

# Results from a 52-Week, Phase 2A Study of an Intra-Articular, Wnt Pathway Inhibitor, SM04690, for Knee Osteoarthritis

Yusuf Yazici<sup>1</sup>, Timothy McAlindon<sup>2</sup>, Allan Gibofsky<sup>3</sup>, Nancy Lane<sup>4</sup>, Daniel Clauw<sup>5</sup>, Christopher Swearingen<sup>1</sup>, Anita DiFrancesco<sup>1</sup>, Jeyanesh R.S. Tambiah<sup>1</sup>, and Marc Hochberg<sup>6</sup>

<sup>1</sup>Samumed LLC, San Diego, CA, USA, <sup>2</sup>Tufts Medical Center, Boston, MA, USA, <sup>3</sup>Hospital for Special Surgery, New York, NY, USA, <sup>4</sup>UC Davis Medical Center, Davis, CA, USA, <sup>5</sup>University of Michigan, Ann Arbor, MI, USA, <sup>6</sup>University of Maryland School of Medicine, Baltimore, MD, USA

# Disclosures

---

Yusuf Yazici	Samumed, LLC, employee and shareholder
Timothy McAlindon	Samumed, LLC, Astellas, Flexion, Pfizer, Regeneron, Seikugaku
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

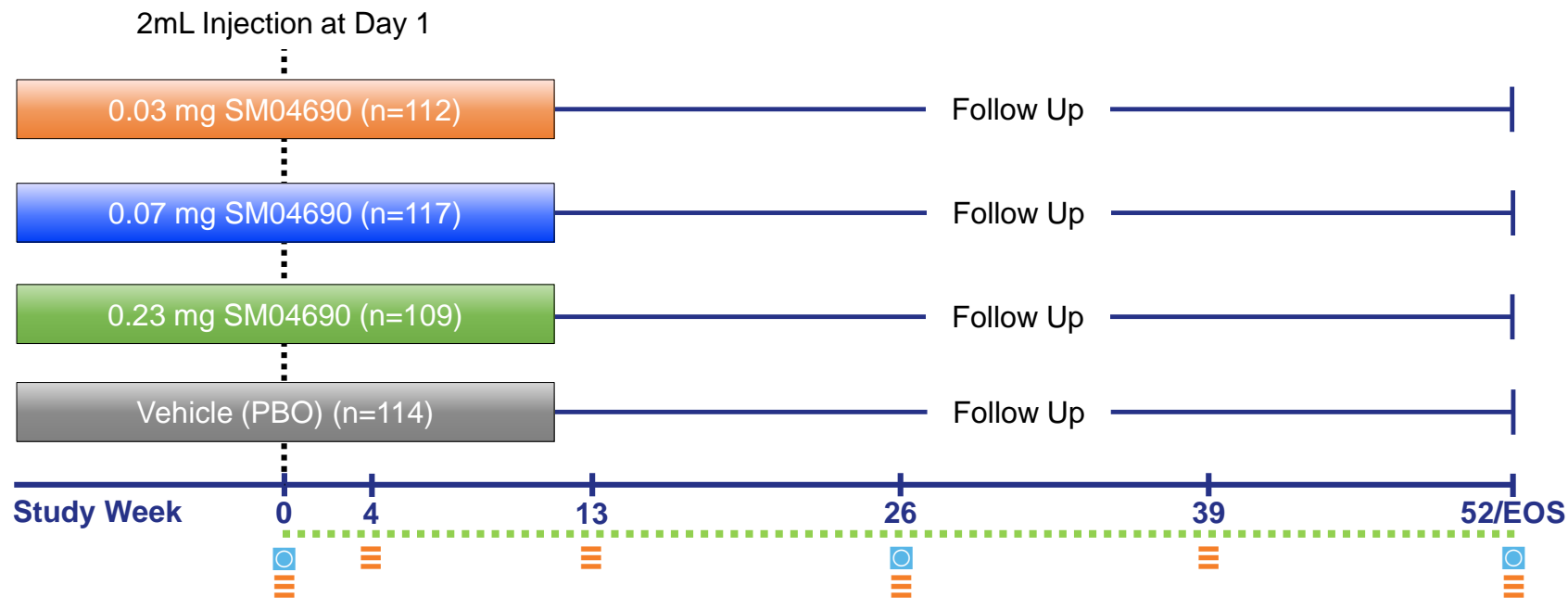
---

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

- The Wnt pathway is upregulated in OA.<sup>1,2</sup> 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<sup>3</sup>
  - Demonstrated sustained local exposure and no systemic toxicity<sup>3,4</sup>
- A phase 1 study suggested a single SM04690 injection had potential for improving symptoms and maintaining joint space in knee OA subjects<sup>4</sup>
- 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

# SM04690-OA-02: Demographics (ITT analysis set)

	0.03 mg	0.07 mg	0.23 mg	Placebo	All subjects
<b>N</b>	<b>112</b>	<b>117</b>	<b>110</b>	<b>116</b>	<b>455</b>
<b>Age at consent (years) [mean (SD)]</b>	59.0 (9.0)	60.0 (8.2)	61.3 (8.7)	60.7 (8.9)	60.3 (8.7)
<b>BMI (kg/m<sup>2</sup>) [mean (SD)]</b>	29.8 (4.8)	30.8 (4.7)	29.6 (4.5)	29.2 (4.4)	29.9 (4.6)
<b>Female [n(%)]</b>	68 (60.7%)	60 (51.3%)	68 (61.8%)	72 (62.1%)	268 (58.9%)
<b>Race [n(%)]</b>					
<i>White</i>	92 (82.1%)	102 (87.2%)	96 (87.3%)	102 (87.9%)	392 (86.2%)
<i>African-American</i>	18 (16.1%)	14 (12.0%)	12 (10.9%)	10 (8.6%)	54 (11.9%)
<i>Asian</i>	1 (0.9%)	0	2 (1.8%)	0	3 (0.7%)
<b>KL grade 3 [n(%)]</b>	74 (66.1%)	74 (63.2%)	70 (63.6%)	74 (63.8%)	292 (64.2%)
<b>Unilateral symptomatic OA [n(%)]</b>	45 (40.2%)	35 (29.9%)	45 (40.9%)	39 (33.6%)	164 (36.0%)

# Incidence of adverse events ([AE], safety analysis set)

<b>AE(s) reported* &gt;2% [#AE / N(%)]</b>	<b>0.03 mg</b>	<b>0.07 mg</b>	<b>0.23 mg</b>	<b>Placebo</b>	<b>All subjects</b>
<i>Arthralgia</i>	16 / 13 (11.7)	14 / 13 (11.4)	13 / 9 (8.7)	12 / 10 (9.3)	61 / 49 (10.8)
<i>Joint swelling</i>	5 / 3 (2.7)	4 / 4 (3.5)	2 / 2 (1.9)	6 / 5 (4.6)	17 / 14 (3.1)
<i>Upper respiratory tract infection</i>	5 / 5 (4.5)	2 / 2 (1.8)	1 / 1 (1.0)	3 / 3 (2.8)	12 / 12 (2.7)
<i>Hypertension</i>	0 / 0 (0.0)	4 / 4 (3.5)	4 / 4 (3.8)	3 / 3 (2.8)	11 / 11 (2.4)
<i>Nasopharyngitis</i>	4 / 4 (3.6)	3 / 3 (2.6)	3 / 3 (2.9)	0 / 0 (0.0)	11 / 11 (2.4)
<i>Osteoarthritis</i>	4 / 3 (2.7)	2 / 2 (1.8)	3 / 3 (2.9)	5 / 3 (2.8)	14 / 11 (2.4)
<i>Headache</i>	0 / 0 (0.0)	6 / 3 (2.6)	2 / 2 (1.9)	4 / 4 (3.7)	13 / 10 (2.2)
<i>Joint effusion</i>	5 / 4 (3.6)	2 / 2 (1.8)	1 / 1 (1.0)	2 / 2 (1.9)	10 / 9 (2.0)
<i>Sinusitis</i>	1 / 1 (0.9)	2 / 2 (1.8)	1 / 1 (1.0)	5 / 5 (4.6)	9 / 9 (2.0)
<i>Urinary tract infection</i>	2 / 2 (1.8)	2 / 2 (1.8)	3 / 2 (1.9)	3 / 3 (2.8)	10 / 9 (2.0)
	<b>0.03 mg (n=111)</b>	<b>0.07 mg (n=114)</b>	<b>0.23 mg (n=104)</b>	<b>Placebo (n=108)</b>	
<b>Subjects reporting AE(s) [N(%)]</b>	61 (55.0)	65 (57.0)	47 (45.2)	53 (49.1)	
<b>Subjects reporting no AE(s) [N(%)]</b>	50 (45.0)	49 (43.0)	57 (54.8)	55 (50.9)	
<b>Subjects reporting SAE(s) [#AE / N(%)]</b>	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

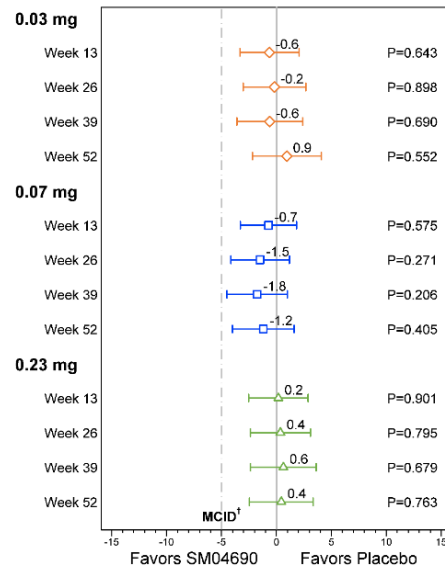
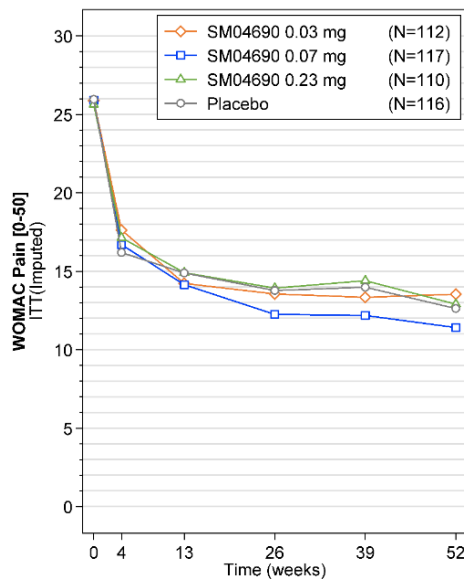
# SM04690-OA-02: Analysis groups

- 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  $\geq$  target knee in 91% of subjects
  - KL grade distribution between UNI and bilateral symptomatic subjects was similar
- Missing data imputed using multiple imputation

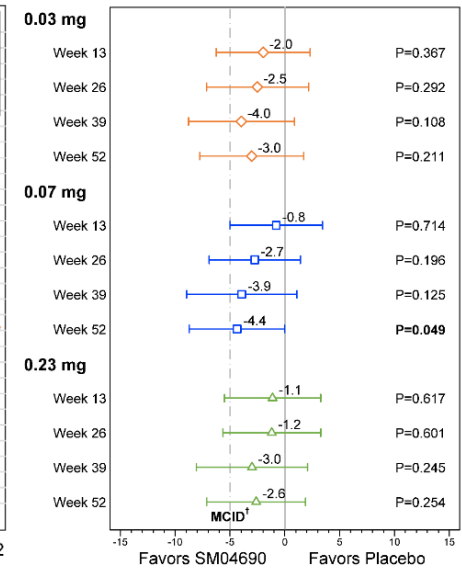
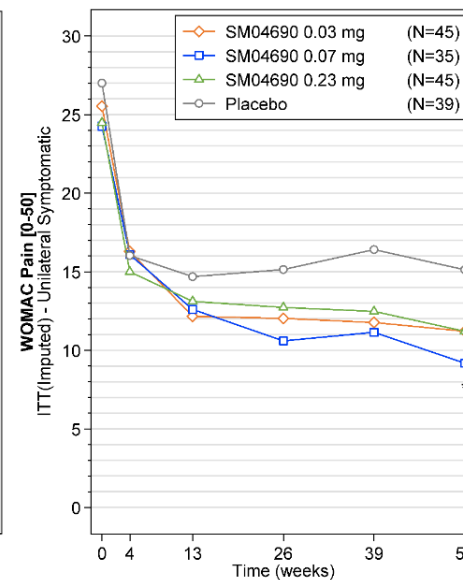
# WOMAC Pain [0-50]

Actual scores (mean) and ladder plots comparing mean ( $\pm$  95%CI) with placebo

## ITT



## Unilateral symptomatic



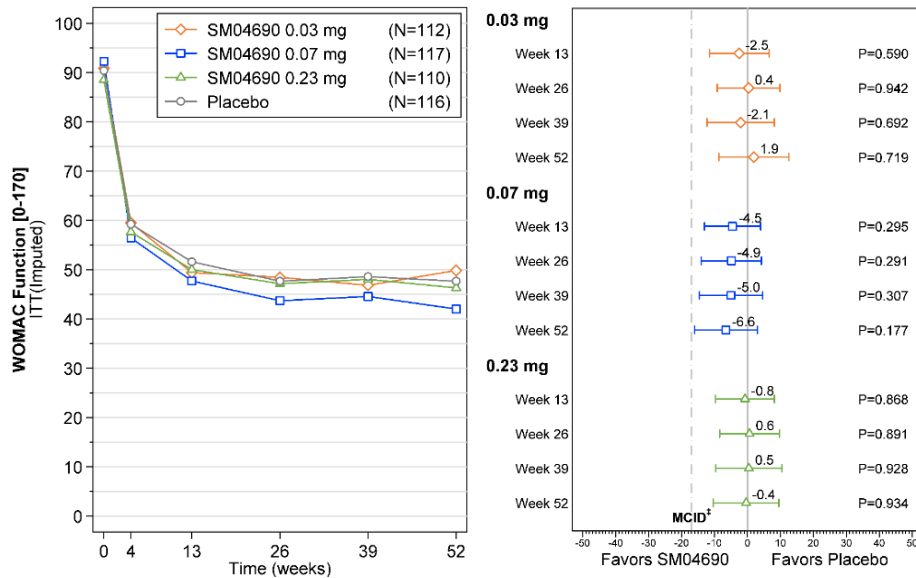
\*Denotes  $P < 0.05$ . Comparisons from baseline-adjusted ANCOVA versus placebo. †**MCID**: Minimal clinically important difference: 10% (5 points) of WOMAC Pain subscore. Cooper C, et al. (2013) *Curr Med Res*.



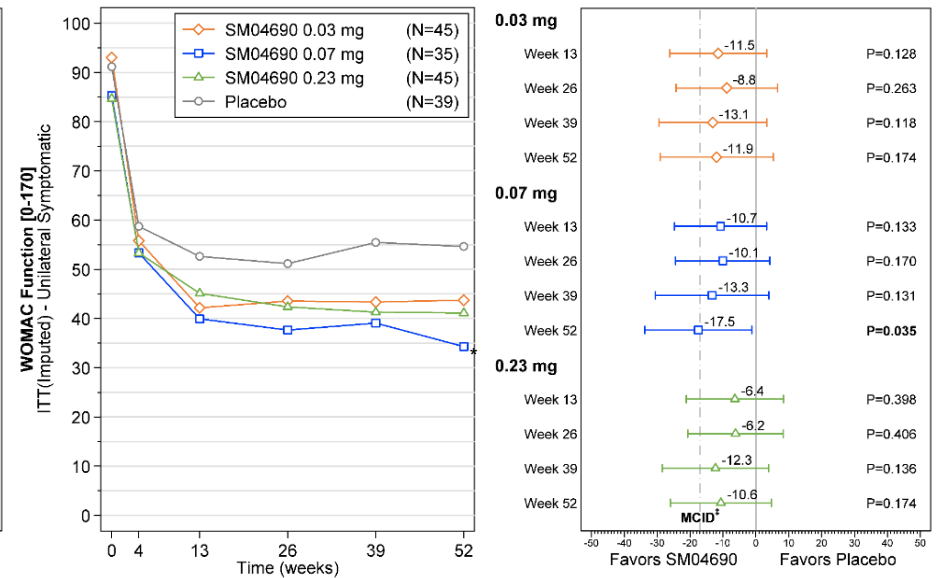
# WOMAC Function [0-170]

Actual scores (mean) and ladder plots comparing mean ( $\pm$  95%CI) with placebo

## ITT



## Unilateral symptomatic

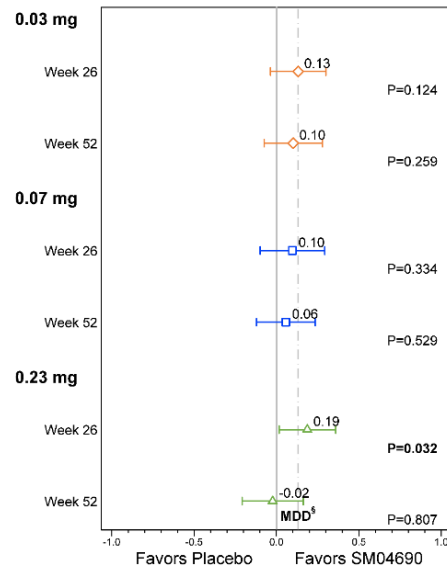
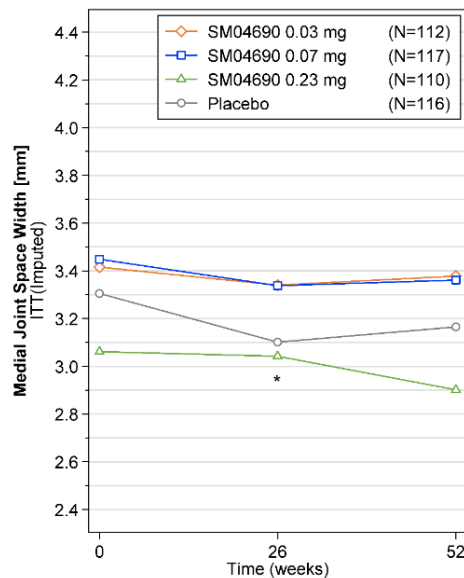


\*Denotes  $P < 0.05$ . Comparisons from baseline-adjusted ANCOVA versus placebo.  $\pm$ MCID: Minimal clinically important difference: 10% (17 points) of WOMAC Function subscore. Cooper C, et al. (2013) *Curr Med Res*.

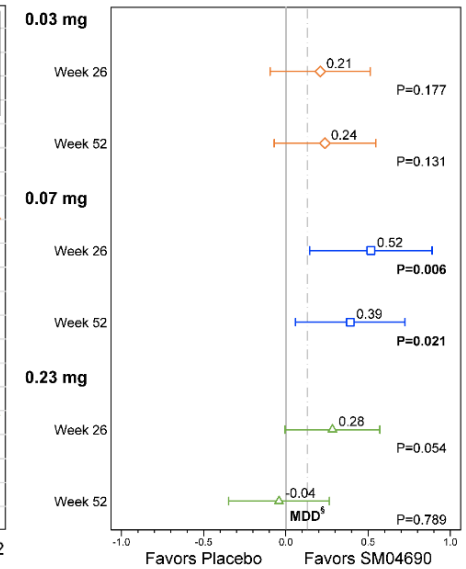
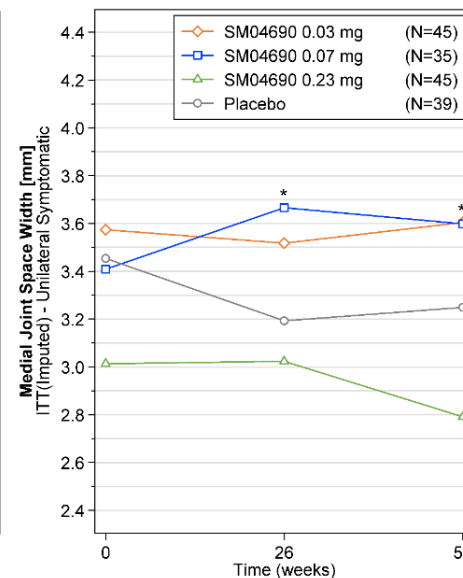
# Medial joint space width ([mJSW], mm)

Actual measurements (mean) and ladder plots comparing mean ( $\pm$  95%CI) with 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<sup>1</sup>
  - We hypothesize treated, relatively unloaded UNI knees provided enhanced environment for SM04690 to improve cartilage regeneration<sup>2,3</sup>
- 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, 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