Eligibility Rates in Axial Spondyloarthritis Clinical Trials Based on Imaging Criteria

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Phase 2 and phase 3 trials in Axial Spondyloarthritis (AxSpA) require the assessment of the sacro-iliac joint (SIJ) either by X-ray or MRI or both in conjunction to establish if the disease is non-radiographic (nr-AxSpA) or radiographic ankylosing spondylitis (AS).

Therefore, for prospective trial design it is important to understand the percentages of subjects likely to be deemed eligible by central imaging review and how many subjects will screen-fail for either AS (mNY+) or nr-AxSpA (mNY-).

INTRODUCTION

Axial Spondyloarthritis (AxSpA) encompasses both non-radiographic (nr-AxSpA) as well as radiographic ankylosing spondylitis (AS) which displays structural changes at the sacroiliac joint (SIJ).[1,2]

The currently accepted modified New York (mNY) criterion includes a radiographic assessment of the SI joint using an AP pelvis X-ray with a good view of the sacroiliac joints.[3]

In clinical trials the subjects deemed locally to be good candidates either for an AS or an nr-AxSpA trial have an SIJ X-ray examination read centrally to determine eligibility (mNY+ for AS and mNY- for nr-AxSpA).

For nr-AxSpA trials, an MRI examination of the SIJ is also obtained to confirm bone marrow edema (BMO) or osteitis per ASAS/OMERACT guidelines;[4] thus, radiographically mNY- subjects with positive MRI (MRI+) for edema are deemed eligible for these trials.

Van den Berg et al[5] describing the results from the DESIR cohort showed that the agreement between local and central reading of sacroiliac joints on plain pelvic x-rays for mNY status is moderate at best and underscored the prevalent phenomenon of site-central discrepancies for this read.

Additionally, van den Berg et al[5] also suggested the necessity of reevaluating the role of radiographic sacroiliitis as a diagnostic criterion for AxSpA.

METHODS

The mNY criteria defines sacroiliitis grades bilaterally ≥Grade 2 or unilaterally as ≥Grade 3 as being modified New York positive (mNY+) and grade 2 unilaterally/grade 0 or 1 unilaterally or less than 2 bilaterally as modified New York negative (mNY-).[3]

Anterio-posterior pelvis (AP Pelvis) x-ray images acquired per centrally provided image acquisition guidelines were analyzed by central review for mNY status in both the right and left SIJ.[3]

According to the ASAS/OMERACT definition, the presence of bone marrow edema (BMO) or osteitis that is highly suggestive of SpA and located in the typical anatomical areas (subchondral or periarticular bone marrow) is required for a positive assessment (MRI+).

The presence of edema (MRI+) is further defined as either more than one bone marrow edema lesion on one slice or a lesion that is present on at least two consecutive slices.

Oblique coronal T1 and STIR sequences of the SIJ acquired per centrally provided image acquisition guidelines were analyzed by central review for having bone marrow lesions (BMO).

A total of 4,736 subjects from seven multi-center clinical trials were assessed for mNY +/- and/or MRI+/-.

- 2 studies (n=1,419) had both an AS and nr-AxSpA cohort and subjects were recruited according to mNY+ (for AS cohort) or mNY- / MRI+ (for nr-AxSpA cohort).
- 3 AS studies (n=821) had mNY+ as the imaging inclusion criteria
- 2 nr-AxSpA studies (n=2496) had mNY- / MRI+ as the imaging inclusion criteria.

X-ray data from the two studies (n=1,419) which had both an AS and nr-AxSpA cohort were used to define the denominators for calculating percentages of "eligible" vs "not eligible" for either of the AS or nr-AxSpA studies based on mNY status, in addition to the total number of subjects for these studies. Therefore, the total subjects analyzed to calculate mNY status was the following:

- AS studies: 821 + 1,419 = 2,240 (2 subjects were deemed "Not Evaluable" by central readers)
- nr-AxSpA studies: 2,496 + 1419 = 3,915 (3 subjects were deemed "Not Evaluable" by central readers)

The read model was either a single or double read. Percentage of subjects deemed either eligible for AS (mNY+) or nr-AxSpA (mNY- / MRI+) was calculated.

We also calculated the percentage of mNY- subjects who were then assessed as MRI- or MRI+ by ASAS OMERACT criteria. A total of 2,635 subjects deemed mNY- by radiographic review were also assessed for the presence of edema and osteitis in the SIJ by MRI (T1 and STIR oblique coronal sequences).

RESULTS

Table 1 lists the mNY scores applied for each SIJ and used in the data presented.

SCORE	FEATURE
0	Normal
1	Suspicious but not definite
2	Minimal; some sclerosis, minimal erosion, no marked joint space narrowing
4	Moderate; definite sclerosis, both sides of the joint with erosions and/or joint space change
5	Ankylosis; complete obliteration of the SIJ with or without sclerosis

Table 1: The modified New York sacroiliitis assessment criteria

Table 2 and Figure 1 list and represent the percent of subjects deemed eligible or ineligible for AS and nr-AxSpA. For AS studies requiring a mNY+ radiograph, out of a total of 2,240 AP Pelvis x-rays evaluated, 52.6% (n=1,180) were deemed mNY+ and thus deemed eligible to be classified as true radiographic AS subjects. However, 47.2% of the total subjects evaluated were deemed to be screen failures due to being mNY- and thus not "radiographic AS." 2 subjects were deemed "Not evaluable" by the central readers.

TYPE OF AXSPA POPULATION	RADIOGRAPHIC INCLUSION CRITERIA	TOTAL # ANALYZED	# MNY+ (%)	# MNY- (%)
AS	mNY+	2240	1180 (52.6%)	1058 (47.2%)
nr-AxSpA	mNY-	3915	1134 (29%)	2778 (70.9%)

Table 2: Percentages of subjects deemed eligible for nr-AxSpA (mNY-) or AS (mNY+) based on central review

Figure 1: Pie Chart representation of eligible vs. non-eligible subjects per central read for radiographic AS (mNY+; fig.1A) and nr-AxSpA (mNY-; fig.1B) studies

Figure 1A: AS

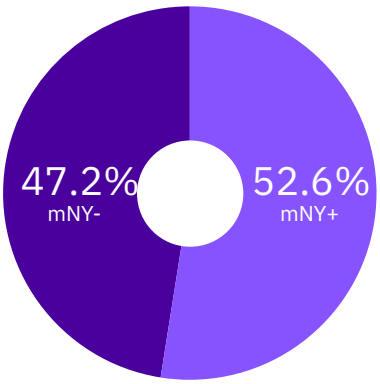
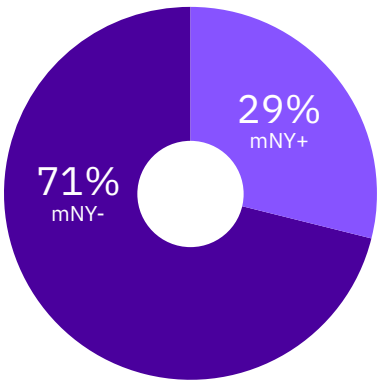


Figure 1B: nr-AxSpA



For nr-AxSpA studies requiring an mNY- radiograph, out of a total of 3,915 AP Pelvis x-rays evaluated, 70.9% (n=2,778) were deemed mNY- and thus deemed eligible to be classified as potentially nr- AxSpA subjects. However, 29% of the total subjects evaluated were deemed to be screen failures due to being mNY+ and thus "radiographic AS." 3 subjects were deemed "Not evaluable" by the central readers.

Table 3 and Figure 2 list and represent the percent of subjects deemed as "true" non-radiographic axial SpA subjects based on the presence of MRI bone marrow edema and osteitis (MRI+) as per ASAS / OMERACT criteria4. From the results it is clear that from a total of 2,635 subjects assessed, 39.7% of hitherto mNY-deemed subjects (n=1,046) show up as MRI+ thus qualifying as 'truly non-radiographic axial SpA" subjects. However, a greater percentage of hitherto mNY- deemed subjects (60.3%, n=1,589) were assessed as MRI- and are thus "false positives" if solely based on the mNY- criteria.

	MRI INCLUSION CRITERIA	TOTAL # ANALYZED	MRI+	MRI-
nr-Ax-SpA	MRI+	2635	1046 (39.7%)	1589 (60.3%)

Table 3: Distribution of nr-AxSpA Subjects (mNY-) into MRI+/- by ASAS OMERACT criteria on central review

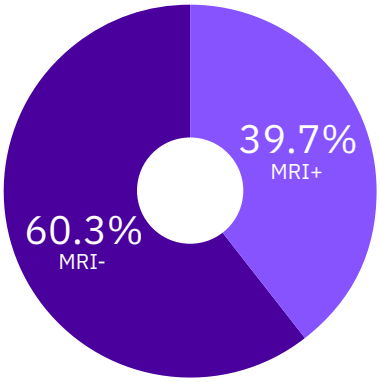


Figure 2: Pie chart showing the distribution of mNY- nonradiographic -AxSpA subjects into MRI+ and MRI-categories based on ASAS/OMERACT scoring for edema and osteitis

CONCLUSIONS

The screen failure rate was high for both AS (47.2%) and nr-AxSpA (29%) studies.

The data suggests that not all subjects screened locally will qualify to enter the trial when the radiographic criteria are applied centrally.

This may be due partly to the deliberate lack of clinical observations during central review of the SIJ.

Not all mNY- subjects initially categorized as nr- AxSpA were MRI+; 60.3% of the mNY- pool did not qualify per the ASAS/OMERACT criteria for inflammation of the SIJ.

Given that MRI positivity is increasingly being used to enroll "true" nr-AxSpA subjects the failure rate is noteworthy.

Our data would suggest that MRI assessment in conjunction with mNY for nr-Ax SpA is in fact warranted and basing enrollment for a nr-AxSpA trial solely on a mNY- result may not be desirable.

In conclusion, the eligibility rates reported herein should be taken into consideration during prospective AS and nr-AxSpA trial design.

REFERENCES

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