SM04690: Potential first-in-class disease modifying treatment for knee osteoarthritis

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Disclosures

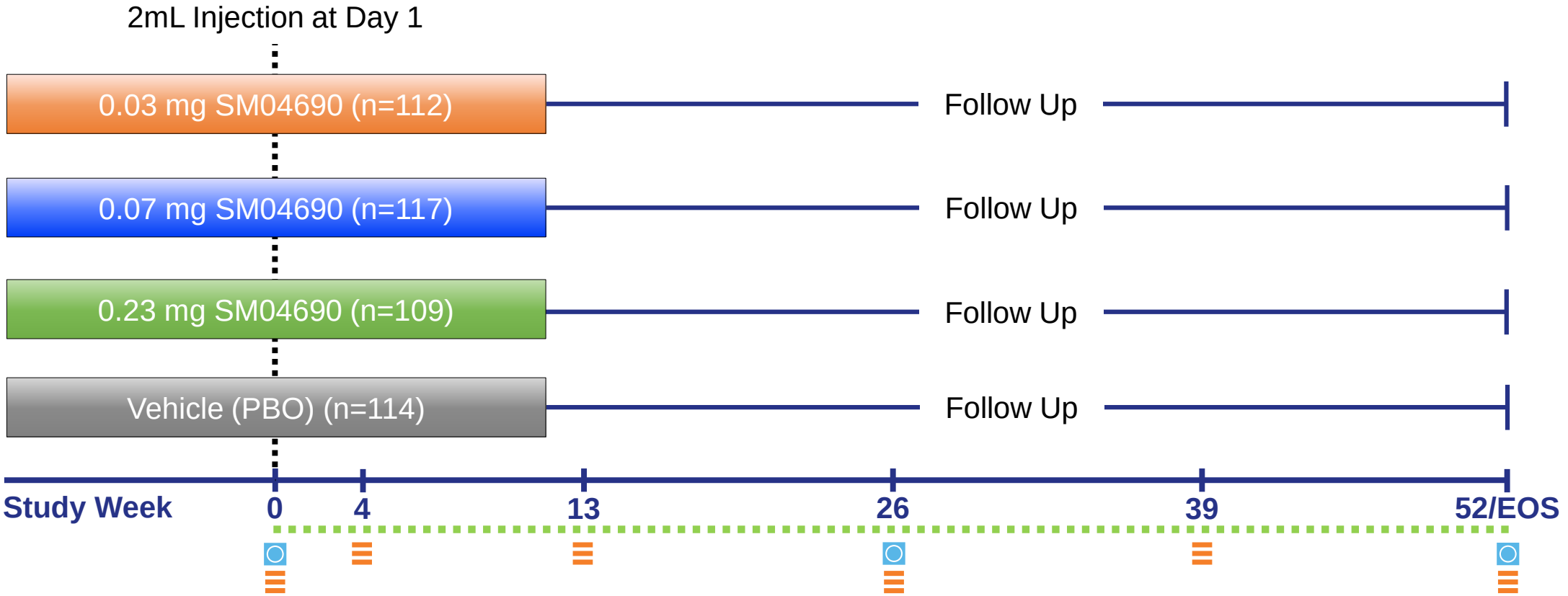
Yusuf Yazici	Samumed, LLC, employee and shareholder
Timothy McAlindon	Samumed, LLC, Astellas, Flexion, Pfizer, Regeneron, Seikagaku
Allan Gibofsky	AbbVie, Amgen, Johnson & Johnson, GSK, Regeneron, Pfizer, Horizon Iroko, Celgene, Novartis/Sandoz, Samumed, LLC
Nancy Lane	Samumed, LLC
Daniel Clauw	AbbVie, Astellas, Cerephex, Eli Lilly, Forest Laboratories, Johnson & Johnson, Merck, Pfizer, Purdue, Theravance, Tonix, UCB, Williams and Connolly LLP, Zynerba, Samumed, LLC
Christopher Swearingen	Samumed, LLC, employee and shareholder
Anita DiFrancesco	Samumed, LLC, employee and shareholder
Jeyanesh Tambiah	Samumed, LLC, employee and shareholder
Marc Hochberg	Bioberica, EMD Serono, Novartis Pharma AG, Plexxikon, Pfizer, Proximagen, Regeneron, Theralogix, LLC, Samumed, LLC

Knee osteoarthritis (OA), the Wnt pathway, and SM04690

- The Wnt pathway is upregulated in OA.[1,2] Inhibition may regenerate and protect articular cartilage.
- SM04690 is a small-molecule Wnt pathway inhibitor for potential treatment of knee OA. In preclinical studies:
  - Inhibited inflammation and cartilage degradation[3]
  - Regenerated cartilage[3]
  - Demonstrated sustained local exposure and no systemic toxicity[3,4]
- A phase 1 study suggested a single SM04690 injection had potential for improving symptoms and maintaining joint space in knee OA subjects[4]
- Results from a 52-week, phase 2a study are presented

1.Rudnicki JA and Brown AM. (1997) *Dev Biol.*
2.Thomas RS, et al. (2011) *Arthritis Res Ther.*
3.Deshmukh V, et al. (2017) *Osteoarthritis Cartilage.*
4.Yazici Y, et al. (2017) *Osteoarthritis Cartilage.*

SM04690-OA-02: Phase 2a study design



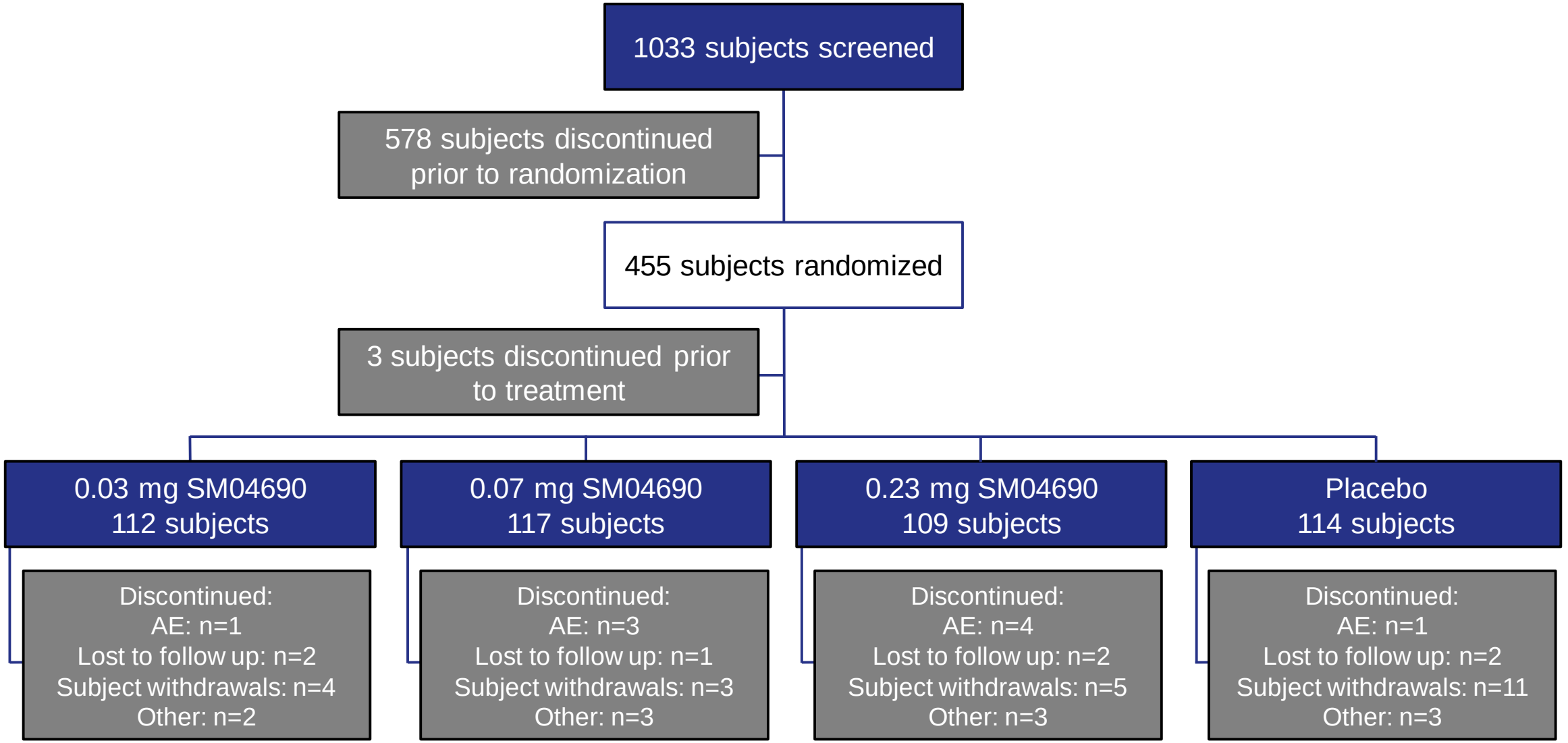
Primary objective: Change from baseline in WOMAC Pain at Week 13

- **Clinical assessments:** WOMAC Function, Pain; Patient and MD Global Assessment; SF-36
- **Imaging:** Knee X-ray for medial joint space width (mJSW)
- **Safety assessments:** Adverse events (AEs), vital signs, physical exam, lab panels

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 Phase 2a: Study participant flow chart



SM04690 Phase 2a: Study subject characteristics (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/m²) [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)

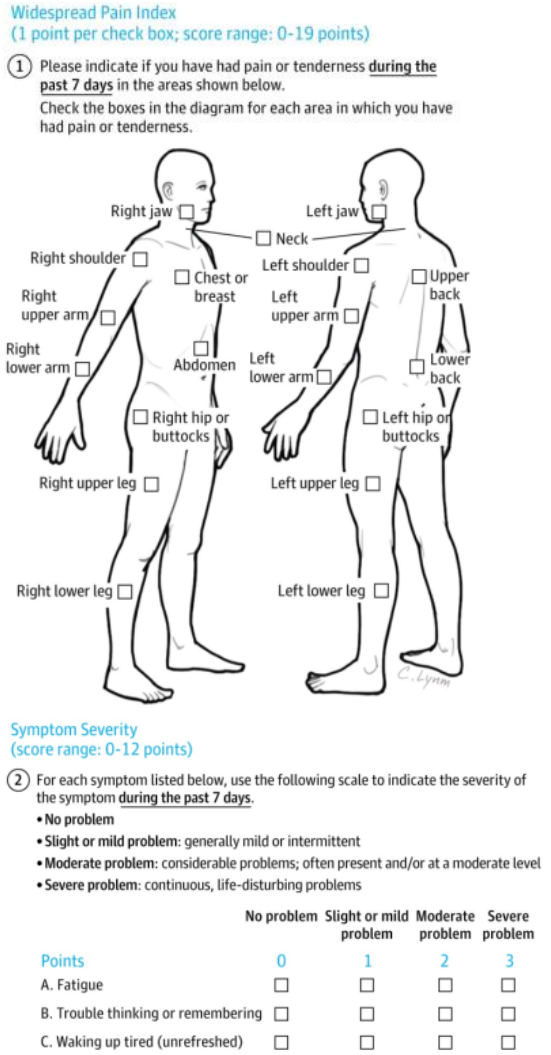
	0.03 mg (n=111)	0.07 mg (n=114)	0.23 mg (n=104)	Placebo (n=108)
Subjects reporting AE(s) [N(%)]	61 (55.0)	65 (57.0)	47 (45.2)	53 (49.1)
Subjects reporting No AE(s) [N(%)]	50 (45.0)	49 (43.0)	57 (54.8)	55 (50.9)
Subjects reporting SAE(s) [#AE / N(%)]	7/5 (4.5)	12/4 (3.5)	5/4 (3.8)	3/3 (2.8)

No SAEs were deemed related to study drug by PI.

*All AEs deemed related to drug per protocol.

SM04690 SM04690 Phase 2a: 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)

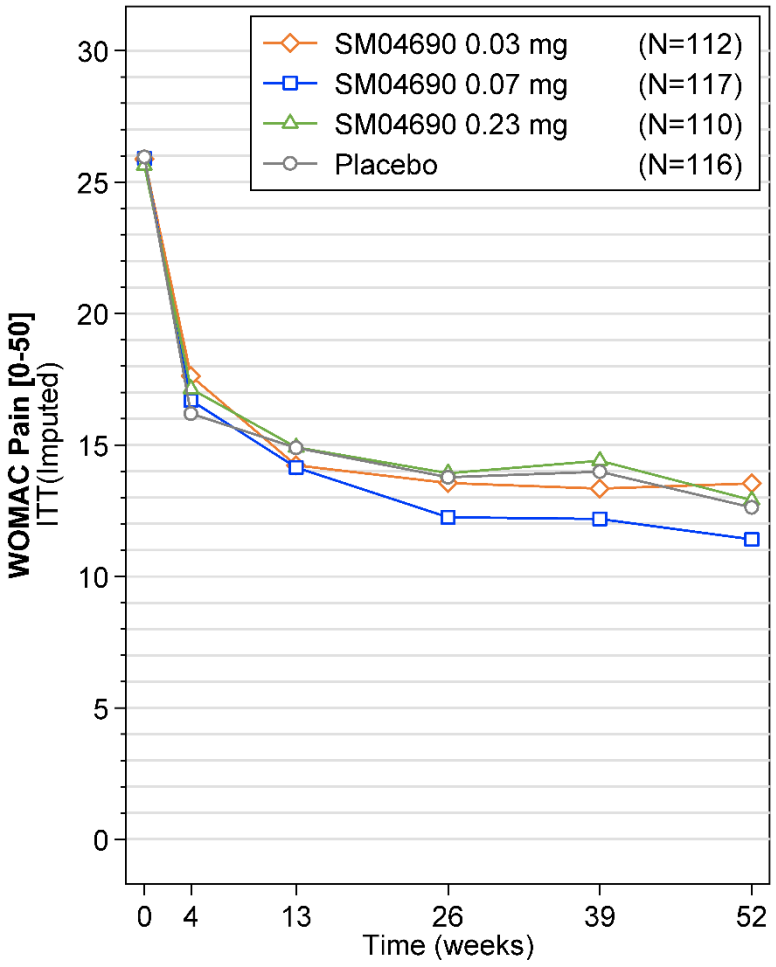
② For each symptom listed below, use the following scale to indicate the severity of the symptom **during the past 7 days**.

- **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

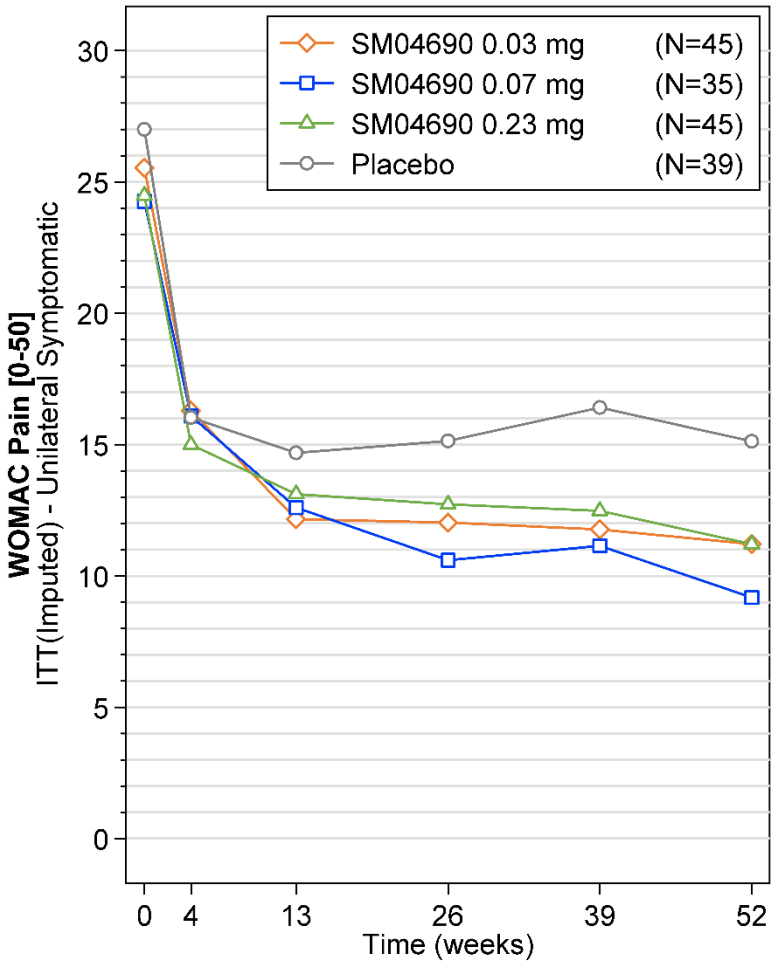
	No problem	Slight or mild problem	Moderate problem	Severe problem
Points	0	1	2	3
A. Fatigue	☐	☐	☐	☐
B. Trouble thinking or remembering	☐	☐	☐	☐
C. Waking up tired (unrefreshed)	☐	☐	☐	☐

WOMAC Pain [0-50]
Actual scores (mean)

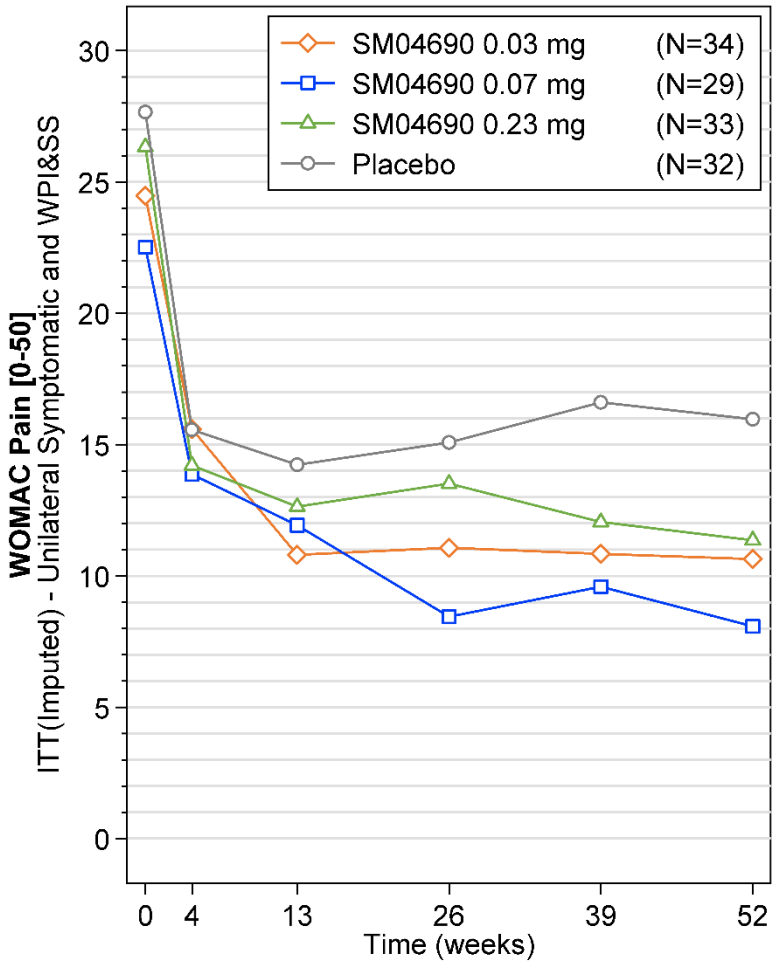
ITT



Unilateral Symptomatic



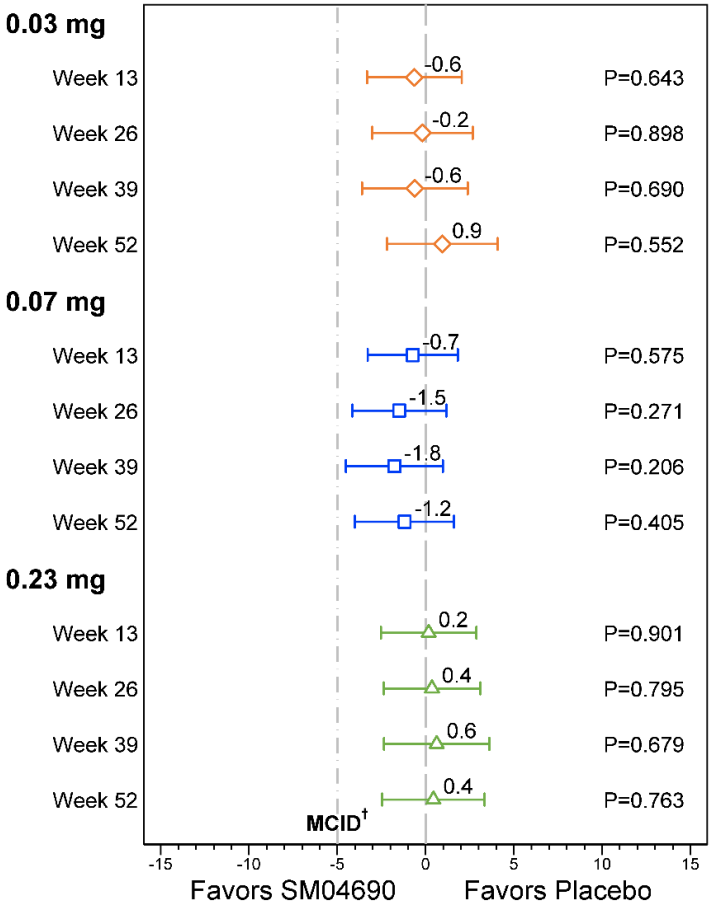
Unilateral Symptomatic without Widespread Pain



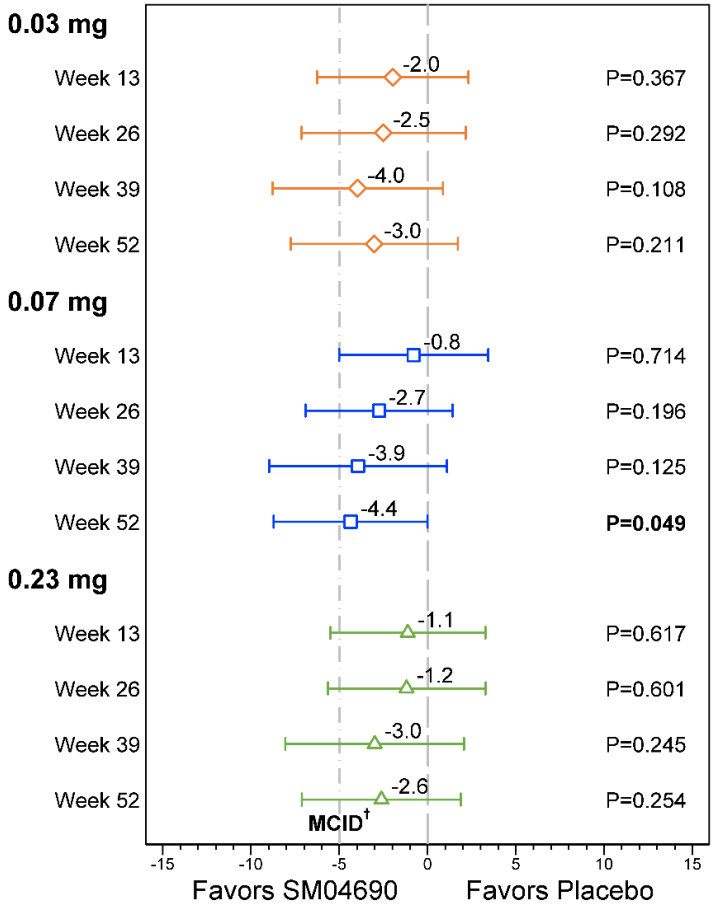
WOMAC Pain [0-50]

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

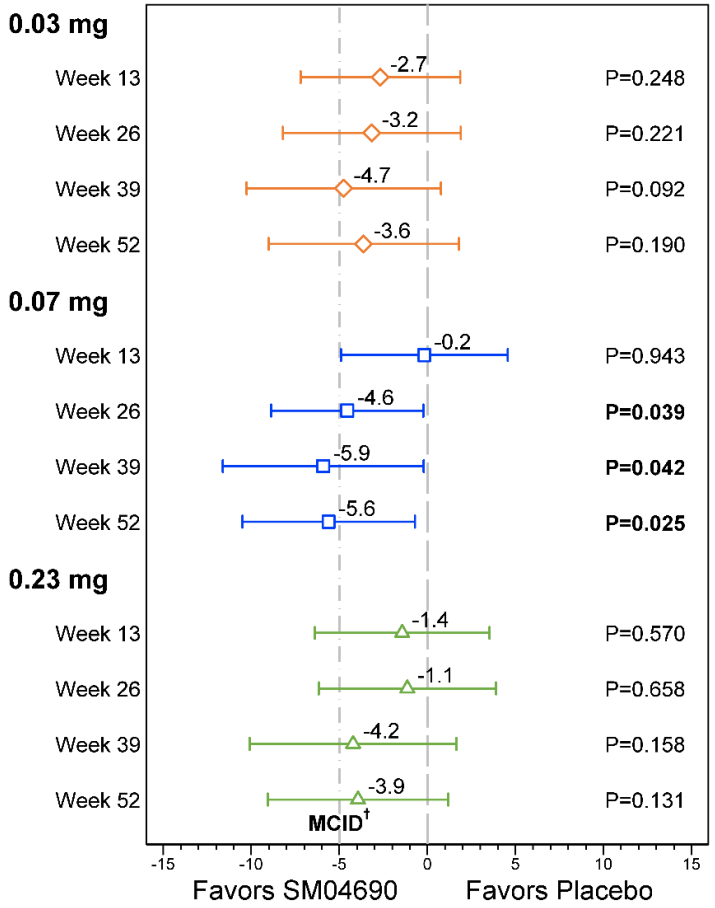
ITT



Unilateral Symptomatic



Unilateral Symptomatic without Widespread Pain

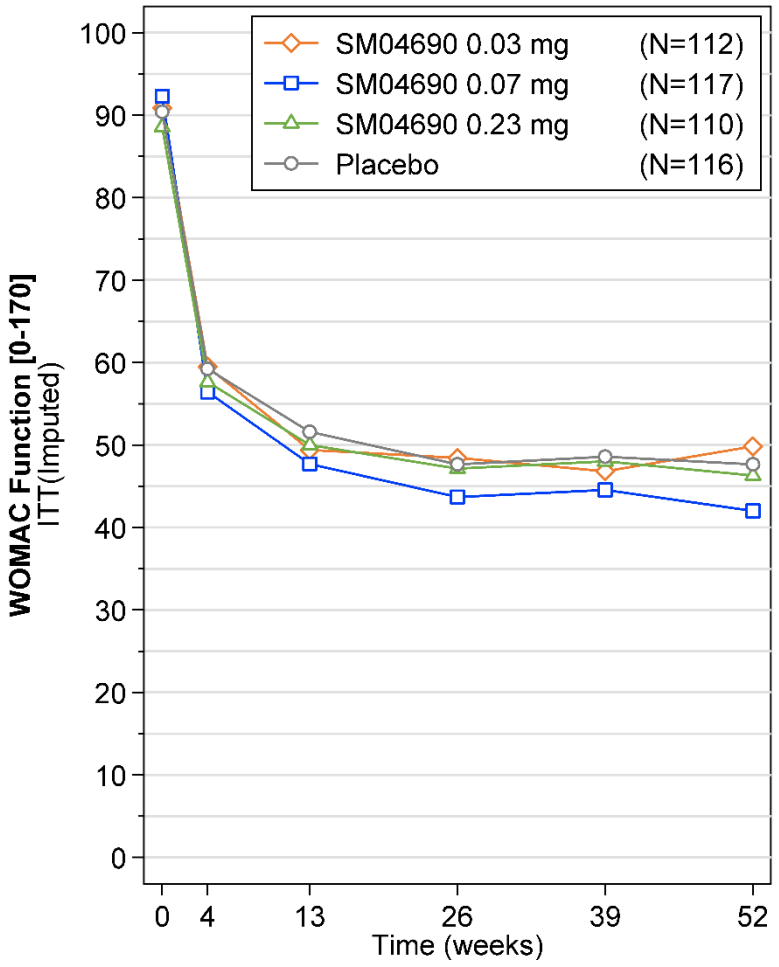


Comparisons from baseline-adjusted ANCOVA versus placebo. †**MCID**: Minimal clinically important difference defined as 10% (5 points) of WOMAC Pain subscore.

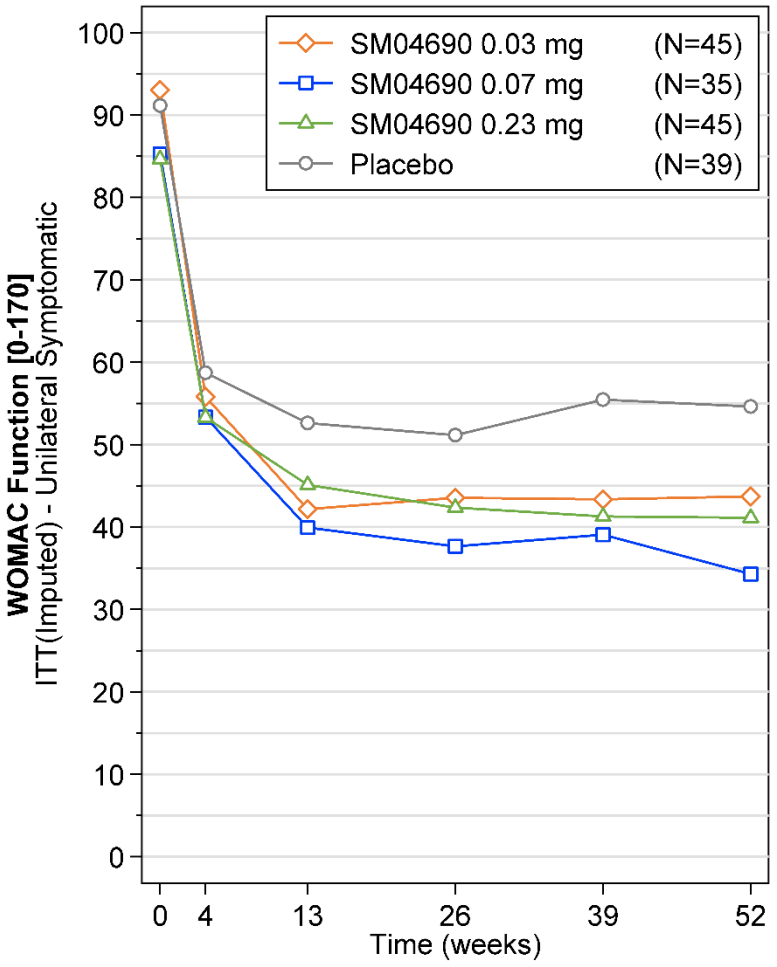
Cooper, et al. (2013) *Curr Med Res.*

WOMAC Function [0-170]
Actual scores (mean)

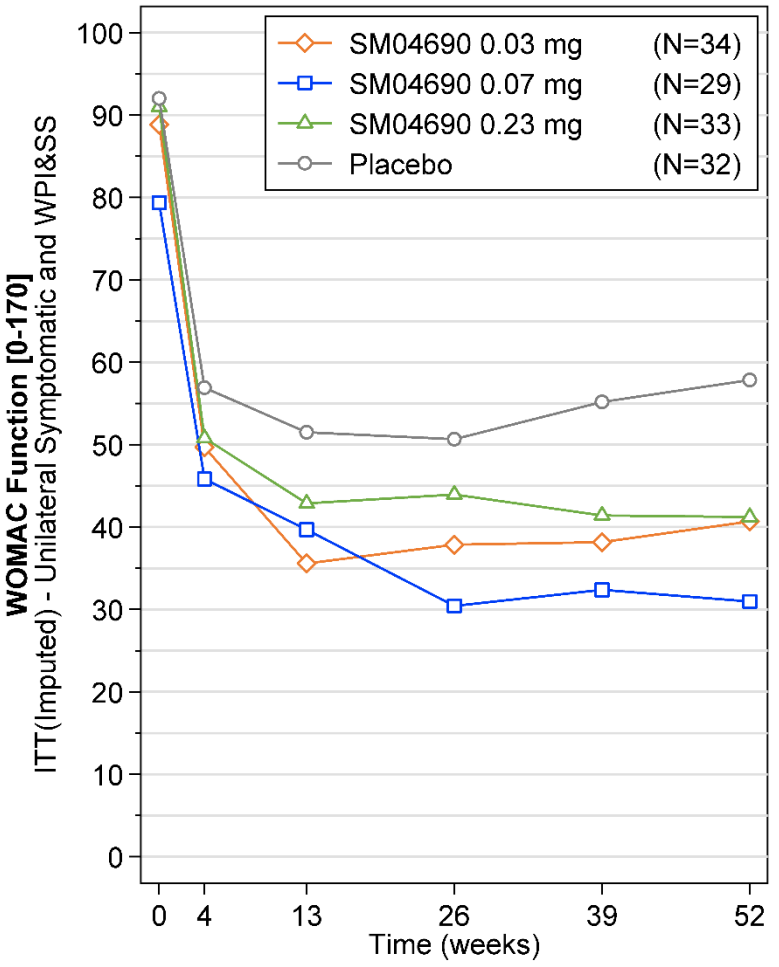
ITT



Unilateral Symptomatic



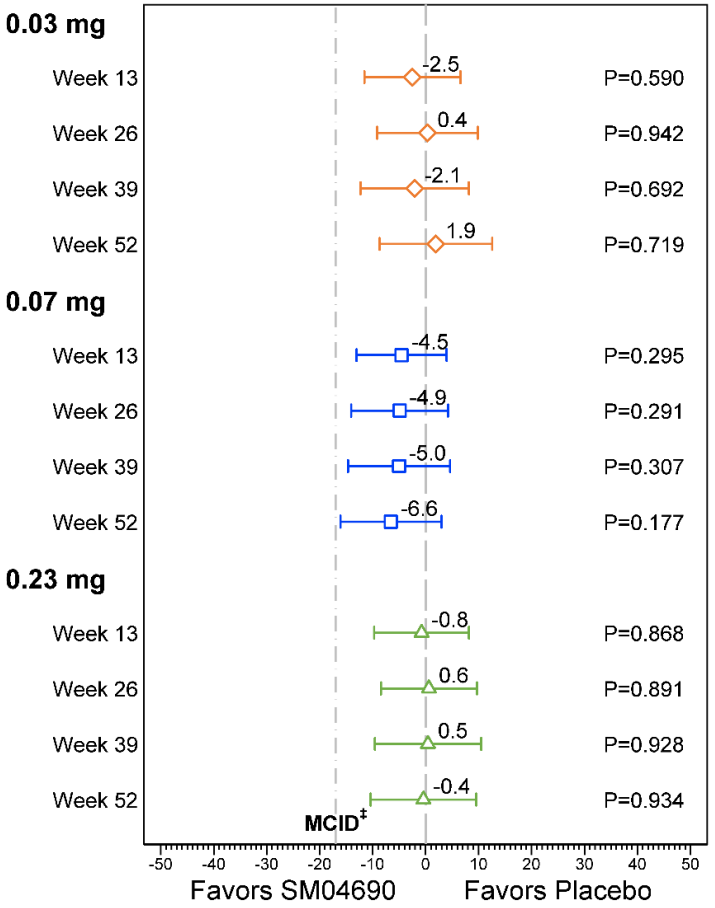
Unilateral Symptomatic without Widespread Pain



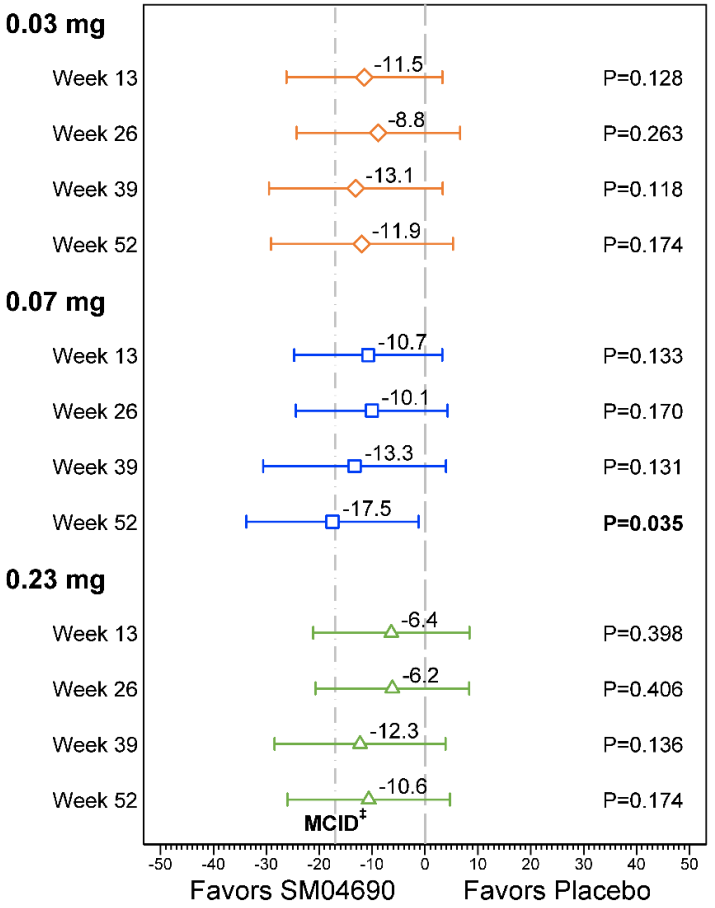
WOMAC Function [0-170]

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

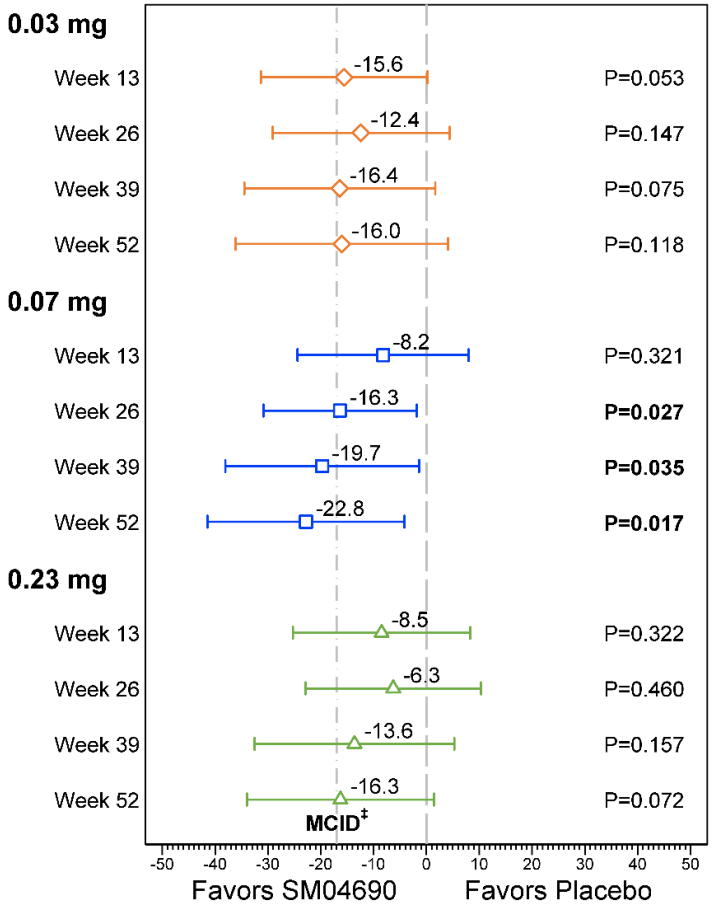
ITT



Unilateral Symptomatic



Unilateral Symptomatic without Widespread Pain



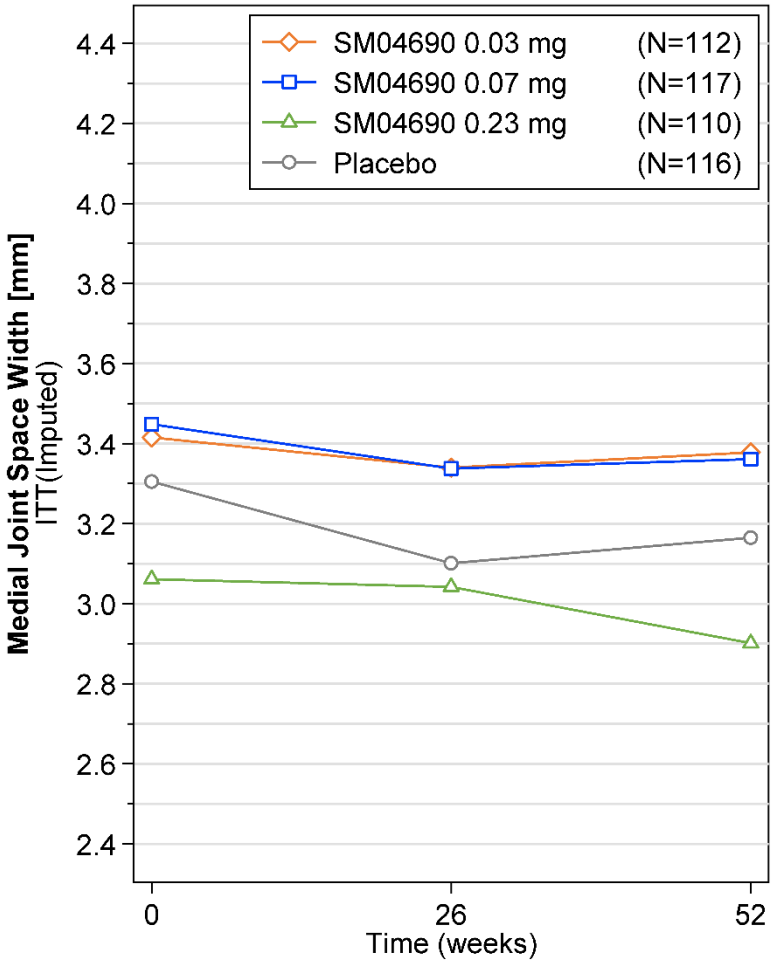
Comparisons from baseline-adjusted ANCOVA versus placebo. ‡**MCID**: Minimal clinically important difference defined as 10% (17 points) of WOMAC Function subscore.

Cooper, et al. (2013) *Curr Med Res.*

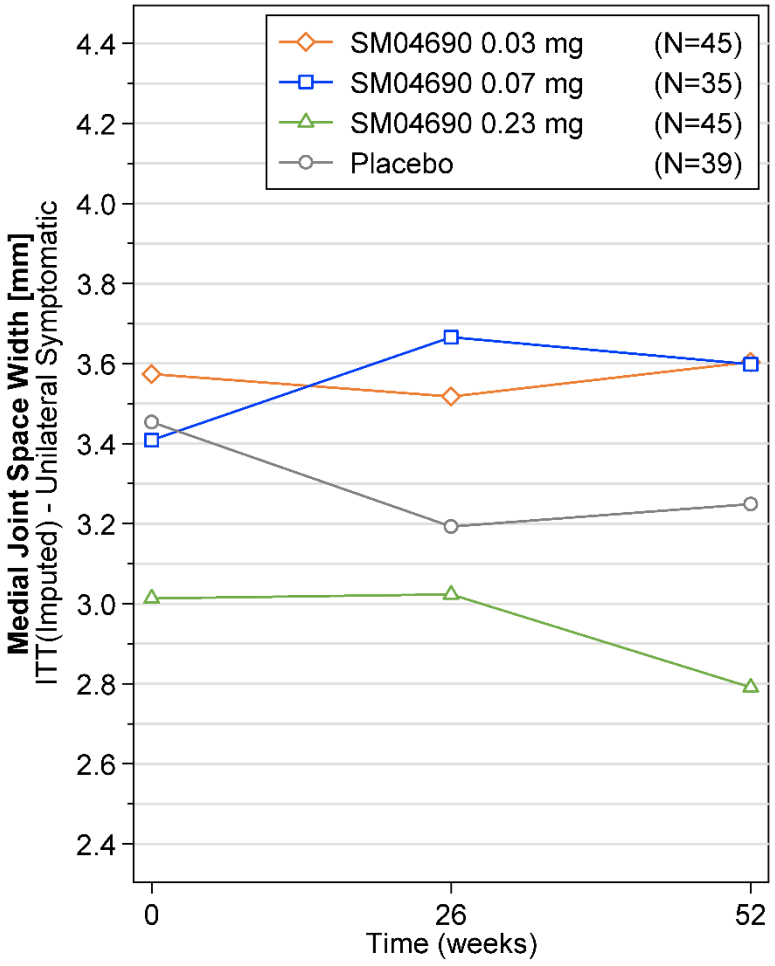
Medial Joint Space Width (mJSW) (mm)

Actual measurements (mean)

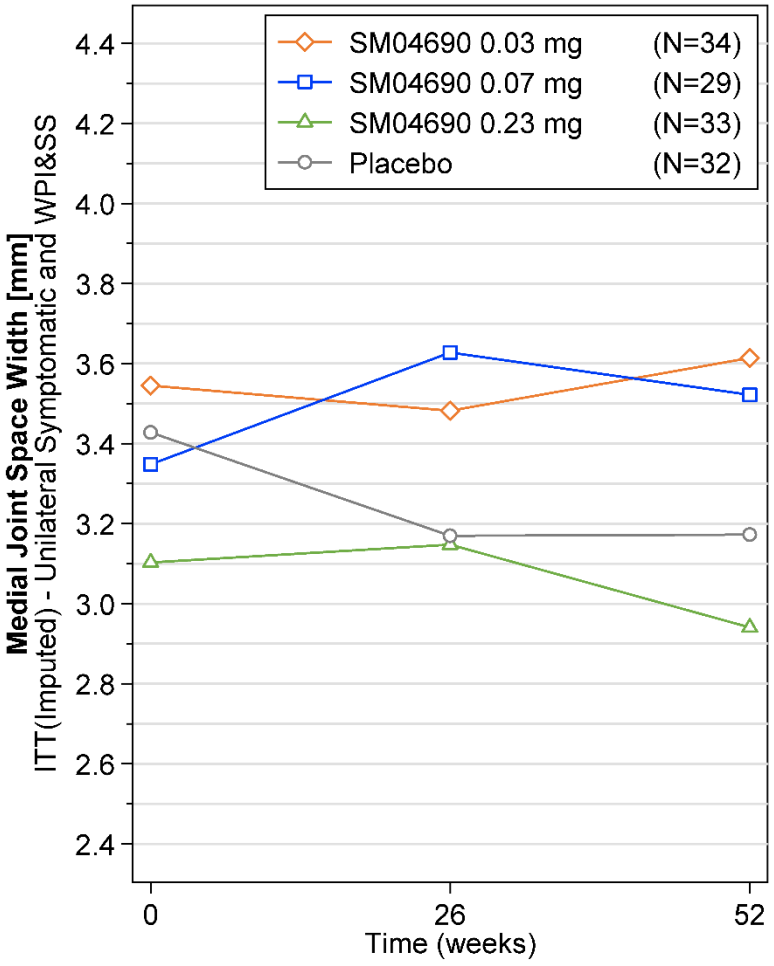
ITT



Unilateral Symptomatic



Unilateral Symptomatic without Widespread Pain

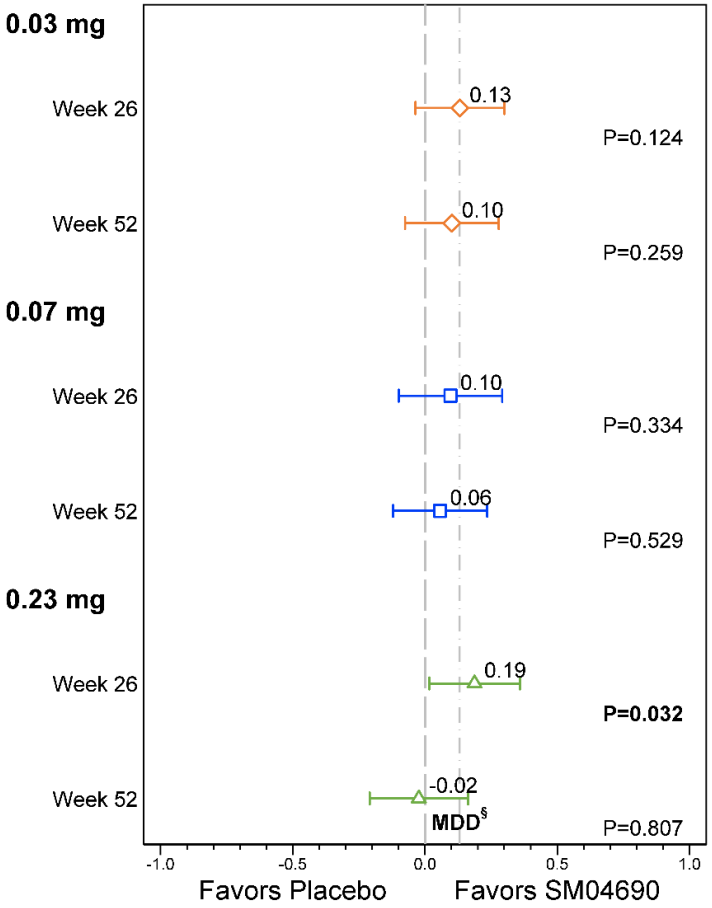


Intra- and inter- observer reproducibility 0.92 & 0.90 respectively. QuAP™ positioner used. Centrally, blinded read.

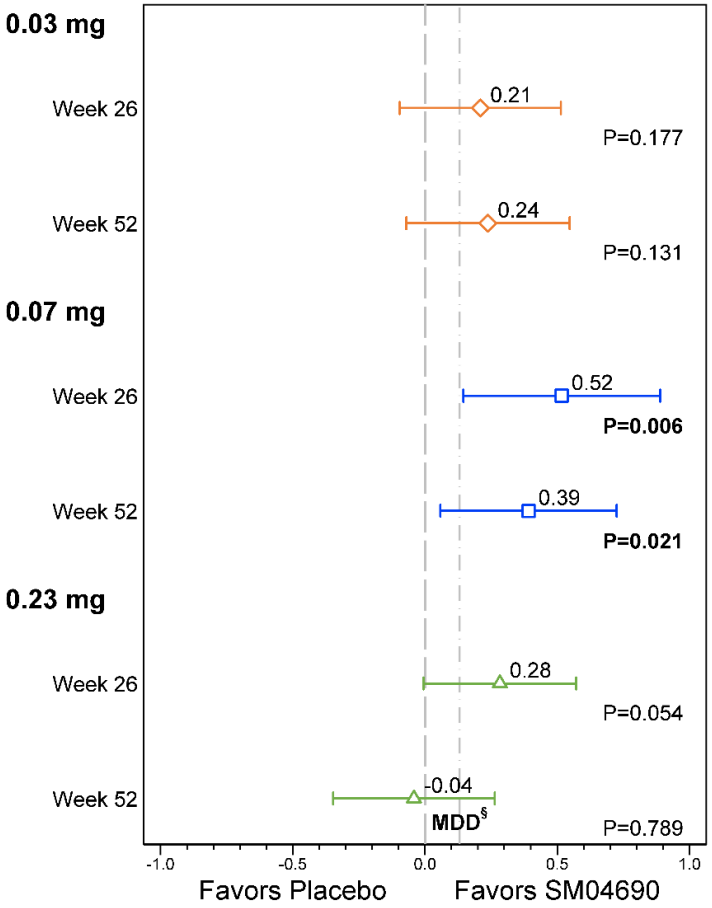
Medial Joint Space Width (mm)

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

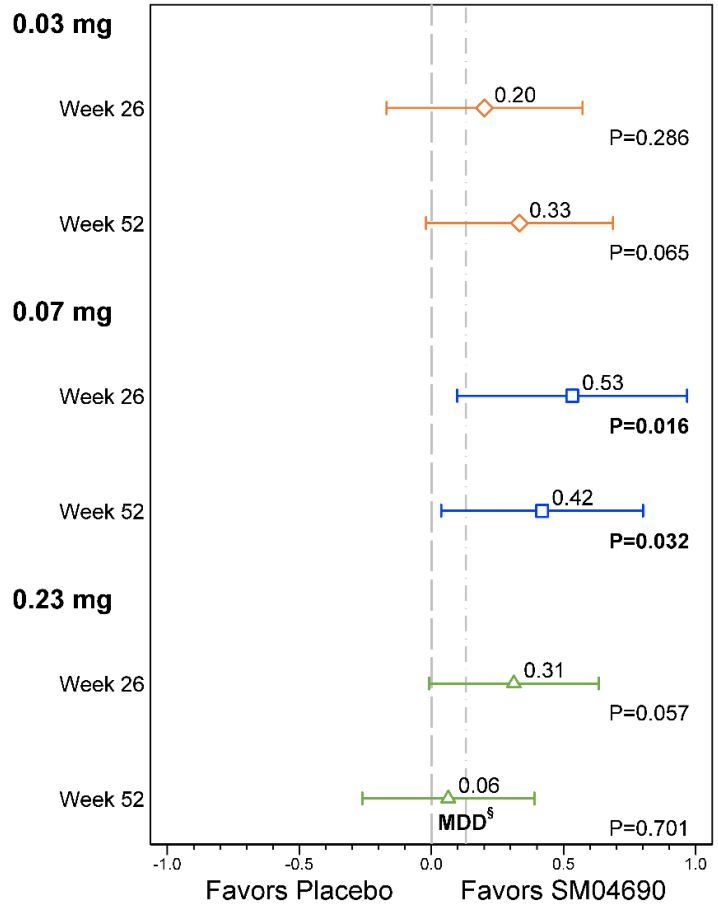
ITT



Unilateral Symptomatic



Unilateral Symptomatic without Widespread Pain



Comparisons from baseline-adjusted ANCOVA versus placebo. **§MDD:** Minimal detectable difference defined as 0.13 mm of mJSW.

Dupuis, et al. (2003) *OAC.*

Discussion

This proof-of-concept study

- Did not meet primary objective for ITT population
- Identified a potential target population
  - UNI subjects probably discriminated target knee WOMAC outcomes better than bilateral symptomatic subjects[1]
  - We hypothesize treated, relatively unloaded UNI knees provided enhanced environment for SM04690 to improve cartilage regeneration[2,3]
- Identified a potential therapeutic dose, SM04690 0.07 mg
  - Non-linear dose response observed
- Study limitations: Study was not powered to analyze subgroups

1. Riddle DL, Stratford PW. (2013) *Rheumatology.*
2. Creaby MW, et al. (2012) *Arch Phys Med Rehabil.*
3. Simic M, et al. (2012) *Arthritis Care Res (Hoboken).*

Conclusions

- SM04690 appeared safe and well-tolerated
- Clinically meaningful improvements in WOMAC Pain and Function observed for all subjects at all time points vs. baseline
- In this proof-of-concept study, a potential therapeutic dose (0.07mg) and target population were identified
  - Pain, function, and radiographic improvements compared with placebo were observed in 0.07 mg SM04690 Unilateral Symptomatic and Unilateral Symptomatic without Widespread Pain subjects at Week 52

Long-term extension data
ITT (As Observed, through 18 months)

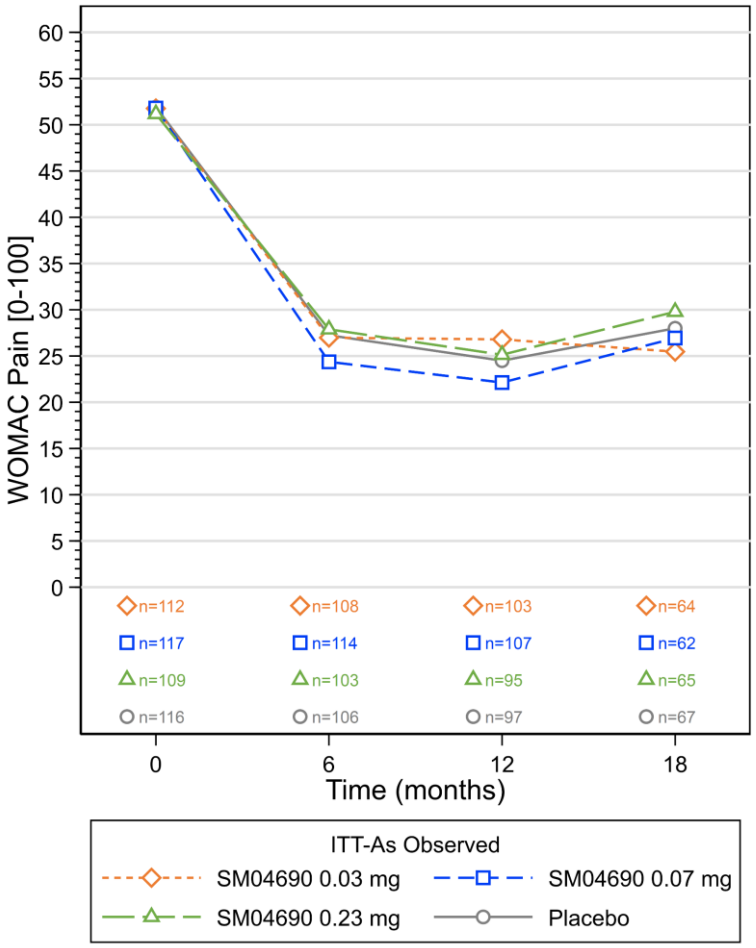
Comparison of enrollees vs non-enrollees in long-term extension

- Phase 2a subjects were enrolled into an open label long-term (5 year) extension study
- Similar demographic data between enrollees and non-enrollees
  - Age ~60, BMI ~29, ~56% female
- Similar OA features between enrollees and non-enrollees
  - ~65% Kellgren-Lawrence grade 3, ~35% Unilateral Symptomatic
- Similar baseline data between enrollees and non-enrollees
  - WOMAC Pain ~52, WOMAC Function ~55, medial JSW ~3.3 mm
- Enrollees improved ~5 points more than non-enrollees on both WOMAC Pain and Function observed in the full Phase 2a population

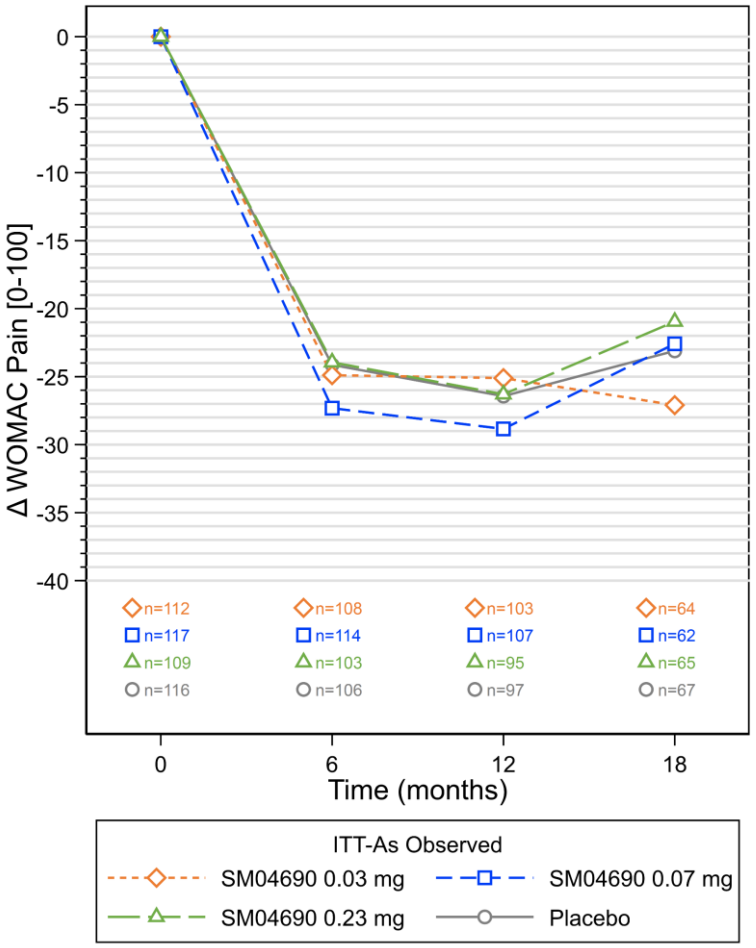
WOMAC Pain [0-100]

ITT (As Observed)

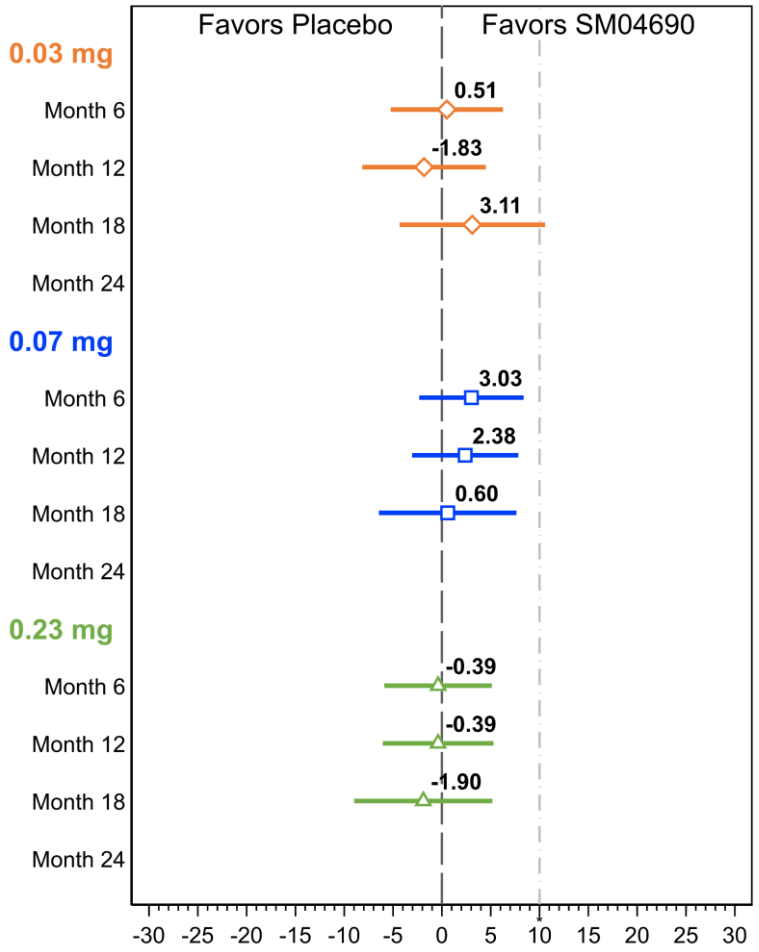
Actual values



Change from baseline



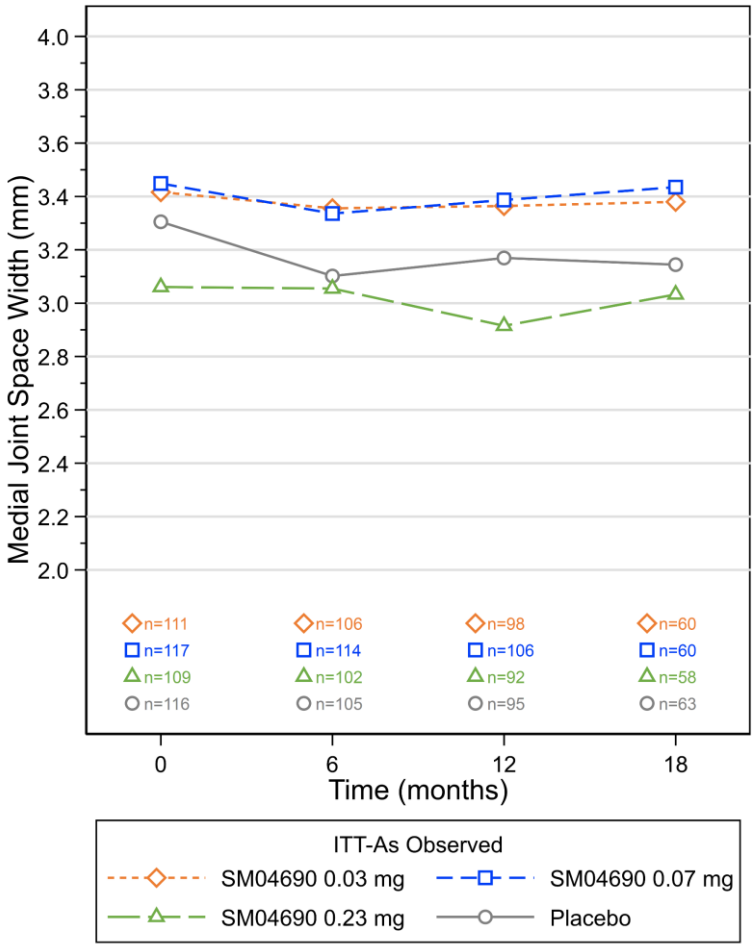
Compared to PBO



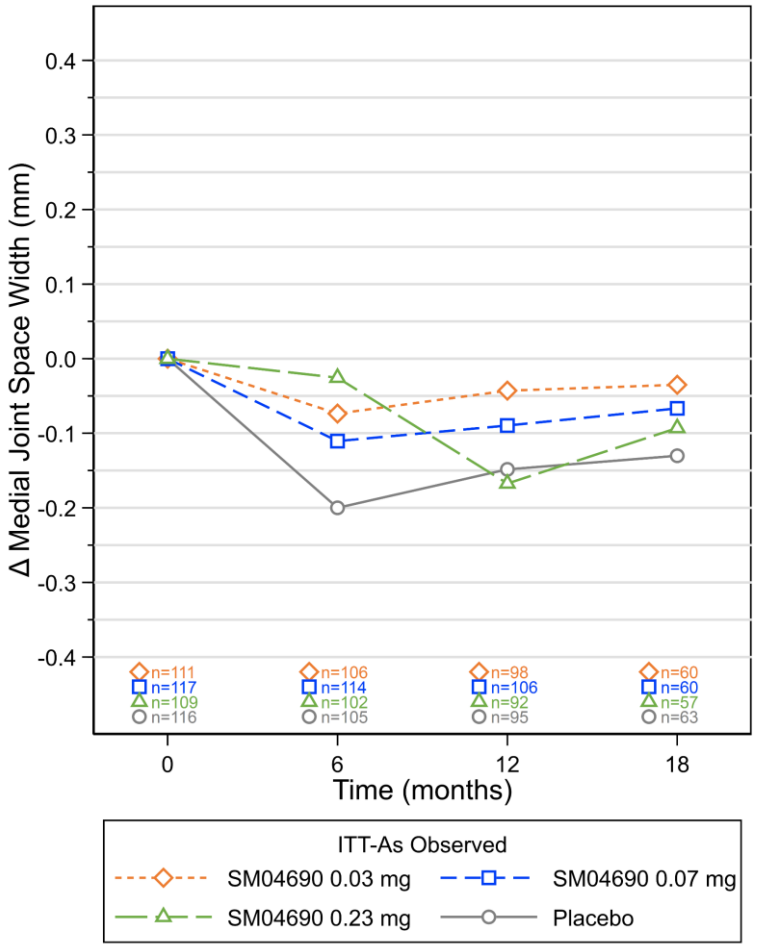
Medial Joint Space Width (mm)

ITT (As Observed)

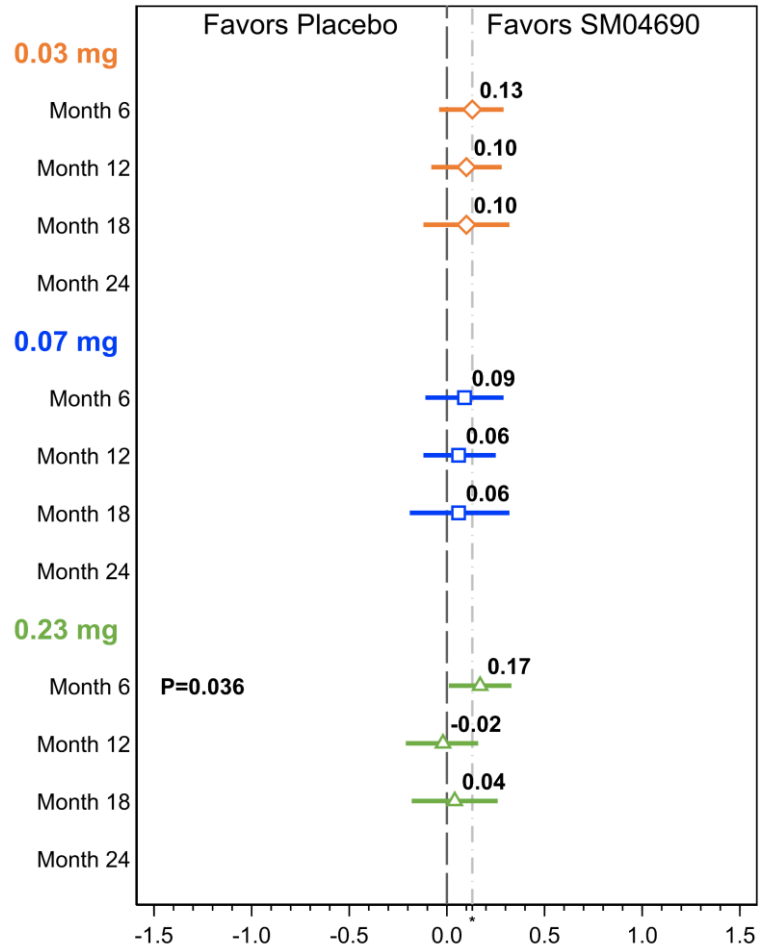
Actual values



Change from baseline



Compared to PBO



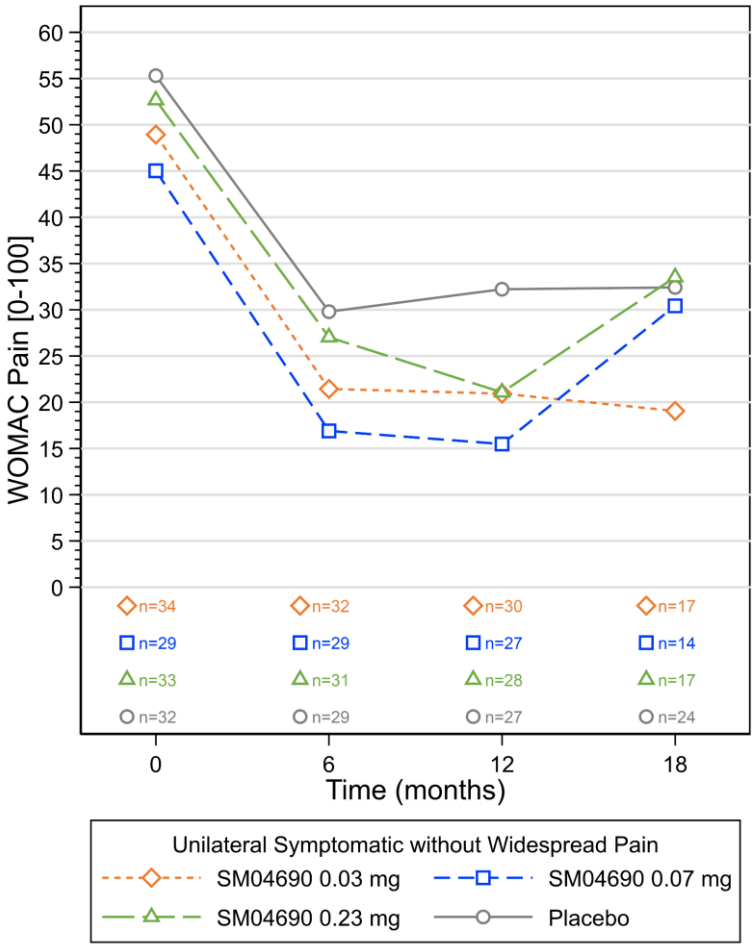
Long-term extension data

Unilateral Symptomatic without Widespread Pain, (As Observed, through 18 months)

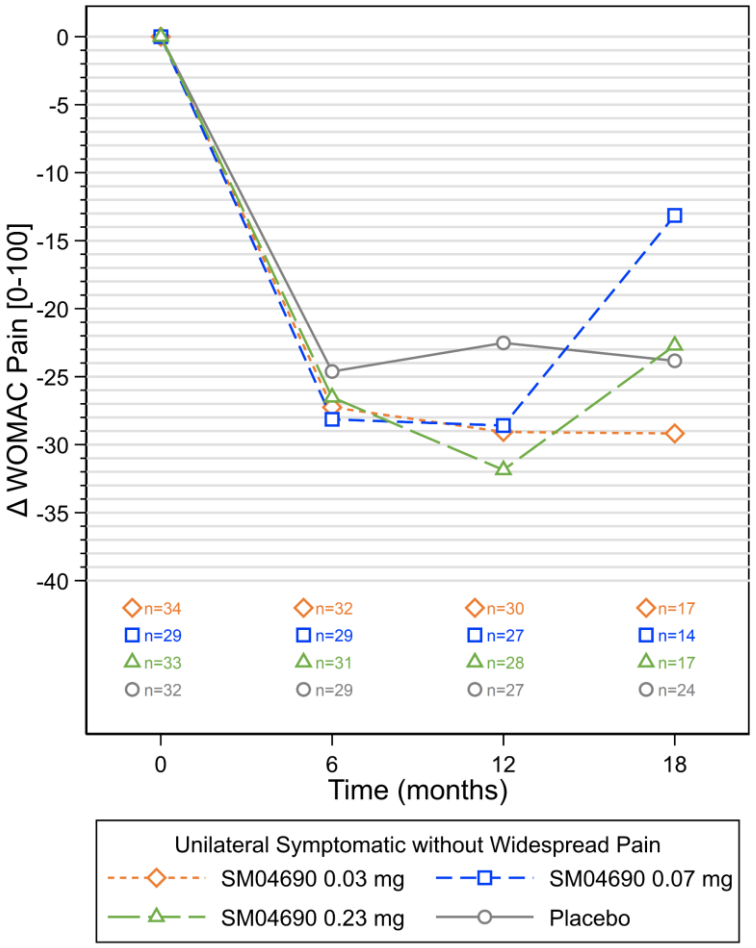
WOMAC Pain [0-100]

Unilateral Symptomatic without Widespread Pain

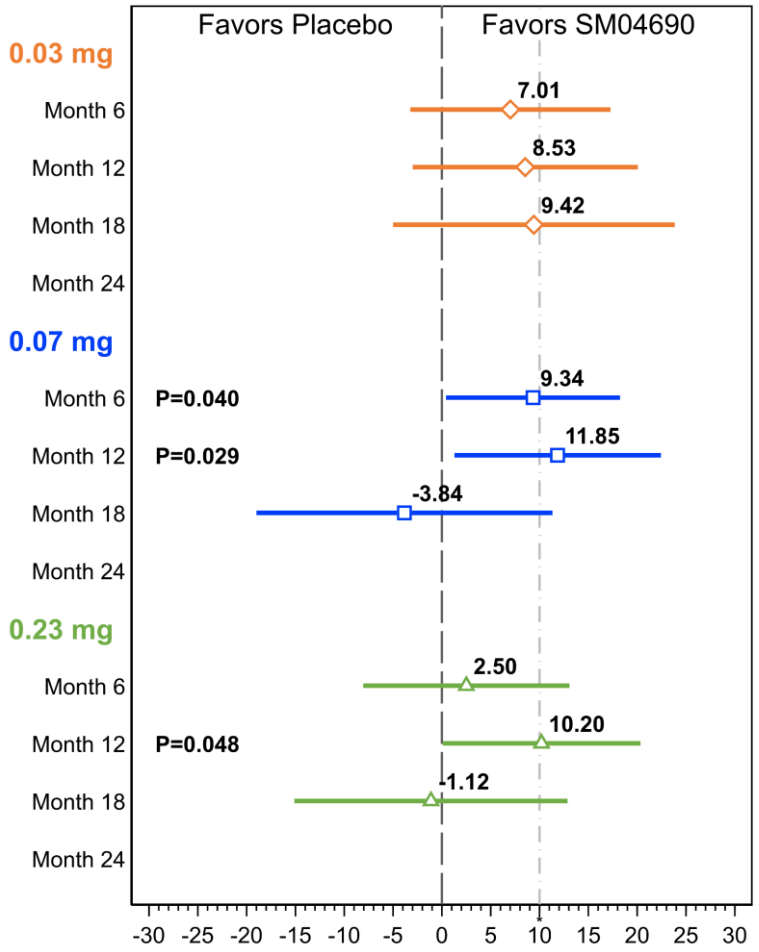
Actual values



Change from baseline



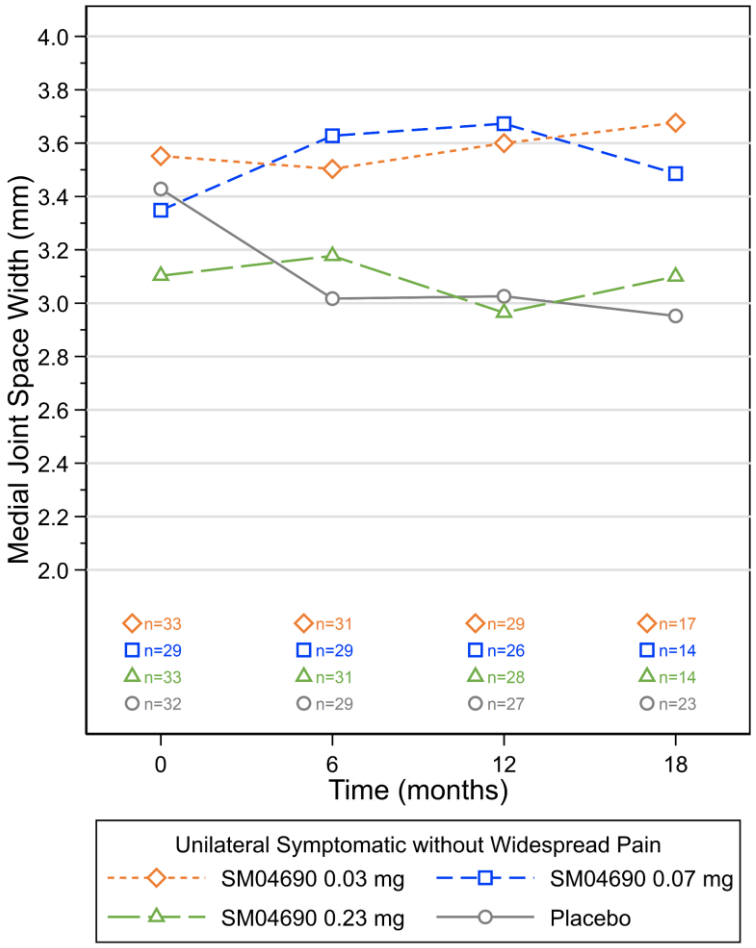
Compared to PBO



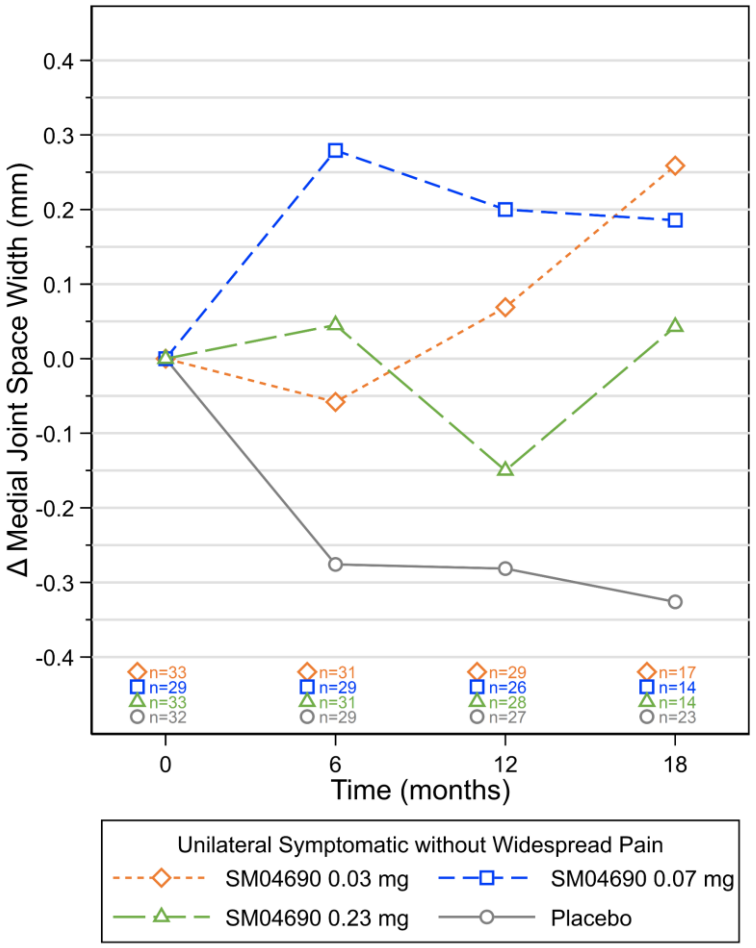
Medial Joint Space Width (mm)

Unilateral Symptomatic without Widespread Pain

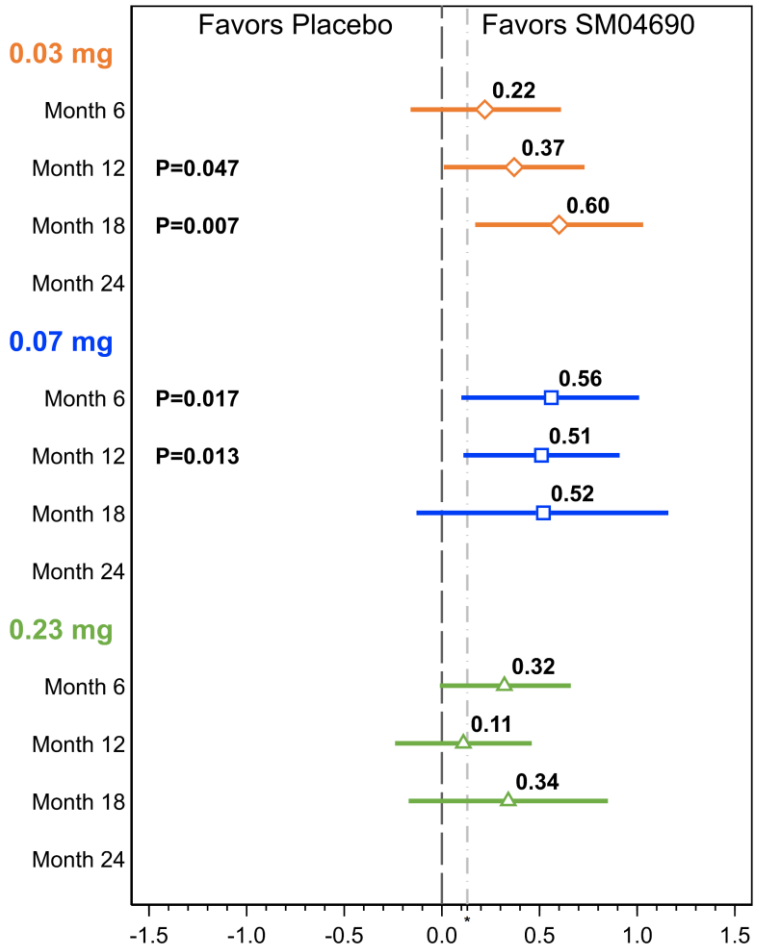
Actual values



Change from baseline



Compared to PBO



SM04690 OA status of clinical development program

- SM04690-OA-04, phase 2b, N=695 (completed, NCT03122860)
  - 24 week single injection, primary endpoints 24 week S&S and JSW
  - Data available fall 2018
- SM04690-OA-05, safety extension (observational with no additional injections, NCT02951026)
  - Started September 2016
  - 5 years, safety with exploratory long-term efficacy including radiographs and WOMAC
- SM04690-OA-06, phase 2, bone health, N=100
  - 52 week two injections, knee qCT, DXA spine/hip, bone health biomarkers
  - Estimated September 2018 start
- SM04690-OA-08, MRI, N=15
  - 52 week single injection, exploratory evaluation of cartilage quality and thickness
  - Estimated October 2018 start

samumed

Thank you