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We thank Mossel and colleagues for their interest in our work.[1, 2] They raise a number of limitations that we acknowledge and have discussed. In addition we agree that an understanding of the pathology underlying the abnormal salivary gland ultrasound findings in Sjögren’s syndrome is an important objective to help establish the validity of this tool as a potential outcome measure in clinical trials. As both we and Mossel and colleagues discuss, we did not observe a difference in hypoechoic areas between rituximab and placebo. Similar hypoechoic areas can be observed in longstanding post-radiotherapy salivary glands where inflammatory cell infiltrate is variable and of a differing pattern.[3-5] Furthermore the pattern of hypoechoic areas on ultrasound in Sjögren’s syndrome is reminiscent of sialography findings which are characterised by contrast defined changes that include destructive and cavitatory stages.[6] Consequently late-stage hypoechoic lesions may reflect potentially irreversible damage rather than ongoing inflammatory lesions. However this would not explain the reported improvement in such hypoechoic lesions following rituximab in a single centre substudy of the French TEARS trial.[7] Our total ultrasound score (TUS) was designed some time ago,[1] and prior to more recent consensus work,[8] and we would not necessarily advocate this score above others for future studies. A greater number of categories for the number and sizing of hypoechoic lesions might offer greater sensitivity to change, be that an improvement or slowing of progression. However, creation of a larger yet reliable dynamic range for the measurement of hypoechoic lesions with such an operator dependent technique, in a multicentre study, may require some form of digital image analysis. Secondly, we also agree that salivary gland histopathology may offer a useful window on drug efficacy or lack thereof in clinical trials in Sjögren’s syndrome. We also advocate the need for standardisation and have argued that the focus
score alone may be insufficient as an outcome measure,[9, 10] although this has yet be proved in
the context of a drug that also clearly improves clinical manifestations in a double blind multicentre
study. Histology may also provide a means of predicting patients that might respond to B cell
depleting therapies; such analyses are underway in the TRACTISS biopsy substudy and it will be
interesting to see if we can replicate the reported associations between B cell infiltration and
response, whether positive or negative.[11-13] However, preliminary data from the ongoing
histopathology analysis of TRACTISS also confirmed that no improvement in the focus score could be
observed between the active and the placebo arm of the study. It will be of interest to correlate
these findings with the baseline and post-treatment number and size of the hypoechoic areas
observed at ultrasound. Although Mossel et al advocate the use of parotid histopathology for such
repeated measures,[2], data from their own group suggest that the diagnostic value of parotid and
minor salivary gland histopathology is very similar,[14] with the exception that lymphoepithelial
lesions that are more common in parotid glands compared with minor salivary glands. We would
argue that minor salivary glands are far more commonly used as a routine diagnostic tool and are
therefore more amenable for use in multicentre studies. Whether the reproducibility of histological
measures, such as focus score, mean focus area and area of infiltration, differ between repeat
biopsies of the parotid versus minor salivary glands is unknown but would help inform this debate. In
conclusion, we agree with Mossel et al that further validation work on ultrasound as a potential
outcome measure, and standardisation of histopathology, is both warranted and highly desirable.

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