EXTENDED REPORT

Title

Efficacy and safety of epicutaneous ketoprofen in Transfersome® (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the knee: multicentre randomised controlled trial

Corresponding author

Matthias Rother
IDEA AG, Frankfurter Ring 193a, 80807 Muenchen, Germany
E-mail: rother@idea-ag.de

Co-authors

Bernard J Lavins
McNeil Consumer & Specialty Pharmaceuticals, a Division of McNeil-PPC, Inc., Fort Washington, USA

Werner Kneer
Orthopaedic outpatient centre, Stockach, Germany

Klaus Lehnhardt
Orthopaedic outpatient centre, Bad Duerrheim, Germany

Egbert J Seidel
Zentrum fuer Physikalische und Rehabilitative Medizin, Sophien- und Hufenland-Klinikum, Weimar, Germany

Stefan Mazgareanu
IDEA AG, Muenchen, Germany

Keywords: osteoarthritis, ketoprofen, celecoxib, ultra-deformable vesicles

Word count: 2646 words

Objective: To compare epicutaneous ketoprofen in Transfersome® (ultra-deformable vesicles, IDEA-033) versus oral celecoxib and placebo for relief of signs and symptoms in knee osteoarthritis.

Methods: Multicentre, randomised, double blind, controlled trial; 397 patients with knee osteoarthritis participated and 324 completed the trial. They were randomly assigned 110 mg epicutaneous ketoprofen in 4.8 g Transfersome® plus oral placebo (n =138), 100 mg oral celecoxib plus placebo gel (n = 132), or both placebo formulations (n = 127) twice daily for six weeks. Primary efficacy outcome measures were the changes from baseline to end of study in Western Ontario and McMaster Universities (WOMAC) Index of Osteoarthritis pain subscale, physical function subscale, and patient global assessment (PGA) of response.

Results: The mean WOMAC pain subscale scores in the intent to treat population were reduced by 18.2 (95% confidence interval -22.1 to -14.3), 20.3 (-24.3 to -16.2), and 9.9 (-13.9 to -5.8) in the IDEA-033, celecoxib, and placebo groups; the physical function subscale score by 14.6 (-18.1 to -11.0), 16.6 (-20.2 to -13.0), and 10.2 (-13.8 to -6.6). The mean PGA of response scores were 1.8 (1.6 to 2.1), 1.7 (1.5 to 1.9), and 1.3 (1.1 to 1.5). The differences in change between IDEA-033 and placebo were statistically significant for pain subscale (p=0.0041) and PGA of response (p=0.0015). Gastrointestinal adverse events for IDEA-033 were similar to placebo.

Conclusion: IDEA-033 is superior to placebo and comparable with celecoxib in relieving pain associated with an acute flare of knee osteoarthritis.

Clinical Trials.gov Identifier: NCT00317733

Osteoarthritis (OA) is the most prevalent form of arthritis and often associated with significant pain, disability, and impaired quality of life due to cartilage degeneration and synovial inflammation.[1] Current treatment recommendations for OA focus on relieving pain and stiffness as well as maintaining physical function. Nonsteroidal antiinflammatory drugs (NSAIDs) are one of the cornerstones of these guidelines but face increasing concerns related to long-term use due to their safety profiles.[2-5] Nonspecific cyclooxygenase inhibitors (COX) have the potential to cause gastrointestinal bleeding in a dose-related manner, and recent studies have shown that COX-2 inhibitors increase the risk of cardiovascular events, such as myocardial infarctions.[6]

IDEA-033 is ketoprofen, a well established NSAID,[7] in Transfersome®. Transfersomes® are ultra-deformable carriers loaded with an active substance and applied epicutaneously in an aqueous suspension. Once the Transfersomes® are on the skin, water starts to evaporate and deprive carriers of their suspending medium. Carriers reaching their solubility limit are attracted by the higher water content in the skin resulting in spontaneous migration of IDEA-033 through the skin barrier.[8] The cutaneous microcirculation cannot clear these carriers due to their large size. The maximum depth of ketoprofen delivery from IDEA-033 in soft tissue is controlled by the applied dose per skin area. We compared this innovative delivery form of ketoprofen with the first approved specific COX-2 inhibitor, celecoxib,[9] and placebo for relief of signs and symptoms in knee osteoarthritis. We selected celecoxib at its approved standard dose for use in OA: 100 mg twice daily.[10]

METHODS

Participants

The study took place at 30 out-patient units in Germany between July 2003 and January 2004. The ethics committees/institutional review boards of each centre approved the protocol.

We considered for inclusion patients with a history of osteoarthritis (OA) of the knee for a minimum of six months meeting two of the following three clinical criteria: morning stiffness of less than 30 minutes duration, crepitus on motion, age ≥ 40 years; rating their pain in the index knee as ≥ 3 on a five point Likert scale; and taking oral nonsteroidal antiinflammatory drugs (NSAIDs) at least three days per week for the past three months or > 25 of the past 30 days. Moreover, patients had to meet three OA flare criteria: pain at walking in the index knee ≥ 40 mm on a visual analogue scale (VAS); increased by ≥ 15 mm compared with pain on prestudy treatment (screening); physician's global assessment of OA 3-5 and at least 1 grade increase from screening.

Exclusion criteria were grade 1 or grade 4 severity of the index knee based on Kellgren and Lawrence radiographic criteria[11]; intraarticular injections or arthroscopy of the index knee within three months prior to screening; signs of any clinically important inflammation of the index knee; crystalline-induced synovitis in the index knee; history, physical examination, or radiographic suggestive of acute inflammatory arthritis, rheumatoid arthritis, psoriatic

arthritis, septic arthritis, gout, pseudogout, fibromyalgia, lupus erythematosus, or other types of inflammatory arthritis of the index knee.

Study design

Patients with pain in the nonindex knee during the two weeks before baseline received epicutaneous treatment of both knees (group 1). Patients with no pain in the nonindex knee received epicutaneous treatment of the index knee only (group 2). We used a computer generated centralised randomisation list in blocks of six patients, balanced per study centre and within groups 1 and 2, respectively. Randomisation to group 2 was restricted to three out of 12 subjects, whereas randomisation to group 1 was unrestricted. Randomisation was performed by a centralised telephone procedure.

Patients returned for study visits after two, four, and six weeks. At each visit, the VAS version of the WOMAC Index of OA,[12,13] PGA of response, physician's global assessment of OA, and safety assessments were performed.

Interventions

Patients received either 110 mg epicutaneous ketoprofen in 4.8 g Transfersome® (a semi-solid formulation, IDEA-033) plus oral placebo or 100 mg oral celecoxib plus placebo gel or both placebo formulations every 12 hours for six weeks. IDEA-033 was accurately dosed using a commercially available applicator. 110 mg ketoprofen in 4.8 g Transfersome® had demonstrated an acceptable safety profile in previous studies and was the maximum feasible dose taking less than 30 minutes to dry on the skin.

Patients could take up to 2000 mg paracetamol per day as rescue medication for knee pain for three days in any week apart from the 48 hours preceding a study visit.

Outcome measures

We assessed all efficacy outcome measures in the index knee.

Primary outcome measures

We selected the following primary efficacy outcome measures: changes from baseline to end of study in WOMAC Index of OA VA3.1 pain subscale, physical function subscale, and PGA of response (five point Likert scale from 0 = none to 4 = excellent) in the intent to treat (ITT) population.

Secondary outcome measures

Secondary efficacy outcome measures were the changes from baseline to end of study in physician's global assessment of OA (five point classification),[14] WOMAC stiffness subscale, use of rescue medication, discontinuation due to lack of efficacy, and primary outcome measures after two and four weeks of treatment.

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

In a post hoc analysis, responder rates were calculated modified in line with the recently updated Outcome Measures in Rheumatology initiative - Osteoarthritis Research Society International (OMERACT-OARSI) criteria.[15]

Safety assessments consisted of physical examination, standard haematology and biochemistry, adverse event questioning, plasma concentrations of ketoprofen, as well as erythema and oedema scoring of the skin area exposed to Transfersome®.

Sample size

We calculated the sample size for this study based on the criteria recommended by the OARSI Standing Committee for Clinical Trial Response Criteria [16]. By these criteria, a patient is classified as a responder if the patient demonstrates the following response in at least two of the following three domains: a 10 mm improvement on pain, a 15 mm improvement on physical function and a 35% improvement on a PGA. This was the first phase II study of IDEA-033. Thus we used the placebo group's mean PGA score of 1.33 from a rofecoxib trial [17] as an expected placebo response. A difference in mean PGA of 0.47 and a standard deviation (SD) estimate of 1.24 were used for the PGA score. Differences of 10 and 15 were used for the WOMAC pain and physical function scores, respectively, as well as a common SD of 27 [18]. 120 patients per treatment group would provide ≥ 80% power to detect differences in all three symptomatic domains. 132 patients per group would account for a 10% dropout rate.

Statistical analysis

Primary efficacy analysis

We performed the primary efficacy analysis on all randomised patients who used at least one dose of study medication, the ITT population. The per protocol (PP) population included patients who did not have significant protocol deviations such as use of rescue medication exceeding three days in any week or within the 48 hours preceding visits. All efficacy outcome measures were additionally analysed in the PP population.

For the primary analysis, we used a closed step-down approach [19]: first we compared celecoxib with placebo, if P value ≤ 0.05, then we compared IDEA-033 with placebo. Thus no adjustment of type I error was necessary. We considered a P value of < 0.05 as statistically significant.

Secondary efficacy analysis

For WOMAC pain and function subscales, we calculated changes from baseline at each visit for each subject based on available data at that visit. We did not impute missing data except for using last observation carried forward in patients who had only baseline data.

We analysed the changes from baseline in WOMAC pain and function subscales using analysis of covariance (ANCOVA) models with treatment and investigator as fixed effects and the corresponding baseline value as a covariate. We included the treatment by investigator interaction in the final model if its P value was < 0.10. We analysed PGA using an ANCOVA model with treatment and investigator as fixed effects and the WOMAC pain

score at baseline as a covariate. We set missing PGA scores at zero, the worst possible outcome. We used least squares means for statistical comparisons between the two active treatments and placebo.

RESULTS

Between July and December 2003, 499 patients were screened and 397 randomised (fig 1). All patients received the allocated treatment. 324 patients completed the study. The number of patients withdrawn due to adverse events was similar in all three groups (fig 1) as were baseline characteristics (table 1).

Fig 1 Flow of patients through trial

Legend to Fig 1:

All results presented are based on the analysis of the intent-to-treat population, i.e. 138, 132 and 127 patients of the three treatment groups, applying the last-observation-carried-forward technique.

Table 1 Baseline characteristics of patients randomised to IDEA-033, celecoxib, or placebo. Values are numbers (percentages) unless stated otherwise

Characteristic	IDEA-033 (n = 138)	Celecoxib (n = 132)	Placebo (n = 127)
Mean (SD) age (years)	63.3 (10.1)	62.4 (9.6)	62.8 (9.8)
Men	63 (45.7)	50 (37.9)	47 (37.0)
Women	75 (54.3)	82 (62.1)	80 (63.0)
WOMAC			
Mean (SD) pain score†	55.1 (18.4)	56.1 (18.6)	59.9 (17.3)
Mean (SD) stiffness score†	49.4 (21.1)	50.6 (22.2)	53.1 (21.1)
Mean (SD) physical function score†	53.8 (20.4)*	54.6 (21.0)	58.9 (19.6)
Mean (SD) physician's global assessment of OA	3.9 (0.5)	3.9 (0.6)	4.0 (0.5)

* One patient did not provide a baseline physical function score (n=137).

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

Efficacy

Primary efficacy analysis

The changes from baseline to end of study in mean WOMAC pain score were similar in the IDEA-033 and celecoxib groups and superior to placebo (table 2). Changes in mean WOMAC physical function score were less pronounced on IDEA-033 compared with celecoxib (ITT population) (table 2). Changes in mean WOMAC physical function score on IDEA-033 turned out to be significantly superior to placebo (table 2). Mean PGA of response at end of study were assessed as fair (2) for both active treatments and poor for placebo (1) (table 2). Thus superiority of IDEA-033 compared with placebo was demonstrated for two of three primary efficacy outcomes for the ITT population.

Table 2 Primary efficacy outcomes observed in patients with osteoarthritis (intent to treat and per protocol populations). Results are given as changes from baseline to end of study unless stated otherwise

Outcomes	**IDEA-033**	**Celecoxib**	**Placebo**
Intent-to treat population (n)	138	132	127
WOMAC			
Mean (SD) change in pain score	-19.4 (21.2)	-20.7 (22.7)	-12.4 (20.8)
LS mean (SE) change	-18.2 (2.0)*	-20.3 (2.1)*	-9.9 (2.1)
95% confidence interval	(-22.1 to -14.3)	(-24.3 to -16.2)	(-13.9 to -5.8)
P value of comparison to placebo	0.0041	0.0004	
Mean (SD) change in physical function score	-16.0 (20.3)	-18.1 (22.5)	-12.3 (19.2)
LS mean (SE) change	-14.6 (1.8)	-16.6 (1.8)*	-10.2 (1.8)
95% confidence interval	(-18.1 to -11.0)	(-20.2 to -13.0)	(-13.8 to -6.6)
P value of comparison to placebo	0.0770	0.0100	
Patient global assessment of response at end of study			
None (0), n (%)	35 (25.4)	34 (25.8)	51 (40.2)
Poor (1), n (%)	16 (11.6)	23 (17.4)	20 (15.7)
Fair (2), n (%)	23 (16.7)	24 (18.2)	21 (16.5)
Good (3), n (%)	48 (34.8)	37 (28.0)	30 (23.6)
Excellent (4), n (%)	16 (11.6)	14 (10.6)	5 (3.9)
Mean (SD) score	2.2 (1.3)	1.9 (1.3)	1.5 (1.3)
LS mean (SE) score	1.8 (0.1)*	1.7 (0.1)*	1.3 (0.1)
95% confidence interval	(1.6 to 2.1)	(1.5 to 1.9)	(1.1 to 1.5)
P value of comparison to placebo	0.0015	0.0145	

* Statistically significant difference ($P<0.05$) compared to placebo.

Table 3 Secondary efficacy outcomes observed in patients with osteoarthritis (intent-to-treat population). Results are given as changes from baseline to end of study unless stated otherwise

Outcomes	IDEA-033 (n = 138)	Celecoxib (n = 132)	Placebo (n = 127)
Physician's global assessment of OA at end of study			
Very good (1), n (%)	12 (8.7%)	13 (9.8%)	4 (3.1%)
Good (2), n (%)	62 (44.9%)	48 (36.4%)	41 (32.3%)
Fair (3), n (%)	47 (34.1%)	50 (37.9%)	46 (36.2%)
Poor (4), n (%)	14 (10.1%)	16 (12.1%)	29 (22.8%)
Very poor (5), n (%)	3 (2.2%)	5 (3.8%)	7 (5.5%)
Mean (SD)	2.5 (0.9)	2.6 (1.0)	3.0 (1.0)
LS mean (SE)	2.5 (0.1)*	2.6 (0.1)*	2.9 (0.1)
95% confidence interval	(2.3 to 2.7)	(2.4 to 2.8)	(2.7 to 3.1)
P value of comparison to placebo	0.0009	0.0141	
WOMAC stiffness score			
Mean (SD) change in stiffness score	-14.7 (22.8)	-16.7 (26.4)	-10.0 (21.3)
LS mean (SE) change	-14.3 (1.9)*	-15.8 (2.0)*	-8.2 (2.0)
95% confidence interval	(-18.1 to -10.5)	(-19.7 to -12.0)	(-12.1 to -4.3)
P value of comparison to placebo	0.0215	0.0044	
Use of rescue medication†			
Mean (SD)	0.24 (0.43)	0.16 (0.34)	0.37 (0.60)
LS mean (SE)	0.26 (0.04)*	0.17 (0.04)*	0.38 (0.04)
95% confidence interval	(0.2 to 0.3)	(0.1 to 0.2)	(0.3 to 0.5)
P value of comparison to placebo	0.0291	0.0002	
OMERACT-OARSI responder‡			
n (%) at end of study	95 (68.8)*	84 (63.6)	70 (55.1)
95% confidence interval	(61.1 to 76.6)	(55.4 to 71.8)	(46.5 to 63.8)
P value of comparison to placebo	0.0247	0.1551	
Number needed to treat (vs placebo)	8.0	12.0	
95% confidence interval	(2.1 to 25.3)	(-3.4 to 20.4)	

* Statistically significant difference (P<0.05) compared to placebo.
† Total Number of rescue medication capsules taken/total number of days in study.
‡ Post hoc analysis of responder rates according to the recently updated OMERACT-OARSI criteria.[15]

Secondary efficacy analysis

Planned secondary efficacy outcomes revealed similar results for both active treatments (table 3). Both active treatments were significantly superior to placebo. The post hoc analysis of responder rates according to the recently updated OMERACT-OARSI criteria[15] essentially confirmed the results in planned efficacy measures (table 3). IDEA-033 had a significantly superior responder rate compared to placebo in contrast to celecoxib.

Safety

Adverse events

All randomised patients were evaluated for safety. No gastrointestinal (GI) bleeding occurred. Nonserious GI adverse events for IDEA-033 (9.4%) were similar to placebo and numerically lower than for celecoxib (13.6%). One patient treated with celecoxib had a myocardial infarction, one patient treated with placebo had angina, and no serious cardiovascular adverse event occurred in patients treated with IDEA-033. Most adverse events were evenly spread throughout all three treatment groups (table 4). There was a tendency for more patients reporting erythema in the IDEA-033 group. IDEA-033 seemed to cause more skin irritations than the matching placebo gel with the popliteal fossa being the predominant skin area concerned.

Plasma ketoprofen concentrations

In the IDEA-033 group, geometric mean (range) ketoprofen plasma concentrations immediately before the next dose of IDEA-033 were 81.2 (4.6 - 677.8) ng/ml and 76.7 (4.6 - 598.8) ng/ml after two and six weeks of treatment, respectively. There were no significant differences between patients who received treatment of both knees and patients who received treatment of the index knee only.

Table 4 Most commonly reported adverse events. Values represent numbers of patients (percentages)*

MedDRA† System Organ Class (SOC) Preferred Term	IDEA-033 (n = 138)	Celecoxib (n = 132)	Placebo (n = 127)
Any SOC, any adverse events	74 (53.6)	66 (50.0)	62 (48.8)
Gastrointestinal disorders, any adverse events	13 (9.4)	18 (13.6)	12 (9.4)
Abdominal pain, upper	2 (1.4)	4 (3.0)	3 (2.4)
Constipation	3 (2.2)	0 (0.0)	1 (0.8)
Diarrhoea NOS‡	1 (0.7)	2 (1.5)	0 (0.0)
Dyspepsia	1 (0.7)	4 (3.0)	1 (0.8)
Flatulence	0 (0.0)	2 (1.5)	0 (0.0)
Gastritis NOS‡	3 (2.2)	0 (0.0)	3 (2.4)
Nausea	2 (1.4)	3 (2.3)	2 (1.6)
Toothache	0 (0.0)	3 (2.3)	1 (0.8)
Musculoskeletal and connective tissue disorders, any adverse events	12 (8.7)	19 (14.4)	20 (15.7)
Arthralgia	3 (2.2)	3 (2.3)	4 (3.1)
Back pain	6 (4.3)	6 (4.5)	4 (3.1)
Joint effusion	2 (1.4)	2 (1.5)	1 (0.8)
Sciatica	0 (0.0)	4 (3.0)	1 (0.8)
Psychiatric disorders	0 (0.0)	6 (4.5)	1 (0.8)
Depression	0 (0.0)	3 (2.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders, any adverse events	17 (12.3)	14 (10.6)	10 (7.9)
Nasopharyngitis	10 (7.2)	11 (8.3)	6 (4.7)
Skin and subcutaneous tissue disorders, any adverse events	39 (28.3)	27 (20.5)	28 (22.0)
Dermatitis allergic	2 (1.4)	1 (0.8)	0 (0.0)
Erythema	29 (21.0)	18 (13.6)	21 (16.5)
Exanthema	3 (2.2)	2 (1.5)	1 (0.8)
Pruritus	0 (0.0)	5 (3.8)	4 (3.1)
Skin irritation	2 (1.4)	0 (0.0)	0 (0.0)
Urticaria NOS‡	2 (1.4)	1 (0.8)	1 (0.8)

* Patients who reported an adverse event more often than once during the study were only counted once.
† Medical Dictionary for Regulatory Activities.
‡ Not otherwise specified.

DISCUSSION

Efficacy

Patients with an acute flare of OA treated epicutaneously with IDEA-033 for six weeks had relief of pain and treatment responses judged by the patients comparable to the prototype of specific COX-2 inhibitors, celecoxib. We selected celecoxib at its approved standard dose for use in OA: 100 mg twice daily.[10] In a recent publication comparing twice-daily doses of 100 mg and 200 mg celecoxib with diclofenac 50 mg and naproxen 500 mg twice daily in a total of 13,274 OA patients, both doses of celecoxib were as effective as diclofenac and naproxen.[20] Thus, the celecoxib dose used in this study is a fully effective dose.

IDEA-033 was superior to placebo in all efficacy outcomes apart from the WOMAC physical function score in the ITT population, whereas in the PP population this outcome was also superior to placebo.

Although widely used for the treatment of OA, conventional topical NSAIDs have been criticised frequently. A particular concern was the absorption of the NSAID through the skin and systemic availability through the intense cutaneous microcirculation which may explain their effects in OA. Topical diclofenac applied to the index knee resulted in similar diclofenac concentrations in the synovial fluids of both index knee and nonindex knee.[21]

Topical NSAIDs applied as a conventional gel or a patch pass the skin barrier which is located in the stratum corneum.[22] The driving force of passive diffusion is the concentration gradient between topical NSAID and skin. Once drug molecules have crossed the stratum corneum, they are subject to clearance through the cutaneous microvasculature.[23] In this aspect, IDEA-033 is totally different to conventional topical NSAIDs. The transport of IDEA-033 into tissues such as muscles and joints deep below the skin application site is driven by the transdermal moisture gradient. The cutaneous microcirculation cannot clear Transfersomes® due to the size of the carrier. In studies in pigs, IDEA-033 showed substantially higher drug concentrations in the target muscle and index knee,[24] in contrast to what was reported on conventional topical NSAIDs.[21]

Safety

IDEA-033 proved to be safe and well tolerated. Although IDEA-033 seemed to cause more skin irritations than the matching placebo gel, the intensity of erythema was generally mild and reversible.[25] All other adverse events were evenly spread throughout all three treatment groups. GI adverse events for IDEA-033 were similar to placebo.

The ketoprofen plasma concentrations detected in the IDEA-033 group (4.6 - 677 ng/ml) corresponded to 0.1 to 10% of the maximum plasma concentrations detected following a usual therapeutic oral dose of 200 mg ketoprofen per day.[26] Thus, the systemic exposure to ketoprofen following IDEA-033 was substantially lower than after oral administration.

Conclusions

An ultra-deformable carrier loaded with ketoprofen for epicutaneous application (IDEA-033) was superior to placebo and similar to oral celecoxib in relieving pain of knee OA over a six-week treatment period

New drug delivery systems may pave the way for evidence-based long-term targeted NSAID use in OA.

Fig 1 Flow of patients through trial

Legend to Fig 1:

All results presented are based on the analysis of the intent-to-treat population, i.e. 138, 132 and 127 patients of the three treatment groups, applying the last-observation-carried-forward technique.

REFERENCES

1 Scott JC, Hochbert MC. Arthritic and other musculosceletal diseases. In: Brownson RC, Remington PL, Davis JR, eds. *Chronic disease epidemiology and control*. Washington: American Public Health Association 1993.

2 Recommendations for the medical management of osteoarthritis of the hip and knee: 2000 update. American College of Rheumatology Subcommittee on Osteoarthritis Guidelines. Arthritis Rheum. 2000;43:1905-15.

3 Pendleton A, Arden N, Dougados M, Doherty M, Bannwarth B, Bijlsma JW, et al. EULAR recommendations for the management of knee osteoarthritis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials (ESCISIT). Ann Rheum Dis. 2000;59:936-44.

4 Mazieres B, Bannwarth B, Dougados M, Lequesne M. EULAR recommendations for the management of knee osteoarthritis. Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutic Trials. Joint Bone Spine. 2001;68:231-40.

5 Roddy E, Doherty M. Guidelines for management of osteoarthritis published by the American College of Rheumatology and the European League Against Rheumatism: why are they so different? Rheum Dis Clin North Am. 2003;29:717-31.

6 Solomon DH, Schneeweiss S, Glynn RJ, Kiyota Y, Levin R, Mogun H, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation. 2004;109:2068-73.

7 Veys EM. 20 years' experience with ketoprofen. Scand J Rheumatol Suppl. 1991;90:Suppl 1-44.

8 Cevc G, Schatzlein A, Richardsen H. Ultradeformable lipid vesicles can penetrate the skin and other semi-permeable barriers unfragmented. Evidence from double label CLSM experiments and direct size measurements. Biochim Biophys Acta. 2002;1564:21-30.

9 FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. N Engl J Med. 2001;345:433-42.

10 CELEBREX (celecoxib capsules) prescribing information: G.D. Searle LLC, a division of Pfizer Inc, New York, NY, USA; 2005.

11 Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16:494-502.

12 Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. 1988;15:1833-40.

13 Bellamy N. Pain assessment in osteoarthritis: experience with the WOMAC osteoarthritis index. Semin Arthritis Rheum. 1989;18:14-7.

14 American Rheumatism Association Glossary Committee. Dictionary of the rheumatic diseases: signs and symptoms. New York: Contact Associates International 1988.

15 Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. Osteoarthritis Cartilage. 2004;12:389-99.

16 Dougados M, Leclaire P, van der Heijde D, Bloch DA, Bellamy N, Altman RD. Response criteria for clinical trials on osteoarthritis of the knee and hip: a report of the Osteoarthritis Research Society International Standing Committee for Clinical Trials response criteria initiative. Osteoarthritis Cartilage. 2000;8:395-403.

17 Ehrich EW, Schnitzer TJ, McIlwain H, Levy R, Wolfe F, Weisman M, et al. Effect of specific COX-2 inhibition in osteoarthritis of the knee: a 6 week double blind, placebo controlled pilot study of rofecoxib. Rofecoxib Osteoarthritis Pilot Study Group. J Rheumatol. 1999;26:2438-47.

18 Davies GM, Watson DJ, Bellamy N. Comparison of the responsiveness and relative effect size of the western Ontario and McMaster Universities Osteoarthritis Index and the short-form Medical Outcomes Study Survey in a randomized, clinical trial of osteoarthritis patients. Arthritis Care Res 1999;12:172-9

19 Maurer W, Hothorn LA, Lehmacher W. Multiple comparisons in drug clinical trials and preclinical assays: a-priori ordered hypotheses. In: Vollmar J, editor. Testing Principles in Clinical and Preclinical Trials. Stuttgart, Germany: Gustav Fischer Verlag; 1995. p. 3-18.

20 Singh G, Fort JG, Goldstein JL, Levy RA, Hanrahan PS, Bello AE, et al. Celecoxib versus naproxen and diclofenac in osteoarthritis patients: SUCCESS-I Study. Am J Med. 2006;119:255-66.

21 Radermacher J, Jentsch D, Scholl MA, Lustinetz T, Frolich JC. Diclofenac concentrations in synovial fluid and plasma after cutaneous application in inflammatory and degenerative joint disease. Br J Clin Pharmacol. 1991;31:537-41.

22 Hadgraft J, Walters KA, Guy RH. Epidermal lipids and topical drug delivery. Semin Dermatol. 1992;11:139-44.

23 Kretsos K, Kasting GB. Dermal capillary clearance: physiology and modeling. Skin Pharmacol Physiol. 2005;18:55-74.

24 Mazgareanu S, Vierl U, Rother M. Transfersome® Carriers for Transdermal Targeted Delivery of NSAID into Muscle and Knee Joint - Pre-Clinical Results with IDEA-033. Osteoarthritis Cartilage. 2004;12:S87.

25 Lin J, Zhang W, Jones A, Doherty M. Efficacy of topical non-steroidal anti-inflammatory drugs in the treatment of osteoarthritis: meta-analysis of randomised controlled trials. Bmj. 2004;329:324.

26 Jamali F, Brocks DR. Clinical pharmacokinetics of ketoprofen and its enantiomers. Clin Pharmacokinet. 1990;19:197-217.

ACKNOWLEDGEMENTS

IDEA AG (Germany) and McNeill Consumer & Specialty Pharmaceuticals (USA) sponsored the study and carried out on-site monitoring of all participants. The sponsors had an opportunity to comment on the manuscript before submission, but the final version was the sole responsibility of the authors.

Further to WK, KL, and ES, the following investigators participated in the study: Drs Gunar Baumann, Juergen Beck, Philipp Bolze, Jaroslaw Boronczyk, Gunter Boy, Hanns-Gerd Dammann, Thorsten Decker, Joachim Deutmarg, Heike Dorow, Patrick Finkbeiner, Maik Lomp, Klaus Hammerle, Klaus Heil, Steffen Hein, Axel Kaden, Reiner Lehmann, Wolfgang Menke, Othard August Moller, Ludwig Radinger, Ulrich Scherer, Wolfgang Schmidl, Hartmut Schneider, Frank-Detlef Stanek, Wilfried Trultzsch, Dieter Veith, Ruediger Zahn, Joerg Zeeh.

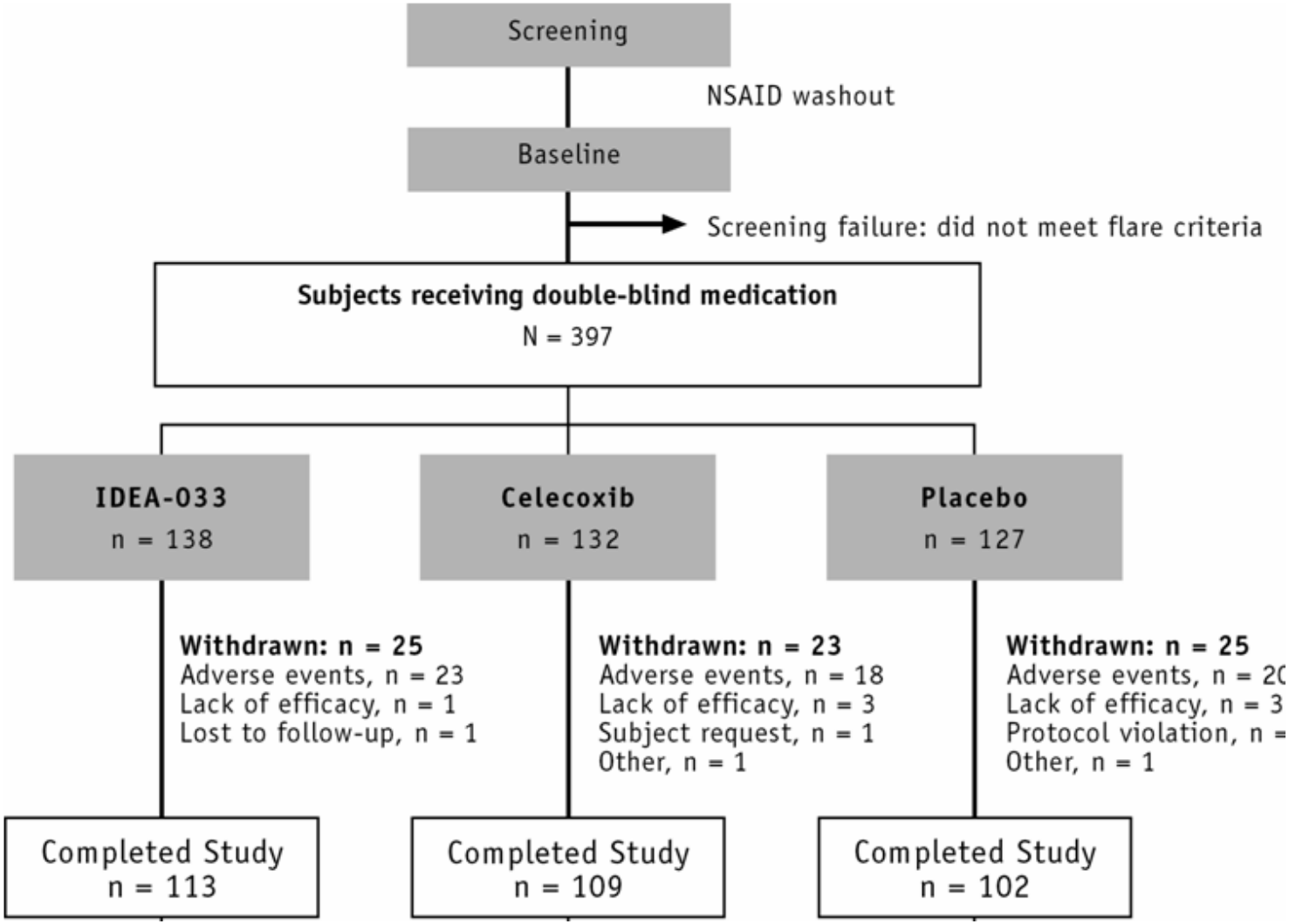

Figure 1