Radiographic Outcomes from a Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of a Novel, Intra-Articular, Wnt Pathway Inhibitor (SM04690) for the Treatment of Osteoarthritis of the Knee: Week 26 Interim Analysis

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DISCLOSURES

• Y. Yazici: Samumed, LLC; salary and equity

• T. McAlindon: Samumed, grant/research support; Astellas, Flexion, Pfizer, Regeneron, Samumed, and Seikugaku, consulting

• A. Gibofsky: AbbVie, Amgen, J&J, GSK, Regeneron, shareholder; AbbVie, Pfizer, Horizon, Iroko, Celgene, Novartis/Sandoz, Samumed, consulting; AbbVie, Amgen, Celgene, Pfizer, speakers bureau

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Osteoarthritis

• 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 CV disease\(^4\)

• Multiple risk factors: age, BMI, joint injury, occupation, genetics\(^5\)

Joint Space Narrowing (JSN) is Indicative of OA Progression and is Predictive of Knee Surgery

- Radiographic JSN remains the current gold standard for assessing disease modification in OA\(^1\)-\(^3\)
- Knee OA natural history rate of JSN 0.18-0.47 mm/year\(^4\)
- Prospective study of 133 subjects: each 0.1 mm increment in JSN over 3 years was associated with a 14\%(CI 3-25%, p=0.02) increase in risk for knee replacement\(^5\)
- Prospective study of 126 patients: minimum JSN of 0.5-0.8 mm over 3 years was predictive of knee surgery within 5 years (p<0.004)\(^6\)

\(^2\)Reginster. 2015. *OAC*.
\(^3\)FDA guidance for industry; 2\(^{nd}\) draft. 1999.
\(^5\)Bruyere. 2013. *Calcif Tiss Int*.
Wnt Signaling Pathway and OA

- Wnt proteins are over-expressed and more active in OA joints\(^1\)-\(^2\)
- Wnt pathway mutations (e.g. FrzB) are associated with OA\(^3\)
- Wnt signaling is involved in increased bone formation and cartilage breakdown
- Progenitor cells reside in the synovium and subchondral bone\(^4\)-\(^6\)

Hypothesis: Inhibiting the Wnt Pathway protects and regenerates cartilage


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\(^1\)
- 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\(^2\)

SM04690-OA-02: Phase 2 Study Design

2mL Single Injection at Week 0

- **0.03mg SM04690 [N=112]**
- **0.07mg SM04690 [N=117]**
- **0.23mg SM04690 [N=109]**
- **Vehicle [N=114]**

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

Imaging: Knee X-ray

Safety Assessments: AEs, Vital signs, Physical exam, Lab panels

- Multicenter study of a single SM04690 injection evaluated safety, clinical outcomes, and JSN as measured by medial joint space width (mJSW) on radiographs.

**Interim analysis:**
- Clinical data to week 39 presented on poster #SAT0552
- Radiographic data to Week 26 presented here
<table>
<thead>
<tr>
<th>Key Inclusion Criteria</th>
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<tbody>
<tr>
<td>40-80 years, good health</td>
<td>BMI &gt;40</td>
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<tr>
<td>Ambulatory (aids allowed if needed &lt;50%)</td>
<td>Major surgery in target knee within 12 months</td>
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<tr>
<td>Clinical and radiological ACR diagnosis of primary femoro-tibial OA in target knee &gt;6 months</td>
<td>IA steroids within 2 months</td>
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<td>Hyaluronic acid within 6 months</td>
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<td></td>
<td>Acupuncture within 1 month</td>
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<tr>
<td>Kellgren-Lawrence Grade 2 / 3 in target knee</td>
<td>Target knee effusion requiring aspiration within 3 months</td>
</tr>
<tr>
<td>Pain VAS score of 30–80 for target knee</td>
<td>Any chronic condition not well controlled &gt;3 months</td>
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SM04690-OA-02: Patient Disposition

1033 subjects screened

578 subjects discontinued prior to randomization

455 subjects randomized

3 subjects discontinued prior to treatment

0.03 mg SM04690
112 subjects

Discontinued: AE: n=1
Lost to follow up: n=1
Subject withdrawals: n=3

0.07 mg SM04690
117 subjects

Discontinued: AE: n=2
Subject withdrawals: n=3

0.23 mg SM04690
109 subjects

Discontinued: AE: n=1
Subject withdrawals: n=4
Other: n=1

PBO
114 subjects

Discontinued: Lost to follow up: n=1
Subject withdrawals: n=7

3 subjects discontinued prior to treatment

455 subjects randomized

1033 subjects screened
### SM04690-OA-02: Study Demographics (ITT)

<table>
<thead>
<tr>
<th></th>
<th>0.03 mg</th>
<th>0.07 mg</th>
<th>0.23 mg</th>
<th>Placebo</th>
<th>All subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>112</td>
<td>117</td>
<td>110</td>
<td>116</td>
<td>455</td>
</tr>
<tr>
<td><strong>Age at Consent (Years) [Mean (SD)]</strong></td>
<td>59.0 (9.0)</td>
<td>60.0 (8.2)</td>
<td>61.3 (8.7)</td>
<td>60.7 (8.9)</td>
<td>60.3 (8.7)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²) [Mean (SD)]</strong></td>
<td>29.8 (4.8)</td>
<td>30.8 (4.8)</td>
<td>29.7 (4.5)</td>
<td>29.2 (4.4)</td>
<td>29.9 (4.6)</td>
</tr>
<tr>
<td><strong>Female [n(%)]</strong></td>
<td>68 (60.7%)</td>
<td>60 (51.3%)</td>
<td>68 (61.8%)</td>
<td>72 (62.1%)</td>
<td>268 (58.9%)</td>
</tr>
<tr>
<td><strong>Race [n(%)]</strong></td>
<td></td>
<td></td>
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<tr>
<td><em>White</em></td>
<td>92 (82.1%)</td>
<td>102 (87.2%)</td>
<td>96 (87.3%)</td>
<td>102 (87.9%)</td>
<td>392 (86.2%)</td>
</tr>
<tr>
<td><em>African-American</em></td>
<td>18 (16.1%)</td>
<td>14 (12.0%)</td>
<td>12 (10.9%)</td>
<td>10 (8.6%)</td>
<td>54 (11.9%)</td>
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<tr>
<td><em>Asian</em></td>
<td>1 (0.9%)</td>
<td>0</td>
<td>2 (1.8%)</td>
<td>0</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td><strong>Kellgren-Lawrence Grade 3 [n(%)]</strong></td>
<td>74 (66.1%)</td>
<td>74 (63.2%)</td>
<td>70 (63.6%)</td>
<td>74 (63.8%)</td>
<td>292 (63.8%)</td>
</tr>
<tr>
<td><strong>Unilateral Symptomatic OA [n(%)]</strong></td>
<td>45 (40.2%)</td>
<td>35 (29.9%)</td>
<td>45 (40.9%)</td>
<td>39 (33.6%)</td>
<td>164 (36.0%)</td>
</tr>
</tbody>
</table>
SM04690-OA-02: Analysis Groups

• Intention-to-treat population (ITT, n=455): all randomized subjects

• ‘Unilateral symptomatic’ population (n=164):
  – 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

• 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
SM04690-OA-02: Clinical Outcomes
WOMAC Pain [0-50] Change through 26 weeks

**ITT**

- SM04690 0.03 mg (N=108)
- SM04690 0.07 mg (N=114)
- SM04690 0.23 mg (N=103)
- Placebo (N=106)

**Unilateral Symptomatic**

- SM04690 0.03 mg (N=43)
- SM04690 0.07 mg (N=35)
- SM04690 0.23 mg (N=42)
- Placebo (N=35)
SM04690-OA-02 Clinical Outcomes
WOMAC Function [0-170] Change through 26 weeks

**ITT**

WOMAC Function [0-170] - All Available Data

**Unilateral Symptomatic**

WOMAC Function [0-170] - Unilateral Symptomatic
SM04690-OA-02: Radiographic Outcomes
Medial Joint Space Width (mJSW) (ITT)

![Graph showing radiographic outcomes for different doses of SM04690-OA-02.](image)

- **0.03 mg**: Week 26, P=0.072
- **0.07 mg**: Week 26, P=0.510
- **0.23 mg**: Week 26, P=0.026
- **All Doses**: Week 26, P=0.090
SM04690-OA-02: Radiographic Outcomes
mJSW (Unilateral Symptomatic)
Response Definitions
- JSW Narrowing: mJSW change < 0 mm
- No Change: mJSW change = 0 mm
- JSW Improvement: mJSW change > 0 mm

Odds of JSW Response compared to Placebo
- 0.03 mg OR=2.07, $P=0.011$
- 0.07 mg OR=1.56, $P=0.124$
- 0.23 mg OR=1.50, $P=0.171$
- All SM04690 OR=1.69, $P=0.029$
**SM04690-OA-02: mJSW Response at Week 26**

*Unilateral Symptomatic*

### Response Definitions

- **JSW Narrowing**: mJSW change < 0 mm
- **No Change**: mJSW change = 0 mm
- **JSW Improvement**: mJSW change > 0 mm

### Odds of JSW Response compared to Placebo

- **0.03 mg**: OR=5.33, \( P=0.001 \)
- **0.07 mg**: OR=5.71, \( P=0.001 \)
- **0.23 mg**: OR=4.63, \( P=0.004 \)
- **All SM04690**: OR=5.18, \( P<0.001 \)
SM04690-OA-02: mJSW Cumulative Probability to Week 26 - Unilateral Symptomatic Group

Change at Week 26 in ITT - Unilateral Symptomatic:

- SM04690 0.03 mg (N=42)
- SM04690 0.07 mg (N=34)
- SM04690 0.23 mg (N=41)
- Placebo (N=35)
Limitations

• Study not formally powered

• Clinical outcomes measured at 0, 4, 13 and 26 weeks

• Radiographs reported at 26 weeks
  – Intra- and inter- observer reproducibility 0.92 & 0.90 respectively
  – QuAP™ positioner used
  – Centrally read
Summary

• Radiographic outcomes from this 26 week interim analysis demonstrated SM04690 treatment maintained or increased mJSW compared to placebo

• Radiographic and clinical outcomes considered together suggested SM04690 has potential as a DMOAD for the treatment of knee OA

• For safety and clinical results, see poster #SAT0552
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
  - Completed April 2017, Data available May 2017
- **SM04690-OA-04, Phase 2, N=330 (ongoing)**
  - 24 weeks, primary endpoints 24 week S&S and JSW
  - Started April 2017, estimated completion January 2018
- **SM04690-OA-05, safety extension (ongoing)**
  - Started September 2016
  - 5 years, safety with exploratory long-term efficacy including radiographs and WOMAC (observational; no additional injections)
- **SM04690-OA-08, MRI, N=10**
  - 24 weeks, exploratory evaluation of cartilage quality and thickness
  - Estimated September 2017 start