CONSIDERATIONS WHEN DESIGNING A DISEASE-MODIFYING OSTEOPATHRITIS DRUG (DMOAD) TRIAL USING RADIOGRAPHY

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Study Objectives and Design

• To inform study design of future radiographic trials using placebo data from a recently completed, randomized clinical DMOAD trial

• Primary endpoint: rate of radiographic JSN
  – Modified Lyon-Schuss X-rays at BL, 1 and 2 years
  – minJSW in medial TF compartment using DIA software

• Inclusion/Exclusion criteria
  – 25 ≤ BMI ≤ 40 kg/m²
  – KLG2 and KLG3
  – Medial JSW ≥ 2 mm and more narrowed than the lateral JSW
  – 174 ≤ AAA ≤ 184 degrees

• Multifaceted quality control throughout
**X-ray Acquisition and JSW Measurement**

**Imaging CRO - BioClinica**
- Imaging charter
- Team of X-ray technologists and radiologists
  - Worldwide Training meetings
    - >300 X-ray technologists/radiologists trained with modified LS protocol
    - Yearly refresher trainings
  - QC of X-ray and MR images
  - Requests for repeat exams
- Team of central radiologists
  - QC
  - Eligibility

**JSW and IMD Measurement**
- Single expert reader (E. Vignon)
- Quantitative software measurement
- Blinded to sequence

**Multifaceted Quality Control Process**

- Data Login
  - Check patient
  - Query for missing data

- Imaging Core Laboratory
  - Review Central Reader input
  - Check discrepancies

- Image Analysis Technology
  - Assess image quality
  - Query for repeat, if needed
  - Calibrate edge detection software
  - Measure ROI (JSW, IMD, AAA)

- 2nd QC Team
  - Second independent review
  - Technical differences

- Conflict Resolution Team
  - Assess for pathophysiology
  - Final image quality review
  - Verify ROI measures
  - Integrate changes as needed
  - Request repeat images
  - Determine disease severity (KLG)

- Adjudication
  - Verify
  - Decide final decision
Quality Control Criteria

- MTP alignment (IMD ≤1.5 mm)
- Knee rotation/flexion
- Knee centering on film

Quality Control Results

- Repeat images requested when QC criteria not met
  - Repeat request rate: 20%

<table>
<thead>
<tr>
<th></th>
<th>BL</th>
<th>48 weeks</th>
<th>96 Weeks</th>
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<tbody>
<tr>
<td>IMD (mm) Mean ± SD</td>
<td>0.54 ± 0.44</td>
<td>0.55 ± 0.44</td>
<td>0.55 ± 0.46</td>
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*IMD = intermargin distance of the medial tibial plateau*
Modified Kellgren and Lawrence Grading (KLG) Criteria for Radiographic Severity of Knee OA

<table>
<thead>
<tr>
<th>Grade</th>
<th>OA severity</th>
<th>Radiographic findings</th>
</tr>
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<tbody>
<tr>
<td>Grade 0</td>
<td>None</td>
<td>No features of OA</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Doubtful</td>
<td>Minute osteophyte of doubtful significance or equivocal diminution of joint space of doubtful significance</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Minimal</td>
<td>Definite osteophyte, with mild diminution of joint space</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Moderate</td>
<td>Definite diminution of joint space with at least a minimal osteophyte</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Severe</td>
<td>Joint space greatly impaired with sclerosis of subchondral bone</td>
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Baseline Characteristics of the Placebo-treated Population, and Stratified by KLG

<table>
<thead>
<tr>
<th></th>
<th>KLG2</th>
<th>KLG3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All (N, %)</td>
<td>Male (N, %)</td>
</tr>
<tr>
<td><strong>Patients, N, (%)</strong></td>
<td>486 (100)</td>
<td>49 (22.1)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>61.3 ± 9.1</td>
<td>60.9 ± 11.0</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>31.6 ± 4.1</td>
<td>29.7 ± 3.0</td>
</tr>
<tr>
<td><strong>Medial JSW</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>3.22 ± 0.71</td>
<td>3.91 ± 0.54</td>
</tr>
<tr>
<td><strong>AAA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean ± SD</td>
<td>181.2 ± 2.16</td>
<td>181.5 ± 1.55</td>
</tr>
</tbody>
</table>
Distribution of Percent Change from Baseline to Week 96 in JSW

(A) All randomized patients

(B) KLG2

(C) KLG3

Percent Change from Baseline in JSW (mm)

Percent Change from Baseline to Week 48 in JSW
All Randomized Patients by KLG and Gender

SRM = 0.25      0.28      0.24

SRM = 0.42      0.49      0.40

*p≤0.05; **p≤0.01; ***p≤0.001
Percent Change from Baseline to Week 96 in JSW All Randomized Patients by KLG and Gender

Sample Size Calculations Overall and by KLG for a Study to Demonstrate 50% Improvement in JSN

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment difference (mm)</th>
<th>SD</th>
<th>Sample size (N/arm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.104</td>
<td>0.481</td>
<td>340</td>
</tr>
<tr>
<td>KLG2</td>
<td>0.071</td>
<td>0.407</td>
<td>520</td>
</tr>
<tr>
<td>KLG3</td>
<td>0.130</td>
<td>0.526</td>
<td>260</td>
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Conclusions

- First large-scale field test of the utility of the non-fluoroscopic mL/S protocol for imaging OA of the knee
- Using a tightly controlled methodology, JSN was detected in the placebo population as early as 1 year in both KLG2 and 3 subjects
- Power maintained by limited number of dropouts, and homogeneous population from strict entry criteria
- Observed mean loss of JSW in both KLG2 and KLG3 patients consistent with the population enrolled, which excluded strong risk factors for OA progression (i.e., genu varum and valgum, and severe JSN at BL)

Thank You!