

Reducing Heterogeneity in OA Clinical Trials: Data from a Phase 2 Study of SM04690, a Novel, Intra-Articular, Wnt Pathway Inhibitor in Knee Osteoarthritis

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Poster 1201

Background

- Kellgren-Lawrence [KL] radiographic grading is used to classify knee osteoarthritis (OA), but may not accurately reflect disease progression.¹
- Classifying subjects by baseline medial joint space width (mJSW) instead may be more specific and identify a more homogenous clinical trial population.² This hypothesis was assessed in a post-hoc analysis of phase 2, 52-week, randomized controlled trial of SM04690, a small molecule Wnt pathway inhibitor and potential disease modifying knee OA drug (NCT02536833). A subgroup (n=258) with baseline mJSW of 2-4 mm was compared to the intention-to-treat (ITT) population.

Methods

- 455 subjects with KL grade 2-3 knee OA were randomized to receive a single, 2 mL, intra-articular injection of 0.03 mg, 0.07 mg, 0.23 mg SM04690 or placebo (PBO) into their target (most painful) knee at Day 0. Western and McMaster Universities Osteoarthritis Index (WOMAC) Pain and Function were assessed at 0, 4, 13, 26, 39 and 52 weeks. Fixed-flexion PA knee radiographs with fixed location mJSW assessments were performed at Weeks 0, 26, and 52. Primary results are reported elsewhere (abstract 935).
- A post-hoc, exploratory analysis of clinical outcomes in the ITT population conducted by analysis of covariance adjusted for baseline mJSW with multiple imputation.

Results

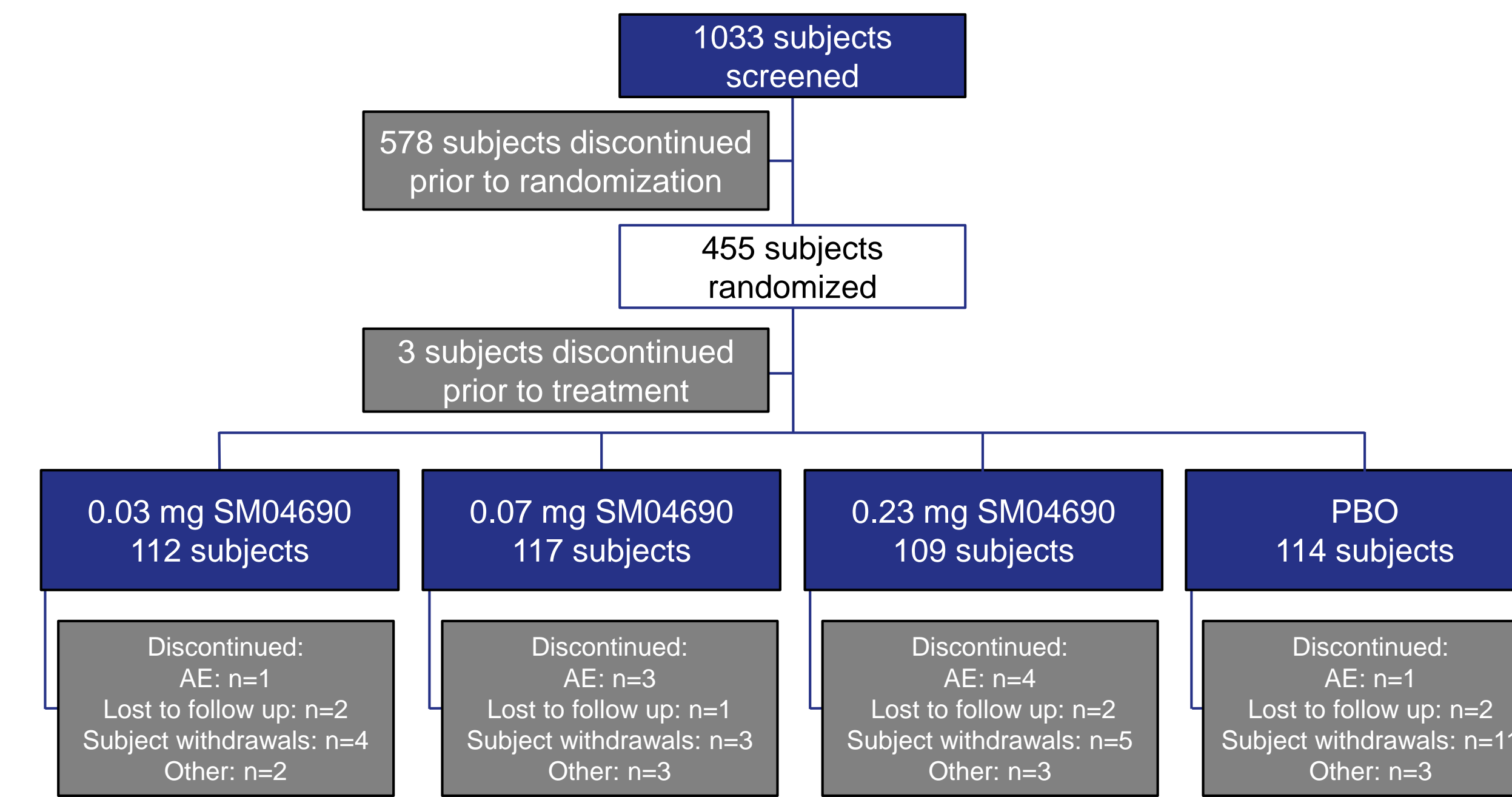
ITT (N=455) Week 52 mean mJSW:

- PBO group change from baseline was -0.14 [SE 0.06] mm.
- Mean changes from baseline compared to PBO were 0.10 [SE 0.09] mm and 0.06 [SE 0.06] mm in 0.03 mg (NS) and 0.07 mg (NS) SM04690 doses and a slight decrease of -0.02 [SE 0.09] mm was seen in 0.23 mg dose.

2-4 mm subgroup (n=258) Week 52 mean mJSW post-hoc analysis:

- Between group heterogeneity at baseline, including mean and interquartile differences, were reduced in the 2-4 mm subgroup (Figure 1).
- The magnitude of mJSW changes (adjusted for baseline) in all SM04690 groups compared to PBO increased in the 2-4 mm subgroup when compared to ITT.
- WOMAC Function change in 0.07 mg SM04690 was statistically significantly improved compared to PBO at Week 52 within the mJSW 2-4 mm subgroup (change -13.6, 95% CI: [-25.5, -1.7], P=0.025).
- Changes in WOMAC Pain from PBO were not statistically significant.

SM04690-OA-02 Subject Disposition



SM04690-OA-02 Demographics (ITT)

| | 0.03 mg | 0.07 mg | 0.23 mg | PBO | All subjects |
|---|------------|-------------|------------|-------------|--------------|
| N | 112 | 117 | 110 | 116 | 455 |
| Age at Consent (Years) [Mean (SD)] | 59.0 (9.0) | 60.0 (8.2) | 61.3 (8.7) | 60.7 (8.9) | 60.3 (8.7) |
| BMI (kg/m²) [Mean (SD)] | 29.8 (4.8) | 30.8 (4.7) | 29.6 (4.5) | 29.2 (4.4) | 29.2 (4.4) |
| Female [n(%)] | 68 (60.7%) | 60 (51.3%) | 68 (61.8%) | 72 (62.1%) | 268 (58.9%) |
| Race [n(%)] | | | | | |
| White | 92 (82.1%) | 102 (87.2%) | 96 (87.3%) | 102 (87.9%) | 392 (86.2%) |
| African-American | 18 (16.1%) | 14 (12.0%) | 12 (10.9%) | 10 (8.6%) | 54 (11.9%) |
| Asian | 1 (0.9%) | 0 | 2 (1.8%) | 0 | 3 (0.7%) |
| Kellgren-Lawrence Grade 3 [n(%)] | 74 (66.1%) | 74 (63.2%) | 70 (63.6%) | 74 (63.8%) | 292 (64.2%) |
| Unilateral Osteoarthritis [n(%)] | 45 (40.2%) | 35 (29.9%) | 45 (40.9%) | 39 (33.6%) | 164 (36.0%) |

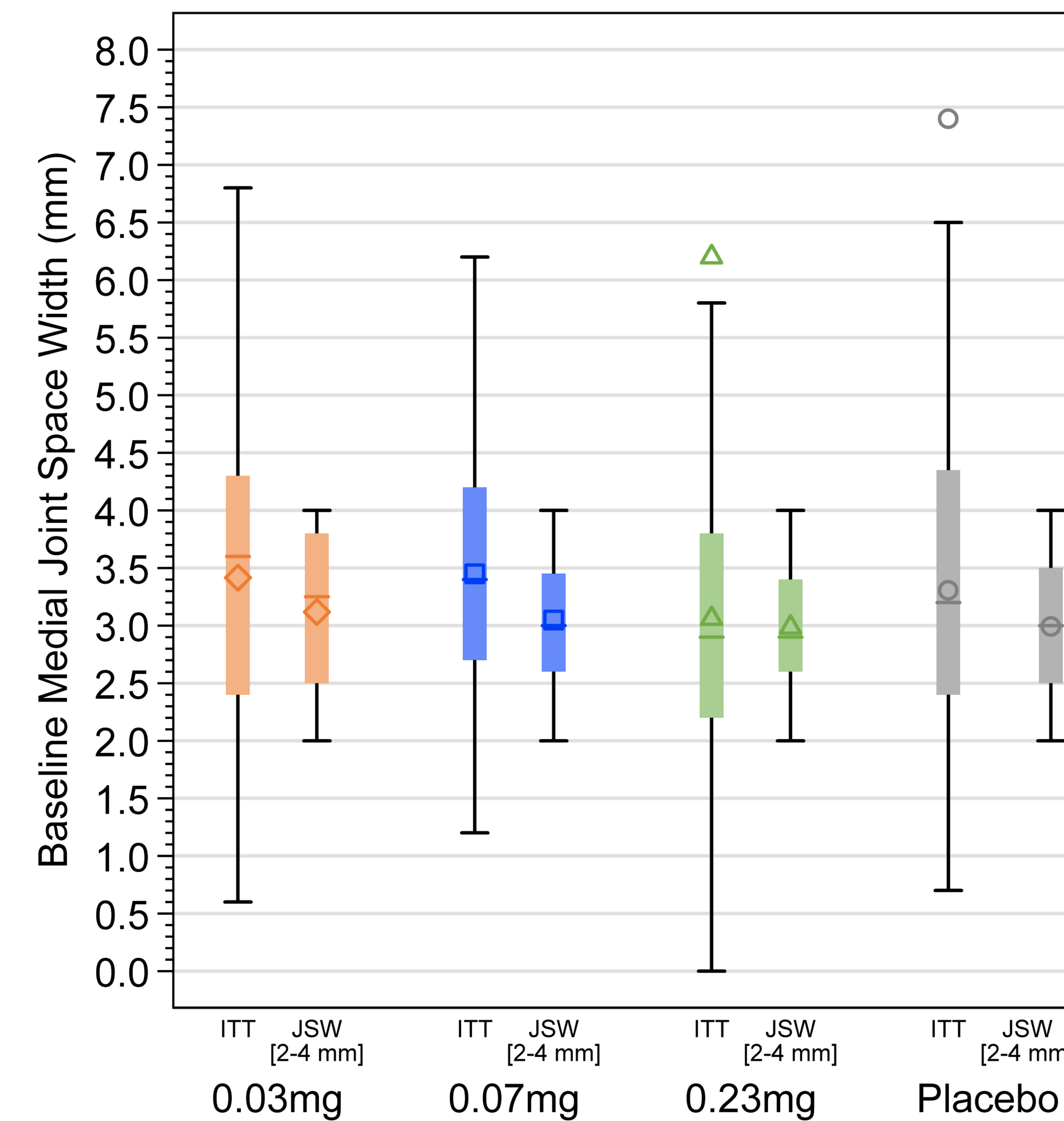
mJSW Measurements

| | ITT | | | |
|-------------------------------------|--------------|--------------|--------------|--------------|
| mJSW | 0.03 mg | 0.07 mg | 0.23 mg | PBO |
| N | 112 | 117 | 110 | 116 |
| Baseline (mm) [Mean (SE)] | 3.42 (0.12) | 3.45 (0.10) | 3.06 (0.12) | 3.31 (0.13) |
| Week 52 Change from Baseline | -0.04 (0.06) | -0.09 (0.06) | -0.16 (0.07) | -0.14 (0.06) |
| Week 52 Compared to PBO | 0.10 (0.09) | 0.06 (0.09) | -0.02 (0.09) | |
| P-value | 0.259 | 0.529 | 0.807 | |

| | Baseline JSW between 2 to 4 mm | | | |
|-------------------------------------|--------------------------------|--------------|--------------|--------------|
| mJSW | 0.03 mg | 0.07 mg | 0.23 mg | PBO |
| N | 56 | 72 | 65 | 65 |
| Baseline (mm) [Mean (SE)] | 3.12 (0.09) | 3.05 (0.06) | 2.98 (0.07) | 2.99 (0.07) |
| Week 52 Change from Baseline | -0.03 (0.08) | -0.03 (0.08) | -0.16 (0.09) | -0.22 (0.09) |
| Week 52 Compared to PBO | 0.19 (0.13) | 0.19 (0.12) | 0.06 (0.13) | |
| P-value | 0.144 | 0.121 | 0.624 | |

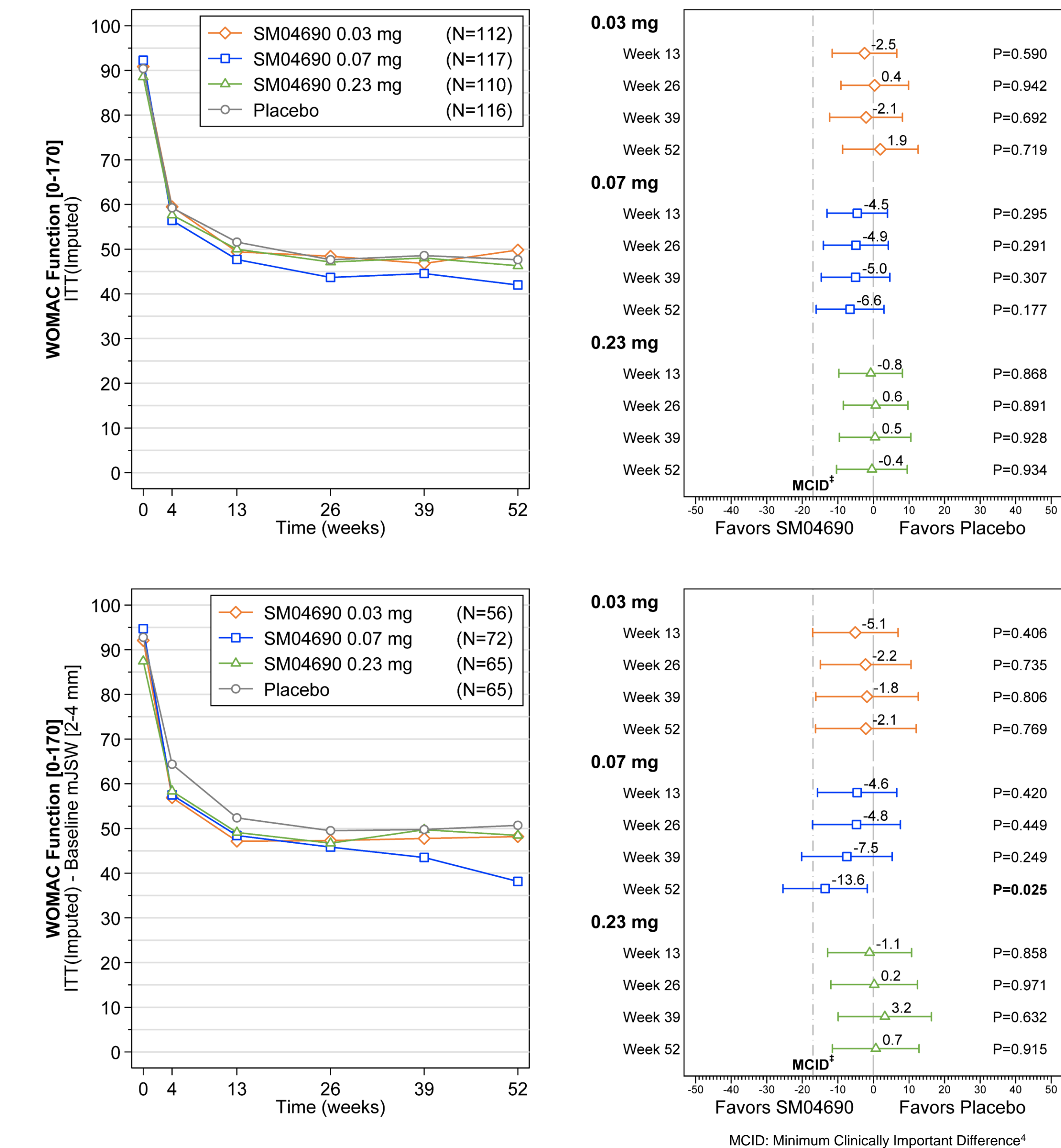
Results

Fig. 1. JSW at Baseline



Box and Whisker plot of Baseline JSW in the ITT and restricted within 2-4 mm. Interior Bar: Median; Box: Interquartile [25th-75th] range; Whisker: 1.5x Interquartile Range; Interior Symbol: Mean; Exterior Symbol: Outlier

Fig. 2. WOMAC Function change by analysis set



Conclusions

- Within this 2-4 mm subgroup post-hoc analysis, mJSW changes beyond radiographic measurement error (>0.13 mm)³ were observed with 0.03 mg and 0.07 mg SM04690 groups compared to PBO suggesting baseline cartilage thickness is an important determinant for detection of change.
- Additionally, WOMAC Function showed significant improvement compared to placebo at Week 52 within the 2-4 mm subgroup, supporting a possible association between joint space width and function.
- Future trials using radiography to assess structure modification in knee OA should consider specific mJSW inclusion criteria. A less heterogenous baseline reduces measurement variability, which may therefore reduce the required population size in a clinical trial, whilst maintaining statistical power.

References

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