Reply to eLetter from Cai et al.

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We would like to thank Cai *et al.* [1]for the interest they have expressed in our recently published article « Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial»[2] and the ARD editorial team to give us the opportunity to address their comments.

First, Cai et al pinpoint another reason behind the lack of statistical significance of our primary outcome, i.e. the shortage of our sample size. As suggested by Cai et al we have performed a post-hoc power calculation based on our estimated results (and sample), with p1= 0.47 and p2 = 0.36 (p1 and p2 being the proportion of responders in the active arm and control arms, respectively) and an α risk of 5%, the post-hoc-calculated power is 29.9%. However, we have also performed a post-hoc power calculation based on the sample size that we aimed for (i.e. 116 patients per arm) and the results observed in the trial: with an α risk of 5% and the p1 and p2 mentioned above, the power was still 41%, i.e. very low. Indeed, in our trial, the difference across arms was only 11.6%; the post-hoc calculation of the sample size needed based on this difference in a classic randomized clinical trial , with an alpha risk of 5% and a power set at 80%, would be 303 patients per arm, i.e. 606 patients in total; in the particular case of a

Cluster-randomized clinical trial (i.e. after multiplying the estimated sample size by 1.45 ,e.g. the "inflation factor" defined as 1 + (m-1)*ρ where m is equal to the size of the cluster (in our study, the number of patients per centre = 10) and ρ is the intra-cluster correlation, 0.05.[3]) the sample needed to take the cluster-randomised design into account would be of 880 patients, i.e. 440 patients per arm.

Cai et al also suggest to present the 95% confidence interval around the point-estimate of the primary and secondary outcomes. Here below we present a table with the estimates at the last visit and their 95% confidence intervals. It is worth of mentioning that in the manuscript we modelled the change in the outcomes over time, not only the estimate at the last visit.

	Estimated outcomes at week 48 and 95% Confidence internal	
	TC/T2T	**UC**
ASAS HI significant improvement	47.3% (95% CI 36.2% - 59.0%)	36.1% (95% CI 25.6% - 46.6%)
ASDAS LDA	76.5% (95% CI 67.2% - 85.8%)	59.5% (95% CI 48.7% - 70.3%)
ASDAS ID	25.9% (95% CI 16.3%-35.5%)	18.7% (95% CI 10.2%-27.2%)
ASDAS CII	61.2% (95% CI 50.5%- 71.9%)	46.0% (95% CI 35.1%; 56.9%)
ASDAS MI	16.5% (95% CI 8.4%- 24.6%)	14.9% (95% CI 7.1%-22.7%)
ASAS40	52.3% (95% CI 41.4%; 63.2%)	34.7% (95% CI 24.3%-45.1%)
ASAS20	94.9% (95% CI 90.1%-99.7%)	85.9% (95% CI 78.0%-93.0%)
BASDAI 50	79.0% (95% CI 70.1%-87.9%)	43.8% (95% CI 32.9%-54.7%)
Physician Global (0-10)	2.0 (95% CI 1.9 -2.1)	1.8 (95% CI 1.78- 1.8)
CRP (mg/L)	3.9 (95% CI 3.6 - 4.2)	3.5 (95% CI 3.2 - 3.8)
BASG (0-10)	2.6 (95% CI 2.5 - 2.7)	3.4 (95% CI 3.3 - 3.5)
BASFI (0-10)	1.7 (95% CI 1.6 - 1.8)	2.4 (95% CI 2.3- 2.5)
EQ5D-5L	0.7 (95% CI 0.7- 0.7)	0.8 (95% CI 0.8 to 0.8)
ASAS-NSAID score	1.5 (95% CI 1.0 – 2.0)	-4.9 (95% CI -5.5 ; -4.3)

Footnote: Abbreviations: ASAS-HI: ASAS health index; ASDAS: Ankylosing Spondylitis Disease Activity Score; LDA: low disease activity; ID: inactive disease; CII= Clinically Important Improvement; MI: Major improvement; BASDAI= Bath Ankylosing Spondylitis Disease Activity Index; EQ5D: EuroQol 5 domains and 5 levels. NS: non-significant

Cai et al also refer to contamination bias, which they admit to be almost unavoidable in pragmatic trials. We can only agree with this remark, and indeed that was the reason behind the rationale to run a cluster-based randomized trial: i.e. centres underwent randomization, not patients. This meant that rheumatologists from "UC" centres were not aware of the "T2T/TC" algorithm, and even participated in separate study meetings during the whole duration of the study. Nevertheless, as pointed out in our manuscript, all participating centres were axSpA expert centres and many of them have participated in the formulation of the recommendations that fed the TICOSPA algorithm[4,5] and thus it is highly likely that many of the investigators from the UC were indeed consciously or unconsciously applying a TC/T2T approach in their clinics.

Finally, Cai et al suggest also to look, particularly for continuous outcomes at the changes from baseline to week 48. This is indeed exactly what was done: mixed models for repeated measures were applied to estimate the changes on the outcomes over time in both groups.

Competing interests:

Dr. Molto reports grants from UCB during the conduct of the study; personal fees from Abbvie, grants and personal fees from UCB, personal fees from BMS, grants and personal fees from Pfizer, grants and personal fees from MSD, personal fees from Novartis, personal fees from Gilead, personal fees from Lilly, outside the submitted work; .

Dr. van der Heijde reports personal fees from AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Cyxone, Daiichi, Eisai, Eli-Lilly, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, UCB Pharma, outside the submitted work; and Director of Imaging Rheumatology bv. Dr. Van den Bosch reports personal fees from Abbvie, personal fees from Celgene, personal fees from Eli Lilly, personal fees from Galapagos, personal fees from Janssen, personal fees from Novartis, personal fees from Pfizer, personal fees from UCB, outside the submitted work.

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Contributorship statement:

- AM, analysis of the data
- AM, drafted the manuscript
- All authors critically reviewed the results and contributed to the interpretation of data
- All authors read and approved the final manuscript, as well as the answer to the reviewers**.**

Data sharing statement: the relevant anonymised patient level data can be available upon reasonable request

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Ethics information: the study was approved by the ethics committee CPP Ile de France III (Réf. Am7156-1-S.C.3394). All patients gave their informed consent.

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References:

1 Cai G, Peng X. Correspondence on 'Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial' by Molto et al. Ann Rheum Dis 2021.

2 Molto A, López-Medina C, Van den Bosch FE, *et al.* Efficacy of a tight-control and treat-to-target strategy in axial spondyloarthritis: results of the open-label, pragmatic, cluster-randomised TICOSPA trial. *Ann Rheum Dis* Published Online First: 6 May 2021. doi:10.1136/annrheumdis-2020-219585

3 Hemming K, Girling AJ, Sitch AJ, *et al.* Sample size calculations for cluster randomised controlled trials with a fixed number of clusters. *BMC Med Res Methodol* 2011;**11**:102. doi:10.1186/1471-2288-11-102

4 Smolen JS, Braun J, Dougados M, *et al.* Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Ann Rheum Dis* 2014;**73**:6–16. doi:10.1136/annrheumdis-2013-203419

5 van der Heijde D, Ramiro S, Landewé R, *et al.* 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. *Ann Rheum Dis* 2017;**76**:978–91. doi:10.1136/annrheumdis-2016-210770