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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Asunto: Radicación No. 11-181661
Resolución No. 33176
Actuación: Recurso de Reposición

MAURICIO JARAMILLO CAMPUZANO, abogado, identificado con la cédula de ciudadanía No. 80.421.942 de Bogotá y la tarjeta profesional No. 74.555 del Consejo Superior de la Judicatura, actuando en calidad de apoderado de la sociedad **SEQUESSOME TECHNOLOGY HOLDINGS LIMITED**, solicitante del asunto, interpongo el presente Recurso de Reposición, de conformidad con el artículo 52 del Código Contencioso Administrativo, con los argumentos que demuestran que lo definido en las reivindicaciones de este expediente presenta Novedad y Mérito Inventivo:

Ante la Resolución No. 33176 que Deniega esta Solicitud de Patente se interpone el presente Recurso de Reposición ante el Superintendente de Industria y Comercio, en el que someten argumentos que demuestran que lo definido en las reivindicaciones de este expediente presenta Novedad y Mérito Inventivo.

El Examinador en su rechazo sostiene que no se demuestra que la presente invención tenga "alguna ventaja o efecto superior de las composiciones reclamadas frente a las composiciones del estado de la técnica cercano, por lo cual el objeto de la reivindicación 1 se considera como una alternativa obvia de las composiciones previamente conocidas.

En relación con lo anterior se advierte que el Examinador hace mención a la falta de los Anexos A y B que resultan de importancia para sustentar la Novedad y Efectos diferenciadores de la presente invención. Ahora se acompañan tales Anexos. En el Anexo A y el Anexo B que ahora se adjuntan, el Examinador podrá ver los datos experimentales en apoyo al uso terapéutico de las formulaciones de la reivindicación 1. Los datos indiscutiblemente demuestran que las formulaciones

vesiculares de la presente invención son eficaces en el tratamiento del dolor asociado con la osteoartritis en los pacientes, según lo expuesto abajo.

El Anexo A muestra los resultados de seis ensayos clínicos de Fase II/III investigando el efecto de la aplicación tópica de Diractin®, una formulación vesicular que incluye el analgésico Ketoprofeno. Se incluyó la formulación X en el ensayo como un placebo (una medicación sin ingrediente activo, un paliativo). Es decir, es la misma formulación vesicular de Diractin®, pero las vesículas no contienen Ketoprofeno, o analgésico o cualquier otra droga. Estos ensayos fueron llevados a cabo para probar la eficacia de Diractin®. El placebo fue incluido en los ensayos a los fines de cubrir los requerimientos de los procedimientos de ensayo clínicos. Sin embargo, sorprendentemente, los datos mostraron que el placebo de la Formulación X (es decir la Formulación de las reivindicaciones) dieron como resultado una reducción de hasta 49.5%” en el dolor asociado con la osteoartritis, tal como se muestra en la Fig. 1 de la presente solicitud. Además, estos datos señalan que el efecto de la Formulación X en el dolor era comparable con aquella de Celecoxib oral (un muy fuerte analgésico) y superior al placebo oral (ver Tabla 2). También estos datos demuestran que los pacientes evaluaron su respuesta a la terapia como “buena/excelente”, tal como se indica en la página 8 de la solicitud, y que el alivio del dolor obtenido a raíz de la Formulación X era sostenible, tal como muestra la Figura 3.

Además, el Anexo B muestra un estudio de “meta-análisis” de los resultados de los ensayos clínicos de la Fase III, que investigaron el cambio desde el comienzo en cuanto a los niveles de dolor del paciente después de la aplicación de la Formulación X. El estudio demuestra que los efectos vistos con la Formulación X en los ensayos clínicos representan mejoras genuinas en los resultados relacionados con pacientes con osteoartritis más que debido a una respuesta de efecto placebo. Por lo tanto, estos datos muestran que las vesículas vacías, incluidas como placebo, inesperadamente se comportaron como las vesículas conteniendo una droga para el tratamiento del dolor asociado a la osteoartritis. Esto es muy sorprendente. Las vesículas de la presente invención, por supuesto, son ventajosas dado que no incluyen los efectos colaterales de la droga y los costos de producción, al no tener la droga, son notablemente inferiores. La Formulación X fue hecha de acuerdo con el Ejemplo 96 que se brinda en el capítulo descriptivo y este corresponde a la Reivindicación 1.

En virtud de todo lo anterior y de las nuevas reivindicaciones que ahora se acompañan y que corresponden a aquellas concedidas por la Oficina de Patentes Británica bajo el No. GB 2483419 B, se considera que la presente solicitud cumple con todos los requisitos de patentabilidad y, por tal, se solicita su concesión.

Pretensiones:

Revocar la Resolución No. 33176 que denegó la patente titulada "FORMULACIONES PARA EL TRATAMIENTO DEL DOLOR TISULAR PROFUNDO", a favor de la sociedad TECHNOLOGY HOLDINGS LIMITED y es su lugar conceder el registro de la misma

Anexos:

1. Anexo A
2. Anexo B
3. Capítulo reivindicatorio

Notificaciones:

Recibiré notificaciones en la secretaría de su Despacho; en mis oficinas de abogado ubicadas en la Calle 67 No. 7 – 35, oficina 1204, teléfono 3192900, fax 3210295, Bogotá D.C., Colombia, o; al correo electrónico dbotero@gpzlegal.com.

Atentamente,

MAURICIO JARAMILLO C.
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T.P. 74.555 del C.S. de la J.

Annex A

Formulation X: summary of clinical efficacy data

1: Formulation X clinical trial overview

Data are currently available from one Phase II and five Phase III randomised, double-blind, studies of Formulation X for pain associated with OA of the knee (Table 1).

Studies CL-033-III-02, CL-033-III-03 and CL-033-III-06 examined the efficacy and safety of epicutaneously applied Formulation X (4.4 g or 2.2 g twice daily) or ketoprofen in Transfersome® gel (Diractin®) administered for 12 weeks. CL-033-III-03 was an active-controlled study comparing 12 weeks of Formulation X (4.4 g or 2.2 g twice daily) with celecoxib (100 mg twice daily), oral placebo or ketoprofen in Transfersome® gel.

Studies CL-033-II-03, CL-033-III-04 and CL-033-III-05 provided additional supportive efficacy and safety data for Formulation X combination regimens. Study CL-033-II-03 evaluated 6 weeks' treatment with Formulation X (4.8 g twice daily) in combination with celecoxib (100 mg twice daily) or oral placebo versus ketoprofen in Transfersome® gel (Diractin®). Study CL-033-III-04 compared 12 weeks' treatment with Formulation X (4.95 g, 2.65 g and 1.45 g twice daily) in combination with oral naproxen (500 mg twice daily) or oral placebo versus ketoprofen in Transfersome® gel (Diractin®). CL-033-III-05 was a double-blind extension of study CL-033-III-04 over 52 weeks in which patients received Formulation X 4.95 g in combination with oral naproxen (500 mg twice daily) versus ketoprofen in Transfersome® gel (Diractin®) plus oral placebo.

Efficacy outcomes reported here focus on the 943 patients who received Formulation X alone, while safety data are described for the overall safety population of 1,675 patients who received Formulation X alone or in combination with an active comparator or oral placebo.

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Table 1. Overview of the six key clinical trials of Formulation X.

Study no.	Title	Main inclusion criteria	Treatment duration	Total no. of patients across all study arms (ITT population)	No. of patients on Formulation X (ITT population)	Volume of Formulation X applied, frequency
Phase III studies of Formulation X alone						
CL-033-III-02	A double-blind, placebo-controlled evaluation of dose related safety and efficacy of epicutaneously applied Diractin® (ketoprofen in Transfersome® gel) for 3 months treatment of osteoarthritis of the knee	Age 18–75 y; clinical OA diagnosis in ≥1 knee for ≥6 mo; oral/rectal NSAID on ≥3 d per wk during 3 mo. before screening or on ≥25 of the 30 d before screening, but dissatisfaction with current NSAID; ≥2 of following: morning stiffness <30 min; crepitus on motion; age ≥40 y	12 weeks	828	190	1.1, 2.2 and 4.4 g, twice daily
CL-033-III-03	Multicenter, randomized, double-blind, placebo- and active-controlled study of safety and efficacy of two dosages of epicutaneously applied Diractin® (Ketoprofen in Transfersome® gel) for the treatment of osteoarthritis of the knee	Age >45 y (if aged 18–45, radiological confirmation of knee OA diagnosis); primary diagnosis of Functional Class I–III knee OA and ACR criteria for knee OA defined as knee pain and ≥4 of following: age >50 y; morning stiffness <30 min; crepitus on active motion; bony tenderness; bony enlargement; no palpable warmth of synovium	12 weeks	1,395	238 (2.2 g) 234 (4.4 g)	2.2 and 4.4 g, twice daily
CL-033-III-06	Multicentre, randomized, double-blind, placebo-controlled study of safety and efficacy of epicutaneously applied Diractin® (ketoprofen in Transfersome® gel) for the treatment of osteoarthritis of the knee	As for CL-033-III-03	12 weeks	555	281	4.4 g, twice daily

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Study no.	Title	Main inclusion criteria	Treatment duration	Total no. of patients across all study arms (ITT population)	No. of patients on Formulation X (ITT population)	Volume of Formulation X applied, frequency
Phase II/III studies of Formulation X in combination with an active comparator or oral placebo						
CL-033-II-03	A double-blind, placebo-controlled evaluation of safety and efficacy of epicutaneously applied Diractin® (ketoprofen in Transfersome® gel) in comparison to oral celecoxib for the treatment of pain associated with osteoarthritis of the knee	OA of index knee for ≥6 mo; subject rating of pain in index knee when not taking NSAIDs ≥3 using a 5-point Likert scale; presence of 2 of the 3 following criteria: morning stiffness <30 min; crepitus on motion; age ≥40 y. Use of oral NSAIDs ≥3 d per wk during 3 mo prior to screening or on >25 of 30 d at a therapeutic level for ≥30 d prior to screening and OA flare criteria met: index knee pain assessment at walking ≥40 mm on VAS at baseline; increase of index knee pain at walking by ≥15 mm on VAS at baseline versus screening; physician's global assessment of OA of grade 3–5 and ≥1 grade increase from screening. Radiographic evidence of OA (<12 mo from screening). Laboratory tests consistent with OA	6 weeks	397	132 (alongside celecoxib) 127 (alongside oral placebo)	4.8 g, twice daily
CL-033-III-04	A double-blind, placebo-controlled evaluation of the safety and efficacy of three doses of topically applied Diractin® (ketoprofen in Transfersome® gel) in comparison to oral naproxen for the treatment of the signs and symptoms of osteoarthritis of the knee	OA of both knees for ≥6 mo (may be based on subject history); subject rating of pain in index knee when not taking NSAIDs ≥2 using a 5-point Likert scale; use of oral NSAIDs ≥3 d per wk during 3 mo prior to screening or on ≥25 of the 30 d prior to screening; radiographic evidence of OA (<6 mo from baseline); WOMAC pain subscale score (based on a normalised 0–100 mm VAS scale) of ≥40 mm and ≥15 mm greater than at screening visit	12 weeks	837	164	1.1 g, 2.2 g and 4.95 g, twice daily
CL-033-III-05	A double-blind, long-term evaluation of the safety of topically applied Diractin® (ketoprofen in Transfersome® gel) in comparison to oral naproxen for the treatment of the signs and symptoms of osteoarthritis of the knee	As for CL-033-III-04; completion of 12 wks of this study or discontinuation due to lack of efficacy	52 weeks	345	138 (alongside naproxen)	4.4 g, twice daily

ACR, American College of Rheumatology; d, days; min, minutes; mo, month; ITT, intention to treat; wk, week; y, years.

2: Summary of Formulation X efficacy

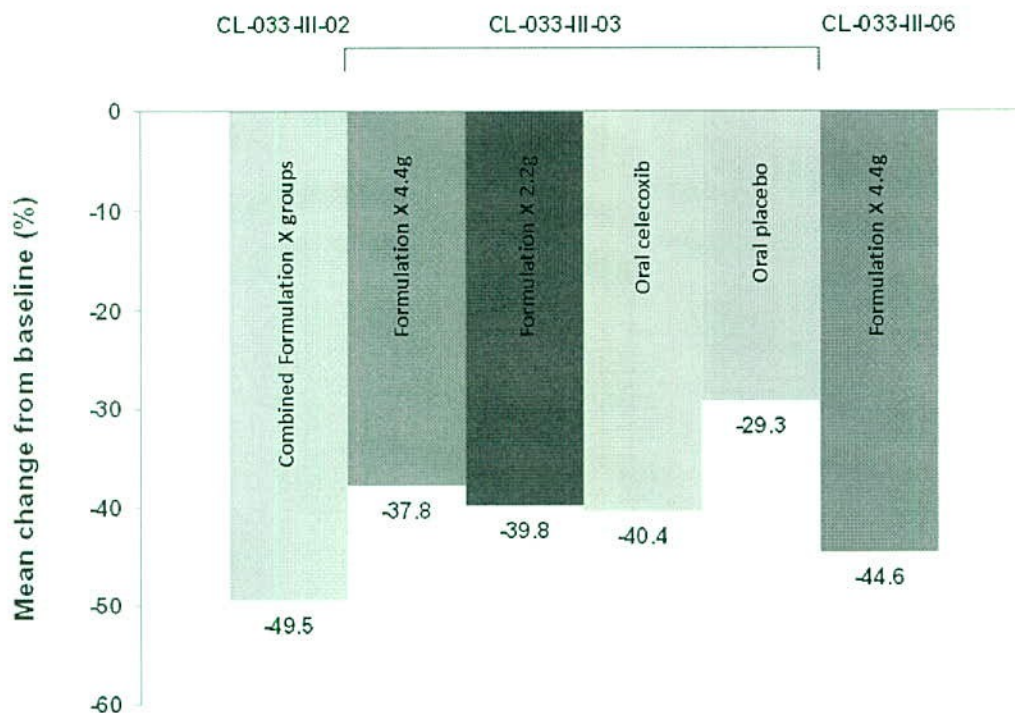
This section summarises available clinical data supporting the efficacy of Formulation X in the treatment of OA. These data are based on trials of Formulation X in OA of the knee.

2.1 Reducing knee pain

The primary efficacy measure in the six clinical trials of Formulation X was the change from baseline to the end of the study in patients' perception of pain, measured on a visual analogue scale (VAS) or using an 11-point numerical rating scale (NRS) on the pain subscale of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index (version 3.1) instrument.

At the end of the 3-month treatment period in the three clinical trials assessing Formulation X alone, pain was reduced by up to 49.5% in 943 patients (Figure 1) (CSR CL-033-III-02; Stucki & Rother 2007; Conaghan et al. 2012; Rother et al. 2012a). The effect of Formulation X on pain was comparable with that of oral celecoxib in Study CL-033-III-03. Both Formulation X doses demonstrated non-inferiority to oral celecoxib, and superiority to oral placebo at a magnitude comparable to celecoxib (see Table 2.).

Figure 1. Mean percentage change from baseline in WOMAC Pain Subscale scores (with adjustment for analgesics) after 3 months of therapy (n=943, ITT population).



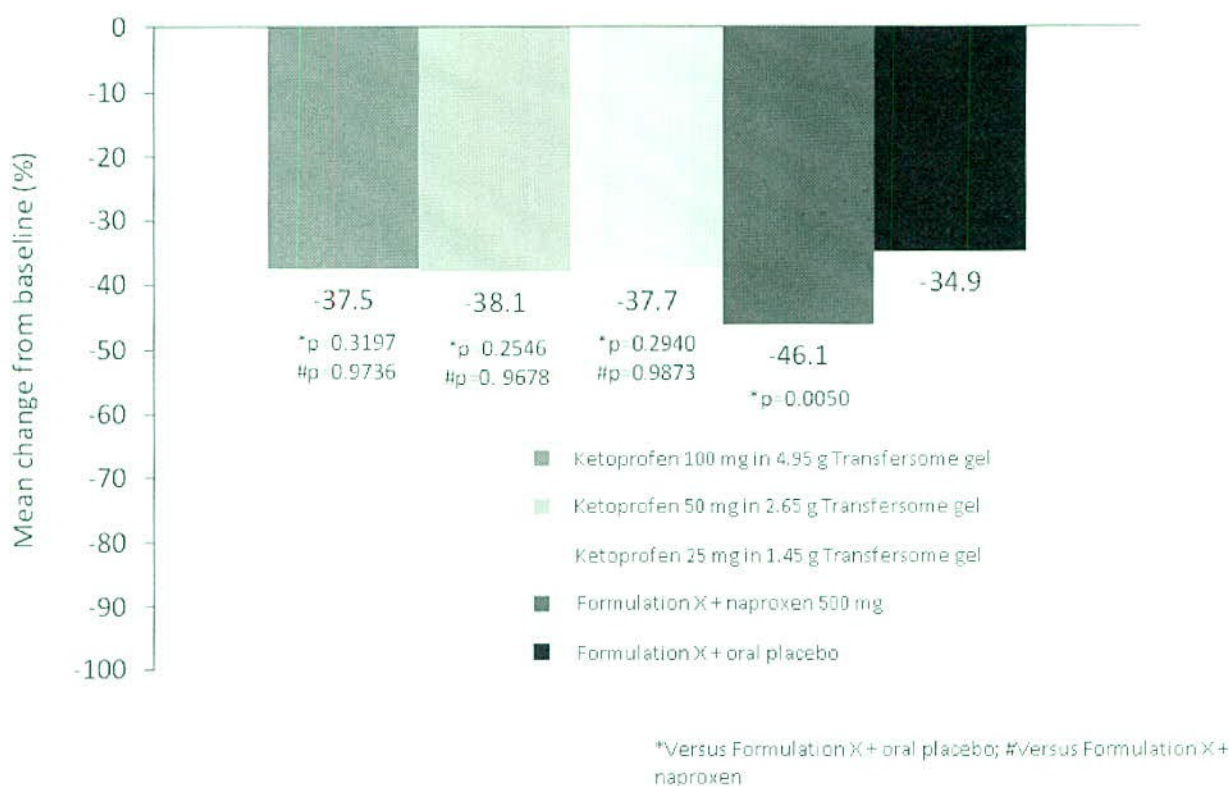
Source: Table 11.4-2, CSR CL-033-III-02; Conaghan et al. 2012; Rother et al. 2012a.

2.1.1 Supportive data from Phase II/III studies of Formulation X in combination with an active comparator or oral placebo

In study CL-033-II-03, Formulation X with oral placebo, or in combination with celecoxib, was effective in reducing pain at the 6-week study endpoint (CSR CL-033-II-03). The least squares (LS) mean change in VAS WOMAC Pain Subscale score from baseline was -9.9 for Formulation X with oral placebo, versus -20.3 for Formulation X in combination with celecoxib ($p=0.0004$) and -18.2 for topical ketoprofen in Transfersome® gel ($p=0.0041$). The reduction in pain in all treatment groups in this study was smaller than that observed in similar treatment groups in the Phase III studies; it is not unusual for Phase II studies with fewer patients and a shorter duration of treatment to demonstrate smaller treatment effects.

As well as showing efficacy in combination with oral placebo, pain was significantly ($p=0.005$) reduced when Formulation X was combined with naproxen for 12 weeks in study CL-033-III-04 (46.1% vs 34.9% for Formulation X plus oral placebo) (Rother et al. 2012b) (Figure 2). This pain relief was maintained out to 52 weeks of treatment in study CL-033-III-05 (25.3% vs 9.2% topical ketoprofen in Transfersome® gel [$p=0.22$]) (CSR CL-033-III-05), although limited conclusions regarding pain relief can be drawn from this study as there was no Formulation X or naproxen-only treatment arm.

Figure 2. Mean percentage change from baseline in WOMAC Pain Subscale scores after 3 months of therapy in study CL-033-III-04 (ITT population).



CL-033-III-04

Source: Table 72 and Figures 59-65, CSR CL-033-III-04; Rother et al. 2012b.

2.1.2 Response to therapy

Response measured by OMERACT-OARSI criteria

Response in several studies was defined according to the modified Outcomes Measures in Rheumatology Clinical Trials-Osteoarthritis Research Society International Index (OMERACT-OARSI) criteria (Pham et al. 2004)¹. In study CL-033-III-02, 77.5% of 190 patients had responded to twice-daily treatment with Formulation X by study end (CSR CL-033-III-02). After 6 weeks of treatment in study CL-033-II-03, response rates (OMERACT-OARSI) with Formulation X and Formulation X/celecoxib were comparable at 55.1% and 63.6%, respectively (Rother et al. 2007). Formulation X combined with naproxen or placebo in study CL-033-III-04 yielded response rates of 66.5% and 56.8%, respectively (OMERACT-OARSI) (CSR CL-033-III-04). A response rate of 81.2% (OMERACT-OARSI) was seen in study CL-033-III-05, only in the subset of patients who were previously enrolled in study CL-033-III-04, following up to 52 weeks of Formulation X/naproxen treatment (CSR CL-033-III-05).

Response according to reduction in pain (WOMAC pain subscale)

Of the patients who received Formulation X in study CL-033-III-03, 40.6% (4.4 g dose) and 40.8% (2.2 g dose) of patients achieved a $\geq 50\%$ reduction in the WOMAC Pain Subscale score from baseline, with 60.7% (4.4 g dose) and 66.0% (2.2 g dose) had a $\geq 30\%$ reduction in the WOMAC Pain Subscale score from baseline, with 12.8% (4.4 g dose) and 9.7% (2.2 g dose) of patients achieving an 80% reduction in pain after 12 weeks of therapy (CSR CL-033-III-03). In study CL-033-III-06, 50.5% of patients treated with Formulation X for 12 weeks experienced a $\geq 50\%$ reduction in WOMAC Pain Subscale score from baseline (CSR CL-033-III-06).

Patients' assessment of therapy

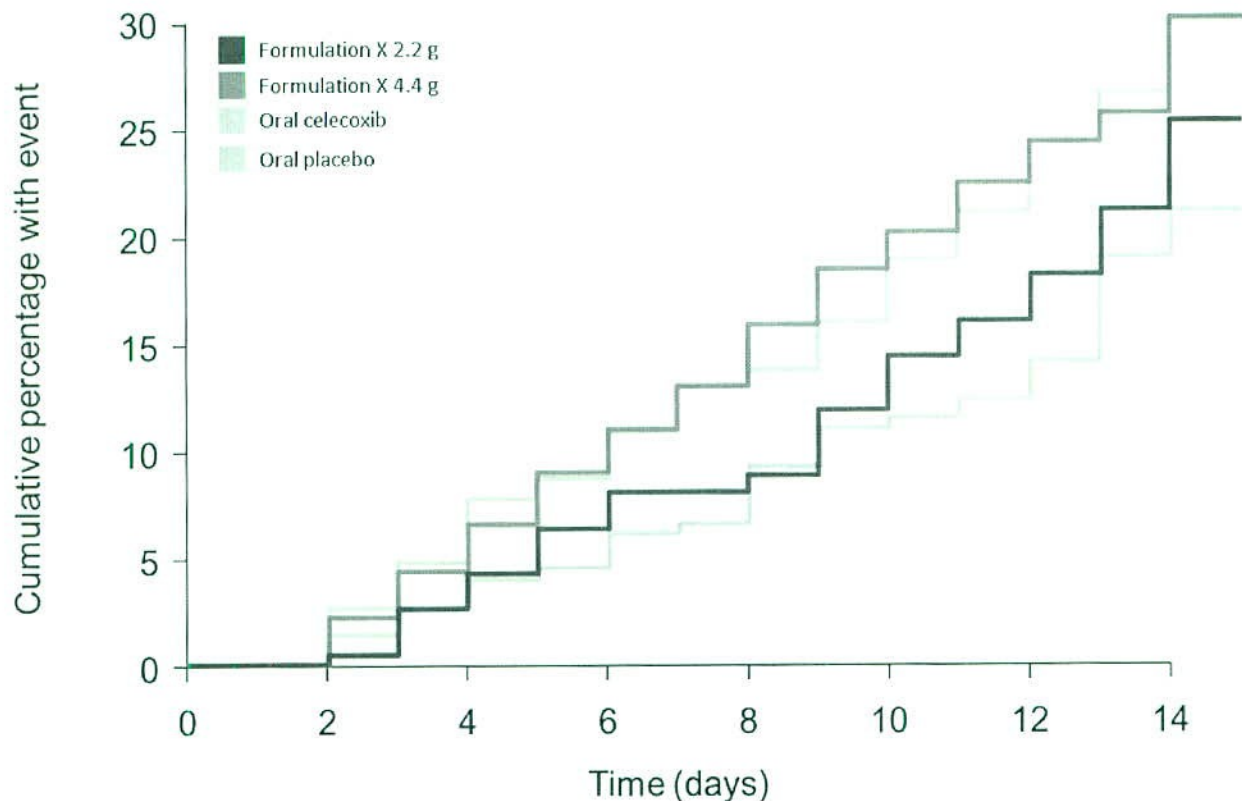
Patients' global assessment of response to therapy was rated as 'good/excellent' by approximately 60% of patients receiving Formulation X/naproxen in studies CL-033-III-04 and CL-033-III-05, and in patients receiving Formulation X alone in study CL-033-III-06 (Rother et al. 2012b; CSR CL-033-III-05; Rother et al. 2012a).

2.1.3 Onset of sustainable pain relief

Sustainable meaningful pain relief, defined as the time until a 2-point improvement on an 11-point NRS pain scale, with ≥ 2 -point improvement sustained until Day 14, was achieved with Formulation X after 2 days (the earliest measured time point). These data are comparable to pain relief provided with other OA therapies, including celecoxib (Figure 3) (CSR CL-033-III-03; CSR CL-033-III-06).

¹ Defined as $\geq 50\%$ improvement in pain or function plus an absolute improvement of 50 mm, or at least two of the following: $\geq 20\%$ improvement in pain together with an absolute improvement of ≥ 10 mm; $\geq 20\%$ improvement in function together with an absolute change of 10 mm; response of 'good' or 'excellent' on the Patient's Global Assessment of Response to Therapy

Figure 3. Time to onset of sustainable meaningful pain relief with Formulation X and celecoxib in study CL-033-III-03 (ITT population). Clinical relevance of treatment differences was judged according to Hasselblad-Hedges criteria for odds ratios.



Source: Figure 71, CSR CL-033-III-03.

2.1.4 Comparison of pain outcomes

At the end of 3 month treatment period in study CL-033-III-03, Formulation X was associated with reductions in joint pain (up to 39.8%) that was comparable with the effects of oral celecoxib (40.4%) (CSR CL-033-III-03; Conaghan et al. 2012). Reductions in pain achieved with Formulation X were statistically significantly non-inferior to oral celecoxib, and superior to oral placebo at a magnitude similar to that of celecoxib (Table 2). These response rates for Formulation X compare favourably with those reported for patients who received therapy with oral celecoxib for 12 weeks (percentage reduction in WOMAC pain approximately 30% [estimated data]) in a large double-blind, placebo-controlled study by Bensen et al. (1999). This demonstrates consistency between the efficacy data for Formulation X in Study CL-033-III-03 and published celecoxib data.

Table 2. Confirmatory analysis of effect size (Mann-Whitney estimator) for WOMAC pain after 3 months of therapy with Formulation X in Study CL-033-III-03. The pre-specified benchmark for superiority was MW >0.5. Non-inferiority versus celecoxib was tested for pain in exploratory and post hoc analyses using a pre-specified lower equivalence margin of MW = 0.4.

	2.2 g Formulation X (n=238)	4.4 g Formulation X (n=234)	Oral celecoxib 100 mg b.i.d. (n=233)	Oral placebo matching celecoxib (n=227)
WOMAC pain subscale score				
Effect size versus oral placebo	MW=0.6006 LB: 0.5404 *p=0.0001	MW=0.5779 LB: 0.5176 *p=0.0019	MW=0.5873 LB: 0.5268 *p=0.0006	—
Effect size versus oral celecoxib	MW=0.5101 LB: 0.4506 **p=0.3526	MW=0.4897 LB: 0.4299 **p=0.6504	—	—

LB, lower boundary of confidence interval; MW, Mann-Whitney estimator; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities.

*P-values calculated using Wilcoxon-Mann-Whitney U test based on one-sided 98.75% confidence intervals.

**P-values represent test for superiority.

References:

1. Bensen WG, Fiechtner JJ, McMillen JI, Zhao WW, Yu SS, Woods EM, et al. Treatment of osteoarthritis with celecoxib, a cyclooxygenase-2 inhibitor: a randomized controlled trial. *Mayo Clin Proc* 1999;74:1095–105.
2. Conaghan P, Dickson JD, Bolten W, Cevc G, Rother M. A large randomised, controlled trial comparing the efficacy and safety of topical ketoprofen in Transfersome® gel with oral celecoxib for osteoarthritis knee pain. Annual EULAR Congress 2012 Abstract no. EULAR12-3366.
3. Pham T, van der Heijde D, Altman RD, Anderson JJ, Bellamy N, Hochberg M, Simon L, Strand V, Woodworth T, Dougados M. OMERACT-OARSI Initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis and Cartilage* 2004;12(5):389–399.
4. Rother M, Lavins BJ, Kneer W, Lehnhardt K, Seidel EJ, Mazgareanu S. Efficacy and safety of epicutaneous ketoprofen in Transfersome® (IDEA-033) versus oral celecoxib and placebo in osteoarthritis of the knee: multicentre randomised controlled trial. *Ann Rheum Dis* 2007 66(9):1178–1183.

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5. Rother M, Lipetz R, Dunmyer S. A double-blind, randomised, placebo-controlled trial to evaluate the safety and efficacy of epicutaneously applied ketoprofen in Transfersome® gel for the treatment of pain associated with osteoarthritis (OA) of the knee. Annual EULAR Congress 2012a Abstract no. EULAR12-3378.
 6. Rother M, Yeoman G, Ekman E. Double-blind, placebo-controlled trial comparing the safety and efficacy of epicutaneously applied ketoprofen in Transfersome® gel with naproxen for the treatment of pain associated with osteoarthritis (OA) of the knee. Annual EULAR Congress 2012b Abstract no. EULAR12-3375.
 7. Stucki G, Rother M. Randomized, double-blind, placebo-controlled study of three dosages of epicutaneously applied IDEA-033 (Ketoprofen in Transfersome®) in patients with osteoarthritis of the knee [abstract]. Ann Rheum Dis. 2007;66(Suppl II):510.

Annex B

Example 1

A meta-analysis was carried out of Phase III clinical trials investigating the effect of Formulation X in osteoarthritis knee pain.

A Transfersome is an ultradeformable phospholipid vesicle originally developed to deliver high concentrations of drug (eg NSAIDs) transdermally. Transfersome vesicles containing ketoprofen (Formulation Y) and drug-free vehicle (Sequessome vesicles, Formulation X) were compared in large interventional trials in osteoarthritis (OA) of the knee, with conflicting results for Formulation Y [1,2,3]. However, all trials showed pronounced treatment effects of the vehicle itself (Formulation X) that, in one study [4], were non-inferior to daily 200 mg celecoxib and statistically significantly superior to oral placebo [4]. We used a meta-analytical approach to investigate how the treatment effects seen with Formulation X compare with the results reported for the placebo arm of other OA interventional studies [5].

The efficacy of Formulation X gel has been evaluated in randomised, double-blind, parallel-group multicentre, Phase III studies of Formulation Y in knee OA that included Formulation X as a drug-free vesicle control group. This meta-analysis combines the results of the WOMAC pain subscales from studies with up to the 12 weeks of treatment, standardised to a 0–100 scale. The resulting pre-post effect size (ES) is the standardised difference (Cohen [6]) of the changes from baseline of the WOMAC pain subscale score (based on the standard deviation of the changes of the corresponding Formulation X group). ES of 0.2, 0.5 and 0.8 are used to represent small, medium and large effect sizes, respectively [6]. The results of the meta-analysis are presented as two-sided tests with two-sided 95.0% confidence intervals (CIs; Hedges'g). These results are compared with those of a meta-analysis of placebo responses from other conventional OA trials published by Zhang et al. [5]. Other analyses and sub-group analyses are ongoing.

The ES calculated for a total of 1061 patients with knee OA treated with Formulation X gel at week 12 was 1.15 (CI: 1.09–1.21). The respective values for the individual studies were 1.33 (CI: 1.18–1.47; [1]), 1.12 (CI: 1.03–1.21; [2]), 1.05 (CI: 0.87–1.24; [3]) and 1.12 (CI: 1.00–1.24; [4]). The results were comparable irrespective of whether 2.2 g or 4.4 g of Formulation X gel was used (ES 2.2 g: 1.17 (CI: 1.07–1.28); ES 4.4 g: 1.12 (CI: 1.04–1.20)). This compares with an ES of 0.54 (CI: 0.49–0.60) reported for all placebo applications in studies with knee OA and an ES of 0.63 (CI: 0.47–0.80) for the topical placebo arm investigated with topical formulations of all OA studies in the meta-analysis of Zhang et al. [6].

In comparative, randomised, double-blind studies in painful knee OA in more than 1000 patients, a substantially greater reduction in pain was reported for Formulation X than that reported for the topical placebo arm of other interventional trials. The magnitude of the difference indicates that this effect is unlikely to be due to a placebo response alone. Additional analyses are underway including other studies of Formulation X and comparisons by baseline pain severity and various aspects of study design.

Table 1: Standardised difference (effect size) for 4 individual studies and their meta-analysis.
WOMAC pain after 12 weeks of treatment with Formulation X (ITT analysis)

	Standard difference	95% Confidence interval	N
Individual Study			
CL-033-III-02	1.33	1.18-1.47	190
CL-033-III-03	1.12	1.03-1.21	472
CL-033-III-04	1.05	0.87-1.24	118
CL-033-III-06	1.12	1.00-1.24	281
Meta-analysis Formulation X	1.15	1.09-1.21	1061
Meta-analysis Zhang et al ⁵			
All placebo	0.54	0.49-0.6	
Topical placebo	0.63	0.47-0.8	

References:

1. Stucki G, et al. Ann Rheum Dis 2007;66 (Suppl. II):510.
2. Rother M, et al. EULAR Annual European Congress of Rheumatology 2012. Abstract no. EULAR12-3375.
3. Rother M, et al. EULAR Annual European Congress of Rheumatology 2012. Abstract no. EULAR12-3378.
4. Conaghan P, et al. EULAR Annual European Congress of Rheumatology 2012. Abstract no. EULAR12-3366.
5. Zhang W, et al. Ann Rheum Dis 2008 doi:10.1136/ard2008.092015.
6. Cohen J. Statistical power analysis for the behavioural sciences (2nd ed). Lawrence Erlbaum Associate Publishers: Hillsdale, NJ (1988).

REIVINDICACIONES

1. Una formulación vesicular que comprende fosfatidilcolina, polisorbato 80, amortiguador fosfato, hidroxitolueno butilado (BHT), metabisulfito de sodio, alcohol bencílico o parabeno, glicerol, ácido etilenodioxidi-etilen-dinitrilo-tetraacético (EDTA), etanol y poliacrilato, y estando la formulación libre de cualquier agente farmacéuticamente activo y siendo la formulación un gel.

2. La formulación vesicular de la reivindicación 1, donde la fosfatidilcolina está presente en una cantidad de 68,70 mg/g.

3. La formulación vesicular de la reivindicación 1 ó 2, donde el polisorbato 80 está presente en una cantidad de 8,50 mg/g.

4. La formulación vesicular de cualquiera de las reivindicaciones 1 a 3, donde el hidroxitolueno butilado (BHT) está presente en una cantidad de 0,20 mg/g.

5. La formulación vesicular de cualquiera de las reivindicaciones 1 a 4, donde el metabisulfito de sodio está

presente en una cantidad de 0,50 mg/g.

6. La formulación vesicular de cualquiera de las reivindicaciones 1 a 5, donde el alcohol bencílico o parabeno
5 está presente en una cantidad de 5,00 mg/g.

7. La formulación vesicular de cualquiera de las reivindicaciones 1 a 6, donde el glicerol está presente en una cantidad de 30,00 mg/g.
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8. La formulación vesicular de cualquiera de las reivindicaciones 1 a 7, donde el ácido etilenodioxi-dietilendinitrilo-tetraacético (EDTA) está presente en una cantidad de 1,00 mg/g.
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9. La formulación vesicular de cualquiera de las reivindicaciones 1 a 8, donde el etanol está presente en una cantidad de 36,51 mg/g.
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