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GENERIC NAME / COMPOUND NUMBER: Cindunistat Hydrochloride Maleate / SD-6010

PROTOCOL NO.: A6171016

PROTOCOL TITLE: A Long-Term, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled, Radiographic Study to Investigate the Safety and Efficacy of Orally Administered SD-6010 in Subjects With Symptomatic Osteoarthritis of the Knee

Study Centers: A total of 131 centers took part in the study and randomized subjects; 78 in the United States, 8 in Czech Republic, 7 in Peru, 5 each in Argentina, Hungary, Russian Federation and Germany, 4 in Canada, 3 each in Italy, Poland and Spain, 2 each in Belgium and Slovakia and 1 in Australia.

Study Initiation, Primary Completion and Final Completion Dates:

Study Initiation Date: 20 November 2007
Primary Completion Date: 18 October 2011
Final Completion Date: 09 November 2011

Phase of Development: Phase 2b/3

Study Objectives:

Primary Objective: To evaluate the disease-modifying efficacy of SD-6010 50 mg and 200 mg once daily (QD) compared to placebo in reducing the rate of progression of osteoarthritis (OA) as assessed by radiographic joint space narrowing (JSN) in the medial tibiofemoral compartment of the study knee of subjects with knee OA.

Secondary Objectives:

- To assess the safety and tolerability of SD-6010 50 mg and 200 mg QD administered long-term to subjects with knee OA;
- To assess the clinical benefit of SD-6010 50 mg and 200 mg QD in subjects with knee OA as measured by the clinical endpoints including, but not limited to, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), pain visual analog scale (VAS), changes in background pain therapy, and use of rescue medication in the study knee.

METHODS

Study Design: This was a Phase 2b/3, randomized, double-blind, placebo-controlled, parallel-group, adaptive-design, radiographic study in subjects with a body mass index (BMI) ≥25 kg/m^2 and ≤40 kg/m^2 with symptomatic OA of the knee. Subjects were to be randomized in a 1:1:1 fashion to single, daily doses of SD-6010 50 mg, SD-6010 200 mg, or placebo. The treatment period was 24 months. The adaptive-design feature of this study allowed for the possibility to extend the treatment period depending on the variability (the standard deviation [SD]) of the progression rate in JSN after approximately 350 subjects completed 1-year radiographs. The length of the treatment period could have been extended from 24 months to 30 months depending on the results of the variability assessment.

In a 2-part screening process, subjects at Screen 1 had the study explained to them and, following their consent to participate, provided medical histories and were pre-qualified in accordance with the Screen 1 inclusion and exclusion criteria. A subject with acceptable safety risks and evaluable knees at the Screen 1 visit was allowed to participate in the Screen 2 visit. A subject must have had Kellgren and Lawrence Grades (KLG) 2 or 3 changes in at least 1 knee to be considered eligible for the study (Table 1). As part of the screening process, subjects were stratified according to KLG (KLG 2 or 3) in the study knee. There was no limit on the number of KLG 3s entering the study; however, a limit to the number of KLG 2s was set at ≤40% of the total sample size.

Table 1. Kellgren and Lawrence Grading Criteria for Radiographic Severity of Knee Osteoarthritis

Grade	OA Severity	Radiographic Findings
Grade 0	None	No features of OA
Grade 1	Doubtful	Minute osteophyte, doubtful significance
Grade 2	Minimal	Definite osteophyte, unimpaired joint space
Grade 3	Moderate	Moderate diminution of joint space
Grade 4	Severe	Joint space greatly impaired with sclerosis of subchondral bone

OA = osteoarthritis.

The schedules of all study activities are presented in Table 2 (Screen 1 visit) and Table 3 (Screen 2, treatment, and post-treatment periods).

Table 2. Schedule of Activities for Screen 1

Treatment Periods	Pre	Treatment											Post
	Visits												
Activities	**Scr 1[a]**	**Day 1 (First Dose)**	**Wk 2 (±2 d)**	**Mo 1 (±10 d)**	**Mo 3 (±10 d)**	**Mo 6 (±10 d)**	**Mo 9 (±10 d)**	**Mo 12 (±10 d)**	**Mo 15 (±10 d)**	**Mo 18 (±10 d)**	**Mo 21/27[b] (±10 d)**	**Mo 24/30/EW[c] (±5 d)**	**Mo 25/31[d] (±2 d)**
Investigator level assessments													
Informed consent	X												
Demographics	X												
Criteria for eligibility[e]	X												
Medical and OA histories	X												
Vital signs[f] height, and weight	X												
Prior and concomitant medications	←———												———→
Adverse events[g]	←———												———→
Central imaging core laboratory assessments													
X-ray imaging[h,i,j]	X												

d = day; EW = early withdrawal; JSW = joint space width; KLG = Kellgren and Lawrence Grades; Mo = month; OA = osteoarthritis; Scr = Screen; wk = week.

a. The combined Screen 1 and Screen 2 duration was up to 35 days. The scheduling and central reading of X-ray images was expected to be the longest aspect of the Screen 1 Period.
b. In the event the decision was made to extend the study another 6 months, a Month 27 visit was required that was identical to the Month 21 activities.
c. In the event the decision was made to extend the study another 6 months, the Month 24 visit was shifted to Month 30.
d. The 28-day follow-up visit in the 24-month study was Month 25; if the study was extended another 6 months, the 28-day follow-up visit became the Month 31 visit.
e. Assessed subjects against the Screen 1 inclusion/exclusion criteria. Criteria were divided into Investigator level assessments and the central imaging core laboratory assessments. Once subjects had successfully passed the Investigator level assessments, they were asked to have X-ray images of their knees to complete the Screen 1 qualification process.
f. Vital signs consisted of a cuff blood pressure and heart rate. Height and weight were recorded at the Screen 1 visit with weight recorded every 6 months.
g. Serious adverse event reporting started with the signing of the informed consent document.

Radiology requirements as assessed by the central imaging core laboratory

h. Multiple X-rays of both knees (approximately 3 images per knee) were performed using the modified Lyon-schuss technique.
i. Current radiographic severity of OA in both knees was assessed by KLG by an independent board-certified radiologist. A subject must have had KLG 2 or 3 changes in at least 1 knee to be considered eligible for the study. If the contralateral knee had KLG 4 changes and, in the opinion of the Investigator, the subject was likely to undergo arthroplasty within the next 2 years, the subject was considered ineligible for the study. Moreover, if a subject was at risk of becoming incapacitated in the near future due to KLG 4 changes such that activities of daily living would have been severely curtailed, the subject was not to be considered for the study.
j. Radiological criteria for entry were 1) a JSW of the medial tibiofemoral space ≥2 mm in the study knee, 2) lateral JSW > medial JSW, and 3) an anatomic axis angle between 184° and 174°. If the study knee had KLG 3 changes and a medial JSW smaller than the lateral JSW with an anatomic axis angle >184°, and if the other radiographic eligibility criteria were met, the subject was considered for eligibility.

Table 3. Schedule of Activities for Screen 2, and the Treatment and Post Treatment Periods

Treatment Periods		Pre	Treatment										Post
Activities		**Screen 2[a,b]**	**Day 1 (First Dose)**	**Wk 2 (±2 d)**	**M 1 (±10 d)**	**M 3 (±10 d)**	**M 6 (±10 d)**	**M 9 (±10 d)**	**M 12 (±10 d)**	**M 15 (±10 d)**	**M 18 (±10 d)**	**M 21/27 (±10 d)[c]**	**M 24/30/ EW (±5 d)[d]**	**M 25/31 (±2 d)[e]**
Safety	Criteria for eligibility[f]	X												
	Tuberculosis testing[g]	X												
	12-lead ECG (singlets)[h]	X					X		X		X		X	
	Physical &/or musculoskeletal exam	X[i]		X[j]	X[j]	X[j]	X[j,k]	X[j]	X[j,k]	X[j]	X[j,k]	X[j]	X[i,j]	X[j]
	Safety laboratories	X	X	X	X	X	X	X	X	X	X	X	X	X
	Urinalysis[l]	X	X				X		X		X		X	
	Vital signs		X[m]	X[m]	X[m]	X[m]	X[m,n]	X[m]	X[m,n]	X[m]	X[m,n]	X[m]	X[m,n]	
	Safety PK sample[o]		←										→	
	PK substudy at MRI sites only			X[p]	X[p]									
Efficacy	WOMAC (composite index)		X			X	X		X		X		X	
	Patient Assessment of Arthritis Pain (VAS)		X			X	X		X		X		X	
	Patient/physician global		X			X	X		X		X		X	
	50-ft (15-m) walk pain		X			X	X		X		X		X	
	OA pain assessment tool-knee pain		X			X	X		X		X		X	
	OARSI knee function survey		X			X	X		X		X		X	
	SF-36, EQ-5D		X						X				X	
	Patient global impression of change												X	
	X-ray imaging								X[q]				X[q]	
Exploratory	MRI substudy (selected sites)		X				X		X				X	
	Biomarkers (blood/urine)		X[r]		X[s]	X[s]	X[s]		X[s]		X[s]		X[s]	
	Pharmacogenomics (volunteers)		X[t]											

Table 3. Schedule of Activities for Screen 2, and the Treatment and Post Treatment Periods

Treatment Periods	Pre	Treatment										Post
Activities	**Screen 2[a,b]**	**Day 1 (First Dose)**	**Wk 2 (±2 d)**	**M 1 (±10 d)**	**M 3 (±10 d)**	**M 6 (±10 d)**	**M 9 (±10 d)**	**M 12 (±10 d)**	**M 15 (±10 d)**	**M 18 (±10 d)**	**M 21/27 (±10 d)[c]**	**M 24/30/ EW (±5 d)[d]**	**M 25/31 (±2 d)[e]**
Study medication dispensing		X			X	X	X	X	X	X	X		
Study medication dosing		←	—	—	—	—	—	—	—	—	—	→	
Prior and concomitant medication	←	—	—	—	—	—	—	—	—	—	—	—	→
Adverse events[u]			←	—	—	—	—	—	—	—	—	—	→

d = day; ECG = electrocardiogram; EQ-5D = EuroQol-5 dimensions; EW = early withdrawal; IA = interim analysis; M = month; MRI = magnetic resonance imaging; OA = osteoarthritis; OARSI = Osteoarthritis Research Society International; PK = pharmacokinetic; PPD = purified protein derivative; QoL = quality of life; Scr = Screen; SF-36 = short form-36; TB = tuberculosis; VAS = visual analog scale; Wk = week; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

a. The number of days remaining for Screen 2 to be completed could be calculated by subtracting the number of days in Screen 1 from 35.
b. A visit for PPD skin text read, if needed, could have been completed during Screen 2. A PPD skin test result must have been read by the qualified site personnel within 48-72 hours (extra visit). An induration ≥10 mm disqualified a subject from the study unless a history of treatment for TB could be verified and a chest X-ray was normal. The TB-specific blood test did not require an extra visit; however, a positive result required same evidence as for a positive PPD (evidence of TB treatment and a normal chest X-ray) for entry.
c. In the event the decision was made to extend the study another 6 months, a Month 27 visit was required that was identical to the Month 21 activities.
d. In the event the decision was made to extend the study another 6 months, the primary endpoint visit at 24 months was shifted to Month 30.
e. The 28-day follow-up visit in the 24-month study was Month 25. If the decision was made to extend the study another 6 months, the 28-day follow-up visit became the Month 31 visit.
f. Assessed subjects against the Screen 2 exclusion criteria.
g. Assessed for TB against exclusion criteria. The Investigator had the choice of completing the PPD skin test or collecting a blood sample for the TB-specific blood test, depending on subject status**.**
h. A verified clinically significant ECG abnormality was reason to discontinue screening the subject. A nonclinically significant abnormality was acceptable. The Investigator was to use clinical judgment at subsequent visits.
i. Full physical examination.
j. Musculoskeletal examination of the study knee (exam noting joint swelling and tenderness, erythema, warmth, bone abnormalities, range of motion, and effusion).
k. Brief physical examination.
l. Dipstick analysis at the central laboratory.
m. Arm cuff blood pressure (supine) and heart rate.
n. Recorded weight.
o. Safety PK: A PK sample was to be collected on all subjects requiring a drug holiday attributed to a study-specified adverse events (eg, blood pressure and/or transaminase increases) only if the subject was administered study drug in the last 48 hours of the finding.
p. Population PK was to be collected from subjects in the MRI substudy: subjects were reminded to delay the Week 2 and Month 1 dose until the clinic visit. At these 2 respective visits, a pre-dose sample was collected (beginning of clinic visit), subjects were then administered study drug, and a 2-hour postdose sample was collected. The last 2 previous dosing times were recorded as well. Once the PK requirement (approximately 180 subjects) was met, sites were notified to cease collecting PK samples in this cohort of subjects.
q. Performed X-rays on the study knee only (approximately 3 images). X-rays on the other knee were not required.

Table 3. Schedule of Activities for Screen 2, and the Treatment and Post Treatment Periods

Treatment Periods	Pre		Treatment										Post
Activities	Screen 2[a,b]	Day 1 (First Dose)	Wk 2 (±2 d)	M 1 (±10 d)	M 3 (±10 d)	M 6 (±10 d)	M 9 (±10 d)	M 12 (±10 d)	M 15 (±10 d)	M 18 (±10 d)	M 21/27 (±10 d)[c]	M 24/30/ EW (±5 d)[d]	M 25/31 (±2 d)[e]

r. For the MRI substudy, the site collected a second morning void urine sample (approximately 5 mL) and a blood sample (one 10-mL tube for plasma and one 10-mL tube for serum) from subjects who agreed to provide biomarker blood and/or urine, prior to administering the first dose of study medication at the clinic.
s. No time stipulation was identified for these collections.
t. Collected only from willing volunteers who signed Part 2 of the informed consent. A refusal to contribute a pharmacogenomic sample was not a reason to exclude a subject from the main study.
u. Serious adverse events were collected from the time of the signing of the informed consent document at Screen 1. Non-serious adverse events were collected from the day of first dose.

Number of Subjects (Planned and Analyzed): Approximately 1400 subjects were to be randomized to ensure that 981 subjects (327 subjects/treatment group) completed the study. A total of 1457 subjects were randomized including 760 subjects in USA, 118 subjects in the Czech Republic, 111 subjects in Peru, 75 subjects in Poland, 69 subjects in Germany, 66 subjects in Spain, 65 subjects in Argentina, 62 subjects in Hungary, 49 subjects in Canada, 41 subjects in Russian Federation, 12 subjects each in Belgium and Australia,, 10 subjects in Italy and 7 subjects in Slovakia. A total of 485, 486 and 486 subjects were randomized in the SD-6010 50 mg QD treatment group, SD-6010 200 mg QD treatment group, and placebo group, respectively.

Diagnosis and Main Criteria for Inclusion and Exclusion: The study included male and female subjects aged ≥40 years with a BMI ≥25 and ≤40 kg/m^2 with past diagnosis of knee OA and radiographic evidence of OA in the study knee.

Main Exclusion Criteria: Subjects with a diagnosis of any other rheumatic disease or conditions in the study knee that would have confounded efficacy were excluded from the study.

Study Treatment: Subjects were randomized to daily doses of SD-6010 50 mg, SD-6010 200 mg, or placebo. SD-6010 was supplied to the clinical pharmacy by the Sponsor as tablets containing either 50 mg or 100 mg equivalents of SD-6010 free-base dose or placebo. The study medication tablets were taken orally QD in the morning for 24 or 30 months (if the 6-month extension period was needed).

Efficacy Endpoints: The primary efficacy endpoint of the study was the progression rate of JSN. The secondary efficacy endpoints of the study are presented in Table 4. Endpoints were assessed as a function of change from Baseline, with the exception of the Patient Global Impression of Change.

Table 4. Secondary Efficacy Endpoints

Secondary Endpoints		Monthly Time Points
Outcome measures	WOMAC (composite index) WOMAC pain subscale WOMAC stiffness subscale WOMAC physical function subscale Patient Assessment of Arthritis Pain (VAS) 50-Foot walk (VAS pain) Patient Global Assessment of Arthritic Condition Physician's Global Assessment of Arthritic Condition Osteoarthritis pain assessment tool-knee joint (Total Score) OARSI knee function survey	3, 6, 12, 18, 24, or 30
	SF-36 version.2 (all domains and summary scores) Physical functioning domain Role-physical domain Bodily pain domain General health domain Vitality domain Social functioning domain Role-emotional domain Mental health domain Physical health component Emotional health component EQ-5D (all domains) Mobility domain Self-care domain Usual activity domain Pain/discomfort domain Anxiety/depression domain VAS Total analgesic medication burden	12, 24, or 30
	OMERACT-OARSI Responder Index JSN Progressor Study	24 or 30

EQ-5D = EuroQoL-5 dimensions; JSN = joint space narrowing; OARSI = Osteoarthritis Research Society International; OMERACT = Outcome Measures in Rheumatology; VAS = visual analog scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SF = short form.

Safety Evaluations: The safety and tolerability of SD-6010 were assessed by adverse event (AE) and serious AE (SAE) monitoring, physical examinations, vital signs, electrocardiograms (ECGs), and clinical laboratory measurements.

Statistical Methods: The primary analysis was done in the full analysis set (FAS), which included all subjects randomized to the study. The per protocol analysis set (PPAS) included all subjects in the FAS who completed the study and had at least 80% treatment compliance. Observations following a non-drug procedure or protocol deviation with the potential to affect the evaluation of efficacy were excluded from the PPAS. Type 1 error associated with the comparison of multiple treatment groups to placebo was controlled using the Hochberg procedure with α=0.0499, the amount of Type 1 error remaining after adjustments for the interim analyses (IAs).

The rate of JSN was analyzed using a random coefficients mixed model repeated measures (MMRM) on joint space width (JSW) with the intercept and slope as random effects; treatment group, time, a treatment group × time interaction term, KLG, a KLG × time interaction term, geographic region, gender, age, and BMI as fixed effects; and an unstructured covariance matrix. Time was measured in years using the study day on which the X-ray was taken and entered the model as a continuous variable; JSW was modeled as a linear function of time. The estimated slope and associated 95% confidence interval (CI) were presented for each treatment group, and the estimated difference in slopes, associated 95% CI, and p-value were presented for the comparison of each SD-6010 treatment group to placebo. Also, the first observation, the last observation, the years between first observation and last observation, and the rate of change per year from the first observation to the last observation were summarized by treatment group. The primary analysis was repeated in the following analysis sets: subjects with KLG ≤2, subjects with KLG = 3, subjects randomized in North America/Australia, subjects randomized in Europe, and subjects randomized in South America.

For JSW, secondary endpoints, systolic blood pressure (SBP) and diastolic blood pressure (DBP), changes from Baseline were analyzed by MMRM with treatment group, visit, a treatment group × visit interaction term, KLG, a KLG × visit interaction term, baseline value, geographic region, age, gender, and BMI as fixed effects. Treatment group, visit, KLG, geographic region, and gender entered the model as categorical variables. Baseline value, age, and BMI entered the model as continuous variables. The covariance matrix was unstructured. All secondary analyses were done in the FAS with α=0.05. Type 1 errors associated with multiple endpoints and multiple comparisons to placebo were not controlled.

The safety parameters were summarized using the safety analysis set, which included all subjects who received at least 1 dose of the randomized study medication.

RESULTS

Subject Disposition and Demography: A total of 5077 subjects were screened for inclusion in the study; 485, 486, and 486 subjects were assigned to study treatment in the SD-6010 50 mg QD treatment group, SD-6010 200 mg QD treatment group, and placebo group, respectively. In the SD-6010 50 mg QD treatment group, 482 subjects were treated and 3 subjects were not treated; all but 1 subject each in the SD-6010 200 mg QD and placebo treatment groups received treatment (Table 5). Data sets analyzed are presented in Table 6.

Table 5. Subject Evaluation Groups – Full Analysis Set

Disposition Number (%) of Subjects	SD-6010 50 mg QD	SD-6010 200 mg QD	Placebo
Screened, 5077			
Assigned to study treatment	485	486	486
Treated	482 (99.4)	485 (99.8)	485 (99.8)
Completed	341 (70.3)	351 (72.2)	356 (73.3)
Discontinued	144 (29.7)	135 (27.8)	130 (26.7)
Death	2 (0.4)	1 (0.2)	3 (0.6)
Relation to study drug not defined	101 (20.8)	80 (16.5)	87 (17.9)
Does not meet entrance criteria	1 (0.2)	0	1 (0.2)
Lost to follow-up	10 (2.1)	8 (1.6)	8 (1.6)
No longer willing to participate in study	58 (12.0)	47 (9.7)	48 (9.9)
Other	30 (6.2)	19 (3.9)	26 (5.3)
Protocol violation	2 (0.4)	6 (1.2)	4 (0.8)
Related to study drug	15 (3.1)	22 (4.5)	19 (3.9)
Adverse event	15 (3.1)	22 (4.5)	19 (3.9)
Not related to study drug	26 (5.4)	32 (6.6)	21 (4.3)
Adverse event	26 (5.4)	32 (6.6)	21 (4.3)

Five (5) subjects were assigned to study treatment but were not treated. Two (2) subjects (1 subject in the SD-6010 50 mg QD treatment group and 1 subject in the placebo group) did not meet entrance criteria and 3 subjects (2 subjects in the SD-6010 50 mg QD treatment group and 1 subject in the SD-6010 200 mg QD treatment group) were no longer willing to participate in the study.
QD = once daily.

Table 6. Subject Groups – Full Analysis Set

Number (%) of Subjects	SD-6010 50 mg QD	SD-6010 200 mg QD	Placebo
Assigned to study treatment	485	486	486
Analyzed for efficacy			
Full analysis set	485 (100.0)	486 (100.0)	486 (100.0)
Per protocol analysis set	456 (94.0)	451 (92.8)	460 (94.7)
Analyzed for safety			
Adverse events	482 (99.4)	485 (99.8)	484 (99.6)
Laboratory data	479 (98.8)	480 (98.8)	481 (99.0)
Safety analysis set	482 (99.4)	485 (99.8)	485 (99.8)
Analyzed for pharmacokinetics	30	26	-

QD = once daily.

The demographic characteristics for subjects in the FAS are presented in Table 7.

Table 7. Demographic Characteristics – Full Analysis Set

Characteristics	SD-6010 50 mg QD			SD-6010 200 mg QD			Placebo		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number (%) of subjects	102	383	485	119	367	486	122	364	486
Hormonal status									
Premenopausal	–	37 (9.7)	–	–	35 (9.5)	–	–	25 (6.9)	–
Postmenopausal	–	346 (90.3)	–	–	332 (90.5)	–	–	339 (93.1)	–
Age (years)									
<18	0	0	0	0	0	0	0	0	0
18-44	2 (2.0)	9 (2.3)	11 (2.3)	5 (4.2)	10 (2.7)	15 (3.1)	6 (4.9)	9 (2.5)	15 (3.1)
45-64	62 (60.8)	245 (64.0)	307 (63.3)	75 (63.0)	238 (64.9)	313 (64.4)	65 (53.3)	234 (64.3)	299 (61.5)
≥65	38 (37.3)	129 (33.7)	167 (34.4)	39 (32.8)	119 (32.4)	158 (32.5)	51 (41.8)	121 (33.2)	172 (35.4)
Mean (SD)	61.0 (9.1)	60.9 (8.7)	61.0 (8.7)	61.1 (8.7)	60.7 (8.6)	60.8 (8.6)	61.7 (10.4)	61.1 (8.6)	61.3 (9.1)
Min-max	40-85	42-84	40-85	40-87	41-84	40-87	41-85	40-89	40-89
Race									
White	86 (84.3)	303 (79.1)	389 (80.2)	104 (87.4)	306 (83.4)	410 (84.4)	103 (84.4)	302 (83.0)	405 (83.3)
Black	6 (5.9)	26 (6.8)	32 (6.6)	8 (6.7)	20 (5.4)	28 (5.8)	5 (4.1)	18 (4.9)	23 (4.7)
Asian	6 (5.9)	6 (1.6)	12 (2.5)	1 (0.8)	8 (2.2)	9 (1.9)	9 (7.4)	3 (0.8)	12 (2.5)
Other	4 (3.9)	48 (12.5)	52 (10.7)	6 (5.0)	33 (9.0)	39 (8.0)	5 (4.1)	41 (11.3)	46 (9.5)
Body mass index (kg/m^2)									
N	102 (100.0)	383 (100.0)	485 (100.0)	119 (100.0)	367 (100.0)	486 (100.0)	122 (100.0)	364 (100.0)	486 (100.0)
Mean (SD)	31.1 (3.9)	32.1 (4.2)	31.9 (4.1)	30.1 (3.5)	32.6 (4.1)	32.0 (4.1)	30.6 (3.5)	32.0 (4.3)	31.6 (4.1)
Min-max	25.1-40.3	24.4 (40.2)	24.4-40.3	24.5-39.4	23.7-40.1	23.7-40.1	25.0-39.9	24.6-40.5	24.6-40.5

Body mass index was calculated as weight/(height × 0.01)^2.
QD = once daily; max = maximum; min = minimum; N = number of evaluable subjects; SD = standard deviation.

Efficacy Results: In the primary analysis, the slope over a 2-year period was used to assess the rate of change in JSW. The slopes were similar across the treatment groups: the primary analysis did not demonstrate superiority of SD-6010 over placebo in reducing the rate of JSN for either treatment group (Table 8).

Table 8. Linear Time MMRM Analysis of Joint Space Width – Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
First JSW			
n	485	483	486
Mean (SD)	3.168 (0.748)	3.194 (0.741)	3.224 (0.708)
Median	3.160	3.180	3.205
Min-max	1.420-5.410	1.550-5.980	1.430-5.280
Last JSW			
n	422	428	434
Mean (SD)	2.977 (0.971)	2.973 (0.905)	3.011 (0.900)
Median	3.040	2.975	3.035
Min-max	0.000-5.270	0.000-5.040	0.000-5.040
Change from first JSW to last JSW			
n	422	428	434
Mean (SD)	-0.180 (0.472)	-0.201 (0.437)	-0.202 (0.453)
Median	-0.050	-0.090	-0.100
Min-max	-3.180-0.900	-2.690-0.790	-2.560-1.310
Years from first JSW to last JSW			
n	422	428	434
Mean (SD)	1.735 (0.481)	1.755 (0.446)	1.774 (0.413)
Median	1.925	1.922	1.927
Min-max	0.172-2.234	0.162-2.270	0.219-2.494
Change per year from first JSW to last JSW			
n	422	428	434
Mean (SD)	-0.101 (0.346)	-0.125 (0.298)	-0.109 (0.261)
Median	-0.030	-0.054	-0.055
Min-max	-3.187-1.218	-2.545-1.139	-1.370-0.670
Slopes			
Slope	-0.103	-0.109	-0.115
Standard error	0.013	0.012	0.012
95% CI	-0.128, -0.078	-0.134, -0.085	-0.139, -0.091
Difference in slopes			
Difference versus placebo	0.012	0.005	
Standard error	0.018	0.017	
95% CI	-0.023, 0.046	-0.029, 0.040	
p-Value versus placebo	0.508770	0.754074	

Hypothesis tests used the Hochberg procedure with 2-sided alpha=0.0499.
Slopes, 95% CI, and p-values are from a random coefficients MMRM model, with random intercept and slope for each subject, and fixed effects for treatment group, time (years), a treatment group × time (years) interaction, (collapsed) KLG, a (collapsed) KLG × time (years) interaction, geographic region, gender, age, and body mass index with an unstructured covariance matrix for the random effects.
JSW was measured in millimeters.
CI = confidence interval; JSW = joint space width; KLG = Kellgren and Lawrence grade; max = maximum; min = minimum; MMRM = mixed model repeated measures; N= total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation.

Secondary Analysis Results:

The discrete time MMRM analysis of change from Baseline in WOMAC pain subscale score and physical function subscale score for subjects in the FAS is shown in Table 9. The improvements were similar for all treatment groups and results were not significant versus placebo at any time point.

Table 9. Discrete Time MMRM Analysis of Change From Baseline in WOMAC Pain Subscale Score and Physical Function Subscale Score – Full Analysis Set

	Pain Subscale Score			Physical Function Subscale Score		
	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline						
n	482	484	483	481	482	482
Mean (SD)	7.96 (3.94)	7.44 (3.87)	7.59 (4.03)	27.63 (13.88)	26.49 (13.18)	27.39 (13.81)
Median	8.00	7.00	8.00	28.00	27.00	27.00
Min-max	0.00-20.00	0.00-20.00	0.00-20.00	0.00-68.00	0.00-68.00	0.00-68.00
Month 3/Week 12						
n	452	453	461	451	454	460
Mean (SD)	6.58 (3.89)	6.20 (3.80)	6.29 (3.85)	23.99 (13.77)	23.16 (12.78)	23.47 (13.28)
Median	6.00	6.00	6.00	23.00	24.00	24.00
Min-max	1.00-18.00	0.00-17.00	0.00-19.00	0.00-62.00	0.00-53.00	0.00-63.00
Change from Baseline						
n	451	453	458	449	452	456
Mean (SD)	-1.32 (3.41)	-1.23 (3.19)	-1.25 (3.15)	-3.50 (10.77)	-3.24 (9.71)	-3.72 (9.99)
Median	-1.00	-1.00	-1.00	-2.00	-2.00	-2.00
Min-max	-15.00-14.00	-13.00-8.00	-17.00-9.00	-49.00-32.00	-37.00-25.00	-54.00-26.00
LS-mean (SE)	-1.16 (0.16)	-1.28 (0.15)	-1.24 (0.15)	-3.26 (0.50)	-3.43 (0.49)	-3.59 (0.49)
95% CI	-1.47, -0.86	-1.58, -0.98	-1.54, -0.94	-4.24, -2.27	-4.39, -2.46	-4.56, -2.63
Versus placebo						
LS-mean difference (SE)	0.08 (0.19)	-0.04 (0.19)		0.34 (0.62)	0.17 (0.62)	
95% CI	-0.03, 0.46	-0.42, 0.35		-0.88, 1.55	-1.05, 1.38	
MMRM p-value	0.683	0.853		0.586	0.789	
Month 6/Week 24						
n	427	429	438	426	428	438
Mean (SD)	6.13 (4.05)	6.08 (3.96)	5.94 (3.79)	22.62 (13.87)	22.84 (13.48)	22.33 (13.03)
Median	6.00	6.00	6.00	22.00	24.00	22.50
Min-max	0.00-19.00	0.00-17.00	0.00-20.00	0.00-62.00	0.00-61.00	0.00-66.00
Change from Baseline						
n	426	429	435	424	426	434
Mean (SD)	-1.73 (3.73)	-1.42 (3.58)	-1.59 (3.45)	-4.78 (11.73)	-3.86 (10.81)	-4.82 (11.43)
Median	-1.00	-1.00	-1.00	-3.00	-3.00	-3.00
Min-max	-14.00-10.00	-13.00-10.00	-14.00-10.00	-51.00-30.00	-41.00-39.00	-49.00-35.00

Table 9. Discrete Time MMRM Analysis of Change From Baseline in WOMAC Pain Subscale Score and Physical Function Subscale Score – Full Analysis Set

	Pain Subscale Score			Physical Function Subscale Score		
	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
LS-mean (SE)	-1.57 (0.17)	-1.48 (0.17)	-1.58 (0.17)	-4.53 (0.55)	-3.96 (0.54)	-4.69 (0.54)
95% CI	-1.90, -1.23	-1.81, -1.15	-1.91, -1.26	-5.61, -3.45	-5.02, -2.89	-5.74, -3.63
Versus placebo						
LS-mean difference (SE)	0.02 (0.22)	0.10 (0.22)		0.16 (0.69)	0.73 (0.69)	
95% CI	-0.41, 0.44	-0.32, 0.52		-1.21, 1.52	-0.63, 2.09	
MMRM p-value	0.938	0.648		0.821	0.294	
Month 12/Week 48						
n	373	389	401	372	389	401
Mean (SD)	5.54 (4.25)	5.31 (3.72)	5.54 (3.90)	20.61 (14.59)	19.98 (13.36)	20.67 (13.43)
Median	5.00	5.00	5.00	18.00	19.00	20.00
Min-max	0.00-20.00	0.00-20.00	0.00-20.00	0.00-68.00	0.00-63.00	0.00-63.00
Change from Baseline						
n	372	389	398	370	388	398
Mean (SD)	-2.17 (4.25)	-2.10 (3.66)	-2.08 (3.47)	-6.09 (13.21)	-6.37 (11.34)	-6.79 (11.55)
Median	-2.00	-2.00	-2.00	-4.00	-5.00	-5.00
Min-max	-14.00-12.00	-13.00-9.00	-14.00-11.00	-47.00-37.00	-44.00-31.00	-49.00-25.00
LS-mean (SE)	-2.00 (0.18)	-2.12 (0.18)	-1.97 (0.18)	-5.88 (0.60)	-6.41 (0.59)	-6.35 (0.58)
95% CI	-2.36, -1.64	-2.47, -1.77	-2.32, -1.62	-7.05, -4.70	-7.56, -5.26	-7.49, -5.22
Versus placebo						
LS-mean difference (SE)	-0.02 (0.24)	-0.15 (0.23)		0.48 (0.76)	-0.06 (0.76)	
95% CI	-0.49, 0.44	-0.60, 0.31		-1.02, 1.97	-1.55, 1.43	
MMRM p-value	0.916	0.528		0.532	0.938	
Month 18/Week 72						
n	348	363	362	346	362	361
Mean (SD)	5.37 (4.04)	5.51 (4.00)	5.69 (4.07)	19.86 (14.01)	21.22 (13.95)	21.13 (13.91)
Median	5.00	5.00	5.00	18.00	20.00	20.00
Min-max	0.00-19.00	0.00-17.00	0.00-19.00	0.00-65.00	0.00-60.56	0.00-63.00
Change from Baseline						
n	347	363	359	344	361	358
Mean (SD)	-2.24 (4.16)	-2.00 (3.93)	-1.86 (3.88)	-6.74 (12.95)	-5.49 (12.05)	-6.12 (13.22)
Median	-2.00	-2.00	-2.00	-5.00	-4.00	-5.00

Table 9. Discrete Time MMRM Analysis of Change From Baseline in WOMAC Pain Subscale Score and Physical Function Subscale Score – Full Analysis Set

	Pain Subscale Score			Physical Function Subscale Score		
	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Min-max	-16.00-8.00	-14.00-10.00	-13.00-12.00	-54.00-27.00	-42.00-30.00	-46.00-40.00
LS-mean (SE)	-2.03 (0.20)	-2.05 (0.19)	-1.81 (0.19)	-6.15 (0.64)	-5.52 (0.63)	-5.80 (0.62)
95% CI	-2.42, -1.65	-2.43, -1.68	-2.18, -1.43	-7.40, -4.89	-6.75, -4.29	-7.03, -4.58
Versus placebo						
LS-mean difference (SE)	-0.23 (0.25)	-0.25 (0.25)		-0.34 (0.83)	0.28 (0.82)	
95% CI	-0.73, 0.27	-0.74, 0.25		-1.97, 1.29	-1.33, 1.90	
MMRM p-value	0.365	0.328		0.680	0.730	
Month 24/Week 96						
n	338	342	354	338	340	353
Mean (SD)	5.12 (4.06)	5.28 (4.03)	5.29 (4.06)	19.14 (14.45)	19.17 (13.31)	19.65 (13.98)
Median	4.00	5.00	5.00	16.50	19.00	19.00
Min-max	0.00-19.00	0.00-17.00	0.00-19.00	0.00-66.00	0.00-51.00	0.00-67.00
Change from Baseline						
n	337	342	351	336	339	350
Mean (SD)	-2.48 (4.02)	-2.23 (4.16)	-2.19 (3.79)	-7.42 (13.47)	-7.65 (12.37)	-7.35 (12.54)
Median	-2.00	-2.00	-2.00	-6.00	-6.00	-6.00
Min-max	-16.00-10.00	-14.00-9.00	-13.00-7.00	-56.00-29.00	-47.00-21.00	-41.00-26.00
LS-mean (SE)	-2.26 (0.20)	-2.31 (0.19)	-2.11 (0.19)	-6.93 (0.65)	-7.84 (0.64)	-7.03 (0.63)
95% CI	-2.65, -1.87	-2.69,-1.93	-2.48, -1.73	-8.20, -5.66	-9.10, -6.59	-8.27, -5.80
Versus placebo						
LS-mean difference (SE)	-0.16 (0.26)	-0.21 (0.26)		0.10 (0.84)	-0.81 (0.84)	
95% CI	-0.66, 0.35	-0.71, 0.30		-1.55, 1.76	-2.45, 0.83	
MMRM p-value	0.540	0.423		0.901	0.333	

Table 9. Discrete Time MMRM Analysis of Change From Baseline in WOMAC Pain Subscale Score and Physical Function Subscale Score – Full Analysis Set

	Pain Subscale Score			Physical Function Subscale Score		
	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486

LS-means, 95% CI, and p-values are from a discrete time MMRM model, with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age, and body mass index with an unstructured covariance matrix.
The WOMAC pain subscale score ranged from 0-20, with higher scores indicating worse pain.
The WOMAC physical function subscale score ranged from 0-68, with higher scores indicating worse physical function.
Decreases from Baseline indicate improvement in pain/physical function.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N= total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

All treatment groups improved in WOMAC OA stiffness and composite index from Baseline, but there were no significant differences between the SD-6010 treatment groups and placebo (Table 10).

Table 10. Discrete Time MMRM Analysis of Change From Baseline in WOMAC Stiffness Subscale Score and Composite Index Score - Full Analysis Set

	Stiffness Subscale Score			Composite Index Score		
	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline						
n	481	484	482	481	482	481
Mean	3.48	3.33	3.44	39.07	37.29	38.45
SD	1.8	1.78	1.77	18.85	17.98	18.91
Median	4	3	3	40	38	38
Min-max	0.00-8.00	0.00-8.00	0.00-8.00	0.00-92.00	0.00-95.00	0.00-96.00
Month 3/Week 12						
n	451	455	460	451	452	460
Mean	2.96	2.83	2.91	33.52	32.1	32.69
SD	1.77	1.73	1.76	18.76	17.52	18.18
Median	3	3	3	33	32	33
Min-max	0.00-8.00	0.00-8.00	0.00-8.00	0.00-85.00	0.00-73.00	0.00-90.00
Change from Baseline						
n	449	455	456	449	450	455
Mean	-0.52	-0.51	-0.51	-5.35	-5.08	-5.5
SD	1.67	1.58	1.58	14.73	13.14	13.59
Median	0	0	0	-4	-4	-3
Min-max	-6.00-5.00	-5.00-5.00	-8.00-4.00	-66.00-49.00	-51.00-34.00	-79.00-35.00
LS-mean (SE)	-0.53 (0.08)	-0.60 (0.07)	-0.55 (0.07)	-5.02 (0.69)	-5.37 (0.67)	-5.42 (0.67)
95% CI	-0.68, -0.39	-0.74,-0.45	-0.69, -0.40	-6.37, -3.67	-6.70, -4.05	-6.73, -4.10
Versus placebo						
LS-mean difference (SE)	0.01 (0.09)	-0.05 (0.09)		0.40 (0.84)	0.05 (0.84)	
95% CI	-0.17, 0.20	-0.24, 0.13		-1.26, 2.05	-1.61, 1.70	
MMRM p-value	0.904	0.582		0.639	0.957	
Month 6/Week 24						
n	427	429	438	426	428	438
Mean	2.8	2.78	2.78	31.54	31.72	31.05
SD	1.77	1.82	1.74	19.07	18.69	17.96
Median	3	3	3	30	33	32
Min-max	0.00-8.00	0.00-8.00	0.00-8.00	0.00-89.00	0.00-85.00	0.00-92.00

Table 10. Discrete Time MMRM Analysis of Change From Baseline in WOMAC Stiffness Subscale Score and Composite Index Score - Full Analysis Set

	Stiffness Subscale Score			Composite Index Score		
	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Change from Baseline						
n	425	429	434	424	426	433
Mean	-0.67	-0.56	-0.62	-7.2	-5.84	-7.07
SD	1.7	1.78	1.73	15.99	15.15	15.62
Median	-1	0	0	-5	-4	-5
Min-max	-7.00-5.00	-6.00-7.00	-6.00-4.00	-69.00-39.00	-57.00-54.00	-66.00-48.00
LS-mean (SE)	-0.69 (0.08)	-0.67 (0.08)	-0.67 (0.08)	-6.85 (0.76)	-6.10 (0.75)	-6.98 (0.75)
95% CI	-0.85, -0.53	-0.82, -0.51	-0.82, -0.51	-8.34, -5.35	-7.58, -4.63	-8.44, -5.51
Versus placebo						
LS-mean difference (SE)	-0.02 (0.10)	-0.00 (0.10)		0.13 (0.96)	0.87 (0.96)	
95% CI	-0.22, 0.18	-0.20, 0.20		-1.76, 2.01	-1.01, 2.76	
MMRM p-value	0.818	0.988		0.893	0.365	
Month 12/Week 48						
n	373	389	401	372	389	401
Mean	2.52	2.5	2.5	28.65	27.79	28.71
SD	1.9	1.77	1.76	20.1	18.24	18.49
Median	2	2	2	26	27	28
Min-max	0.00-8.00	0.00-8.00	0.00-8.00	0.00-95.00	0.00-90.00	0.00-87.00
Change from Baseline						
n	371	389	397	370	388	397
Mean	-0.89	-0.79	-0.95	-9.17	-9.25	-9.84
SD	1.89	1.83	1.78	18.19	15.82	15.75
Median	-1	-1	-1	-7	-7	-8
Min-max	-7.00-5.00	-7.00-4.00	-6.00-5.00	-66.00-53.00	-64.00-40.00	-69.00-35.00
LS-mean (SE)	-0.92 (0.09)	-0.89 (0.09)	-0.94 (0.08)	-8.84 (0.83)	-9.41 (0.81)	-9.28 (0.80)
95% CI	-1.09, -0.75	-1.06, -0.72	-1.11, -0.77	-10.47, -7.22	-10.99, -7.82	-10.85, -7.71
Versus placebo						
LS-mean difference (SE)	0.02 (0.11)	0.05 (0.11)		0.44 (1.05)	-0.13 (1.05)	
95% CI	-0.20, 0.24	-0.17, 0.27		-1.63, 2.51	-2.18, 1.93	
MMRM p-value	0.857	0.658		0.678	0.902	

Table 10. Discrete Time MMRM Analysis of Change From Baseline in WOMAC Stiffness Subscale Score and Composite Index Score - Full Analysis Set

	Stiffness Subscale Score			Composite Index Score		
	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Month 18/Week 72						
n	348	363	362	346	362	361
Mean	2.47	2.49	2.58	27.68	29.22	29.4
SD	1.76	1.79	1.74	19.25	19.22	19.18
Median	2	2	2	25	28	28
Min-max	0.00-8.00	0.00-7.00	0.00-8.00	0.00-92.00	0.00-82.56	0.00-89.00
Change from Baseline						
n	346	363	358	344	361	357
Mean	-0.88	-0.87	-0.82	-9.91	-8.35	-8.82
SD	1.86	1.88	1.82	17.98	16.87	18
Median	-1	-1	-1	-8	-7	-8
Min-max	-6.00-4.00	-6.00-5.00	-6.00-4.00	-74.00-38.00	-58.00-44.00	-65.00-56.00
LS-mean (SE)	-0.91 (0.09)	-0.95 (0.09)	-0.85 (0.09)	-9.11 (0.89)	-8.50 (0.87)	-8.47 (0.86)
95% CI	-1.09, -0.74	-1.12, -0.78	-1.02, -0.68	-10.85, -7.37	-10.20, -6.80	-10.16, -6.78
Versus placebo						
LS-mean difference (SE)	-0.06 (0.12)	-0.10 (0.11)		-0.64 (1.15)	-0.03 (1.14)	
95% CI	-0.28, 0.17	-0.32, 0.13		-2.89, 1.61	-2.26, 2.21	
MMRM p-value	0.612	0.391		0.577	0.98	
Month 24/Week 96						
n	338	342	353	338	340	353
Mean	2.4	2.29	2.44	26.66	26.74	27.38
SD	1.82	1.79	1.83	19.73	18.59	19.36
Median	2	2	2	23	26	26
Min-max	0.00-8.00	0.00-6.00	0.00-8.00	0.00-91.00	0.00-71.94	0.00-94.00
Change from Baseline						
n	336	342	349	336	339	349
Mean	-0.94	-1.1	-0.95	-10.85	-10.98	-10.49
SD	1.95	1.95	1.92	18.49	17.62	17.26
Median	-1	-1	-1	-9	-9	-8
Min-max	-7.00-5.00	-8.00-4.00	-6.00-5.00	-75.00-40.00	-66.00-27.94	-58.00-34.00
LS-mean (SE)	-0.96 (0.09)	-1.17 (0.09)	-0.96 (0.09)	-10.16 (0.90)	-11.32 (0.89)	-10.09 (0.88)

Table 10. Discrete Time MMRM Analysis of Change From Baseline in WOMAC Stiffness Subscale Score and Composite Index Score - Full Analysis Set

	Stiffness Subscale Score			Composite Index Score		
	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
95% CI	-1.15, -0.78	-1.35, -0.99	-1.14, -0.78	-11.93, -8.39	-13.06, -9.58	-11.81, -8.36
Versus placebo						
LS-mean difference (SE)	-0.00 (0.12)	-0.21 (0.12)		-0.07 (1.17)	-1.23 (1.17)	
95% CI	-0.24, 0.24	-0.45, 0.03		-2.37, 2.23	-3.53, 1.06	
MMRM p-value	1	0.086		0.95	0.292	

LS-Means, 95% CI and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix.
The WOMAC stiffness subscale score ranges from 0-8, with higher scores indicating worse stiffness. Decreases from Baseline indicate improvement in stiffness.
The WOMAC composite index ranges from 0-96, with higher scores indicating worse osteoarthritis. Decreases from Baseline indicate improvement of osteoarthritis.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N= total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

The discrete time MMRM analysis of change from Baseline in Patient Assessment of Arthritis Pain VAS score for subjects in the FAS is presented in Table 11. The improvement was similar for all treatment groups, and the results were not significant compared to placebo at any time point.

Table 11. Discrete Time MMRM Analysis of Change From Baseline in Patient Assessment of Arthritis Pain VAS Score – Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	478	479	482
Mean (SD)	40.19 (24.77)	37.59 (24.26)	39.37 (23.91)
Median	41.09	36.63	41.00
Min-max	0.00-99.00	0.00-94.00	0.00-100.00
Month 3/Week 12			
n	451	452	459
Mean (SD)	32.79 (24.12)	30.71 (24.28)	30.20 (23.34)
Median	28.00	27.00	26.88
Min-max	0.00-100.00	0.00-98.00	0.00-100.00
Change from Baseline			
n	446	448	455
Mean (SD)	-7.21 (25.49)	-7.02 (23.45)	-9.12 (21.72)
Median	-5.00	-6.00	-5.00
Min-max	-92.00-65.00	-89.32-77.23	-85.00-55.00
LS-mean (SE)	-6.21 (1.08)	-7.44 (1.06)	-8.55 (1.06)
95% CI	-8.33, -4.09	-9.52, -5.35	-10.62, -6.48
Versus placebo			
LS-mean difference (SE)	2.34 (1.36)	1.11 (1.36)	
95% CI	-0.33, 5.01	-1.56, 3.78	
MMRM p-value	0.086	0.415	
Month 6/Week 24			
n	427	428	439
Mean (SD)	29.79 (23.74)	30.04 (24.40)	28.72 (23.02)
Median	25.74	26.00	25.00
Min-max	0.00-99.00	0.00-99.00	0.00-97.00
Change from Baseline			
n	422	424	435
Mean (SD)	-10.13 (24.91)	-7.92 (24.90)	-10.17 (24.07)
Median	-6.66	-7.00	-7.97
Min-max	-88.30-85.00	-82.98-73.35	-99.01-57.00
LS-mean (SE)	-8.99 (1.12)	-8.54 (1.10)	-9.79 (1.09)
95% CI	-11.18, -6.80	-10.70, -6.38	-11.93, -7.66
Versus placebo			
LS-mean difference (SE)	0.80 (1.41)	1.26 (1.41)	
95% CI	-1.97, 3.57	-1.51, 4.02	
MMRM p-value	0.569	0.374	
Month 12/Week 48			
n	374	387	400
Mean (SD)	27.32 (24.63)	26.87 (22.93)	26.09 (22.46)
Median	21.00	21.78	22.00
Min-max	0.00-100.00	0.00-98.00	0.00-97.00
Change from Baseline			
n	370	384	396
Mean (SD)	-11.75 (30.38)	-10.98 (25.28)	-12.97 (24.26)
Median	-8.91	-8.31	-11.54
Min-max	-89.22-77.23	-88.26-61.39	-99.01-10.09
LS-mean (SE)	-10.73 (1.20)	-11.18 (1.17)	-12.36 (1.16)
95% CI	-13.09, -8.37	-13.48, -8.88	-14.63, -10.09

Table 11. Discrete Time MMRM Analysis of Change From Baseline in Patient Assessment of Arthritis Pain VAS Score – Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Versus placebo			
LS-mean difference (SE)	1.63 (1.53)	1.18 (1.52)	
95% CI	-1.38, 4.64	-1.81, 4.17	
MMRM p-value	0.288	0.440	
Month 18/Week 72			
n	346	362	363
Mean (SD)	24.60 (22.90)	27.16 (23.61)	25.63 (23.63)
Median	17.82	21.00	18.00
Min-max	0.00-93.62	0.00-88.30	0.00-92.55
Change from Baseline			
n	342	360	360
Mean (SD)	-13.99 (26.78)	-11.17 (25.60)	-12.86 (26.47)
Median	-9.95	-8.53	-12.00
Min-max	-96.00-57.00	-79.21-65.00	-99.01-62.88
LS-mean (SE)	-12.88 (1.23)	-11.54 (1.19)	-12.68 (1.19)
95% CI	-15.29, -10.48	-13.87, -9.20	-15.01, -10.35
Versus placebo			
LS-mean difference (SE)	-0.21 (1.58)	1.14 (1.56)	
95% CI	-3.30, 2.88	-1.92, 4.20	
MMRM p-value	0.896	0.464	
Month 24/Week 96			
n	337	341	351
Mean (SD)	24.55 (22.69)	25.22 (23.02)	24.79 (23.06)
Median	17.82	19.00	18.81
Min-max	0.00-86.00	0.00-88.00	0.00-100.00
Change from Baseline			
n	333	338	348
Mean (SD)	-14.59 (28.36)	-13.36 (25.69)	-13.29 (23.97)
Median	-10.00	-9.00	-11.40
Min-max	-95.74-74.00	-89.34-53.00	-79.02-58.00
LS-mean (SE)	-13.18 (1.22)	-13.38 (1.19)	-12.99 (1.18)
95% CI	-15.57, -10.79	-15.73, -11.04	-15.31 (-10.67)
Versus placebo			
LS-mean difference (SE)	-0.20 (1.57)	-0.39 (1.56)	
95% CI	-3.27, 2.88	-3.45, 2.66	
MMRM p-value	0.901	0.800	

LS-means, 95% CI, and p-values are from a discrete time MMRM model, with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age, and body mass index with an unstructured covariance matrix. Patient Assessment of Arthritic Pain was a VAS that ranged from 0-100, with higher scores indicating worse pain.

CI = confidence interval; KLG = Kellgren and Lawrence grade; max = maximum; min = minimum; LS = least squares; MMRM = mixed model repeated measures; N= total number of subjects in each treatment group; n =number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; VAS = visual analog scale.

In the discrete time MMRM analysis of change from Baseline in pain after a 50-foot walk VAS score for subjects in the FAS, all treatment groups improved compared to Baseline, but no SD-6010 treatment effect was observed compared to placebo (Table 12).

Table 12. Discrete Time MMRM Analysis of Change From Baseline in Pain After a 50-Foot Walk VAS Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	480	483	482
Mean	38.03	35.13	38.00
SD	26.39	26.10	25.73
Median	36.63	32.98	38.89
Min-max	0.00-100.00	0.00-97.00	0.00-100.00
Month 3/Week 12			
n	448	453	459
Mean	31.95	29.54	30.42
SD	25.80	24.34	24.23
Median	29.00	25.00	26.73
Min-max	0.00-99.01	0.00-100.00	0.00-100.00
Change from Baseline			
n	446	453	456
Mean	-5.78	-5.71	-7.45
SD	25.30	23.20	23.15
Median	-3.84	-2.62	-4.00
Min-max	-87.43-89.00	-82.18-80.00	-83.17-75.55
LS-mean (SE)	-4.25 (1.09)	-5.93 (1.06)	-5.93 (1.06)
95% CI	-6.38, -2.12	-8.01, -3.84	-8.01, -3.86
Versus placebo			
LS-mean difference (SE)	1.68 (1.37)	0.01 (1.36)	
95% CI	-1.00, 4.36	-2.67, 2.68	
MMRM p-value	0.220	0.997	
Month 6/Week 24			
n	426	429	439
Mean	29.53	28.83	29.00
SD	24.72	24.96	23.75
Median	26.94	24.00	25.00
Min-max	0.00-94.00	0.00-99.00	0.00-100.00
Change from Baseline			
n	424	428	436
Mean	-8.13	-7.17	-8.78
SD	25.86	25.42	25.67
Median	-4.21	-4.00	-6.21
Min-max	-83.29-78.00	-84.00-62.24	-99.01-69.00
LS-mean (SE)	-6.65 (1.13)	-7.31 (1.11)	-7.38 (1.10)
95% CI	-8.87, -4.43	-9.50, -5.13	-9.54, -5.21
Versus placebo			
LS-mean difference (SE)	0.73 (1.44)	0.06 (1.44)	
95% CI	-2.09, 3.55	-2.75, 2.88	
MMRM p-value	0.613	0.964	
Month 12/Week 48			
n	372	382	400
Mean	25.35	25.34	26.09
SD	24.68	23.61	23.95
Median	17.35	19.15	20.90
Min-max	0.00-99.00	0.00-98.91	0.00-97.87
Change from Baseline			
n	370	382	397

Table 12. Discrete Time MMRM Analysis of Change From Baseline in Pain After a 50-Foot Walk VAS Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Mean	-11.32	-10.07	-11.91
SD	27.42	25.22	24.04
Median	-7.92	-6.00	-9.00
Min-max	-88.11-56.00	-78.57-65.35	-99.01-64.00
LS-mean (SE)	-9.89 (1.17)	-10.04 (1.15)	-10.13 (1.13)
95% CI	-12.20, -7.59	-12.29, -7.78	-12.35, -7.92
Versus placebo			
LS-mean difference (SE)	0.24 (1.49)	0.10 (1.48)	
95% CI	-2.69, 3.17	-2.81, 3.01	
MMRM p-value	0.872	0.947	
Month 18/Week 72			
n	346	360	360
Mean	25.10	27.33	25.90
SD	24.00	24.65	25.16
Median	18.00	20.21	18.04
Min-max	0.00-93.62	0.00-95.92	0.00-100.00
Change from Baseline			
n	345	360	357
Mean	-11.17	-8.91	-11.86
SD	27.51	27.12	26.04
Median	-7.17	-5.26	-9.63
Min-max	-98.00-73.00	-84.69-58.51	-99.01-69.00
LS-mean (SE)	-9.83 (1.25)	-9.01 (1.22)	-9.98 (1.22)
95% CI	-12.29, -7.37	-11.41, -6.62	-12.37, -7.59
Versus placebo			
LS-mean difference (SE)	0.15 (1.62)	0.97 (1.61)	
95% CI	-3.03, 3.33	-2.18, 4.12	
MMRM p-value	0.927	0.547	
Month 24/Week 96			
n	337	341	354
Mean	24.58	23.14	23.49
SD	24.02	22.74	23.66
Median	16.33	15.31	15.92
Min-max	0.00-94.68	0.00-92.00	0.00-100.00
Change from Baseline			
n	336	340	351
Mean	-12.31	-12.86	-13.77
SD	27.61	26.73	24.53
Median	-8.96	-8.38	-12.00
Min-max	-87.00-70.85	-88.00-57.00	-84.04-60.00
LS-mean (SE)	-10.40 (1.23)	-12.67 (1.20)	-12.02 (1.19)
95% CI	-12.81, -8.00	-15.03, -10.31	-14.36, -9.69
Versus placebo			
LS-mean difference (SE)	1.62 (1.58)	-0.65 (1.57)	
95% CI	-1.47, 4.71	-3.73, 2.43	
MMRM p-value	0.304	0.679	

Table 12. Discrete Time MMRM Analysis of Change From Baseline in Pain After a 50-Foot Walk VAS Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486

LS-means, 95% CI, and p-values are from a discrete time MMRM model, with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age, and body mass index with an unstructured covariance matrix. Pain After a 50-foot Walk was a VAS that ranges from 0-100, with higher scores indicating worse pain. Decreases from Baseline indicate improvement in pain.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n =number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; VAS = visual analog scale.

The discrete time MMRM analysis of change from Baseline in Patient Global Assessment of Arthritic Condition scores for subjects in the FAS is shown in Table 13. The improvements were similar for all treatment groups, and the results were not statistically significant at any time point.

Table 13. Discrete Time MMRM Analysis of Change From Baseline in Patient Global Assessment of Arthritic Condition Score – Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
Very good	45 (9.4)	47 (9.8)	51 (10.6)
Good	150 (31.2)	169 (35.1)	152 (31.5)
Fair	209 (43.5)	199 (41.3)	207 (42.9)
Poor	66 (13.7)	59 (12.2)	69 (14.3)
Very poor	11 (2.3)	8 (1.7)	4 (0.8)
n	481	482	483
Mean (SD)	2.684 (0.904)	2.610 (0.883)	2.634 (0.883)
Median	3.000	3.000	3.000
Min-max	1.000-5.000	1.000-5.000	1.000-5.000
Month 3/Week 12			
Very good	67 (14.9)	75 (16.6)	70 (15.3)
Good	166 (36.8)	167 (36.9)	166 (36.2)
Fair	178 (39.5)	178 (39.3)	187 (40.8)
Poor	34 (7.5)	31 (6.8)	32 (7.0)
Very poor	6 (1.3)	2 (0.4)	3 (0.7)
Versus placebo			
CMH p-value	0.855	0.637	
n	451	453	458
Mean (SD)	2.437 (0.881)	2.377 (0.855)	2.415 (0.854)
Median	2.000	2.000	2.000
Min-max	1.000-5.000	1.000-5.000	1.000-5.000
Change from Baseline			
n	449	452	455
Mean (SD)	-0.232 (0.909)	-0.230 (0.816)	-0.202 (0.787)
Median	0.000	0.000	0.000
Min-max	-4.000-2.000	-3.000-3.000	-3.000-2.000
LSmean (SE)	-0.150 (0.038)	-0.198 (0.037)	-0.151 (0.037)
95% CI	-0.224, -0.076	-0.270, -0.125	-0.224, -0.079
Versus placebo			
LS-mean difference (SE)	0.001 (0.048)	-0.046 (0.048)	
95% CI	-0.093, 0.095	-0.140, 0.047	
MMRM p-value	0.984	0.330	
Month 6/Week 24			
Very good	72 (16.9)	79 (18.5)	75 (17.2)
Good	167 (39.3)	172 (40.2)	157 (35.9)
Fair	161 (37.9)	145 (33.9)	178 (40.7)
Poor	24 (5.6)	29 (6.8)	26 (5.9)
Very poor	1 (0.2)	3 (0.7)	1 (0.2)
Versus placebo			
CMH p-value	0.378	0.257	
n	425	428	437
Mean (SD)	2.329 (0.830)	2.311 (0.873)	2.362 (0.842)
Median	2.000	2.000	2.000
Min-max	1.000-5.000	1.000-5.000	1.000-5.000
Change from Baseline			
n	424	427	435
Mean (SD)	-0.337 (0.876)	-0.319 (0.857)	-0.260 (0.879)
Median	0.000	0.000	0.000
Min-max	-4.000-2.00	-3.000-3.000	-3.000-3.000

Table 13. Discrete Time MMRM Analysis of Change From Baseline in Patient Global Assessment of Arthritic Condition Score – Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
LS-mean (SE)	-0.254 (0.039)	-0.287 (0.038)	-0.204 (0.038)
95% CI	-0.330, -0.178	-0.362, -0.213	-0.278, -0.130
Versus placebo			
LS-mean difference (SE)	-0.050 (0.049)	-0.083 (0.049)	
95% CI	-0.146, 0.046	-0.180, 0.013	
MMRM p-value	0.308	0.089	
Month 12/Week 48			
Very good	78 (21.1)	78 (20.2)	65 (16.3)
Good	159 (43.0)	162 (42.0)	183 (45.9)
Fair	107 (28.9)	126 (32.6)	133 (33.3)
Poor	22 (5.9)	16 (4.1)	16 (4.0)
Very poor	4 (1.1)	4 (1.0)	2 (0.5)
Versus placebo			
CMH p-value	0.677	0.768	
n	370	386	399
Mean (SD)	2.230 (0.886)	2.238 (0.856)	2.266 (0.795)
Median	2.000	2.000	2.000
Min-max	1.000-5.000	1.000-5.000	1.000-5.000
Change from Baseline			
n	368	385	397
Mean (SD)	-0.405 (0.908)	-0.371 (0.930)	-0.370 (0.848)
Median	0.000	0.000	0.000
Min-max	-4.000-2.000	-3.000-3.000	-3.000-3.000
LS-mean (SE)	-0.326 (0.041)	-0.327 (0.040)	-0.291 (0.039)
95% CI	-0.406, -0.246	-0.405, -0.249	-0.369 (-0.214)
Versus placebo			
LS-mean difference (SE)	-0.035 (0.052)	-0.036 (0.052)	
95% CI	-0.137 (0.068)	-0.137 (0.066)	
MMRM p-value	0.508	0.490	
Month 18/Week 72			
Very good	80 (23.1)	85 (23.5)	71 (19.7)
Good	141 (40.8)	138 (38.1)	152 (42.2)
Fair	103 (29.8)	117 (32.3)	117 (32.5)
Poor	18 (5.2)	18 (5.0)	19 (5.3)
Very poor	4 (1.2)	4 (1.1)	1 (0.3)
Versus placebo			
CMH p-value	0.495	0.678	
n	346	362	360
Mean (SD)	2.205 (0.895)	2.221 (0.900)	2.242 (0.838)
Median	2.000	2.000	2.000
Min-max	1.000-5.000	1.000-5.000	1.000-5.000
Change from Baseline			
n	344	361	358
Mean (SD)	-0.442 (0.979)	-0.418 (0.934)	-0.388 (0.903)
Median	0.000	0.000	0.000
Min-max	-4.000-2.000	-4.000-2.000	-3.000-2.000
LS-mean (SE)	-0.337 (0.044)	-0.368 (0.043)	-0.318 (0.043)
95% CI	-0.424, -0.250	-0.453, -0.284	-0.402, -0.233
Versus placebo			
LS-mean difference (SE)	-0.019 (0.057)	-0.050 (0.057)	

Table 13. Discrete Time MMRM Analysis of Change From Baseline in Patient Global Assessment of Arthritic Condition Score – Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
95% CI	-0.132, 0.094	-0.162, 0.061	
MMRM p-value	0.739	0.376	
Month 24/Week 96			
Very good	88 (26.2)	75 (22.0)	89 (25.2)
Good	135 (40.2)	156 (45.7)	146 (41.4)
Fair	95 (28.3)	91 (26.7)	100 (28.3)
Poor	16 (4.8)	18 (5.3)	16 (4.5)
Very poor	2 (0.6)	1 (0.3)	2 (0.6)
Versus placebo			
CMH p-value	0.771	0.900	
n	336	341	353
Mean (SD)	2.134 (0.879)	2.161 (0.837)	2.139 (0.866)
Median	2.000	2.000	2.000
Min-max	1.000-5.000	1.000-5.000	1.000-5.000
Change from Baseline			
n	335	340	351
Mean (SD)	-0.513 (0.950)	-0.488 (0.934)	-0.473 (0.934)
Median	0.000	0.000	0.000
Min-max	-4.000-2.000	-4.000-2.000	-3.000-3.000
LS-mean (SE)	-0.421 (0.044)	-0.436 (0.044)	-0.413 (0.043)
95% CI	-0.508, -0.334	-0.521, -0.350	-0.497, -0.329
Versus placebo			
LS-mean difference (SE)	-0.008 (0.057)	-0.023 (0.057)	
95% CI	-0.121, 0.104	-0.135, 0.089	
MMRM p-value	0.883	0.690	

LS means, 95% CI, and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age, and body mass index with an unstructured covariance matrix.
CMH p-values were from the Cochran-Mantel Haenszel row means test using table scores with (collapsed) KLG and collapsed baseline values as stratification factors.
For Patient Global Assessment of Arthritic Condition, 1 = very good, 2 = good, 3 = fair, 4 = poor, 5 = very poor. Decreases from Baseline indicate improvement of arthritis.
CI = confidence interval; CMH = Cochran-Mantel Haenszel; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min= minimum; MMRM = mixed model repeated measures; N= total number of subjects in each treatment group; n =number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error.

The discrete time MMRM analysis of change from Baseline in Physician's Global Assessment of Arthritic Condition score for subjects in the FAS is presented in Table 14. Aside from superiority of the SD-6010 200 mg group at Month 6/Week 24 (p = 0.033) and Month 12/Week 48 (p = 0.038), no SD-6010 treatment effect was seen versus placebo at any of the 5 on-study time points.

Table 14. Discrete Time MMRM Analysis of Change From Baseline in Physician's Global Assessment of Arthritic Condition Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
Very good	17 (3.5%)	13 (2.7%)	14 (2.9%)
Good	119 (24.8%)	117 (24.2%)	105 (21.9%)
Fair	297 (61.9%)	295 (61.1%)	312 (65.0%)
Poor	44 (9.2%)	53 (11.0%)	46 (9.6%)
Very poor	3 (0.6%)	5 (1.0%)	3 (0.6%)
n	480	483	480
Mean	2.785	2.834	2.831
SD	0.679	0.689	0.655
Median	3.000	3.000	3.000
Min-max	1.000-5.000	1.000-5.000	(1.000-5.000)
Month 3/Week 12			
Very good	42 (9.3%)	38 (8.4%)	47 (10.3%)
Good	206 (45.6%)	212 (47.0%)	191 (41.7%)
Fair	180 (39.8%)	175 (38.8%)	204 (44.5%)
Poor	24 (5.3%)	25 (5.5%)	15 (3.3%)
Very poor	0	1 (0.2%)	1 (0.2%)
n	452	451	458
Mean	2.412	2.421	2.415
SD	0.732	0.733	0.726
Median	2.000	2.000	2.000
Min-max	1.000-4.000	1.000-5.000	1.000-5.000
Change from Baseline			
n	449	448	453
Mean	-0.379	-0.422	-0.415
SD	0.782	0.756	0.764
Median	0.000	0.000	0.000
Min-max	-4.000- 2.000	-2.000-2.000	-3.000-2.000
LS-mean (SE)	-0.394 (0.035)	-0.412 (0.034)	-0.403 (0.034)
95% CI	-0.462, -0.326	-0.479, -0.344	-0.469, -0.336
Versus placebo			
LS-mean difference (SE)	0.008 (0.044)	-0.009 (0.044)	
95% CI	-0.078, 0.095	-0.096, 0.078	
MMRM p-value	0.849	0.837	
Month 6/Week 24			
Very good	45 (10.6%)	58 (13.6%)	50 (11.5%)
Good	204 (48.2%)	198 (46.3%)	187 (43.0%)
Fair	160 (37.8%)	159 (37.1%)	183 (42.1%)
Poor	13 (3.1%)	13 (3.0%)	15 (3.4%)
Very poor	1 (0.2%)	0	0
n	423	428	435
Mean	2.340	2.297	2.375
SD	0.717	0.736	0.731
Median	2.000	2.000	2.000
Min-max	1.000-5.000	1.000-4.000	1.000-4.000
Change from Baseline			
n	420	426	431
Mean	-0.443	-0.561	-0.452
SD	0.823	0.841	0.791
Median	0.000	0.000	0.000

Table 14. Discrete Time MMRM Analysis of Change From Baseline in Physician's Global Assessment of Arthritic Condition Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Min-max	-4.000-2.000	-3.000-2.000	-3.000-2.000
LS-mean (SE)	-0.457 (0.037)	-0.543 (0.036)	-0.443 (0.036)
95% CI	-0.528, -0.385	-0.614, -0.472	-0.513, -0.373
Versus placebo			
LS-mean difference (SE)	-0.013 (0.047)	-0.100 (0.047)	
95% CI	-0.105, 0.078	-0.191, -0.008	
MMRM p-value	0.776	0.033[a]	
Month 12/Week 48			
Very good	55 (14.9%)	61 (15.7%)	48 (12.0%)
Good	193 (52.2%)	195 (50.3%)	196 (49.1%)
Fair	110 (29.7%)	119 (30.7%)	140 (35.1%)
Poor	10 (2.7%)	13 (3.4%)	15 (3.8%)
Very poor	2 (0.5%)	0	0
n	370	388	399
Mean	2.219	2.216	2.306
SD	0.746	0.743	0.728
Median	2.000	2.000	2.000
Min-max	1.000-5.000	1.000-4.000	1.000-4.000
Change from Baseline			
n	367	386	396
Mean	-0.548	-0.627	-0.535
SD	0.873	0.859	0.828
Median	-1.000	-1.000	-1.000
Min-max	-4.000-3.000	-4.000-1.000	-3.000-2.000
LS-mean (SE)	-0.573 (0.039)	-0.612 (0.038)	-0.509 (0.038)
95% CI	-0.650, -0.496	-0.687, -0.537	-0.583, -0.435
Versus placebo			
LS-mean difference (SE)	-0.064 (0.050)	-0.103 (0.050)	
95% CI	-0.163, 0.034	-0.201, -0.006	
MMRM p-value	0.201	0.038[a]	
Month 18/Week 72			
Very good	57 (16.5%)	59 (16.3%)	58 (16.2%)
Good	177 (51.3%)	174 (48.2%)	175 (48.7%)
Fair	104 (30.1%)	119 (33.0%)	111 (30.9%)
Poor	7 (2.0%)	9 (2.5%)	15 (4.2%)
Very poor	0	0	0
n	345	361	359
Mean	2.177	2.216	2.231
SD	0.720	0.740	0.766
Median	2.000	2.000	2.000
Min-max	1.000-4.000	1.000-4.000	1.000-4.000
Change from Baseline			
N	342	359	355
Mean	-0.602	-0.643	-0.628
SD	0.906	0.833	0.862
Median	-1.000	-1.000	-1.000
Min-max	-3.000-2.000	-3.000-2.000	-3.000-1.000
LS-mean (SE)	-0.598 (0.041)	-0.607 (0.040)	-0.588 (0.040)
95% CI	-0.678, -0.518	-0.685, -0.529	-0.666, -0.510
Versus placebo			

Table 14. Discrete Time MMRM Analysis of Change From Baseline in Physician's Global Assessment of Arthritic Condition Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
LS-mean difference (SE)	-0.010 (0.053)	-0.019 (0.052)	
95% CI	-0.114, 0.094	-0.122, 0.084	
MMRM p-value	0.848	0.714	
Month 24/Week 96			
Very good	70 (21.0%)	59 (17.3%)	66 (18.7%)
Good	159 (47.6%)	170 (49.7%)	179 (50.7%)
Fair	99 (29.6%)	106 (31.0%)	100 (28.3%)
Poor	6 (1.8%)	7 (2.0%)	8 (2.3%)
Very poor	0	0	0
n	334	342	353
Mean	2.123	2.178	2.142
SD	0.751	0.731	0.736
Median	2.000	2.000	2.000
Min-max	1.000-4.000	1.000-4.000	1.000-4.000
Change from Baseline			
n	331	340	349
Mean	-0.656	-0.662	-0.711
SD	0.906	0.879	0.867
Median	-1.000	-1.000	-1.000
Min-max	-4.000-1.000	-3.000-3.000	-3.000-2.000
LS-mean (SE)	-0.650 (0.042)	-0.654 (0.041)	-0.674 (0.041)
95% CI	-0.732, -0.568	-0.734, -0.573	-0.754, -0.595
Versus placebo			
LS-mean difference (SE)	0.025 (0.054)	0.021 (0.054)	
95% CI	-0.082, 0.131	-0.085, 0.127	
MMRM p-value	0.652	0.700	

LS means, 95% CI, and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age, and body mass index with an unstructured covariance matrix.
For Physician's Global Assessment of Arthritic Condition, 1=Very Good, 2=Good, 3=Fair, 4=Poor, 5=Very Poor.
Decreases from Baseline indicate improvement of arthritis.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min= minimum; MMRM = mixed model repeated measures; N= total number of subjects in each treatment group; n =number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error.
a. p-Value significant, 2-sided alpha=0.05.

The discrete time MMRM analysis of change from Baseline in OA pain assessment tool-knee joint (Intermittent and Constant Osteoarthritis Pain [ICOAP]) total score for subjects in the FAS is presented in Table 15. No SD-6010 treatment effect in comparison to placebo was apparent.

Table 15. Discrete Time MMRM Analysis of Change From Baseline in Osteoarthritis Pain Assessment Tool - Knee Joint (ICOAP) Total Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	479	480	481
Mean	39.35	36.55	38.79
SD	23.06	21.78	22.29
Median	40.91	36.36	38.64
Min-max	0.00-100.00	0.00-100.00	0.00-100.00
Month 3/Week 12			
n	452	454	454
Mean	31.96	29.63	31.36
SD	23.20	20.81	20.98
Median	29.55	27.27	29.55
Min-max	0.00-95.45	0.00-86.36	0.00-100.00
Change from Baseline			
n	448	450	449
Mean	-7.00	-6.68	-7.08
SD	19.95	17.77	18.15
Median	-4.55	-4.55	-4.55
Min-max	-86.36-54.55	-79.55-47.73	-81.82-52.27
LS-mean (SE)	-6.30 (0.89)	-7.20 (0.87)	-6.67 (0.87)
95% CI	-8.05, -4.56	-8.91, -5.50	-8.38, -4.97
Versus placebo			
LS-mean difference (SE)	0.37 (1.11)	-0.53 (1.11)	
95% CI	-1.80, 2.55	-2.70, 1.64	
MMRM p-value	0.738	0.632	
Month 6/Week 24			
n	426	424	435
Mean	29.88	29.06	30.14
SD	22.58	21.93	21.24
Median	27.27	25.00	27.27
Min-max	0.00-100.00	0.00-86.36	0.00-100.00
Change from Baseline			
n	422	422	430
Mean	-9.09	-7.74	-8.27
SD	21.43	19.36	19.68
Median	-6.82	-4.55	-6.82
Min-max	-86.36-52.27	-84.09-61.36	-75.00-56.82
LS-mean (SE)	-8.33 (0.95)	-8.21 (0.94)	-7.92 (0.93)
95% CI	-10.20, -6.45	-10.05, -6.36	-9.75, -6.09
Versus placebo			
LS-mean difference (SE)	-0.41 (1.21)	-0.29 (1.21)	
95% CI	-2.77, 1.96	-2.66, 2.08	
MMRM p-value	0.736	0.811	
Month 12/Week 48			
n	369	387	401
Mean	24.88	25.43	26.79
SD	22.10	20.70	20.93
Median	18.18	22.73	25.00
Min-max	0.00-100.00	0.00-95.45	0.00-95.45
Change from Baseline			
n	365	384	397

Table 15. Discrete Time MMRM Analysis of Change From Baseline in Osteoarthritis Pain Assessment Tool - Knee Joint (ICOAP) Total Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Mean	-13.00	-10.84	-12.26
SD	21.93	20.58	20.24
Median	-11.36	-9.09	-9.09
Min-max	-77.27-50.00	-79.55-40.91	-90.91-50.00
LS-mean (SE)	-12.35 (1.00)	-11.19 (0.97)	-11.13 (0.96)
95% CI	-14.32, -10.39	-13.09, -9.28	-13.02, -9.25
Versus placebo			
LS-mean difference (SE)	-1.22 (1.27)	-0.05 (1.26)	
95% CI	-3.71, 1.26	-2.52, 2.41	
MMRM p-value	0.335	0.966	
Month 18/Week 72			
n	346	361	362
Mean	24.44	27.13	27.49
SD	22.05	22.40	21.15
Median	18.18	22.73	25.00
Min-max	0.00-97.73	0.00-95.45	0.00-97.73
Change from Baseline			
n	342	359	359
Mean	-12.71	-9.59	-11.23
SD	22.64	21.26	22.13
Median	-11.36	-9.09	-9.09
Min-max	-75.00-47.73	-79.55-70.45	-90.91-54.55
LS-mean (SE)	-11.93 (1.08)	-10.36 (1.05)	-10.49 (1.04)
95% CI	-14.04, -9.82	-12.41, -8.31	-12.53, -8.45
Versus placebo			
LS-mean difference (SE)	-1.44 (1.38)	0.13 (1.37)	
95% CI	-4.16, 1.28	-2.56, 2.82	
MMRM p-value	0.299	0.925	
Month 24/Week 96			
n	334	342	352
Mean	23.84	23.85	24.85
SD	21.79	21.44	21.39
Median	18.18	18.18	20.45
Min-max	0.00-97.73	0.00-81.82	0.00-100.00
Change from Baseline			
n	330	340	349
Mean	-13.02	-12.87	-13.79
SD	22.30	21.53	21.81
Median	-11.36	-10.23	-11.36
Min-max	-79.55-52.27	-79.55-43.18	-72.73-56.82
LS-mean (SE)	-12.44 (1.08)	-13.50 (1.05)	-13.02 (1.04)
95% CI	-14.56, -10.33	-15.56, -11.43	-15.07, -10.98
Versus placebo			
LS-mean difference (SE)	0.58 (1.39)	-0.47 (1.38)	
95% CI	-2.14, 3.30	-3.18, 2.23	
MMRM p-value	0.676	0.732	

Table 15. Discrete Time MMRM Analysis of Change From Baseline in Osteoarthritis Pain Assessment Tool - Knee Joint (ICOAP) Total Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486

LS-Means, 95% CI and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix.
The Osteoarthritis Pain Assessment Tool-Knee Joint (ICOAP) Total Score ranges from 0-100, with higher scores indicating worse pain.
Decreases from Baseline indicate improvement in pain.
CI = confidence interval; KLG = Kellgren and Lawrence grade; ICOAP = Intermittent and Constant Osteoarthritis Pain; max = maximum; min = minimum; LS = least squares; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error.

The discrete time MMRM analysis of change from Baseline in Osteoarthritis Research Society International (OARSI) knee function survey score for subjects in the FAS is presented in Table 16. No treatment effect was apparent.

Table 16. Discrete Time MMRM Analysis of Change From Baseline in OARSI Knee Function Survey Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	382	376	391
Mean	22.19	21.49	21.80
SD	8.96	8.59	8.92
Median	22.00	22.00	22.00
Min-max	0.00-43.00	0.00-44.00	0.00-44.00
Month 3/Week 12			
n	346	354	349
Mean	19.51	19.21	18.96
SD	9.88	8.88	9.60
Median	20.00	20.00	19.00
Min-max	0.00-42.00	0.00-41.00	0.00-43.00
Change from Baseline			
n	309	304	315
Mean	-2.20	-2.24	-2.99
SD	7.70	6.57	7.12
Median	-2.00	-2.00	-2.00
Min-max	-37.00-23.00	-28.00-18.00	-29.00-23.00
LS-mean (SE)	-2.00 (0.43)	-2.45 (0.42)	-2.97 (0.42)
95% CI	-2.84, -1.16	-3.28, -1.62	-3.79, -2.15
Versus placebo			
LS-mean difference (SE)	0.97 (0.53)	0.52 (0.54)	
95% CI	-0.07, 2.02	-0.53, 1.57	
MMRM p-value	0.069	0.335	
Month 6/Week 24			
n	307	328	329
Mean	18.79	18.17	18.50
SD	9.93	9.65	9.61
Median	19.00	19.00	19.00
Min-max	0.00-43.00	0.00-44.00	0.00-43.00
Change from Baseline			
n	270	283	294
Mean	-3.24	-3.29	-3.53
SD	8.42	7.80	8.26
Median	-2.00	-3.00	-3.00
Min-max	-35.00-23.00	-35.00-16.00	-30.00-18.00
LS-mean (SE)	-2.65 (0.49)	-3.28 (0.48)	-3.54 (0.47)
95% CI	-3.61, -1.69	-4.22, -2.34	-4.46, -2.62
Versus placebo			
LS-mean difference (SE)	0.89 (0.62)	0.26 (0.62)	
95% CI	-0.33, 2.11	-0.95, 1.47	
MMRM p-value	0.153	0.672	
Month 12/Week 48			
n	270	310	308
Mean	17.23	17.12	17.70
SD	9.60	9.51	9.72
Median	17.00	17.00	17.00
Min-max	0.00-43.00	0.00-42.00	0.00-43.00
Change from Baseline			
n	240	263	266

Table 16. Discrete Time MMRM Analysis of Change From Baseline in OARSI Knee Function Survey Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Mean	-4.57	-4.35	-4.46
SD	8.65	7.76	7.99
Median	-4.00	-4.00	-4.00
Min-max	-27.00-21.00	-27.00-17.00	-29.00-19.00
LS-mean (SE)	-4.25 (0.50)	-4.18 (0.48)	-4.44 (0.48)
95% CI	-5.23, -3.28	-5.12, -3.24	-5.37, -3.51
Versus placebo			
LS-mean difference (SE)	0.19 (0.63)	0.26 (0.62)	
95% CI	-1.05, 1.43	-0.96, 1.49	
MMRM p-value	0.765	0.675	
Month 18/Week 72			
n	257	281	279
Mean	16.71	16.59	17.17
SD	9.93	9.66	10.09
Median	16.00	16.00	17.00
Min-max	0.00-44.00	0.00-40.00	0.00-44.00
Change from Baseline			
n	225	239	243
Mean	-5.14	-4.61	-4.93
SD	9.37	8.56	9.22
Median	-5.00	-4.00	-5.00
Min-max	-33.00-26.00	-28.00-22.00	-28.00-18.00
LS-mean (SE)	-4.37 (0.56)	-4.23 (0.54)	-4.80 (0.54)
95% CI	-5.47, -3.28	-5.30, -3.17	-5.85, -3.74
Versus placebo			
LS-mean difference (SE)	0.42 (0.72)	0.56 (0.72)	
95% CI	-1.00, 1.84	-0.84, 1.97	
MMRM p-value	0.560	0.433	
Month 24/Week 96			
n	257	261	270
Mean	16.16	16.60	16.06
SD	10.33	9.70	9.96
Median	15.00	17.00	16.00
Min-max	0.00-44.00	0.00-44.00	0.00-43.00
Change from Baseline			
n	227	224	237
Mean	-5.31	-5.13	-5.62
SD	9.40	8.36	9.28
Median	-5.00	-4.00	-5.00
Min-max	-40.00-27.00	-29.00-18.00	-28.00-15.00
LS-mean (SE)	-5.02 (0.56)	-4.99 (0.55)	-5.75 (0.54)
95% CI	-6.11, -3.93	-6.08, -3.91	-6.81, -4.68
Versus placebo			
LS-mean difference (SE)	0.73 (0.73)	0.75 (0.73)	
95% CI	-0.70, 2.16	-0.68, 2.18	
MMRM p-value	0.318	0.303	

Table 16. Discrete Time MMRM Analysis of Change From Baseline in OARSI Knee Function Survey Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486

LS-Means, 95% CI and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix. The OARSI Knee Function Survey ranges from 0-44, with higher scores indicating worse knee function. Decreases from Baseline indicate improvement in knee function.
CI = confidence interval; KLG = Kellgren and Lawrence grade; max = maximum; min = minimum; LS = least squares; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n = number of evaluable subjects at each time point; OARSI = Osteoarthritis Research Society International; QD = once daily; SD = standard deviation; SE = standard error.

The discrete time MMRM analyses of change from Baseline in Short-Form-36 domains and summary scores are presented in Table 17, Table 18, Table 19, Table 20, Table 21, Table 22, Table 23, Table 24, Table 25, and Table 26. Except for significant improvements over placebo in the SF-36 mental health component and social functioning domain scores at Month 12/Week 48 for subjects in the SD-6010 50 mg QD treatment group (p=0.023 and p=0.030, respectively), no SD-6010 treatment effects were apparent when compared to placebo.

Table 17. Discrete Time MMRM Analysis of Change From Baseline in SF-36 Physical Function Domain Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	481	482	485
Mean	35.67	36.84	36.32
SD	9.74	9.42	9.15
Median	34.60	36.65	36.65
Min-max	16.18-57.11	16.18-57.11	16.18-57.11
Month 12/Week 48			
n	370	382	398
Mean	38.78	39.30	38.96
SD	9.57	9.90	9.69
Median	38.69	38.69	38.69
Min-max	16.18-57.11	16.18-57.11	16.18-57.11
Change from Baseline			
n	368	381	397
Mean	2.59	2.41	2.55
SD	8.80	8.66	8.84
Median	2.05	2.05	2.05
Min-max	-26.60-34.79	-28.65-40.93	-28.65-40.93
LS-mean (SE)	2.62 (0.47)	2.64 (0.45)	2.57 (0.45)
95% CI	1.69, 3.54	1.75, 3.53	1.69, 3.45
Versus placebo			
LS-mean difference (SE)	0.04 (0.57)	0.07 (0.56)	
95% CI	-1.07, 1.16	-1.04, 1.17	
MMRM p-value	0.938	0.906	
Month 24/Week 96			
n	334	342	352
Mean	39.91	39.87	40.15
SD	10.27	9.93	10.12
Median	40.74	38.69	40.74
Min-max	16.18-57.11	16.18-57.11	16.18-57.11
Change from Baseline			
n	332	341	352
Mean	3.53	3.23	3.51
SD	9.50	9.66	9.54
Median	4.09	2.05	4.09
Min-max	-34.79-34.79	-24.56-32.74	-26.60-28.65
LS-mean (SE)	3.45 (0.52)	3.41 (0.50)	3.67 (0.50)
95% CI	2.43, 4.47	2.42, 4.40	2.70, 4.65
Versus placebo			
LS-mean difference (SE)	-0.23 (0.65)	-0.26 (0.64)	
95% CI	-1.50, 1.04	-1.52, 1.00	
MMRM p-value	0.726	0.681	

LS-Means, 95% CI and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix.
The SF-36 Physical Function domain score was a norm-based (50, 10) score, with higher scores indicating better physical function.
Increases from Baseline indicate improvement in physical function.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; SF-36 = Short form-36.

Table 18. Discrete Time MMRM Analysis of Change From Baseline in SF-36 Role-Physical Domain Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	481	482	485
Mean	39.99	40.37	40.14
SD	9.85	9.73	10.03
Median	39.92	39.92	39.92
Min-max	18.45-56.62	18.45-56.62	18.45-56.62
Month 12/Week 48			
n	370	382	398
Mean	42.55	42.84	42.45
SD	10.16	9.58	10.03
Median	42.31	42.31	42.31
Min-max	18.45-56.62	18.45-56.62	18.45-56.62
Change from Baseline			
n	368	381	397
Mean	2.06	2.35	2.22
SD	9.55	8.75	8.85
Median	2.39	2.39	2.39
Min-max	-23.86-28.63	-21.48-28.63	-38.18-38.18
LS-mean (SE)	1.98 (0.48)	2.27 (0.46)	1.90 (0.45)
95% CI	1.04, 2.91	1.37, 3.17	1.02, 2.79
Versus placebo			
LS-mean difference (SE)	0.07 (0.58)	0.36 (0.58)	
95% CI	-1.07, 1.21	-0.77, 1.50	
MMRM p-value	0.900	0.528	
Month 24/Week 96			
n	335	342	352
Mean	42.78	42.91	43.09
SD	10.24	9.85	9.69
Median	42.31	42.31	42.31
Min-max	18.45-56.62	18.45-56.62	18.45-56.62
Change from Baseline			
n	333	341	352
Mean	2.44	2.44	2.70
SD	9.53	9.34	9.35
Median	2.39	2.39	2.39
Min-max	-28.63-33.41	-38.18-35.79	-33.41-33.41
LS-mean (SE)	2.22 (0.50)	2.38 (0.49)	2.51 (0.48)
95% CI	1.24, 3.20	1.43, 3.34	1.57, 3.45
Versus placebo			
LS-mean difference (SE)	-0.29 (0.62)	-0.12 (0.62)	
95% CI	-1.51, 0.94	-1.34, 1.09	
MMRM p-value	0.647	0.841	

LS-Means, 95% CI and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix.
The SF-36 Role-Physical domain score is a norm-based (50, 10) score, with higher scores indicating better role-physical. Increases from Baseline indicate improvement in role-physical.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; SF-36 = Short form-36.

Table 19. Discrete Time MMRM Analysis of Change From Baseline in SF-36 Bodily Pain Domain Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	481	482	485
Mean	38.81	39.77	38.90
SD	8.63	8.34	8.22
Median	36.31	40.47	36.73
Min-max	19.23-60.88	19.23-60.88	19.23-60.88
Month 12/Week 48			
n	370	382	398
Mean	43.42	43.60	43.15
SD	9.47	9.21	9.46
Median	45.06	45.06	42.77
Min-max	19.23-60.88	19.23-60.88	19.23-60.88
Change from Baseline			
n	368	381	397
Mean	4.07	3.72	4.06
SD	9.64	8.32	8.97
Median	4.17	4.17	4.17
Min-max	-29.99-32.49	-17.91-25.82	-21.66-34.99
LS-mean (SE)	4.44 (0.48)	4.36 (0.47)	4.12 (0.46)
95% CI	3.49, 5.39	3.44, 5.27	3.22, 5.02
Versus placebo			
LS-mean difference (SE)	0.32 (0.59)	0.24 (0.58)	
95% CI	-0.84, 1.48	-0.91, 1.38	
MMRM p-value	0.587	0.687	
Month 24/Week 96			
n	334	342	352
Mean	43.70	44.28	43.72
SD	9.44	9.98	9.27
Median	45.06	45.06	45.06
Min-max	19.23-60.88	19.23-60.88	19.23-60.88
Change from Baseline			
n	332	341	352
Mean	4.25	4.65	4.46
SD	9.54	9.90	9.44
Median	4.17	4.17	4.17
Min-max	-21.66-34.99	-22.08-32.49	-34.99- 32.49
LS-mean (SE)	4.36 (0.52)	5.10 (0.51)	4.63 (0.50)
95% CI	3.33, 5.39	4.10, 6.10	3.65, 5.62
Versus placebo			
LS-mean difference (SE)	-0.27 (0.65)	0.47 (0.65)	
95% CI	-1.56, 1.01	-0.80, 1.74	
MMRM p-value	0.677	0.469	

LS-Means, 95% CI and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix.
The SF-36 Bodily Pain domain score is a norm-based (50, 10) score, with higher scores indicating better bodily pain. Increases from Baseline indicate improvement in bodily pain.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; SF-36 = Short form-36.

Table 20. Discrete Time MMRM Analysis of Change From Baseline in SF-36 General Health Domain Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	481	481	484
Mean	44.77	46.49	45.19
SD	10.15	9.79	9.63
Median	45.87	48.22	45.87
Min-max	16.75-63.72	16.75-63.72	21.45-63.72
Month 12/Week 48			
n	369	382	397
Mean	46.51	47.36	46.21
SD	9.71	9.31	9.52
Median	45.87	48.22	45.87
Min-max	16.75-63.72	21.45-63.72	21.45-63.72
Change from Baseline			
n	367	381	395
Mean	1.33	1.10	1.20
SD	7.52	7.64	6.93
Median	0.00	0.00	0.00
Min-max	-21.14-31.47	-18.79-29.12	-19.73-23.49
LS-mean (SE)	1.03 (0.40)	1.28 (0.38)	0.80 (0.38)
95% CI	0.25, 1.80	0.54, 2.03	0.06, 1.53
Versus placebo			
LS-mean difference (SE)	0.23 (0.48)	0.49 (0.48)	
95% CI	-0.71, 1.17	-0.45, 1.42	
MMRM p-value	0.632	0.308	
Month 24/Week 96			
n	333	342	352
Mean	45.93	46.66	46.53
SD	9.68	10.01	9.73
Median	45.87	48.22	47.75
Min-max	16.75-63.72	19.10-63.72	21.45-63.72
Change from Baseline			
n	331	341	352
Mean	1.13	0.40	1.25
SD	8.43	7.76	7.77
Median	0.00	0.00	0.94
Min-max	-28.18-29.12	-23.49-31.47	-24.43-22.08
LS-mean (SE)	0.70 (0.43)	0.54 (0.42)	0.97 (0.41)
95% CI	-0.15, 1.55	-0.28, 1.36	0.16, 1.78
Versus placebo			
LS-mean difference (SE)	-0.27 (0.54)	-0.43 (0.53)	
95% CI	-1.33, 0.79	-1.48,0.62	
MMRM p-value	0.615	0.425	

LS-Means, 95% CI and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix.
The SF-36 General Health domain score is a norm-based (50, 10) score, with higher scores indicating better general health. Increases from Baseline indicate improvement in general health.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; SF-36 = Short form-36.

Table 21. Discrete Time MMRM Analysis of Change From Baseline in SF-36 Vitality Domain Score- Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	481	481	484
Mean	47.57	49.00	48.08
SD	9.44	9.20	9.53
Median	48.96	48.96	48.96
Min-max	22.02-69.92	22.02-69.92	22.02-69.92
Month 12/Week 48			
n	370	382	397
Mean	49.82	49.78	49.19
SD	9.07	9.48	9.38
Median	48.96	50.46	48.96
Min-max	22.02-69.92	25.01-69.92	22.02-69.92
Change from Baseline			
n	368	381	396
Mean	1.52	0.48	1.04
SD	8.51	8.04	8.22
Median	0.00	0.00	0.00
Min-max	-26.94-44.90	-23.95-41.91	-26.94-35.92
LS-mean (SE)	1.83 (0.44)	1.15 (0.43)	1.17 (0.42)
95% CI	0.97, 2.70	0.31, 1.99	0.34, 1.99
Versus placebo			
LS-mean difference (SE)	0.67 (0.54)	-0.01 (0.53)	
95% CI	-0.39, 1.72	-1.06, 1.03	
MMRM p-value	0.214	0.980	
Month 24/Week 96			
n	334	342	352
Mean	49.88	50.14	49.45
SD	9.08	9.45	9.80
Median	51.95	51.95	48.96
Min-max	22.02-69.92	22.02-69.92	22.02-69.92
Change from Baseline			
n	332	340	351
Mean	1.53	0.78	1.42
SD	8.71	8.62	8.70
Median	0.00	0.00	0.00
Min-max	-26.94-44.90	-32.93-32.93	-23.95-35.92
LS-mean (SE)	1.85 (0.47)	1.51 (0.46)	1.52 (0.45)
95% CI	0.92, 2.78	0.60, 2.41	0.63, 2.41
Versus placebo			
LS-mean difference (SE)	0.33 (0.59)	-0.01 (0.59)	
95% CI	-0.83, 1.49	-1.16, 1.14	
MMRM p-value	0.575	0.986	

LS-Means, 95% CI and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix.
The SF-36 Vitality domain score is a norm-based (50, 10) score, with higher scores indicating better vitality.
Increases from Baseline indicate improvement in vitality.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; SF-36 = Short form-36.

Table 22. Discrete Time MMRM Analysis of Change From Baseline in SF-36 Social Functioning Domain Score- Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	481	482	485
Mean	45.15	46.23	45.64
SD	11.06	10.19	10.36
Median	45.65	45.65	45.65
Min-max	13.38-56.40	13.38-56.40	13.38-56.40
Month 12/Week 48			
n	370	382	398
Mean	46.77	46.25	45.62
SD	10.42	9.69	10.54
Median	51.03	45.65	45.65
Min-max	13.38-56.40	18.76-56.40	13.38-56.40
Change from Baseline			
n	368	381	397
Mean	1.11	-0.28	-0.15
SD	10.28	9.16	9.74
Median	0.00	0.00	0.00
Min-max	-32.27-43.02	-32.27- 26.89	-37.64- 32.27
LS-mean (SE)	0.62 (0.50)	-0.28 (0.48)	-0.71 (0.48)
95% CI	-0.37, 1.60	-1.23, 0.67	-1.64, 0.23
Versus placebo			
LS-mean difference (SE)	1.33 (0.61)	0.43 (0.60)	
95% CI	0.13, 2.52	-0.76, 1.61	
MMRM p-value	0.030[a]	0.480	
Month 24/Week 96			
n	335	342	352
Mean	46.90	47.13	45.91
SD	10.66	9.82	10.53
Median	51.03	51.03	45.65
Min-max	13.38-56.40	18.76-56.40	13.38-56.40
Change from Baseline			
n	333	341	352
Mean	1.31	0.88	0.12
SD	10.62	10.15	10.03
Median	0.00	0.00	0.00
Min-max	-43.02- 43.02	-32.27- 26.89	-37.64- 32.27
LS-mean (SE)	0.54 (0.54)	0.58 (0.52)	-0.46 (0.51)
95% CI	-0.51, 1.60	-0.44, 1.60	-1.47, 0.55
Versus placebo			
LS-mean difference (SE)	1.01 (0.67)	1.04 (0.66)	
95% CI	-0.30, 2.32	-0.26, 2.34	
MMRM p-value	0.132	0.117	

LS-Means, 95% CI and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix.
The SF-36 Social Function domain score is a norm-based (50, 10) score, with higher scores indicating better social function.
Increases from Baseline indicate improvement in social function.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; SF-36 = Short form-36.
a. p-Value significant, 2-sided alpha=0.05.

Table 23. Discrete Time MMRM Analysis of Change From Baseline in SF-36 Role-Emotional Domain Score- Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	481	482	485
Mean	43.73	43.27	43.37
SD	12.79	12.09	12.35
Median	48.11	44.32	44.32
Min-max	10.25-55.68	10.25-55.68	10.25-55.68
Month 12/Week 48			
n	370	382	397
Mean	44.56	43.55	43.05
SD	12.05	11.55	11.92
Median	48.11	44.32	44.32
Min-max	10.25-55.68	10.25-55.68	10.25-55.68
Change from Baseline			
n	368	381	396
Mean	0.05	-0.18	-0.25
SD	12.06	10.55	11.47
Median	0.00	0.00	0.00
Min-max	-45.43-45.43	-37.86-30.29	-37.86-45.43
LS-mean (SE)	0.13 (0.58)	-0.49 (0.56)	-0.93 (0.55)
95% CI	-1.01, 1.26	-1.58, 0.61	-2.01, 0.15
Versus placebo			
LS-mean difference (SE)	1.06 (0.71)	0.44 (0.70)	
95% CI	(-0.32, 2.44)	-0.93, 1.82	
MMRM p-value	0.133	0.524	
Month 24/Week 96			
n	335	342	352
Mean	44.31	44.24	43.39
SD	12.23	11.84	12.20
Median	44.32	44.32	44.32
Min-max	10.25-55.68	10.25-55.68	10.25-55.68
Change from Baseline			
n	333	341	352
Mean	-0.28	0.60	0.32
SD	12.77	11.69	11.98
Median	0.00	0.00	0.00
Min-max	-45.43-45.43	-34.07-34.07	-45.43-45.43
LS-mean (SE)	-0.26 (0.62)	0.27 (0.61)	-0.51 (0.60)
95% CI	-1.48, 0.97	-0.92, 1.46	-1.68, 0.66
Versus placebo			
LS-mean difference (SE)	0.26 (0.78)	0.78 (0.77)	
95% CI	-1.27, 1.78	-0.73, 2.30	
MMRM p-value	0.743	0.310	

LS-Means, 95% CI and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix.
The SF-36 Role-Emotional domain score is a norm-based (50, 10) score, with higher scores indicating better role-emotional.
Increases from Baseline indicate improvement in role-emotional.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; SF-36 = Short form-36.

Table 24. Discrete Time MMRM Analysis of Change From Baseline in SF-36 Mental Health Domain Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	481	481	484
Mean	47.01	47.70	47.26
SD	10.80	10.73	11.15
Median	49.58	49.58	49.58
Min-max	8.02-63.43	10.79-63.43	10.79-63.43
Month 12/Week 48			
n	370	382	397
Mean	48.32	48.20	47.25
SD	10.58	10.34	11.22
Median	50.96	49.58	49.58
Min-max	13.56-63.43	19.10-63.43	16.33-63.43
Change from Baseline			
n	368	381	396
Mean	0.95	0.19	-0.31
SD	10.08	9.10	9.50
Median	0.00	0.00	0.00
Min-max	-33.25-44.33	-41.56-30.48	-36.02-41.56
LS-mean (SE)	0.64 (0.51)	0.23 (0.49)	-0.53 (0.48)
95% CI	-0.35, 1.64	-0.73, 1.19	-1.47, 0.42
Versus placebo			
LS-mean difference (SE)	1.17 (0.62)	0.76 (0.61)	
95% CI	-0.04, 2.38	-0.44, 1.96	
MMRM p-value	0.058	0.213	
Month 24/Week 96			
n	334	342	352
Mean	48.29	48.42	47.56
SD	10.41	10.75	11.46
Median	49.58	49.58	49.58
Min-max	13.56-63.43	10.79-63.43	13.56-63.43
Change from Baseline			
n	332	340	351
Mean	1.12	0.26	-0.01
SD	10.26	10.01	9.81
Median	0.00	0.00	0.00
Min-max	-36.02-44.33	-36.02-33.25	-36.02-38.79
LS-mean (SE)	0.79 (0.54)	0.31 (0.52)	-0.19 (0.52)
95% CI	-0.27, 1.85	-0.72, 1.34	-1.20, 0.82
Versus placebo			
LS-mean difference (SE)	0.98 (0.67)	0.50 (0.67)	
95% CI	-0.33, 2.30	-0.80, 1.81	
MMRM p-value	0.143	0.450	

LS-Means, 95% CI and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix.
The SF-36 Mental Health domain score is a norm-based (50, 10) score, with higher scores indicating better mental health. Increases from Baseline indicate improvement in mental health.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; SF-36 = Short form-36.

Table 25. Discrete Time MMRM Analysis of Change From Baseline in SF-36 Physical Health Component Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	481	480	483
Mean	37.38	38.69	37.84
SD	8.84	8.35	8.46
Median	37.15	38.48	37.65
Min-max	11.83-61.35	14.55-59.22	11.50-63.58
Month 12/Week 48			
n	369	382	397
Mean	41.13	41.92	41.49
SD	8.55	9.00	8.74
Median	41.21	42.49	41.59
Min-max	15.66-60.76	14.95-61.84	14.51-62.37
Change from Baseline			
n	367	381	395
Mean	3.26	3.31	3.58
SD	7.98	7.69	7.87
Median	2.86	2.56	3.47
Min-max	-24.84-27.80	-17.81- 33.13	-25.92- 33.98
LS-mean (SE)	3.32 (0.42)	3.66 (0.41)	3.51 (0.40)
95% CI	2.49, 4.14	2.87, 4.46	2.73, 4.29
Versus placebo			
LS-mean difference (SE)	-0.20 (0.51)	0.15 (0.50)	
95% CI	-1.19, 0.80	-0.84, 1.14	
MMRM p-value	0.701	0.764	
Month 24/Week 96			
n	331	342	352
Mean	41.68	42.04	42.36
SD	9.13	8.92	8.63
Median	41.77	41.78	42.46
Min-max	10.36- 62.37	20.18-64.15	17.26-62.85
Change from Baseline			
n	329	340	351
Mean	3.77	3.66	4.18
SD	8.48	8.32	8.48
Median	3.57	3.58	3.64
Min-max	-27.08-32.28	-30.34-35.59	-30.70-33.55
LS-mean (SE)	3.61 (0.46)	3.93 (0.44)	4.30 (0.44)
95% CI	2.72, 4.51	(3.06, 4.80)	3.44, 5.15
Versus placebo			
LS-mean difference (SE)	-0.68 (0.57)	-0.37 (0.56)	
95% CI	-1.80, 0.43	-1.47, 0.74	
MMRM p-value	0.228	0.514	

LS-Means, 95% CI and p-values are from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix.
The SF-36 Physical Health Component score is a norm-based (50, 10) score, with higher scores indicating better physical health.
Increases from Baseline indicate improvement in physical health.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; SF-36 = Short form-36.

Table 26. Discrete Time MMRM Analysis of Change From Baseline in SF-36 Mental Health Component Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	481	480	483
Mean	49.65	49.97	49.65
SD	11.79	11.11	11.62
Median	52.34	51.52	52.02
Min-max	8.77-68.82	14.24-70.67	12.27-69.58
Month 12/Week 48			
n	369	382	397
Mean	50.12	49.27	48.48
SD	10.86	10.60	11.13
Median	52.52	51.48	49.31
Min-max	15.63-68.37	19.76-70.25	19.38-74.59
Change from Baseline			
n	367	381	395
Mean	-0.13	-1.17	-1.27
SD	10.64	9.48	9.65
Median	-0.45	-0.57	-0.84
Min-max	-34.35-44.50	-38.66-35.41	-33.93-31.65
LS-mean (SE)	-0.32 (0.51)	-1.21 (0.50)	-1.74 (0.49)
95% CI	-1.33, 0.69	-2.18, -0.23	-2.70, -0.78
Versus placebo			
LS-mean difference (SE)	1.42 (0.62)	0.53 (0.62)	
95% CI	0.19, 2.65	-0.68, 1.75	
MMRM p-value	0.023[a]	0.391	
Month 24/Week 96			
n	331	342	352
Mean	49.78	49.81	48.50
SD	11.04	10.79	11.62
Median	52.40	52.71	51.00
Min-max	13.80-69.46	13.23-69.75	13.02-69.77
Change from Baseline			
n	329	340	351
Mean	-0.41	-0.70	-1.09
SD	11.24	10.08	10.18
Median	-0.30	-0.29	-0.65
Min-max	-36.19-54.21	-37.50-30.03	-45.34-37.10
LS-mean (SE)	-0.63 (0.55)	-0.78 (0.54)	-1.65 (0.53)
95% CI	-1.72, 0.45	-1.84, 0.28	-2.69, -0.61
Versus placebo			
LS-mean difference (SE)	1.02 (0.69)	0.87 (0.68)	
95% CI	-0.34, 2.37	-0.47, 2.21	
MMRM p-value	0.142	0.204	

LS-Means, 95% CI and p-values ae from a discrete time MMRM model with fixed effects for treatment group, visit, a treatment group × visit interaction, (collapsed) KLG, a (collapsed) KLG × visit interaction, baseline value, geographic region, gender, age and body mass index with an unstructured covariance matrix.
The SF-36 Mental Health Component score is a norm-based (50, 10) score, with higher scores indicating better mental health.
Increases from Baseline indicate improvement in mental health.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; MMRM = mixed model repeated measures; N = total number of subjects in each treatment group; n = number of evaluable subjects at each time point; QD = once daily; SD = standard deviation; SE = standard error; SF-36 = Short form-36.
a. p-Value significant, 2-sided alpha=0.05.

A summary of the EQ-5D domain scores is presented in Table 27, Table 28, Table 29, Table 30, Table 31, Table 32. The results were similar across treatment groups.

Table 27. Summary of EQ-5D Mobility Domain Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
	n (%)	n (%)	n (%)
Baseline			
No problem	132 (27.4)	135 (28.1)	163 (33.6)
Some problems	348 (72.3)	345 (71.7)	322 (66.4)
Confined to bed	1 (0.2)	1 (0.2)	0
Missing	4	5	1
Month 12/Week 48			
No problem	174 (46.9)	186 (48.7)	178 (44.6)
Some problems	197 (53.1)	196 (51.3)	221 (55.4)
Confined to bed	0	0	0
Missing	114	104	87
Month 24/Week 96			
No problem	167 (50.0)	161 (47.2)	178 (50.4)
Some problems	165 (49.4)	180 (52.8)	175 (49.6)
Confined to bed	2 (0.6)	0	0
Missing	151	145	133

EQ-5D = EuroQol-5 dimension; N = number of subjects in each treatment group; n = number of subjects meeting specific criteria; QD = once daily.

Table 28. Summary of EQ-5D Self-Care Domain Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
	n (%)	n (%)	n (%)
Baseline			
No problem	383 (79.8)	387 (80.5)	386 (79.6)
Some problems	92 (19.2)	93 (19.3)	97 (20.0)
Unable to wash/dress	5 (1.0)	1 (0.2)	2 (0.4)
Missing	5	5	1
Month 12/Week 48			
No problem	305 (82.2)	327 (85.6)	331 (83.0)
Some problems	66 (17.8)	51 (13.4)	67 (16.8)
Unable to wash/dress	0	4 (1.0)	1 (0.3)
Missing	114	104	87
Month 24/Week 96			
No problem	280 (83.8)	286 (83.9)	299 (84.9)
Some problems	54 (16.2)	55 (16.1)	51 (14.5)
Unable to wash/dress	0	0	2 (0.6)
Missing	151	145	134

EQ-5D = EuroQol-5 dimension; N = number of subjects in each treatment group; n = number of subjects meeting specific criteria; QD = once daily.

Table 29. Summary of EQ-5D Usual Activity Domain Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
	n (%)	n (%)	n (%)
Baseline			
No problem	186 (38.7)	185 (38.5)	190 (39.2)
Some problems	285 (59.3)	291 (60.5)	289 (59.6)
Unable to perform usual activities	10 (2.1)	5 (1.0)	6 (1.2)
Missing	4	5	1
Month 12/Week 48			
No problem	192 (51.8)	201 (52.6)	193 (48.4)
Some problems	176 (47.4)	180 (47.1)	204 (51.1)
Unable to perform usual activities	3 (0.8)	1 (0.3)	2 (0.5)
Missing	114	104	87
Month 24/Week 96			
No problem	187 (56.0)	186 (54.7)	205 (58.2)
Some problems	140 (41.9)	151 (44.4)	144 (40.9)
Unable to performed usual activities	7 (2.1)	3 (0.9)	3 (0.9)
Missing	151	146	134

EQ-5D = EuroQol-5 dimension; N = number of subjects in each treatment group; n = number of subjects meeting specific criteria; QD = once daily.

Table 30. Summary of EQ-5D Pain/Discomfort Domain Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
	n (%)	n (%)	n (%)
Baseline			
No pain/discomfort	42 (8.7)	48 (10.0)	38 (7.8)
Moderate pain/discomfort	383 (79.6)	391 (81.3)	403 (83.1)
Extreme pain/discomfort	56 (11.6)	42 (8.7)	44 (9.1)
Missing	4	5	1
Month 12/Week 48			
No pain/discomfort	91 (24.5)	89 (23.3)	82 (20.6)
Moderate pain/discomfort	259 (69.8)	280 (73.3)	293 (73.4)
Extreme pain/discomfort	21 (5.7)	13 (3.4)	24 (6.0)
Missing	114	104	87
Month 24/Week 96			
No pain/discomfort	92 (27.5)	89 (26.1)	98 (27.8)
Moderate pain/discomfort	226 (67.7)	232 (68.0)	240 (68.2)
Extreme pain/discomfort	16 (4.8)	20 (5.9)	14 (4.0)
Missing	151	145	134

EQ-5D = EuroQol-5 dimension; N = number of subjects in each treatment group; n = number of subjects meeting specific criteria; QD = once daily.

Table 31. Summary of EQ-5D Anxiety/Depression Domain Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
	n (%)	n (%)	n (%)
Baseline			
Not anxious/depressed	297 (61.7)	306 (63.6)	303 (62.5)
Moderately anxious/depressed	166 (34.5)	164 (34.1)	168 (34.6)
Extremely anxious/depressed	18 (3.7)	11 (2.3)	14 (2.9)
Missing	4	5	1
Month 12/Week 48			
Not anxious/depressed	251 (67.7)	256 (67.0)	261 (65.4)
Moderately anxious/depressed	111 (29.9)	116 (30.4)	127 (31.8)
Extremely anxious/depressed	9 (2.4)	10 (2.6)	11 (2.8)
Missing	114	104	87
Month 24/Week 96			
Not anxious/depressed	235 (70.4)	244 (71.6)	237 (67.3)
Moderately anxious/depressed	93 (27.8)	89 (26.1)	109 (31.0)
Extremely anxious/depressed	6 (1.8)	8 (2.3)	6 (1.7)
Missing	151	145	134

EQ-5D = EuroQol-5 dimension; N = number of subjects in each treatment group; n = number of subjects meeting specific criteria; QD = once daily.

Table 32. Summary of EQ-5D VAS Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	480	479	484
Mean (SD)	66.75 (21.52)	68.59 (19.69)	67.86 (19.36)
Median	70.0	70.0	70.0
Min-max	0.0-100	2.0-100	1.0-100
Month 12/Week 48			
n	369	381	399
Mean (SD)	72.34 (19.01)	72.55 (19.48)	70.58 (19.91)
Median	75.0	75.0	75.0
Min-max	5.0-100	1.0-100	5.0-100
Month 24/Week 96			
n	334	341	352
Mean (SD)	73.18 (19.64)	73.95 (18.85)	72.36 (19.36)
Median	80.0	79.0	75.0
Min-max	5.0-100	6.0-100	8.0-100

The EQ-5D VAS score is a VAS that ranges from 0-100, with higher scores indicating a better health state.
EQ-5D = EuroQol-5 dimension; max = maximum; min = minimum; N = number of subjects in each treatment group; n = number of evaluable subjects at specific time point; QD = once daily; SD = standard deviation; VAS = visual analog scale.

There were similar increases in total analgesic medication burden apparent in all treatment groups at both time points assessed for subjects in the FAS (Table 33).

Table 33. Logistic Regression Analyses of Total Analgesic Medication Burden Increase - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
	n (%)	n (%)	n (%)
Baseline			
OA knee pain medication	485	486	486
No pain medications	106 (21.9%)	128 (26.3%)	110 (22.6%)
Symptomatic slow-acting drugs for OA	41 (8.5%)	37 (7.6%)	40 (8.2%)
Acetaminophen	101 (20.8%)	98 (20.2%)	98 (20.2%)
Duloxetine	0	0	0
NSAIDs/Coxibs/ASA	304 (62.7%)	295 (60.7%)	309 (63.6%)
Weak opioids	33 (6.8%)	16 (3.3%)	24 (4.9%)
Strong opioids	4 (0.8%)	5 (1.0%)	3 (0.6%)
Glucocorticoids	1 (0.2%)	1 (0.2%)	1 (0.2%)
Month 12/Week 48			
OA knee pain medication	372	395	408
No pain medications	96 (25.8%)	121 (30.6%)	115 (28.2%)
Symptomatic slow-acting drugs for OA	30 (8.1%)	30 (7.6%)	31 (7.6%)
Acetaminophen	68 (18.3%)	75 (19.0%)	79 (19.4%)
Duloxetine	0	0	0
NSAIDs/Coxibs/ASA	223 (59.9%)	220 (55.7%)	238 (58.3%)
Weak opioids	20 (5.4%)	17 (4.3%)	21 (5.1%)
Strong opioids	5 (1.3%)	6 (1.5%)	4 (1.0%)
Glucocorticoids	3 (0.8%)	1 (0.3%)	2 (0.5%)
Added a class	17 (4.6%)	26 (6.6%)	16 (3.9%)
More in a class	4 (1.1%)	3 (0.8%)	8 (2.0%)
Increase in medication burden			
Yes	21 (5.6%)	29 (7.3%)	24 (5.9%)
No	351 (94.4%)	366 (92.7%)	384 (94.1%)
Missing	113	91	78
LS-mean Pr (Resp)	3.2%	4.3%	3.4%
95% CI	1.8%, 5.8%	2.5%, 7.3%	(1.9%, 5.9%)
Versus placebo			
Adjusted OR	0.952	1.273	
95% CI	0.516, 1.756	0.721, 2.247	
p-Value	0.875	0.406	
Month 24/Week 96			
OA knee pain medication	344	353	354
No pain medications	89 (25.9%)	99 (28.0%)	110 (31.1%)
Symptomatic slow-acting drugs for OA	25 (7.3%)	28 (7.9%)	25 (7.1%)
Acetaminophen	57 (16.6%)	69 (19.5%)	70 (19.8%)
Duloxetine	0	0	0
NSAIDs/Coxibs/ASA	209 (60.8%)	206 (58.4%)	196 (55.4%)
Weak opioids	21 (6.1%)	14 (4.0%)	18 (5.1%)
Strong opioids	6 (1.7%)	7 (2.0%)	7 (2.0%)
Glucocorticoids	2 (0.6%)	2 (0.6%)	1 (0.3%)
Added a class	17 (4.9%)	28 (7.9%)	21 (5.9%)
More in a class	7 (2.0%)	6 (1.7%)	9 (2.5%)
Increase in medication burden			
Yes	24 (7.0%)	34 (9.6%)	30 (8.5%)

Table 33. Logistic Regression Analyses of Total Analgesic Medication Burden Increase - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
	n (%)	n (%)	n (%)
No	320 (93.0%)	319 (90.4%)	324 (91.5%)
Missing	141	133	132
LS-Mean Pr (Resp)	5.3%	7.5%	6.6%
95% CI	3.2%, 8.5%	4.9%, 11.4%	4.3%, 10.1%
Versus placebo			
Adjusted OR	0.787	1.154	
95% CI	0.448, 1.384	0.685, 1.942	
p-Value	0.406	0.591	

Estimated Pr (Resp), adjusted OR, 95% CI and p-values are from a logistic regression model, with treatment group, (collapsed) KLG, geographic region, and gender as factors, age and body mass index as covariates. Medications used in the 28 days leading up to and including the Baseline visit were included in the analyses. Medications used for the entire 28 day period leading up to and including the post-randomization visit, or for injections, used at any time during the 28 day period were included in the analyses.
ASA = acetylsalicylic acid; CI = confidence interval; Coxib = cyclooxygenase-2 inhibitors; KLG = Kellgren and Lawrence grade; LS = least squares; N = number of subjects in each treatment group;
NSAID = nonsteroidal anti-inflammatory drug; OA = osteoarthritis; OR = odds ratio; Pr = probability; QD = once daily; Resp = response.

There were no SD-6010 treatment effects versus placebo observed in the analysis of covariance (ANCOVA) on Patient Global Impression of Change score for subjects in the FAS (Table 34). Similarly, there were no SD-6010 treatment effects versus placebo observed in the analysis of response on Patient Global Impression of Change for subjects in the FAS. Outcome Measures in Rheumatology-Osteoarthritis Research Society International Responder Index (OMERACT-OARSI) results are presented in Table 35. The results were similar across the 3 treatment groups.

Table 34. Analysis of Covariance of Patient Global Impression of Change Score - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Patient Global Impression			
n	434	426	434
Mean	2.97	3.02	3.00
SD	1.26	1.34	1.35
Median	3.00	3.00	3.00
Min-max	1.00-7.00)	1.00-7.00	1.00-7.00
LS-mean (SE)	2.86 (0.07)	2.92 (0.07)	2.89 (0.07)
95% CI	2.72, 3.01	2.77, 3.06	2.75, 3.03
Versus placebo			
LS-mean difference (SE)	-0.03 (0.09)	0.02 (0.09)	
95% CI	-0.21, 0.14	-0.15, 0.20	
p-Value	0.709	0.798	

LS-Means, 95% CI and p-values are from an analysis of covariance model, with treatment group, (collapsed) KLG, geographic region, and gender as factors and age and body mass index as covariates.
For the Patient Global Impression of Change, 1=Very Much Improved, 2=Much Improved, 3=Minimally Improved, 4=No Change, 5=Minimally Worse, 6=Much Worse, 7=Very Much Worse, 8=Missing.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; max = maximum; min = minimum; N = number of subjects in each treatment group; n = number of evaluable subjects; QD = once daily; SD = standard deviation; SE = standard error.

Table 35. Analysis of OMERACT-OARSI Responder Index - Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
	n (%)	n (%)	n (%)
Pain Response	469	470	471
High response	125 (26.7%)	127 (27.0%)	115 (24.4%)
Improvement	126 (26.9%)	109 (23.2%)	110 (23.4%)
No improvement	218 (46.5%)	234 (49.8%)	246 (52.2%)
Missing	16	16	15
Function Response	468	468	470
High response	89 (19.0%)	97 (20.7%)	90 (19.1%)
Improvement	112 (23.9%)	100 (21.4%)	113 (24.0%)
No improvement	267 (57.1%)	271 (57.9%)	267 (56.8%)
Missing	17	18	16
Global Improvement Response	468	468	471
Improvement	206 (44.0%)	206 (44.0%)	201 (42.7%)
No improvement	262 (56.0%)	262 (56.0%)	270 (57.3%)
Missing	17	18	15
OMERACT-OARSI Response	468	469	470
Responder	222 (47.4%)	226 (48.2%)	219 (46.6%)
Non-responder	246 (52.6%)	243 (51.8%)	251 (53.4%)
Missing	17	17	16
LS-mean Pr (resp)	48.4%	49.2%	47.6%
95% CI	43.0%, 53.8%	43.9%, 54.5%	42.3%, 52.9%
Versus placebo			
Adjusted OR	1.032	1.068	
95% CI	0.797, 1.337	0.824, 1.383	
p-Value	0.810	0.620	

Estimated Pr (Response), adjusted OR, 95% CI and p-values are from a logistic regression model, with treatment group, (collapsed) KLG, geographic region, and gender as factors, age and body mass index as covariates.
For the WOMAC Pain Subscale Score, a high responsewas a decrease from Baseline of at least 4 points that was also a 50% reduction from Baseline; an improvement was a decrease from Baseline of at least 2 points that was also a 20% reduction from Baseline.
For the WOMAC Physical Function Subscale Score, a high response was a decrease from Baseline of at least 14 points that was also a 50% reduction from Baseline; an improvement was a decrease of at least 7 points that was also a 20% reduction from Baseline.
For the Patient Global Assessment of Arthritic Condition, an improvement was a decrease of 1 point that was also 20% reduction from Baseline.
An OMERACT-OARSI responder was defined as a high response on the WOMAC Pain Subscale score, a high response on the WOMAC Physical Function Subscale Score, or improvement on at least 2 of the 3 domains.
CI = confidence interval; KLG = Kellgren and Lawrence grade; LS = least squares; N = number of subjects in each treatment group; n = number of subjects meeting specific criteria; OMERACT-OARSI = Outcome Measures in Rheumatology-Osteoarthritis Research Society International; OR = odds ratio; Pr = probability; QD = once daily; Resp = response; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

The analysis of JSN progressors in the FAS is shown in Table 36. Statistically significantly fewer JSN progressors were observed in the SD-6010 50 mg QD treatment group, compared to placebo (p=0.047). No difference was observed between the SD-6010 200 mg QD treatment group and placebo (p=0.317).

Table 36. Analysis of JSN Progressors – Full Analysis Set

	SD-6010 50 mg QD N=485	SD-6010 200 mg QD N=486	Placebo N=486
Baseline			
n	481	477	481
Mean (SD)	3.169 (0.746)	3.195 (0.741)	3.221 (0.709)
Median	3.160	3.180	3.200
Min-max	1.560-5.410	1.550-5.980	1.430-5.280
Last post-baseline observation			
n	432	429	434
Mean (SD)	2.979 (0.971)	2.975 (0.905)	3.011 (0.900)
Median	3.050	2.980	3.035
Min-max	0.00-5.270	0.00-5.040	0.00-5.040
Change from Baseline			
n	419	423	429
Mean (SD)	-0.180 (0.474)	-0.201 (0.438)	-0.205 (0.455)
Median	-0.050	-0.090	-0.100
Min-max	-3.180-0.900	-2.690-0.790	-2.560-1.310
Joint space narrowing progressor			
Progression	136 (32.5)	153 (36.2)	165 (38.5)
Non-progression	283 (67.5)	270 (63.8)	264 (61.5)
Missing	66	63	57
Estimated Pr (Resp)	33.7	37.1	40.6
95% CI	28.5, 39.5	31.8, 42.8	35.1, 46.3
Versus placebo			
Adjusted OR	0.745	0.864	
95% CI for OR	0.557, 0.997	0.650, 1.150	
p-Value	0.047[a]	0.317	

Estimated Pr (resp), adjusted OR, 95% CI, and p-values are from a logistic regression model, with treatment group, (collapsed) KLG, geographic region, and gender as factors; baseline JSW, age, and body mass index as covariates.
JSW was measured in millimeters.
JSN progressors were those subjects with a decrease from Baseline greater than the SDD (0.199 mm). The SDD was defined as 1.96 × square root (2) × the within subject standard deviation determined from the test-retest JSW data.
CI = confidence interval; JSN = joint space narrowing; JSW = joint space width; KLG = Kellgren and Lawrence grade; max = maximum; min = minimum; N = number of subjects in each treatment group; n = number of evaluable subjects at specific time point; OR = odds ratio; Pr = probability; QD = once daily; Resp = response; SD = standard deviation; SDD = smallest detectable difference.
a. p-Value significant, 2-sided alpha=0.05.

The number of subjects who were considered potential candidates for virtual joint replacement was the same for the SD-6010 50 mg QD treatment group and the placebo group (28 subjects each, 6.9% and 6.6%, respectively), and was slightly higher for the SD-6010 200 mg QD treatment group (34 subjects, 8.3%). There were no statistically significant differences between the SD-6010 treatment groups and placebo.

Safety Results: A summary of all-causality SAEs is presented in Table 37.

Table 37. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With AEs By: System Organ Class and MedDRA (v14.1) Preferred Term	SD-6010 50 mg QD N=482	SD-6010 200 mg QD N=485	Placebo N=485
Number (%) of subjects:			
Evaluable for adverse events	482	485	485
With adverse events	43 (8.9)	61 (12.6)	49 (10.1)
Blood and lymphatic system disorders	0	0	1 (0.2)
Anaemia	0	0	1 (0.2)
Coagulopathy	0	0	1 (0.2)
Thrombocytopenia	0	0	1 (0.2)
Cardiac disorders	2 (0.4)	12 (2.5)	8 (1.6)
Acute myocardial infarction	0	2 (0.4)	0
Angina unstable	0	1 (0.2)	0
Arrhythmia	0	0	1 (0.2)
Atrial fibrillation	1 (0.2)	1 (0.2)	3 (0.6)
Bradyarrhythmia	0	0	1 (0.2)
Bradycardia	0	0	1 (0.2)
Cardiac arrest	0	0	1 (0.2)
Cardiac disorder	0	1 (0.2)	0
Cardiac failure	0	1 (0.2)	0
Cardiac failure chronic	0	0	1 (0.2)
Cardiac failure congestive	0	1 (0.2)	0
Coronary artery disease	0	0	2 (0.4)
Coronary artery occlusion	0	0	1 (0.2)
Coronary artery stenosis	1 (0.2)	0	0
Myocardial infarction	0	3 (0.6)	1 (0.2)
Prinzmetal angina	0	1 (0.2)	0
Ventricular tachycardia	0	1 (0.2)	0
Ear and labyrinth disorders	0	1 (0.2)	0
Vertigo	0	1 (0.2)	0
Gastrointestinal disorders	6 (1.2)	4 (0.8)	5 (1.0)
Abdominal hernia	0	0	1 (0.2)
Colonic polyp	1 (0.2)	0	0
Constipation	1 (0.2)	0	0
Diverticulum	1 (0.2)	0	0
Duodenal ulcer	0	1 (0.2)	0
Gastric disorder	0	0	1 (0.2)
Gastric ulcer	0	0	1 (0.2)
Gastritis	0	1 (0.2)	0
Gastritis erosive	0	0	1 (0.2)
Gastrointestinal haemorrhage	0	0	1 (0.2)
Gastrooesophageal reflux disease	1 (0.2)	1 (0.2)	0
Hernial eventration	1 (0.2)	0	0
Hiatus hernia	0	0	1 (0.2)
Internal hernia	0	0	1 (0.2)
Pancreatitis acute	1 (0.2)	0	0
Small intestinal obstruction	1 (0.2)	1 (0.2)	0
Umbilical hernia	0	1 (0.2)	0
Vomiting	0	0	1 (0.2)
General disorders and administration site conditions	4 (0.8)	7 (1.4)	3 (0.6)
Chest pain	4 (0.8)	3 (0.6)	2 (0.4)

Table 37. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With AEs By: System Organ Class and MedDRA (v14.1) Preferred Term	SD-6010 50 mg QD N=482	SD-6010 200 mg QD N=485	Placebo N=485
Device dislocation	0	1 (0.2)	0
Fatigue	0	1 (0.2)	0
Medical device complication	0	1 (0.2)	0
Non-cardiac chest pain	0	1 (0.2)	0
Pyrexia	0	0	1 (0.2)
Hepatobiliary disorders	2 (0.4)	4 (0.8)	0
Cholecystitis	0	2 (0.4)	0
Cholelithiasis	1 (0.2)	2 (0.4)	0
Gallbladder polyp	1 (0.2)	0	0
Infections and infestations	6 (1.2)	13 (2.7)	8 (1.6)
Abdominal abscess	0	0	1 (0.2)
Abdominal wall abscess	1 (0.2)	0	0
Abscess limb	0	1 (0.2)	0
Appendicitis	1 (0.2)	2 (0.4)	0
Clostridium difficile colitis	0	1 (0.2)	0
Diverticulitis	0	2 (0.4)	1 (0.2)
Enterocolitis infectious	0	0	1 (0.2)
Gastric ulcer helicobacter	1 (0.2)	0	0
Gastroenteritis	1 (0.2)	0	0
Helicobacter infection	0	1 (0.2)	0
Infectious peritonitis	0	0	1 (0.2)
Meningitis bacterial	0	0	1 (0.2)
Osteomyelitis	0	1 (0.2)	0
Pneumonia	1 (0.2)	2 (0.4)	0
Pseudomembranous colitis	0	1 (0.2)	0
Pyelonephritis	0	1 (0.2)	0
Sepsis	0	0	1 (0.2)
Septic shock	1 (0.2)	0	0
Tonsillitis	0	1 (0.2)	0
Urinary tract infection	0	2 (0.4)	0
Viral infection	0	0	1 (0.2)
Wound infection	0	0	1 (0.2)
Injury, poisoning and procedural complications	9 (1.9)	4 (0.8)	7 (1.4)
Anastomotic ulcer	0	0	1 (0.2)
Ankle fracture	1 (0.2)	0	0
Arthropod bite	1 (0.2)	0	0
Clavicle fracture	0	1 (0.2)	0
Comminuted fracture	0	1 (0.2)	0
Concussion	0	0	1 (0.2)
Contusion	0	1 (0.2)	0
Craniocerebral injury	0	1 (0.2)	0
Deep vein thrombosis postoperative	1 (0.2)	0	0
Fall	2 (0.4)	2 (0.4)	0
Femoral neck fracture	1 (0.2)	0	0
Femur fracture	0	1 (0.2)	0
Laceration	0	1 (0.2)	0
Ligament injury	0	1 (0.2)	0
Limb injury	0	0	1 (0.2)

Table 37. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With AEs By: System Organ Class and MedDRA (v14.1) Preferred Term	SD-6010 50 mg QD N=482	SD-6010 200 mg QD N=485	Placebo N=485
Meniscus lesion	1 (0.2)	1 (0.2)	1 (0.2)
Operative haemorrhage	0	0	1 (0.2)
Radius fracture	1 (0.2)	0	1 (0.2)
Rib fracture	1 (0.2)	1 (0.2)	0
Skull fracture	0	1 (0.2)	0
Splenic rupture	0	0	1 (0.2)
Tendon rupture	1 (0.2)	0	0
Ulna fracture	1 (0.2)	0	0
Investigations	1 (0.2)	0	2 (0.4)
Blood pressure increased	1 (0.2)	0	1 (0.2)
Borrelia test positive	0	0	1 (0.2)
Metabolism and nutrition disorders	0	1 (0.2)	1 (0.2)
Dehydration	0	1 (0.2)	0
Diabetic ketoacidosis	0	0	1 (0.2)
Musculoskeletal and connective tissue disorders	8 (1.7)	8 (1.6)	10 (2.1)
Arthralgia	2 (0.4)	3 (0.6)	2 (0.4)
Intervertebral disc protrusion	0	1 (0.2)	0
Limb discomfort	0	0	1 (0.2)
Musculoskeletal chest pain	0	1 (0.2)	1 (0.2)
Osteoarthritis	6 (1.2)	1 (0.2)	7 (1.4)
Osteonecrosis	0	1 (0.2)	0
Rhabdomyolysis	0	1 (0.2)	0
Spinal column stenosis	0	1 (0.2)	0
Systemic lupus erythematosus	0	0	1 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	4 (0.8)	7 (1.4)	10 (2.1)
Adenocarcinoma	0	1 (0.2)	0
Basal cell carcinoma	1 (0.2)	0	2 (0.4)
Breast cancer	1 (0.2)	2 (0.4)	2 (0.4)
Chronic lymphocytic leukaemia	0	1 (0.2)	0
Endometrial cancer	0	0	1 (0.2)
Lung neoplasm malignant	0	1 (0.2)	0
Malignant melanoma	0	1 (0.2)	0
Malignant melanoma in situ	1 (0.2)	0	0
Nasal cavity cancer	1 (0.2)	0	0
Neoplasm malignant	0	0	1 (0.2)
Ovarian cancer stage III	0	0	1 (0.2)
Prostate cancer recurrent	0	0	1 (0.2)
Squamous cell carcinoma	0	0	1 (0.2)
Thyroid cancer	0	0	1 (0.2)
Uterine cancer	0	0	1 (0.2)
Uterine leiomyoma	0	1 (0.2)	0
Nervous system disorders	6 (1.2)	6 (1.2)	5 (1.0)
Cerebral haemorrhage	0	1 (0.2)	0
Facial paresis	0	1 (0.2)	0
Haemorrhagic stroke	1 (0.2)	0	0
Lacunar infarction	0	0	1 (0.2)
Loss of consciousness	0	0	1 (0.2)

Table 37. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With AEs By: System Organ Class and MedDRA (v14.1) Preferred Term	SD-6010 50 mg QD N=482	SD-6010 200 mg QD N=485	Placebo N=485
Orthostatic intolerance	0	0	1 (0.2)
Presyncope	1 (0.2)	1 (0.2)	0
Sciatica	0	1 (0.2)	0
Spinal cord compression	1 (0.2)	0	0
Spinal vascular disorder	1 (0.2)	0	0
Subarachnoid haemorrhage	0	1 (0.2)	0
Transient ischaemic attack	1 (0.2)	1 (0.2)	2 (0.4)
Tremor	1 (0.2)	0	0
Psychiatric disorders	1 (0.2)	1 (0.2)	1 (0.2)
Depression	1 (0.2)	0	0
Mental status changes	0	0	1 (0.2)
Suicide attempt	0	1 (0.2)	0
Renal and urinary disorders	0	3 (0.6)	1 (0.2)
Bladder perforation	0	1 (0.2)	0
Haematuria	0	1 (0.2)	0
Renal failure	0	1 (0.2)	1 (0.2)
Urinary incontinence	0	1 (0.2)	0
Urinary retention	0	1 (0.2)	0
Urogenital disorder	0	1 (0.2)	0
Reproductive system and breast disorders	1 (0.2)	6 (1.2)	2 (0.4)
Cystocele	0	3 (0.6)	0
Endometrial disorder	0	0	1 (0.2)
Metrorrhagia	1 (0.2)	2 (0.4)	0
Uterine haemorrhage	0	1 (0.2)	1 (0.2)
Uterine prolapse	0	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	1 (0.2)	0	3 (0.6)
Asthma	1 (0.2)	0	0
Dyspnoea	0	0	2 (0.4)
Lung disorder	0	0	1 (0.2)
Vascular disorders	1 (0.2)	4 (0.8)	0
Deep vein thrombosis	1 (0.2)	1 (0.2)	0
Hypertension	0	2 (0.4)	0
Hypertensive crisis	0	1 (0.2)	0

Subjects are only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v14.1) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; QD = once daily; v = version.

The incidence of treatment-related SAEs is presented in Table 38.

Table 38. Incidence of Treatment-Related Serious Adverse Events - Safety Analysis Set

Number (%) of Subjects With AEs By: System Organ Class and MedDRA (v14.1) Preferred Term	SD-6010 50 mg QD N=482	SD-6010 200 mg QD N=485	Placebo N=485
Cardiac disorders	0	3 (0.6)	0
Acute myocardial infarction	0	1 (0.2)	0
Myocardial infarction	0	2 (0.4)	0
General disorders and administration site conditions	0	0	1 (0.2)
Chest pain	0	0	1 (0.2)
Injury, poisoning and procedural complications	0	1 (0.2)	0
Femur fracture	0	1 (0.2)	0
Investigations	1 (0.2)	0	1 (0.2)
Blood pressure increased	1 (0.2)	0	1 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (0.2)	1 (0.2)
Chronic lymphocytic leukaemia	0	1 (0.2)	0
Prostate cancer recurrent	0	0	1 (0.2)
Nervous system disorders	0	1 (0.2)	0
Transient ischaemic attack	0	1 (0.2)	0
Vascular disorders	1 (0.2)	0	0
Deep vein thrombosis	1 (0.2)	0	0
Total preferred term events	2	6	3

Subjects were counted only once in each row.
All data on or after the first dose of study medication are included.
MedDRA (v14.1) coding dictionary applied.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; QD = once daily; v = version.

The incidence of treatment-emergent AEs (all causalities) was similar across treatment groups (Table 39).

Table 39. Treatment-Emergent Adverse Events (All Causalities) – Safety Analysis Set

Number (%) of Subjects	SD-6010 50 mg QD	SD-6010 200 mg QD	Placebo
Subjects evaluable for AEs	482	485	485
Number of AEs	1466	1561	1369
Subjects with AEs	371 (77.0)	381 (78.6)	364 (75.1)
Subjects with SAEs	43 (8.9)	61 (12.6)	49 (10.1)
Subjects with severe AEs	71 (14.7)	79 (16.3)	70 (14.4)
Subjects discontinued due to AEs	41 (8.5)	55 (11.3)	40 (8.2)
Subjects with dose interruption due to AEs	65 (13.5)	72 (14.8)	59 (12.2)
Subjects with dose reduction due to AEs	6 (1.2)	18 (3.7)	13 (2.7)

All data on or after the first dose of study medication were included.
Except for the number of AEs, subjects were counted only once in each row.
SAEs – according to the Investigator's assessment.
MedDRA (v14.1) coding dictionary was applied.
SAE/non-SAE results are not separated out.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; SAE = serious adverse event; v = version.

The incidence of treatment-emergent, treatment-related AEs was similar across treatment groups (Table 40).

Table 40. Treatment-Emergent Adverse Events (Treatment-Related) – Safety Analysis Set

Number (%) of Subjects	SD-6010 50 mg QD	SD-6010 200 mg QD	Placebo
Subjects evaluable for AEs	482	485	485
Number of AEs	209	174	148
Subjects with AEs	111 (23.0)	100 (20.6)	91 (18.8)
Subjects with SAEs	2 (0.4)	6 (1.2)	3 (0.6)
Subjects with severe AEs	7 (1.5)	7 (1.4)	5 (1.0)
Subjects discontinued due to AEs	15 (3.1)	23 (4.7)	19 (3.9)
Subjects with dose interruption due to AEs	20 (4.1)	16 (3.3)	12 (2.5)
Subjects with dose reduction due to AEs	6 (1.2)	14 (2.9)	11 (2.3)

All data on or after the first dose of study medication were included.
Except for the number of AEs, subjects were counted only once per treatment in each row.
SAEs – according to the Investigator's assessment.
MedDRA (v14.1) coding dictionary was applied.
SAE/non-SAE results are not separated out.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; SAE = serious adverse event; v= version.

A summary of all-causality treatment-emergent AEs that were experienced by ≥2% of subjects in any treatment group is provided in Table 41.

Table 41. Treatment-Emergent Non-Serious Adverse Events Occurring in ≥2% of Subjects in Any Treatment Group by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With AEs By: System Organ Class and MedDRA (v14.1) Preferred Term	SD-6010 50 mg QD N=482	SD-6010 200 mg QD N=485	Placebo N=485
Number (%) of subjects:			
Evaluable for adverse events	482	485	485
With adverse events	365 (75.7)	371 (76.5)	360 (74.2)
Gastrointestinal disorders	103 (21.4)	117 (24.1)	104 (21.4)
Abdominal pain	8 (1.7)	11 (2.3)	14 (2.9)
Abdominal pain upper	9 (1.9)	13 (2.7)	12 (2.5)
Diarrhoea	22 (4.6)	27 (5.6)	29 (6.0)
Dyspepsia	10 (2.1)	14 (2.9)	14 (2.9)
Gastritis	4 (0.8)	11 (2.3)	4 (0.8)
Gastrooesophageal reflux disease	10 (2.1)	12 (2.5)	9 (1.9)
Nausea	20 (4.1)	15 (3.1)	14 (2.9)
Vomiting	9 (1.9)	12 (2.5)	3 (0.6)
General disorders and administration site conditions	52 (10.8)	52 (10.7)	46 (9.5)
Fatigue	10 (2.1)	12 (2.5)	13 (2.7)
Oedema peripheral	15 (3.1)	15 (3.1)	19 (3.9)
Infections and infestations	176 (36.5)	180 (37.1)	163 (33.6)
Bronchitis	25 (5.2)	30 (6.2)	20 (4.1)
Influenza	13 (2.7)	12 (2.5)	14 (2.9)
Nasopharyngitis	33 (6.8)	41 (8.5)	25 (5.2)
Pharyngitis	7 (1.5)	16 (3.3)	7 (1.4)
Sinusitis	18 (3.7)	18 (3.7)	14 (2.9)
Upper respiratory tract infection	40 (8.3)	31 (6.4)	30 (6.2)
Urinary tract infection	24 (5.0)	21 (4.3)	26 (5.4)
Injury, poisoning, and procedural complications	63 (13.1)	86 (17.7)	71 (14.6)
Contusion	12 (2.5)	12 (2.5)	10 (2.1)
Fall	26 (5.4)	41 (8.5)	28 (5.8)
Ligament sprain	8 (1.7)	11 (2.3)	7 (1.4)
Investigations	54 (11.2)	74 (15.3)	57 (11.8)
Blood pressure increased	13 (2.7)	24 (4.9)	21 (4.3)
Gamma-glutamyltransferase increased	0	10 (2.1)	4 (0.8)
Musculoskeletal and connective tissue disorders	165 (34.2)	167 (34.4)	182 (37.5)
Arthralgia	69 (14.3)	65 (13.4)	66 (13.4)
Back pain	31 (6.4)	32 (6.6)	43 (8.9)
Bursitis	12 (2.5)	2 (0.4)	7 (1.4)
Joint swelling	14 (2.9)	8 (1.6)	7 (1.4)
Muscle spasms	12 (2.5)	9 (1.9)	3 (0.6)
Musculoskeletal pain	12 (2.5)	13 (2.7)	17 (3.5)
Neck pain	6 (1.2)	12 (2.5)	7 (1.4)
Osteoarthritis	21 (4.4)	23 (4.7)	14 (2.9)
Pain in extremity	13 (2.7)	19 (3.9)	21 (4.3)
Tendonitis	9 (1.9)	14 (2.9)	11 (2.3)
Nervous system disorders	86 (17.8)	80 (16.5)	63 (13.0)
Dizziness	17 (3.5)	22 (4.5)	11 (2.3)
Headache	32 (6.6)	27 (5.6)	18 (3.7)
Sciatica	4 (0.8)	10 (2.1)	2 (0.4)
Psychiatric disorders	26 (5.4)	27 (5.6)	19 (3.9)
Depression	12 (2.5)	12 (2.5)	6 (1.2)

Table 41. Treatment-Emergent Non-Serious Adverse Events Occurring in ≥2% of Subjects in Any Treatment Group by System Organ Class and Preferred Term (All Causalities)

Number (%) of Subjects With AEs By: System Organ Class and MedDRA (v14.1) Preferred Term	SD-6010 50 mg QD N=482	SD-6010 200 mg QD N=485	Placebo N=485
Respiratory, thoracic and mediastinal disorders	53 (11.0)	47 (9.7)	34 (7.0)
Cough	10 (2.1)	9 (1.9)	8 (1.6)
Skin and subcutaneous tissue disorders	45 (9.3)	43 (8.9)	46 (9.5)
Rash	13 (2.7)	12 (2.5)	8 (1.6)
Vascular disorders	47 (9.8)	39 (8.0)	36 (7.4)
Hypertension	34 (7.1)	27 (5.6)	19 (3.9)

Subjects were counted only once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v14.1) coding dictionary was applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in each treatment group; QD = once daily; v = version.

A summary of treatment-related treatment-emergent AEs that were experienced by ≥2% of subjects in any treatment group is provided in Table 42.

Table 42. Incidence of Treatment-Emergent Adverse Events in ≥2% of Subjects in Any Treatment Group (Treatment-Related) – Safety Analysis Set

Number (%) of Subjects With AEs By: System Organ Class and MedDRA (v14.1) Preferred Term	SD-6010 50 mg QD N=482	SD-6010 200 mg QD N=485	Placebo N=485
Investigations	20 (4.1)	30 (6.2)	25 (5.2)
Blood pressure increased	7 (1.5)	12 (2.5)	13 (2.7)
Nervous system disorders	24 (5.0)	20 (4.1)	16 (3.3)
Headache	14 (2.9)	8 (1.6)	8 (1.6)
Vascular disorders	22 (4.6)	13 (2.7)	14 (2.9)
Hypertension	20 (4.1)	10 (2.1)	11 (2.3)

Subjects were counted only once in each row.
All data on or after the first dose of study medication were included.
MedDRA (v14.1) coding dictionary was applied.
SAE/non-SAE results are not separated out.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects in each treatment group; QD = once daily; SAE = serious adverse event; v = version.

A summary of all-causality treatment-emergent AEs leading to discontinuation from the study is provided in Table 43.

Table 43. Treatment-Emergent Adverse Events Leading to Discontinuation From the Study (All Causalities) – Safety Analysis Set

Number (%) of Subjects With AEs By: System Organ Class and MedDRA (v14.1) Preferred Term	SD-6010 50 mg QD N=482	SD-6010 200 mg QD N=485	Placebo N=485
Blood and lymphatic system disorders	1 (0.2)	1 (0.2)	1 (0.2)
Eosinophilia	0	0	1 (0.2)
Leukocytosis	0	1 (0.2)	0
Neutropenia	1 (0.2)	0	0
Cardiac disorders	1 (0.2)	8 (1.6)	1 (0.2)
Acute myocardial infarction	0	1 (0.2)	0
Angina unstable	0	1 (0.2)	0
Cardiac flutter	1 (0.2)	0	0
Myocardial infarction	0	3 (0.6)	0
Palpitations	0	3 (0.6)	1 (0.2)
Gastrointestinal disorders	6 (1.2)	12 (2.5)	8 (1.6)
Abdominal discomfort	0	1 (0.2)	1 (0.2)
Abdominal pain	1 (0.2)	0	0
Abdominal pain upper	0	1 (0.2)	1 (0.2)
Colitis	1 (0.2)	1 (0.2)	0
Constipation	0	0	1 (0.2)
Diarrhoea	2 (0.4)	2 (0.4)	1 (0.2)
Dyspepsia	0	2 (0.4)	2 (0.4)
Enteritis	0	1 (0.2)	0
Flatulence	0	0	1 (0.2)
Gastritis	1 (0.2)	2 (0.4)	0
Gastrointestinal haemorrhage	1 (0.2)	0	0
Gastrooesophageal reflux disease	0	0	1 (0.2)
Haematochezia	0	0	1 (0.2)
Nausea	1 (0.2)	4 (0.8)	1 (0.2)
Pancreatitis chronic	1 (0.2)	0	0
Vomiting	0	1 (0.2)	1 (0.2)
General disorders and administration site conditions	2 (0.4)	4 (0.8)	3 (0.6)
Chest pain	0	1 (0.2)	0
Fatigue	0	1 (0.2)	0
Irritability	1 (0.2)	0	0
Medical device complication	0	1 (0.2)	0
Oedema peripheral	1 (0.2)	1 (0.2)	1 (0.2)
Pain	0	0	1 (0.2)
Ulcer haemorrhage	0	0	1 (0.2)
Hepatobiliary disorders	1 (0.2)	0	0
Hepatic function abnormal	1 (0.2)	0	0
Infections and infestations	4 (0.8)	4 (0.8)	2 (0.4)
Appendicitis	1 (0.2)	0	0
Cystitis	1 (0.2)	0	0
Diverticulitis	0	1 (0.2)	0
Enterocolitis infectious	0	0	1 (0.2)
Gastric ulcer helicobacter	1 (0.2)	0	0
Gastroenteritis	0	1 (0.2)	0
Pseudomembranous colitis	0	1 (0.2)	0
Upper respiratory tract infection	0	1 (0.2)	1 (0.2)
Urinary tract infection	1 (0.2)	0	0
Injury, poisoning, and procedural complications	4 (0.8)	1 (0.2)	3 (0.6)
Ankle fracture	1 (0.2)	0	0

Table 43. Treatment-Emergent Adverse Events Leading to Discontinuation From the Study (All Causalities) – Safety Analysis Set

Number (%) of Subjects With AEs By: System Organ Class and MedDRA (v14.1) Preferred Term	SD-6010 50 mg QD N=482	SD-6010 200 mg QD N=485	Placebo N=485
Deep vein thrombosis postoperative	1 (0.2)	0	0
Fall	1 (0.2)	0	0
Femoral neck fracture	1 (0.2)	0	0
Ligament sprain	1 (0.2)	0	1 (0.2)
Meniscus lesion	0	1 (0.2)	2 (0.4)
Investigations	5 (1.0)	7 (1.4)	6 (1.2)
Blood amylase increased	0	1 (0.2)	0
Blood creatinine increased	0	0	2 (0.4)
Blood glucose increased	1 (0.2)	0	0
Blood pressure increased	1 (0.2)	2 (0.4)	3 (0.6)
Cardiac murmur	1 (0.2)	0	0
Gamma-glutamyltransferase increased	0	1 (0.2)	0
Hepatic enzyme increased	1 (0.2)	0	0
Lipase increased	0	2 (0.4)	0
Liver function test abnormal	2 (0.4)	0	1 (0.2)
Transaminases increased	0	1 (0.2)	0
Weight increased	0	1 (0.2)	0
Metabolism and nutrition disorders	1 (0.2)	0	0
Type 2 diabetes mellitus	1 (0.2)	0	0
Musculoskeletal and connective tissue disorders	7 (1.5)	10 (2.1)	5 (1.0)
Arthralgia	5 (1.0)	5 (1.0)	3 (0.6)
Back pain	0	0	1 (0.2)
Chondrocalcinosis pyrophosphate	0	0	1 (0.2)
Meniscal degeneration	0	1 (0.2)	0
Muscle spasms	0	1 (0.2)	0
Myalgia	1 (0.2)	0	0
Osteoarthritis	1 (0.2)	1 (0.2)	0
Osteonecrosis	0	1 (0.2)	0
Osteopenia	1 (0.2)	0	0
Polyarthritis	0	1 (0.2)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (0.4)	4 (0.8)	4 (0.8)
Adenocarcinoma	0	1 (0.2)	0
Breast cancer	1 (0.2)	2 (0.4)	1 (0.2)
Lung neoplasm malignant	0	1 (0.2)	0
Nasal cavity cancer	1 (0.2)	0	0
Ovarian cancer stage III	0	0	1 (0.2)
Prostate cancer recurrent	0	0	1 (0.2)
Squamous cell carcinoma	0	0	1 (0.2)
Nervous system disorders	5 (1.0)	5 (1.0)	3 (0.6)
Burning sensation	1 (0.2)	0	1 (0.2)
Cerebral haemorrhage	0	1 (0.2)	0
Dizziness	0	2 (0.4)	0
Headache	1 (0.2)	3 (0.6)	1 (0.2)
Hemiparesis	0	1 (0.2)	0
Lethargy	0	0	1 (0.2)
Neuralgia	1 (0.2)	0	0
Neuropathy peripheral	1 (0.2)	0	0
Spinal cord compression	1 (0.2)	0	0

Table 43. Treatment-Emergent Adverse Events Leading to Discontinuation From the Study (All Causalities) – Safety Analysis Set

Number (%) of Subjects With AEs By: System Organ Class and MedDRA (v14.1) Preferred Term	SD-6010 50 mg QD N=482	SD-6010 200 mg QD N=485	Placebo N=485
Psychiatric disorders	3 (0.6)	0	1 (0.2)
Confusional state	1 (0.2)	0	0
Depression	1 (0.2)	0	1 (0.2)
Insomnia	2 (0.4)	0	0
Renal and urinary disorders	1 (0.2)	1 (0.2)	0
Proteinuria	0	1 (0.2)	0
Urinary incontinence	1 (0.2)	0	0
Reproductive system and breast disorders	0	1 (0.2)	0
Fallopian tube cyst	0	1 (0.2)	0
Respiratory, thoracic and mediastinal disorders	0	0	0
Asthma	0	0	1 (0.2)
Dysphonia	0	0	1 (0.2)
Skin and subcutaneous tissue disorders	2 (0.4)	1 (0.2)	1 (0.2)
Erythema	0	1 (0.2)	0
Haemorrhage subcutaneous	0	0	1 (0.2)
Hyperhidrosis	1 (0.2)	0	0
Pruritus	0	1 (0.2)	0
Rash	1 (0.2)	0	0
Vascular disorders	5 (1.0)	4 (0.8)	3 (0.6)
Deep vein thrombosis	0	0	1 (0.2)
Hypertension	5 (1.0)	3 (0.6)	2 (0.4)
Hypertensive crisis	0	1 (0.2)	0
Total preferred team events	56	70	46

Subjects were counted only once in each row.
All data on or after the first dose of study medication were included.
MedDRA (v14.1) coding dictionary was applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects; QD = once daily; v = version.

Events with fatal outcome and cause of death for subjects are presented in Table 44.

Table 44. Subject Deaths by Treatment

Serial Number	Sex/Age[a] (Years)	Day of Death[b]	Event With Fatal Outcome Preferred Term	Cause of Death
SD-6010 50 mg QD				
1	Female/71	680	Septic shock	Septic shock
2	Male/49	154	Haemorrhagic stroke	Haemorrhagic stroke
SD-6010 200 mg QD				
3	Male/77	661	Acute myocardial infarction	Acute myocardial infarction
Placebo				
4	Male/54	584	Diabetic ketoacidosis	Diabetic ketoacidosis
5	Female/66	190	Meningitis bacterial	Meningitis bacterial
6	Female/65	376	Sepsis	Sepsis

MedDRA v14.1 coding dictionary was applied.
MedDRA = Medical Dictionary for Regulatory Activities; OC = oracle clinical (database); QD = once daily; SDW = safety data warehouse; v = version.
a. Age at death.
b. Day of death was calculated as SDW death date minus OC first active therapy date plus 1.

Monitoring of BP was implemented with triplicate measurements of both SBP and DBP at each visit to establish secondary pharmacodynamic effects related to potential loss of inducible nitric oxide synthase (iNOS) selectivity. SBP and DBP were significantly increased compared to placebo for the SD-6010 200 mg QD group at several time points. The increases were most pronounced in the subset of subjects who were normotensive at Baseline and were not taking antihypertension medication. This elevation in SBP and DBP observed within the first 6 months of treatment with the SD-6010 200 mg dose suggests loss of iNOS selectivity and inhibition of the constitutive endothelial nitric oxide synthase and/or neuronal NOS isozymes at higher exposures. At all-time points, >97% of ECGs results were either normal, or abnormal but not clinically significant.

CONCLUSIONS:

- Neither SD-6010 treatment group was superior to placebo in reducing the primary endpoint of rate of JSN.

- In an exploratory discrete time MMRM analysis of KLG ≤2 subjects, the loss of JSW after 48 weeks was significantly smaller with SD-6010 50 mg than placebo; however, this improvement was not sustained at 96 weeks. SD-6010 did not slow OA progression in KLG 3 subjects.

- Although there were some sporadic significant improvements over placebo for the secondary endpoints, there was no overall pattern of improvement for SD-6010 at either dose over placebo for the WOMAC (composite index or subscales), Patient Assessment of Arthritic Pain (VAS), pain after a 50-foot walk, Patient Global Assessment of Arthritic Condition, Physician's Global Assessment of Arthritic Condition, OA Pain Assessment tool-knee Joint (ICOAP) (total score or subscales), OARSI knee function survey, Knee Injury and Osteoarthritis Outcome Score – Physical Function Short Form, SF-36 (components or subscales), medication burden (increases or decreases), patient global impression of change, OMERACT-OARSI responder index, or virtual joint replacement.

- SD-6010 50 mg QD and 200 mg QD were generally safe and well-tolerated for subjects with symptomatic knee OA.

- Small but statistically significant increases that resolved before the end of study in SBP and DBP were observed for the SD-6010 200 mg QD treatment group. These changes in the population as a whole were not considered clinically significant. These elevations were more pronounced in subset of subjects who were normotensive at Baseline and were not receiving antihypertension medication at Baseline. Some of these elevations in SBP were clinically important. No differences from placebo in SBP or DBP were observed with SD-6010 50 mg QD.

- Deaths were similarly distributed across the treatment groups and judged to be not related to study medication.

- SAEs were similarly distributed across treatment groups.

- The rate of SAEs leading to discontinuation from the study was similar between the SD-6010 50 mg QD treatment group and placebo group, and higher in the SD-6010 200 mg QD treatment group.

- Treatment-emergent AEs leading to discontinuation from the study were similarly distributed across the treatment groups.

- Incidence of AEs was similar across the treatment groups.

- Laboratory and ECG abnormalities were similarly distributed across the treatment groups.