SUPPLEMENTAL METHODS

Subjects

Subjects had to have discontinued use of analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and nutraceuticals (e.g., glucosamine, chondroitin sulfate, shark cartilage, diacerein, soy extract, avocado–soybean unsaponifiables) for at least 5 half-lives of each agent or 48 hours, whichever was longer, before beginning study drug.

Efficacy

The subdomain pain score of the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) was chosen to evaluate the primary endpoint, consistent with recommendations of the Osteoarthritis Research Society International Task Force that were current when the study was designed, which suggested use of that instrument or a single-item global pain scale.[1]

Randomization and Blinding

Subjects were assigned a unique identification number at the screening visit via an interactive response system. Eligible subjects were randomized at the baseline visit, in equal ratios to either study treatment, according to a schedule previously created by the statistics group of the study sponsor and stratified by country. The active and placebo treatments, labeled on their vials with the unique subject identification numbers, were shipped to each study site for reconstitution by an unblinded pharmacist, physician, or their qualified designee. An unblinded monitor at each site was responsible for study drug accountability. All other study staff, the subjects, and the sponsor remained blinded to the treatment assignments throughout the course of the study.

However, an unblinded committee of sponsor personnel not otherwise directly involved with the study monitored safety.

Pharmacokinetics

Blood samples for determination of lutikizumab serum concentrations and detection of antidrug antibodies were collected before the first dose of lutikizumab at baseline and weeks 2, 4, 6, 8, 12, 16, 20, and 26. In a subset of subjects, additional blood samples for determination of lutikizumab concentrations were obtained on days 3, 7, and 10. Values for pharmacokinetic parameters of lutikizumab, including apparent clearance and apparent volume of distribution, were estimated using population pharmacokinetic modeling analysis (NONMEM software version VII or higher, ICON, Dublin, Ireland).

Target Engagement and Pharmacodynamics

Serum IL-1α and IL-1β levels were quantified using high-sensitivity immunoassays on either the Singulex (IL-1α kit from EMD Millipore, catalog # 03-0072-00) or Simoa (IL-1 β homebrew assay) platform, respectively. Both validated assays measure only the unbound cytokine (either free IL-1α or IL-1β) in the presence of lutikizumab, with assay lower limits of quantitation of 1 and 0.1 pg/mL, respectively. High-sensitivity C-reactive protein (hsCRP) was measured at ICON using the Abbott Laboratories ARCHITECT 16000 in Ireland and the United States and ARCHITECT 8000 in Singapore and China, with global correlations performed between all locations. Other biomarkers were analyzed at the BioClinica Molecular Marker Lab (Lyon, France) using validated enzyme-linked immunosorbent assays (provided by Nordic Bioscience [Herlev, Denmark; metalloproteinase-degraded collagen types I and III and matrix

metalloproteinase-generated fragment of CRP], Corgenix [Broomfield, CO, United States; hyaluronic acid], EMD Millipore [Darmstadt, Germany; N-propeptide of collagen IIA], and Roche Diagnostics [Indianapolis, IN, United States; C-terminal telopeptide fragments of type II collagen]), with the analysis performed following standard operating procedures adhering to regulatory guidance for clinical trials.

Radiography

Modified Verbruggen-Veys [2, 3]

Four distal interphalangeal joints (DIPs 2–5) and 4 proximal interphalangeal joints (PIPs 2–5) of both hands were scored using the Verbruggen-Veys system on a scale from 0 to 5, as follows:

0 (N)=Normal phase – no signs of osteoarthritis

1 (S)=Stationary phase – small ossification centers and osteophytes are present at the joint margins

2 (J)=Loss of joint space phase – some joints become destroyed

3 (E)=Erosive phase – subchondral plate becomes eroded

4 (E/R)=Erosive and remodeling phase – disappearance of the osteolytic areas in the subchondral bone and reconstruction of the subchondral bone plate accompanied by the reappearance of a distinct joint space

5 (R)=Remodeling phase – new irregular sclerotic subchondral plates are formed, and a new joint space becomes visible. Huge osteophytes are formed during this phase

The total score in each hand could range from 0 to 40; the total score in both hands could range from 0 to 80.

Osteoarthritis Research Society International Atlas[4]

Six osteoarthritis features in each hand were assessed: osteophytes, joint space narrowing, malalignment, erosion, subchondral sclerosis, and subchondral cyst. Each feature was scored on a scale from 0 to 3, as follows: 0=normal; 1=mild change; 2=moderate change; 3=severe change or 0=absent and 1=present. Osteophytes and joint space narrowing data are presented based on scoring DIPs 2 to 5 (0–3 in each joint), PIPs 2 to 5 (0–3 in each joint), carpometacarpal joint of the thumb (0–3), interphalangeal joint of the thumb (0–1), and scaphotrapeziotrapezoid joint (0–1). The total score in each hand could range from 0 to 29; the total score in both hands could range from 0 to 58.

Modified Kellgren-Lawrence[5]

Ten joints (DIP joints 2–5, PIP joints 2–5, carpometacarpal joint of the thumb, and interphalangeal joint of the thumb) of each hand were assessed for features consistent with osteoarthritis, including the formation of osteophytes on the joint margins, periarticular ossicles, narrowing of joint cartilage associated with sclerosis of subchondral bone, small pseudocystic areas with sclerotic walls situated usually in the subchondral bone, and altered shape of the bone ends. Scoring of each joint was based on a scale from 0 to 4, as follows: 0=none; 1=doubtful; 2=minimal; 3=moderate; 4=severe. The total score in each hand could range from 0 to 40; the total score in both hands could range from 0 to 80.

Magnetic Resonance Imaging

Image Acquisition

Target hands were imaged using whole-body 1.5 or 3.0 T MRI scanners, with each index hand bandaged onto a special positioning frame and inserted into a knee coil. The hand was meticulously and consistently aligned in the coronal and axial planes to ensure a similar orientation at measurements separated in time. Pulse sequences included coronal Short Tau Inversion Recovery (STIR) and axial 3-dimensional T1-weighted gradient-echo with and without intravenous gadolinium-based contrast and with fat saturation.

Modified Outcome Measures in Rheumatology/Hand Osteoarthritis MRI scoring system (HOAMRIS)[6]

For each magnetic resonance imaging time point, 15 joints were assessed on the index hand (DIP joints 2–5, PIP joints 2–5, first interphalangeal joint of the thumb, metacarpophalangeal joints 1–5, and carpometacarpal joint of the thumb) for synovitis, erosive damage, bone marrow lesions, and cartilage space loss. Synovitis, erosive damage, and bone marrow lesions were scored on a scale from 0 to 3.5, as follows:

HOAMRIS Synovitis Scoring

Score	Description
0.0	Normal: no synovitis
0.5	Minimal: >0 but decreased from a comparison time point scored 1
1.0	Mild: 1%–33% of volume enhanced
1.5	Mild–Moderate: >0 and <2, but increased from a comparison time point scored 1 or decreased from a comparison time point scored 2
2.0	Moderate: 34%–67% volume enhancement
2.5	Moderate–Severe: >1 and <3, but increased from a comparison time point scored 2 or decreased from a comparison time point scored 3
3.0	Severe: 68%–100% volume enhanced
3.5	Very Severe: increased from a comparison time point scored 3

HOAMRIS Erosive Damage Scoring

Score	Description
0.0	Normal: no erosive damage
0.5	Minimal: >0 but decreased from a comparison time point scored 1
1.0	Mild: ≤10% of bone volume or ≤25% of joint surface affected
1.5	Mild–Moderate: >0 and <2, but increased from a comparison time point scored 1 or decreased from a comparison time point scored 2
2.0	Moderate: 11%–20% of bone volume and/or 26%–50% of joint surface affected
2.5	Moderate–Severe: >1 and <3, but increased from a comparison time point scored 2 or decreased from a comparison time point scored 3
3.0	Severe: >20% of bone volume and/or >50% of joint surface affected
3.5	Very Severe: increased from a comparison time point scored 3

HOAMRIS Bone Marrow Lesions Scoring

Score	Description
0	Normal: no bone marrow lesions
0.5	Minimal: >0 but decreased from a comparison time point scored 1
1	Mild: lesions are 1%–33% of bone volume
1.5	Mild–Moderate: >0 and <2, but increased from a comparison time point scored 1 or decreased from a comparison time point scored 2
2	Moderate: lesions are 34%–66% of bone volume
2.5	Moderate–Severe: >1 and <3, but increased from a comparison time point scored 2 or decreased from a comparison time point scored 3
3	Severe: lesions are 67%–100% of bone volume
3.5	Very Severe: increased from a comparison time point scored 3

The total scores for synovitis, erosive damage, or bone marrow lesions in a hand could range from 0 to 52.5.

Cartilage space loss was scored on a scale from 0 to 3, as follows:

HOAMRIS Cartilage Space Loss Scoring

Score	Description
0	Normal, no loss of cartilage space
1	Mild, loss of cartilage space without bone-to-bone contract
2	Moderate, focal complete loss of cartilage space
3	Severe, complete cartilage space loss affecting >50% of the articulating joint area

The total score for cartilage space loss in a hand could range from 0 to 45.

Safety

Adverse events were coded using the *Medical Dictionary for Regulatory Activities, version 19.0,* preferred term and system organ class.

Statistics and Analyses

In a post hoc analysis on the primary efficacy endpoint, subjects were split into two groups: those who had either never used NSAIDs or stopped NSAIDs before screening and those who took NSAIDs during the screening period but stopped NSAIDs before randomization and the first dose of study drug.

References

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