Response to: 'Correspondence on 'Long-term efficacy and safety of canakinumab in patients with colchicine-resistant familial Mediterranean fever: results from the randomised phase III CLUSTER trial" by Satis *et al*

We thank Satis *et al*[1] for their interest in our article,[2] and will try to address their queries. Our colleagues suggest that flares with musculoskeletal symptoms as predominant signs may not be remembered by the patients when they report them. We reported that in Epoch 4 of the CLUSTER study, >90% of the patients treated with canakinumab experienced no flares or one flare throughout the 72-week period, while a median of 17.5 flares per year was reported before baseline. As detailed in the methods section and according to the study protocol, during the trial patients were considered to experience a flare when they present with a physician global assessment (which includes the assessment of musculoskeletal symptoms) ≥2 and C-reactive protein (CRP) ≥30 mg/L. On the other hand, if the phenomenon that Satis *et al*[1] mentioned occurred when patients reported the number of flares before the trial, it could have potentially led to an underestimation of the number of flares experienced in the previous year, thus making the difference with the rate of flares during the study even higher. Overall, we believe that it is unlikely that this phenomenon would affect significantly the results and conclusions in our manuscript. However, as we mentioned in the discussion of the limitations of the study, we acknowledge that a more standardised definition of flare would help to better define the target of familial Mediterranean fever (FMF) treatment.

Satis *et al*[1] suggest that there is an inconsistency between the reported number of patients receiving <2700 or ≥2700 mg as cumulative doses of canakinumab in the text and elsewhere. As explained in the patient disposition section, from the 60 patients who entered Epoch 4 of the CLUSTER study, three discontinued the study and 57 completed it. We correctly mentioned in the text that overall, 44 patients received <2700 mg canakinumab and 16 received ≥2700 mg. Figure 1 of our referred paper[2] indicates the patients in the lower boxes (ie, those who completed the study) who received each cumulative dose, and as Satis *et al*[2] mentioned, when we add the numbers in the boxes, these were 42 and 15. This is also correct as it refers only to the 57 patients who completed the study. What the figure does not mention explicitly is the cumulative dose received by the three patients who discontinued the study, it was ≥2700 mg for the patient receiving 150 mg every 4 weeks who discontinued the study due to pregnancy, and <2700 mg for the other two patients.

Satis *et al*[1] ask why baseline CRP levels were high. As mentioned in the article, patients had to have active disease with an ongoing flare when they entered the study (ie, baseline flare), and this is the reason for which their CRP levels were high. This is also mentioned specifically in the figure legend. Average CRP levels decreased quickly during Epoch 2 in patients treated with canakinumab, as previously reported.[3]

We would also like to point out that none of the patients had amyloidosis nor renal failure during the study. All patients entered the study with normal renal function, and the effect of canakinumab on proteinuria was not systematically analysed in this trial. Renal function was studied by creatinine clearance, as reported. However, only two adult patients with colchicine-resistant FMF presented with isolated events of newly occurring proteinuria during the whole study, as measured by protein urine dipstick. One of these patients presented with proteinuria at the last visit of the study and one with intermittent low levels of proteinuria at four different visits during Epochs 2, 3 and 4.

We hope that this additional information helps to further clarify some aspects of our study, and thank again Satis *et al*[1] for their correspondence.

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Acknowledgements We thank Marco Migliaccio for medical writing assistance.

Contributors Both authors have had: substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data, and drafting the work or revising it critically for important intellectual content, and final approval of the version published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests SO has received consultancy and speaker fees from Novartis and SOBI. FDB reports receiving grant support from AbbVie, F Hoffmann–La Roche, Novartis, Novimmune, Pfizer, R-Pharm, Sanofi and SOBI.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

To cite Ozen S, De Benedetti F. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2020-218942

Received 28 August 2020
Accepted 30 August 2020

Linked

► http://dx.doi.org/10.1136/annrheumdis-2020-218901

Ann Rheum Dis 2020;**0**:1. doi:10.1136/annrheumdis-2020-218942

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