Response to: Can ultrasound of the major salivary glands assess histopathological changes induced by treatment with rituximab in primary Sjögren's syndrome?

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 long-standing postradiotherapy 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 cavitary 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 Tolerance and Efficacy of Rituximab in Primary Sjögren's Syndrome (TEARS) trial.⁷ Our total ultrasound score 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. Second, 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 to 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 under way in the TRial of Anti-B-Cell Therapy In patients with primary Sjögren's Syndrome (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 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, differs 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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