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SHORT REPORT

Comparison of established and preliminarily proposed ASAS MRI working group cut-offs for inflammatory MRI lesions in the sacroiliac joints in radiographic and non-radiographic axial spondyloarthritis

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ABSTRACT

Background A consensus definition for active sacroiliitis by MRI, mentioned in the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axial spondyloarthritis (axSpA), was published in 2009 and included a qualitative and quantitative MRI cut-off component. In 2021, updates to the quantitative component were preliminarily proposed. This post hoc analysis of part A of the phase 3 open-label C-OPTIMISE study (NCT02505542) explores the differences by applying the 2009 and preliminary 2021 inflammatory cut-offs on clinical outcomes of axSpA patients treated with certolizumab pegol.

Methods Baseline MRI scans were used to classify 657 patients as MRI+ or MRI– according to the quantitative components of the 2009 and preliminary 2021 MRI cut-offs for inflammatory lesions. Clinical outcomes, including ASAS ≥40% improvement (ASAS40), Ankylosing Spondylitis Disease Activity Score and Bath Ankylosing Spondylitis Disease Activity Index, were reported to week 48.

Results Across all analysed outcomes, 2009 MRI+ and preliminary 2021 MRI+ subgroups showed similar results. Notably, clinical outcomes for the discordant group (2009 MRI+but preliminary 2021 MRI– group; 53/657 [8.1%]) were close to those seen in MRI– patients according to either 2009 or preliminary 2021 inflammatory cut-offs, and notably different from the totality of MRI+ subgroups.

Conclusion This analysis suggests that the preliminary 2021 cut-offs for MRI inflammatory lesions may slightly increase the specificity of the quantitative part of the 2009 MRI inflammatory lesion definition. The effects of the updated MRI cut-offs need to be assessed on the basis of efficacy outcomes and with the inclusion of aspects of structural changes.

Trial registration number NCT02505542.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Assessment of SpondyloArthritis International Society (ASAS)/Outcomes Measures in Rheumatology working group published a consensus definition for 'active sacroiliitis by MRI' in 2009.

⇒ However, there are concerns about insufficient specificity of the quantitative component of the 2009 MRI cut-offs so new MRI cut-offs for inflammatory and structural lesions were, therefore, proposed in 2021.

WHAT THIS STUDY ADDS

⇒ We explored the differences in the quantitative component of the 2009 and preliminarily proposed 2021 ASAS cut-offs for active sacroiliitis by MRI on clinical outcomes of patients with axial spondyloarthritis treated with certolizumab pegol.

⇒ Our analysis suggests that the preliminary 2021 ASAS cut-offs for MRI inflammatory lesions may increase the specificity of the quantitative part of the 2009 definition.

⇒ However, the effects on the clinical outcomes of the study did not differ substantially based on the cut-offs used for patient selection.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings could have important implications for the recruitment of patients during trial enrolment.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease, affecting the spine and sacroiliac joints (SIJ).[1] axSpA can be classified as radiographic (r-axSpA, or ankylosing spondylitis [AS]) or non-radiographic (nr-axSpA), subject to the presence or absence of definite radiographic sacroiliitis fulfilling the modified New York classification criteria.[2 3]

Several treatments have been developed to manage axSpA. In many patients, after the

failure of non-steroidal antirheumatic drugs, improvements can be reached using treatment with tumour necrosis factor inhibitors (TNFis). This may include certolizumab pegol (CZP), a PEGylated Fc-free TNFi.[4] CZP is indicated for the treatment of adult patients with active axSpA by several regulatory authorities, and it is the only Food and Drug Administration (FDA)-approved TNFi for both AS and nr-axSpA.[5]

Magnetic resonance imaging (MRI) can provide objective evidence of inflammatory lesions in patients with axSpA, even in the absence of radiographic sacroiliitis. For this reason, 'active sacroiliitis by MRI' is one of the key features in the Assessment of SpondyloArthritis International Society (ASAS) classification criteria for axSpA.[6] The ASAS/Outcomes Measures in Rheumatology working group published a consensus definition for 'active sacroiliitis by MRI' in 2009.[6] This definition had a qualitative component (bone marrow oedema [BME] highly suggestive of axSpA) and a quantitative component (one BME lesion on two consecutive MRI slices or more than one BME on a single slice; '2009 MRI cut-offs'). The MRI definition was revisited by the ASAS working group in 2016. This study pointed out the qualitative impression of MRI inflammatory lesions reflecting sacroiliitis, and that MRI always has to be reviewed in the wider clinical context, but maintained the 2009 cut-offs as a non-strict recommendation.[7]

However, concerns remained about insufficient specificity of the quantitative component of the 2009 MRI cut-offs, as it was reported that false-positive BME lesions meeting the 2009 definition may be observed in 20%–40% of healthy individuals as well as in those with non-specific back disorders.[8–13] New MRI cut-offs for inflammatory (BME) and structural lesions were, therefore, proposed in 2021. Unlike the 2009 cut-offs which were based on expert opinion, the 2021 cut-offs were data derived; it was suggested that the cut-offs that best reflect a definitive inflammatory lesion typical of axSpA were either ≥4 SIJ quadrants with BME at any location, or at the same location in ≥3 consecutive slices ('preliminary 2021 MRI cut-offs'; figure 1).[14]

There is some evidence that introducing more stringent MRI cut-offs could contribute to higher specificity for axSpA classification without substantial decrease in sensitivity.[14] However, to our knowledge, no study has yet compared the preliminary 2021 cut-offs with the 2009 cut-offs in a large clinical trial setting.

In this post hoc analysis, we investigate the effect of applying the preliminary 2021 cut-offs vs 2009 cut-offs for inflammatory MRI lesions on the clinical outcomes of patients with axSpA treated with CZP in part A of the C-OPTIMISE trial.

METHODS

C-OPTIMISE (ClinicalTrials.gov identifier: NCT02505542) was a two-part phase 3b multicentre study in adult patients with early active axSpA.[15] From baseline to week 48 (part A) patients received open-label CZP 200 mg every 2 weeks.

Key patient inclusion criteria were being 18–45 years of age, having a clinical diagnosis of adult-onset axSpA, meeting ASAS classification criteria, symptom duration ≥3 months and <5 years, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ≥4 and spinal pain ≥4 on a 0–10 numerical rating acale. Baseline MRI scans of the SIJ were performed at the screening visit and assessed centrally. For part A, MRI scans were assessed by one reader and classified according to the 2009 definition, with consideration of the qualitative aspect of the lesions.[7]

This post hoc analysis includes patients from C-OPTIMISE part A who had an available baseline MRI reading. In this analysis, we used the results of the efficacy scoring campaign to reclassify patients as MRI-positive (MRI+) or MRI-negative (MRI−) according to the quantitative aspect of either the 2009 or preliminary 2021 MRI cut-offs for inflammatory lesions only; structural lesions were not obtained in the original scorings and so could not be analysed.

MRI positivity according to the 2009 definition was defined as BME highly suggestive of axSpA based on T1-weighted (T1W) and Short-TI Inversion Recovery (STIR) scans (ie, the qualitative component as published in 2016[7]) in addition to two positive BME scores in a single slice, or one BME in the same location in two consecutive slices. MRI positivity according to the preliminary 2021 definition was defined as BME highly suggestive of axSpA (ie, the same qualitative component as above) in addition to four SIJ quadrants with BME at any location, or one BME in the same quadrant in three consecutive slices (figure 1).

Patients classified as 2009 MRI+ but 2021 MRI− were termed the 'discordant group' since the preliminary 2021 cut-offs are more stringent than the 2009 cut-offs; due to the nature of the analysis based on patient recruitment, it was not possible to score 2009 MRI− but 2021 MRI+.

We report the following outcomes to week 48, stratified by axSpA diagnosis (nr-axSpA or r-axSpA) and baseline MRI classification according to either 2009 or preliminary 2021 quantitative cut-offs: ASAS ≥40% improvement (ASAS40) response, BASDAI change from baseline (CfB), Ankylosing Spondylitis Disease Activity Score (ASDAS) CfB, C reactive protein (CRP) CfB and ASDAS disease states.

In patients with elevated CRP at baseline (defined as CRP greater than the upper limit of normal [ULN]), we also report ASAS40 response, stratified by axSpA diagnosis and baseline MRI classification.

For continuous outcomes, p values were calculated using a t-test; for dichotomous outcomes, p values were calculated using a McNemar test. Due to the post hoc nature of this study, reported p values were not prespecified and are, therefore, nominal and should be interpreted with caution. Missing ASAS40 response data were imputed using non-responder imputation; missing

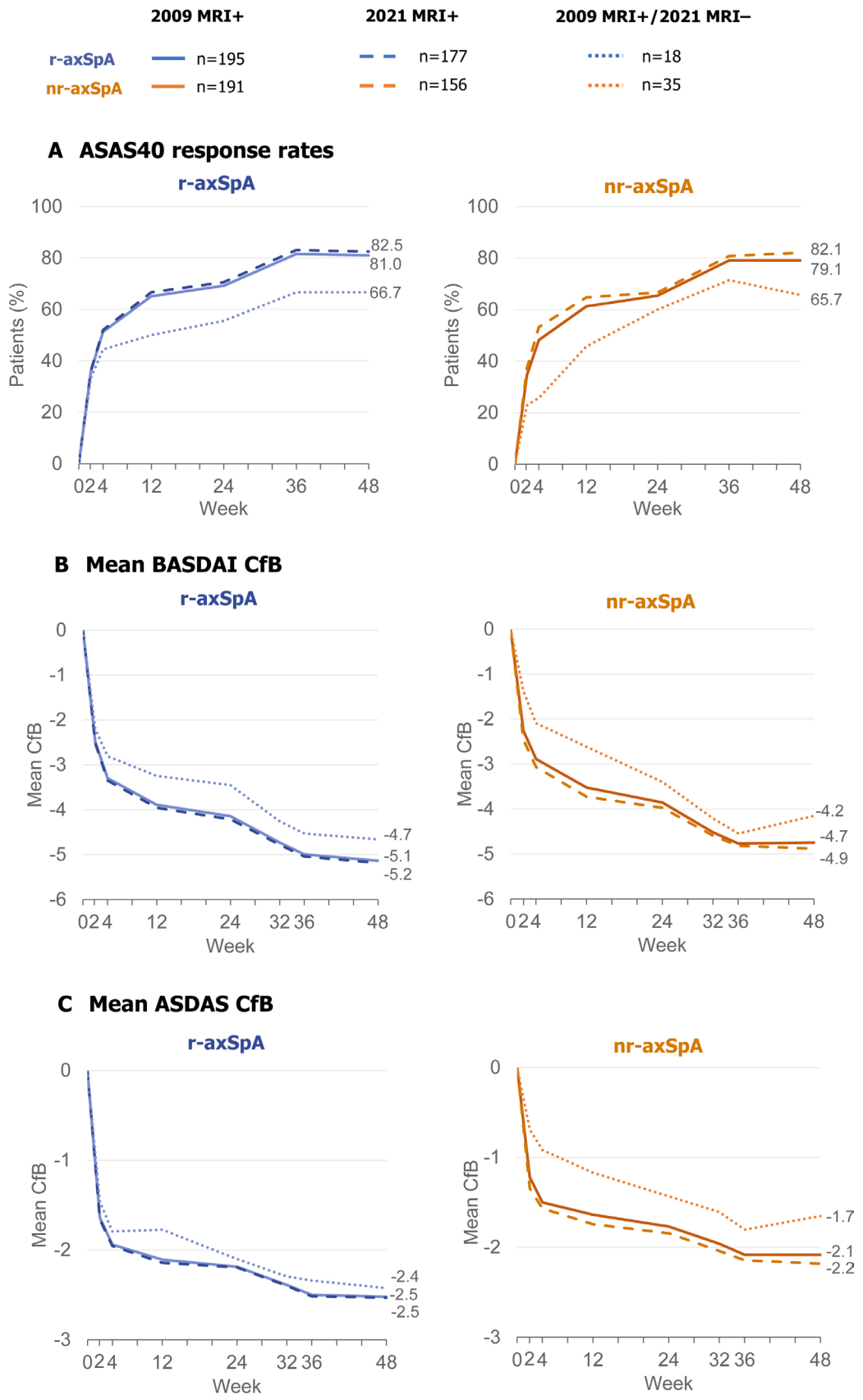

Figure 1 ASAS definition of active sacroiliitis by MRI, including 2009 and preliminary 2021 MRI cut-offs for inflammatory lesions. Sources: Rudwaleit *et al*,[6] Lambert *et al*,[7] Maksymowych *et al*.[14] ASAS, Assessment of SpondyloArthritis International Society; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CfB, change from baseline; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axSpA; r-axSpA, radiographic axSpA.

Table 1 Patient demographics and baseline characteristics stratified by 2009 and preliminary 2021 MRI cut-offs for inflammatory lesions

	2009 MRI+ N=386 (58.8%)		2021 MRI+ N=333 (50.7%)		2009 MRI+/2021 MRI– N=53 (8.1%)	
	r-axSpA (n=195)	nr-axSpA (n=191)	r-axSpA (n=177)	nr-axSpA (n=156)	r-axSpA (n=18)	nr-axSpA (n=35)
Age, years, mean (SD)	32.7 (6.8)	31.9 (7.0)	32.7 (6.9)	31.1 (6.5)	32.4 (5.5)	35.4 (8.0)
Male, n (%)	154 (79.0)	123 (64.4)	138 (78.0)	109 (69.9)	16 (88.9)	14 (40.0)
CRP, mg/L, mean (SD)	17.3 (17.7)	11.0 (18.5)	17.1 (17.1)	11.5 (19.0)	19.6 (23.3)	8.6 (15.9)
HLA-B27 positive, n (%)	169 (86.7)	148 (77.5)	153 (86.4)	127 (81.4)	16 (88.9)	21 (60.0)
Symptom duration, years						
Mean (SD)	3.5 (2.1)	2.9 (1.6)	3.6 (2.2)	2.9 (1.6)	3.2 (1.3)	3.2 (1.8)
Median (range)	3.9 (0.2–19.4)	2.9 (0.2–8.4)	4.0 (0.2–19.4)	2.9 (0.2–7.9)	3.2 (0.6–5.0)	3.3 (0.3–8.4)
Disease duration, years						
Mean (SD)	2.2 (1.6)	1.9 (1.6)	2.2 (1.7)	1.8 (1.5)	2.5 (1.6)	2.1 (1.6)
Median (range)	1.9 (0.2–5.6)	1.2 (0.2–5.0)	1.8 (0.2–5.6)	1.2 (0.2–5.0)	2.8 (0.2–4.6)	2.0 (0.2–5.0)
BASDAI, mean (SD)	6.8 (1.4)	6.6 (1.4)	6.8 (1.4)	6.5 (1.4)	6.2 (1.7)	6.9 (1.4)
ASDAS, mean (SD)	4.0 (0.8)	3.5 (0.8)	4.0 (0.7)	3.5 (0.8)	3.8 (1.0)	3.5 (0.7)
ASDAS disease state, n (%)						
ID	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LDA	2 (1.0)	4 (2.1)	1 (0.6)	4 (2.6)	1 (5.6)	0 (0)
HDA	52 (26.7)	95 (49.7)	45 (25.4)	78 (50.0)	7 (38.9)	17 (48.6)
vHDA	141 (72.3)	92 (48.2)	131 (74.0)	74 (47.4)	10 (55.6)	18 (51.4)

Patient demographics and baseline characteristics for patients categorised as MRI—according to the 2009 and preliminary 2021 MRI cut-offs for inflammatory lesions are given in online supplemental table 1.

ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C reactive protein; CRP, C-reactive protein; HDA, high disease activity; HLA-B27, human leukocyte antigen B27; ID, inactive disease; LDA, low disease activity; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axSpA; r-axSpA, radiographic axSpA; SD, standard deviation; vHDA, very high disease activity.

ASDAS disease states, ASDAS CfB, BASDAI CfB and CRP CfB data were imputed using the last observation carried forward.

RESULTS

Of the 736 patients enrolled into C-OPTIMISE, baseline MRI data were available for 657/736 (89.3%) patients, 358/657 (54.5%) of whom had r-axSpA and 299/657 (45.5%) nr-axSpA. 386/657 patients (58.8%, 195 patients with r-axSpA and 191 with nr-axSpA) were classified as MRI+ according to 2009 cut-offs compared with 333/657 patients (50.7%, 177 with r-axSpA and 156 with nr-axSpA) using preliminary 2021 cut-offs; the discordant group (8.1% [53/657] of the entire cohort) comprised 18/358 (5.0%) patients with r-axSpA and 35/299 patients (11.7%) with nr-axSpA (table 1).

Only a slightly higher proportion of patients fulfilling the preliminary 2021 MRI+ inflammatory lesion cut-offs achieved ASAS40 at week 48 (146/177 [82.5%] for r-axSpA and 128/156 [82.1%] for nr-axSpA) vs the 2009 MRI+ patients (158/195 [81.0%] for r-axSpA [p<0.001] and 151/191 [79.1%] for nr-axSpA [p<0.001]). Compared with the totality of MRI+ subgroups, a notably lower proportion of patients in the discordant group achieved ASAS40 at week 48 (12/18 [66.7%] for r-axSpA and 23/35 [65.7%] for nr-axSpA; figure 2).

At week 48, mean change from baseline was similar in patients fulfilling the preliminary 2021 MRI+ inflammatory lesion cut-offs vs the 2009 MRI+ patients (mean BASDAI CfB: −5.2 vs −5.1 for r-axSpA [p=0.837] and −4.9 vs −4.7 for nr-axSpA [p=0.613]; mean ASDAS CfB: −2.5 vs −2.5 for r-axSpA [p=0.93] and −2.2 vs −2.1 for nr-axSpA [p=0.404]; figure 2). Outcomes at week 48 for the discordant group were notably different from the 2009 or 2021 MRI+ groups (online supplemental materials).

At week 48, a lower proportion of patients in the discordant group achieved ASDAS inactive disease (ASDAS<1.3) compared with the totality of the MRI+ subgroups; differences between subgroups were more notable among patients with nr-axSpA than with r-axSpA (discordant group: 15/35 [42.9%] nr-axSpA, 10/18 [55.6%] r-axSpA; 2009 MRI+: 112/191 [58.6%] nr-axSpA, 118/195 [60.5%] r-axSpA; preliminary 2021 MRI+:

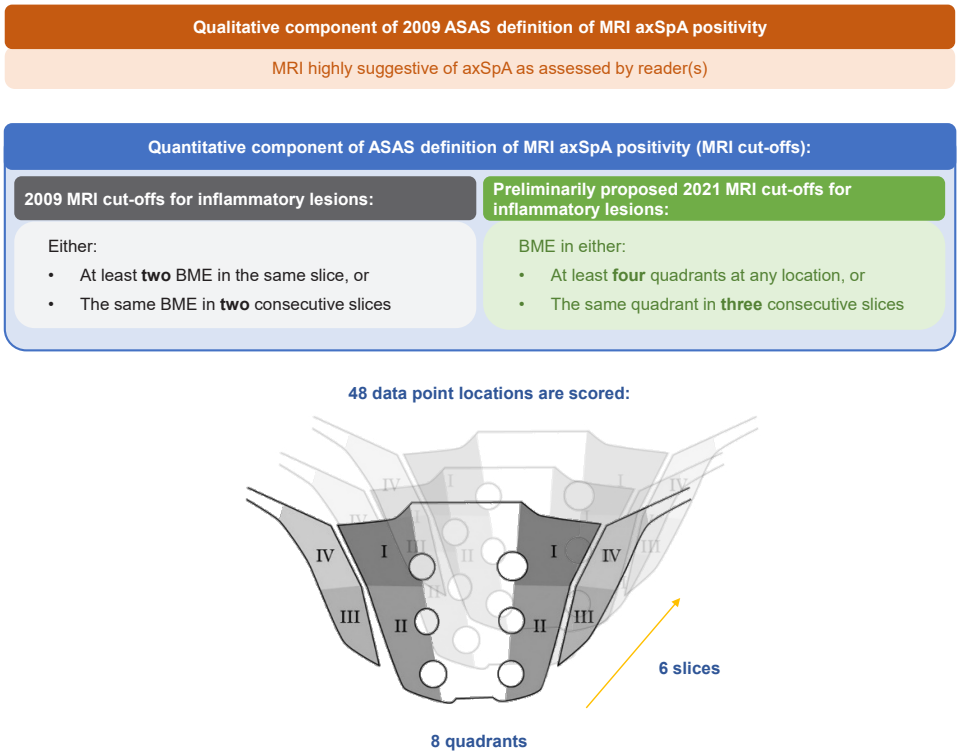

Figure 2 ASAS40 response rates, mean BASDAI CfB and mean ASDAS CfB to week 48 stratified by applying 2009 and preliminary 2021 MRI cut-offs for inflammatory lesions (open-label population). Missing ASAS40 response data were imputed using NRI; missing BASDAI CfB and ASDAS CfB data were imputed using LOCF. ASAS, Assessment of SpondyloArthritis International Society; ASAS40, ASAS ≥40% improvement; ASDAS, Ankylosing Spondylitis Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BME, bone marrow oedema; CfB, change from baseline; LOCF, last observation carried forward; MRI, magnetic resonance imaging; nr-axSpA, non-radiographic axSpA; NRI, non-responder imputation; r-axSpA, radiographic axSpA.

97/156 [62.2%] nr-axSpA, 108/177 [61.0%] r-axSpA; online supplemental figure 3).

Outcomes in patients without elevated CRP at baseline

Of the 386 patients from the primary analysis classified as MRI+ according to 2009 cut-offs, 216 (56.0%) had CRP≤ULN at baseline, of whom 85/216 (39.4%) had r-axSpA and 131/216 (60.6%) had nr-axSpA. Of the 333 patients from the main analysis classified as MRI+ according to preliminary 2021 cut-offs, 180 (54.1%) had CRP≤ULN at baseline, 76/180 (42.2%) of whom had r-axSpA and 104/180 (57.8%) nr-axSpA.

In those without elevated CRP at baseline, fewer patients with r-axSpA achieved ASAS40 at week 48 compared with those with elevated CRP (2009 MRI+: 76.5% vs 84.5%; 2021 MRI+: 77.6% vs 86.1%). However, in agreement with the results of the primary analysis, only a slightly higher proportion of patients fulfilling the preliminary 2021 MRI+ compared with the 2009 inflammatory lesion cut-offs achieved ASAS40 at week 48 (r-axSpA: 59/76 [77.6%] vs 65/85 [76.5%, p<0.001]; nr-axSpA: 85/104 [81.7%] vs 103/131 [78.6%; p<0.001]). Compared with the totality of MRI+ subgroups, a notably lower proportion of patients in the discordant group with CRP≤ULN achieved ASAS40 at week 48 (r-axSpA: 6/9 [66.7%]; nr-axSpA: 18/27 [66.7%]; online supplemental figure 4).

DISCUSSION AND CONCLUSIONS

Accurate diagnosis and classification of axSpA patients is important for appropriate trial enrolment, and MRI identification of inflammatory lesions forms a key part of the clinical assessment. Therefore, a reliable definition of MRI positivity for axSpA is needed.

This is the first study to compare the quantitative components of the preliminary 2021 cut-offs with the 2009 cut-offs for inflammatory lesions on MRI SIJ in a large clinical trial setting. The results seen for the MRI+ groups based on the 2009 and preliminary 2021 quantitative cut-offs were similar across all clinical outcomes, both for r-axSpA and nr-axSpA (figure 2). Similarly, the outcomes for the MRI– groups based on either quantitative cut-offs were comparable (online supplemental materials). Overall, a small group (<8.1%) of discordant (2009 MRI+ but 2021 MRI–) patients were identified in this analysis. Across all outcomes, this discordant group was similar to the patients classified as MRI– by either 2009 or preliminary 2021 quantitative cut-offs, but notably different from the totality of MRI+ patients (figure 2, online supplemental materials). These findings support the argument that the quantitative components of the 2009 cut-offs are associated with a lower specificity and that the more stringent preliminary 2021 quantitative

cut-offs may be able to produce higher specificity in the depiction of patients with inflammatory MRI lesions. Importantly, the clinical outcomes of the patients classified using 2009 or 2021 inflammatory lesion quantitative cut-offs were similar apart from the discordant group, suggesting that the majority (91.9%) of patients recruited in C-OPTIMISE based on the 2009 criteria had substantial inflammation on MRI, and therefore, also fulfilled the preliminary 2021 MRI cut-offs. This is likely the case since the qualitative component (BME highly suggestive of axSpA) was applied during MRI reading. Nevertheless, it is important to mention that for both the eligibility and the efficacy assessment of the images of the present study, both the STIR (for the depiction of the inflammatory lesions) and the T1W (for the structural lesions in the context of axSpA) sequences were considered for qualitative evaluation of the images. This may have led to the more stringent evaluation of the accounted BME lesions since the images had to meet the qualitative component (both during eligibility screening and during the efficacy analysis).

There has been debate in the literature around the difficulty in diagnostic distinction between nr-axSpA and other undefined lower back pain due to the low specificity of the 2009 classification criteria.[16] Classification criteria should not be applied in the context of solely back pain—clinical diagnosis of axSpA also entails careful consideration and exclusion of differential diagnoses, a process which is not captured by classification criteria. These criteria are intended to classify patients in clinical trials, rather than for diagnosis. In clinical practice, diagnosis of axSpA relies on skilful pattern recognition rather than imaging alone.[17] A previous study found that applying the criteria '≥5 fatty lesions and/or erosions' on MRI-SIJ, as well as '≥5 spinal inflammatory lesions' or '≥5 spinal fatty lesions' was highly specific while still assuring an acceptable and useful level of discrimination between patients with and patients without spondyloarthritis.[18] In future analyses, the combination of inflammatory and structural MRI-SIJ lesions, as proposed in full by the preliminary definitions discussed here, should be considered.[14]

A limitation of this study is that part A of the C-OPTIMISE study was open-label so it was not possible to determine how differences in patient selection based on the different MRI definitions would have affected treatment group discrimination between active treatment and placebo, especially for nr-axSpA patients. Patients in C-OPTIMISE also had a symptom duration <5 years, which is less than that observed in other trials in patients with axSpA. Furthermore, T1W MRIs, although obtained and considered during assessment, were not scored in this study and we, therefore, cannot provide the effect of assessment of structural changes in the reported outcomes.

In conclusion, the findings of this post hoc analysis suggest a potential to improve the specificity of the quantitative part of the 2009 MRI definition of inflammatory lesions, which may be possible with the preliminary 2021 cut-offs. However, since this finding was shown in only a small proportion of the patients included here, this result needs to be reassessed in future prospective studies due to the possible inclusion of false positive patients recruited during trial enrolment. The impact of postinflammatory, structural lesions, as well as the consequences of any new cut-off proposals, on the effect of treatment remains to be clarified in future studies.

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Competing interests XB: Speakers' bureau: AbbVie, BMS, Chugai, Eli Lilly, Galapagos, Gilead, MSD, Novartis, Pfizer, UCB Pharma; Paid instructor for AbbVie, BMS, Chugai, Eli Lilly, Galapagos, Gilead, MSD, Novartis, Pfizer, UCB Pharma; Consultant of AbbVie, BMS, Chugai, Eli Lilly, Galapagos, Gilead, MSD, Novartis, Pfizer, UCB Pharma. PMM: Personal fees from: AbbVie, Bristol Myers Squibb, Celgene, Eli Lilly, Galapagos, GSK, Janssen, MSD, Novartis, Orphazyme, Pfizer, Roche and UCB Pharma. LB, BH: Employee and stockholder of UCB Pharma. MK, TK: Employee of UCB Pharma. RT: Veramed statistical consultant for UCB Pharma. MR: Speakers' bureau from: AbbVie, Boehringer Ingelheim, Chugai, Eli Lilly, Janssen, Novartis, Pfizer, UCB Pharma; Consultant of AbbVie, Eli Lilly, Novartis, UCB Pharma.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the study protocol, amendments and patient informed consent were reviewed by a national, regional or Independent Ethics Committee (IEC) or Institutional Review Board (IRB). This study was conducted in accordance with the current version of the applicable regulatory and International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP) requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki and the local laws of the countries involved. Participants gave informed consent to participate in the study before taking part.

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