Treatment of Knee Osteoarthritis with SM04690 Improved WOMAC A1 “Pain on Walking” – Results from a 52 Week, Randomized, Double Blind, Placebo Controlled, Phase 2 Study of a Novel, Intra-Articular, Wnt Pathway Inhibitor

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DISCLOSURES

- Sarah Kennedy: Samumed, LLC employee and shareholder
- Heli Ghandehari: Samumed, LLC employee and shareholder
- Christopher Swearingen: 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

WOMAC question A1 commonly used as an endpoint in osteoarthritis (OA) trials

- Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) knee score
  - extensively used patient reported outcome measure
  - 24 items in 3 subscales: A = pain [5], B = stiffness [2], C = physical function [17]
- Question A1, walking pain on a flat surface
  - major symptom of tibio-femoral OA and differentiates from patello-femoral OA[1,2]
  - multi-dimensional, incorporating pain and function
  - onset usually earlier than rest pain
  - used as a clinical trial endpoint for many intra-articular (IA) compounds in knee OA

1. Peat et al. *Arth Res Ther. 14:R63.*
2. Stefanik et al. *Arthritis Care Res (Hoboken).* 2018;70:15761.

WOMAC A1: ‘pain when walking on a flat surface’ question is multi-dimensional

- ‘How much pain have you had when walking on a flat surface?’
- ‘How much difficulty have you had when walking on a flat surface?’

Pain

Think about the pain you felt in your _____ (study joint) caused by the arthritis during the last 48 hours.

(Please mark your answers by putting an "X" in one of the boxes.)

QUESTION: **How much pain have you had . . .**

		0	1	2	3	4	5	6	7	8	9	10	
1. when walking on a flat surface?	No Pain												Extreme Pain
2. when going up or down stairs?	No Pain												Extreme Pain
3. at night while in bed? (that is - pain that disturbs your sleep)	No Pain												Extreme Pain
4. while sitting or lying down?	No Pain												Extreme Pain
5. while standing?	No Pain												Extreme Pain

Physical Function

QUESTION: **How much difficulty have you had . . .**

		0	1	2	3	4	5	6	7	8	9	10	
8. when going down the stairs?	No Difficulty												Extreme Difficulty
9. when going up the stairs?	No Difficulty												Extreme Difficulty
10. when getting up from a sitting position?	No Difficulty												Extreme Difficulty
11. while standing?	No Difficulty												Extreme Difficulty
12. when bending to the floor?	No Difficulty												Extreme Difficulty
13. when walking on a flat surface?	No Difficulty												Extreme Difficulty

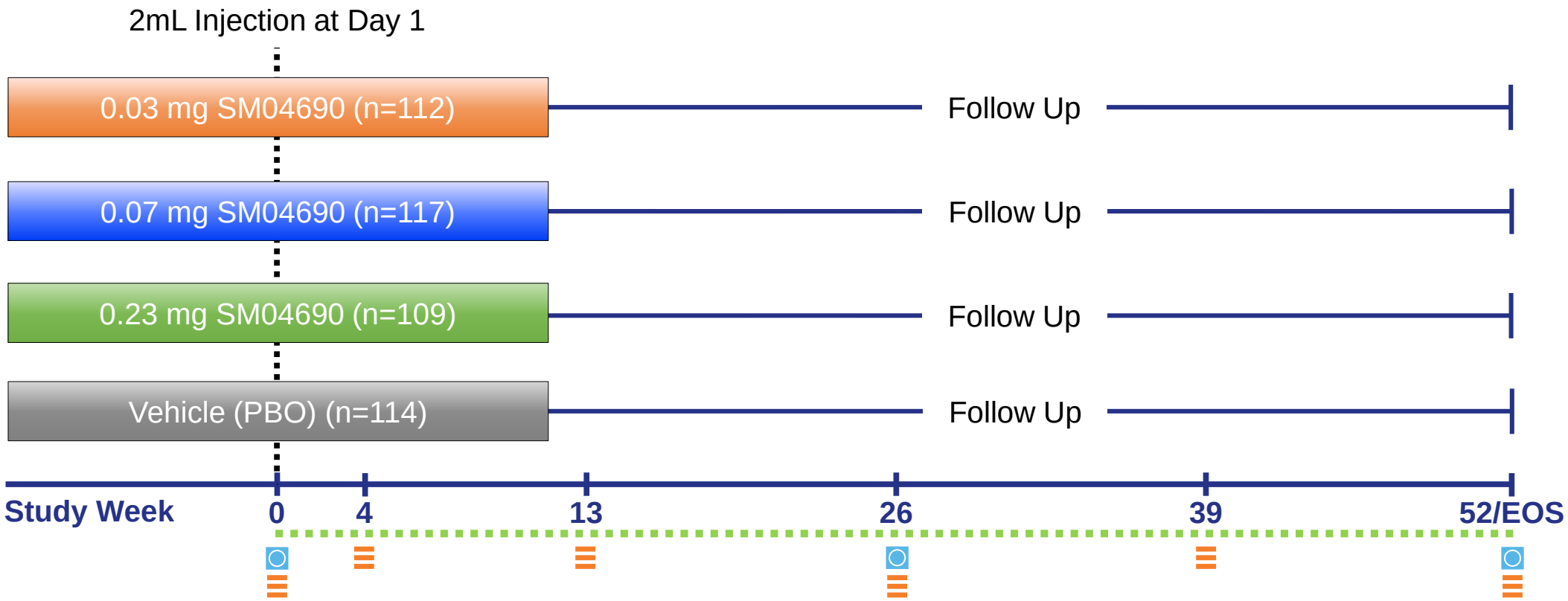
Bellamy N. *WOMAC Osteoarthritis Index User Guide. Version V.* Brisbane, Australia 2002.

Knee OA, the Wnt pathway, and SM04690

- The Wnt pathway is upregulated in OA.[1,2] Inhibition may regenerate and protect articular cartilage
- SM04690: an IA Wnt pathway inhibitor for potential treatment of knee OA
  - preclinical studies demonstrated inhibition of inflammation and cartilage degradation *in vitro* and *in vivo* compared with vehicle[3]
  - phase 2 study demonstrated improvements in WOMAC Pain, Function, and radiographic medial joint space width compared to placebo (PBO) in clinically relevant subgroups for 0.07 mg dose at 52 weeks[4]
- This post-hoc analysis evaluated SM04690 effects measured by WOMAC A1

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 Physician 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

Incidence of adverse events

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: Demographics

	0.03 mg	0.07 mg	0.23 mg	Placebo	All subjects
N	**112**	**117**	**110**	**116**	**455**
Age (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%)
KL grade 3 [n(%)]	74 (66.1%)	74 (63.2%)	70 (63.6%)	74 (63.8%)	292 (64.2%)
Unilateral Symptomatic [n(%)]	45 (40.2%)	35 (29.9%)	45 (40.9%)	39 (33.6%)	164 (36.0%)
Unilateral Symptomatic WP- [n(%)]	34 (30.4%)	29 (24.8%)	33 (30.0%)	32 (27.6%)	128 (28.1%)

KL: Kellgren-Lawrence

SM04690-OA-02: Analysis groups

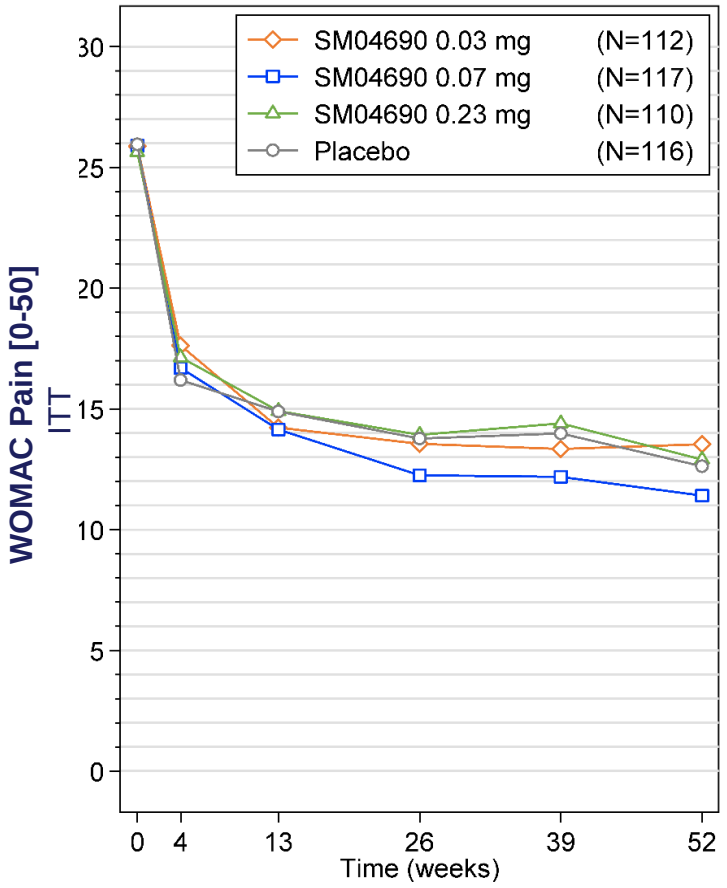
- **Intention to treat population (ITT, n=455):** All randomized subjects
  - contra-lateral knee pain threshold not limited at enrollment
- **Unilateral Symptomatic (UNI, n=164):**
  - prespecified, investigator-designated target knee with most pain
- **Unilateral Symptomatic without Widespread Pain (UNI WP-, n=128):**
  - excludes subjects with comorbid pain
  - post-hoc, Unilateral Symptomatic **excluding** subjects with Widespread Pain Index > 4 and Symptom Severity > 2

- KL grade: Non-target knee ≥ target knee in 91% of subjects
  - KL distribution between unilateral and bilateral symptomatic subjects similar
- Multiple imputation for missing data

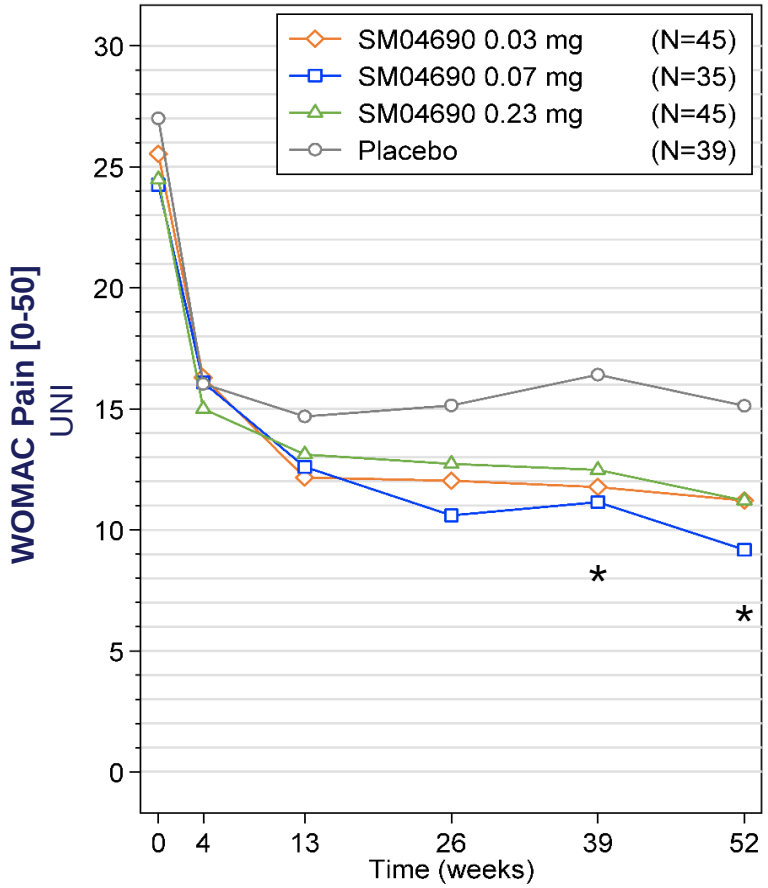
WOMAC Pain [0-50]

Actual scores (mean)

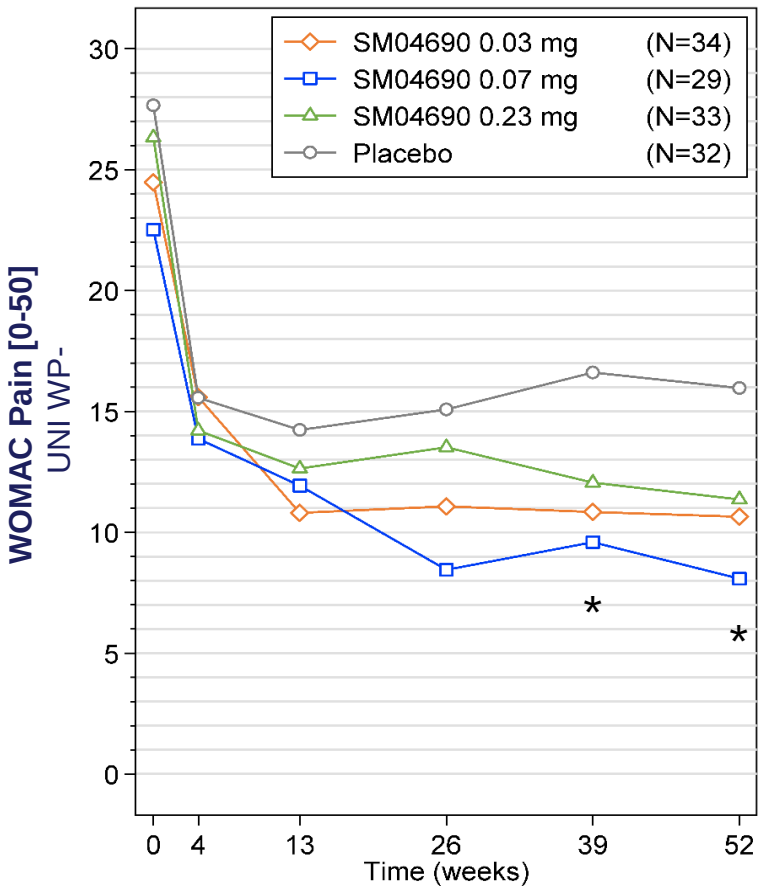
ITT



Unilateral Symptomatic



Unilateral Symptomatic without Widespread Pain

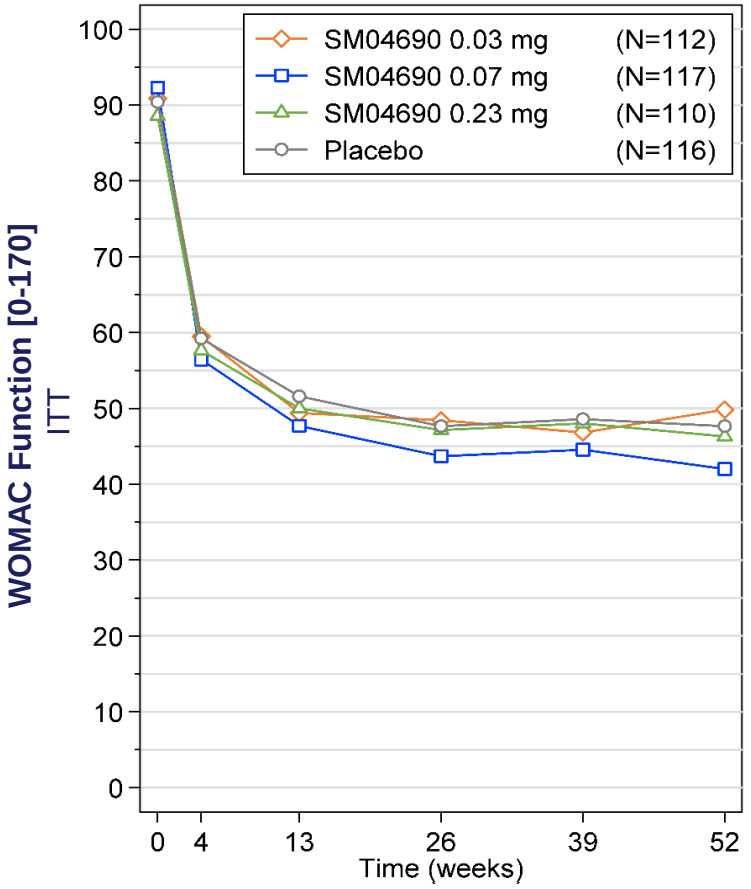


**P*<0.05 Baseline adjusted ANCOVA comparing 0.07 mg SM04690 to PBO

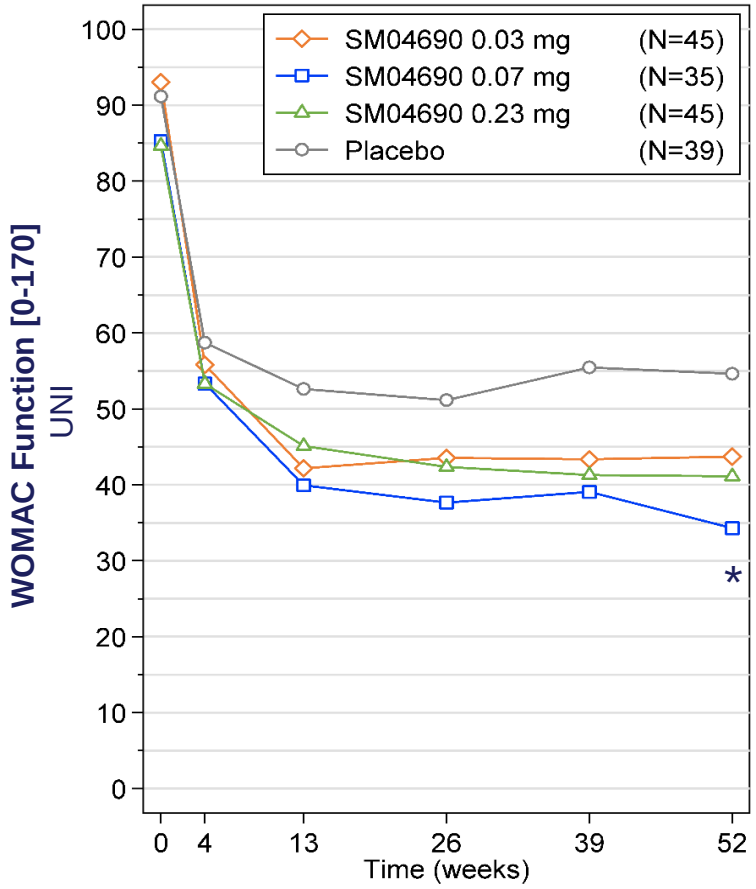
WOMAC Function [0-170]

Actual scores (mean)

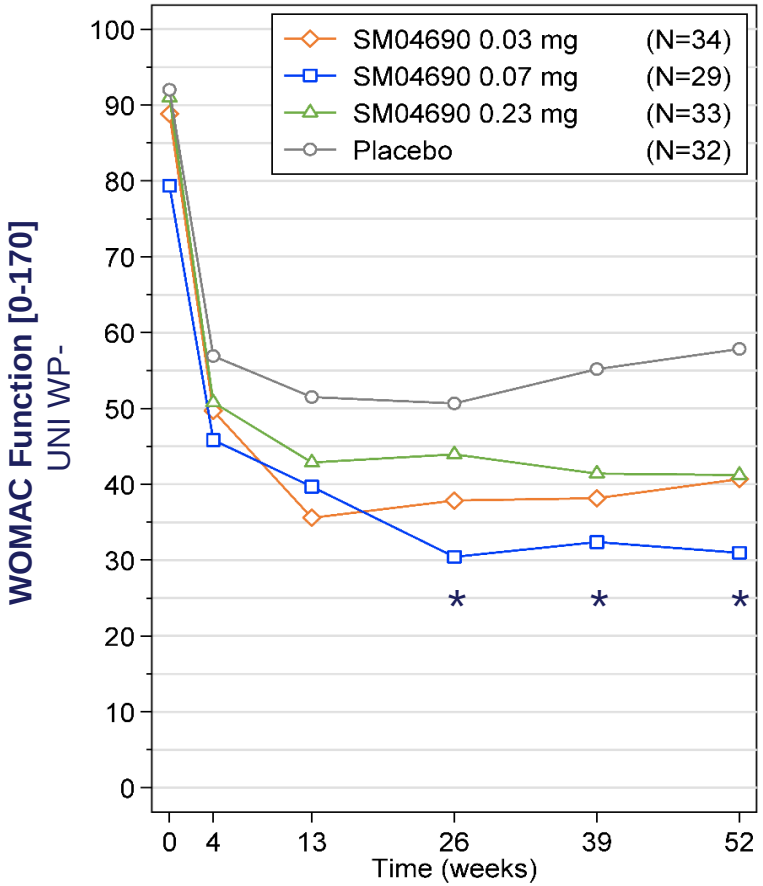
ITT



Unilateral Symptomatic



Unilateral Symptomatic without Widespread Pain

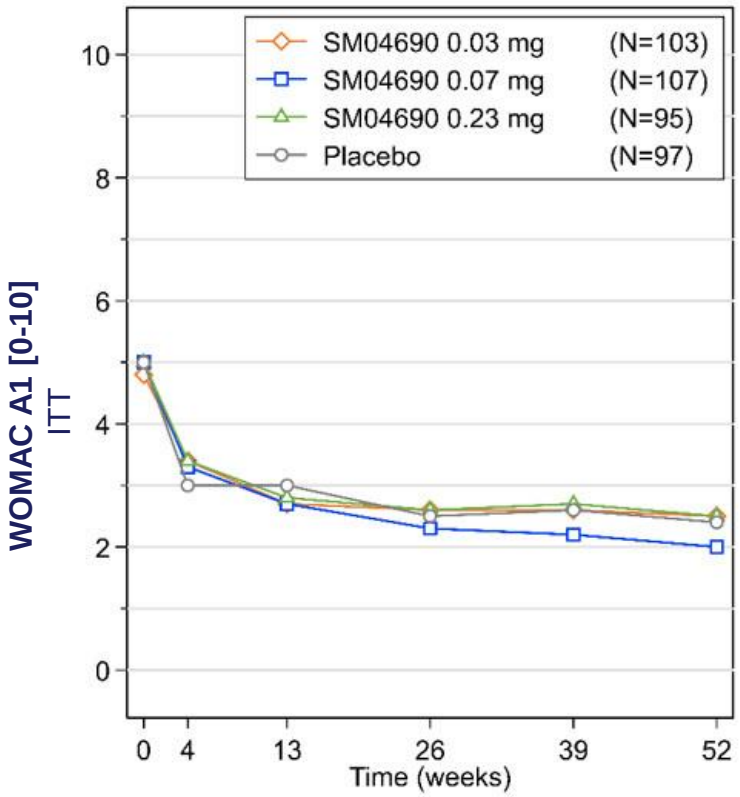


**P*<0.05 Baseline adjusted ANCOVA comparing 0.07 mg SM04690 to PBO

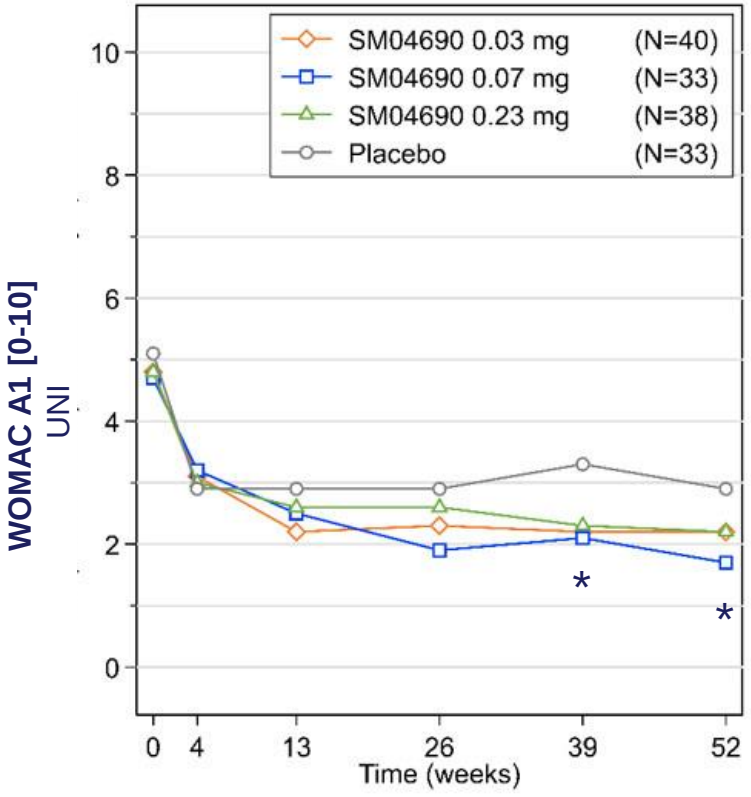
WOMAC A1 Pain [0-10]

Actual scores (mean)

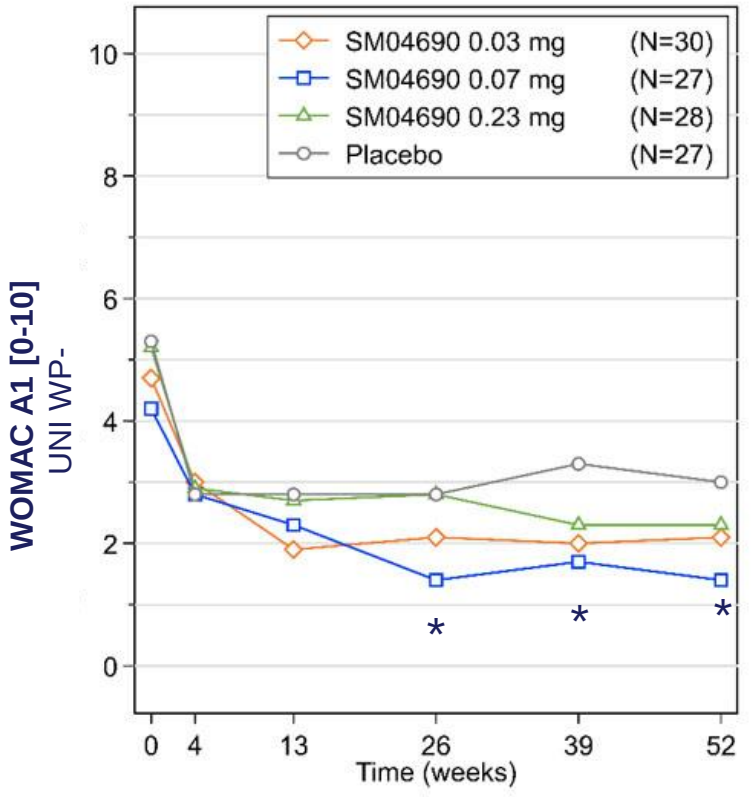
ITT



Unilateral Symptomatic



Unilateral Symptomatic without Widespread Pain



*P<0.05 Baseline adjusted ANCOVA comparing 0.07 mg SM04690 to PBO

SM04690 0.07 mg average (scaled) improvement over PBO

	WOMAC Pain [0-10]			WOMAC Function [0-10]			WOMAC A1 [0-10]		
	ITT	UNI	UNI WP-	ITT	UNI	UNI WP-	ITT	UNI	UNI WP-
Week 13	0.14	0.16	0.00	0.26	0.63	0.48	0.25	0.23	0.05
Week 26	0.30	0.92	**0.92**	0.29	0.59	**0.96**	0.28	0.80	**1.18**
Week 39	0.36	1.18	**1.18**	0.29	0.78	**1.16**	0.42	**1.15**	**1.77**
Week 52	0.24	**1.12**	**1.12**	0.39	**1.03**	**1.34**	0.35	**1.09**	**1.40**

*Improvement is absolute value of 0.07 mg treatment effect over PBO from a baseline adjusted ANCOVA.
Statistically significant *P*<0.05.

SM04690 0.07 mg effect size versus PBO at Week 52: Unilateral Symptomatic without Widespread Pain subjects

	0.07 mg SM04690 vs. PBO		
Outcome	**Improvement**	**Mean Square Error**	**Effect Size**
WOMAC A1	1.4	3.4	0.764
WOMAC Pain	5.9	81.7	0.655
WOMAC Physical Function	24.7	1061.0	0.757

This post-hoc analysis of SM04690 0.07 mg and WOMAC A1

Supports a previous study assessing WOMAC signal and aggregate score responsiveness[1]

At 52 weeks compared with PBO, Unilateral Symptomatic with and without Widespread Pain subgroups demonstrated significant WOMAC A1 pain improvements, corresponding with significant WOMAC Pain and Function improvements

In the Unilateral Symptomatic without Widespread Pain subgroup, effect size comparisons among WOMAC A1, Pain, and Function subscores at Week 52 were similar, supporting the responsiveness of the A1 question

1. Barr, S. et al. J. Rheum 1999; 21: 210612.

Thank you

Samumed posters:

SM04690-OA-02 52-Week Data – SAT0586

SM04755 Tendinopathy – THU0522

SM04755 Psoriasis – THU0046

SM04690-OA-02 Radiographic Outcomes – FRI0534

Meta-Analysis: Intra-Articular Saline Control – FRI0542

SM04690 Preclinical OA – FRI0552

Intra-Articular Placebo Effect in Knee OA Therapies – SAT0565