Radiographic Outcomes from a Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of a Novel, Intra-Articular, Wnt Pathway Inhibitor (SM04690) for the Treatment of Osteoarthritis of the Knee: Week 26 Interim Analysis

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DISCLOSURES

- Y. Yazici: Samumed, LLC; salary and equity
- T. McAlindon: Samumed, grant/research support; Astellas, Flexion, Pfizer, Regeneron, Samumed,and Seikugaku, consulting
- A. Gibofsky: AbbVie, Amgen, J&J, GSK, Regeneron, shareholder; AbbVie, Pfizer, Horizon, Iroko, Celgene, Novartis/Sandoz, Samumed, consulting; AbbVie, Amgen, Celgene, Pfizer, speakers bureau
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- C. Swearingen: Samumed, LLC; salary and equity
- A. DiFrancesco: Samumed, LLC; salary and equity
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Osteoarthritis

- The most common form of arthritis
  - Affects over 250 million persons worldwide[1]
  - Knee OA has a global prevalence of 3.8%[2]
- Accounts for more functional limitation, work loss and physical disability than any other chronic disease[1,3]

- Most common indication for total joint arthroplasty[3]
- Associated with excess mortality due to CV disease[4]
- Multiple risk factors: age, BMI, joint injury, occupation, genetics[5]

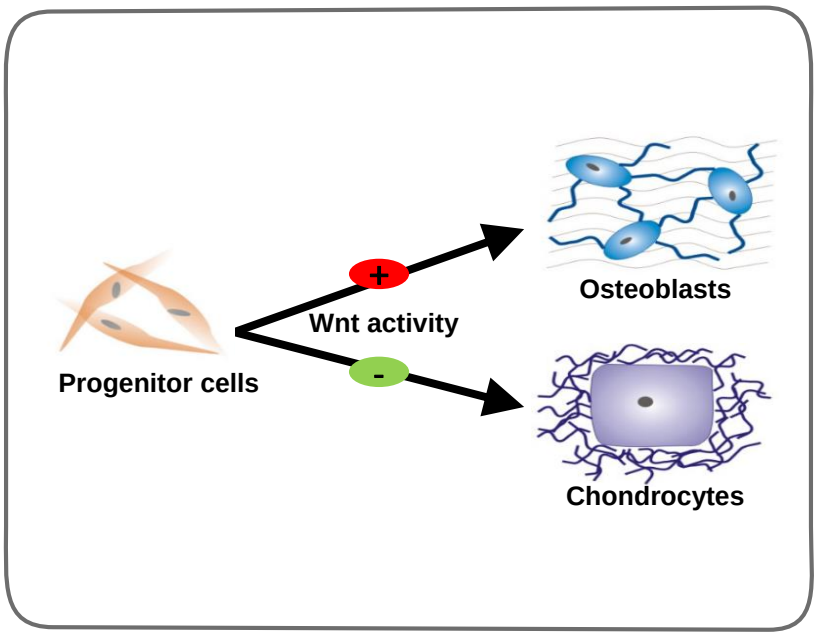
1. Vos T, et al. (2015) *Lancet.*
2. Cross et al. (2014) *Ann Rheum Dis*.
3. The Burden of Musculoskeletal Diseases in the US, Third Edition. (2014)
4. Rahman MM, et al. (2013) *BMJ.*
5. Felson DT, et al. (2000) *Ann Intern Med.*

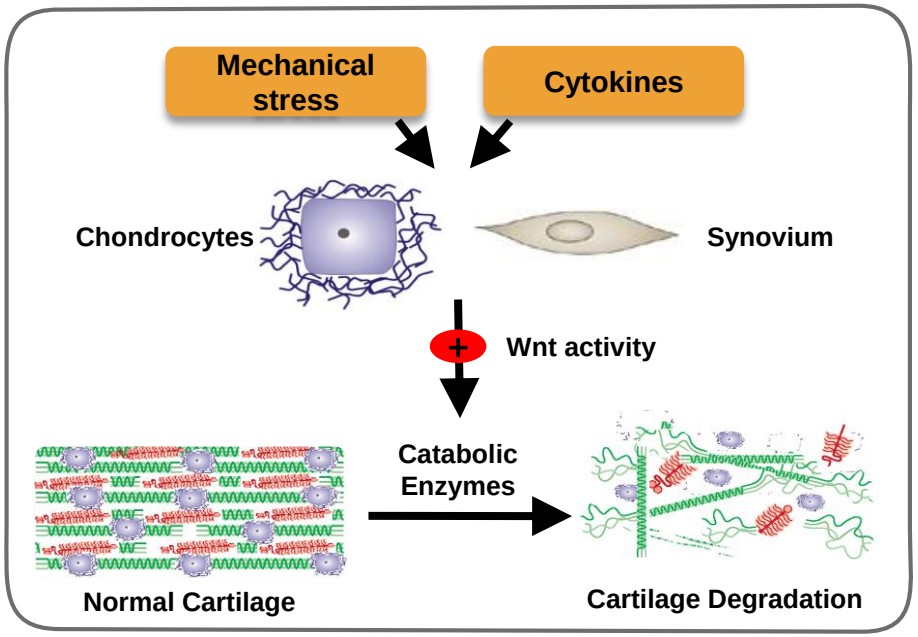
Joint Space Narrowing (JSN) is Indicative of OA Progression and is Predictive of Knee Surgery

- Radiographic JSN remains the current gold standard for assessing disease modification in OA[1-3]
- Knee OA natural history rate of JSN 0.18-0.47 mm/year[4]
- Prospective study of 133 subjects: each 0.1 mm increment in JSN over 3 years was associated with a 14%(CI 3-25%, p=0.02) increase in risk for knee replacement[5]
- Prospective study of 126 patients: minimum JSN of 0.5-0.8 mm over 3 years was predictive of knee surgery within 5 years ($p<0.004$)[6]

[1]Cooper. 2013. *Curr Med Res Op*.
[2]Reginster. 2015. *OAC*.
[3]FDA guidance for industry; 2nd draft. 1999.
[4]Parastu S. et al. 2008. *Osteoarthritis Cartilage.*
[5]Bruyere. 2013. *Calcif Tiss Int*.
[6]Bruyere. 2005. *ARD*.

Wnt Signaling Pathway and OA





- Wnt proteins are over-expressed and more active in OA joints[1-2]
- Wnt pathway mutations (e.g. FrzB) are associated with OA[3]
- Wnt signaling is involved in increased bone formation and cartilage breakdown
- Progenitor cells reside in the synovium and subchondral bone[4-6]

Hypothesis: Inhibiting the Wnt Pathway protects and regenerates cartilage

1. Rudnicki JA & Brown AM. 1997.*Dev Biol.*
2. Thomas RS, et al. 2011. *Arthritis Res Ther*.
3. Blom AB, et al. 2009. *Arthritis Rheum*.
4. Loughlin J. 2004. *Proc Natl Acad Sci USA*.
5. Im GI, et al. 2011. *Biotechnol Lett*.
6. Loughlin J. 2005. *Curr Opin Rheumatol*.

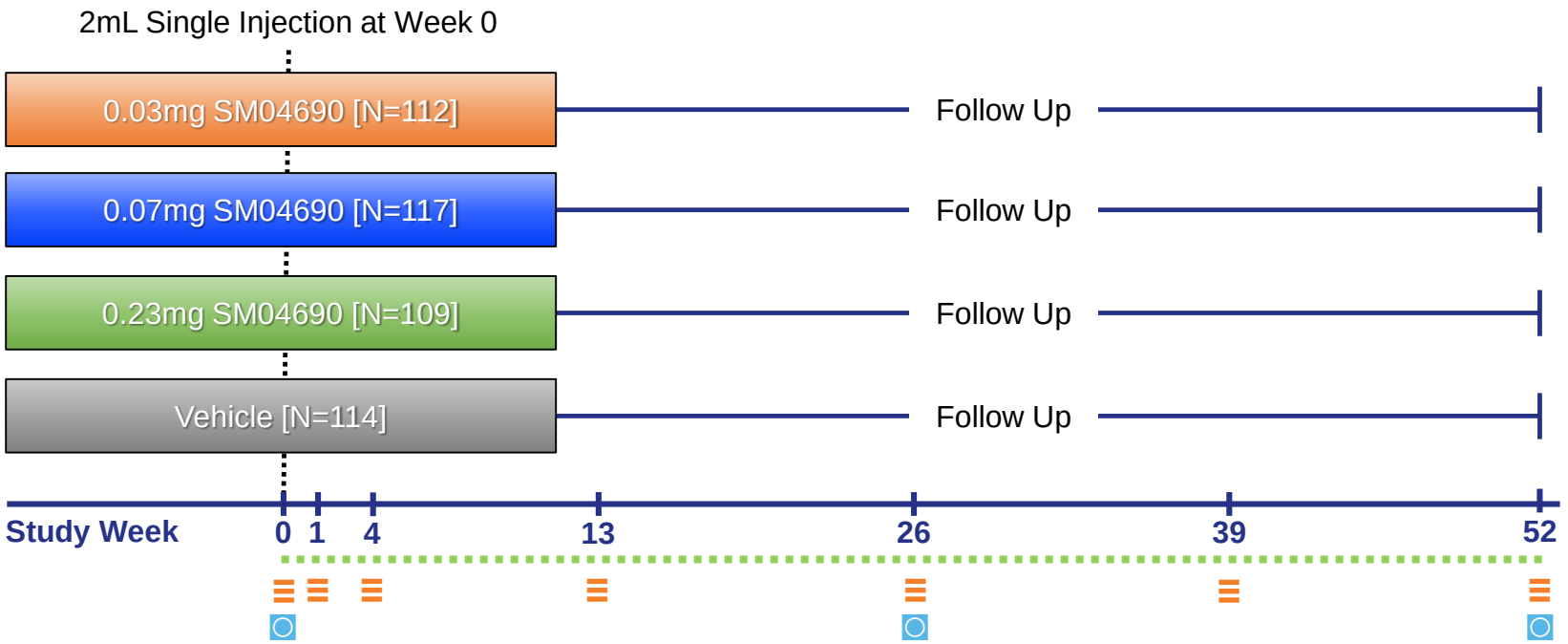
Figure adaptations: www.york.ac.uk and Bush J & Beier F. 2013. *Nature Med*.

SM04690: A Proposed Treatment for Knee OA

- A small molecule, intra-articular, Wnt pathway inhibitor in development for the treatment of knee OA[1,2]
- In preclinical studies, inhibited inflammation, decreased cartilage degradation, and regenerated cartilage[1]
- Demonstrated sustained local exposure and no observable systemic toxicity[1,2]
- Previous phase 1 study suggested a single intra-articular SM04690 injection appeared well-tolerated, and showed potential for improving symptoms, and maintaining joint space width in knee OA subjects[2]

[1]Hood J. 2016. Abstract. *Ann. Rheum. Dis.*
[2]Yazici Y. 2016. Abstract. *Ann. Rheum. Dis.*

SM04690-OA-02: Phase 2 Study Design



- Multicenter study of a single SM04690 injection evaluated safety, clinical outcomes, and JSN as measured by medial joint space width (mJSW) on radiographs.

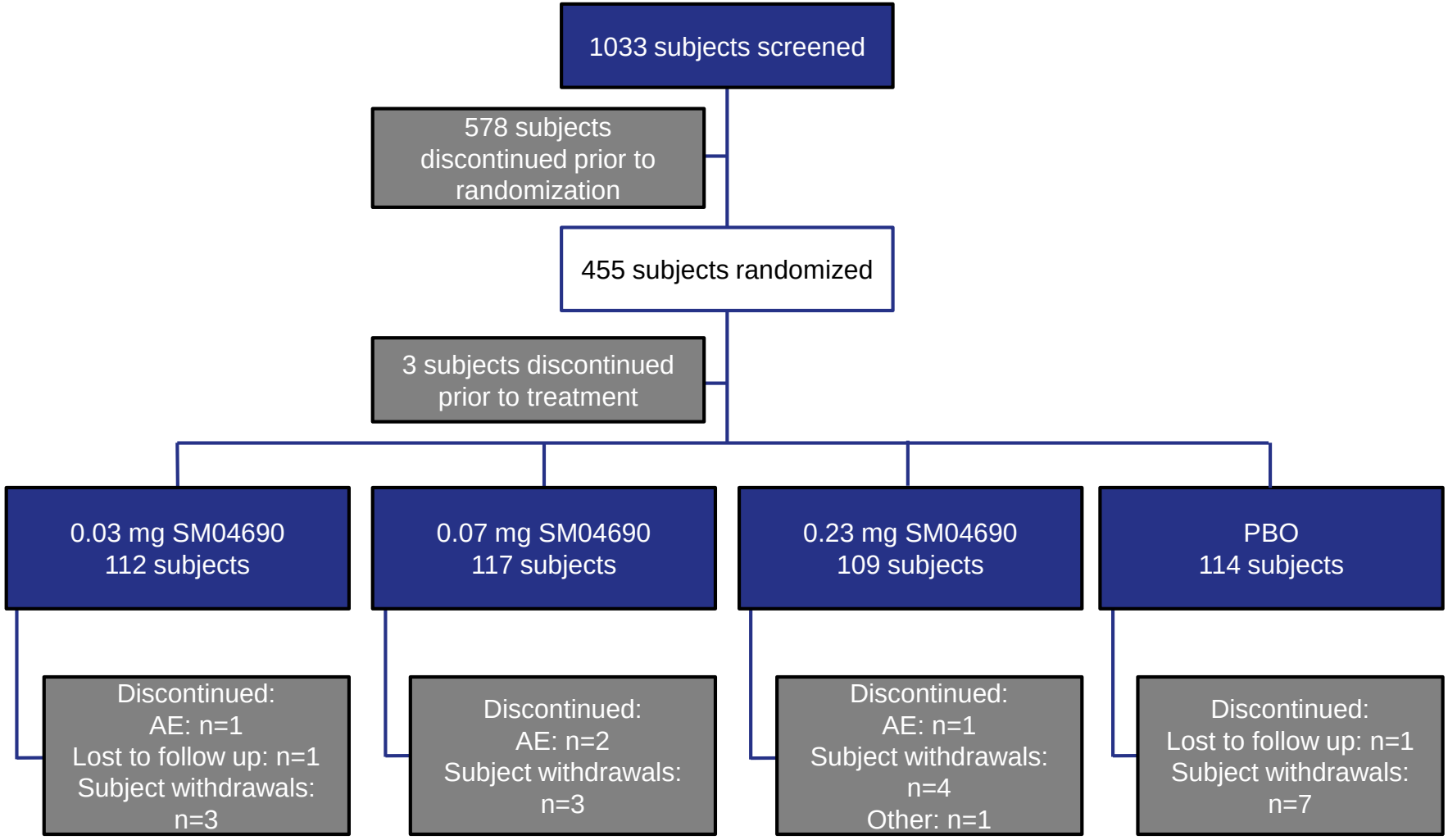
Interim analysis:

- Clinical data to week 39 presented on poster #SAT0552
- Radiographic data to Week 26 presented here

Key Inclusion / Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
40-80 years, good health	BMI >40
Ambulatory (aids allowed if needed <50%)	Major surgery in target knee within 12 months
Clinical and radiological ACR diagnosis of primary femoro-tibial OA in target knee >6 months	IA steroids within 2 months Hyaluronic acid within 6 months Acupuncture within 1 month
Kellgren-Lawrence Grade 2 / 3 in target knee	Target knee effusion requiring aspiration within 3 months
Pain VAS score of 30–80 for target knee	Any chronic condition not well controlled >3 months

SM04690-OA-02: Patient Disposition



SM04690-OA-02: Study Demographics (ITT)

	0.03 mg	0.07 mg	0.23 mg	Placebo	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/m^2) [Mean (SD)]	29.8 (4.8)	30.8 (4.8)	29.7 (4.5)	29.2 (4.4)	29.9 (4.6)
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 (63.8%)
Unilateral Symptomatic OA [n(%)]	45 (40.2%)	35 (29.9%)	45 (40.9%)	39 (33.6%)	164 (36.0%)

SM04690-OA-02: Analysis Groups

- Intention-to-treat population (ITT, n=455): all randomized subjects

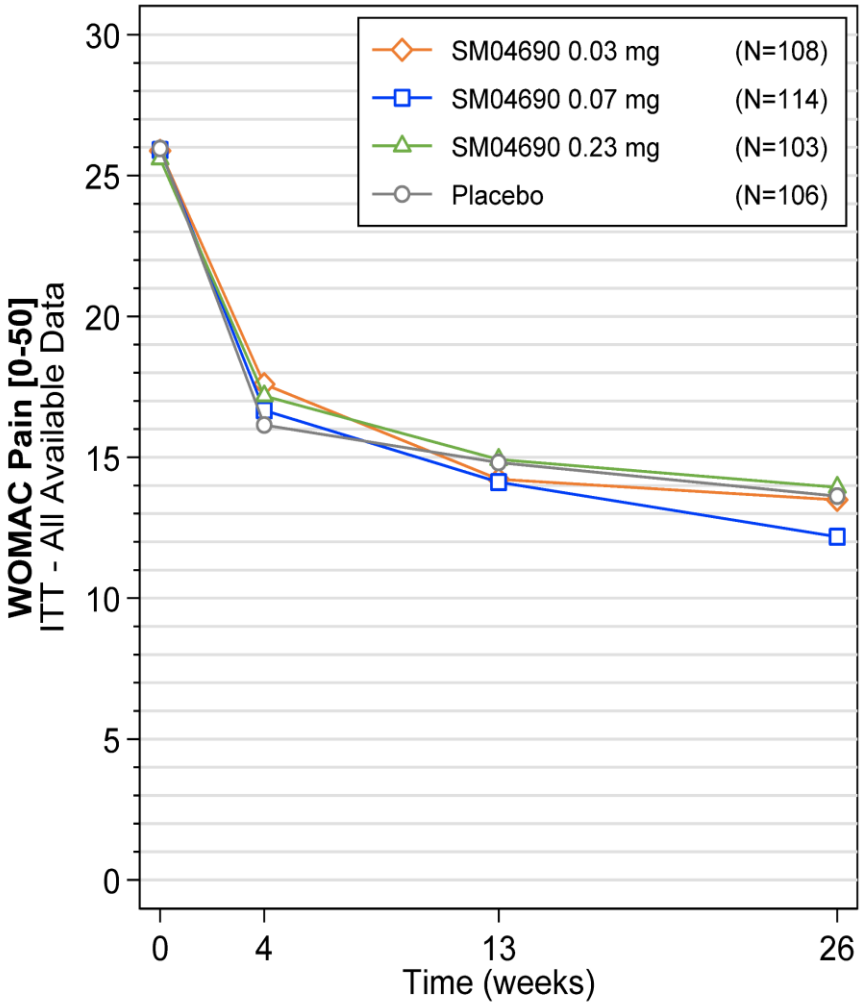
- 'Unilateral symptomatic' population (n=164):
  - Investigator designated 'target knee' as knee with most pain
  - Determined per protocol on patient history and examination
  - Contralateral knee pain threshold not limited at enrollment

- KL grade: Non-target knee equal or worse than target knee in 91% of subjects (n=386 of 424 non-target KLs)
  - KL grades were equivalent between unilateral symptomatic and bilateral symptomatic subjects

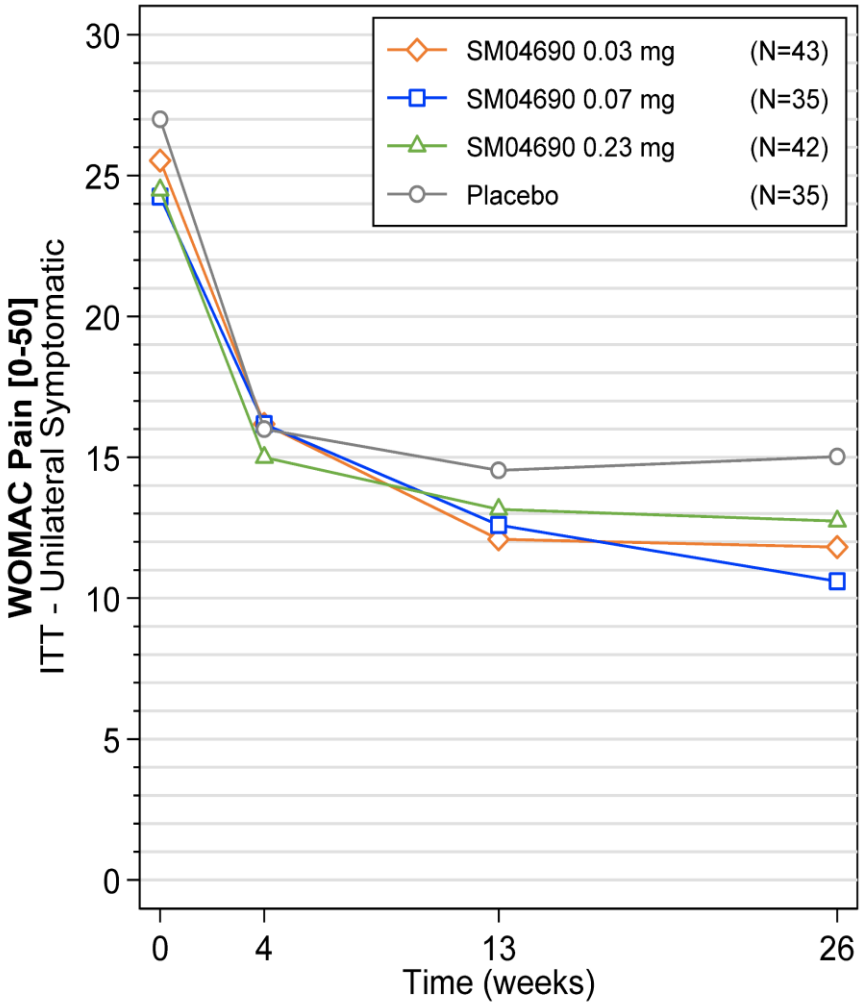
SM04690-OA-02: Clinical Outcomes

WOMAC Pain [0-50] Change through 26 weeks

ITT



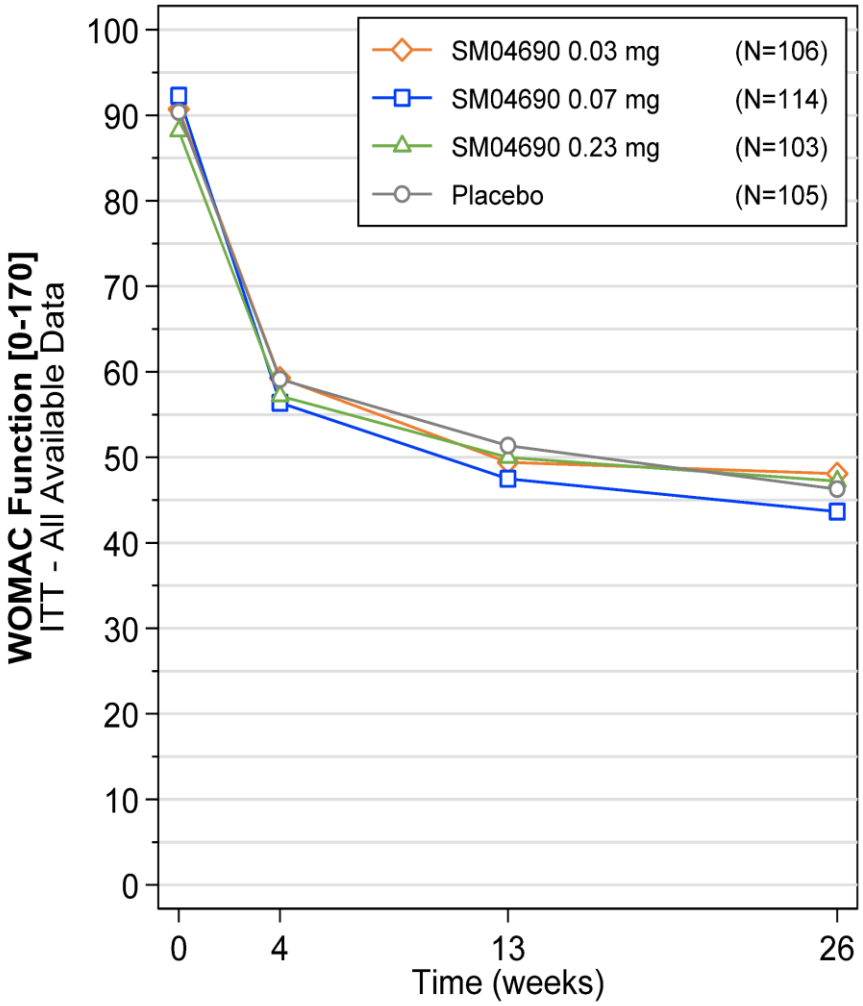
Unilateral Symptomatic



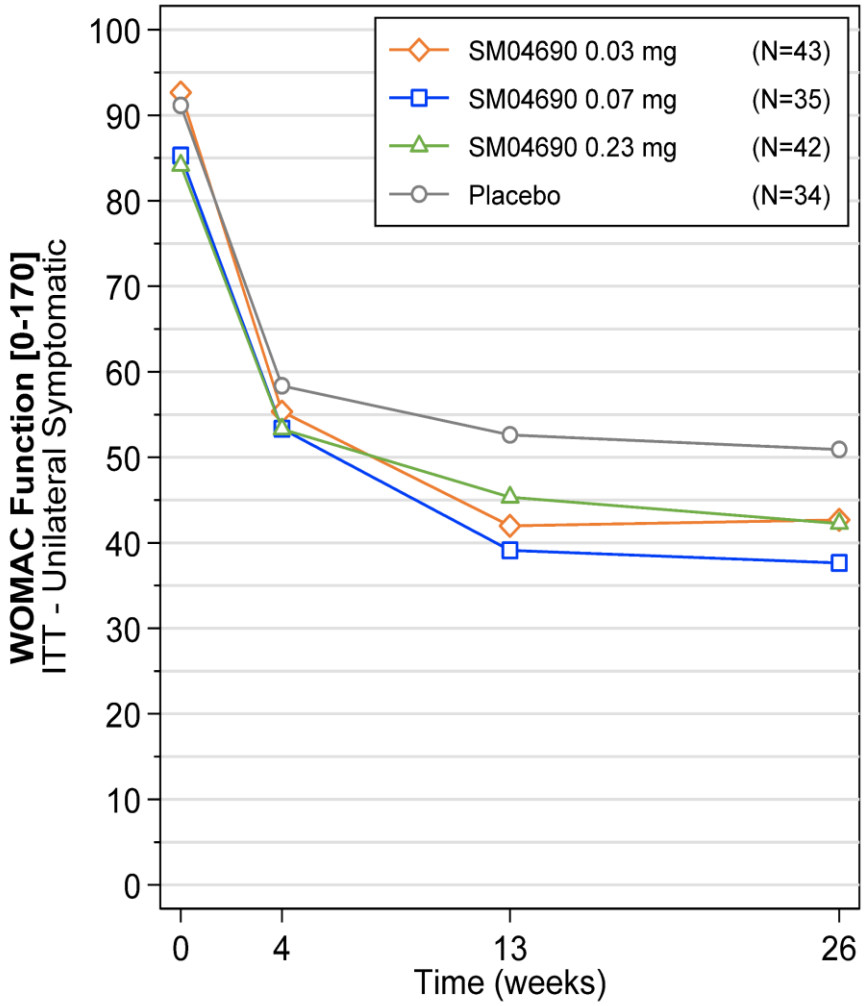
SM04690-OA-02 Clinical Outcomes

WOMAC Function [0-170] Change through 26 weeks

ITT

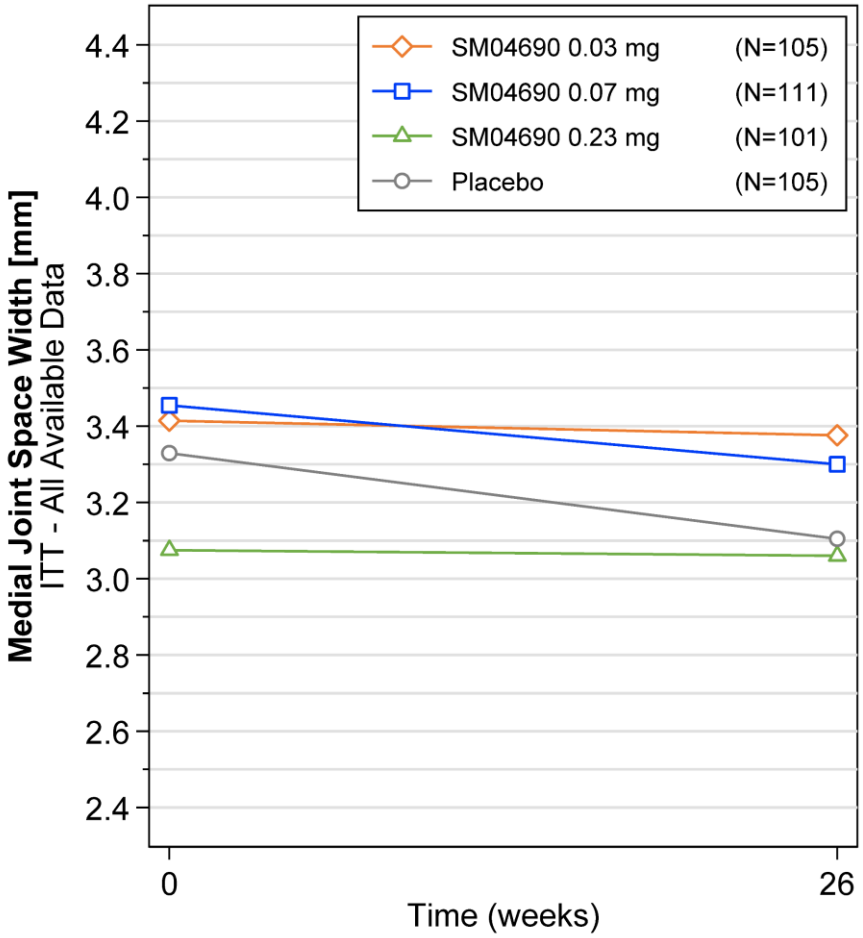


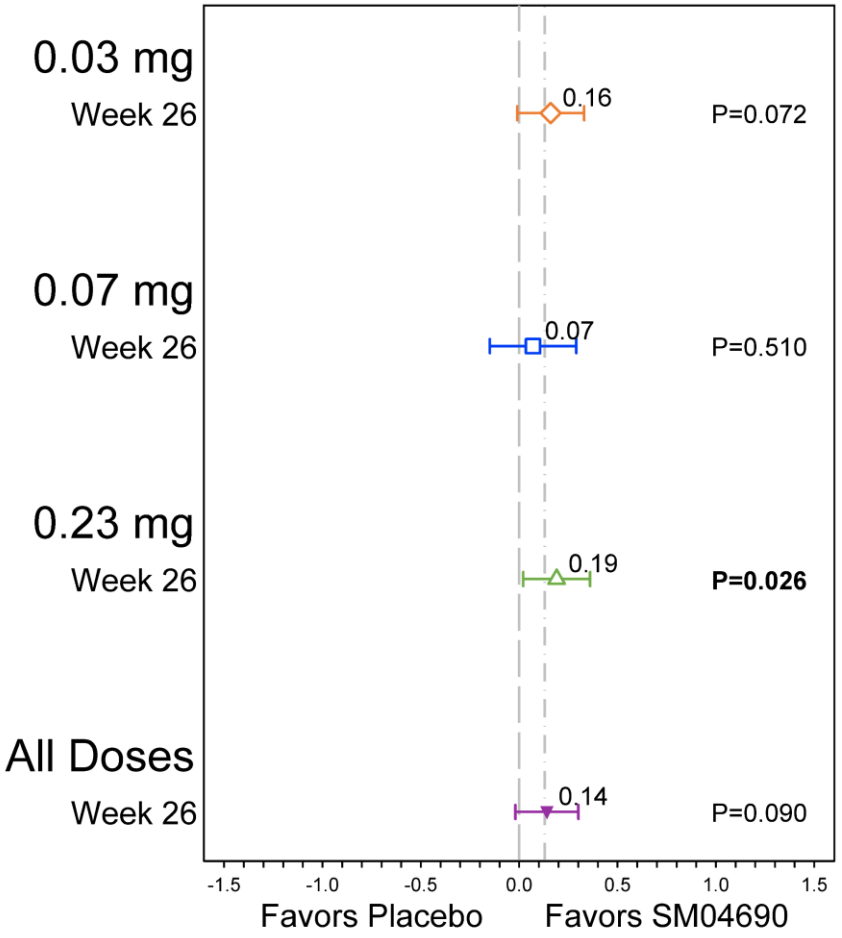
Unilateral Symptomatic



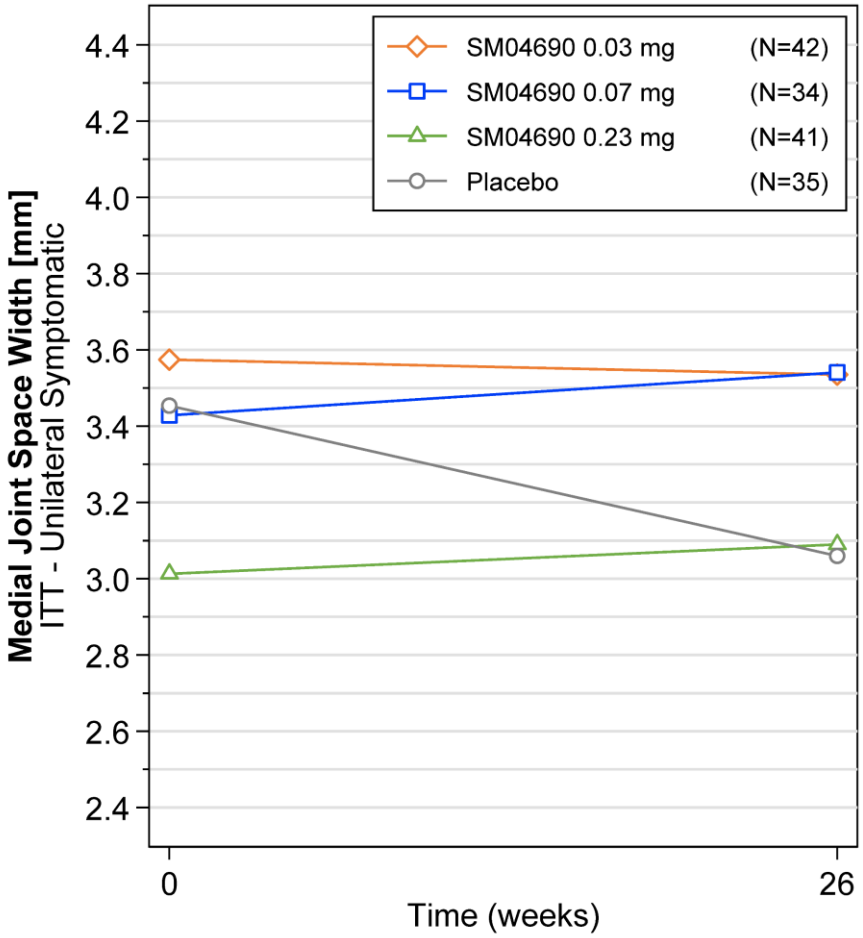
SM04690-OA-02: Radiographic Outcomes

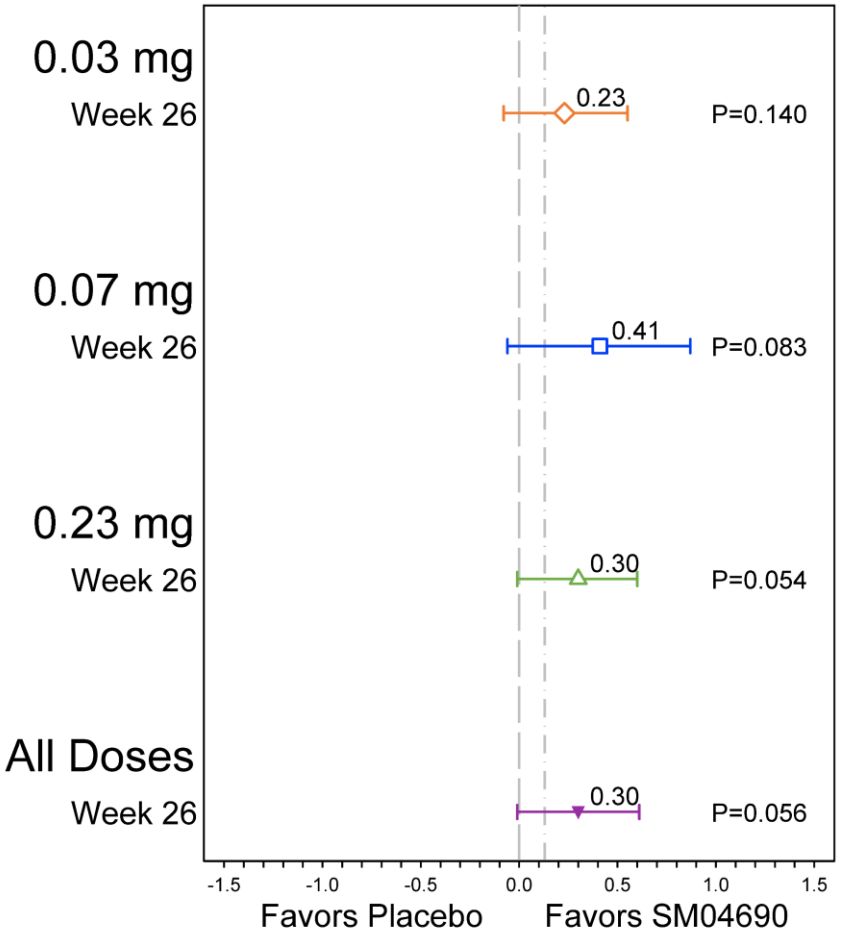
Medial Joint Space Width (mJSW) (ITT)



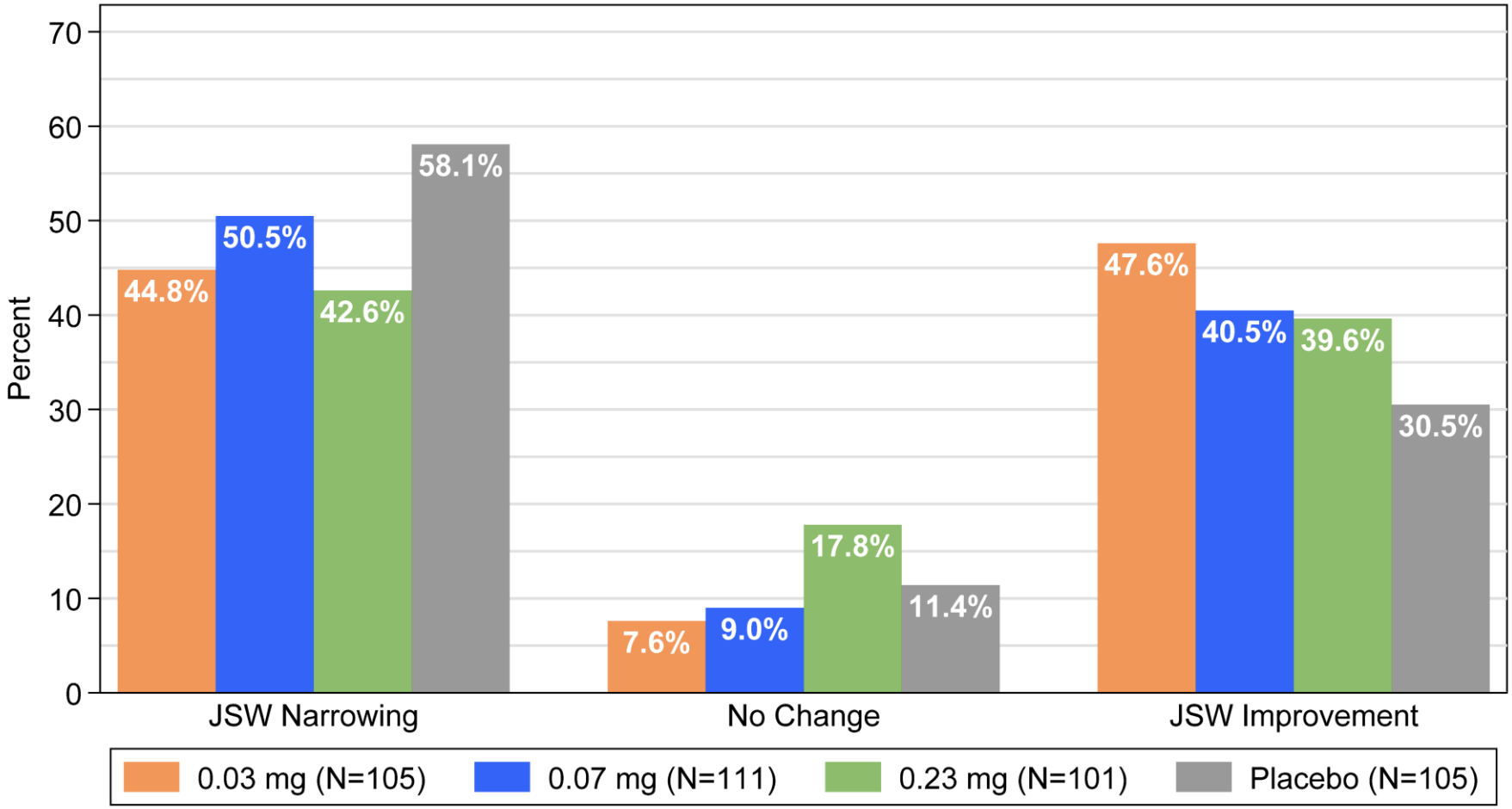


SM04690-OA-02: Radiographic Outcomes
mJSW (Unilateral Symptomatic)





SM04690-OA-02: mJSW Response at Week 26 ITT



Response Definitions

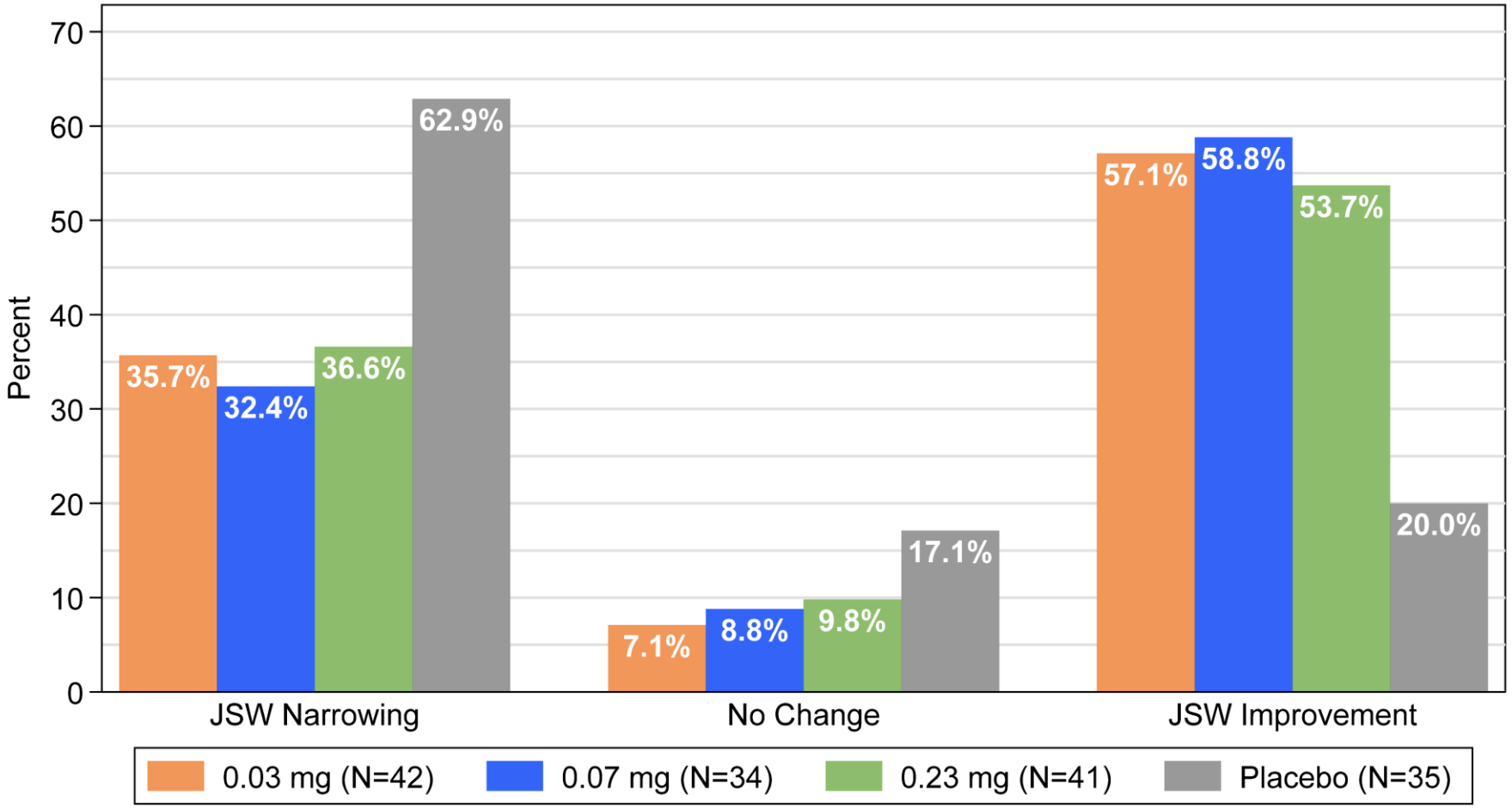
- JSW Narrowing: mJSW change < 0 mm
- No Change: mJSW change = 0 mm
- JSW Improvement: mJSW change > 0 mm

Odds of JSW Response compared to Placebo

- 0.03 mg OR=2.07, **P=0.011**
- 0.07 mg OR=1.56, P=0.124
- 0.23 mg OR=1.50, P=0.171
- All SM04690 OR=1.69, **P=0.029**

SM04690-OA-02: mJSW Response at Week 26

Unilateral Symptomatic



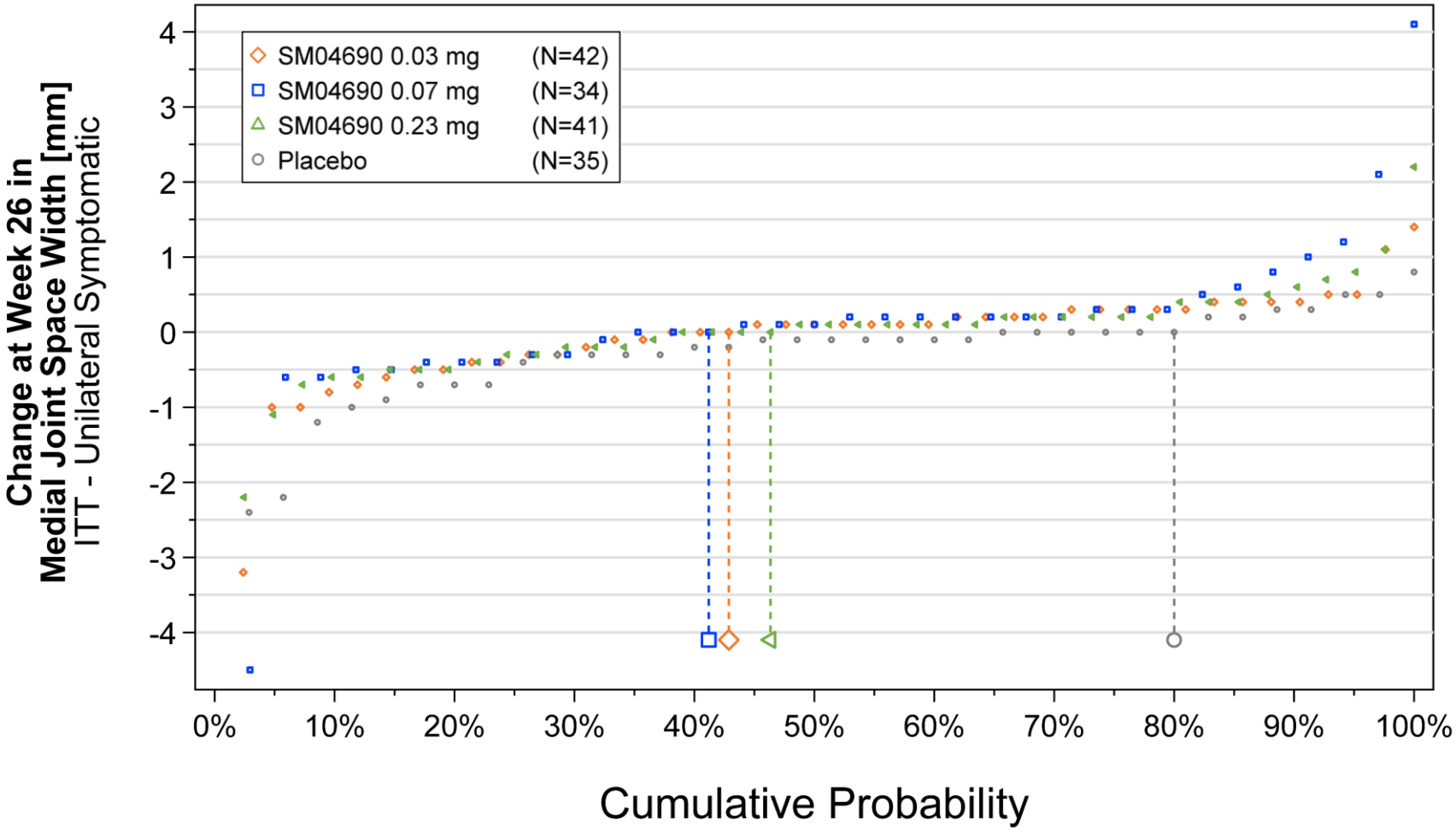
Response Definitions

- JSW Narrowing: mJSW change < 0 mm
- No Change: mJSW change = 0 mm
- JSW Improvement: mJSW change > 0 mm

Odds of JSW Response compared to Placebo

- 0.03 mg OR=5.33, **P=0.001**
- 0.07 mg OR=5.71, **P=0.001**
- 0.23 mg OR=4.63, **P=0.004**
- All SM04690 OR=5.18, **P<0.001**

SM04690-OA-02: mJSW Cumulative Probability to Week 26 - Unilateral Symptomatic Group



Limitations

- Study not formally powered
- Clinical outcomes measured at 0, 4, 13 and 26 weeks
- Radiographs reported at 26 weeks
  - Intra- and inter- observer reproducibility 0.92 & 0.90 respectively
  - QuAP™ positioner used
  - Centrally read

Summary

- Radiographic outcomes from this 26 week interim analysis demonstrated SM04690 treatment maintained or increased mJSW compared to placebo

- Radiographic and clinical outcomes considered together suggested SM04690 has potential as a DMOAD for the treatment of knee OA

- For safety and clinical results, see poster #SAT0552

SM04690 OA clinical program

- SM04690-OA-01, Phase 1, N=61 (completed)
  - 24 weeks, safety with exploratory efficacy
- SM04690-OA-02, Phase 2, N=455 (completed)
  - 52 weeks, primary endpoint 13 week WOMAC pain
  - Completed April 2017, Data available May 2017
- SM04690-OA-04, Phase 2, N=330 (ongoing)
  - 24 weeks, primary endpoints 24 week S&S and JSW
  - Started April 2017, estimated completion January 2018
- SM04690-OA-05, safety extension (ongoing)
  - Started September 2016
  - 5 years, safety with exploratory long-term efficacy including radiographs and WOMAC (observational; no additional injections)
- SM04690-OA-08, MRI, N=10
  - 24 weeks, exploratory evaluation of cartilage quality and thickness
  - Estimated September 2017 start