Response to: 'Correspondence on 'Interleukin 6 receptor inhibition in primary Sjögren syndrome: a multicentre double-blind randomised placebo-controlled trial" by Wang *et al*

We read with interest the correspondence related to our article, 'Interleukin 6 receptor inhibition in primary Sjögren syndrome: a multicentre double-blind randomised placebo-controlled trial', by Wang *et al*[1] who discuss the disappointing results of recent trials of primary Sjögren syndrome (pSS).

To explain recent negative results of tocilizumab and abatacept, apart from the inefficacy of these biologicals in pSS, Wang *et al* discuss the contribution of the design of the study. First, they discuss the choice of a primary endpoint based on the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI). As mentioned by the authors, this score captures only the systemic complications of the disease, observed in 30%–50% of patients with pSS overall, but in all patients in our trials (requiring ESSDAI ≥ 5 at inclusion).[2] Until now, 17 controlled trials have used ESSDAI as the primary endpoint (table 1), including at least three positive trials (leflunomide and hydroxychloroquine, iscalimab, ianalumab).[3–6]

Second, Wang *et al* propose to use exocrine gland-centred outcome measures such as salivary gland biopsy and salivary gland ultrasonography. We agree that salivary gland ultrasonography requires improved standardisation. In addition, there might be a disconnect between salivary gland biopsy and salivary gland function findings. We preferred to use the routine Schirmer's test and unstimulated salivary flow in this academic multicentre trial as well as a patient-reported outcome visual analogue scale score for dryness. In our trial, none of these exocrine gland-centred outcomes revealed any effect of tocilizumab on pSS, but missing data on Schirmer test and unstimulated salivary flow limit the interpretation of these results.

Finally, Wang *et al* suggest that the poor response to treatment of pSS in terms of glandular function may be due to damage rather than activity in advanced stages of the disease. They suggest including patients at earlier disease stages. Of note, for more than half of the patients included in our trial, the disease duration was <5 years after diagnosis. In addition, restricting the study to patients with recently diagnosed pSS would make inclusion in clinical trials of pSS even more difficult.

Thus, regardless concerns regarding trial design in pSS, our negative results for clinical, patient-reported and also immunological outcomes indicate that interleukin 6 does not represent a relevant therapeutic target in pSS.

However, we agree with Wang *et al* that we have to continue our efforts to improve the design of future trials. NECESSITY, a European initiative, will combine data from our trial with those of previous randomised trials to determine new clinical composite outcomes in pSS, capturing both systemic and glandular features of the disease. An initiative from OMERACT on clinical outcomes in pSS is also progressing on this crucial topic.

Renaud Felten [1,2] **Jacques-Eric Gottenberg** [1,2]

[1]Service de Rhumatologie, CHU de Strasbourg, Centre National de Référence pour les Maladies Auto-Immunes Systémiques Rares Est Sud-Ouest RESO, Hôpitaux universitaires de Strasbourg, Strasbourg, France
[2]IBMC, CNRS, UPR3572, Université de Strasbourg, Strasbourg, Alsace, France

Correspondence to Dr Jacques-Eric Gottenberg, Service de Rhumatologie, CHU de Strasbourg, Centre National de Référence pour les Maladies Auto-Immunes Systémiques Rares Est Sud-Ouest RESO, Hôpitaux universitaires de Strasbourg, Strasbourg, Alsace, France; jacques-eric.gottenberg@chru-strasbourg.fr

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Table 1 Major recent or ongoing clinical trials using EULAR Sjögren's Syndrome Disease Activity Index as their primary endpoint

NCT or EudraCT no.	Treatment and mode of action	Phase	Status	Patients (n)	Time of evaluation of primary endpoint	Results	Reference
NCT01782235	Tocilizumab	III	Completed	110	Week 24	Negative	2
NCT02067910	Abatacept	III	Completed	80	Week 24	Negative	7
NCT02915159	Abatacept	III	Completed	187	Day 169	Negative	8
NCT02962895	Ianalumab anti-BAFFR	IIb	Active, not recruiting	195	Week 24	Positive	5
NCT02291029	Iscalimab anti-CD40	II	Completed	44	Week 12	Positive	4
NCT03905525	Iscalimab anti-CD40	II	Recruiting	260	Week 24	Not yet reported	
2014-003140-12	Leflunomide+hydroxychloroquine	IIa	Completed	29	Week 24	Positive	3
NCT02334306	Prezalumab anti-ICOSL	IIa	Terminated	32	Day 99	Negative	Not published
NCT02464319	Low dose IL-2	II	Completed	60	Week 24	Not yet reported	
NCT02701985	Petesicatib cathepsine-S inhibitor	II	Completed	75	Week 12	Negative	Not published
NCT02775916	Leniolisib PI3Kδ inhibitor	II	Completed	30	Week 12	Negative	Not published
NCT03100942	Filgotinib anti-JAK1 Lanraplenib SYK inhibitor Tirabrutinib BTK inhibitor	II	Completed	152	Week 12	Negative	Not published
NCT04035668	LOU064 BTK inhibitor	II	Recruiting	252	Week 24	Not yet reported	
NCT04078386	RC18 TACI fusion protein	II	Recruiting	30	Week 24	Not yet reported	
NCT02610543	Seletalisib PI3Kδ inhibitor	II	Terminated (enrolment challenges)	27	Week 12	Negative	9
NCT02843659	Lulizumab anti-CD28, BMS-986142 BTK inhibitor	II	Terminated	45	Week 24	Not yet reported	
NCT03023592	Iguratimod	I/II	Recruiting	30	Week 24	Not yet reported	

Eudra-CT, European Union Drug Regulating Authorities Clinical Trials; IL, interleukin; NCT, ClinicalTrials.gov Identifier.

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ORCID iDs
Renaud Felten http://orcid.org/0000-0002-4951-4032
Jacques-Eric Gottenberg http://orcid.org/0000-0002-9469-946X

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