same cartilage lesions in order to establish the validity of this procedure.

Methods Articular cartilage of medial compartments of three OA knee joints were magnified evaluated and recorded using a 2,7 mm scope. 34 different areas of lesion were individualised and fissures; III: deep fissures; IV: exposure of subchondral bone. 73 sections of arthroscopically normal and OA cartilage were microscopically examined and graded twice by two observers according to Mankin's histopathological grading system (0–14) (MHHGS). Mathematic categorization in five groups was done to correlate with chondroscopic grades of lesion: normal (0–2), mild (3–5), moderate (6–8), severe (9–11), and very severe (12–14).

Results Intra and interobserver variability for MHHGS score was determined with Sperman's correlation coefficient for both observers: $r = 0,890$ $p < 0,001$; $r = 0,835$ $p < 0,001$ and $r = 0,906$ $p < 0,001$; $r = 0,822$ $p < 0,001$. Average MHHGS score for chondroscopic grade 0 ($1,7 \pm 0,59$ $n = 20$), grade I ($3,62 \pm 2,33$ $n = 28$), grade II ($6,82 \pm 1,75$ $n = 52$) were as expected, but for grade III ($8,13 \pm 2,13$ $n = 34$) and grade IV ($11,5 \pm 3,18$ $n = 14$) were lower. Correlation between CHGS and MHHGS scores were measure computing the kappa index for categorical variables for both observers: $k_p = 0,50$ $k_p = 0,58$.

Conclusion CHGS score of cartilage might be considered a relevant tool of OA outcome for research. The low tendency to overestimate lesions in advanced stages may be related to the mathematic categorization of the histopathological score.

SAT0080 INSIGHT INTO THE STRUCTURAL BASIS OF SELECTIVE CYCLOOXYGENASE-2 INHIBITION

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Background Cyclooxygenase-1 and -2 (COX-1/COX-2) catalyse the rate-limiting step in prostaglandin (PG) synthesis and are the targets of non-steroidal anti-inflammatory drugs (NSAIDs). The evidence is strong that the selective COX-2 inhibitors have reduced GI side effects in patients treated for rheumatic conditions, including osteoarthritis.

Objectives The molecular basis of binding affinities and COX-2/COX-1 selectivity are explored using an approach that combines experimental results from X-ray analyses and docking experiments from computational chemistry.

Methods The reported X-ray structures of COX-1 and COX-2 were used for computational optimisation of the interaction between the different NSAIDs and COX isoforms using the established computer program Sybyl/Molcad.

Results The inhibition of COX can occur by compounds with high degree of structural diversity and various types of mechanisms. The results show that COX-2 selective inhibitors are belonging to several different, structural distinct classes: arylalkanoic acids, enolcarboxamids, acidic sulfonamids and diarylheterocycles.

Two fundamental differences between the active site of COX-2 and COX-1 are responsible for the COX-2 selectivity and are caused by several amino acid substitution in COX-2 vs. COX-1: The volume of the COX-2 channel is extended by the substitution of Iso 523 by Val 523, Iso 434 by Val 434, His 513 by Arg 513 and Phe 503 by Leu 503.

COX-selective diaryl-heterocycles (DuP 697, celecoxib, rofecoxib) are exploiting the side pocket and enolcarboxamid (meloxicam) and acidic sulfonamids (L745,733, NS 398, nimesulide) the extra space at the top of the channel.

Conclusion This work illustrates the value of novel docking procedure for determining the binding of NSAIDs to the COX-enzyme. The structural insights into the binding mechanism indicate that COX-2 selectivity can be obtained by at least three chemically distinct classes of NSAIDs of which meloxicam, nimesulide and celecoxib are representatives.

SAT0081 EFFECT OF BODY MASS INDEX AND BONE MINERAL DENSITY ON KNEE OSTEOARTHRITIS

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Background

Objectives The aim of this study was to investigate the influence of the bone mineral density (BMD) and body mass index (BMI) on the knee osteoarthritis (OA).

Methods Seventyfive patients were taken in this study. BMD was measured using dual X-ray absorptiometry (Dexa). Measurements of the spine were made at L1-L4 and of the hip at three sites (femoral neck, Ward's region and trochanter). The BMI, an indicator of obesity was calculated as the weight divided by the height squared (kg/m^2). The knee OA was assessed from a weight-bearing anteroposterior radiograph. Osteophytes and joint space narrowing were evaluated separately. Individual radiographic features (IRF) rating method was used for grading of osteophytes (0–3) and joint space narrowing (0–3).

Results The mean age of the women was 67 years (48–75) and of the 23 men was 61 years (45–66). There was a highly positive correlation between BMD and OA with BMI ($p < 0,01$, $p < 0,01$ respectively). The density of the lumbar spine and the 3 proximal femur sites was significantly larger in men than in women. Mean femoral BMD was correlated with joint space narrowing but not with osteophytosis ($p < 0,05$). There was no relationship between the density of the lumbar spine with knee OA.

Conclusion There is a clear link between BMD and BMI with the knee OA. These results suggest that mechanical factors are important in the pathophysiology of these diseases.

SAT0082 A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, ORAL SINGLE DOSE, DOSE ESCALATION TRIAL, INVESTIGATING THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SVT-2016 IN HEALTHY MALE SUBJECTS. PRELIMINARY REPORT

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Background As a pivotal enzyme in the inflammatory response, inhibition of cyclooxygenase is an established mechanism of action for many anti-inflammatory agents. Non-selective inhibition of COX reduces pain, fever and inflammation but is often associated with gastrointestinal or renal injury. In the past decade, the existence of multiple isoforms of COX has become

established.¹ Selective inhibitors of COX-2 are thought to reduce pain, fever and inflammation without causing the gastrointestinal or renal injury associated with inhibition of COX-1.² SVT-2016 is a new COX-2 inhibitor being developed for the treatment of pain and inflammation associated with osteoarthritis and rheumatoid arthritis.

Objectives Evaluate the safety and tolerability of rising doses (16 mg, 32 mg and 64 mg) of SVT-2016, in healthy male volunteers. In addition, the pharmacokinetics (PK) of SVT-2016 following a single oral dose was examined.

Methods Three groups of 6 healthy male volunteers, aged 23–43 years, were exposed to a single oral dose of SVT-2016 or matching placebo (Group 1: 16 mg SVT-2016, Group 2: 32 mg SVT-2016 and Group 3: 64 mg SVT-2016). For each group, subjects were randomised to receive either SVT-2016 or matching placebo (2:1 active to placebo). All volunteers provided informed written consent prior to participation. The study was approved by the Simbec Independent Ethics Committee. Following administration of SVT-2016, blood samples were taken for the determination of plasma SVT-2016 levels at the following time points: Pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36 and 48 h post dose. Vital signs were measured and a 12-lead ECG performed throughout the 48 h post dose. Continuous ECG monitoring took place until 4 h after dosing. Laboratory safety tests were conducted prior to dosing and at 24 h and 48 h post dose. Adverse events were monitored throughout the study. Validated LCMS method was used for the determination of plasma SVT-2016 concentrations.

Results There were no clinically significant changes in vital signs, ECG or laboratory safety tests during the study. A total of three adverse events were recorded (2 events of mild headache and 1 event of mild dizziness). No serious or severe adverse events were recorded. All events were considered to be mild in severity. The pharmacokinetic profile obtained following a single oral dose of SVT-2016 demonstrates that, SVT-2016 was absorbed in a dose dependent manner, C_{max} increasing with increasing dose level administered. This peak plasma concentration occurs at approximately 1.7 h (range: 1.5 h ? 1.9 h) following administration of SVT-2016, suggesting a rapid onset of action. The elimination half-life of SVT-2016 appears to increase with increasing dose level and would support the suitability of this compound for the treatment of patients with osteoarthritis and rheumatoid arthritis.

Conclusion SVT-2016 was considered to be safe and well tolerated at the dose levels investigated. The PK obtained favour the development of SVT-2016 as a novel COX-2 inhibitor for the treatment of pain and inflammation associated with osteoarthritis and rheumatoid arthritis. To further examine the safety, tolerability and PK of SVT-2016, it is proposed that further dose levels be investigated.

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SAT0083 ULTRASONOGRAPHIC EVIDENCE OF INTRA-ARTICULAR INJECTIONS IN THE HIP

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Background In order to validate intra-articular medical treatment of osteoarthritis in the hip joints it is imperative to have documentation of the correct placement of the injection.

Radiographic methods imply a radiation load, while ultrasound (US) is harmless.

Objectives Our goal was to evaluate the use of US as guidance when performing injections in osteoarthritic hips using air as contrast medium.^{1–3}

Methods A total of 30 injections were given to 11 Patients with hip-osteoarthritis (ACR criteria)(Mean age 60 years (Range 44–86)).

The femoral head and neck was scanned with a 8–13 MHz linear transducer.

The probe was placed below the inguinal ligament in parallel with the axis of the femoral neck.

Placement of a gauge 21 needle into the hip joint (anterior/inferior capsule below the femoral head) was monitored with a B mode (grey scale) scanning allowing a continuous visual guidance.

Preceding the treatment, a small (0,5–2 ml) amount of atmospheric air was injected.

Results The position of the needle was evident on the screen in all cases. The injections of air into the joint was demonstrated in 29 cases presenting a small hyperechoic brim inside the joint capsule. However, in one case in spite of a seemingly correct placement of the needle the hyperechoic air brim was clearly positioned outside the joint. Placement of the needle was subsequently corrected.

Still picture of the setting as documentation revealed the presence of air without difficulty, however the needle tended to be less recognisable when not in motion.

Conclusion The sole use of grey scale US as guidance device gives a good view of the intra-articular placement of a needle. However use of air as US contrast before an injection or aspiration, enhances the precision and allows photographic documentation of the set-up.

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SAT0084 DEVELOPMENT AND INITIAL PSYCHOMETRIC VALIDATION OF THE ARTHRITIS TREATMENT SATISFACTION QUESTIONNAIRE (ARTS)

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Background

Objectives To develop and examine the reliability and validity of a questionnaire assessing patient satisfaction with their osteoarthritis treatment.

Methods Item generation: Semi-structured interviews were performed among 20 French patients (6 suffering from arthritis of the knee, 6 of the hip and 8 of the hand), and 10 clinicians (5 rheumatologists and 5 general practitioners (GPs)). Interviews were recorded, transcribed and analysed. The first version of the questionnaire was produced in French and reviewed by 5 rheumatologists and 5 GPs. Content validity and cognitive debriefing