoms by EULAR Sjögren's Syndrome Patient Reported Index, assessed by a decrease of at least 1 point or at least 15% from baseline; (3) tear gland item by Schirmer's test and ocular staining score, assessed by an increase of at least 5 mm or decrease of at least 2 points, respectively, in patients with abnormal Schirmer's test or ocular staining score findings at baseline, or, in patients with normal baseline values, assessed by no change to abnormal for both; (4) salivary gland item, assessed by unstimulated whole saliva secretion (increase of at least 25%) and salivary gland ultrasonography (decrease of at least 25%); and (5) serology, assessed by rheumatoid factor (decrease of at least 25%) and IgG (decrease of at least 10%). Total CRESS response is defined as response on at least three of five items. Post-hoc assessment of phase 3 trial data showed that CRESS response rates at the primary endpoint visits were 60% (24 of 40) for abatacept versus 18% (seven of 39) for placebo ($p < 0.0001$) in ASAP-III, 49% (33 of 67) for rituximab versus 30% (20 of 66) for placebo ($p = 0.026$) in the TRACTISS trial, 45% (41 of 92) for abatacept versus 32% (30 of 95) for placebo ($p = 0.067$) in the multinational abatacept trial, and 18% (10 of 55) for tocilizumab versus 24% (13 of 55) for placebo ($p = 0.48$) in the ETAP trial.

Interpretation The CRESS is a feasible, well-balanced, composite endpoint for use in trials of primary Sjögren's syndrome. As a next step, the CRESS will require validation in a prospective RCT.

Funding None.

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Introduction

Primary Sjögren's syndrome is a systemic autoimmune disease with a highly heterogeneous presentation. The most common symptoms are ocular and oral sicca, fatigue, and arthralgias. Many systemic symptoms can manifest, including arthritis, renal, cutaneous, and pulmonary involvement, and peripheral neuropathy. Laboratory

abnormalities can also occur, such as lymphocytopenia, hypergammaglobulinemia, and presence of autoantibodies, including anti-SSA/SSB and rheumatoid factor.¹

To date, treatment of primary Sjögren's syndrome relies on symptomatic treatment of sicca complaints and broad-spectrum immunosuppression, since no immunomodulatory systemic therapies have been registered for

Lancet Rheumatol 2021;
3: 553–62

Published Online
May 26, 2021
[https://doi.org/10.1016/S2665-9913\(21\)00122-3](https://doi.org/10.1016/S2665-9913(21)00122-3)
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For the Dutch translation of the abstract see [Online](#) for appendix 1

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Research in context

Evidence before this study

Currently, no systemic immunomodulatory treatments have been approved for use against primary Sjögren's syndrome. Several randomised controlled trials (RCTs) studying the efficacy of various drugs in primary Sjögren's syndrome have not met their primary endpoint. In most RCTs in primary Sjögren's syndrome, the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) was used as the primary endpoint. We searched PubMed and EULAR/American College of Rheumatology congress abstract archives with the terms "Sjögren's syndrome", "randomised controlled trial" and "ESSDAI" up to Jan 31, 2021, to identify RCTs of various immunomodulatory therapies using ESSDAI as primary endpoint, and how they performed. Our search returned eight RCTs. Two phase 2 RCTs (prezalumab and seletalisib) did not meet their primary endpoint, whereas three phase 2 RCTs (iscalimab, leflunomide-hydroxychloroquine, and ionalumab) reported significant effects of active treatment compared with placebo. These results still need to be confirmed in phase 3 RCTs. Three phase 3 RCTs (two with abatacept, one with tocilizumab) did not meet their primary endpoint, showing large responses on ESSDAI in both active and placebo-treated patients; at the group level, responses were greater than the minimal clinically important improvement of at least 3 points compared with baseline. Given the heterogeneous nature of primary Sjögren's syndrome, there is a need for a composite endpoint that includes multiple clinically relevant aspects.

use in these patients.² Effective therapy is urgently needed, and many promising biological drugs are in development.

Several open-label studies with multiple immunomodulatory drugs have shown positive results,^{3,4} but larger randomised controlled trials (RCTs) did not show clinical efficacy.⁵⁻⁹ So far, various single endpoints have been used in trials, the most frequent of which is currently the European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI). RCTs using ESSDAI as their primary endpoint showed large response rates in both the active treatment and placebo groups,^{5,6} which could help to explain why these trials did not meet their primary efficacy endpoints.

A primary study endpoint that is feasible, valid, reliable, clinically relevant, sensitive to change, and able to discriminate between active treatment and placebo is crucial to prove clinical efficacy. Recent results bring into question whether the ESSDAI is fit to be used as a primary endpoint on its own.¹⁰ ESSDAI only measures systemic disease activity, whereas there are other prominent and relevant primary Sjögren's syndrome features, such as sicca symptoms, fatigue, and decreased saliva and tear production. Moreover, although the ESSDAI includes a biological domain, additional

Such a composite endpoint is presumed to be more appropriate in showing drug efficacy than one that reports on a single aspect of this heterogeneous disease.

Added value of this study

We report on the development of a new composite endpoint, the Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS) to be used in future clinical trials. The CRESS consists of five complementary, clinically relevant items: systemic disease activity, patient-reported symptoms, tear gland item, salivary gland item, and serology. In RCTs that previously showed negative primary endpoint results, post-hoc analysis of the trial data using the CRESS resulted in higher response rates in patients treated with abatacept and rituximab than in those given placebo. Use of CRESS also resulted in decreased placebo response rates compared with use of the ESSDAI minimal clinically important improvement, which is essential to be able to show treatment efficacy.

Implications of all the available evidence

The CRESS is suitable for use as a primary endpoint in future clinical trials in primary Sjögren's syndrome, particularly because this comprehensive tool includes a combination of disease activity, functional, and serological parameters, which are all important dimensions of this heterogeneous, systemic autoimmune disease. This development is crucial for the search of new, effective therapies for a broad selection of patients with primary Sjögren's syndrome.

serological markers are used in daily clinical practice to monitor disease activity. Our hypothesis is that, given the complexity of primary Sjögren's syndrome, a composite endpoint that includes measures of multiple clinically relevant aspects of disease might be more appropriate than a single endpoint. This theory is in line with the use of composite measures in other heterogeneous, immune-mediated diseases.^{11,12} Furthermore, the use of a composite endpoint might facilitate inclusion in trials of a broad selection of patients with different levels of disease activity and manifestations. A combined response at multiple items might also lower placebo response rates, facilitating the ability to detect between-group differences.

We aimed to develop and validate a composite endpoint for assessing treatment efficacy in patients with primary Sjögren's syndrome based on expert opinion and trial data, called the Composite of Relevant Endpoints for Sjögren's Syndrome (CRESS).

Methods

To develop the CRESS, we set up a multidisciplinary team, consisting of experts in the primary Sjögren's syndrome field, including a rheumatologist (HB), ophthalmologist (JV), oral medicine expert (AV), immunologist (FGMK), pharmacologist (GMPJV), clinical trialist (NR), and

epidemiologist (SA). This team selected clinically relevant items to include in a composite endpoint. For each item, experts selected candidate measurements based on clinical relevance and practical feasibility. For CRESS items, we defined response on the basis of clinical relevance according to expert opinion, previously published data on minimal clinically important improvement (MCII), and trial data, primarily data from the Abatacept Sjögren Active Patients phase 3 (ASAP-III) trial,⁵ and for some items, from rituximab trials.^{4,13} We assessed CRESS response in the ASAP-III trial data, including the balance between CRESS items, and criterion validity with physician global disease activity as a comparator. We validated CRESS using data from three independent RCTs.^{6–8}

CRESS development

To develop CRESS, we used data from three trials done in the multidisciplinary, tertiary referral centre for primary Sjögren's syndrome at the University Medical Center Groningen (Groningen, Netherlands). ASAP-III was a single-centre, phase 3, randomised, double-blind, placebo-controlled, trial in 80 patients with primary Sjögren's syndrome treated with weekly subcutaneous injections of abatacept (125 mg) or placebo for 24 weeks.⁵ We used available data from the intention-to-treat population at 24 weeks (abatacept group $n=40$, placebo group $n=39$). We combined data from two rituximab trials, an RCT and an open-label trial,^{13,4} thereby including 31 patients with primary Sjögren's syndrome treated with rituximab (1000 mg intravenous infusion at days 1 and 15). For baseline characteristics of patients in the ASAP-III and rituximab trials see appendix 2 (p 3).

Statistical analyses of CRESS development

We used receiver operating characteristic (ROC) analysis to assess discrimination between treatment groups in ASAP-III (abatacept vs placebo) for absolute improvement, relative improvement, or both, in the selected candidate measurements, reported as area under the curve (AUC)

with 95% CI. When possible, we derived cutoff points from the ROC analysis, based on the highest sum of sensitivity and specificity. Otherwise, cutoff points were based on expert opinion, taking measurement variation into account. We selected the definition of total CRESS response by calculating the number of responders on one to five of the individual items and based on optimal discrimination between abatacept and placebo treatment. To explore the balance between CRESS items, we calculated the number of CRESS responders who were responders on single items. We also calculated the number of responders when leaving out single items one by one. We used IBM SPSS Statistics (version 23.0) for all statistical analyses.

External validation

We externally validated CRESS using data from three multi-centre, phase 3, randomised, double-blind, placebo-controlled trials of rituximab (TRial of Anti-B Cell Therapy In patients with primary Sjögren's Syndrome [TRACTISS], $n=133$)⁸, abatacept (multinational abatacept, $n=187$),⁶ and tocilizumab (Efficacy of TocilizumAb in Primary Sjögren's syndrome [ETAP], $n=110$)⁷ using available data on CRESS items. We identified the TRACTISS and multinational abatacept trials as potentially positive trials because, although these trials had negative primary endpoint results, they showed improvement in secondary outcome measures. We identified the ETAP trial as a negative trial because clinical, patient-reported, glandular, and immunological outcome measures showed negative results.⁷ Baseline characteristics and treatment regimens can be found in the original publications.^{6–8}

See Online for appendix 2

For all three trials, we calculated the number and percentage of responders for separate CRESS items and total CRESS at the primary endpoint visit (week 48 for TRACTISS, week 24 for the other two trials). We assessed early CRESS response using week 24 data from the TRACTISS trial and week 12 data from the other two trials. Patients with available data for fewer than

	Measurement	Definition of response
Systemic disease activity	ClinESSDAI	Score of lower than 5 points indicating low disease activity
Patient-reported symptoms	ESSPRI	Decrease of at least 1 point or at least 15% from baseline
Tear gland*	Schirmer's test and OSS	If abnormal Schirmer (5 mm or less) at baseline: increase of at least 5 mm in Schirmer from baseline; or if abnormal OSS (at least 3 points) at baseline: decrease of at least 2 points in OSS from baseline; or if both Schirmer and OSS normal score at baseline (Schirmer greater than 5 mm and OSS of less than 3 points): no change to abnormal in Schirmer and OSS
Salivary gland	UWS and SGUS	UWS: increase of at least 25% or, if score is 0 mL/min at baseline, any increase from baseline; or SGUS: decrease of at least 25% in total Hocevar score from baseline
Serological	Rheumatoid factor† and IgG	Rheumatoid factor: decrease of at least 25% from baseline; or IgG: decrease of at least 10% from baseline
CRESS responder	Not applicable	Responder on at least 3 of 5 items

CRESS can be used without OSS and SGUS (concise CRESS) leaving Schirmer's test for assessment of tear gland function, and UWS for assessment of salivary gland function. ClinESSDAI=Clinical 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 saliva secretion. SGUS=salivary gland ultrasonography. CRESS=Composite of Relevant Endpoints for Sjögren's Syndrome. *Mean of both eyes. †Total rheumatoid factor or rheumatoid factor-IgM.

Table 1: CRESS items and definition of response per item

three CRESS items were imputed as non-responders. We used χ^2 tests to test the significance of total CRESS response. We compared total CRESS response with the previously validated MCII of a decrease of at least 3 points in ESSDAI.

Results

Based on expert opinion, five complementary items were selected for inclusion in the CRESS: systemic disease activity, patient-reported symptoms, tear gland item, salivary gland item, and serology (table 1). Physician global disease activity was not selected as an item because the use of specific tests for separate items was preferred to a global disease activity measurement. Candidate outcome measurements, selected by the multidisciplinary experts based on clinical relevance and feasibility, are shown in appendix 2 (p 4), including previously validated definitions of normal or low scores and validated cutoff points indicating improvement, where available.

An extensive glossary with CRESS instructions (pp 5–8) and response rates of ROC and expert cutoff points for all items in the ASAP-III and rituximab trials (where available; pp 9–10) are shown in appendix 2.

Because ESSDAI is currently used as a primary outcome measure in most RCTs of primary Sjögren's syndrome, we evaluated ESSDAI and Clinical ESSDAI (ClinESSDAI) for the systemic disease activity item of CRESS. ROC analyses of absolute and relative change showed no difference between abatacept and placebo treatment both for ESSDAI and ClinESSDAI in data from ASAP-III (appendix 2 p 11). The MCII of at least 3 points decrease^{14,15} did not differ between treatment groups, with high response rates in the placebo group (>50%).

Analysis of ASAP-III data on the proportion of patients who reached the validated cutoff for low disease activity (<5 points)^{14,15} at week 24 showed that response rates for ESSDAI (<5 points) were 35% (14 of 40) for patients treated with abatacept and 22% (eight of 37) for those given placebo; for ClinESSDAI (<5 points) response rates were 45% (18 of 40) for abatacept and 27% (10 of 37) for placebo (table 2). ClinESSDAI was preferred by the experts as a measure of low disease activity because ClinESSDAI does not include the biological domain (ie, serology), and the CRESS includes serology as a separate item. Of patients with high disease activity (ClinESSDAI of at least 14 points) at baseline, eight (36%) of 22 abatacept patients versus

	Abatacept group (n=40)	Placebo group (n=39)
Systemic disease activity, ClinESSDAI		
Less than 5 points at week 24	18/40 (45%)	10/37 (27%)
Patient-reported symptoms, ESSPRI decrease		
At least 1 point	23/40 (58%)	8/36 (22%)
At least 15%	21/40 (53%)	8/36 (22%)
At least 1 point or 15%	23/40 (58%)	8/36 (22%)
Tear gland		
Increase in Schirmer's test of at least 5 mm	4/23 (17%)	0/23 (0%)
Decrease in OSS of at least 2 points	12/26 (46%)	8/26 (31%)
Stable*	3/5 (60%)	4/8 (50%)†
An increase in Schirmer's test of at least 5 mm; or a decrease in OSS of at least 2 points; or stable	18/40 (45%)	12/37 (32%)
Salivary gland		
Increase in UWS of at least 25%‡	14/29 (48%)	8/30 (27%)
Any increase in UWS if baseline is 0	3/8 (38%)	3/5 (60%)
Decrease in SGUS of at least 25%	11/37 (30%)	4/35 (11%)
Increase in UWS of at least 25%; or any increase if baseline is 0; or decrease in SGUS of at least 25%	23/40 (58%)	15/37 (41%)
Serology		
Decrease in rheumatoid factor of at least 25%§	24/36 (67%)	3/34 (9%)
Decrease in IgG of at least 10%	7/38 (18%)	5/37 (14%)
Decrease in rheumatoid factor of at least 25% or decrease in IgG of at least 10%	25/40 (63%)	7/37 (19%)
Total CRESS response		
Responder on at least three of five items	24/40 (60%)	7/37 (19%)
Including two non-responders¶	24/40 (60%)	7/39 (18%)
Data are n/N (%). We used available data from the intention-to-treat population of the ASAP-III trial at 24 weeks. ClinESSDAI=Clinical 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 saliva secretion. SGUS=salivary gland ultrasonography. CRESS=Composite of Relevant Endpoints for Sjögren's Syndrome. *Stable was defined as more than 5 mm for Schirmer's test and less than 3 points for OSS. †Including one patient with a missing Schirmer's test result. ‡13 patients with a baseline value of 0 were excluded. §7 patients with a baseline value of 0 were excluded. ¶Including two placebo-treated patients with missing data at week 24 (non-responders).		
Table 2: CRESS response rates using 24 week data from the ASAP-III trial, in which patients were treated with abatacept or placebo		

two (13%) of 16 placebo patients reached ClinESSDAI low disease activity (<5 points) at week 24, indicating that reaching low disease activity for patients with high disease activity at baseline is possible, and showing that this measure also allows for discrimination between treatment groups in patients with a high disease activity at baseline.

For the patient-reported symptoms item, EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) was selected for analysis by the experts. ROC analyses showed cutoff points similar to the previously validated MCII in ESSPRI: a decrease of at least 1 point or at least 15% (appendix 2 p 11).¹⁴ Using this definition of response, response rates were 58% (23 of 40) for abatacept-treated patients and 22% (eight of 36) for placebo-treated patients (table 2).

For the tear gland item, the experts selected Schirmer's test, measured without anesthesia, ocular staining score (OSS), and tear breakup time for analyses, using mean scores of both eyes. Relative change for Schirmer's test is not suitable as an endpoint because small changes over time (ie, <5 mm) most likely reflect normal variability. ROC analysis of Schirmer's test showed a cutoff point of 0.3 mm increase. Since this falls within measurement variation, the set definition for the minimal clinically important difference of at least 5 mm increase was selected.¹⁶ The OSS is a sum score ranging from 0 to 12, taking into account corneal and conjunctival staining scores, scored on a logarithmic scale, with extra points given for the presence of filaments, staining in the pupillary area, and patches of confluent staining.¹⁷ Therefore, relative change in OSS as an endpoint is not mathematically justifiable. ROC analysis of OSS could not discriminate between treatment groups, and no cutoff point could be calculated. For OSS, the minimal clinically important difference has not been studied yet. Based on expert opinion and a clinical trial using OSS as an endpoint, a cutoff of at least 2 points decrease was selected.¹⁸ ROC analyses of tear breakup time could not discriminate between treatment groups (appendix 2 p 11). Schirmer's test and OSS, but not tear breakup time, were selected, because they are complementary tests that measure glandular function and ocular surface disease, respectively, and both are part of the ACR-EULAR classification criteria.¹⁹

Because improvement within the normal range was considered not clinically relevant for the Schirmer's test and OSS, separate definitions of response were developed for patients with normal and abnormal values at baseline. For patients with abnormal values of Schirmer's test (≤ 5 mm) at baseline, response was defined as an increase of at least 5 mm; for patients with abnormal OSS values (at least 3 points) at baseline, response was defined as a decrease in OSS of at least 2 points. For patients with normal scores at baseline, response was defined as no change in score to abnormal values in both Schirmer's test and OSS. Combining patients who responded based on Schirmer's test or OSS (or both), response rates were 45%

(18 of 40) for patients treated with abatacept and 32% (12 of 37) for patients treated with placebo (table 2).

For the salivary gland item, unstimulated whole saliva secretion (UWS), stimulated whole saliva secretion (SWS), and salivary gland ultrasonography (SGUS) were selected for analysis. For UWS and SWS, relative change was explored because of wide inter-patient variation in secretion rates. ROC analysis for UWS showed a cutoff point of 0.0% (appendix 2 p 11), which falls within measurement variation. Therefore, a stricter cutoff point of at least 25% increase was selected.²⁰ ROC analysis for SWS showed a cutoff point of 44.2% increase. In line with UWS, a cutoff point of at least 25% increase was also analysed. For patients with no saliva production (0 mL/min) at baseline, any increase in saliva secretion was defined as a response.

Because UWS showed higher response rates than SWS in rituximab trials (appendix 2 p 9), is more commonly applied in patients with primary Sjögren's syndrome, and is more uniform and easier to collect than SWS, UWS was included in the CRESS. ROC analyses for absolute and relative change in total Hocevar score (via SGUS) showed somewhat better discrimination for relative change than absolute change, with a cutoff point of 14.7% decrease (appendix 2 p 11).²¹ To minimise response due to natural variation, the cutoff point was set at a decrease of at least 25% in total Hocevar score. For additional SGUS analyses see appendix 2 (pp 13–14). Because UWS and SGUS are complementary tests, measuring gland function and structural changes in the glands, respectively, both were selected. Response rates based on UWS or SGUS (or both) for patients enrolled in ASAP-III were 58% (23 of 40) for abatacept-treated patients and 41% (15 of 37) for placebo-treated patients (table 2).

For the serological item, levels of rheumatoid factor, IgG, complement (C3 and C4), and lymphocyte count were considered as possible measurements by the experts. Relative change in serological markers was explored because of wide inter-patient variation in these measures. ROC analysis for rheumatoid factor showed a cutoff point of 23.0% decrease, with good discrimination between treatment groups. Therefore, the cutoff point was set at a decrease of at least 25%. ROC analysis for IgG showed a cutoff point of 2.2% decrease (appendix 2 p 11). Because of the relatively small effect on IgG of abatacept (table 2), and because different biological drugs might induce different serological responses, IgG response was also evaluated in patients on rituximab (appendix 2 p 9). The cutoff point of a decrease of at least 10% was selected, giving acceptable sensitivity and specificity. Serum complement and lymphocyte count did not improve discrimination between groups (appendix 2 p 15). Response rates for rheumatoid factor or IgG (or both) in participants in ASAP-III were 63% (25 of 40) for patients treated with abatacept and 19% (seven of 37) for those treated with placebo (table 2).

	≥1 item	≥2 items	≥3 items	≥4 items	5 items
Abatacept group (n=40)	39 (98%)	34 (85%)	24 (60%)*	9 (23%)	1 (3%)
Placebo group (n=37)	30 (81%)	15 (41%)	7 (19%)*	0	0

*Highest sum of sensitivity and specificity.

Table 3: Abatacept and placebo patients who were responders on 1–5 items at week 24

Figure 1: Number of CRESS responders who were responders or non-responders on the single items for abatacept and placebo treatment

CRESS=Composite of Relevant Endpoints for Sjögren's Syndrome. ClinESSDAI=Clinical EULAR Sjögren's Syndrome Disease Activity Index. ESSPRI=EULAR Sjögren's Syndrome Patient Reported Index. OSS=ocular staining score. SGUS=salivary gland ultrasonography. UWS=unstimulated whole saliva secretion.

Response on at least three of five items provided the best discrimination between treatment groups and was selected as the definition of total CRESS response (table 3). Total CRESS response rates among participants in the ASAP-III trial were 60% (24 of 40) for abatacept-treated patients and 18% (seven of 37) for placebo-treated patients ($p<0.0001$; table 2, figure 1A).

If OSS and SGUS are not available, the concise CRESS (cCRESS) can be used, with Schirmer's test used to assess tear gland function and UWS used to assess salivary gland function. Total cCRESS response rates were 63% (25 of 40) for abatacept-treated patients and 8% (three of 39) for placebo-treated patients ($p<0.0001$; appendix 2 p 16).

The number of CRESS responders who responded on single items was well-balanced for all items (figure 1B; appendix 2 p 17). Criterion validity was confirmed by

exploring the agreement of total CRESS response with physician global disease activity (appendix 2 p 18).

For external validation, cCRESS was analysed in TRACTISS and ETAP trials because OSS and SGUS Hocevar score were not available in these trials. The serological item in the ETAP trial was based on IgG only, since numeric rheumatoid factor values were not available. Furthermore, IgG was only measured at week 12 and imputed at week 24. In the multinational abatacept trial, the CRESS without SGUS was analysed.

Calculation of CRESS or cCRESS response rates using data from the TRACTISS and multinational abatacept trials, which were identified as potentially positive trials, showed superior responses in the treatment arms. Analysis of data from the primary endpoint visit (week 48) in the TRACTISS trial showed that 33 (49%) of 67 patients treated with rituximab had a cCRESS response, compared with 20 (30%) of 66 patients treated with placebo ($p=0.026$; figure 2). Analysis of data from the multinational abatacept trial showed that 41 (45%) of 92 patients in the abatacept group had a CRESS response compared with 30 (32%) of 95 patients in the placebo group ($p=0.067$; figure 2). Data from the ETAP trial confirmed this trial as a negative trial, with low response rates in both treatment groups; cCRESS response was achieved by 10 (18%) of 55 patients in the tocilizumab group compared with 13 (24%) of 55 in the placebo group ($p=0.48$).

Use of CRESS resulted in low response rates among patients treated with placebo in our post-hoc analysis of clinical trial data (figure 3). In the multinational abatacept and ETAP trials, placebo response rates were 24–32% when using CRESS compared with 58–64% when using ESSDAI MCII (decrease of at least 3 points). In the TRACTISS trial, use of CRESS resulted in a higher response rate for rituximab than for placebo at the primary endpoint visit, whereas no distinction between the groups could be made based on ESSDAI MCII response. When we excluded patients with fewer than three CRESS items available, placebo response in all trials remained low (27–35%). External validation results of separate CRESS items (pp 20–25) and supportive analyses of selected CRESS items (pp 26–27) are shown in appendix 2.

Discussion

The choice of a primary study endpoint is a crucial step in designing clinical trials. Owing to the heterogeneity and complexity of primary Sjögren's syndrome, a composite endpoint is needed to reflect all of the important aspects of the disease. We developed and validated the CRESS, a feasible composite endpoint that combines disease activity, functional parameters, and serological parameters, and enabled discrimination between active treatment and placebo in post-hoc analysis of clinical trial data.

Our multidisciplinary expert team selected five complementary, clinically relevant items for the CRESS, and all five CRESS items contributed equally to total

CRESS response in data from the ASAP-III trial. When evaluating disease activity, systemic and patient-reported symptoms are both important. As a validated instrument, ESSDAI is widely used by physicians and researchers to assess systemic disease activity, and ESSPRI is used by patients to report prominent symptoms. High systemic disease activity might lead to severe complications of primary Sjögren's syndrome, whereas patient-reported symptoms have greater impact on quality of life of patients.^{22,23} Previous studies have shown that correlation between ESSDAI and ESSPRI is poor,²⁴ suggesting that these indices are complementary. As such, we included both in the CRESS. We selected ClinESSDAI low disease activity for the systemic disease activity item to include in CRESS because it better discriminated between treatment and placebo groups than did the ClinESSDAI MCII (decrease of at least 3 points); this measure might also be more relevant for patients. Low disease activity as a response criterion has also been used in systemic lupus erythematosus. The Lupus Low Disease Activity State (LLDAS) was developed and validated using data from several RCTs²⁵ and was found to be associated with reduced damage accrual and higher health-related quality of life.^{26,27} The ESSPRI, which consists of three questions regarding dryness, fatigue, and pain, was preferred to more elaborate questionnaires assessing separate patient-reported features, which might be more appropriate to use as secondary endpoints in trials.

For the tear and salivary gland items, we included two complementary tests assessing glandular function and structural abnormalities: Schirmer's test and OSS for the tear gland and UWS and SGUS for the salivary gland. For Schirmer's test, variability is high, especially within normal scores.²⁸ Therefore, improvement in Schirmer's test was considered clinically relevant only for patients with abnormal values at baseline; thus we separated the definitions of response for patients with normal and abnormal values at baseline. UWS was preferred to SWS because UWS is also included as an ACR-EULAR classification criterion¹⁹ and is more uniform and samples are more feasible to collect. By contrast, SWS is done using gustatory (eg, citric acid) or mechanical stimulation (chewing). We included SGUS in CRESS because it is a non-invasive tool for imaging that can reveal structural changes to salivary glands. Because it is not yet clear which items of SGUS scores are most important in the evaluation of therapeutic response and what each of these items reflect, we selected the widely applied total Hocevar score for inclusion in the CRESS. Previously, we found that reliability varies between individual items of the Hocevar score. Total Hocevar score showed excellent intra-observer and good inter-observer reliability, although total scores varied more between observers in patients with high ultrasonographic scores.²⁹ Therefore, relative change in total Hocevar score was considered the most applicable, and

Figure 2: CRESS and cCRESS response rates

(A) CRESS and cCRESS response rates using data from the ASAP-III trial at weeks 12 and 24. At week 12 only CRESS without SGUS was available. (B) cCRESS response rates using data from the TRACTISS trial at weeks 24 and 48. (C) CRESS without SGUS response rates using data from the multinational abatacept trial at weeks 12 and 24. (D) cCRESS without rheumatoid factor response rates using data from the ETAP trial at weeks 12 and 24. ASAP-III=Abatacept Sjögren Active Patients phase 3. CRESS=Composite of Relevant Endpoints for Sjögren's Syndrome. cCRESS=concise CRESS. ETAP=Efficacy of Tocilizumab in Primary Sjögren's syndrome. OSS=ocular staining score. SGUS=salivary gland ultrasonography. TRACTISS=TRial of Anti-B Cell Therapy in patients with primary Sjögren's Syndrome.

the cutoff selected was a decrease of at least 25%. Further research and international collaboration is needed to determine the optimal SGUS scoring system for assessment of therapeutic response.

We included the ClinESSDAI and serology as separate items because the biological domain of the ESSDAI is too global and is based on absolute cutoff values for IgG, meaning that improvement in IgG can go undetected. Moreover, the biological domain of the ESSDAI does not include rheumatoid factor autoantibodies, which is an important marker for disease activity and has been associated with development of mucosa-associated lymphoid tissue.³⁰ Rheumatoid factor can be evaluated as total rheumatoid factor or IgM-rheumatoid factor, depending on the assay method. The majority of total rheumatoid factor comprises IgM, and response on this

Figure 3: CRESS and cCRESS response rates versus ESSDAI MCII response rates

(A) CRESS response rates versus ESSDAI MCII response rates in the ASAP-III trial at week 24. Median baseline ESSDAI scores were 14.0 (IQR 9.0–16.8) for abatacept and 13.0 (8.0–18.0) for placebo. (B) cCRESS response rates versus ESSDAI MCII response rates in the TRACTISS trial at week 48. Mean baseline ESSDAI scores were 5.3 (SD 4.7) for rituximab and 6.0 (4.3) for placebo. (C) CRESS without SGUS response rates versus ESSDAI MCII response rates in the multinational abatacept trial at week 24. Mean baseline ESSDAI scores were 8.7 (SD 3.4) for abatacept and 10.1 (5.0) for placebo. (D) cCRESS without rheumatoid factor response rates versus ESSDAI MCII response rates in the ETAP trial at week 24. Median baseline ESSDAI scores were 11.0 (IQR 8.0–13.5) for tocilizumab and 10.0 (8.0–14.8) for placebo. For all trials, we calculated ESSDAI response percentages by imputing missing patients as non-responders. ASAP-III=Abatacept Sjögren Active Patients phase 3. CRESS=Composite of Relevant Endpoints for Sjögren's Syndrome. cCRESS=concise CRESS. ESSDAI=EULAR Sjögren's Syndrome Disease Activity Index. ETAP=Efficacy of Tocilizumab in Primary Sjögren's syndrome. MCII=minimal clinically important improvement. TRACTISS=TRial of Anti-B Cell Therapy In patients with primary Sjögren's Syndrome.

serological item is defined using relative change. Therefore, the cutoff point of at least 25% can be used for different assays, as was the case in the trials used for validation. Immunological and kinetic differences between the formation of IgM-rheumatoid factor and IgG provide a rationale for combined analysis in clinical trials; IgM-rheumatoid factor has a shorter half-life and is mainly produced by short-lived plasma cells,³¹ whereas IgG has a longer half-life and is mainly produced by long-lived plasma cells. This difference is illustrated by the modest effect of B-cell depletion therapy on IgG levels and persistence of Ig-producing cells in salivary gland tissue.^{9,32}

Using data from two RCTs that were identified as having potentially positive results, use of the cCRESS showed significant between-group discrimination at the primary endpoint visit in data from the TRACTISS trial (49% vs 30% at week 48), and use of CRESS showed substantial between-group discrimination in data from the multinational abatacept trial (45% vs 32% at week 24). The ETAP trial was identified as a negative trial, and this was confirmed by calculating cCRESS using these trial

data; low response rates were seen in both treatment groups (18% vs 24% at week 24).

Using data from trials in which patient inclusion required high baseline ESSDAI scores (multinational abatacept and ETAP), use of CRESS resulted in decreased placebo response rates compared with use of ESSDAI MCII (24–32% vs 58–64%). Patients lacking sufficient data to evaluate CRESS response were imputed as non-responders. Even when excluding patients with fewer than three CRESS items available, discrimination between treatment groups remained similar, and placebo response in all trials remained low (27–35%). This improvement is important, since a relatively small placebo response is essential to show treatment efficacy.

In the TRACTISS trial, no early treatment effect was seen at week 24. A longer follow-up period of 48 weeks with repeated cycles of rituximab might be needed to establish a treatment effect. The relatively high placebo response at week 24 might be explained by the high dose of glucocorticoids. When analysing the individual CRESS items, there was a high response for ClinESSDAI (<5 points) in both treatment groups of TRACTISS (appendix 2 pp 20–21). This response can be explained by the fact that TRACTISS did not require patients to have moderate to high systemic disease activity at baseline for inclusion. However, the alternative of assessing the ESSDAI or ClinESSDAI MCII would have resulted in low response rates; for patients with already low ESSDAI scores it would be impossible to improve, thereby restricting response on at least three or four items. As seen from our additional analyses, replacing ClinESSDAI low disease activity with ClinESSDAI MCII in the cCRESS led to smaller between-group differences in the TRACTISS trial (appendix 2 p 26). It is also important that therapeutic drugs become available for patients with a high symptom burden and a relatively low systemic disease activity, which is often the case in patients newly diagnosed with primary Sjögren's syndrome. All recent RCTs that used the ESSDAI as the primary endpoint included patients with moderate to high systemic disease activity (at least 5 points on ESSDAI) at baseline. Use of CRESS as a trial outcome would allow inclusion of patients with relatively low systemic disease activity.

Limitations to this study are that data are not yet available on sensitivity to change of the CRESS in patients with primary Sjögren's syndrome with long-standing disease, since patients with long disease duration were not included in RCTs. If patients with long-standing disease and damaged glands were included, certain CRESS items might be less sensitive to change, especially the tear and salivary gland items, and the dryness component of the ESSPRI. However, objectively measured glandular function and sicca symptoms are not always coupled. It is also unclear whether dryness can improve in damaged glands. Given that symptoms due to damage are not scored in the

ClinESSDAI, this item and the serological item are expected to remain sensitive to change.

The CRESS was developed on the basis of expert opinion. Another composite endpoint, the Sjögren's Syndrome Responder Index, includes five domains (visual analogue score for fatigue, ocular and oral dryness, UWS, and ESR) and was developed in 2015 with a more data-driven approach using data from rituximab trials.³³ This endpoint lacks important measures for primary Sjögren's syndrome, such as systemic disease activity and objective measures for tear gland function. Moreover, the Sjögren's Syndrome Responder Index response was inferior to the CRESS response in the ASAP-III trial, with response rates at week 24 of 33% (13 of 40) in the abatacept group and 23% (9 of 39) in the placebo.⁵ An Innovative Medicines Initiative project, NECESSITY,³⁴ is working to identify a new composite endpoint based on a data-driven approach of candidate criteria and a Delphi procedure, and the CRESS will be included in these analyses.

In summary, the CRESS is a feasible composite endpoint that consists of well-balanced, complementary, and clinically relevant items for all patients with primary Sjögren's syndrome. We showed that the CRESS is able to discriminate between active treatment and placebo in patients with primary Sjögren's syndrome and thus show clinical efficacy of these treatments. As the next step, validation of the CRESS in a future, prospective RCT is warranted. This study is an important advance in the search for valid composite endpoints for use in future clinical trials of primary Sjögren's syndrome.

Contributors

SA, JV, GMPJV, AV, NR, FGMK, and HB were part of the multidisciplinary expert team. Statistical analysis was done by SA and LdW for development and validation, EP for validation in the TRACTISS trial, and MN for validation in the multinational abatacept trial. SA and LdW wrote the first draft of the manuscript. SA and LdW verified the data. All authors had full access to the data in the study, interpreted the data, contributed to writing, critically revised the article, had final responsibility for the decision to submit for publication, and approved the final submitted version.

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Declaration of interests

ANB reports personal fees from Bristol-Myers Squibb and Sanofi-Aventis, outside the submitted work. MB reports grants and personal fees from Amgen/Medimmune, Janssen, and GSK, and personal fees from UCB, outside the submitted work. HB reports grants and personal fees from Bristol Myers Squibb and Roche, and personal fees from Novartis,

Medimmune, personal fees and Union Chimique Belge, outside the submitted work. SJB reports consulting fees from Novartis, AstraZeneca, and Abbvie/Galapagos, outside the submitted work. J-EG reports grants and personal fees from Bristol Myers Squibb and Pfizer, and personal fees from CSL Behring, Lilly, Janssen, UCB, and Roche, outside the submitted work. FGMK reports grants and personal fees from Bristol Myers Squibb and Roche, and personal fees from Janssen-Cilag, outside the submitted work. MN and NR are employees and shareholders of Bristol-Myers Squibb. JFvN reports personal fees from Bristol Myers Squibb, outside the submitted work. JV reports personal fees from Santen and Tramedico, outside the submitted work. AV reports grants from Bristol Myers Squibb and Roche, during the conduct of the study. SA, LdW, GMPJV, EP, and RF declare no competing interests.

Data sharing

We have no plans to share additional data beyond what is shared in this article.

Acknowledgments

We thank M Nowak, D Grasela, and S Banerjee (Bristol-Myers Squibb) and K Hammitt (Sjögren's Foundation) for valuable discussions.

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