directed against CGRP, were assessed in a phase 2 clinical trial NCT02192190 in patients with moderate to severe osteoarthritis (OA) knee pain. Patients were randomized to placebo, galcanezumab (5, 25, 120 and 300 mg subcutaneously every 4 weeks, at weeks 0 and 4) or celecoxib (200 mg once daily) for 16 weeks in a 2:1:1:1:1 ratio. The study was terminated after an interim analysis due to inadequate efficacy for OA pain.

Objectives: This study assessed the correlation of baseline plasma CGRP concentrations with signs, symptoms and radiographic severity of OA, and response to galcanezumab and celecoxib treatments.

Methods: Plasma samples were collected at baseline and weeks 4, 8, 12 and 16 after study drug treatment. CGRP concentrations were determined by a validated high sensitivity (HS) assay. Correlation of baseline CGRP levels to WOMAC scores, PGA and radiographic Kellgren-Lawrence (K-L) grades were assessed using Spearman's correlation and Wilcoxon test. Patients were stratified into high vs low groups by baseline CGRP concentrations and post-treatment changes from baseline WOMAC scores evaluated by mixed effect model repeated measures for each subset.

Results: At the interim analysis, baseline plasma CGRP samples were available for 262 patients with 54 patients providing samples at study termination through the week 8 visit. The median CGRP concentration at baseline was 1.07 pg/ml, range <0.78 to 33.91, and 31% of patients were below the level of quantitation (BLQ, <0.78 pg/ml). Median baseline CGRP levels were 1.0 pg/ml for K-L grade 2 (N=178), and 1.2 pg/ml for K-L grade 3 (N=84) (p=0.06). Correlations of WOMAC or PGA scores with baseline CGRP levels were all $r < 0.01$ (showed no significant correlations). In OA patients receiving galcanezumab 300mg SC at week 0 and week 4, those with high baseline CGRP levels demonstrated a 14mm improvement in WOMAC Pain response at week 12, (95% CI 0, 29mm). The pain response to galcanezumab 300mg did not reach the magnitude of celecoxib response and no effects were seen at 5–120mg doses. Celecoxib treatment had larger pain reduction among patients with high baseline CGRP compared to low baseline CGRP levels. Treatment with celecoxib did not alter plasma CGRP concentrations.

Conclusions: At baseline, CGRP levels in OA patients were not associated with WOMAC or PGA scores. There was a modest association to radiographic K-L grade. Subgroup analyses of patients with high (>median) CGRP levels at baseline suggested a potential response to galcanezumab for the highest dose, 300mg, but not lower doses. Celecoxib response was greater in those with higher CGRP levels. However, interpretation was limited by small samples sizes at the latter time points. Further studies may determine if enriching the OA population for higher CGRP levels at baseline, or if increased or longer dosing of galcanezumab would improve pain responses or if CGRP blockade is relevant in relieving OA knee pain.

Disclosure of Interest: T. McNearney Shareholder of: Eli Lilly stock, Employee of: Eli Lilly and Company, C. Smith Shareholder of: Eli Lilly stock, Employee of: Eli Lilly and Company, R. Brown Shareholder of: Eli Lilly and Company, Employee of: Eli Lilly and Company, A. Camporeale Shareholder of: Eli Lilly stock, Employee of: Eli Lilly and Company, M. Deeg Shareholder of: Eli Lilly stock, Employee of: Eli Lilly and Company, D. Montieth Shareholder of: Eli Lilly stock, E. Collins Employee of: Eli Lilly and Company, T. Schnitzer Consultant for: Eli Lilly and Company, A. Kivitz: None declared, J. Talbot Shareholder of: Eli Lilly stock, Employee of: Eli Lilly and Company, Y. Jin Shareholder of: Eli Lilly stock, Employee of: Eli Lilly and Company

DOI: 10.1136/annrheumdis-2017-eular.2155

SAT0549 ANTI-INFLAMMATORY PROPERTIES OF SM04690, A SMALL MOLECULE INHIBITOR OF THE WNT PATHWAY AS A POTENTIAL TREATMENT FOR KNEE OSTEOARTHRITIS

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Background: Osteoarthritis (OA) is characterized by pain, deformity, and reduced function in the knee joint. Upregulated Wnt signaling affects the pathogenesis of OA through increased inflammation, increased subchondral bone and thinning cartilage. SM04690, a novel small molecule, was previously shown to inhibit the Wnt pathway and induce chondrogenesis *in vitro* and *in vivo*.¹

Objectives: SM04690 was evaluated in preclinical studies to determine its capacity to reduce inflammation, and reduce pain in OA.

Methods: Anti-inflammatory activity was evaluated by measuring cytokine (IL-6 and TNF- α) secretion using ELISA with IL1- β stimulated synovial fibroblasts. A panel of pro-inflammatory cytokines (TNF- α , IL-1 α , IL-1 β , IL-2, IL-6, IL-8, IL-17A, IL-17F, IFN- γ and PGE2) was evaluated by ELISA; T and B cell proliferation by flow cytometry in peripheral blood mononuclear cells (PBMCs), and T and B cell co-cultures stimulated with super-antigen (SAg) or lipopolysaccharides (LPS), compared to vehicle or benchmark immunosuppressant or steroid (cyclosporin A and prednisolone). SM04690 effects on LPS-induced expression and phosphorylation of JNK, NFkB, Erk, cJun, Akt, Stat3 in THP-1 cells were measured by qPCR and Western Blot. *In vivo* SM04690 activity was evaluated in a rat monosodium iodoacetate (MIA) injection-induced OA model, immediately followed by a single intra-articular SM04690 or vehicle injection. Joint inflammation was evaluated by measuring synovial thickness and infiltrating cells histology; inflammatory cytokines (IL-1 α , IL-1 β , IL-2, IL-5, IL-6, IL-8, TNF- α and IFN- γ) by qPCR and ELISA and cartilage protection by qPCR for matrix metalloproteinases (MMPs). Pain was measured as paw withdrawal threshold using Von Frey apparatus.

Results: SM04690 inhibited IL-1 β -induced TNF- α and IL-6 secretion in synovial fibroblasts (EC₅₀ @30nM). SM04690 significantly inhibited ($p < 0.01$) SAg and LPS stimulated pro-inflammatory cytokine production (TNF- α , IL-1 α , IL-1 β , IL-2, IL-6, IL-8, IL-17A, IL-17F, IFN- γ , PGE2), T and B cell proliferation in PBMCs and T and B cell co-cultures (Figure A), with activity comparable to or better than cyclosporin A and prednisolone. SM04690 treatment specifically decreased LPS-induced gene expression ($p < 0.01$) and phosphorylation of NFkB in THP-1 cells with no effect on JNK, Erk, cJun, Akt and Stat3. Compared to vehicle in the rat MIA OA model, SM04690 injection reduced inflammatory cells, decreased synovial thickness ($p < 0.05$, Figure B), inhibited production of pro-inflammatory cytokines and MMPs ($p < 0.05$). SM04690 increased ($p < 0.01$) paw withdrawal threshold in treated rats compared to vehicle at multiple time points (Figure C).

Figure. SM04690 inhibited inflammatory cytokine production *in vitro* and decreased inflammation and pain in the MIA model of OA

Conclusions: SM04690 demonstrated potent anti-inflammatory properties, comparable to or greater than cyclosporin A and prednisolone. In a rat knee OA model, SM04690 injection reduced inflammation, protease production and pain compared to vehicle. The anti-inflammatory properties of SM04690 may provide beneficial effects in the treatment of OA. Clinical studies are ongoing.

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Disclosure of Interest: V. Deshmukh Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, C. Barroga Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, M. Ibanez Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, T. Seo Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, S. Kc Shareholder of: Samumed, LLC, Employee of: Samumed, LLC, Y. Yazici Shareholder of: Samumed, LLC, Employee of: Samumed, LLC

DOI: 10.1136/annrheumdis-2017-eular.6460

SAT0550 NEUROPATHIC PAIN AMONG PATIENTS WITH PRIMARY KNEE OSTEOARTHRITIS- RESULTS OF A CROSS SECTIONAL STUDY FROM A TERTIARY CARE CENTRE IN SOUTHERN INDIA

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Background: Pain in osteoarthritis (OA) is generally believed to be nociceptive because of local structural pathology and joint failure which so characterizes OA. However, there is often a discordance between the radiographic knee OA and pain, suggesting that the pain can be contributed by other mechanisms other than nociception.¹ Recently it is shown that pain in knee OA may have a neuropathic component.²

Objectives: The objective of the study was to assess the level of neuropathic pain in patients with knee OA, and identify the clinical and socio-demographical factors associated with neuropathic pain

Study design: Cross sectional study.

Setting: Medicine and Orthopaedic outpatient department (OPD) of a tertiary care centre located in southern India

Methods: One-hundred and sixty-one patients with knee OA satisfying the American College of Rheumatology 1986 clinical and radiographic classification criteria for knee OA were studied. Neuropathic pain was assessed by the Douleur Neuropathique in 4 questions (DN4) questionnaire,³ score of 4/10 or more was classified as diagnostic for neuropathic pain. The Indian version of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)⁴ was used to assess pain, stiffness and physical function of the patients. Factors associated with neuropathic pain were explored.

Results: Mean age was 55.7 $\pm$ 8.8 years. The mean total Indian WOMAC was

75.07±13.8, WOMAC pain score was 16.1±3.6. Eighty-two patients of 161 (50.9%) had neuropathic pain. When diabetics were excluded (n=58), the proportion of patients with neuropathic pain reduced to 45.6%. The most frequently described pain characteristic was sensation of electric shock (58.4%). Mean total WOMAC and physical function subscale was significantly higher in neuropathic pain group when compared to no neuropathic pain group (DN4 score 3 or less), 77.5±11.5 versus 72.6±15.5, $p=0.024$; and 54.3±8.8 and 49.8±12.6 respectively, $p=0.008$.

Conclusions: Neuropathic pain was seen in up to 50% patients with knee OA. Centrally acting drugs like tricyclic anti-depressants or duloxetine can be used to improve pain and physical function in patients of knee OA with neuropathic pain.

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Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.6192

SAT0551 INCREASED SERUM AND SYNOVIAL LEVELS OF MIDKINE ARE ASSOCIATED WITH RADIOLOGICAL PROGRESSION IN KNEE OSTEOARTHRITIS PATIENTS

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Background: Midkine is a heparin-binding growth factor that plays an important role in mesoderm remodeling as in chondrogenesis and adipocyte formation. There is an increased expression of midkine in damaged tissues and it is believed to have functional antagonism, as it helps in tissue repair and survival while, on the other hand it can enhance inflammatory reactions resulting in more tissue injury [1].

Objectives: This study aimed to determine serum and synovial fluid (SF) levels of midkine in patients with primary knee osteoarthritis (KOA) and to examine the relationship between these levels with the clinical and functional parameters as well as radiological progression of KOA.

Methods: We measured midkine in the serum (n=52) and SF samples (n=23) from 52 KOA patients as well as in the serum from 20 healthy control (n=20). In the patients, numerical rating scale of pain (NRS), body mass index (BMI) and The Western Ontario Mc Master scale (WOMAC) were recorded. Graded plain radiographs using Thomas score, and musculoskeletal ultrasound examination (MSUS) of both knees were performed at baseline and after 24 months to assess radiological progression [2,3]. Radiological progression was considered if there is an increase in the Thomas grading score or MSUS transition to a higher grade at the 24 months follow up period compared to baseline evaluation.

Results: Serum and SF midkine levels were significantly increased in KOA patients (mean ± SD 80.79±31.8 pg/mL and 216.31±94.93 pg/mL respectively) compared to serum level in the healthy controls (mean ± SD 65.6±14.76 pg/mL), $p<0.05$ and $p<0.001$ respectively. In KOA patients, the serum and SF concentrations of midkine significantly correlated with the baseline thickness of the cartilage on the medial condyle ($r = -0.41$ and -0.52 respectively, $p<0.05$) but not on the lateral condyle of the femur ($r=0.12$ and 0.15 respectively, $p>0.05$). Patients with elevated serum and SF midkine (defined as midkine level more than the mean plus 2 standard deviation of healthy controls's level) had a twofold increased risk of radiological progression with MSUS (age, sex and BMI adjusted RR 2.4 and 2.6, 95% CI respectively). With elevated serum and SF midkine levels, there was no increased risk of radiological progression detected with plain radiography in KOA Patients (age, sex and BMI adjusted RR 1.3 and 1.6, 95% CI respectively).

Conclusions: Osteoarthritis patients have significantly elevated serum and synovial levels of midkine that were obviously associated with radiological progression on MSUS suggesting that it could be a useful marker to reflect OA severity and implies a possible role in the pathogenesis of OA.

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Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.5439

SAT0552 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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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.

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)
	Week 26	90.7 (28.7)	92.3 (25.7)	88.2 (28.9)	90.4 (25.4)
WOMAC Function [0-170]	Baseline	41.6 (37.4)	44.2 (36.4)	38.7 (37.7)	39.0 (37.7)
	Week 13	-43.3 (38.4)	-48.4 (37.0)	-41.3 (36.0)	-43.5 (36.3)
	Week 26	52.7 (20.0)	53.2 (18.4)	53.0 (20.5)	52.0 (18.2)
	Week 26	-23.2 (25.1)	-26.0 (23.5)	-23.3 (25.5)	-20.8 (25.8)
Physician Global [0-100]	Baseline	25.3 (28.9)	26.8 (23.6)	25.6 (25.8)	21.5 (24.8)
	Week 13	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)					
n*	Timepoint	0.03 mg	0.07 mg	0.23 mg	Placebo
		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)
	Week 26	92.7 (29.6)	85.3 (27.7)	84.2 (28.6)	91.2 (22.7)
WOMAC Function [0-170]	Baseline	51.3 (34.9)	44.8 (28.7)	39.7 (40.7)	39.7 (39.3)
	Week 13	-50.5 (39.5)	-47.6 (28.0)	-42.7 (38.0)	-40.8 (34.2)
	Week 26	54.5 (18.5)	50.6 (20.5)	52.8 (24.2)	50.5 (17.8)
	Week 26	-30.6 (24.6)†	-25.6 (19.7)	-24.5 (27.1)	-17.4 (26.5)
Physician Global [0-100]	Baseline	29.2 (29.8)	27.6 (25.7)†	27.9 (24.6)	17.4 (25.9)
	Week 13	44.2 (23.1)	44.3 (24.1)	48.8 (19.7)	45.7 (19.9)
	Week 26	-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)					
n*	Timepoint	0.03 mg	0.07 mg	0.23 mg	Placebo
		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)
	Week 26	90.6 (25.6)	88.7 (26.7)	93.6 (21.5)	91.1 (24.9)
WOMAC Function [0-170]	Baseline	47.6 (39.2)	44.0 (35.7)	43.4 (36.2)	35.9 (39.7)
	Week 13	-46.1 (41.2)	-49.8 (36.9)	-46.6 (34.2)	-39.5 (36.4)
	Week 26	53.2 (19.5)	53.4 (19.7)	56.9 (18.6)	51.6 (18.1)
	Week 26	-24.8 (25.7)	-26.1 (24.4)	-24.9 (27.5)	-18.7 (26.9)
Physician Global [0-100]	Baseline	24.5 (29.6)	28.4 (25.2)†	26.2 (27.3)	18.0 (24.9)
	Week 13	44.3 (23.0)	43.9 (23.7)	47.8 (22.4)	42.8 (21.1)
	Week 26	-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