Medical or Research Professionals/Clinicians

Topic area: Clinical topics by disease

Topic: 23. Osteoarthritis

Submission N°: EULAR17-6382

CLINICAL OUTCOMES FROM A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2 STUDY OF A NOVEL, INTRA-ARTICULAR, INJECTABLE, WNT PATHWAY INHIBITOR (SM04690) FOR THE TREATMENT OF KNEE OSTEOARTHRITIS: WEEK 26 INTERIM ANALYSIS

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My abstract has been or will be presented at a scientific meeting during a 12 months period prior to EULAR 2017: No

Is the first author applying for a travel bursary and/or an award for undergraduate medical students?: No

Background: Knee osteoarthritis (OA) is characterized by pain, disability and joint deformity due to degradation of articular cartilage and bone remodeling. The Wnt signaling pathway has a role in these cellular processes, and it is also linked to inflammation. SM04690, a small molecule Wnt pathway inhibitor, is in development for the treatment of knee OA as a potential disease modifying drug. A phase 2, multicenter, 52-week, randomized controlled trial of a single intra-articular (IA) injection of SM04690 is ongoing in subjects with moderate to severe knee OA. Clinical results from an interim analysis are reported.

Objectives: To evaluate clinical outcomes from the treatment of moderate to severe knee OA by SM04690.

Methods: Subjects with ACR defined knee OA, Kellgren-Lawrence (KL) grades 2-3, received a 2 mL injection of 0.03 mg, 0.07 mg, 0.23 mg SM04690 or placebo in the target (most painful) knee. Clinical outcomes (Western Ontario and McMaster Universities Arthritis Index [WOMAC], patient global assessment [PTGA], physician global assessment [MDGA]), were assessed at 4, 13 and 26 weeks by analysis of covariance adjusted for subject baseline in the intention-to-treat (ITT) population and two subgroups: 1) with unilateral knee OA (pre-specified); 2) without chronic pain (Widespread Pain Index [WPI]≤4, post-hoc).

Results: 455 subjects (average age 60.3 [±8.7], female 58.9%, average BMI 29.9 [±4.6] kg/m2, KL 3 [64.4%], and bilateral OA [64.0%]) were enrolled. SM04690 appeared well tolerated. In the ITT population clinically meaningful improvements in all clinical outcomes compared to baseline were seen for all groups and placebo at weeks 13 and 26 (Table). Moreover, clinically meaningful improvements in clinical outcomes were also seen in multiple groups over several outcomes at various time points compared to placebo. In the unilateral knee OA subgroup, PTGA (0.03 mg) and MDGA (0.07 mg) were significantly improved compared to placebo. In the WPI≤4 subgroup, WOMAC Pain (0.07 mg), PTGA (0.03 mg) and MDGA (0.07 mg) were significantly improved compared to placebo.

Image/graph:

Table. Mean (SD) Baseline and Change in Clinical Outcomes over Time by Treatment Groups

All Subjects (ITT)	Timepoint	0.03 mg	0.07 mg	0.23 mg	Placebo
n*		106	114	103	105
WOMAC Pain [0-50]	*Baseline*	25.9 (8.3)	25.9 (8.2)	25.6 (7.7)	26.0 (7.6)
	Week 13	-11.9 (11.3)	-11.8 (11.2)	-10.8 (11.4)	-11.1 (11.1)
	Week 26	-12.4 (12.0)	-13.7 (10.8)	-12.0 (10.6)	-12.1 (10.8)
WOMAC Function [0-170]	*Baseline*	90.7 (28.7)	92.3 (25.7)	88.2 (28.9)	90.4 (25.4)
	Week 13	-41.6 (37.4)	-44.2 (36.4)	-38.7 (37.7)	-39.0 (37.7)
	Week 26	-43.3 (38.4)	-48.4 (37.0)	-41.3 (36.0)	-43.5 (36.3)
Physician Global [0-100]	*Baseline*	52.7 (20.0)	53.2 (18.4)	53.0 (20.5)	52.0 (18.2)
	Week 13	-23.2 (25.1)	-26.0 (23.5)	-23.3 (25.5)	-20.8 (25.8)
	Week 26	-25.3 (28.9)	-26.8 (23.6)	-25.6 (25.8)	-21.5 (24.8)
Patient Global [0-100]	*Baseline*	45.4 (22.0)	45.3 (20.5)	45.2 (20.9)	44.1 (21.1)
	Week 13	-18.5 (24.1)	-13.8 (24.8)	-15.0 (26.8)	-13.9 (24.1)
	Week 26	-21.7 (24.7)	-17.9 (25.2)	-17.8 (27.2)	-15.9 (27.4)
Unilateral Subjects (ITT)	Timepoint	**0.03 mg**	**0.07 mg**	**0.23 mg**	**Placebo**
n*		43	35	42	34
WOMAC Pain [0-50]	*Baseline*	25.5 (8.5)	24.3 (8.9)	24.5 (7.1)	27.0 (7.1)
	Week 13	-13.7 (11.1)	-11.7 (8.7)	-11.7 (12.0)	-12.6 (10.7)
	Week 26	-13.7 (11.9)	-13.7 (7.9)	-12.3 (10.6)	-11.7 (10.1)
WOMAC Function [0-170]	*Baseline*	92.7 (29.6)	85.3 (27.7)	84.2 (28.6)	91.2 (22.7)
	Week 13	-51.3 (34.9)	-44.8 (28.7)	-39.7 (40.7)	-39.7 (39.3)
	Week 26	-50.5 (39.5)	-47.6 (28.0)	-42.7 (38.0)	-40.8 (34.2)
Physician Global [0-100]	*Baseline*	54.5 (18.5)	50.6 (20.5)	52.8 (24.2)	50.5 (17.8)
	Week 13	-30.6 (24.6)†	-25.6 (19.7)	-24.5 (27.1)	-17.4 (26.5)
	Week 26	-29.2 (29.8)	-27.6 (25.7)†	-27.9 (24.6)	-17.4 (25.9)
Patient Global [0-100]	*Baseline*	44.2 (23.1)	44.3 (24.1)	48.8 (19.7)	45.7 (19.9)
	Week 13	-22.9 (24.0)†	-13.3 (24.3)	-20.0 (28.1)	-13.8 (24.4)
	Week 26	-26.8 (23.6)‡	-20.4 (29.1)	-20.2 (30.4)	-13.8 (31.0)
WPI ≤ 4 (ITT)	Timepoint	**0.03 mg**	**0.07 mg**	**0.23 mg**	**Placebo**
n*		64	66	63	64
WOMAC Pain [0-50]	*Baseline*	25.6 (7.4)	25.5 (8.7)	26.7 (5.8)	26.5 (7.0)
	Week 13	-13.4 (11.3)	-12.2 (11.5)	-11.6 (11.9)	-11.0 (11.6)
	Week 26	-12.4 (12.0)	-14.8 (11.1)†	-12.9 (10.5)	-11.5 (11.2)
WOMAC Function [0-170]	*Baseline*	90.6 (25.6)	88.7 (26.7)	93.6 (21.5)	91.1 (24.9)
	Week 13	-47.6 (39.2)	-44.0 (35.7)	-43.4 (36.2)	-35.9 (39.7)
	Week 26	-46.1 (41.2)	-49.8 (36.9)	-46.6 (34.2)	-39.5 (36.4)
Physician Global [0-100]	*Baseline*	53.2 (19.5)	53.4 (19.7)	56.9 (18.6)	51.6 (18.1)
	Week 13	-24.8 (25.7)	-26.1 (24.4)	-24.9 (27.5)	-18.7 (26.9)
	Week 26	-24.5 (29.6)	-28.4 (25.2)‡	-26.2 (27.3)	-18.0 (24.9)
Patient Global [0-100]	*Baseline*	44.3 (23.0)	43.9 (23.7)	47.8 (22.4)	42.8 (21.1)
	Week 13	-21.6 (24.9)‡	-15.1 (26.7)	-18.1 (28.6)	-12.1 (26.2)
	Week 26	-23.8 (25.7)†	-21.1 (27.6)	-21.1 (28.6)	-14.3 (29.1)

*Ns represent observations at Week 26.†P<0.05 compared to placebo. ‡ P<0.01 compared to placebo.

Conclusions: In this phase 2 interim analysis, the ITT population (SM04690 and placebo groups) demonstrated clinically relevant improvements in clinical outcomes at weeks 13 and 26 compared to baseline. In two subgroups, consistent improvements over placebo were seen in 0.03 mg and 0.07 mg treatment arms, achieving statistical significance for PTGA and MDGA. Further studies to identify relevant sub-populations and evaluate the safety and efficacy of SM04690 are ongoing.

Disclosure of Interest: Y. Yazici: None declared, A. Gibofsky Shareholder of: AbbVie, Amgen, J&J, GSK, Regneron, Consultant for: AbbVie, Pfizer, Horizon, Iroko, Celgene, Novartis/Sandoz, Samumed, Speakers bureau: AbbVie, Amgen, Celgene, Pfizer, N. Lane Consultant for: Samumed, LLC, N. Skrepnik Grant/research support from: Samumed, LLC, Consultant for: Orthofix and Sanofi, E. Armas Grant/research support from: Samumed, LLC, C. Swearingen Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, A. DiFrancesco Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, J. Tambiah Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, T. McAlindon Grant/research support from: Samumed, Consultant for: Astellas, Flexion, Pfizer, Regeneron, Samumed,and Seikugaku