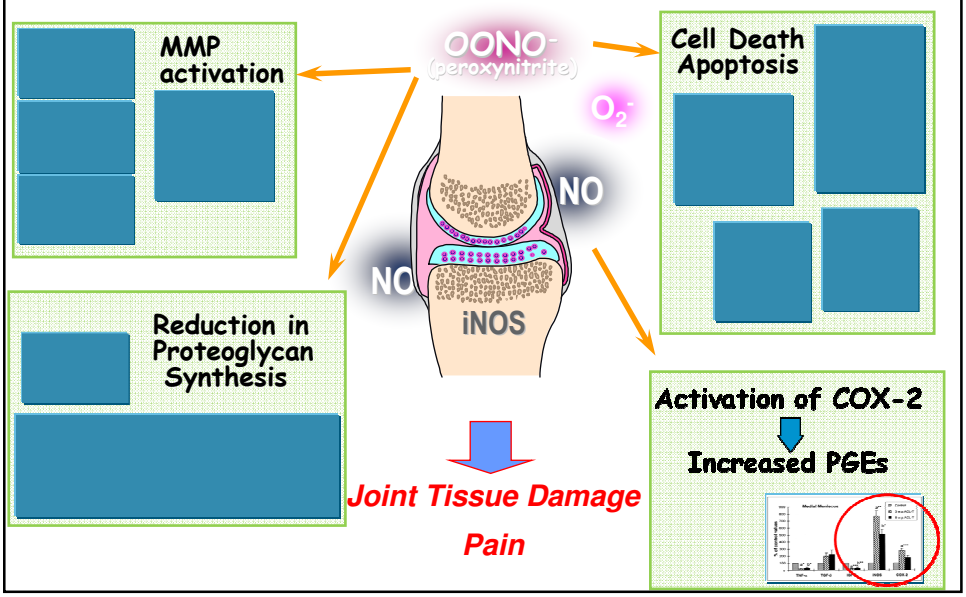
A 2-YEAR RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF AN ORAL SELECTIVE INOS INHIBITOR IN SUBJECTS WITH SYMPTOMATIC OSTEOARTHRITIS OF THE KNEE

Marie-Pierre Hellio le Graverand; Ray Clemmer; Patricia Redifer; Robert M. Brunell; Curtis W. Hayes; Kenneth Brandt; Steven B. Abramson
Pamela T. Manning; Colin G Miller; and Eric Vignon

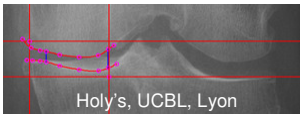
Pfizer Primary Care

Inducible NOS (iNOS) in OA

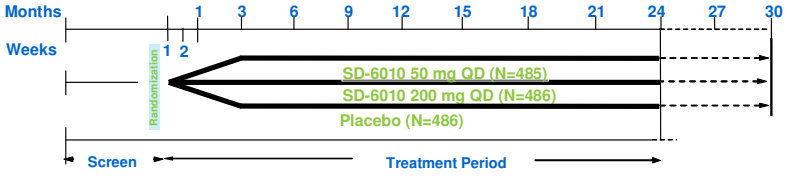


Study Objectives and Design

- To evaluate the disease-modifying efficacy, safety and tolerability of cindunistat/SD-6010 50 mg and 200 mg QD compared to placebo in patients with symptomatic knee OA
- 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
  - BMI ≥25 to ≤40 kg/m^2
  - KLG2 and KLG3
  - Medial JSW ≥2 mm and more narrowed than the lateral JSW
  - 174 ≤ AAA ≤ 184 degrees
- 5077 subjects screened at 131 sites in 14 countries



Demographic Characteristics

		Cindunistat	
	Placebo N=486	50 mg N=485	200 mg N=486
Age, mean (SD)	61.3 (9.1)	61.0 (8.7)	60.8 (8.6)
Female, n (%)	364 (74.9%)	383 (79.0%)	367 (75.5%)
Race White, n (%)	405 (83.3%)	389 (80.2%)	410 (84.4%)
BMI, kg/m^2, (SD)	31.6 (4.1)	31.9 (4.1)	32.0 (4.1)
Region, n (%)			
North America/ Australia	273 (56.2%)	286 (59.0%)	262 (53.9%)
Europe	152 (31.3%)	142 (29.3%)	166 (34.2%)
South America	61 (12.6%)	57 (11.8%)	58 (11.9%)

OA Disease Characteristics

	Placebo N=486	Cindunistat 50 mg N=485	Cindunistat 200 mg N=486
Duration of Osteoarthritis Since Diagnosis			
Mean (SD)	6.8 (7.2)	6.4 (6.3)	6.7 (7.2)
Kellgren-Lawrence X-ray Grade – n (%)			
Grade ≤2 Grade 3	222 (45.7%) 264 (54.3%)	216 (44.5%) 269 (55.5%)	203 (41.8%) 283 (58.2%)
JSW (mm) at Baseline			
Mean (SD) Range	3.22 (0.71) 1.43- 5.28	3.17 (0.75) 1.56- 5.41	3.19 (0.74) 1.55- 5.98

Baseline OA Symptoms

	Placebo N=486	Cindunistat 50 mg N=485	Cindunistat 200 mg N=486
WOMAC Pain subscale score at Baseline (range 0-20)			
Mean (SD)	7.6 (4.0)	8.0 (3.9)	7.4 (3.9)
WOMAC Physical Function subscale score at Baseline (range 0-68)			
Mean (SD)	27.4 (13.8)	27.6 (13.9)	26.5 (13.2)
Patient Global Assessment of Osteoarthritis at Baseline – n (%)			
Very good Good Fair Poor Very Poor	51 (10.6%) 152 (31.5%) 207 (42.9%) 69 (14.3%) 4 (0.8%)	45 (9.4%) 150 (31.2%) 209 (43.5%) 66 (13.7%) 11 (2.3%)	47 (9.8%) 169 (35.1%) 199 (41.3%) 59 (12.2%) 8 (1.7%)

Baseline OA Pain Medications

	Placebo N=486	Cindunistat 50 mg N=485	Cindunistat 200 mg N=486
Pain Medications at Baseline			
None	115 (23.7%)	109 (22.5%)	133 (27.4%)
SYSADOA*	40 (8.2%)	41 (8.5%)	36 (7.4%)
Acetaminophen	94 (19.3%)	100 (20.6%)	97 (20.0%)
NSAIDs/Coxibs	306 (63.0%)	301 (62.1%)	292 (60.1%)
Weak Opioids	22 (4.5%)	32 (6.6%)	15 (3.1%)
Strong Opioids	3 (0.6%)	4 (0.8%)	5 (1.0%)
Corticosteroids	1 (0.2%)	1 (0.2%)	0 (0.0%)

** Symptomatic Slow-Acting Drugs for Osteoarthritis*

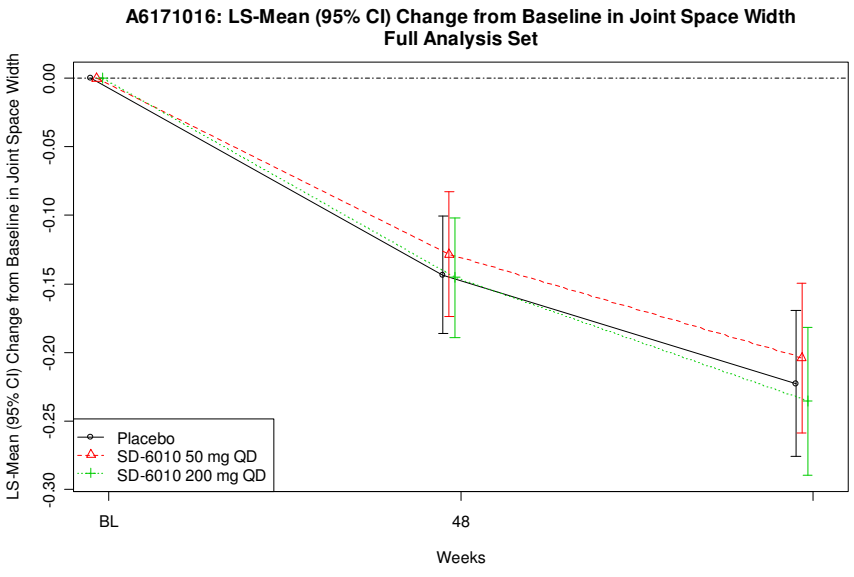
Subject Disposition

	Placebo N=486	Cindunistat 50 mg N=485	Cindunistat 200 mg N=486
Discontinued	130 (26.7%)	144 (29.7%)	135 (27.8%)
Death	3 (0.6%)	2 (0.4%)	1 (0.2%)
Adverse event	40 (8.2%)	41 (8.5%)	54 (11.1%)
Lost to follow-up	8 (1.6%)	10 (2.1%)	8 (1.6%)
No longer willing to participate in study	48 (9.9%)	58 (12.0%)	47 (9.7%)
Other/Entry Criteria	31(6.4%)	33 (6.8%)	25 (5.1%)
Completed	356 (73.3%)	341 (70.3%)	351 (72.2%)

Primary Endpoint Analysis
Linear Time MMRM Analysis of JSW

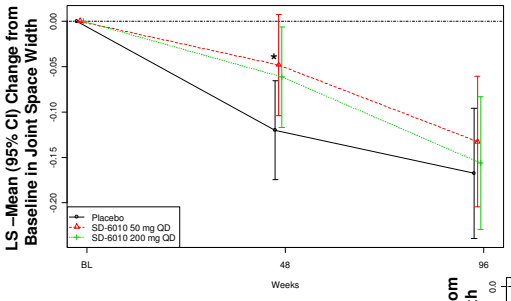
	Placebo N=486	Cindunistat 50 mg N=485	Cindunistat 200 mg N=486
JSW (mm) at Baseline			
Mean (SD)	3.22 (0.71)	3.17 (0.75)	3.19 (0.74)
Slopes			
Slope Std. Error 95% CI	-0.115 0.012 (-0.139, -0.091)	-0.103 0.013 (-0.128, -0.078)	-0.109 0.012 (-0.134, -0.085)
Difference in Slopes			
Difference vs Pbo 95% CI P-value vs Pbo		0.012 (-0.023, 0.046) 0.509	0.005 (-0.029, 0.040) 0.754

Change from Baseline in JSW (JSN)
Discrete Time MMRM Analysis



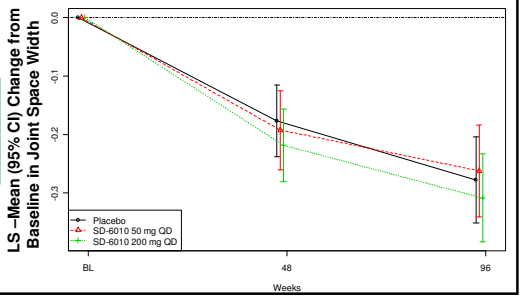
Change from Baseline in JSW (JSN)
Discrete Time MMRM Analysis by KLG

KLG ≤ 2



*p = 0.032 indicates statistical significance compared to placebo

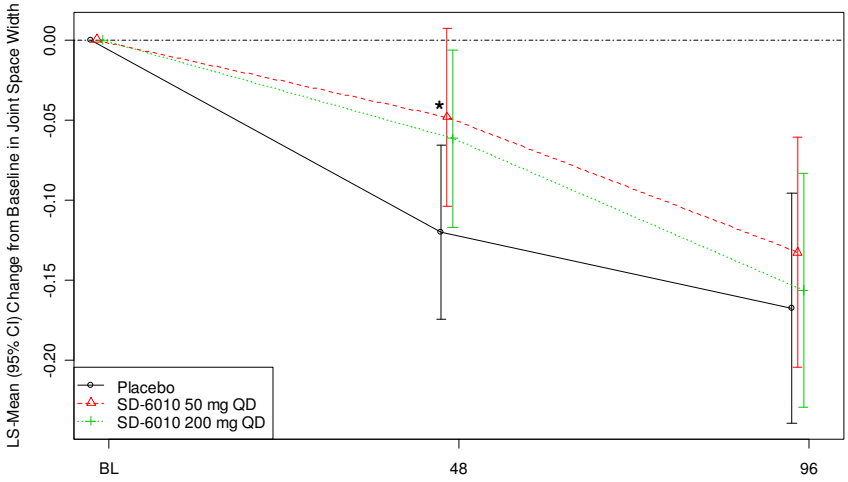
KLG = 3



The rate of JSN differed with disease severity

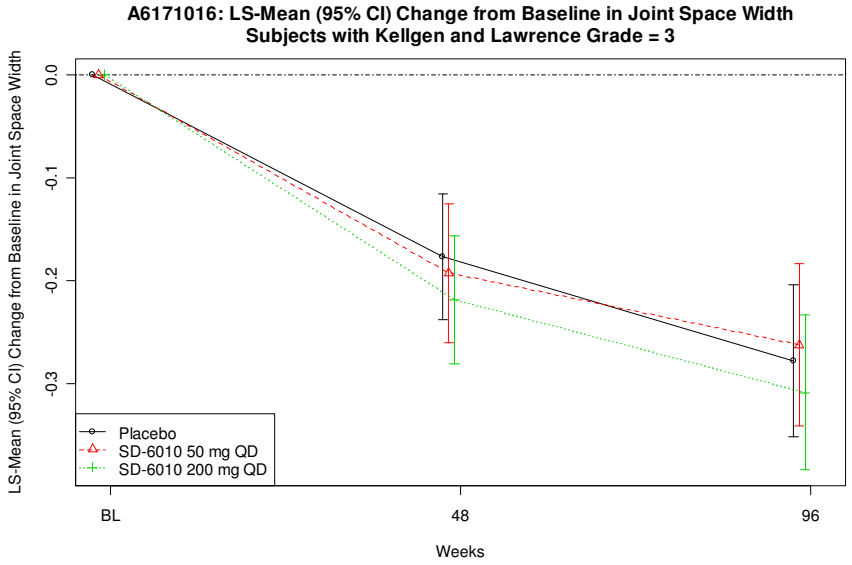
Change from Baseline in JSW in KLG ≤ 2
Discrete Time MMRM Analysis

A6171016: LS-Mean (95% CI) Change from Baseline in Joint Space Width
Subjects with Kellgen and Lawrence Grade <= 2

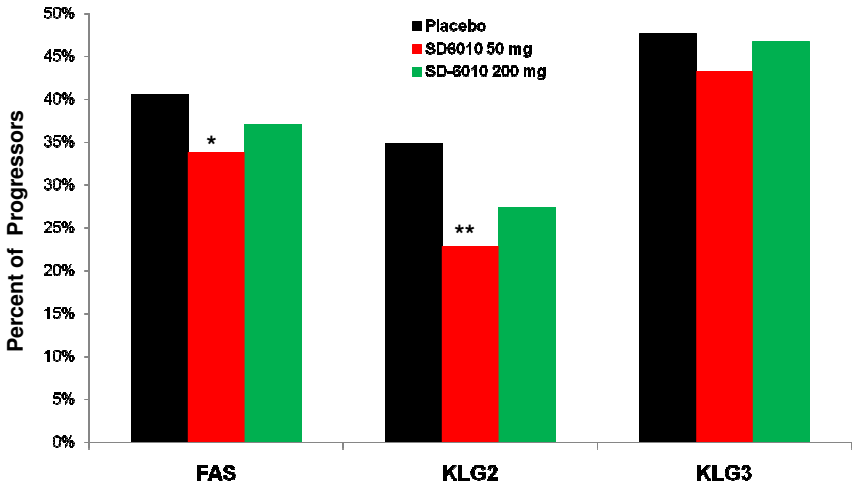


***p = 0.032 indicates statistical significance compared to placebo**

Change from Baseline in JSW in KLG = 3
Discrete Time MMRM Analysis



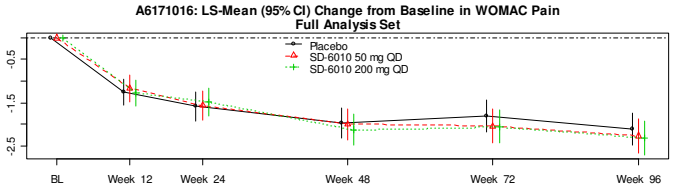
JSN Progressors



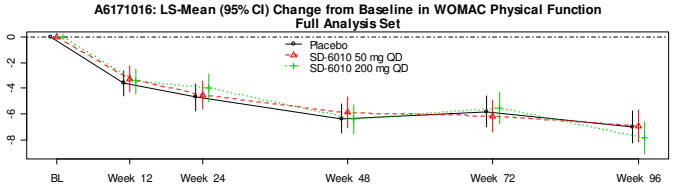
Progressors: subjects with a decrease in JSW from baseline >SDD (0.199mm)
*p = 0.047; **p=0.01 indicate statistical significance compared to placebo
FAS: full analysis set

Clinical Benefit Endpoints

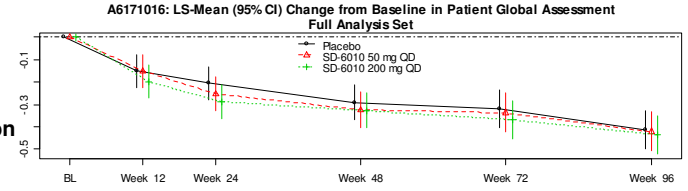
WOMAC Pain



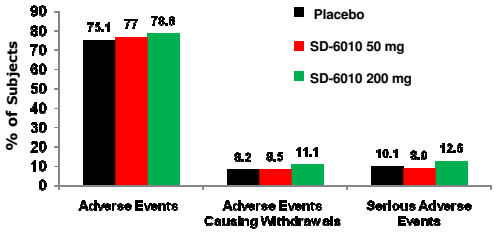
WOMAC Physical Function



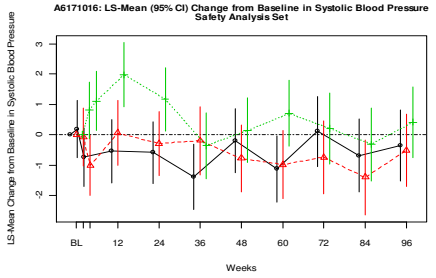
Patient Global Assessment of Arthritic Condition

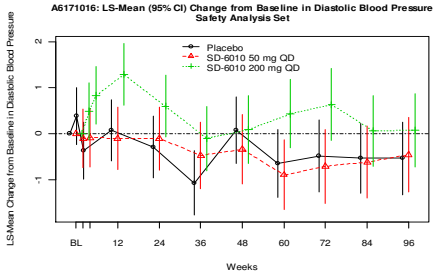


Summary of Safety



	placebo N=486	cindunistat 50 mg N=485	cindunistat 200 mg N=486
AEs Occurring in ≥ 5% of Any Treatment Group			
Arthralgia	66 (13.6%)	71 (14.7%)	67 (13.8%)
Back Pain	43 (8.9%)	31 (6.4%)	32 (6.6%)
Upper Respiratory Infection	30 (6.2%)	40 (8.3%)	31 (6.4%)
Nasopharyngitis	25 (5.2%)	33 (6.8%)	41 (8.5%)
Fall	28 (5.8%)	28 (5.8%)	43 (8.9%)
Hypertension	19 (3.9%)	34 (7.1%)	29 (6.0%)
Diarrhoea	29 (6.0%)	22 (4.6%)	27 (5.6%)
Headache	18 (3.7%)	32 (6.6%)	27 (5.6%)
Bronchitis	20 (4.1%)	25 (5.2%)	30 (6.2%)
Urinary Tract Infection	26 (5.4%)	24 (5.0%)	22 (4.5%)
Osteoarthritis	21 (4.3%)	26 (5.4%)	24 (4.9%)





Conclusions

- Cindunistat was generally safe and well tolerated in this OA population
- Cindunistat was not superior to placebo in the primary endpoint, rate of JSN, in subjects with knee OA
  - During the first year of treatment, subjects with KLG2 had a slower rate of JSN
  - This early improvement was not sustained at 2 years
  - iNOS inhibition did not slow OA progression in subjects with KLG3
- The observed early effect on JSN in subjects with mild OA supports the role of iNOS in OA pathogenic mechanisms
- Alternative biochemical catabolic pathways may have overcome the effects of nitric oxide inhibition alone
- In more severe OA, biomechanical factors may not be amenable to iNOS inhibition

Additional Thoughts

- At some point in the progression of OA, joint tissue deterioration may not be reversible through inhibition of iNOS
  - We attempted to select patients with less aberrant biomechanics (no valgus and only mild varus), although patients were overweight and obese
- Certain pathophysiological pathways, such as the iNOS-NO pathway, may be more relevant targets for pharmacological intervention early in disease
  - Other DMOAD studies suggest reduced disease progression after 1-year but lost after 2, or improvement in less severe OA
- No systematic measure of changes by MRI
- The current method of staging severity for clinical trials may be insufficient to adequately identify suitable candidates
- Research efforts must continue to validate biomarkers to improve patient selection and the detection of structure modification, particularly for patients with early OA where the potential for slowing progression is greater

Additional Thoughts

- Demonstration of structure modification in OA must be related to clinical benefit
  - By the time an OA joint becomes symptomatic, damage may already have progressed beyond the capability of pharmacological modification, making DMOAD trials in patients presenting with OA pain inappropriate
  - Limitation of our study was access to standard-of-care which may have introduced noise and/or bias
- Altered mechanics in even radiographic "mild-to-moderate" OA might be overwhelming and may not be effectively altered with a pharmacological or biological structure-modifying agent
  - iNOS may have been too limited a target to retard progression of OA in established disease
  - A broad-based target may be more successful
  - Evidence from surgical approaches to OA, (i.e., distraction procedures, osteotomy) indicate that joints can heal when biomechanical stresses are normalised

NIH-NCATS
National Center for Advancing Translational Sciences

- Discovering New Therapeutic Uses for Existing Molecules
  - A collaborative program that will match academic researchers with molecules form pharmaceutical companies to help scientists explore new treatments for patients
  - Provide access to molecules that are no longer in development due to a lack of efficacy in their primary indication(s)
  - http://ncats.nih.gov/therapeutics.html
- Abbott, AZ, BMS, E.Lilly, GSK, Janssen, Pfizer and Sanofi
- 58 compounds available
- NIH/NCATS XO2 Request for Proposals announced June 12, 2012

Thank You!