A 52 Week Randomized, Double-Blind Phase 2 Study of Intra-Articular, Wnt Pathway Inhibitor (SM04690) for Osteoarthritis

Jeyanesh R.S. Tambiah[1], Sarah Kennedy[1], Christopher J. Swearingen[1], Ismail Simsek[1], Andreas H. Gomoll[2], Deryk G. Jones[3], Morgan Jones[4], and John Bergfeld[4]

[1]Samumed LLC, San Diego, CA, USA, [2]Hospital for Special Surgery, New York, NY, USA, [3]Ochsner Health System, Jefferson, LA, USA, [4]Cleveland Clinic, Cleveland, OH, USA

Disclosures

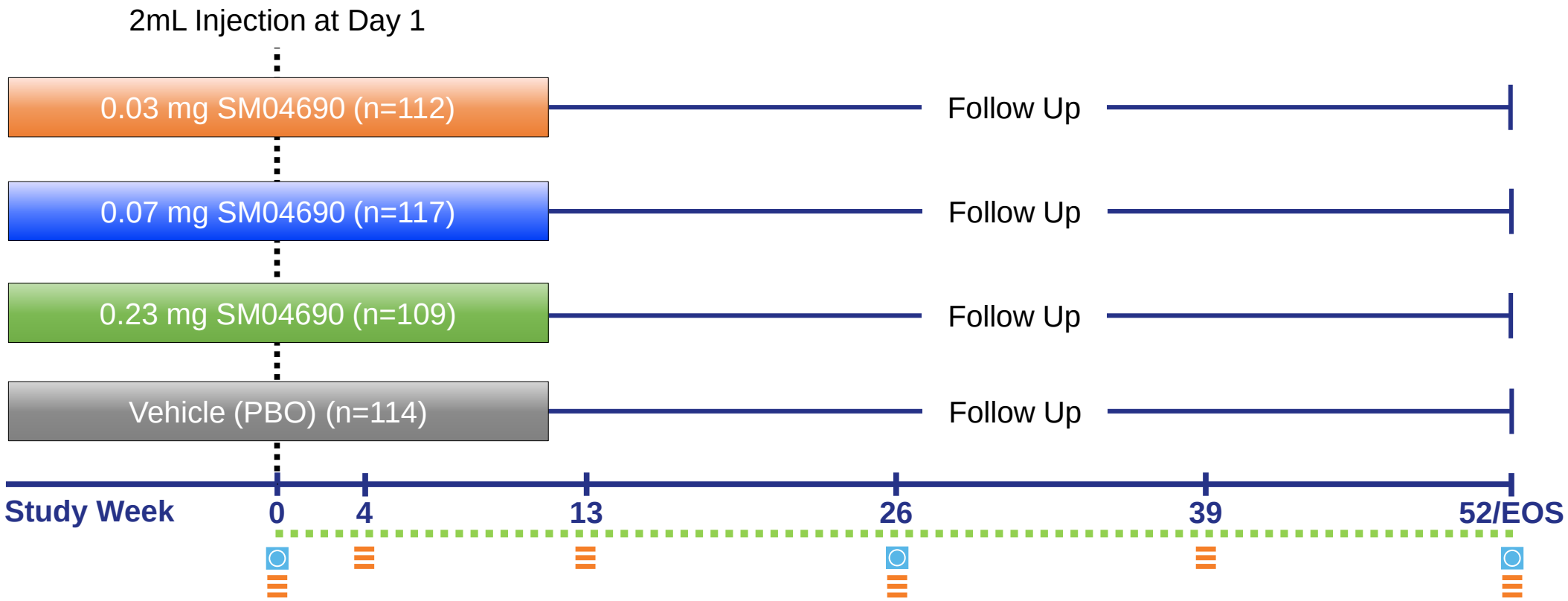
Jeyanesh Tambiah	Samumed, LLC, employee and shareholder
Sarah Kennedy	Samumed, LLC, employee and shareholder
Christopher Swearingen	Samumed, LLC, employee and shareholder
Ismail Simsek	Samumed, LLC, employee and shareholder
Andreas Gomoll	NuTech, consulting

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, 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 2 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 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:** Fixed flexion knee X-ray with QuAP™ positioner
- **Safety Assessments:** Adverse events (AEs), Vital signs, Physical exam, Lab panels

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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%)
KL 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%)

KL: Kellgren-Lawrence

Incidence of Adverse Events ([AE], 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

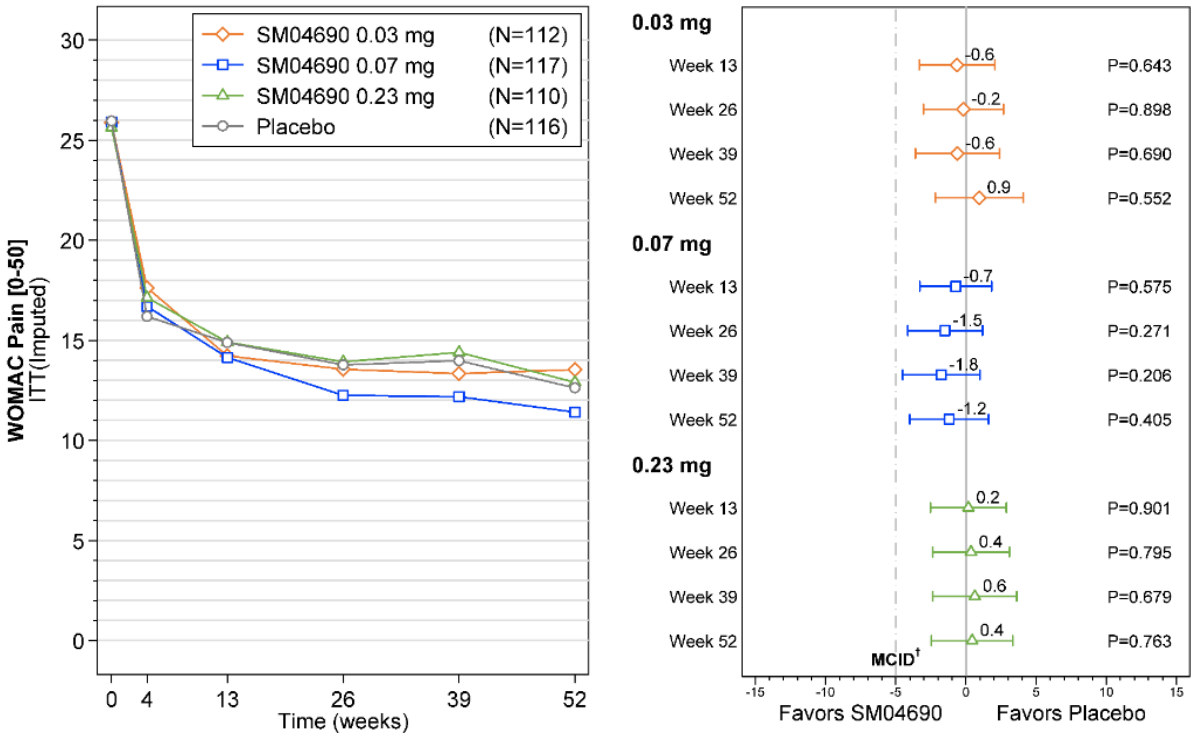
SM04690-OA-02: Analysis groups

- Intention-to-treat population (ITT, n=455): all randomized subjects
  - ‘Unilateral symptomatic’ population (UNI, n=164):
    - Pre-specified, investigator designated target knee with most pain
    - Determined per protocol on patient history and examination
    - Contralateral knee pain threshold not limited at enrollment
- KL: Non-target knee ≥ target knee in 91% of subjects
  - KL grade distribution between UNI and bilateral symptomatic subjects was similar
- Missing data imputed using multiple imputation

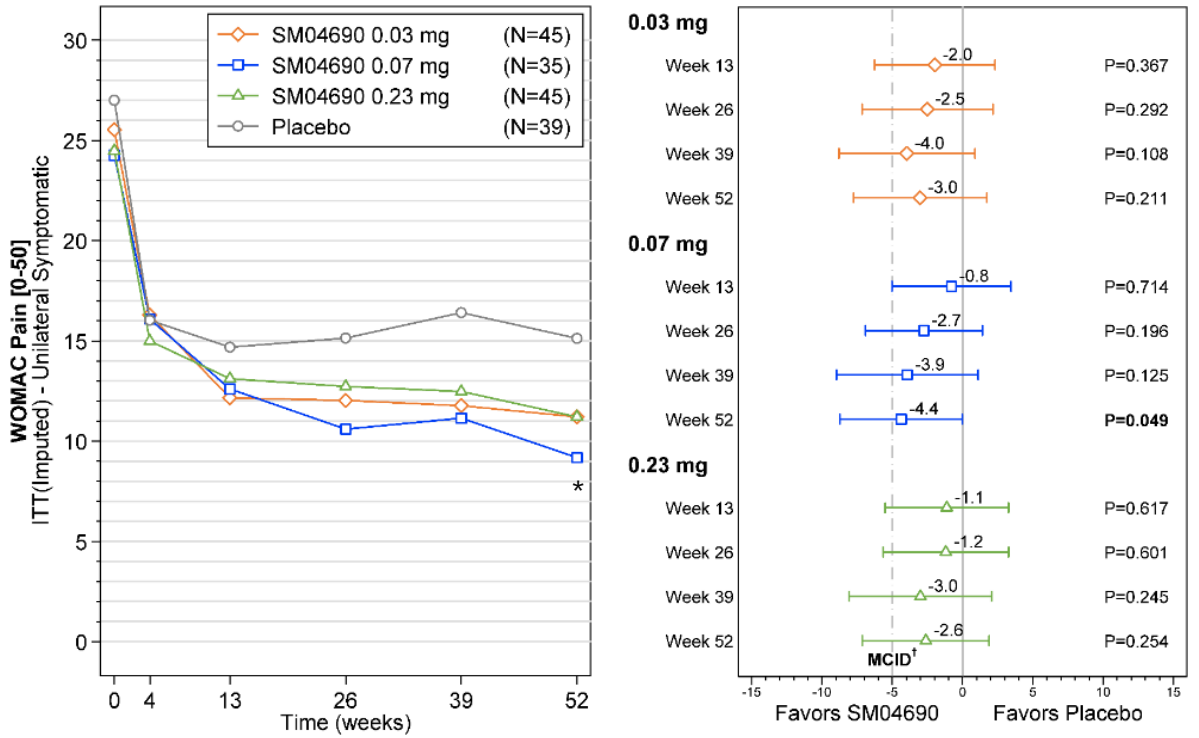
WOMAC Pain [0-50]

Actual scores (mean) and ladder plots comparing mean (± 95%CI) to placebo

ITT



Unilateral Symptomatic



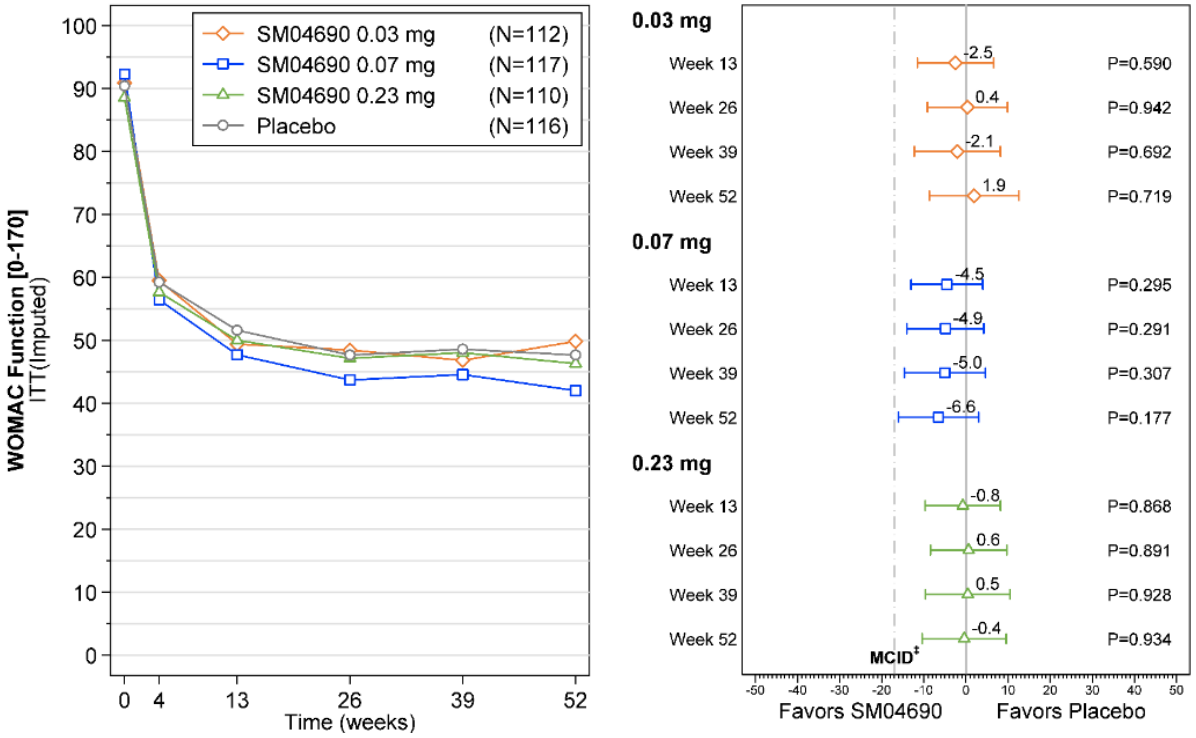
*Denotes P<0.05. Comparisons from Baseline-adjusted ANCOVA versus Placebo. †**MCID**: Minimal Clinically Important Difference: 10% (5 points) of WOMAC Pain subscore.

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

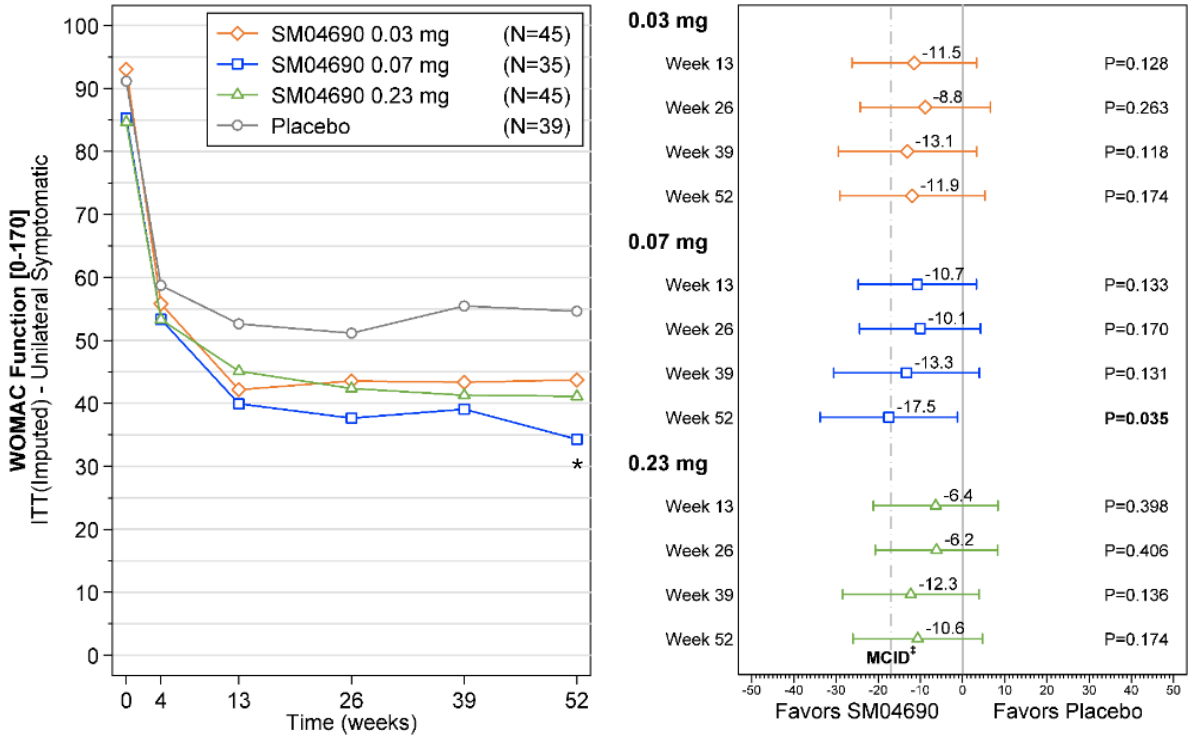
WOMAC Function [0-170]

Actual scores (mean) and ladder plots comparing mean (± 95%CI) to placebo

ITT



Unilateral Symptomatic



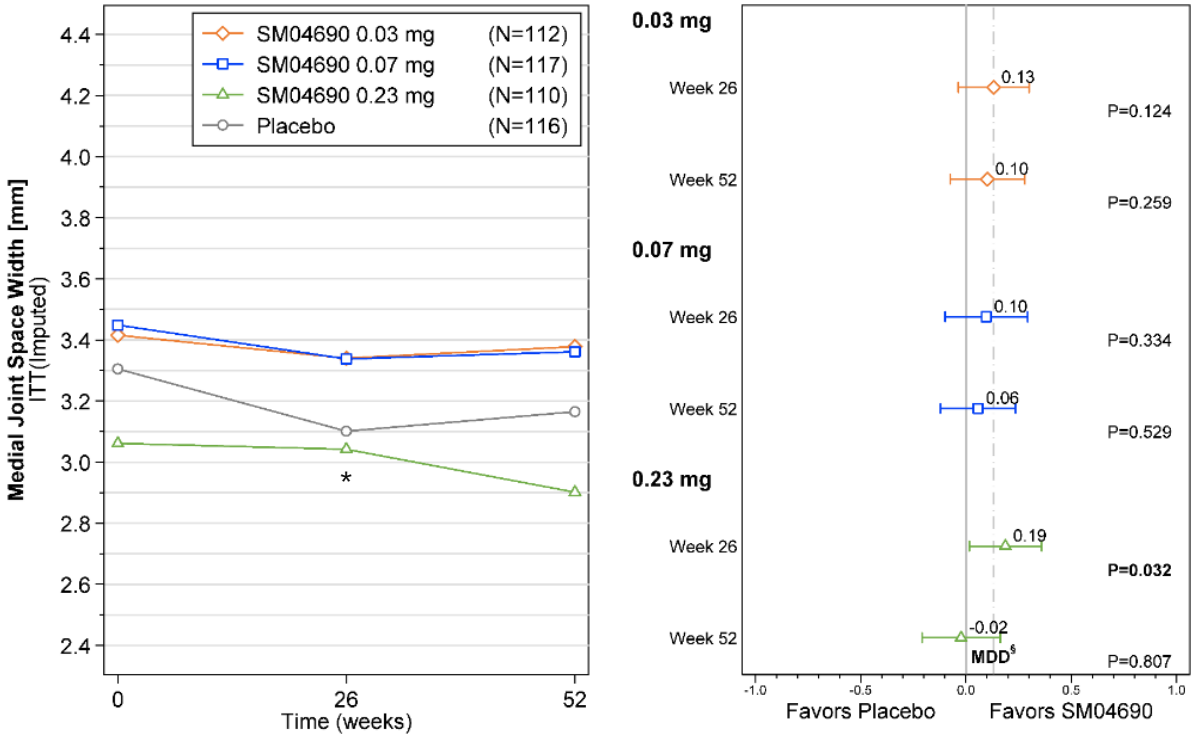
*Denotes P<0.05. Comparisons from Baseline-adjusted ANCOVA versus Placebo. ‡**MCID**: Minimal Clinically Important Difference defined as 10% (17 points) of WOMAC Function subscore.

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

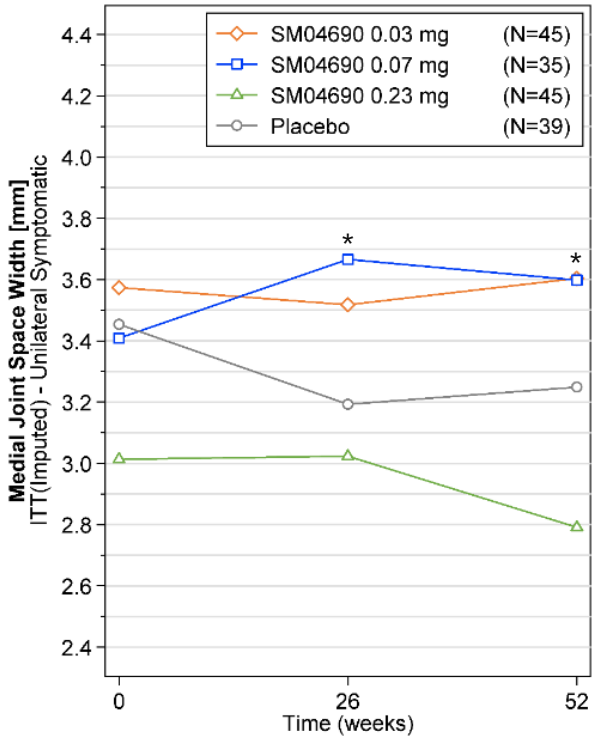
Medial joint space width ([mJSW], mm)

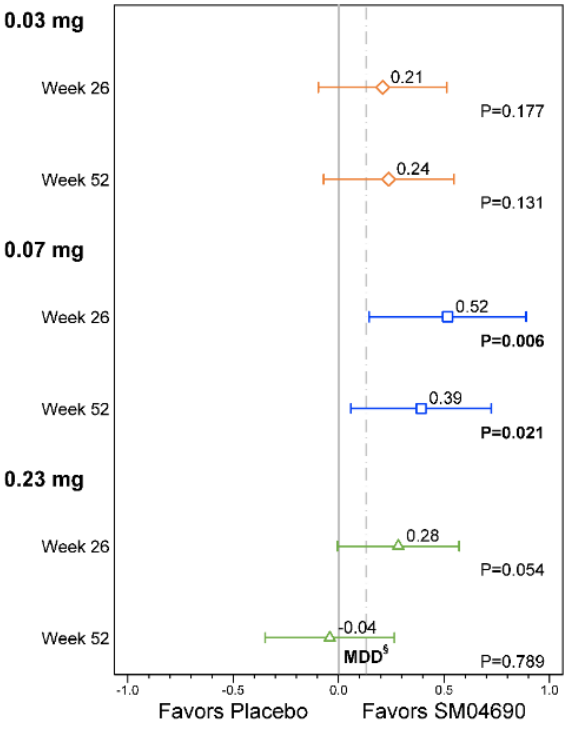
Actual measurements (mean) and ladder plots comparing mean (± 95%CI) to placebo

ITT



Unilateral Symptomatic





*Denotes P<0.05. Comparisons from Baseline-adjusted ANCOVA versus Placebo. **§MDD:** Minimal Detectable Difference defined as 0.13 mm of medial joint space width.

Dupuis DE, 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: no formal sample size, small subgroups

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

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 with baseline
- Unilateral Symptomatic 0.07 mg SM04690 subgroup showed significant WOMAC Pain, Function, and mJSW improvements compared with PBO at 52 weeks

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

Thank you