

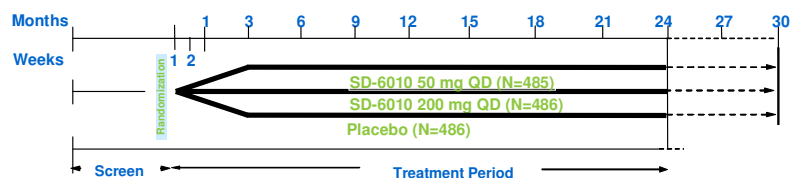
## CONSIDERATIONS WHEN DESIGNING A DISEASE-MODIFYING OSTEOARTHRITIS DRUG (DMOAD) TRIAL USING RADIOGRAPHY

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## Study Objectives and Design

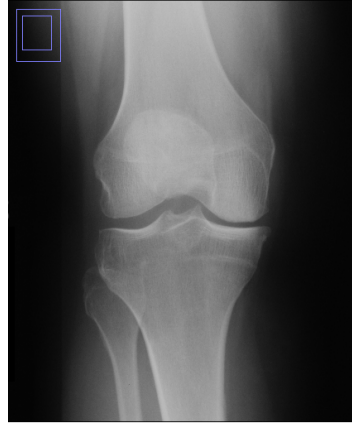
- To inform study design of future radiographic trials using placebo data from a recently completed, randomized clinical DMOAD trial
- Primary endpoint: rate of radiographic JSN
  - Modified Lyon-Schuss X-rays at BL, 1 and 2 years
  - minJSW in medial TF compartment using DIA software
- Inclusion/Exclusion criteria
  - $25 \leq \text{BMI} \leq 40 \text{ kg/m}^2$
  - KLG2 and KLG3
  - Medial JSW  $\geq 2 \text{ mm}$  and more narrowed than the lateral JSW
  - $174 \leq \text{AAA} \leq 184 \text{ degrees}$
- Multifaceted quality control throughout



## X-ray Acquisition and JSW Measurement

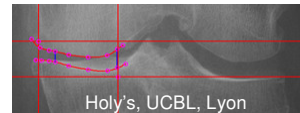
### Imaging CRO - BioClinica

- 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

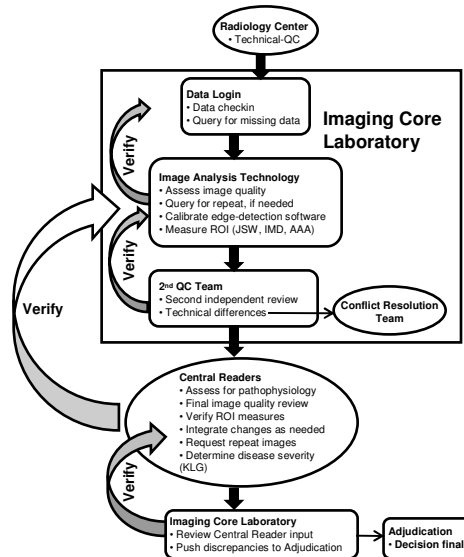


### JSW and IMD Measurement

- Single expert reader (E. Vignon)
- Quantitative software measurement
- Blinded to sequence

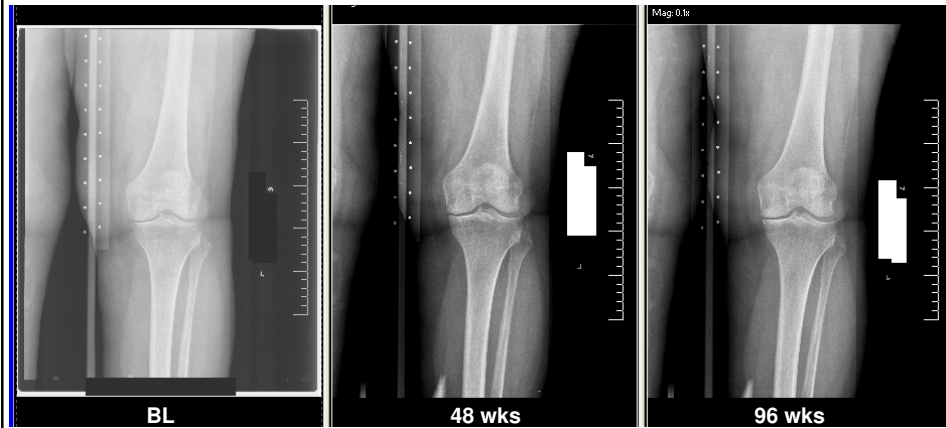


## Multifaceted Quality Control Process



## Quality Control Criteria

- MTP alignment (IMD  $\leq 1.5$  mm)
- Knee rotation/flexion
- Knee centering on film



## Quality Control Results

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

	BL	48 weeks	96 Weeks
IMD (mm)	0.54	0.55	0.55
Mean $\pm$ SD	$\pm 0.44$	$\pm 0.44$	$\pm 0.46$

*IMD = intermargin distance of the medial tibial plateau*



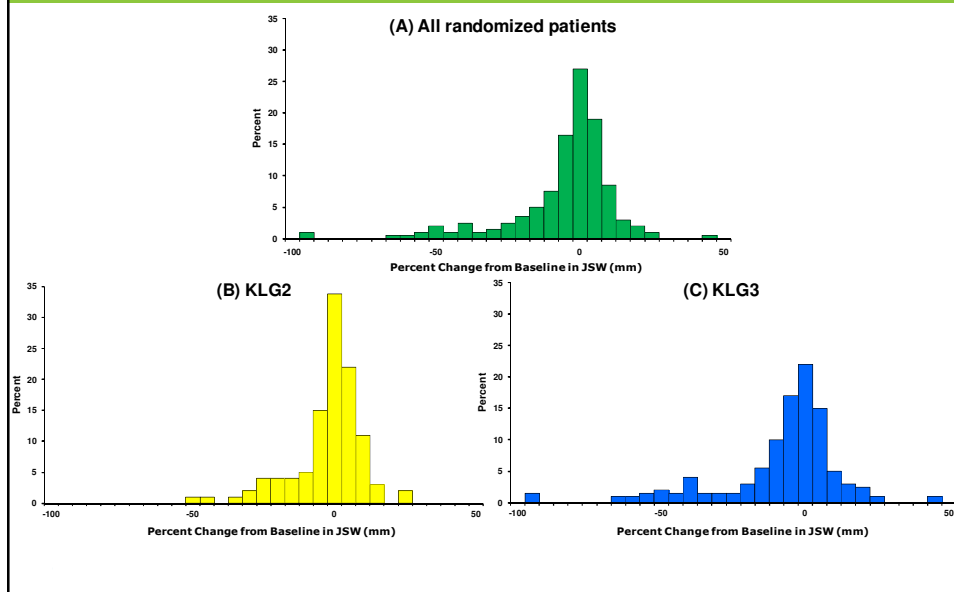
## Modified Kellgren and Lawrence Grading (KLG) Criteria for Radiographic Severity of Knee OA

Grade	OA severity	Radiographic findings
Grade 0	None	No features of OA
Grade 1	Doubtful	Minute osteophyte of doubtful significance or equivocal diminution of joint space of doubtful significance
Grade 2	Minimal	Definite osteophyte, with <i>mild diminution</i> of joint space
Grade 3	Moderate	Definite diminution of joint space with at least a minimal osteophyte
Grade 4	Severe	Joint space greatly impaired with sclerosis of subchondral bone

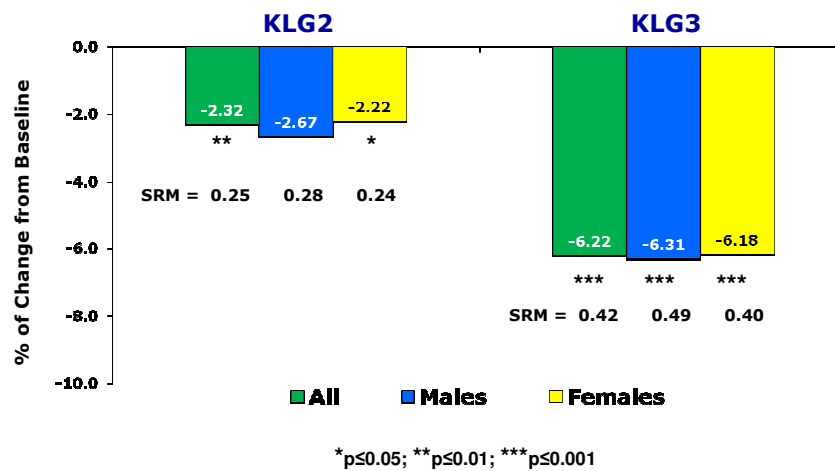
## Baseline Characteristics of the Placebo-treated Population, and Stratified by KLG

	All	KLG2		KLG3	
		Male	Female	Male	Female
<b>Patients, N, (%)</b>	486 (100)	49 (22.1)	173 (77.9)	73 (27.7)	191 (72.3)
<b>Age (years)</b>					
mean	61.3	60.9	59.1	62.2	62.9
± SD	(9.1)	± 11.0	± 8.7	± 10.1	± 8.1
<b>BMI (kg/m<sup>2</sup>)</b>					
mean	31.6	29.7	31.2	31.1	32.7
± SD	(4.1)	± 3.0	± 4.2	± 3.7	± 4.3
<b>Medial JSW</b>					
mean	3.22	3.91	3.69	2.89	2.76
± SD	(0.71)	± 0.54	± 0.5	± 0.58	± 0.53
<b>AAA</b>					
mean	181.2	181.5	181.9	180.6	180.7
± SD	± 2.16	± 1.55	± 1.80	± 2.28	± 2.34

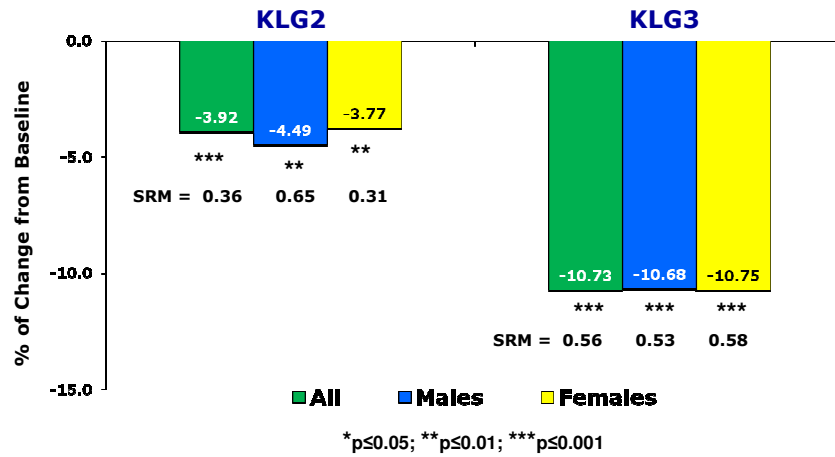
## Distribution of Percent Change from Baseline to Week 96 in JSW



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



## 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

Population	Treatment difference (mm)	SD	Sample size (N/arm)
All	0.104	0.481	340
KLG2	0.071	0.407	520
KLG3	0.130	0.526	260

## 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!

