THU0414

COMPARISON OF INTRA-ARTICULAR SHAM AND VEHICLE INJECTIONS FROM A PHASE 2B TRIAL OF SM04690, A SMALL-MOLECULE WNT PATHWAY INHIBITOR FOR KNEE OSTEOARTHRITIS

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Background: Intra-articular (IA) saline, commonly used as a placebo (PBO) comparator in knee osteoarthritis (OA) trials, has consistently shown improvements from baseline in patient-reported outcomes (PROs).¹ These effects have been attributed to contextual and/or physiological benefits of saline, thus causing interpretation of potential IA therapeutics trial results to be questioned.^{2,3}

Objectives: A prospective, randomized, controlled, 24-week phase 2b study compared effects of vehicle PBO to sham and SM04690 (an IA Wnt pathway inhibitor in development as a potential disease-modifying knee OA drug (DMOAD)) injections. Potential unblinding impact of PBO or sham was also tested. Primary study results are presented separately.

Methods: Knee OA subjects with Kellgren-Lawrence (KL) grades 2-3 and Pain Numeric Rating Scale (NRS) ≥ 4 and ≤ 8 in the target knee and < 4 in the contralateral knee were randomized to receive a single blinded IA injection of 2 mL vehicle (PBO, 0.5% carboxymethylcellulose sodium, 0.05% polysorbate 80 in pH 7.4 saline), sham (dry needle), or SM04690 in the target knee on Day 0. PROs included change from baseline in weekly average of daily pain in the target knee by NRS, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain, WOMAC Physical Function, and Patient Global Assessment (PtGA). Subjects were asked which treatment assignment they thought they received; their accuracy was compared using Bang's Blinding Index (BBI), a method used to evaluate blinding across clinical trial treatment arms. The index scale is $-1 < 0 < +1$, with values toward -1 indicating more subjects incorrectly guessing treatment allocations, toward 0 indicating perfect blinding, and toward $+1$ indicating more subjects correctly identifying treatment allocations.

Results: In the full analysis set of PBO and sham subjects (N=233; 207 [89%] completed), both groups showed clinically relevant improvements ($>10\%$ of full scale⁴) from baseline at first measurement that persisted through Week 24. However, no clinically meaningful or statistically significant differences were evident between the two groups at any timepoints (Figure). BBI did not indicate unblinding.

Conclusion: Subjects with knee OA receiving a single IA injection of PBO reported no differences in changes from baseline in knee OA PROs compared to subjects who received sham injections. These data suggested the effects were "contextual," meaning they resulted from the injection procedure, rather than from direct therapeutic effects of PBO or saline in the joint.

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Figure: Observations over time depicting mean improvements ($\pm$ 95% CI) of PBO compared to sham injection adjusted for baseline. A. Pain NRS, B. WOMAC Pain, C. WOMAC Function, and D. Patient Global; in all subjects.

Disclosure of Interests: Yusuf Yazici Shareholder of: Samumed, LLC, Consultant for: Celgene Corporation, BMS, Genentech, Sanofi, Employee of: Samumed, LLC, Jeyanesh Tambiah Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, Christopher Swearingen Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, Sarah Kennedy Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, Vibeke Strand Consultant for: Samumed, LLC, AbbVie, Amgen, EMD Serono, Eupraxia, Flexion, Iroko, Novartis, Pfizer, Regeneron, Sanofi, SKK, Brian Cole Shareholder of: Ossio, Regentis, Grant/research support from: Aesculap/B. Braun, Arthrex, Inc, Regentis, Consultant for: Arthrex, Inc, Regentis, Samumed LLC, Marc Hochberg Shareholder of: BriOri Biotech, Theralogix LLC., Consultant for: Bristol Myers Squibb, Eli Lilly, EMD Serono, Novartis Pharma AG, Pfizer Inc., Samumed LLC, Symbio Bio Inc., Theralogix LLC, TissueGene Inc., TLC Biopharmaceuticals, Inc., Zynherba, Galapagos, IQVIA, Hoffman LaRoche., Raveendhara Bannuru Consultant for: Samumed, LLC, Bioventus, Timothy McAlindon Grant/research support from: Samumed, LLC, Consultant for: Samumed, LLC, Astellas, Flexion, Pfizer, Regeneron, Seikugaku

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THU0415

EXPLORATORY PROTEIN PROFILING OF HUMAN SYNOVIAL FLUID FROM KNEE OSTEOARTHRITIS

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Background: There is a lack of valid and robust biomarkers in the field of OA diagnosis, prognosis, and treatment evaluation [1]. Synovial fluid is in direct contact with articular cartilage, ligament, meniscus and joint capsule it is therefore an excellent sample to explore the protein profile in which could provide pathogenesis information from several surrounding parts.

Objectives: The aim with this project was to perform mass spectrometry (MS) of human synovial fluid using a global discovery approach, to identify biomarker candidates associated with meniscus degradation and/or knee OA.

Methods: Synovial fluid was sampled from 3 different subject groups: i) end-stage medial compartment knee OA patients undergoing arthroplasty (n=11, age range 55-80 years), ii) knee arthroscopy patients who typically had a degenerative meniscal tear (n=7, age range 50-64 years), and iii) deceased human donors without known chronic knee disease (n=13, age range 19-79 years). All synovial fluids were centrifuged and freshly frozen and stored at -80°C . For the analysis, 50 μL of synovial fluid was mixed with MS-safe proteinase inhibitor cocktail, hyaluronidase, depleted, reduced, alkylated, precipitated, digested with sequencing grade trypsin (Promega), filtered and desalted. The samples were further analyzed with an EASY-nLC 1000 coupled to an Orbitrap Fusion mass spectrometer