Results from a 52 Week Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of a Novel, Intra-Articular, Wnt Pathway Inhibitor (SM04690) for the Treatment of Knee Osteoarthritis

Yusuf Yazici, Timothy E. McAlindon, Allan Gibofsky, Nancy E. Lane, Daniel J. Clauw, Eddie Armas, Nebojsa Skrepnik, Christopher J. Swearingen, Anita DiFrancesco, Jeymi R. Tambiah, and Marc C. Hochberg

Disclosures

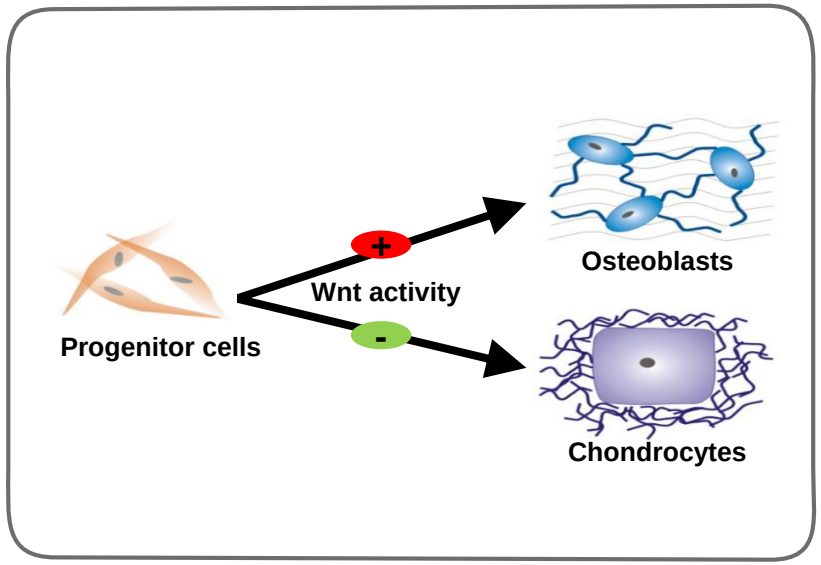
- **Y. Yazici**: Samumed, LLC; salary and equity
- **T. McAlindon**: Samumed, LLC, grant/research support; Astellas, Flexion, Pfizer, Regeneron, Samumed, LLC, and Seikugaku, consulting
- **A. Gibofsky**: AbbVie, Amgen, Johnson &Johnson, GSK, Regeneron, shareholder; AbbVie, Pfizer, Horizon, Iroko, Celgene, Novartis/Sandoz, Samumed, LLC, consulting; AbbVie, Celgene, Pfizer, speakers bureau
- **N. Lane**: Samumed, LLC, consulting
- **D. Clauw:** AbbVie, Astellas, Cerephex, Eli Lillly, Forest Laboratories, Johnson and Johnson, Merck, Pfizer, Purdue, Samumed, LLC, Theravance, Tonix, UCB, Williams and Connolly LLP, Zynerba, consulting
- **N. Skrepnik**: Samumed, LLC, grant/research support; Orthofix and Sanofi, consulting
- **E. Armas**: Samumed, LLC, grant/research support
- **C. Swearingen**: Samumed, LLC; salary and equity
- **A. DiFrancesco**: Samumed, LLC; salary and equity
- **J. Tambiah**: Samumed, LLC; salary and equity
- **M. Hochberg**: Bioberica, EMD Serono, Novartis Pharma AG, Plexxikon, Pfizer, Proximagen, Regeneron, Samumed, LLC, Theralogix LLC, consulting

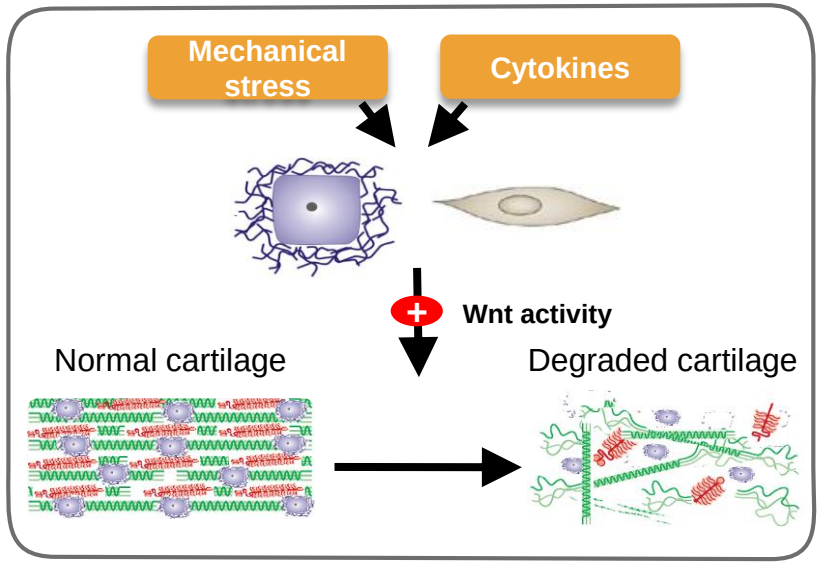
Osteoarthritis (OA)

- 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 cardiovascular 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. Burden of Musculoskeletal Diseases in the US, 3rd Ed. (2014)
4. Rahman MM, et al. (2013) *BMJ.*
5. Felson DT, et al. (2000) *Ann Intern Med.*

Wnt signaling pathway and OA





- Wnt proteins are over-expressed and more active in OA joints[1-2]
- Wnt pathway mutations (e.g. FrzB, DOT1L) are associated with OA[3-4]
- Wnt signaling is involved in increased bone formation and cartilage breakdown
- Progenitor cells reside in the synovium and subchondral bone[5-7]

Hypothesis: Inhibiting the Wnt Pathway protects and regenerates cartilage

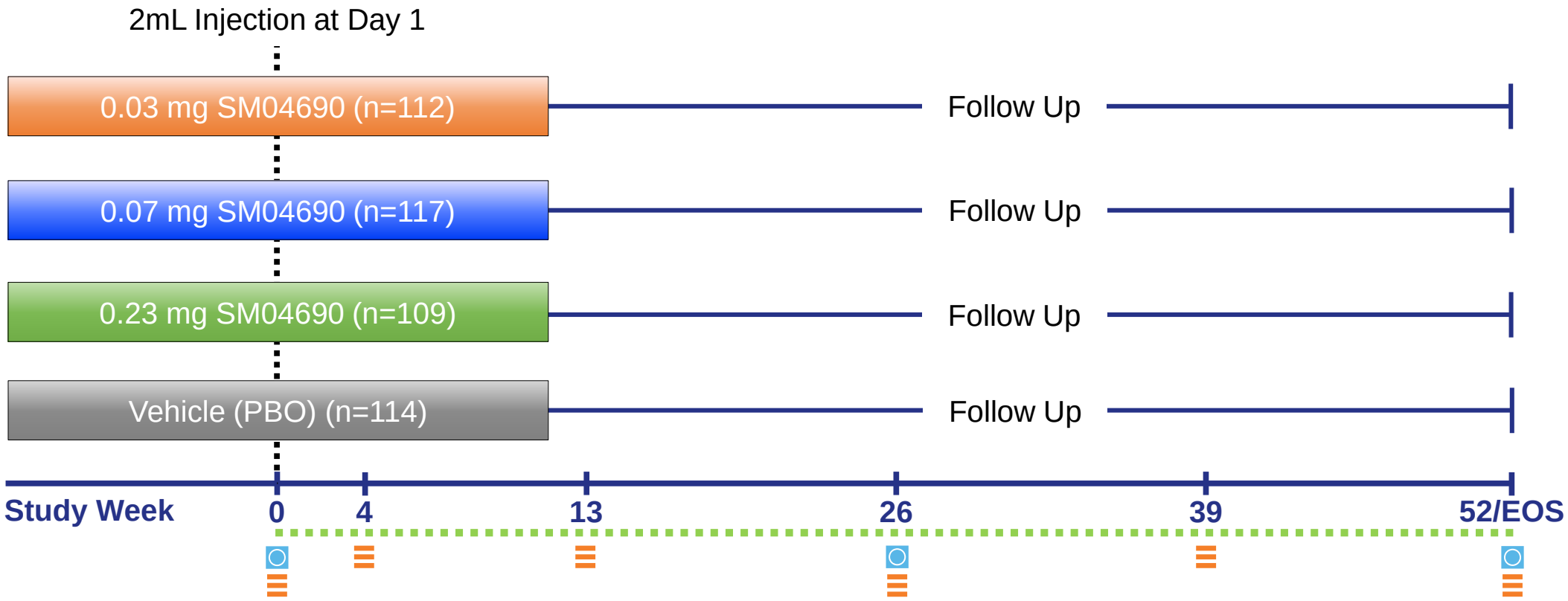
1. Rudnicki JA and Brown AM. (1997) *Dev Biol.*
2. Thomas RS, et al. (2011) *Arthritis Res Ther*.
3. Blom AB, et al. (2009) *Arthritis Rheum*.
4. Monteagudo S, et al. (2017) *Nat Commun.*
5. Loughlin J, et al. (2004) *Proc Natl Acad Sci.*
6. Im GI, et al. (2011) *Biotechnol Lett*.
7. Loughlin J, et al. (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]
- In preclinical studies, 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. Deshmukh V, et al.(2017) *OAC.*
2. Yazici Y, et al. (2017) *OAC.*

SM04690-OA-02: Phase 2 study design



Primary objective: Change from baseline in WOMAC pain at Week 13

Clinical Assessments: WOMAC Function, Pain; Patient and MD Global Assessment; SF-36

Imaging: Knee X-ray

Safety Assessments: Adverse Events (AEs), Vital signs, Physical exam, Lab panels

SM04690-OA-02: Radiographic methodology

Study	N	Lin's Concordance Coeff.	Difference (mm)	BA LOA[1] (mm)
431 Intra-observer[2]	64	0.92	0.13 ± 0.35	-0.56 to 0.83
431 Inter-observer[2]	64	0.90	0.04 ± 0.42	-0.78 to 0.86
OAI Inter-observer[3]	63	0.96	-0.05 ± 0.27	-0.58 to 0.48

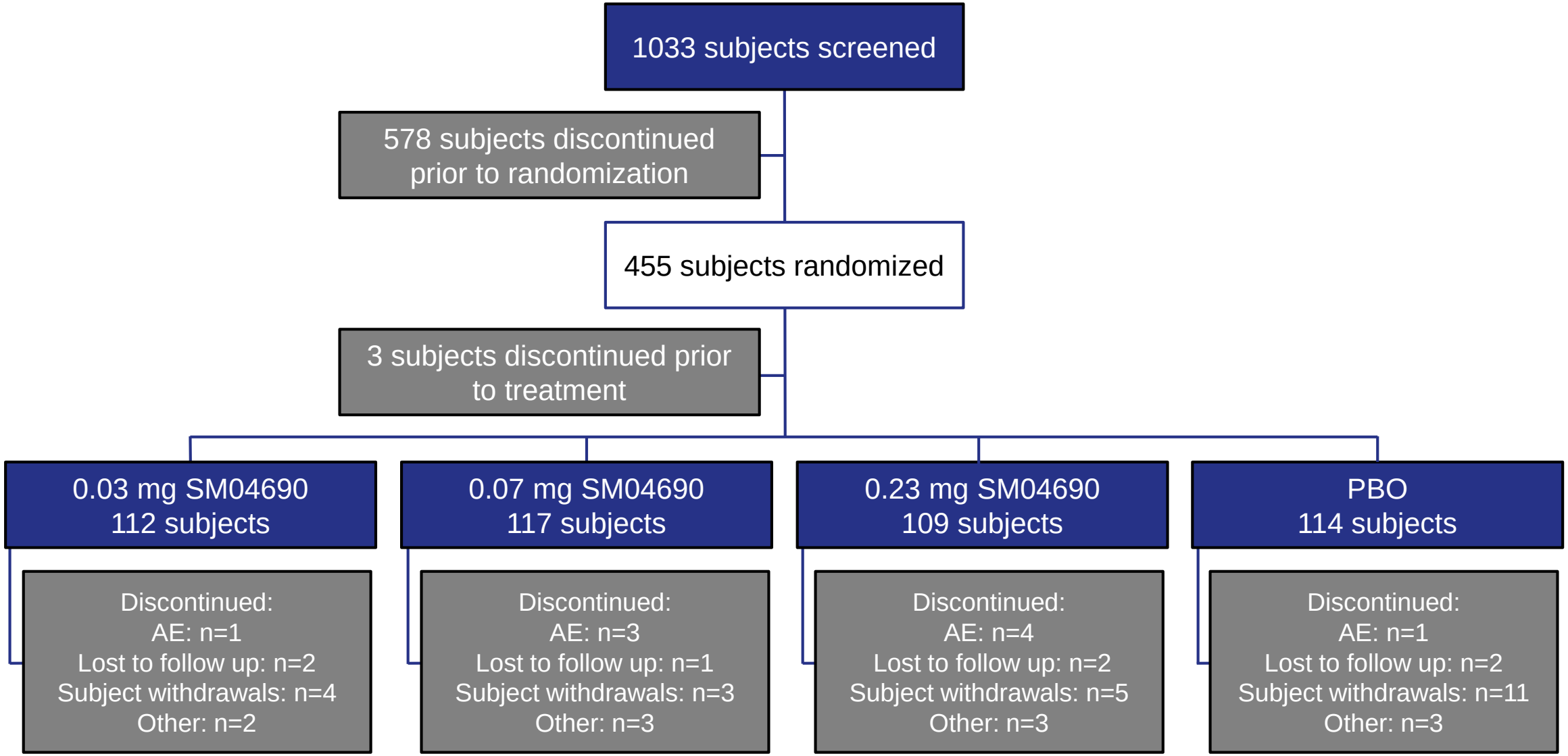
- Images obtained using QuAP™ positioner, centrally read in 72 hours
- Mean baseline KL Grade 2 in OAI, KL Grade 3 in SM04690-OA-02
- Radiographic JSN remains current 'gold standard' for assessing disease modification in OA[4-7]
- Radiographic changes >0.13 mm represent actual or true change in JSN[8]
- Knee OA natural history of JSN rate is 0.18-0.47 mm/year[9]
- Worsening pain and function occur in tandem with radiographic progression[10]

1. Bland-Altman's Limits of Agreement
2. Using QMA® technique for JSN
3. Using **Osteoarthritis Initiative (OAI)** protocol for JSN measurements
4. Cooper et al. (2013) *Curr Med Res Op*.
5. Reginster et al. (2015) *OAC*.
6. FDA guidance for industry; 2nd draft. 1999.
7. EMA guidline on clin invest in OA 2010.
8. Depuis, et al. (2003) *OAC*.
9. Parastu S, et al. (2008) *OAC*.
10. Riddle and Juranek (2015) *OAC*.

Key inclusion / exclusion criteria

Key Inclusion Criteria	Key Exclusion Criteria
40-80 years	BMI >40
Ambulatory (aids allowed if needed <50%)	Major surgery in target knee within 12 months
Clinical and radiological ACR diagnosis of primary femorotibial 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: Demographics
(ITT analysis set)

	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 (4.7)	29.6 (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 (64.2%)
Unilateral Symptomatic OA [n(%)]	45 (40.2%)	35 (29.9%)	45 (40.9%)	39 (33.6%)	164 (36.0%)

Incidence of AEs
(Safety analysis set)

AE(s) Reported* >2% [#AE / N(%)]	0.03 mg	0.07 mg	0.23 mg	Placebo	All Subjects
Arthralgia	16 / 13 (11.7)	14 / 13 (11.4)	13 / 9 (8.7)	12 / 10 (9.3)	61 / 49 (10.8)
Joint swelling	5 / 3 (2.7)	4 / 4 (3.5)	2 / 2 (1.9)	6 / 5 (4.6)	17 / 14 (3.1)
Upper respiratory tract infection	5 / 5 (4.5)	2 / 2 (1.8)	1 / 1 (1.0)	3 / 3 (2.8)	12 / 12 (2.7)
Hypertension	0 / 0 (0.0)	4 / 4 (3.5)	4 / 4 (3.8)	3 / 3 (2.8)	11 / 11 (2.4)
Nasopharyngitis	4 / 4 (3.6)	3 / 3 (2.6)	3 / 3 (2.9)	0 / 0 (0.0)	11 / 11 (2.4)
Osteoarthritis	4 / 3 (2.7)	2 / 2 (1.8)	3 / 3 (2.9)	5 / 3 (2.8)	14 / 11 (2.4)
Headache	0 / 0 (0.0)	6 / 3 (2.6)	2 / 2 (1.9)	4 / 4 (3.7)	13 / 10 (2.2)
Joint effusion	5 / 4 (3.6)	2 / 2 (1.8)	1 / 1 (1.0)	2 / 2 (1.9)	10 / 9 (2.0)
Sinusitis	1 / 1 (0.9)	2 / 2 (1.8)	1 / 1 (1.0)	5 / 5 (4.6)	9 / 9 (2.0)
Urinary tract infection	2 / 2 (1.8)	2 / 2 (1.8)	3 / 2 (1.9)	3 / 3 (2.8)	10 / 9 (2.0)

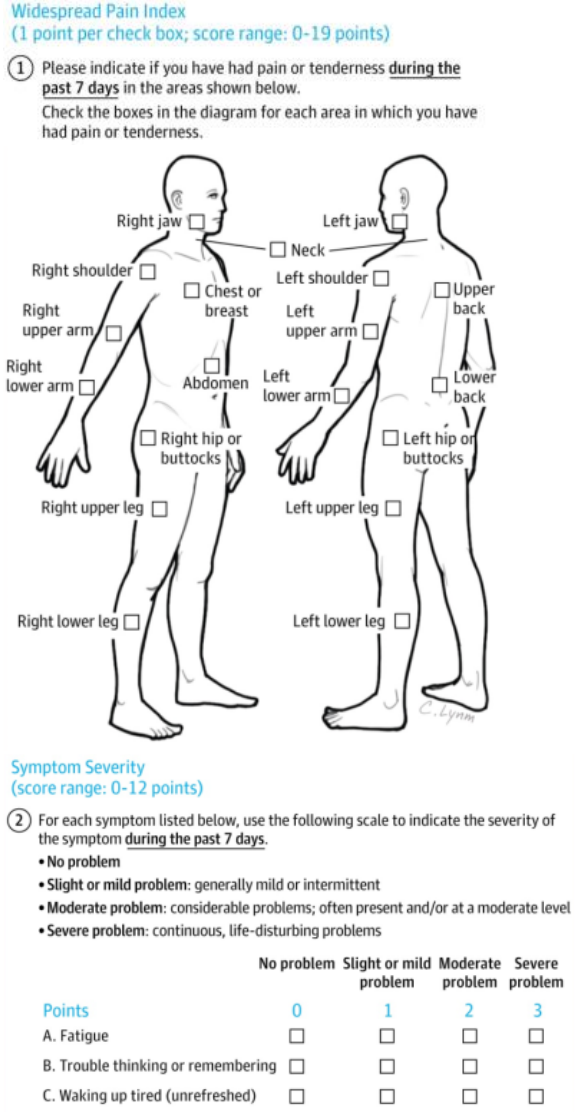
	0.03 mg (n=111)	0.07 mg (n=114)	0.23 mg (n=104)	Placebo (n=108)
Subjects Reporting AE(s) [N(%)]	61 (55.0)	65 (57.0)	47 (45.2)	53 (49.1)
Subjects Reporting No AE(s) [N(%)]	50 (45.0)	49 (43.0)	57 (54.8)	55 (50.9)
Subjects Reporting SAE(s) [#AE / N(%)]	7/5 (4.5)	12/4 (3.5)	5/4 (3.8)	3/3 (2.8)

No SAEs were deemed related to study drug by PI.

*All AEs deemed related to drug per protocol.

SM04690-OA-02: Analysis groups

- Intention-to-treat population (ITT, n=455): all randomized subjects
- 'Unilateral symptomatic' population (n=164):
  - Pre-specified, 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
- 'Unilateral symptomatic without widespread pain' population (n=128):
  - Post-hoc, unilateral symptomatic as above plus:
  - Widespread Pain Index score ≤ 4 and Symptom Severity score ≤ 2
- Missing data were imputed using multiple imputation
- 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



Widespread Pain Index
(1 point per check box; score range: 0-19 points)

(1) Please indicate if you have had pain or tenderness **during the past 7 days** in the areas shown below.
Check the boxes in the diagram for each area in which you have had pain or tenderness.

Symptom Severity
(score range: 0-12 points)

(2) For each symptom listed below, use the following scale to indicate the severity of the symptom **during the past 7 days**.

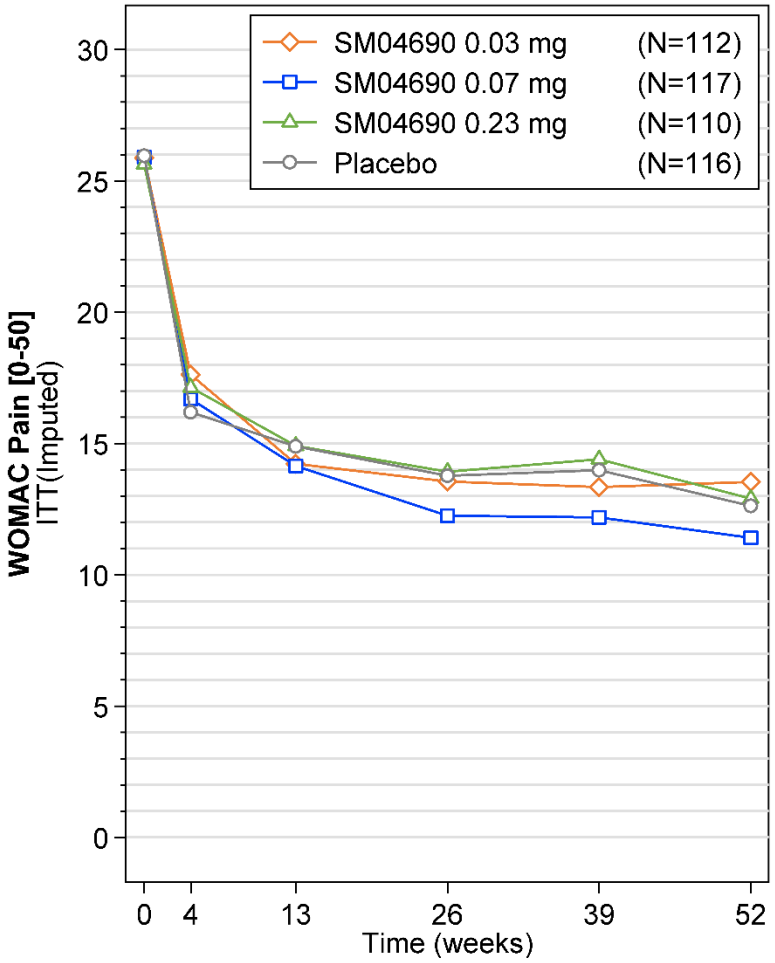
- **No problem**
- **Slight or mild problem**: generally mild or intermittent
- **Moderate problem**: considerable problems; often present and/or at a moderate level
- **Severe problem**: continuous, life-disturbing problems

	No problem	Slight or mild problem	Moderate problem	Severe problem
Points	0	1	2	3
A. Fatigue	☐	☐	☐	☐
B. Trouble thinking or remembering	☐	☐	☐	☐
C. Waking up tired (unrefreshed)	☐	☐	☐	☐

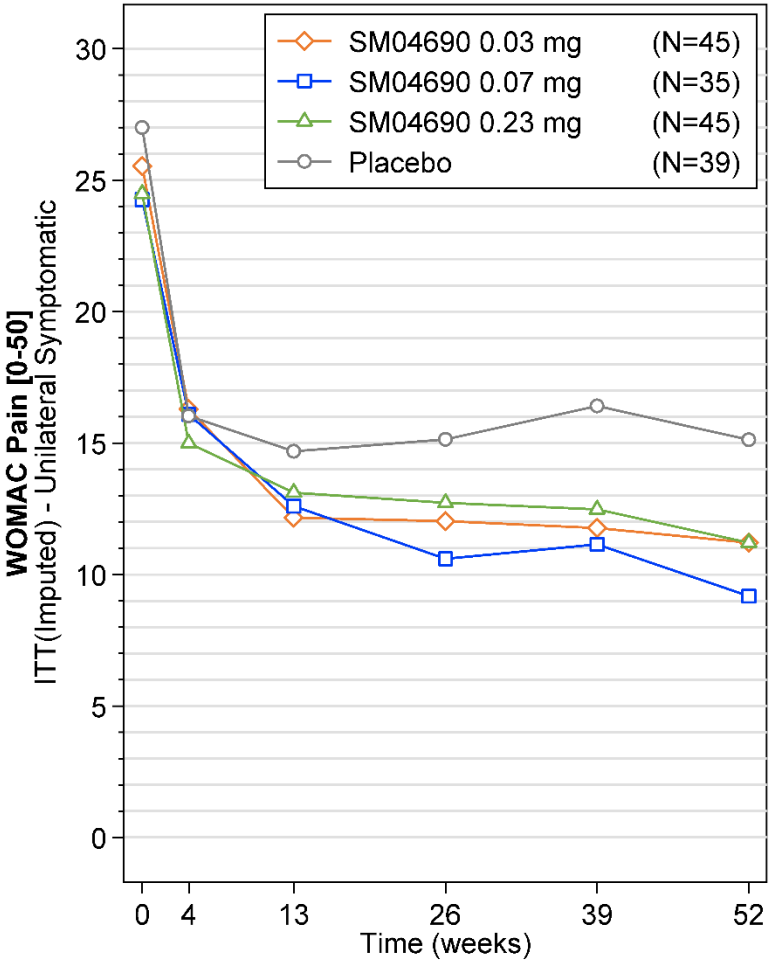
WOMAC Pain [0-50]

Actual scores (mean)

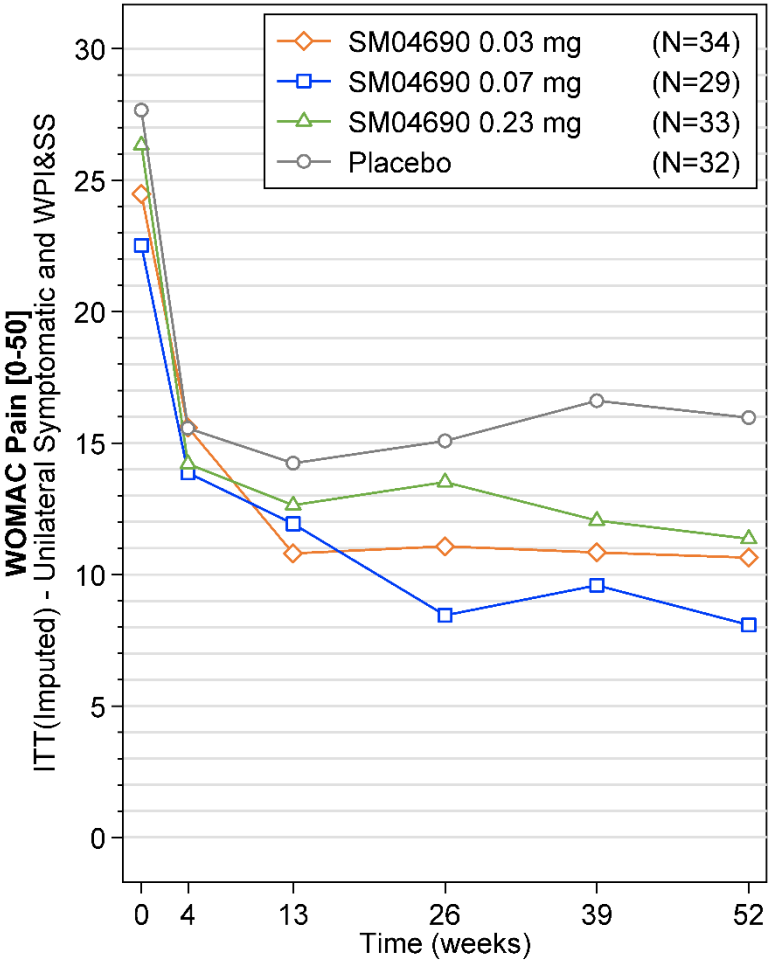
ITT



Unilateral Symptomatic



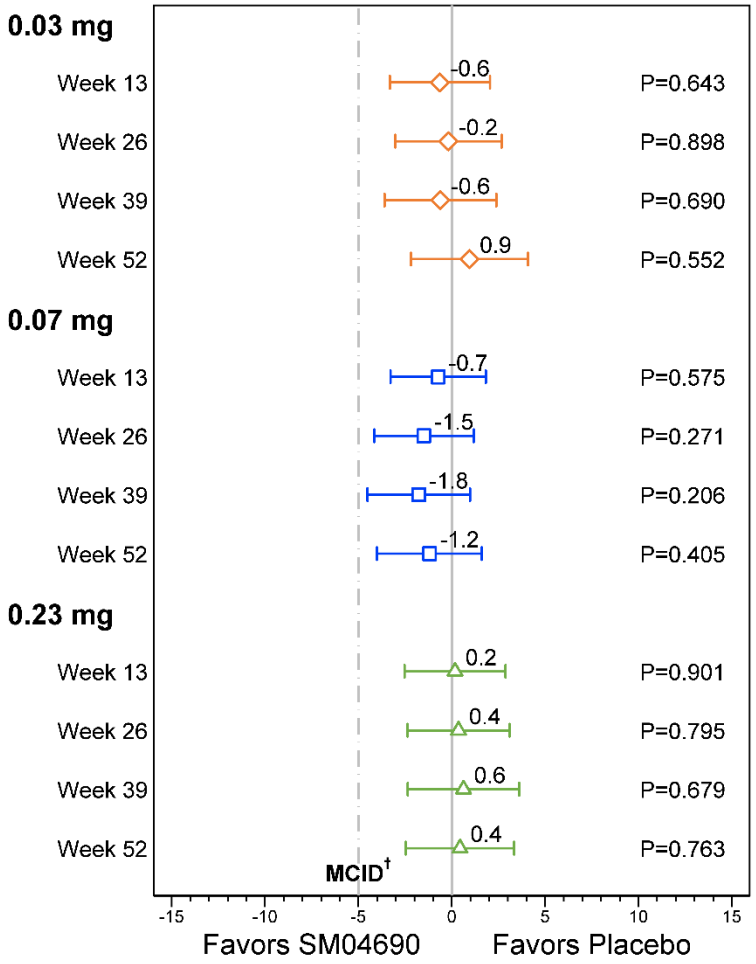
Unilateral Symptomatic without Widespread Pain



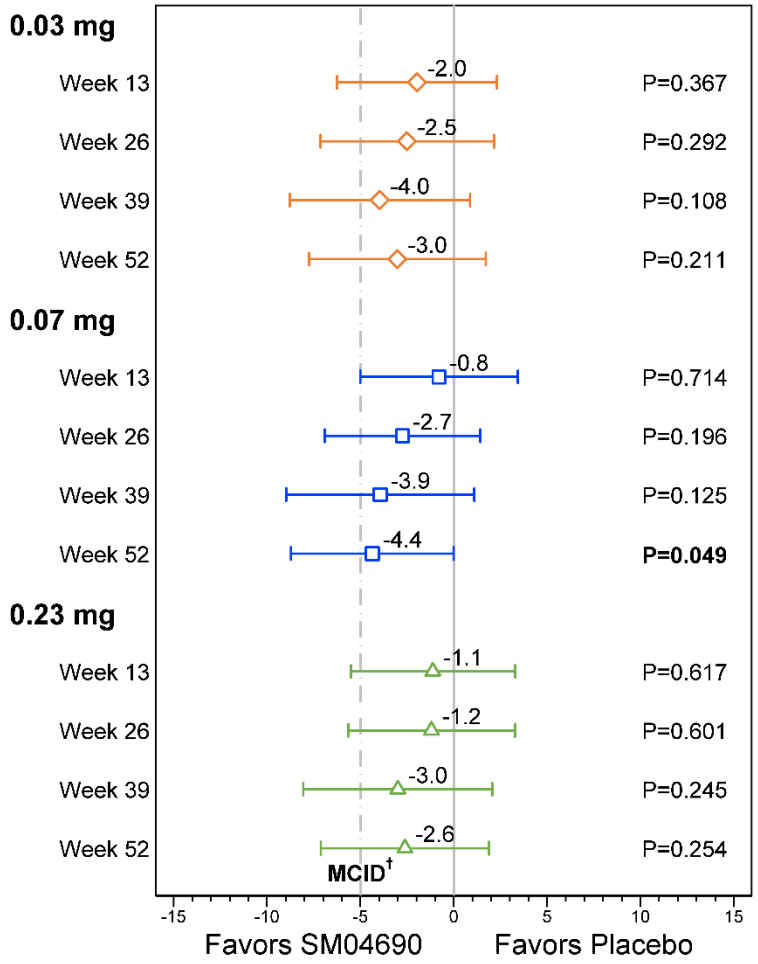
WOMAC Pain [0-50]

Ladder plots comparing mean (± 95%CI) to placebo

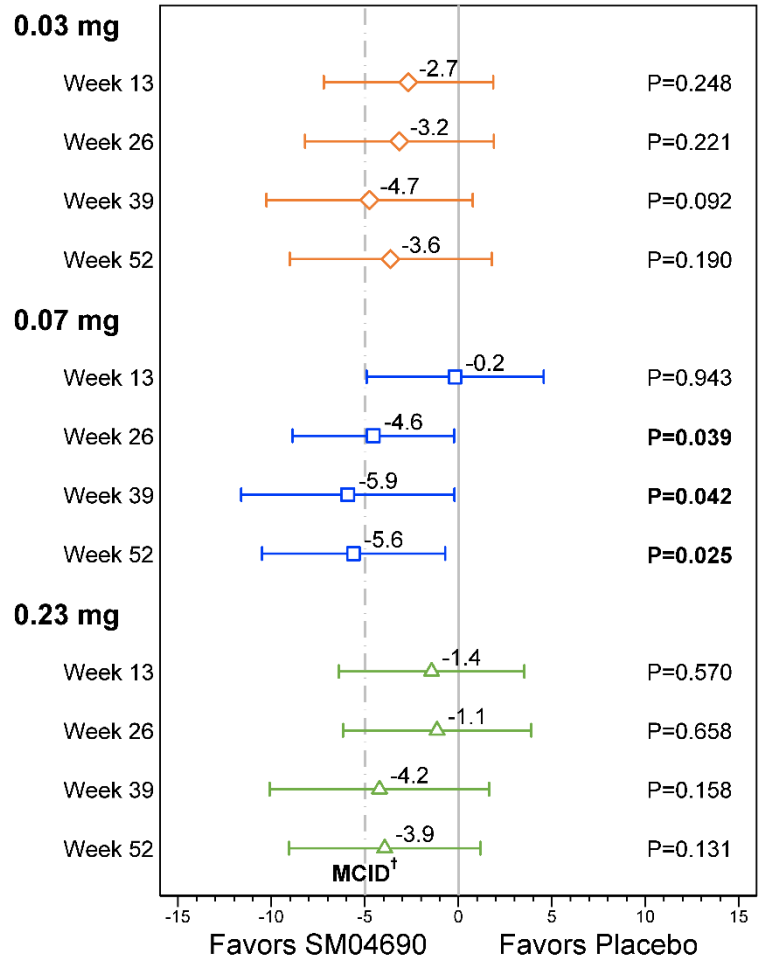
ITT



Unilateral Symptomatic



Unilateral Symptomatic without Widespread Pain

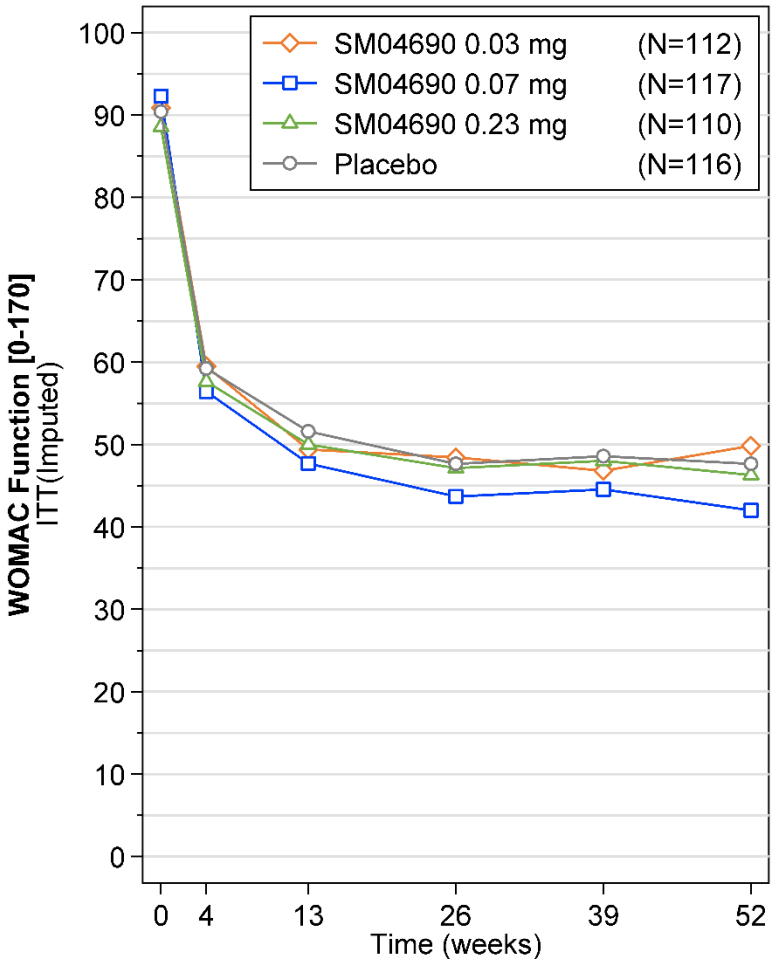


Comparisons from Baseline-adjusted ANCOVA versus Placebo. †**MCID**: Minimal Clinically Important Difference defined as 10% (5 points) of WOMAC Pain subscore. Cooper, et al. (2013) *Curr Med Res.*

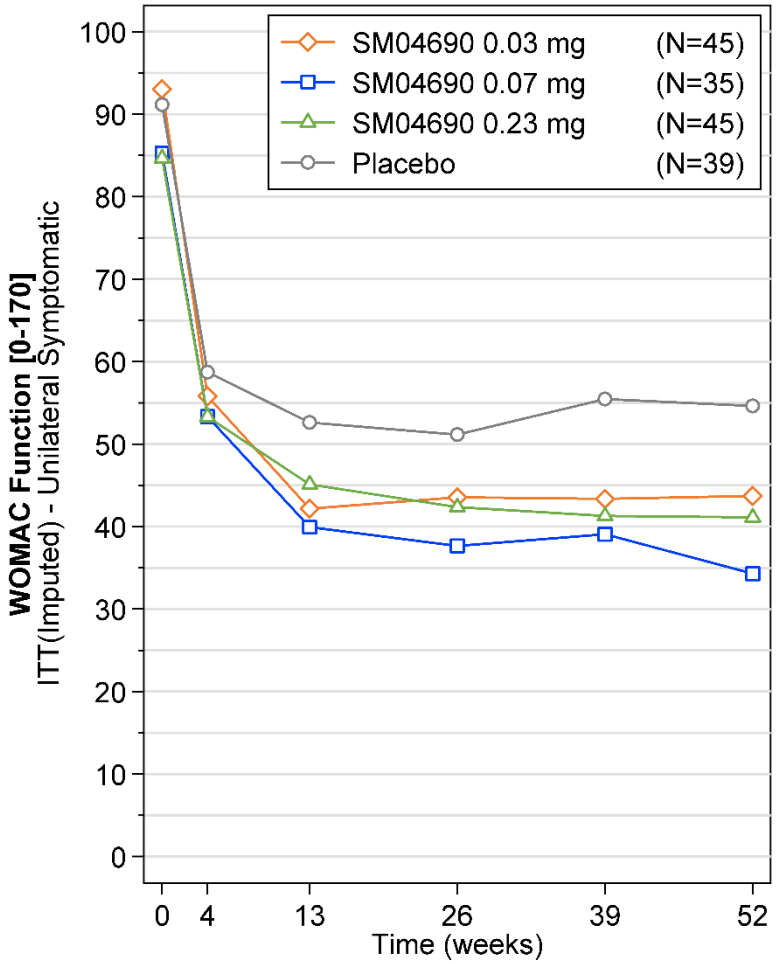
WOMAC Function [0-170]

Actual scores (mean)

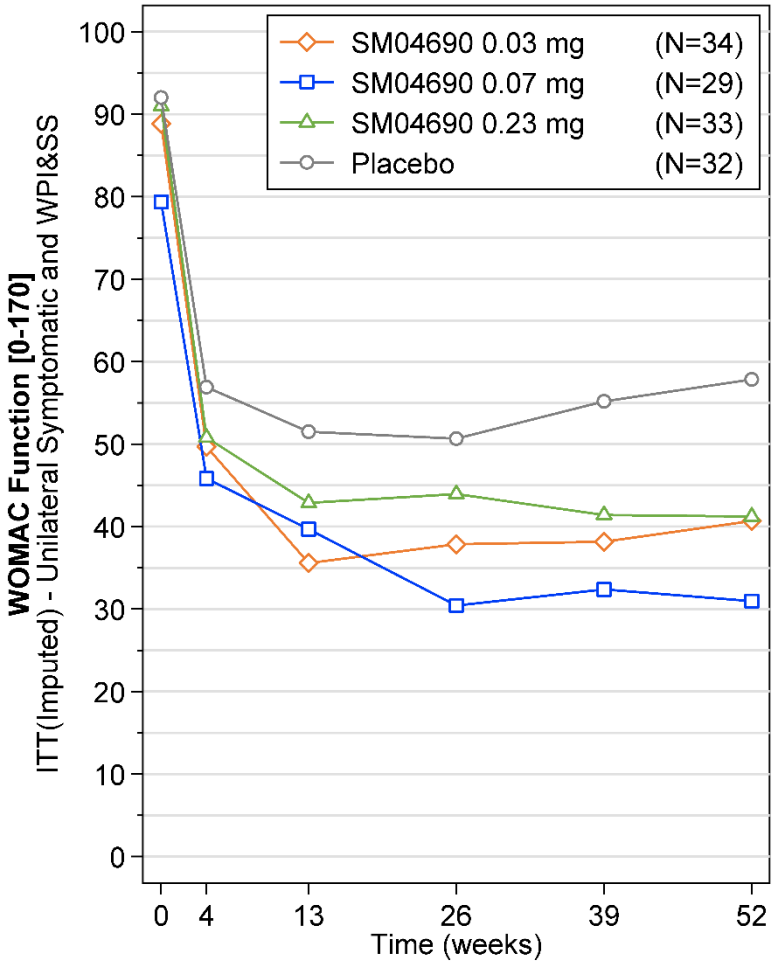
ITT



Unilateral Symptomatic

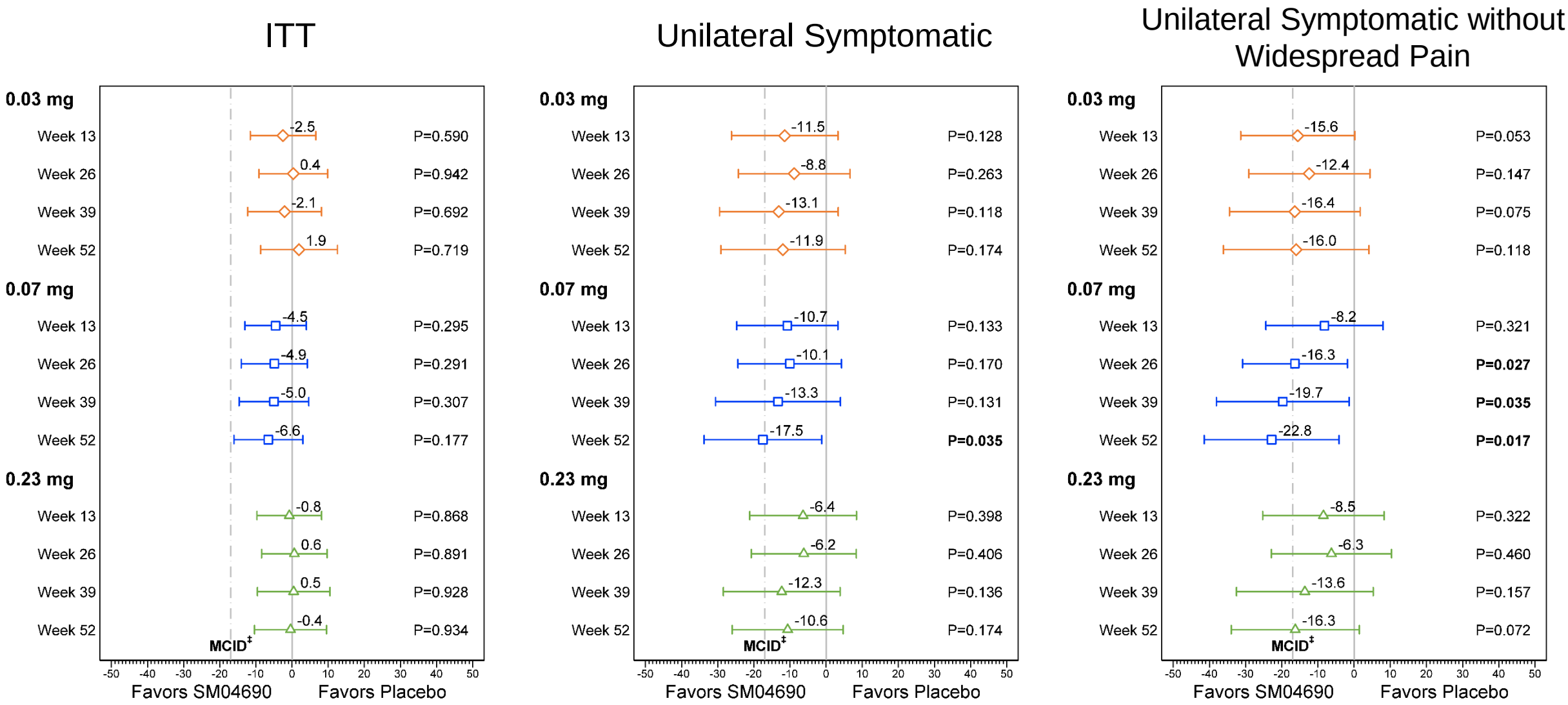


Unilateral Symptomatic without Widespread Pain



WOMAC Function [0-170]

Ladder plots comparing mean (± 95%CI) to placebo

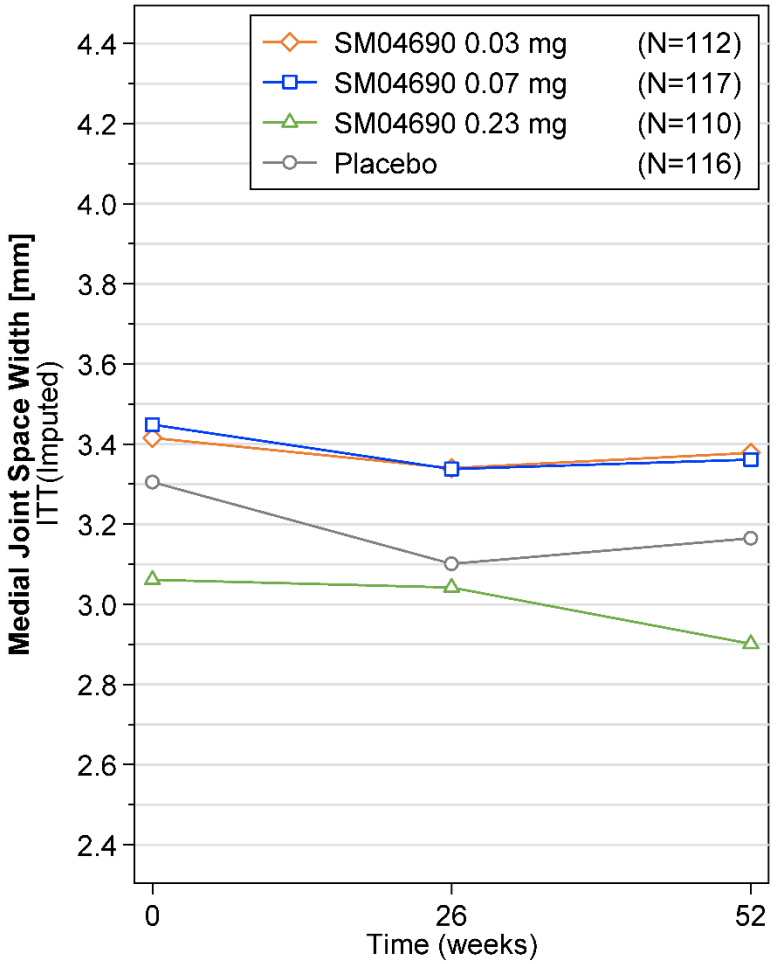


Comparisons from Baseline-adjusted ANCOVA versus Placebo. ‡**MCID**: Minimal Clinically Important Difference defined as 10% (17 points) of WOMAC Function subscore. Cooper, et al. (2013) *Curr Med Res.*

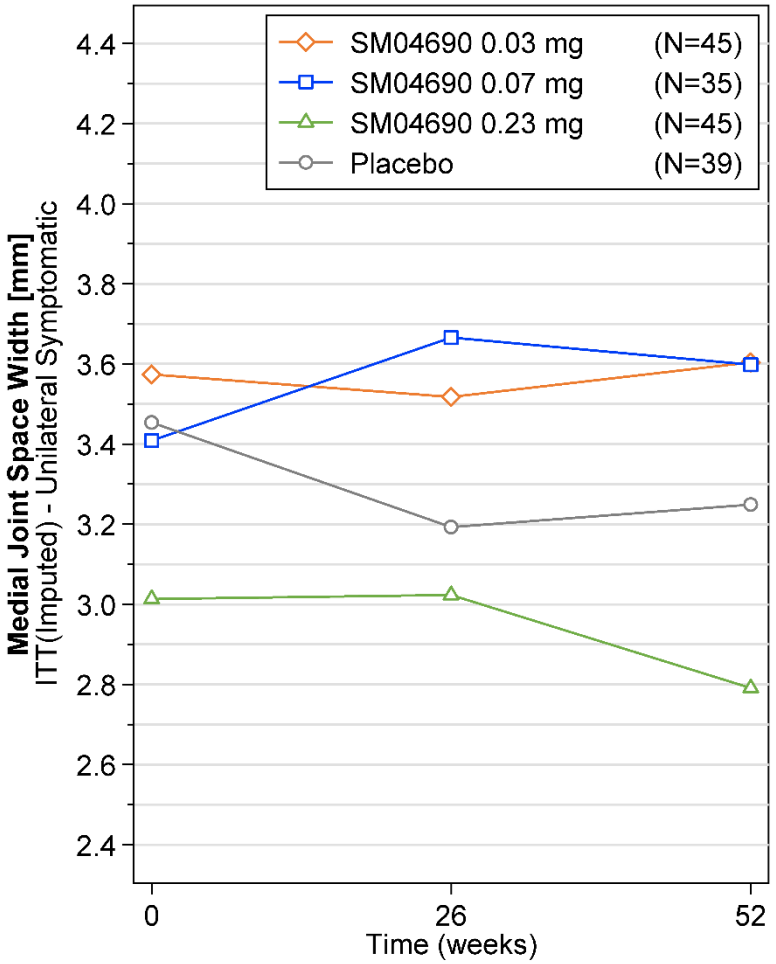
Medial joint space width (mm)

Actual measurements (mean)

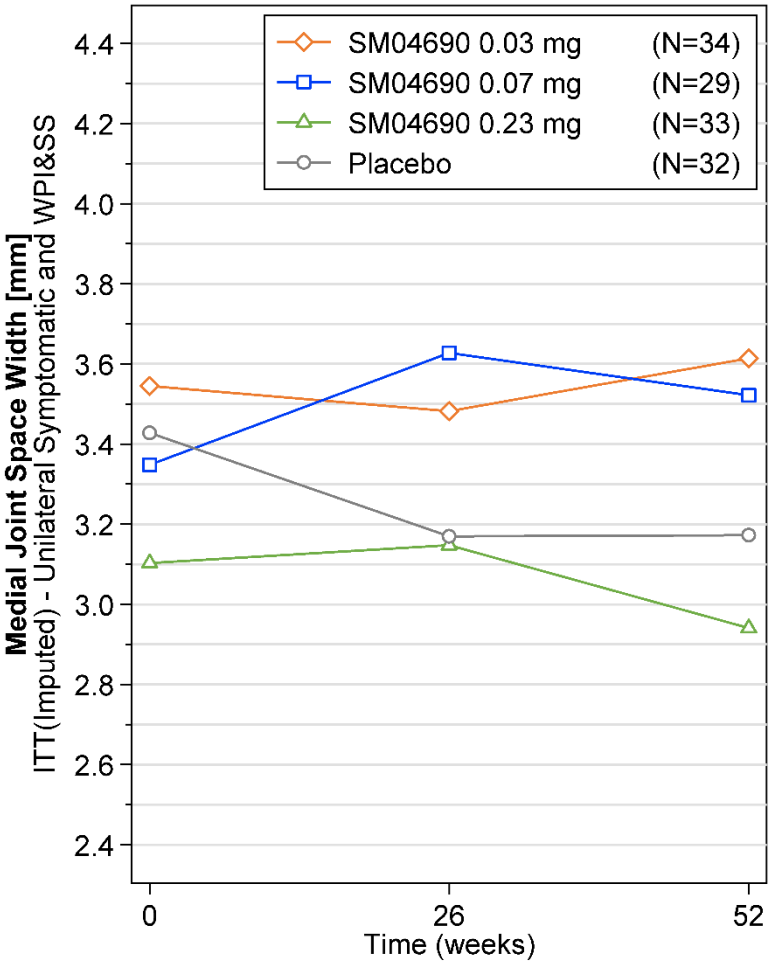
ITT



Unilateral Symptomatic



Unilateral Symptomatic without Widespread Pain

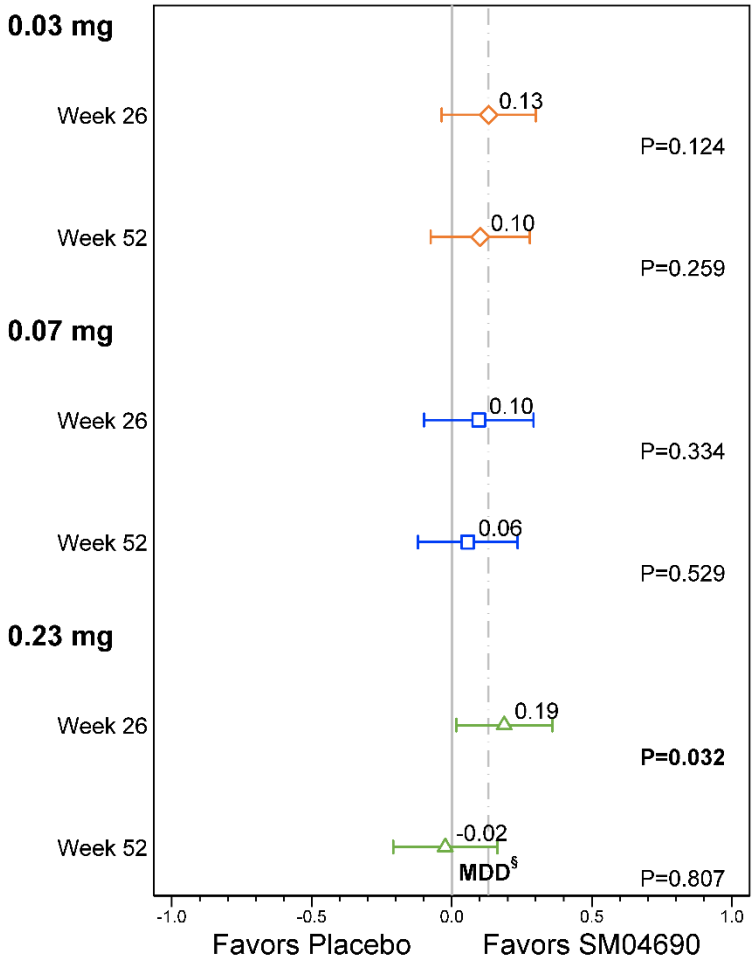


Intra- and inter- observer reproducibility 0.92 & 0.90 respectively. QuAP™ positioner used. Centrally, blinded read.

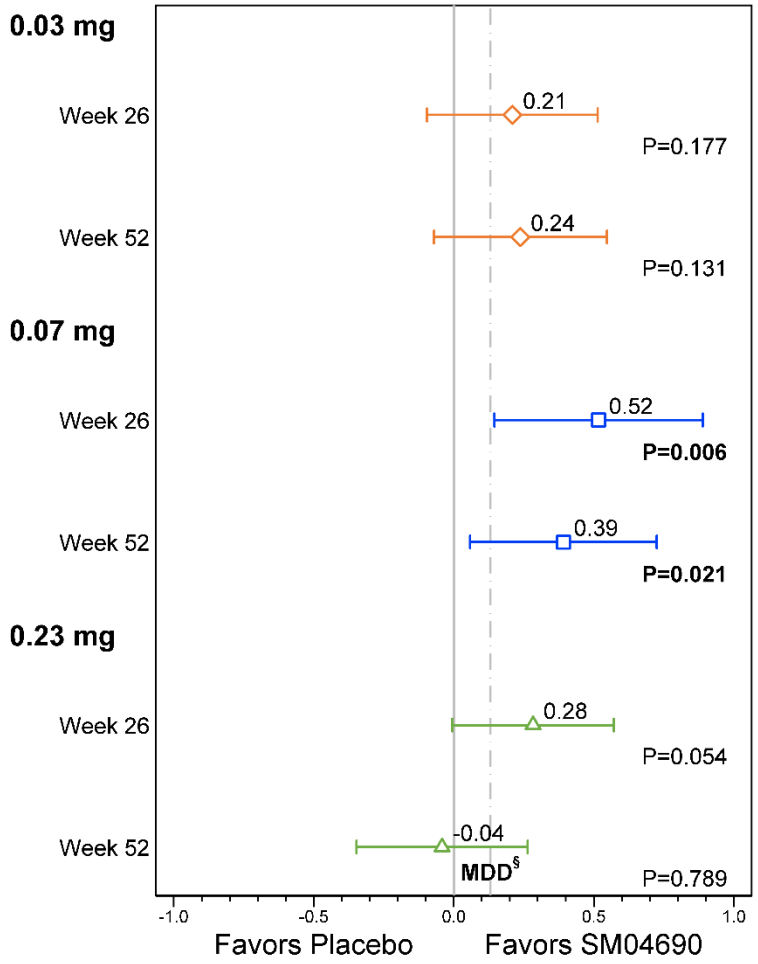
Medial joint space width (mm)

Ladder plots comparing mean (± 95%CI) to placebo

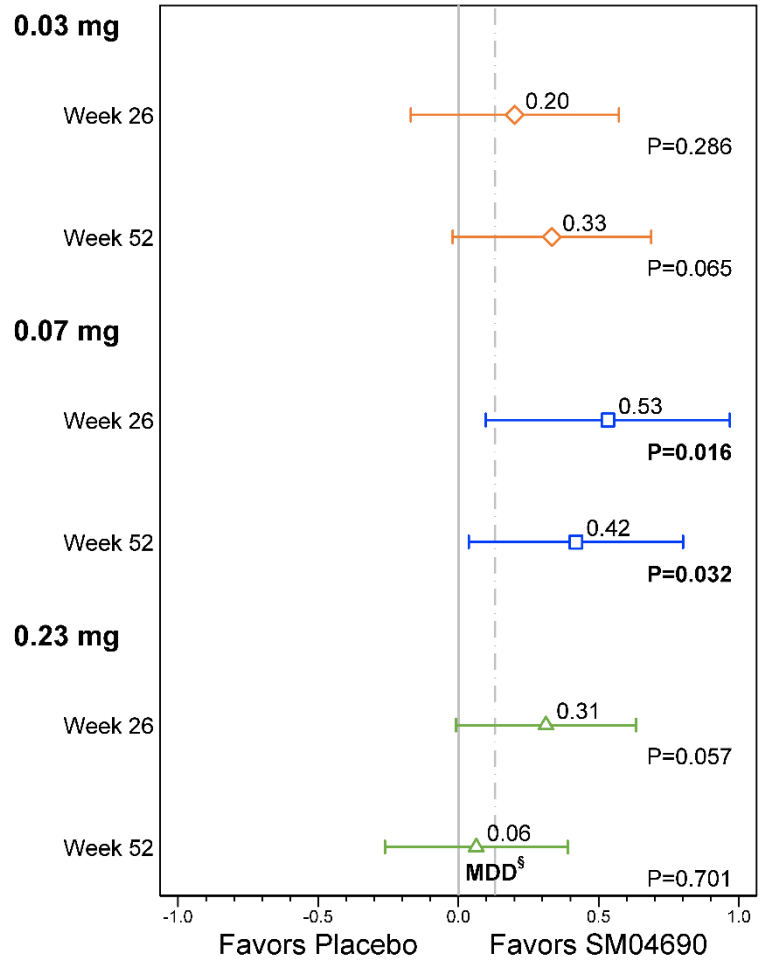
ITT



Unilateral Symptomatic



Unilateral Symptomatic without Widespread Pain



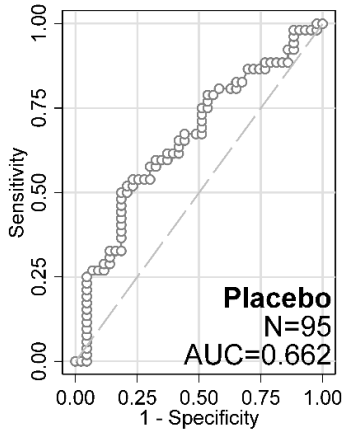
Comparisons from Baseline-adjusted ANCOVA versus Placebo. **§MDD:** Minimal Detectable Difference defined as 0.13 mm of medial joint space width. Dupuis, et al. (2003) *OAC.*

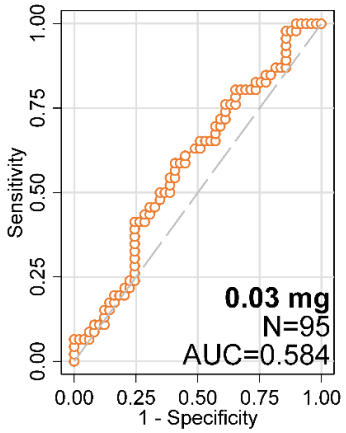
mJSW change concordance with WOMAC Pain and Function response (post-hoc analysis)

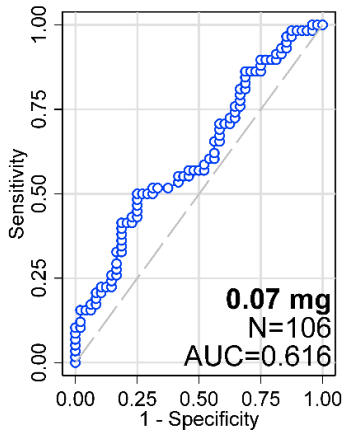
mJSW change concordance with WOMAC Pain and Function

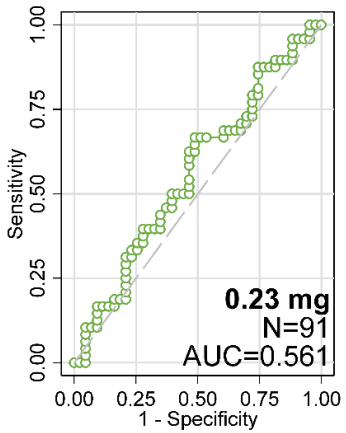
Outcomes measured at Week 52

ITT

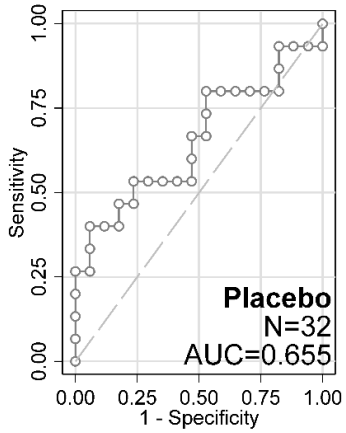


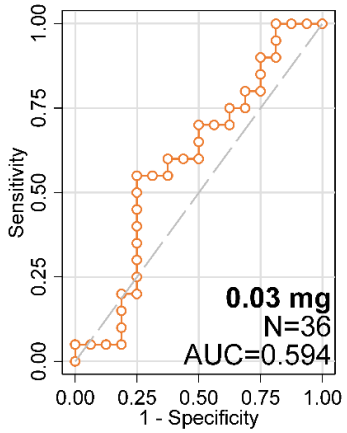


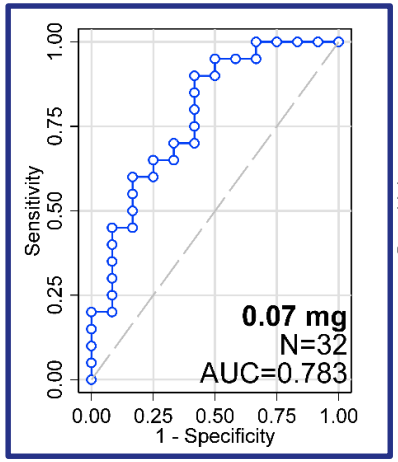


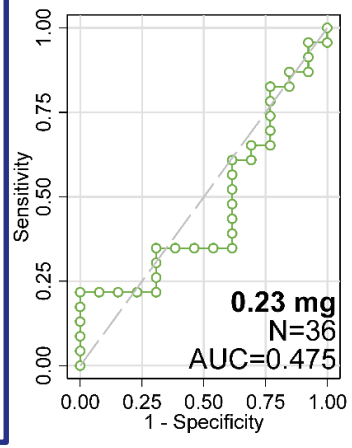


Unilateral Symptomatic

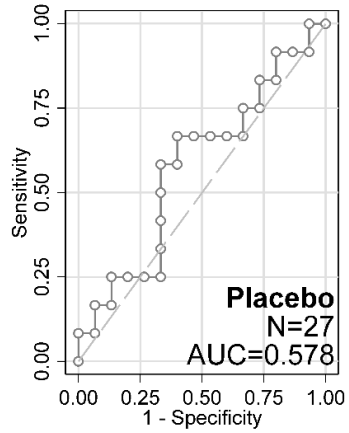


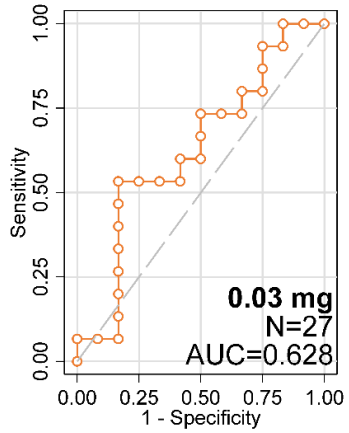


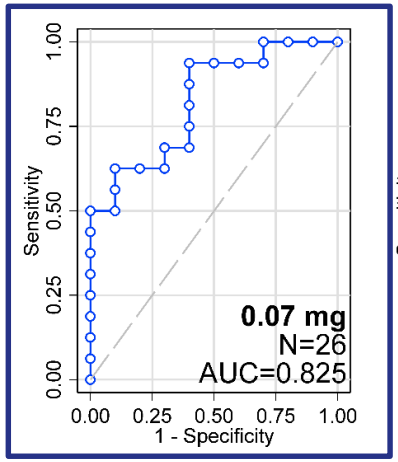


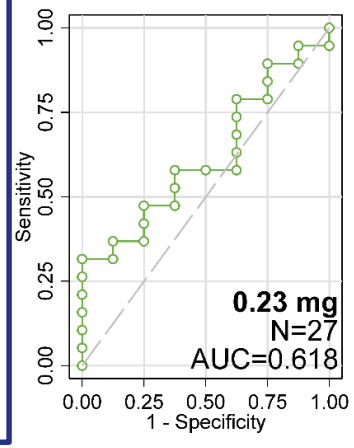


Unilateral Symptomatic without Widespread Pain









Pain and Function response defined as having both Pain and Function responses separately. Baseline mJSW-adjusted logistic regression used to estimate concordance.

Discussion

This proof-of-concept study:

- Did not meet its primary objective for the ITT population
- Identified a potential therapeutic dose, 0.07 mg SM04690
- Identified a potential target population
  - Unilateral symptomatic knee OA subjects without widespread pain discriminate target knee WOMAC outcomes better than bilateral symptomatic subjects and those with widespread pain[1]
  - We hypothesize that when the target knee in an unilateral symptomatic subject was injected, biomechanical load was normalized between both knees. In bilateral symptomatic subjects, after the target knee was injected (and on average improved), it gained increased biomechanical loading as the non-treated knee remained painful[2]
  - We hypothesize that the relatively unloaded unilateral symptomatic knee provided an enhanced environment for SM04690 to improve cartilage degradation and regeneration over PBO[3]
- Study limitations included no formal sample size estimation and small subgroups

1. Riddle and Stratford. (2013) *Rheumatology.*
2. Creaby, et al. (2012) *Arch Phys Med Rehab.*
3. Lefeber, et al. (2006) *Curr Opin Rheum.*

Summary

This phase 2 trial demonstrated:

- SM04690 appeared safe and well-tolerated
- Clinically meaningful improvements in WOMAC Pain and Function for all subjects at all time points compared to baseline
- Pain, function, and radiographic improvements compared to PBO were observed in 0.07 mg SM04690 Unilateral Symptomatic and Unilateral Symptomatic without Widespread Pain subjects
- Additional analyses presented Monday, 9-11 AM:
  - Poster #1201: Reducing Heterogeneity in OA Clinical Trials
  - Poster #1204: Radiographic Outcomes Were Associated with Pain and Function Responses
- Innovation Theater, Monday 3:30-4:15, Exhibit Hall Theater B

A Phase 2b study to confirm target population and dose is ongoing (NCT03122860)

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
- SM04690-OA-04, Phase 2, N=700 (enrollment complete)
  - 24 weeks, primary endpoints 24 week S&S and JSW
  - Started April 2017, data available May 2018
- SM04690-OA-05, safety extension (observational with no additional injections; ongoing)
  - Started September 2016
  - 5 years, safety with exploratory long-term efficacy including radiographs and WOMAC
- SM04690-OA-08, MRI, N=15
  - 52 weeks, exploratory evaluation of cartilage quality and thickness
  - Estimated November 2017 start

Thank you