STUDY PROTOCOL

a. Scientific Premise

Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line treatment of ankylosing spondylitis (AS) and axial spondyloarthritis (axSpA). More than 20 different NSAIDs are available, but limited evidence is available to guide the choice of different NSAIDs, for short-term symptom control and for long-term disease modifying effect. None of the previous trials has addressed the question of whether each individual patient responds to NSAIDs differently. Mean responses in treatment groups, rather than individual responses, were compared in previous trials. And therefore, a N-of-1 trial of the most commonly used NSAIDs is needed to answer the question of how to optimize NSAID use in each individual patient.

When designing an N-of-1 trial, treatment length, carryover effect, blinding and outcome measures are the major elements to consider. For treatment length, it has been shown in clinical trials that the therapeutic effects of celecoxib were similar at six weeks and at 52 weeks. In clinical practice, shorter duration, such as two to four weeks, is commonly used to make a treatment decision to switch NSAID. Whether a shorter duration is as sufficient as six weeks remains unknown. Therefore, we propose this pilot study to determine the treatment length for NSAIDs in patients with AS and axial SpA.

b. Overview and Hypothesis: This is a 6-week randomized, double-blind trial of 4 different NSAIDs in patients with axSpA to compare the change of pain score from baseline (Δ_{pain}) at 4 weeks to Δ_{pain} at 6 weeks. The hypothesis is that Δ_{pain} at 4 weeks is not significantly different from Δ_{pain} at 6 weeks, and 4 weeks of treatment is sufficient to determine efficacy of NSAIDs.

c Study Subject: Study subjects will be outpatients at CUMC rheumatology outpatient clinic with a diagnosis of AS by treating rheumatologists, or a diagnosis of axial SpA with a pelvis MRI with significant bone marrow edema on STIR sequence. Other inclusion criteria include 1) minimum of 18 years old; 2) are taking NSAIDs on a regular basis for AS or SpA (defined as more than 20 days in the past month), or having active symptoms that require initiation of NSAIDs; 3) if using antirheumatic drugs concomitantly, stable dose for the past three months; 4) have active disease after initial washout period, defined by BASDAI >=4/10, or back pain VAS >=4/10. Exclusion criteria include: patients who have concurrent rheumatic diseases other than AS or axial SpA; patients who have oral corticosteroid in the past two weeks; patients who have acute peripheral arthritis; patients with high fibromyalgia score; patients with extensive cardiac history, history of gastrointestinal bleeding that required blood transfusion, chronic kidney disease, or pregnancy. Use of low dose of aspirin (<100mg daily) is allowed in the study.

c.3 Intervention: Patients will be randomized at Week 0 (Randomization Visit) using a randomization table to one of the following four arms: indomethacin ER 75mg twice a day; diclofenac DR 75mg twice a day; meloxicam 7.5mg twice a day; celecoxib 200mg twice a day, with omeprazole 20mg daily. Treatment length will be 6 weeks. Clinicians, investigators and subjects will be blinded to the treatment allocation.

c.4 Outcome Assessment: The primary outcome of the study is the change of pain score from Week 0 (Randomization Visit) (Δ_{pain}) at 4 weeks and Δ_{pain} at 6 weeks, on a 0 to 100 VAS. The secondary outcomes include change of Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI). In addition, patient global assessment of response to therapy (PGART), by a 0-4 Likert scale, physician global assessment (NRS), Ankylosing Spondylitis Disease Activity Score (ASDAS, a composite score), sedimentation rate, C-reactive protein. These outcomes will be assessed face to face at Week 0 (Randomization Visit) and Week 6 (End Visit). We will also remotely collect patient-report outcomes at week 2 and week 4, including spinal pain (NRS), patient global score (NRS), BASDAI, BASFI. A link to the questionnaire will be emailed to patients via RedCap. By clicking the link, patients will be able to answer the questionnaires using either a mobile device or a desktop computer. If a patient does not respond in 24 hours, another email with link to questionnaires will be sent as a reminder. After three attempts, if there is still no reply, the patient will be contacted via phone to collect the answers to questionnaires. Adverse events will be assessed by remote data collection and at Week 6 (End Visit).

c.5 Statistical analysis and sample size calculation: We will use a paired-t test to examine whether Δ_{pain} at 4 weeks is significantly different from Δ_{pain} at 6 weeks. The primary analysis will be the pooled result from patients randomized to different NSAIDs, and will be limited to patients who complete the 6-week study. <u>The study is not designed to compare medication efficacy</u>.

We will test the hypothesis that Δ_{pain} at 4 weeks is not significant different from Δ_{pain} at 6 weeks. For sample size calculation, we use a paired *t*-test to compare Δ_{pain} at 4 weeks and at 6 weeks. For α=0.05, two-sided,

β=0.2, minimal clinically important difference for pain = 17/100, standard deviation of change of pain score 22-30/100, the sample size will be 15-26 . We anticipate a dropout rate of 20-25%, so we plan to enroll 30 patients.