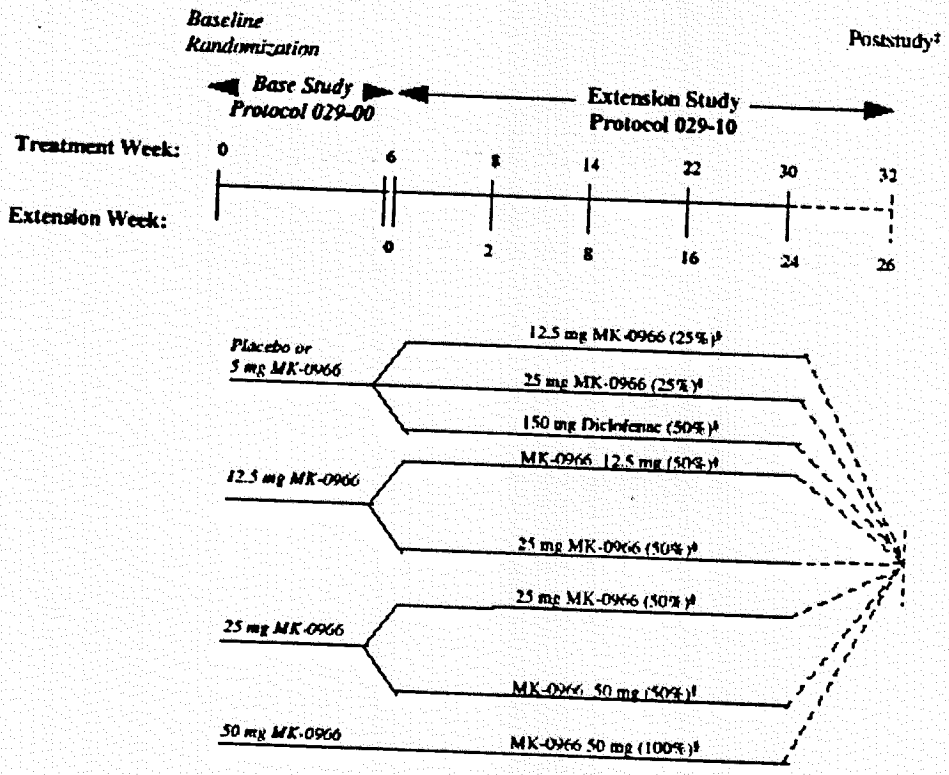
Appendix 7.2. Comparison of studies 010 and 029.

	010	029
Design	R,DB,PC	R,DB,PC
Doses	Placebo, 25mg, 125mg,	Placebo, 5mg, 12.5mg, 25mg, 50mg
Patients randomized per arm	72 73 74	145 149 144 137 97
Formulation	Formulation A (25% formulation)	Three different formulations (5 %, 7.5% and 25% formulation)
Baseline Demographics		
Age, gender, race, weight, years of disease:	Similar for both studies	
ARA functional class: I, II, III	22.8%, 66.7%, 10.5%	15.8%, 66.7%, 17.6%
Efficacy endpoints:	Similar for both studies	
Affected joint	Knee only	Hip and knee (except the 50 mg group that included knee only)
Comparison of results		
Efficacy outcomes:	25mg – 125mg	25mg - 50mg comparison
Pt assessment of Arthritic Pain (VAS)	No Different	Not measured
WOMAC Pain Subscale (VAS)	" "	50mg SS Different from 25
WOMAC pain walking on flat surface	" "	" "
Pt Global of Response to Therapy	" "	" "
Investigator Global or Disease Status	" "	" "
WOMAC Physical Function Subscale	" "	" "
WOMAC Stiffness Subscale	" "	" "
WOMAC Total Score Average	" "	" "
Patient Global of Disease Status	" "	no SS different
Discontinuation due to Lack of Efficay	5.6% 1.4%	4.4% 3.1% (no SS diff)
Safety: Disc due to Adverse Events	5.6% 15.1%	5.1% 5.2%

Appendix 7.3. Study 029-10 design.



Appendix 7.4. 029-10 randomization and accounting

Base:	LO			HI		
	Placebo or 5 mg MK-0966			12.5 mg or 25 mg or 50 mg MK-0966		
Extension:	MK-0966		Diclofenac	MK-0966		
	12.5 mg	25 mg	150 mg	12.5 mg	25 mg	50 mg
ENTERED THE EXTENSION:	54	47	92	50	101	123
Male (age range)[c]	22 (46-76)	13 (46-74)	28 (44-78)	14 (50-73)	23 (46-92)	35 (40)80
Female (age range)[c]	32 (40-75)	34 (39-83)	64 (40-81)	36 (39-81)	78 (44-80)	88 (39-83)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
COMPLETED:	40 (74.1)	35 (74.5)	69 (75.0)	38 (76.0)	69 (68.3)	89 (72.4)
DISCONTINUED:	14 (25.9)	12 (25.5)	23 (25.0)	12 (24.0)	32 (31.7)	34 (27.6)
Clinical adverse experiences	4 (7.4)	5 (10.6)	7 (7.6)	4 (8.0)	6 (5.9)	15 (12.2)
Laboratory adverse experiences	0 (0.0)	0 (0.0)	7 (7.6)	0 (0.0)	0 (0.0)	1 (0.8)
Deviation from protocol	4 (7.4)	0 (0.0)	1 (1.1)	0 (6.0)	2 (2.0)	1 (0.8)
Patient withdrew consent	0 (0.0)	0 (0.0)	1 (1.1)	3 (6.0)	6 (5.9)	6 (4.9)
Lost to follow up	0 (0.0)	1 (2.1)	1 (1.1)	0 (0.0)	1 (1.0)	0 (0.0)
Lack of efficacy	4 (7.4)	3 (6.4)	3 (3.3)	5 (10.0)	17 (16.8)	9 (7.3)
Other reasons[d]	2 (3.7)	3 (6.4)	3 (3.3)	0 (0.0)	0 (0.0)	2 (1.6)

Appendix 7.5. Study 029 changes in primary endpoints.

4.2.1: Pain Walking on a Flat Surface (WOMAC),
Mean Change From Baseline at Screening, Weeks 2, 4, 6, 8, 14, 22, and 30,
(Intention-to-Treat Approach) (Cont.)

Treatment (Base/Extension)	N	Baseline Mean	On-Rx Mean	On-Rx Mean Change	SD Change	LS Mean Change	95% CI for Mean Change*
			Week 22				
Placebo/12.5 mg	23	75.57	32.22	-43.35	29.85	-42.45	(-53.80,-31.10)
Placebo/25 mg	20	72.95	27.05	-45.90	21.91	-47.41	(-59.36,-35.46)
Placebo/Diclofenac	47	72.11	32.19	-39.91	28.13	-42.37	(-51.13,-33.62)
5 mg/12.5 mg	31	77.68	34.84	-42.84	26.37	-41.56	(-51.90,-31.22)
5 mg/25 mg	27	78.33	31.04	-47.30	27.26	-46.08	(-56.51,-35.66)
5 mg/Diclofenac	43	72.28	29.16	-43.12	29.68	-46.51	(-55.29,-37.73)
12.5 mg/12.5 mg	48	69.33	35.58	-33.75	29.66	-38.01	(-46.37,-29.65)
12.5 mg/25 mg	50	70.80	40.84	-29.96	25.75	-32.30	(-40.66,-23.93)
25 mg/25 mg	51	75.63	38.51	-37.12	25.90	-36.99	(-45.14,-28.84)
25 mg/50 mg	50	76.20	43.12	-33.08	27.55	-33.46	(-41.90,-25.03)
50 mg/50 mg	73	74.04	29.42	-44.62	27.98	-42.90	(-50.36,-35.44)
			Week 30				
Placebo/12.5 mg	23	75.57	37.70	-37.87	31.88	-35.19	(-47.02,-23.36)
Placebo/25 mg	20	72.95	31.50	-41.45	25.98	-41.73	(-54.19,-29.27)
Placebo/Diclofenac	47	72.11	34.74	-37.36	31.90	-37.71	(-46.83,-28.58)
5 mg/12.5 mg	31	77.68	35.84	-41.84	28.25	-38.59	(-49.37,-27.81)
5 mg/25 mg	27	78.33	33.37	-44.96	24.38	-41.95	(-52.81,-31.08)
5 mg/Diclofenac	43	72.28	28.28	-44.00	29.37	-45.87	(-55.02,-36.71)
12.5 mg/12.5 mg	48	69.33	37.46	-31.88	30.49	-34.74	(-43.45,-26.02)
12.5 mg/25 mg	50	70.80	41.42	-29.38	26.79	-29.81	(-38.54,-21.09)
25 mg/25 mg	51	75.63	38.20	-37.43	27.58	-35.60	(-44.10,-27.10)
25 mg/50 mg	50	76.20	42.04	-34.16	24.76	-32.70	(-41.50,-23.91)
50 mg/50 mg	73	74.04	32.70	-41.34	30.71	-37.33	(-45.11,-29.56)

* Derived from LS mean.

4.2.2: Patient Global Assessment of Disease Status (VAS),
Mean Change From Baseline at Screening, Weeks 2, 4, 6, 8, 14, 22, and 30,
(Intention-to-Treat Approach) (Cont.)

Treatment (Base/Extension)	N	Baseline Mean	On-Rx Mean	On-Rx Mean Change	SD Change	LS Mean Change	95% CI for Mean Change*
			Week 22				
Placebo/12.5 mg	23	65.61	33.39	-32.22	31.97	-34.88	(-45.86,-23.90)
Placebo/25 mg	20	64.50	26.85	-37.65	19.41	-42.58	(-54.15,-31.02)
Placebo/Diclofenac	47	64.96	30.45	-34.51	31.25	-39.12	(-47.60,-30.65)
5 mg/12.5 mg	31	73.23	30.26	-42.97	29.12	-40.82	(-50.83,-30.82)
5 mg/25 mg	27	72.89	32.22	-40.67	27.65	-39.46	(-49.53,-29.39)
5 mg/Diclofenac	43	71.40	29.33	-42.07	29.20	-42.77	(-51.27,-34.28)
12.5 mg/12.5 mg	48	61.96	38.88	-23.08	30.02	-30.20	(-38.29,-22.11)
12.5 mg/25 mg	49	69.27	39.76	-29.51	26.70	-29.53	(-37.73,-21.34)
25 mg/25 mg	51	68.61	37.53	-31.08	29.76	-32.42	(-40.31,-24.54)
25 mg/50 mg	49	71.86	41.00	-30.86	25.83	-30.54	(-38.74,-22.33)
50 mg/50 mg	73	68.58	31.55	-37.03	29.56	-35.92	(-43.14,-28.70)
			Week 30				
Placebo/12.5 mg	23	65.61	36.13	-29.48	31.64	-30.07	(-41.30,-18.85)
Placebo/25 mg	20	64.50	35.05	-29.45	21.02	-32.40	(-44.23,-20.58)
Placebo/Diclofenac	47	64.96	31.47	-33.49	30.84	-35.32	(-43.99,-26.66)
5 mg/12.5 mg	31	73.23	32.48	-40.74	26.83	-35.96	(-46.19,-25.73)
5 mg/25 mg	27	72.89	34.30	-38.59	26.70	-35.65	(-45.95,-25.35)
5 mg/Diclofenac	43	71.40	31.02	-40.37	31.01	-38.34	(-47.03,-29.65)
12.5 mg/12.5 mg	48	61.96	38.96	-23.00	30.42	-27.19	(-35.47,-18.92)
12.5 mg/25 mg	49	69.27	40.86	-28.41	26.44	-25.83	(-34.21,-17.46)
25 mg/25 mg	51	68.61	38.43	-30.18	30.96	-29.29	(-37.35,-21.23)
25 mg/50 mg	49	71.86	42.12	-29.73	24.89	-26.96	(-35.35,-18.57)
50 mg/50 mg	73	68.58	32.16	-36.41	29.46	-32.74	(-40.13,-25.36)

* Derived from LS mean.

A.7.5 (cont).

4.2.3: Investigator Global Assessment of Disease Status (Likert), Mean Change From Baseline at Screening, Weeks 2, 4, 6, 8, 14, 22, and 30, (Intention-to-Treat Approach) (Cont.)

Treatment (Base/Extension)	N	Baseline Mean	On-Rx Mean	On-Rx Mean Change	SD Change	LS Mean Change	95% CI for Mean Change[1]
			Week 22				
Placebo/12.5 mg	23	3.04	1.00	-2.04	1.40	-2.01	(-2.41, -1.61)
Placebo/25 mg	20	2.75	1.10	-1.65	0.88	-1.91	(-2.33, -1.49)
Placebo/Diclofenac	46	2.85	1.09	-1.76	1.18	-1.94	(-2.25, -1.63)
5 mg/12.5 mg	31	2.97	1.03	-1.94	0.96	-1.95	(-2.31, -1.58)
5 mg/25 mg	27	2.93	1.33	-1.59	1.28	-1.71	(-2.08, -1.34)
5 mg/Diclofenac	43	2.84	1.07	-1.77	1.23	-1.97	(-2.28, -1.66)
12.5 mg/12.5 mg	48	2.92	1.27	-1.65	1.19	-1.74	(-2.03, -1.45)
12.5 mg/25 mg	50	2.94	1.44	-1.50	0.97	-1.53	(-1.82, -1.23)
25 mg/25 mg	51	2.92	1.24	-1.69	0.99	-1.76	(-2.05, -1.48)
25 mg/50 mg	49	2.92	1.51	-1.41	1.10	-1.49	(-1.79, -1.19)
50 mg/50 mg	72	2.86	1.08	-1.78	1.06	-1.81	(-2.07, -1.54)
			Week 30				
Placebo/12.5 mg	23	3.04	1.04	-2.00	1.21	-1.86	(-2.28, -1.45)
Placebo/25 mg	20	2.75	1.10	-1.65	0.88	-1.83	(-2.26, -1.39)
Placebo/Diclofenac	47	2.87	1.04	-1.83	1.26	-1.86	(-2.18, -1.54)
5 mg/12.5 mg	31	2.97	1.03	-1.94	1.00	-1.85	(-2.23, -1.48)
5 mg/25 mg	27	2.93	1.37	-1.56	1.15	-1.57	(-1.95, -1.19)
5 mg/Diclofenac	43	2.84	1.05	-1.79	1.04	-1.91	(-2.23, -1.58)
12.5 mg/12.5 mg	47	2.89	1.34	-1.55	1.19	-1.59	(-1.89, -1.28)
12.5 mg/25 mg	50	2.94	1.42	-1.52	1.01	-1.45	(-1.75, -1.14)
25 mg/25 mg	51	2.92	1.37	-1.55	1.17	-1.54	(-1.84, -1.24)
25 mg/50 mg	49	2.92	1.51	-1.41	1.08	-1.36	(-1.67, -1.05)
50 mg/50 mg	72	2.86	1.01	-1.85	1.12	-1.81	(-2.08, -1.53)

[1] Derived from LS mean.

Appendix 8.1. Study 033.

Patient Accounting

	Placebo	MK-0966 12.5 mg	MK-0966 25 mg	Ibuprofen 2400 mg	Total
ENTERED:	69	219	227	221	736
Male (age range)†	13 (42 to 70)	52 (39 to 91)	65 (39 to 84)	58 (43 to 82)	188 (39 to 91)
Female (age range)†	56 (40 to 87)	167 (39 to 86)	162 (39 to 85)	163 (41 to 81)	548 (39 to 87)
	n (%)	n (%)	n (%)	n (%)	n (%)
COMPLETED:	50 (72.5)	186 (84.9)	200 (88.1)	189 (85.5)	625 (84.9)
DISCONTINUED:	19 (27.5)*	33 (15.1)	27 (11.9)	32 (14.5)	111 (15.1)
Clinical adverse experience	4 (5.8)	12 (5.5)	15 (6.6)	8 (3.6)	39 (5.3)
Laboratory adverse experience	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)
Deviation from protocol	0 (0.0)	1 (0.5)	1 (0.4)	0 (0.0)	2 (0.3)
Patient withdrew consent	2 (2.9)	1 (0.5)	2 (0.9)	2 (0.9)	7 (1.0)
Lost to follow up	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.1)
Lack of efficacy	13 (18.8)*	17 (7.8)	9 (4.0)	19 (8.6)	58 (7.9)
Other reasons‡	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.9)	3 (0.4)

* p<0.05 vs. MK-0966 and ibuprofen.

† Birth date masking to 12/31/XX in database, where XX is the true year of birth, may cause patient's age to appear 1 year younger than the actual age, depending on the date of randomization. All patients were ≥39 years of age when randomized.

‡ Includes reasons other than those listed.

Data Source: [4.23; 4.33]

Appendix A.8.2

Analysis of End Point: Pain Walking on a Flat Surface (WOMAC)†
Mean Change From Baseline (Flare/Randomization Visit)
Averaged Over 6-Week Treatment Period
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean (mm)	Treatment Period Mean (mm)	Mean Change (mm)	SD of Change	LSMean‡ Change (mm)	95% CI for LSMean Change
Placebo	69	73.51	55.68	-17.82	26.11	-17.21	(-22.83, -11.59)
12.5 mg	218	73.30	44.03	-29.28	25.21	-29.62	(-32.89, -26.34)
25 mg	222	76.45	41.28	-35.18	25.25	-33.71	(-36.97, -30.45)
Ibuprofen	218	75.62	43.86	-31.76	22.52	-30.66	(-33.93, -27.39)

Comparisons Between Active-Treatment Groups	LSMean (mm)	95% CI	p-Value	Posterior Probability§
<u>With Active Comparator</u>				
25 mg vs. Ibuprofen	-3.05	(-7.28, 1.18)	0.158	>0.999
12.5 mg vs. Ibuprofen	1.04	(-3.23, 5.31)	0.632	>0.999
<u>Between MK-0966 Doses</u>				
25 mg vs. 12.5 mg	-4.09	(-8.36, 0.18)	0.060	0.997
<u>With Placebo</u>				
12.5 mg vs. Placebo	-12.40	(-18.56, -6.24)	<0.001	
25 mg vs. Placebo	-16.49	(-22.68, -10.31)	<0.001	
Ibuprofen vs. Placebo	-13.45	(-19.64, -7.26)	<0.001	

Effect:	p-Value	Pooled SD
History of Ulcer or Upper GI Bleeding	0.762	22.57
Study Center	<0.001	
Baseline Covariate	<0.001	
Treatment	<0.001	

† 2d-0.5cm-mm VAS.

‡ Least square mean.

§ Posterior probability that the true mean difference is within the predefined comparability bounds

Appendix 8.3. Study 033

Analysis of End Point: Patient Global Assessment of Response to Therapy (Likert†) Averaged Over 6-Week Treatment Period (Intention-to-Treat Approach)

Treatment Group	N	Treatment Period Mean	SD	LSMean‡	95% CI for LSMean
Placebo	69	-1.38	1.25	-1.37	(-1.62, -1.12)
12.5 mg	218	-2.19	0.99	-2.24	(-2.38, -2.09)
25 mg	223	-2.34	0.99	-2.38	(-2.52, -2.23)
Ibuprofen	218	-2.21	1.08	-2.24	(-2.39, -2.10)

Comparisons Between Active-Treatment Groups	LSMean	95% CI	p-Value	Posterior Probability¶
With Active Comparator				
25 mg vs. Ibuprofen	-0.13	(-0.32, 0.05)	0.163	>0.999
12.5 mg vs. Ibuprofen	0.01	(-0.18, 0.20)	0.955	>0.999
Between MK-0966 Doses				
25 mg vs. 12.5 mg	-0.14	(-0.33, 0.05)	0.149	>0.999
With Placebo				
12.5 mg vs. Placebo	-0.87	(-1.14, -0.59)	<0.001	
25 mg vs. Placebo	-1.01	(-1.28, -0.73)	<0.001	
Ibuprofen vs. Placebo	-0.87	(-1.15, -0.60)	<0.001	

Effect:	p-Value	Pooled SD
History of Ulcer or Upper GI Bleeding	0.918	1.01
Study Center	<0.001	
Baseline Covariate	<0.001	
Treatment	<0.001	

Analysis of End Point: Investigator Global Assessment of Disease Status (Likert)† Mean Change From Baseline (Flare/Randomization Visit) Averaged Over 6-Week Treatment Period (Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LSMean‡ Change	95% CI for LSMean Change
Placebo	68	2.87	2.10	-0.77	1.01	-0.80	(-1.00, -0.60)
12.5 mg	217	2.82	1.52	-1.30	0.98	-1.37	(-1.49, -1.26)
25 mg	225	2.90	1.45	-1.46	0.91	-1.46	(-1.58, -1.34)
Ibuprofen	219	2.89	1.58	-1.31	0.96	-1.33	(-1.45, -1.21)

Comparisons Between Active-Treatment Groups	LSMean	95% CI	p-Value	Posterior Probability¶
With Active Comparator				
25 mg vs. Ibuprofen	-0.13	(-0.28, 0.02)	0.085	>0.999
12.5 mg vs. Ibuprofen	-0.05	(-0.20, 0.11)	0.562	>0.999
Between MK-0966 Doses				
25 mg vs. 12.5 mg	-0.09	(-0.24, 0.06)	0.259	>0.999
With Placebo				
12.5 mg vs. Placebo	-0.58	(-0.80, -0.35)	<0.001	
25 mg vs. Placebo	-0.66	(-0.89, -0.44)	<0.001	
Ibuprofen vs. Placebo	-0.53	(-0.75, -0.31)	<0.001	

Effect:	p-Value	Pooled SD
History of Ulcer or Upper GI Bleeding	0.926	0.81
Study Center	<0.001	
Baseline Covariate	<0.001	
Treatment	<0.001	

† 0- to 4-point Likert.
‡ Least square mean.
¶ Posterior probability that the true mean difference is within the predefined comparability bounds (± 0.5 Likert scale; ± 10 mm VAS).

A. 8.4. Study 033. Secondary and other endpoints

End Point	Pairwise Treatment Difference in LSMean (95% CI)		
	12.5 mg—Placebo	25 mg—Placebo	Ibuprofen—Placebo
Key Secondary End Points			
Physical Function Subscale (WOMAC) (0- to 100-mm VAS)	-11.36 (-16.87, -5.85)	-14.61 (-20.13, -9.10)	-11.52 (-17.05, -5.99)
Pain Subscale (WOMAC) (0- to 100-mm VAS)	-12.05 (-17.85, -6.24)	-15.57 (-21.39, -9.75)	-13.00 (-18.83, -7.17)
Stiffness Subscale (WOMAC) (0- to 100-mm VAS)	-13.32 (-19.24, -7.39)	-15.33 (-21.26, -9.40)	-13.08 (-19.02, -7.14)
Patient Global Assessment of Disease Status (0- to 100-mm VAS)	-14.57 (-20.57, -8.57)	-18.25 (-24.26, -12.24)	-15.29 (-21.31, -9.26)
	Difference in Percentage Points (95% CI)		
Discontinuation Due to Lack of Efficacy	-11.08% (-20.96%, -1.19%)	-14.88% (-24.45%, -5.31%)	-10.24% (-20.18%, -0.30%)
Other End Points			
Investigator Global Assessment of Response to Therapy (0- to 4-point Likert)	-0.76 (-1.03, -0.50)	-0.91 (-1.18, -0.64)	-0.80 (-1.07, -0.53)
Study Joint Tenderness (0- to 3-point Likert)	-0.25 (-0.41, -0.08)	-0.34 (-0.50, -0.17)	-0.32 (-0.49, -0.16)
Acetaminophen Use (for Rescue) (tabs/day)	-0.48 (-0.75, -0.21)	-0.47 (-0.74, -0.20)	-0.59 (-0.86, -0.32)
Total Score Average (WOMAC) (0- to 100-mm VAS)	-12.07 (-17.52, -6.62)	-15.28 (-20.75, -9.82)	-12.30 (-17.77, -6.82)
Subscale Average (WOMAC) (0- to 100-mm VAS)	-12.13 (-17.67, -6.58)	-15.19 (-20.75, -9.63)	-12.42 (-17.98, -6.85)
	Difference in Percentage Points (95% CI)		
Study Joint Swelling at Week 6 (0=Absent, 1=Present)	-11.67% (-28.83%, 5.50%)	-7.67% (-24.92%, 9.58%)	-15.55% (-32.65%, 1.55%)

Data Source: 14.341

Appendix 9.1. Study 040.

Patient Accounting

	Placebo	MK-0966 12.5 mg	MK-0966 25 mg	Ibuprofen 2400 mg	Total
ENTERED:	74	244	242	249	809
Male (age range)†	11 (44 to 76)	46 (45 to 78)	51 (40 to 79)	54 (46 to 84)	162 (40 to 84)
Female (age range)†	63 (44 to 83)	198 (40 to 86)	191 (40 to 85)	195 (41 to 90)	647 (40 to 90)
	n (%)	n (%)	n (%)	n (%)	n (%)
COMPLETED:	62 (83.8)	217 (88.9)	217 (89.7)	213 (85.5)	709 (87.6)
DISCONTINUED:	12 (16.2)	27 (11.1)	25 (10.3)	36 (14.5)	100 (12.4)
Clinical adverse experience	1 (1.4)	10 (4.1)	9 (3.7)**	21 (8.4)*	41 (5.1)
Laboratory adverse experience	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)	2 (0.2)
Deviation from protocol	0 (0.0)	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)
Patient withdrew consent	1 (1.4)	4 (1.6)	5 (2.1)	4 (1.6)	14 (1.7)
Lost to follow-up	0 (0.0)	1 (0.4)	2 (0.8)	1 (0.4)	4 (0.5)
Lack of efficacy	9 (12.2)	8 (3.3)*	7 (2.9)*	9 (3.6)*	33 (4.1)
Patient discontinued for other reasons	1 (1.4)	1 (0.4)	1 (0.4)	0 (0.0)	3 (0.4)

* $p < 0.05$ vs. placebo.
** $p < 0.05$ vs. ibuprofen.
† Birth date masking to 12/31/XX in database, where XX is the true year of birth, may cause patient's age to appear 1 year younger than the actual age, depending on the date of randomization. All patients were ≥40 years of age when randomized.

Data Source: 14,281

A.9.2

Table 2.1

Analysis of Primary End Point: Pain Walking on a Flat Surface (WOMAC)
Mean Change From Baseline (Flare/Randomization Visit)
Averaged Over 6-Week Treatment Period
(Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LSMean† Change	95% CI for LSMean† Change
Placebo	74	71.49	53.39	-18.10	23.42	-18.92	(-23.72, -14.12)
12.5 mg	243	72.66	38.37	-34.29	20.51	-34.32	(-37.03, -31.60)
25 mg	237	72.37	37.30	-35.07	20.59	-35.07	(-37.82, -32.33)
Ibuprofen	247	72.57	39.05	-33.52	22.95	-33.55	(-36.26, -30.84)

Comparisons Between Treatment Groups	Difference in LSMean	95% CI for Difference	p-Value	Posterior Probability‡
With Active Comparator				
25 mg vs. Ibuprofen	-1.52	(-5.14, 2.09)	0.408	>0.999
12.5 mg vs. Ibuprofen	-0.77	(-4.37, 2.83)	0.675	>0.999
Between MK-0966 Doses				
25 mg vs. 12.5 mg	-0.76	(-4.39, 2.88)	0.683	>0.999
With Placebo				
12.5 mg vs. Placebo	-15.40	(-20.72, -10.08)	<0.001	
25 mg vs. Placebo	-16.15	(-21.48, -10.83)	<0.001	
Ibuprofen vs. Placebo	-14.63	(-19.92, -9.33)	<0.001	

Effect:	p-Value	Pooled SD
History of Ulcer or Upper GI Bleeding	0.298	20.25
Study Center	<0.001	
Baseline Covariate	<0.001	
Treatment	<0.001	

† Least squares mean.
‡ Posterior probability that the true mean difference is within the predefined clinical comparability bounds (±0.5 Likert scale; ±10 mm VAS).

Data Source: [4.29]

A.9.3. Study 040. Efficacy Endpoints.

Analysis of Primary End Point: Patient Global Assessment of Response to Therapy (Likert) Averaged Over 6-Week Treatment Period (Intention-to-Treat Approach)

Treatment Group	N	Treatment Period Mean	SD	LSMean[†]	95% CI for LSMean[†]
Placebo	74	-1.50	0.97	-1.56	(-1.77, -1.36)
12.5 mg	242	-2.23	0.94	-2.28	(-2.39, -2.16)
25 mg	235	-2.41	0.77	-2.44	(-2.56, -2.33)
Ibuprofen	245	-2.17	0.94	-2.22	(-2.34, -2.11)

Comparisons Between Treatment Groups	Difference in LSMean	95% CI for Difference	p-Value	Posterior Probability[‡]
With Active Comparator				
25 mg vs. Ibuprofen	-0.22	(-0.38, -0.07)	0.005	>0.999
12.5 mg vs. Ibuprofen	-0.06	(-0.21, 0.10)	0.471	>0.999
Between MK-0966 Doses				
25 mg vs. 12.5 mg	-0.17	(-0.32, -0.01)	0.036	>0.999
With Placebo				
12.5 mg vs. Placebo	-0.72	(-0.94, -0.49)	<0.001	
25 mg vs. Placebo	-0.88	(-1.11, -0.65)	<0.001	
Ibuprofen vs. Placebo	-0.66	(-0.88, -0.43)	<0.001	

Effect:	p-Value	Pooled SD
History of Ulcer or Upper GI Bleeding	0.736	0.86
Study Center	<0.001	
Baseline Covariate	<0.001	
Treatment	<0.001	

A.9.4. Study 040

Analysis of Primary End Point: Investigator Global Assessment of Disease Status (Likert) Mean Change From Baseline (Flare/Randomization Visit) Averaged Over 6-Week Treatment Period (Intention-to-Treat Approach)

Treatment Group	N	Baseline Mean	Treatment Period Mean	Mean Change	SD of Change	LSMean* Change	95% CI for LSMean† Change
Placebo	74	2.99	2.02	-0.96	0.74	-1.00	(-1.17, -0.83)
12.5 mg	243	3.00	1.55	-1.45	0.87	-1.47	(-1.56, -1.37)
25 mg	238	2.97	1.41	-1.55	0.79	-1.59	(-1.68, -1.49)
Ibuprofen	247	3.01	1.62	-1.40	0.88	-1.40	(-1.50, -1.31)

Comparisons Between Treatment Groups	Difference in LSMean	95% CI for Difference	p-Value	Posterior Probability‡
With Active Comparator				
25 mg vs. Ibuprofen	-0.18	(-0.31, -0.05)	0.005	>0.999
12.5 mg vs. Ibuprofen	-0.06	(-0.19, 0.06)	0.320	>0.999
Between MK-0966 Doses				
25 mg vs. 12.5 mg	-0.12	(-0.25, 0.01)	0.072	>0.999
With Placebo				
12.5 mg vs. Placebo	-0.46	(-0.65, -0.28)	<0.001	
25 mg vs. Placebo	-0.58	(-0.77, -0.39)	<0.001	
Ibuprofen vs. Placebo	-0.40	(-0.59, -0.21)	<0.001	

Effect:	p-Value	Pooled SD
History of Ulcer or Upper GI Bleeding	0.740	0.72
Study Center	<0.001	
Baseline Covariate	<0.001	
Treatment	<0.001	

* Least squares mean.
‡ Posterior probability that the true mean difference is within the predefined clinical comparability bounds (±0.5 Likert scale; ±10 mm VAS).

Data Source: [4.29]

Appendix 10. O34 randomization and accounting

	MK-0966				Diclofenac 150 mg		Total	
	12.5 mg		25 mg					
Entered:	231		232		230		693	
Male (age range)	44 (47 to 82)		52 (39 to 79)		42 (38 to 81)		138 (38 to 82)	
Female (age range)	187 (39 to 85)		180 (43 to 79)		188 (40 to 85)		555 (39 to 85)	
	n	(%)	n	(%)	n	(%)	n	(%)
CONTINUING TRIAL:	169	(73.1)	183	(78.9)	174	(75.6)	526	(75.9)
DISCONTINUED:	62	(26.8)	49	(21.1)	56	(24.3)	167	(24.1)
Clinical adverse experience	18	(7.7)*	14	(6.0)*	22	(9.6)	54	(7.8)
Laboratory adverse experience	0	(0)*	1	(0.4)*	10	(4.3)	11	(1.6)
Deviation from protocol	8	(3.4)	6	(2.6)	2	(0.9)	16	(2.3)
Patient withdrew consent	8	(3.4)	3	(1.3)	4	(1.7)	15	(2.2)
Lost to follow-up	2	(0.9)	2	(0.9)	2	(0.9)	6	(0.9)
Lack of efficacy	22	(9.5)	19	(8.2)	13	(5.6)	54	(7.8)
Other reasons†	4	(1.7)	4	(1.7)	3	(1.3)	11	(1.6)

* $p<0.05$ vs. diclofenac.
† Includes reasons other than those listed.
Birth date masking to 12/31/XX in database, where XX is the true year of birth, may cause patient's age to appear 1 year younger than the actual age, depending on the date of randomization. All patients were ≥35 years of age when randomized.

Data Source: [4.16; 4.34]

Appendix 10.1. Studies 034 and 035 primary endpoint results

Table D-39 Pairwise Difference in LS Mean for the Primary End Points
Mean Change From Baseline (Randomization Visit)
Averaged Over 12-Week Treatment Period
(Protocols 034 and 035)

End Point	Difference in LS Mean (95% CI)	
	25 mg Minus Diclofenac	12.5 mg Minus Diclofenac
Pain Walking on a Flat Surface (WOMAC) (0- to 100-mm VAS)*		
034	2.98 (-0.50, 6.45)	5.27 (1.79, 8.75)
035	2.75 (-0.93, 6.43)	3.74 (0.07, 7.40)
Combined Analysis 034 and 035	2.84 (0.30, 5.37)	4.45 (1.91, 6.99)
Patient Global Assessment of Response to Therapy (0- to 4-Point Likert Scale)†,**		
034	0.16 (0.01, 0.31)	0.21 (0.06, 0.36)
035	0.19 (0.05, 0.33)	0.24 (0.10, 0.38)
Combined Analysis 034 and 035	0.17 (0.07, 0.27)	0.23 (0.13, 0.33)
Investigator Global Assessment of Disease Status (0- to 4-Point Likert Scale)**		
034	0.13 (0.00, 0.25)	0.16 (0.04, 0.29)
035	0.17 (0.05, 0.30)	0.18 (0.06, 0.31)
Combined Analysis 034 and 035	0.15 (0.06, 0.24)	0.18 (0.09, 0.26)

Difference in LS Means (MK-0966 minus diclofenac) greater than zero favor MK-0966.
Differences less than zero favor MK-0966.
† Scale reversed so decreasing values indicate improvement to be consistent with presentation of the other end points.
* All 95% CIs within prespecified comparability bounds ±10 mm.
** All 95% CIs within prespecified comparability bounds ±0.50.

[P034: P035: 236]

Appendix 10.2 Study 034 secondary endpoints, 12 weeks.

Table 36

Summary of Key Secondary and Other End Points
Pairwise Treatment Differences in Least-Squares Mean Change
Averaged Over 12-Week Treatment Period
(Intention-to-Treat Approach)

Key Secondary End Point	Pairwise Treatment Difference in LSMean (95% CI)		
	25 mg—Diclofenac	12.5 mg—Diclofenac	25 mg—12.5 mg
Physical Function Subscale (WOMAC) (0 to 100-mm VAS)	2.22 (-0.72, 5.15)	3.70 (0.76, 6.64)	-1.48 (-4.43, 1.46)
Pain Subscale (WOMAC) (0- to 100-mm VAS)	1.84 (-1.09, 4.76)	4.40 (1.47, 7.33)	-2.57 (-5.50, 0.36)
Stiffness Subscale (WOMAC) (0- to 100-mm VAS)	1.80 (-1.55, 5.14)	3.86 (0.50, 7.22)	-2.07 (-5.44, 1.30)
Patient Global Assessment of Disease Status (VAS) (0- to 100-mm VAS)	3.89 (0.52, 7.26)	4.33 (0.95, 7.71)	-0.44 (-3.83, 2.94)
Other End Point	Pairwise Treatment Difference in LSMean (95% CI)		
	25 mg—Diclofenac	12.5 mg—Diclofenac	25 mg—12.5 mg
Investigator Global Assessment of Response to Therapy (0 to 4 point Likert)	0.12 (-0.02, 0.26)	0.19 (0.05, 0.33)	-0.07 (-0.21, 0.08)
Study-joint Tenderness (0 to 3 point Likert)	0.02 (-0.09, 0.13)	-0.01 (-0.11, 0.10)	0.02 (-0.08, 0.13)
Paracetamol Usage (For Rescue) (tabs/day)	0.08 (-0.02, 0.18)	0.13 (0.03, 0.23)	-0.05 (-0.15, 0.05)
Total Score Average (WOMAC) (0- to 100-mm VAS)	2.16 (-0.71, 5.04)	3.71 (0.83, 6.59)	-1.55 (-4.44, 1.33)
Subscale Average (WOMAC) (0- to 100-mm VAS)	2.02 (-0.89, 4.93)	3.71 (0.79, 6.63)	-1.69 (-4.61, 1.23)
	Pairwise Difference in Percent of Patients (95% CI) at Week 12		
	25 mg—Diclofenac	12.5 mg—Diclofenac	25 mg—12.5 mg
Patients with swelling in study joints at Week 12	-5.94 (-14.17, 2.29)	-3.88 (-12.35, 4.58)	-2.06 (-9.82, 5.70)

Data Source: [4.35]

Appendix 10.3. Primary endpoints, studies 034 and 035, 6 months.

Table D-40 Pairwise Difference in LS Mean for the Primary End Points Mean Change From Baseline (Randomization Visit) Averaged Over 6-Month Treatment Period (Protocols 034 and 035)

End Point	Difference in LS Mean[‡] (95% CI)	
	25 mg Minus Diclofenac	12.5 mg Minus Diclofenac
Pain Walking on a Flat Surface (WOMAC) (0- to 100-mm VAS)*		
034	3.40 (-0.07, 6.87)	5.53 (2.06, 9.00)
035	2.06 (-1.59, 5.71)	2.62 (-1.02, 6.26)
Combined Analysis 034 and 035	2.66 (0.13, 5.19)	3.98 (1.45, 6.50)
Patient Global Assessment of Response to Therapy (0- to 4-Point Likert Scale)[†]**		
034	0.16 (0.01, 0.31)	0.21 (0.06, 0.36)
035	0.18 (0.05, 0.32)	0.21 (0.07, 0.34)
Combined Analysis 034 and 035	0.17 (0.07, 0.27)	0.21 (0.11, 0.31)
Investigator Global Assessment of Disease Status (0- to 4-Point Likert Scale)**		
034	0.14 (0.01, 0.26)	0.17 (0.04, 0.29)
035	0.16 (0.04, 0.28)	0.15 (0.03, 0.28)
Combined Analysis 034 and 035	0.15 (0.06, 0.24)	0.16 (0.07, 0.25)

* All 95% CIs within prespecified comparability bounds ±10 mm.
** All 95% CIs within prespecified comparability bounds ±0.50.
Difference in LS Means (MK-0966 minus diclofenac) greater than zero favor ibuprofen.
Differences less than zero favor MK-0966.
† Scale reversed so decreasing values indicate improvement to be consistent with presentation of the other end points.
‡ Decreasing values represent improvement.

[P034; P035; 236]

Appendix 10.4. 034 secondary endpoints (6 month analysis)

Summary of Key Secondary and Other End Points
Pairwise Treatment Differences in Least-Squares Mean Change
Averaged Over 6-Month Treatment Period
(Intention-to-Treat Approach)

Key Secondary End Points	Pairwise Treatment Difference in LSMean (95% CI)		
	25 mg—Diclofenac	12.5 mg—Diclofenac	25 mg—12.5 mg
Physical Function Subscale (WOMAC) (0- to 100-mm VAS)	2.54 (-0.44, 5.52)	3.98 (0.99, 6.96)	-1.43 (-4.42, 1.56)
Pain Subscale (WOMAC) (0- to 100-mm VAS)	2.25 (-0.69, 5.20)	4.60 (1.65, 7.55)	-2.35 (-5.30, 0.60)
Stiffness Subscale (WOMAC) (0- to 100-mm VAS)	2.24 (-1.11, 5.59)	4.38 (1.01, 7.74)	-2.14 (-5.51, 1.24)
Patient Global Assessment of Disease Status (VAS) (0- to 100-mm VAS)	4.15 (0.76, 7.54)	4.73 (1.33, 8.13)	-0.58 (-3.99, 2.82)
	Difference in Percentage Points (95% CI)		
Discontinuation Due to Lack of Efficacy (Difference in Percent)	2.54 (-2.08, 7.16)	3.87 (-0.95, 8.69)	-1.33 (-6.51, 3.84)
	Pairwise Treatment Difference, in LSMean (95% CI)		
Other End Points	25 mg—Diclofenac	12.5 mg—Diclofenac	25 mg—12.5 mg
Investigator Global Assessment of Response to Therapy (0 to 4 point Likert)	0.13 (-0.01, 0.27)	0.19 (0.05, 0.33)	-0.06 (-0.20, 0.08)
Study-joint Tenderness (0 to 3 point Likert)	0.08 (-0.03, 0.19)	0.04 (-0.07, 0.14)	0.04 (-0.06, 0.15)
Paracetamol Usage (For Rescue) (tablets/day)	0.09 (-0.00, 0.19)	0.13 (0.03, 0.22)	-0.03 (-0.13, 0.06)
Total Score Average (WOMAC) (0- to 100-mm VAS)	2.51 (-0.40, 5.43)	4.00 (1.08, 6.92)	-1.48 (-4.41, 1.44)
Subscale Average (WOMAC) (0- to 100-mm VAS)	2.43 (-0.51, 5.37)	4.03 (1.09, 6.98)	-1.61 (-4.56, 1.35)
	Difference in Percent of Patients (95% CI) at Month 6		
	25 mg—Diclofenac	12.5 mg—Diclofenac	25 mg—12.5 mg
Patients with swelling in study joints at Month 6	-5.05 (-13.53, 3.43)	-1.11 (-10.16, 7.93)	-3.94 (-12.24, 4.38)

Data Source: [4.35]

Appendix 11. Study 035 randomization and accounting. (6- month data)

Patient Accounting

	MK-0966			
	12.5 mg	25 mg	Diclofenac 150 mg	Total
ENTERED:	259	257	268	784
Male (age range)†	90 (39 to 79)	82 (40 to 83)	83 (40 to 84)	255 (39 to 84)
Female (age range)†	169 (39 to 86)	175 (39 to 87)	185 (39 to 91)	529 (39 to 91)
	n (%)	n (%)	n (%)	n (%)
COMPLETED:	183 (70.7)	166 (64.6)	173 (64.6)	522 (66.6)
DISCONTINUED:	76 (29.3)	91 (35.4)	95 (35.4)	262 (33.4)
Clinical adverse experience	29 (11.2)	25 (9.7)	35 (13.1)	89 (11.4)
Laboratory adverse experience	1 (0.4)*	2 (0.8)*	14 (5.2)	17 (2.2)
Deviation from protocol	6 (2.3)	6 (2.3)	7 (2.6)	19 (2.4)
Patient withdrew consent	3 (1.2)	4 (1.6)	10 (3.7)	17 (2.2)
Lost to follow-up	1 (0.4)	1 (0.4)	1 (0.4)	3 (0.4)
Lack of efficacy	34 (13.1)	50 (19.5)**	27 (10.1)	111 (14.2)
Other reasons‡	2 (0.8)	3 (1.2)	1 (0.4)	6 (0.8)

* p<0.001 vs. diclofenac.

** p=0.003 vs. diclofenac.

† Birth date masking to 12/31/XX in database, where XX is the true year of birth, may cause patient's age to appear 1 year younger than the actual age, depending on the date of randomization. All patients were ≥39 years of age when randomized.

‡ Includes reasons other than those listed.

Data Source: [4.13.1; 4.21.1; 4.31]

A.11.1

Summary of Key Secondary and Other End Points
Pairwise Treatment Differences Averaged Over 12-Week Treatment Period
(Intention-to-Treat Approach)

End Point	Pairwise Treatment Difference		
	25 mg vs. Diclofenac	12.5 mg vs. Diclofenac	25 mg vs. 12.5 mg
Key Secondary End Points			
	Difference in LSMean (95% CI)		
Physical Function Subscale (WOMAC) (0- to 100-mm VAS)	2.39 (-0.92, 5.71)	3.92 (0.61,7.23)	-1.53 (-4.87, 1.81)
Pain Subscale (WOMAC) (0- to 100-mm VAS)	2.79 (-0.59, 6.17)	3.83 (0.46,7.21)	-1.05 (-4.45, 2.36)
Stiffness Subscale (WOMAC) (0- to 100-mm VAS)	3.24 (-0.26, 6.75)	5.13 (1.63, 8.62)	-1.88 (-5.41, 1.65)
Patient Global Assessment of Disease Status (0- to 100-mm VAS)	5.11 (1.57, 8.66)	5.32 (1.79, 8.85)	-0.21 (-3.77, 3.36)
Other End Points			
End Point	Differences in LSMean (95% CI)		
	25 mg vs. Diclofenac	12.5 mg vs. Diclofenac	25 mg vs. 12.5 mg
Investigator Global Assessment of Response to Therapy (0- to 4-point Likert)	0.23 (0.09, 0.36)	0.17 (0.03, 0.30)	0.06 (-0.07, 0.20)
Study Joint Tenderness (0- to 3-point Likert)	-0.06 (-0.17, 0.06)	-0.04 (-0.15, 0.07)	-0.02 (-0.13, 0.10)
Acetaminophen Use (for Rescue) (tabs/day)	0.08 (-0.04, 0.20)	0.12 (-0.00, 0.24)	-0.04 (-0.16, 0.09)
Total Score Average (WOMAC) (0- to 100-mm VAS)	2.51 (-0.77, 5.79)	3.94 (0.67, 7.21)	-1.44 (-4.74, 1.87)
Subscale Average (WOMAC) (0- to 100-mm VAS)	2.74 (-0.54, 6.03)	4.21 (0.93, 7.48)	-1.46 (-4.77, 1.84)
	Differences in Percentage Points (95% CI)		
Study Joint Swelling (0=Absent, 1=Present) at Week 12 (regardless of baseline swelling status)	5.53% (-4.18%, 15.23%)	2.25% (-6.94%, 11.43%)	3.28% (-6.61%, 13.16%)

Data Source: [4.32]

A.11.2. Study 035. Secondary efficacy endpoints. 6- month data.

Table 38

Summary of Key Secondary and Other End Points
Pairwise Treatment Differences in Least Square Mean
Averaged Over 6-Month Treatment Period
(Intention-to-Treat Approach)

End Point	Pairwise Treatment Difference		
	25 mg vs. Diclofenac	12.5 mg vs. Diclofenac	25 mg vs. 12.5 mg
Key Secondary End Points			
	Difference in LSMean (95% CI)		
Physical Function Subscale (WOMAC) (0- to 100-mm VAS)	2.03 (-1.27, 5.33)	3.10 (-0.20, 6.39)	-1.07 (-4.39, 2.26)
Pain Subscale (WOMAC) (0- to 100-mm VAS)	2.31 (-1.06, 5.68)	2.90 (-0.46, 6.26)	-0.59 (-3.99, 2.80)
Stiffness Subscale (WOMAC) (0- to 100-mm VAS)	2.59 (-0.87, 6.06)	4.09 (0.63, 7.55)	-1.50 (-4.99, 1.99)
Patient Global Assessment of Disease Status (0- to 100-mm VAS)	4.46 (0.96, 7.96)	3.97 (0.48, 7.46)	0.49 (-3.04, 4.01)
	Difference in Percentage Points (95% CI)		
Discontinuation Due to Lack of Efficacy Over 6 Months	9.37% (3.35%, 15.41%)	3.06% (-2.42%, 8.52%)	6.33% (-0.02%, 12.68%)
Other End Points			
	Difference in LSMean (95% CI)		
End Point	25 mg vs. Diclofenac	12.5 mg vs. Diclofenac	25 mg vs. 12.5 mg
Investigator Global Assessment of Response to Therapy (0- to 4-point Likert)	0.23 (0.09, 0.36)	0.17 (0.03, 0.30)	0.06 (-0.07, -0.20)
Study Joint Tenderness (0- to 3-point Likert)	-0.06 (-0.17, 0.05)	-0.06 (-0.16, 0.05)	-0.00 (-0.11, 0.10)
Acetaminophen Use (for Rescue) (tabs/day)	0.07 (-0.05, 0.18)	0.09 (-0.03, 0.20)	-0.02 (-0.14, 0.10)
Total Score Average (WOMAC) (0- to 100-mm VAS)	2.10 (-1.17, 5.37)	3.08 (-0.18, 6.34)	-0.98 (-4.27, 2.31)
Subscale Average (WOMAC) (0- to 100-mm VAS)	2.25 (-1.02, 5.52)	3.28 (0.02, 6.54)	-1.03 (-4.32, 2.26)
	Difference in Percentage Points (95% CI)		
Study Joint Swelling (0=Absent, 1=Present) at Month 6 (regardless of baseline swelling status)	-0.46% (-10.38%, 9.47%)	0.45% (-9.24%, 10.13%)	-0.91% (-10.59%, 8.78%)

Data Source: [4.3; 4.32]