

The Efficacy of Topically Applied Ketoprofen Versus Celecoxib and Placebo in Osteoarthritis of the Knee

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Abstract

Purpose: Transfersome[®] carriers are ultradeformable vesicles designed to deliver drugs noninvasively through the skin barrier to target muscles and joints without being cleared by the cutaneous microcirculation. Ketoprofen is an NSAID analgesic with potent additional local anti-inflammatory properties. This study compared the safety and efficacy of 110 mg of ketoprofen in Transfersome[®] Gel (IDEA-033) applied epicutaneously twice daily (bid) with that of celecoxib (100 mg orally bid) and placebo in treating the signs and symptoms of osteoarthritis (OA) of the knee.

Methods: This 6-week, multicenter, randomized, double-blind, double-dummy, parallel-group study was conducted in 397 subjects with OA of the knee who were experiencing at least moderate pain when not taking analgesic medication. To qualify for the study, subjects met the following flare criteria for the index knee at the baseline visit: pain with walking of at least 40 mm on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) visual analogue scale (VAS), an increase in pain with walking of at least 15 mm on the WOMAC VAS at baseline compared with screening, and a physician's global assessment of OA of grade 3 to 5 and at least a 1-grade increase from screening.

Results: Three co-primary endpoints were defined a priori. In the intent-to-treat (ITT) analysis, for the WOMAC pain subscale, both IDEA-033 ($P = .0041$) and celecoxib ($P = .0004$) showed a statistically significant improvement in the least squares (LS) mean change from baseline at Week 6/End of Study versus placebo. For the WOMAC physical function subscale, celecoxib showed a significant ($P = .0100$) improvement in the LS mean change from baseline at Week 6/End of Study versus placebo; the improvement for IDEA-033 versus placebo approached statistical significance ($P = .0770$). For Patient Global Assessment, both IDEA-033 ($P = .0015$) and celecoxib ($P = .0145$) showed a statistically significantly higher response to therapy at Week 6/End of Study for the LS mean values versus placebo. Analysis of the efficacy endpoints by study week demonstrated that both IDEA-033 and celecoxib were associated with progressive improvement over the 6-week study period. The results of the per-protocol analysis were generally consistent with the ITT analysis; however, for the WOMAC physical function subscale, the improvement after 6 weeks with IDEA-033 was significantly ($P = .0118$) greater than with placebo. IDEA-033 was well tolerated. Overall, 53.6% of subjects treated with IDEA-033, 50.0% of subjects treated with celecoxib, and 48.8% of subjects treated with placebo reported adverse events; the differences were not statistically significant ($P = .7116$).

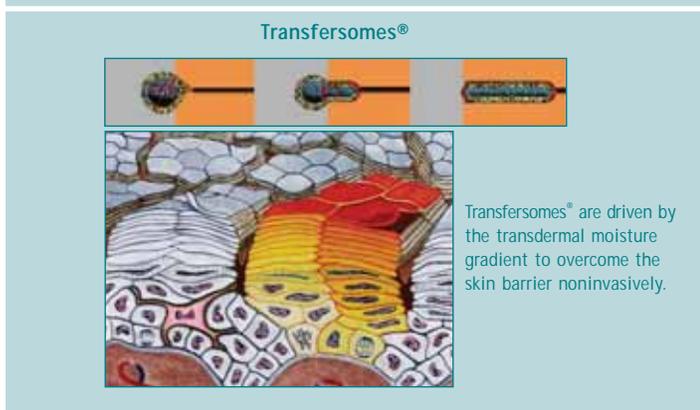
Conclusions: IDEA-033 was superior to placebo for 2 of the 3 primary efficacy measures in the ITT population and for all 3 primary efficacy measures in the per-protocol population. The study medications were generally well tolerated. The severity and nature of adverse events were generally similar among groups.

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Introduction

- Osteoarthritis (OA) is the most prevalent form of arthritis and is often associated with significant pain, disability, and impaired quality of life^{1,2}
- OA affects approximately 40 million Americans and has an estimated prevalence of 30% to 90% based on radiographic evidence^{3,4}
- Risk factors for OA include obesity, chondrocalcinosis, occupational exposures involving repetitive knee bending and lifting, and prior knee injuries⁵
- Current OA therapy is focused upon symptom relief and maintenance or improvement of functional status⁶; oral nonsteroidal anti-inflammatory drugs (NSAIDs) such as ketoprofen are often employed to provide symptom relief, but these agents may be associated with systemic adverse effects
- Transfersomes[®] are highly adaptable lipid aggregate drug carriers (Figure 1) that transport drug across the skin; their high adaptability allows them to transverse the skin barrier in a spontaneous and nondiffusive manner, and their large size limits their clearance by the cutaneous microcirculation
- This poster describes the results of a clinical trial in which ketoprofen was administered using this novel technology to subjects with OA of the knee

Figure 1. Transfersomes[®] for targeted drug delivery.



Objectives

- This study assessed the efficacy and safety of 110 mg of ketoprofen in Transfersome[®] Gel (IDEA-033) applied epicutaneously to each affected knee twice daily (bid), as compared with placebo and oral celecoxib 200 mg daily given in divided doses (100 mg/bid) for the relief of signs and symptoms of OA of the knee

Methods

Subjects

- Subjects who presented with the following clinical criteria for OA were eligible for the study:
 - OA of the index knee for a minimum of 6 months
 - Subject rating of pain in the index knee while not taking NSAIDs of at least 3 using a 5-point Likert scale

- Presenting 2 of the 3 following criteria: morning stiffness of less than 30 minutes in duration, crepitus on motion, and at least 40 years of age
- All subjects must have used oral NSAIDs for at least 3 days per week for the 3 months before screening or on at least 25 of the 30 days before screening
- After a washout period from usual OA medication (3 to 14 days depending on half-life), subjects had to meet the following OA flare criteria in their index knee at baseline:
 - Pain on walking of at least 40 mm on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)⁷ visual analogue scale (VAS)
 - An increase in pain with walking of at least 15 mm on the WOMAC VAS at baseline compared with screening
 - A physician's global assessment of OA of 3 to 5 and at least a 1-grade increase from screening

Study Design

- This randomized, double-blind, double-dummy, parallel-group, placebo- and active-controlled study was conducted at multiple sites in Germany
- Eligible subjects were allocated to 2 target groups: subjects with OA of both knees (Group 1) and subjects with OA of 1 knee (Group 2); no more than 25% of subjects could be in Group 2
- Subjects were stratified by group and randomly assigned by a centralized procedure to 6 weeks of therapy with 1 of 3 treatments:
 - Ketoprofen 110 mg in Transfersome[®] Gel epicutaneously bid + 1 placebo capsule bid (IDEA-033 group)
 - Celecoxib 100 mg bid + placebo Transfersome[®] Gel epicutaneously bid (celecoxib group)
 - Placebo Transfersome[®] Gel epicutaneously bid + 1 placebo capsule bid (placebo group)
- Acetaminophen (500 mg up to 4 times per day; maximum, 2000 mg) was used as rescue medicine; it was permitted on no more than 3 days in any 7-day period and was not allowed within 48 hours before visits

Assessments

- Subjects returned for visits at Weeks 2, 4, and 6 (or upon early discontinuation from the study) for clinical evaluation
- WOMAC pain and physical function subscales and Patient Global Assessment of Response to Therapy, based on a 5-point Likert scale, were assessed at each visit
- There were 3 predefined co-primary efficacy endpoints:
 - Change from baseline at Week 6 (or End of Study measurements) on the VAS version of the WOMAC pain subscale
 - Change from baseline at Week 6 (or End of Study measurements) on the VAS version of the WOMAC physical function subscale
 - Patient Global Assessment of Response to Therapy at Week 6 (or End of Study measurements)
- Adverse events were monitored throughout the study

Statistical Analysis

- The intent-to-treat (ITT) population was used for all analyses and included all randomized subjects who received at least 1 dose of study medication

- Demographic and baseline characteristics were compared among the treatment groups using a Chi-square test for categorical variables and 1-way analysis of variance (ANOVA) with treatment as a factor for continuous variables
- Efficacy endpoints were compared among the treatment groups using an analysis of covariance (ANCOVA), with study site and treatment as factors and baseline value as covariate
- The incidence of adverse events was compared among the treatment groups using Fisher's exact test

- Significant differences between the active treatment groups and placebo were observed as early as Week 2, with progressive improvement through Week 6/End of Study (Figure 3)

Results

- A total of 397 subjects were randomized, and 324 completed the 6-week study (Figure 2)
- No statistically significant differences were observed among the treatment groups in baseline mean age, gender, allocation to target group (involvement of 1 or both knees), and mean WOMAC pain and physical function subscale scores (Table 1)

Figure 2. Subject disposition.

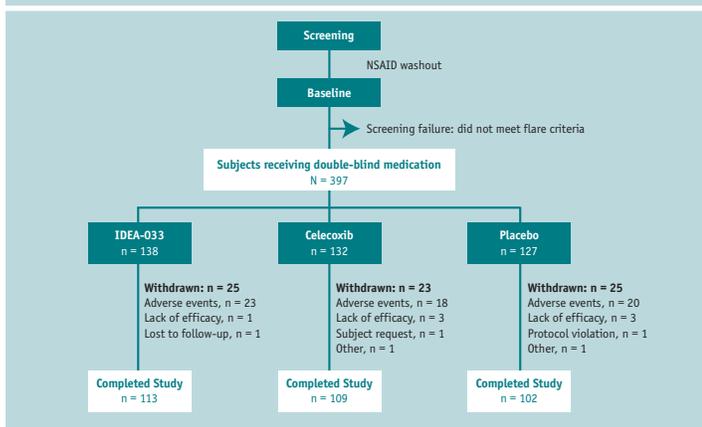


Table 1. Baseline Demographic and Disease Characteristics

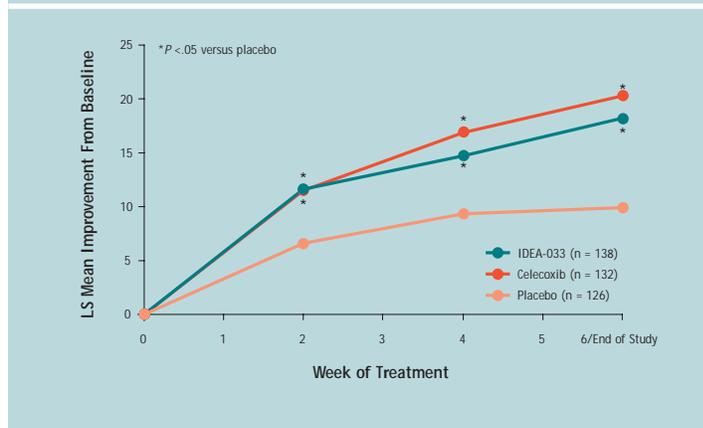
Characteristic	IDEA-033 n = 138	Celecoxib n = 132	Placebo n = 127	P Value
Mean (SD) age, yr	63.3 (10.1)	62.4 (9.6)	62.8 (9.8)	.7711
Gender, n (%)				.2813
Male	63 (45.7)	50 (37.9)	47 (37.0)	
Female	75 (54.3)	82 (62.1)	80 (63.0)	
Allocation to target group, n (%)				.5382
Both knees	107 (77.5)	103 (78.0)	105 (82.7)	
One knee	31 (22.5)	29 (22.0)	22 (20.6)	
Mean (SD) WOMAC pain subscale score*	55.1 (18.4)	56.1 (18.6)	59.9 (17.3)	.0791
Mean (SD) WOMAC physical function subscale score*	53.8 (20.4)	54.6 (21.0)	58.9 (19.6)	.0976

*All WOMAC subscale scores were normalized to a scale of 0 to 100 by dividing the sum subscale score by the number of questions for each subscale score.

Efficacy

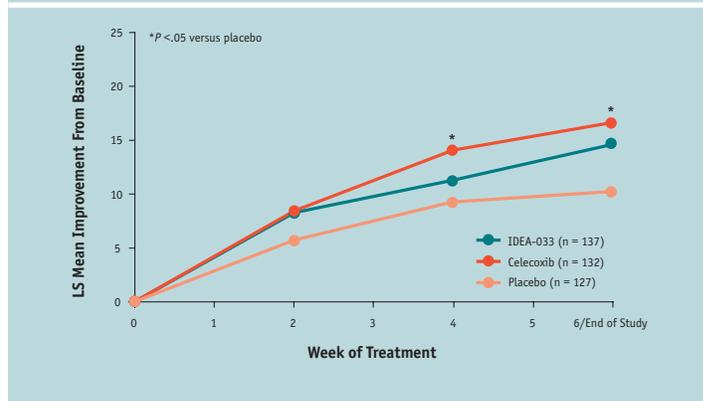
- For the WOMAC pain subscale, subjects receiving either IDEA-033 or celecoxib showed a significant improvement in least squares (LS) mean change from baseline at Week 6/End of Study versus placebo ($P = .0041$ and $P = .0004$, respectively; Figure 3)

Figure 3. WOMAC pain subscale: least squares (LS) mean improvement from baseline in the ITT population.



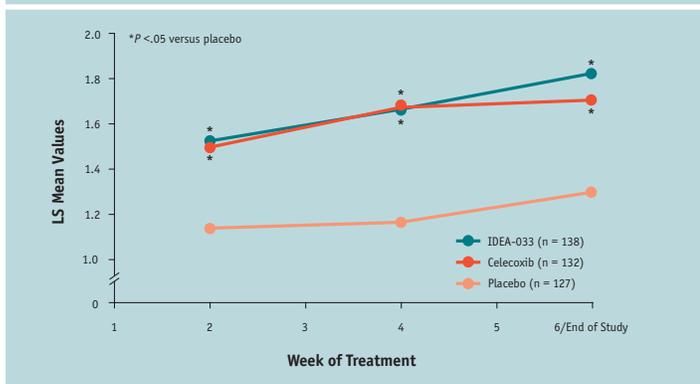
- For the WOMAC physical function subscale, subjects receiving celecoxib showed a significant improvement in LS mean change from baseline at Week 6/End of Study versus placebo ($P = .0100$; Figure 4); the improvement in the IDEA-033 group approached significance at this timepoint ($P = .0770$ versus placebo)

Figure 4. WOMAC physical function subscale: LS mean improvement from baseline in the ITT population.



- For the Patient Global Assessment of Response to Therapy, subjects receiving either IDEA-033 or celecoxib had significantly higher ratings of response to therapy at Week 6/End of Study versus placebo ($P = .0015$ and $P = .0145$, respectively; Figure 5)
- Statistically significant differences between the active treatment groups and placebo were observed as early as Week 2, with additional improvement through Week 6/End of Study (Figure 5)
- The results of a per-protocol analysis, which included subjects without major protocol deviations ($N = 299$), were generally consistent with those of the ITT analysis; however, for the WOMAC physical function subscale, the improvement after 6 weeks of treatment with IDEA-033 was significantly greater than with placebo ($P = .0118$)

Figure 5. Patient Global Assessment of Response to Therapy: LS mean values in the ITT population.



Safety

- Both IDEA-033 and celecoxib were well tolerated
- There were no significant differences among the treatment groups in the proportions of subjects who reported adverse events, serious adverse events, or who discontinued because of adverse events (Table 2)
- No significant differences were observed among the treatment groups in the incidences of gastrointestinal or dermatological adverse events (Table 3)

Table 2. Summary of Adverse Events

Evaluation, n (%)	IDEA-033 n = 138	Celecoxib n = 132	Placebo n = 127	P Value
Subjects reporting adverse events	74 (53.6)	66 (50.0)	62 (48.8)	.7116
Subjects with serious adverse events	2 (1.4)	3 (2.3)	2 (1.6)	.8986
Subjects discontinuing because of adverse events	24 (17.4)	18 (13.6)	20 (15.7)	.6864

Table 3. Gastrointestinal and Dermatological Adverse Events Occurring in at Least 1% of Subjects

Adverse Event, n (%)	IDEA-033 n = 138	Celecoxib n = 132	Placebo n = 127	P Value
Any gastrointestinal disorder	13 (9.4)	18 (13.6)	12 (9.4)	.4727
Upper abdominal pain	2 (1.4)	4 (3.0)	3 (2.4)	.6457
Nausea	2 (1.4)	3 (2.3)	2 (1.6)	.8986
Dyspepsia	1 (0.7)	4 (3.0)	1 (0.8)	.3321
Gastritis	3 (2.2)	0	3 (2.4)	.2250
Constipation	3 (2.2)	0	1 (0.8)	.2752
Toothache	0	3 (2.3)	1 (0.8)	.1711
Diarrhea	1 (0.7)	2 (1.5)	0	.5399
Flatulence	0	2 (1.5)	0	.2118
Any skin and subcutaneous tissue disorder	39 (28.3)	27 (20.5)	28 (22.0)	.2893
Erythema	29 (21.0)	18 (13.6)	21 (16.5)	.2844
Pruritus	0	5 (3.8)	4 (3.1)	.0530
Exanthema	3 (2.2)	2 (1.5)	1 (0.8)	.8751
Urticaria	2 (1.4)	1 (0.8)	1 (0.8)	1.0000
Allergic dermatitis	2 (1.4)	1 (0.8)	0	.7765
Skin irritation	2 (1.4)	0	0	.3320

Conclusions

- IDEA-033 was more effective than placebo and nearly as effective as celecoxib at treating OA of the knee
- IDEA-033 was well tolerated; the severity and nature of adverse events were generally similar among the treatment groups
- IDEA-033 represents a promising alternative to systemic anti-inflammatory therapy for OA of the knee

References

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