Response to: 'Changing the outcome measures, changing the results? The urgent need of a specific Disease Activity Score to adult-onset Still's disease' by Ruscitti *et al*

We would like to thank Ruscitti *et al*[1] for their interest in our recent publication, in which we presented the results of the Canakinumab for treatment of adult onset Still's disease to achieve reduction ofarthritic manifestation (CONSIDER) trial. In this study, we investigated the efficacy of canakinumab for the treatment of patients with adult-onset Still's disease (AOSD) with articular involvement (tender and swollen joint counts≥4 each) by means of a multicentre, double-blind, randomised, placebo-controlled trial.[2] Patients were randomised to receive either canakinumab 4 mg/kg body weight (maximum 300 mg) every 4 weeks or placebo. According to the study goal, the primary endpoint was defined as the proportion of patients with a clinically relevant reduction in Disease Activity Score (DAS 28 >1.2) at week 12.

Since no controlled studies existed in this indication at that time of the study initiation, we were not able to base our statistical considerations on known facts of response rates to placebo or any immunosuppressive regimen. After careful consideration, our sample size calculation indicated that it requires a total of n=68 randomised patients to show a significant difference between the groups. Of note, due to a conditional approval of the drug for AOSD by the European Medicines Agency (EMA), which was partially based on the results of the biomarker analyses of our CONSIDER trial[3] and ethical considerations of a placebo-controlled trial in a potentially severe disease, we had to stop the trial prematurely. Thus, we did not reach the planed sample size, but recruited only 51% of the required patients. Of course, this situation had a strong impact on our statistical analysis. Unfortunately, our predictions of response rates were almost correct and it was not possible to show a significant difference between the groups with this limited number of patients. In the intention-to treat analysis, 67% in the canakinumab but also 41% in the placebo group reached the primary endpoint (p=0.18). We cannot extrapolate these results to a fully recruited study, but it is clear that the p value would be different for the same response rates with a higher patient number. The high placebo rate seems to be strange with this targeted approach in AOSD based on broad clinical experience and Ruscitti *et al* mention that this finding seems to be in contrast with the strong scientific rationale, which is behind the study, of inhibiting IL-1β in AOSD. However, we would like to point out that the placebo response rate should not be underestimated in this condition. The same problem led evidently also to a failure in the recently published study with tocilizumab in AOSD.[4]

We fully agree with Ruscitti *et al* that it is of upmost relevance to develop a new and reliable DAS for AOSD. In our study, DAS28 has been chosen as a primary outcome measure after discussion and in accordance with the health authorities (EMA) as an established score in rheumatology, which could support approval of the drug also in AOSD, especially in arthritic manifestations. At least this goal was achieved which is of great relevance to our patients. Of course, keeping in mind that AOSD is a systemic autoinflammatory disease, predominant articular manifestation characterises only a subgroup of patients. We still believe that to capture the outcome of articular manifestation, a placebo-controlled study design and even joint based scores like DAS28 or American College of Rheumatology (ACR) could be appropriate as done in the CONSIDER study. For patient with predominant systemic manifestations also other approaches should be discussed such as a flare design and a different primary outcome need to be used. One candidate would be the known Pouchot score (first published in 1991, modified by Rau in 2010), and validated in 2016, after approval of CONSIDER study protocol.[5–7] In fact, this score has been increasingly used in trials with AOSD recently. However, it is clear that also the modified Pouchot score has its limits, for example, due to the fact that the different captured domains are not weighted. In our mind, another example of an imperfect efficacy outcome was used in the tadekining alpha study.[8] Therefore, we fully agree with Ruscitti *et al* that there is still an urgent need to further improve management of patients with AOSD and a standardised outcome measure is the sine qua non condition to better characterise and evaluate disease and treatment response. The development and validation of a new DAS in AOSD: the Developement And Validation of a European League Against Rheumatism (EULAR) disease activity score in adult onset Stiull's Disease (DAVID) project supported by EULAR and convened by Giacomelli could provide the missing instrument and facilitate clinical studies is AOSD.

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Handling editor Josef S Smolen

Contributors CK undertook the primary duties in writing, editing and submitting the response letter. JL advised on statistical analysis of data. JZ revised the letter. EF revised the letter critically, advised on additional information to statistical analysis, references, adding important information to the letter.

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 CK has received personal advisory board and congress fees from Novartis, Pfizer, Roche and Sobi. EF has received advisory board and speaker fees from Novartis, Roche, Sobi, Lilly, Pfizer, Abbvie, BMS, MSD and Sanofi.

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 Kedor C, Listing J, Zernicke J, *et al*. *Ann Rheum Dis* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/annrheumdis-2020-218143

Received 5 June 2020
Revised 9 June 2020
Accepted 10 June 2020

Linked

► http://dx.doi.org/10.1136/annrheumdis-2020-218032

Ann Rheum Dis 2020;**0**:1–2. doi:10.1136/annrheumdis-2020-218143

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REFERENCES

1 Ruscitti P, Stamm R G. Changing the outcome measures, changing the results? The urgent need of a specific disease activity score to adult onset Still's disease. *Ann Rheum Dis* 2020.

2 Kedor C, Listing J, Zernicke J, *et al*. Canakinumab for Treatment of Adult-Onset Still's Disease to Achieve Reduction of Arthritic Manifestation (CONSIDER): phase II, randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial. *Annals of the Rheumatic Diseases* 2020;annrheumdis-2020-217155.
3 Nirmala N, Brachat A, Feist E, *et al*. Gene-Expression analysis of adult-onset still's disease and systemic juvenile idiopathic arthritis is consistent with a continuum of a single disease entity. *Pediatr Rheumatol Online J* 2015;13:50.
4 Pouchot J, Sampalis JS, Beaudet F, *et al*. Adult still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine* 1991;70:118–36.
5 Kaneko Y, Kameda H, Ikeda K, *et al*. Tocilizumab in patients with adult-onset still's disease refractory to glucocorticoid treatment: a randomised, double-blind, placebo-controlled phase III trial. *Ann Rheum Dis* 2018;77:1720–9.
6 Rau M, Schiller M, Krienke S, *et al*. Clinical manifestations but not cytokine profiles differentiate adult-onset still's disease and sepsis. *J Rheumatol* 2010;37:2369–76.
7 Ruscitti P, Cipriani P, Masedu F, *et al*. Adult-Onset still's disease: evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. *BMC Med* 2016;14:194.
8 Gabay C, Fautrel B, Rech J, *et al*. Open-label, multicentre, dose-escalating phase II clinical trial on the safety and efficacy of tadekinig alfa (IL-18BP) in adult-onset Still's disease. *Ann Rheum Dis* 2018;13:annrheumdis-2017-212608–7.