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Brief review

Drug-free gel containing ultra-deformable phospholipid vesicles (TDT 064) as topical therapy for the treatment of pain associated with osteoarthritis: a review of clinical efficacy and safety

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Abstract

Background:
Many patients with osteoarthritis (OA) experience side effects with available systemic therapies, some of which can be life threatening. The widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs), often without prescription, is concerning given their potential risks. New treatments for OA are therefore required. This review discusses evidence supporting the use of TDT 064, a drug-free, topical gel containing ultra-deformable phospholipid vesicles (Sequessome* vesicles), for OA-associated pain.

Scope:
Preclinical and clinical studies investigating TDT 064 in patients with OA-associated knee pain were identified in searches of PubMed and congress abstracts.

Findings:
The ultra-deformable phospholipid vesicles (sequessome vesicles) in TDT 064 pass through the skin intact to reach the synovial space within the joint. The mechanism of action is not yet certain, but the phospholipid-based structure of these ultra-deformable phospholipid vesicles, and the observation that they localize to the cartilage surface, support biolubrication as a possible mechanism of action of TDT 064. Data from randomized, phase III studies in OA knee pain in which TDT 064 was used as the drug-free vehicle control for IDEA-033 (ketoprofen in ultra-deformable phospholipid vesicles) demonstrate a marked and consistent response to TDT 064 in terms of pain, stiffness, and function. In a 12 week study of >1300 patients, the effects of TDT 064 on pain and function were statistically noninferior to those of oral celecoxib, and superior to oral placebo. TDT 064 was well tolerated in all studies, and adverse events were typically mild-to-moderate effects on the skin.

Conclusions:
Evidence from clinical studies supports the use of TDT 064 as a drug-free topical treatment for patients with OA. Further experience with TDT 064, particularly among patients with comorbidities or NSAID contraindications, will provide more information on its potential use.

Introduction

Osteoarthritis (OA) is a leading cause of disability[1]. In addition to joint pain and stiffness, patients experience significant functional disability and impaired quality of life, placing a substantial burden on healthcare resources[2–4].

*Sequessome is a registered trade name of Pro Bono Bio Entrepreneur Ltd, UK

Lifestyle changes with a focus on self-management and a variety of pharmacotherapies are recommended for the treatment of OA, including acetaminophen (paracetamol), topical or oral nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and intra-articular glucocorticoid injections[5–8]. Many patients, however, do not experience satisfactory symptom relief with their initial therapies and therefore switch, modify, or discontinue their medication[9].

The side effects associated with some widely used drugs may result in patients changing or modifying therapy[9] and can be serious. Concerns about hepatotoxicity with long-term use of acetaminophen may lead to patients taking intermittent doses[10]. Use of selective and nonselective NSAIDS is associated with an increased risk of cardiovascular (CV) events and death among both those with a history of CV disease and healthy individuals[11–14]. Gastrointestinal (GI) complications are also associated with the use of NSAIDs, and can be life threatening[11,15,16]. A high proportion of the elderly OA population have comorbidities and risk factors for NSAID-related side effects[17]. Consequently, guidelines recommend that if oral NSAIDs are prescribed, they should be used at low doses for the shortest period of time possible, and with caution (e.g., with gastroprotection)[5,6,18–20]. Recommendations for short-term drug use, however, present a challenge for the management of chronic conditions, such as OA.

Given the potential for oral NSAIDs to interact with concomitant medications widely used by the OA population (e.g., aspirin, anti-coagulants, anti-depressants, and anti-hypertensives)[21,22], extensive use of oral NSAIDs without prescription is concerning, as patients may be self-administering these drugs[23]. Additionally, many patients with established risk factors for NSAID use are reported to be receiving oral NSAIDs on prescription, in some cases at higher than the recommended doses, regardless of their use of contraindicated medications[24,25]. Thus, there is a need to develop new treatment strategies for patients with OA.

Topical therapy may be a suitable alternative to oral NSAIDs[5–8,26], either alone or with low doses of other oral analgesics. There is, however, uncertainty about the extent or variability of systemic absorption of drugs from topical preparations[27]; users of topical NSAIDs may experience systemic adverse events (AEs)[28].

Targeted delivery of ketoprofen in ultra-deformable phospholipid vesicles, Transfersome* vesicles (IDEA-033), was investigated in a series of randomized trials in individuals with OA as a means of achieving high concentrations of ketoprofen in sub-dermal tissue, while avoiding systemic effects (Table 1)[29–35]. While pain reduction in response to IDEA-033 treatment was consistent across multiple trials, it did not demonstrate significant superiority to the drug-free vehicle TDT 064 in all studies. A contributing factor was the magnitude of the response to the vehicle itself, which in a study with the active comparator oral celecoxib showed comparable efficacy[33]. These observations, as well as its potential biolubricant activity, led to an interest in TDT 064 as a drug-free topical therapy for OA. TDT 064 is now registered as a class IIa medical device in the EU (Certificate no. 1244719-00). This review focuses on this novel drug-free technology, its potential mechanism of action (MoA), and the clinical evidence supporting its use for the treatment of OA. English-language clinical trial publications and preclinical study publications were identified through searches of the PubMed database, and the European League Against Rheumatism and the American College of Rheumatology congress abstracts (from 2003 to June 2013) using the terms 'IDEA-033', 'TDT 064', 'ketoprofen in Transfersome', and 'ketoprofen in ultra-deformable phospholipid vesicles'. Only clinical studies of IDEA-033 without a vehicle control were excluded.

*Transfersome is a registered trade name of IDEA AG, Munich, Germany

Structure and mechanism of action of TDT 064

Sequessome vesicles: structure, properties and transdermal transport

TDT 064 is an aqueous gel containing hydrophilic, nano-scale lipid vesicles with a phospholipid bilayer (Sequessome vesicles) that are able to pass through the skin permeability barrier to reach the joint[36] (Figure 1A). These vesicles were originally developed as carriers for targeted delivery of active pharmaceutical substances (known as Transfersome vesicles when carrying drug). These preparations carrying different drugs have been used in thousands of patients in various disease areas (e.g., musculoskeletal and joint disorders, including OA, soft tissue inflammation, inflammatory skin disorders, and onychomycosis), with minimal AEs and no systemic safety concerns with continued use (up to 36 months)[37–41].

The components of IDEA-033 and TDT 064 are identical except for the absence of drug in TDT 064; the excipients are widely used in pharmaceuticals, foodstuffs, and cosmetics. Due to the incorporation of the nonionic surfactant polysorbate, the vesicles are in a liquid crystalline phase, and their resulting ultra-deformability enables them to pass intact through the intercellular spaces of the skin, despite their large size (70–198 nm in diameter[42]), relative to the width of the skin channels (44 nm[43,44]; Figure 1B). This movement of hydrophilic vesicles between cells in the stratum corneum is driven by the osmotic gradient

Table 1. Overview of randomized, double-blind, controlled clinical trials of IDEA-033 in OA in which TDT 064 was included as the drug-free vehicle.

Study	Key inclusion/exclusion criteria	Treatment regimens (no. of patients randomized)	Duration (weeks)	Key endpoints	Reference
Studies with NSAID responder enrichment					
CL-033-II-03 (NCT00317733)	OA in ≥1 knee for ≥6 months NSAIDs on ≥3 days/week during 3 months before screening or on ≥25 of the 30 days before screening and OA flare criteria met ≥2 of the following: morning stiffness <30 minutes; crepitus on motion; age ≥40 years	IDEA-033 (110 mg ketoprofen) bid + oral placebo bid ($n=138$) TDT 064 4.8 g bid + 100 mg oral celecoxib bid ($n=132$) TDT 064 4.8 g bid + oral placebo bid ($n=127$)	6	Change from baseline on WOMAC pain subscale Change from baseline on WOMAC function subscale PGA of response to therapy	Rother *et al.*, 2007[29]
CL-033-III-02 (NCT00316784)	OA in ≥1 knee for ≥6 months Age 18–75 years NSAIDs on ≥3 days/week during 3 months before screening or on ≥25 of the 30 days before screening, but dissatisfaction with current NSAID ≥2 of the following: morning stiffness <30 minutes; crepitus on motion; age ≥40 years	IDEA-033 (25 mg ketoprofen) bid ($n=223$) IDEA-033 (50 mg ketoprofen) bid ($n=223$) IDEA-033 (100 mg ketoprofen) bid ($n=221$) TDT 064 1.1 g, 2.2 g, or 4.4 g bid ($n=199$)	12	Change from baseline on WOMAC pain subscale Change from baseline on WOMAC function subscale PGA of response to therapy	Kneer *et al.*, 2013[30]
CL-033-III-04 (NCT00211549)	OA of both knees for ≥6 months NSAIDs on ≥3 days/week during 3 months before screening or on ≥25 of the 30 days before screening ≥2 of the following: morning stiffness ≥30 minutes; crepitus on motion; age ≥40 years (patients who met the first two criteria must be aged >18 years)	IDEA-033 (25 mg ketoprofen) bid ($n=172$) IDEA-033 (50 mg ketoprofen) bid ($n=173$) IDEA-033 (100 mg ketoprofen) bid ($n=179$) TDT 064 1.1 g, 2.2 g, or 4.4 g bid + oral naproxen 500 mg bid ($n=165$) TDT 064 1.1 g, 2.2 g, or 4.4 g bid + oral placebo bid ($n=164$)	12	Change from baseline on WOMAC pain subscale Change from baseline on WOMAC function subscale PGA of response to therapy	Rother *et al.*, 2009[31]; Rother *et al.*, 2012[32]
Studies with nonenrichment design					
CL-033-III-03 (NCT00716547)	OA of the index knee with/without concurrent analgesic medication Age >45 years (if aged 18–45, radiologic evidence of knee OA) Moderate pain	IDEA-033 (100 mg ketoprofen) bid ($n=230$) IDEA-033 (50 mg ketoprofen) bid ($n=233$) TDT 064 2.2 g bid ($n=238$) TDT 064 4.4 g bid ($n=235$) Oral celecoxib 100 mg bid ($n=235$) Oral placebo bid ($n=228$)	12	Change from baseline on WOMAC pain subscale Change from baseline on WOMAC function subscale PGA of response to therapy	Conaghan *et al.*, 2013[33]
CL-033-III-06 (NCT00722852)	OA of the index knee with/without concurrent analgesic medication Age >45 years (if aged 18–45, radiologic evidence of knee OA) Mild-to-moderate pain	IDEA-033 (100 mg ketoprofen) bid ($n=274$) TDT 064 4.4 g bid ($n=281$)	12	Change from baseline on WOMAC pain subscale Change from baseline on WOMAC function subscale PGA of response to therapy	Rother and Conaghan, 2013[34]
Additional studies					
CL-033-III-05 (NCT00265304)	Patients who had completed study CL-033-III-04 or had discontinued due to lack of efficacy, or patients meeting entry criteria for study CL-033-III-04	IDEA-033 (100 mg ketoprofen) bid + oral placebo ($n=207$) TDT 064 4.4 g bid + oral naproxen 500 mg bid ($n=138$)	52[a]	Change from baseline on WOMAC pain subscale Change from baseline on WOMAC function subscale PGA of response to therapy	Rother *et al.*, 2008[35]

[a]Study CL-033-III-05 was an extension of study CL-033-III-04; 52 weeks represents the maximum time on treatment from randomization in study CL-033-III-04.
bid, twice daily; NSAID, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; PGA, patient global assessment; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

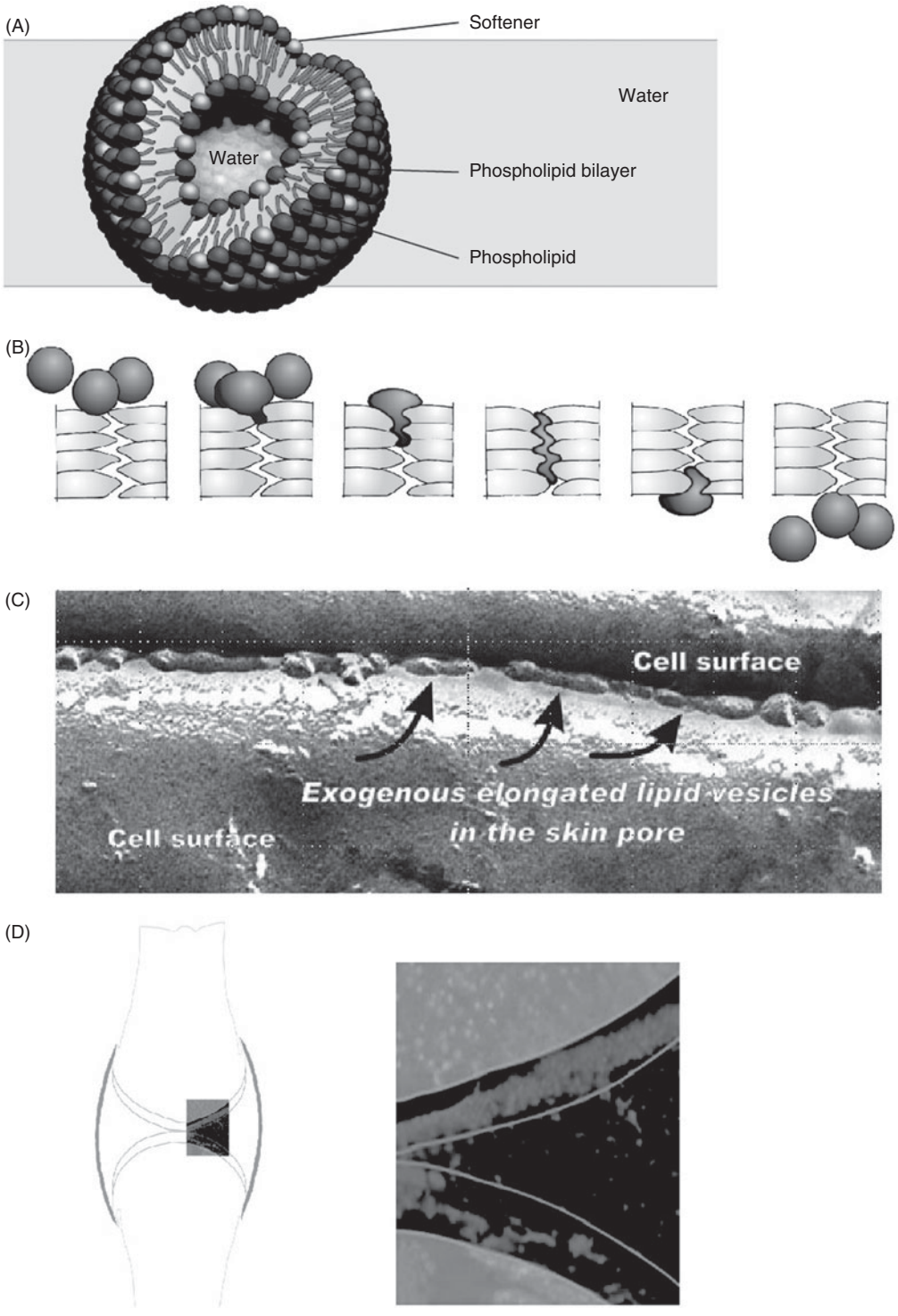

Figure 1. Structure and properties of drug-free, ultra-deformable phospholipid vesicles in TDT 064. (A) Schematic of the structure of ultra-deformable phospholipid vesicles contained in TDT 064 showing phospholipid molecules with the hydrophilic heads on the exterior and the hydrophobic tails aggregating in the interior of the bilayer. Insertion of surfactant molecules into the bilayer softens the membrane, resulting in highly deformable and compressible vehicles. (B) Schematic of the movement of the ultra-deformable phospholipid vesicles across the stratum corneum to sub-dermal tissue. Following application of TDT 064 to non-occluded skin, the water in the gel formulation evaporates, triggering the movement of the ultra-deformable phospholipid vesicles through the intercellular spaces in the skin towards the aqueous environment of the synovial fluid within the joint. The ultra-deformability of the vesicles gives them the flexibility to compress as they move through the natural gaps in the skin. (C) Electron micrograph of elongated ultra-deformable phospholipid vesicles passing through intercellular spaces in the skin. Image courtesy of Professor J. Bouwstra, Leiden Amsterdam Centre for Drug Research, University of Leiden, Amsterdam. (D) Localization of fluorescently (DiO) labeled ultra-deformable phospholipid vesicles to the synovial space of isolated knee joints following application of TDT 064 containing the labeled vesicles to rat knee. The fluorescent signal is evident in the synovial space and accumulates on the surface of the articular cartilage[36].

between the surface of the skin and sub-dermal tissues. As the vesicles move through the skin channels, they elongate and compress due to their deformability, but remain intact (Figure 1C). Microscopy studies in rats have shown that the intact vesicles move to the synovial space following topical application to the joint[36] (Figure 1D).

Mechanism of action of TDT 064

Although the exact analgesic MoA of TDT 064 has not been fully elucidated, some insight can be obtained from the localization study in rats using TDT 064 containing fluorescently labeled ultra-deformable phospholipid vesicles[36]. Analysis of rat joints isolated after local dermal application of TDT 064, at a dose comparable with that used in clinical studies, revealed localization of labeled vesicles in the synovial space on the cartilage surface (Figure 1D). It is plausible that, once localized on the articular surface, the ultra-deformable phospholipid vesicles may act as a biolubricant. This is supported by several lines of evidence. Firstly, it is known that naturally occurring surface-acting phospholipids, which play a key role in lubricating articular cartilage[45], are depleted in synovial fluid from the affected joints of patients with OA[46–49]. Injection of surface-acting phospholipids into the affected joints of patients with OA improves joint mobility[50]. Secondly, liposomes, which have a similar phospholipid-based structure to these ultra-deformable phospholipid vesicles, have shown a biolubricant effect in human joints *in vitro*[51]. Finally, the ultra-deformable phospholipid vesicles in TDT 064 have characteristics that research has shown to increase the biolubricant effect of liposomes. These include high surface head hydration of the phospholipids and compressibility. Although a biolubricant action would not be expected to mediate an analgesic effect directly, the reduction in friction between cartilage surfaces may minimize further inflammation, and might reduce the release of fragments and debris from the damaged cartilage, an effect that has been demonstrated after hyaluronan injections[52].

Pharmacokinetics and clearance of TDT 064

Following dermal application of these ultra-deformable phospholipid vesicles, the vesicles are not cleared by the cutaneous blood microcirculation due to their relatively large size[43]. Instead, they are transported with the interstitial fluid and penetrate into other and/or deeper tissues below the application site[43,53]. This was demonstrated in a preclinical study comparing the biodistribution of ketoprofen applied to the skin of mini-pigs either in a conventional gel or in IDEA-033[54]. Ketoprofen concentrations in subcutaneous tissue after application of IDEA-033 were more sustained than those with a conventional gel (estimated local bioavailability ~10-fold higher with a terminal half-life of 4–6 hours), and there was low systemic bioavailability. Following dermal application of labeled ultra-deformable vesicles in mice, label from the vesicles has been detected in the liver[55], suggesting that, like naturally occurring phospholipids, this is the route by which the vesicles are eliminated and broken down by the body.

Clinical efficacy of TDT 064 in osteoarthritis

Data on the efficacy of TDT 064 in OA are available from the clinical development program for IDEA-033, which included six randomized, comparative trials with TDT 064 as the drug-free vehicle control (Table 1). More than 1600 patients across these studies were treated with TDT 064. The studies were based on a nonenrichment design, or enrolled patients experiencing flare following withdrawal of their NSAID treatment. In all studies, patients were permitted to use acetaminophen for rescue medication at a dose of up to 2 g/day for a limited period but not within ≥24 hours of study visits. Efficacy analyses were formally adjusted for analgesic use in Studies CL-033-III-03 and CL-033-III-06. In all studies, the per-protocol analysis excluded subjects with use of any analgesic within five times its half-life time. Since the per-protocol analysis showed comparable results to the intention to treat analysis, the effect of usage of rescue medication and/or other analgesics should have had no major impact on the results.

Nonenrichment studies

The largest and most informative of these was CL-033-III-03, which evaluated two doses of TDT 064, and included 200 mg daily oral celecoxib as an active comparator (Figure 2)[33]. Celecoxib provided a reference against which to compare the treatment effects of the topical formulations. The 1399 patients with moderate OA-associated knee pain who were randomized in the study were typical of OA patients seen in clinical practice (Figure 2). The incorporation of a double baseline visit was a unique feature of this trial, ensuring that patients entering the study were not experiencing disease flare.

Patients treated with 2.2 g or 4.4 g of TDT 064 showed progressive and clinically relevant improvements in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) subscales for pain, function, and stiffness (Figure 3), comparable in magnitude with those observed among patients receiving IDEA-033 and oral celecoxib. After 12 weeks' treatment, pain had

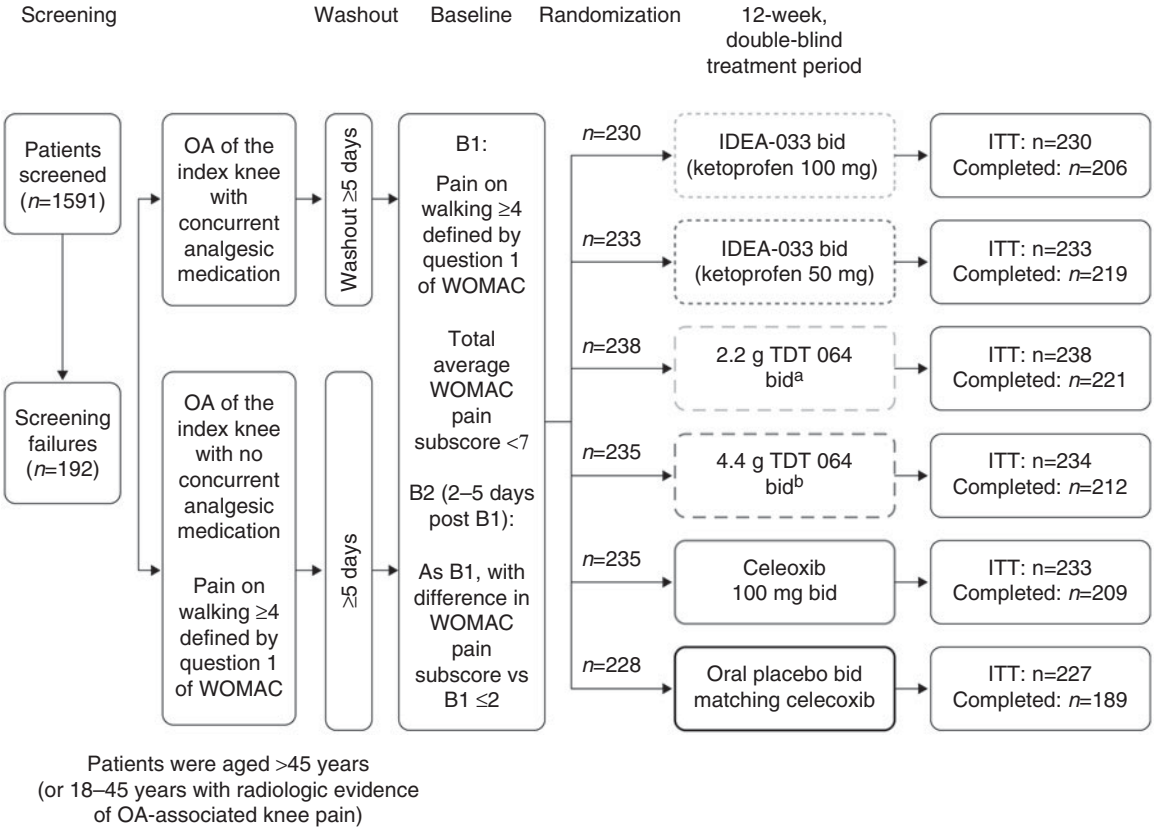

Figure 2. Design of the randomized, phase III study CL-033-III-03 comparing TDT 064 and oral celecoxib. [a]Vehicle matching 50 mg ketoprofen dose of IDEA-033. [b]Vehicle matching 100 mg ketoprofen dose of IDEA-033. bid, twice daily; ITT, intent-to-treat; OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

improved by up to 39.8% from baseline, compared with 40.4% for oral celecoxib. Corresponding improvements in function and stiffness were up to 37.0% and 35.9%, respectively, for TDT 064, and up to 38.2% and 37.9%, respectively, for oral celecoxib. Confirmatory analyses of the effect sizes (ES; Mann–Whitney estimators) for pain and function endpoints demonstrated that IDEA-033 was not superior to TDT 064, indicating no significant benefit of the addition of ketoprofen to the vesicles. Furthermore, these analyses demonstrated the statistically significant noninferiority of TDT 064 versus oral celecoxib, and statistically significant superiority to oral placebo[33].

The clinical significance of the results observed in study CL-033-III-03 is further supported by the comparable magnitude of the improvements in pain reported in pivotal registration trials of oral celecoxib and topical diclofenac[56–59]. The extent of the improvement exceeded the threshold level of ~30% determined to be clinically important for relief of chronic pain measured using a similar 11-point (0–10) numerical rating scale (NRS)[60].

A comparable response to TDT 064 was observed in study CL-033-III-06 (Table 2)[34]. In studies CL-033-III-03 and CL-033-III-06, TDT 064 showed sustainable, clinically meaningful pain relief (defined as a decrease of ≥2 points on a 0–10 point NRS sustained to 14 days) at the earliest timepoint measured (2 days), which in study CL-033-III-03 was comparable to the time to onset of effect of celecoxib[33,34].

Studies with NSAID-responder enrichment (flare) design

In study CL-033-III-02, the effects of TDT 064 administered alone were evaluated in patients experiencing flare. Patients were randomized to treatment with IDEA-033 (25 mg, 50 mg, or 100 mg doses of ketoprofen) or 1.1 g, 2.2 g, or 4.4 g TDT 064 (analyzed as a combined dosage group). All four treatment groups experienced improvements in pain of ≥50% from baseline following 12 weeks' therapy (Table 2)[30], and a substantial proportion of patients in all groups met the OMERACT-OARSI responder criteria[61]. The effects of the 50 mg and 100 mg ketoprofen doses of IDEA-033 were, in this particular study, significantly superior to TDT 064, with a small between-group difference[30]. Superiority was not demonstrated for function[30]. NSAID-responder enrichment

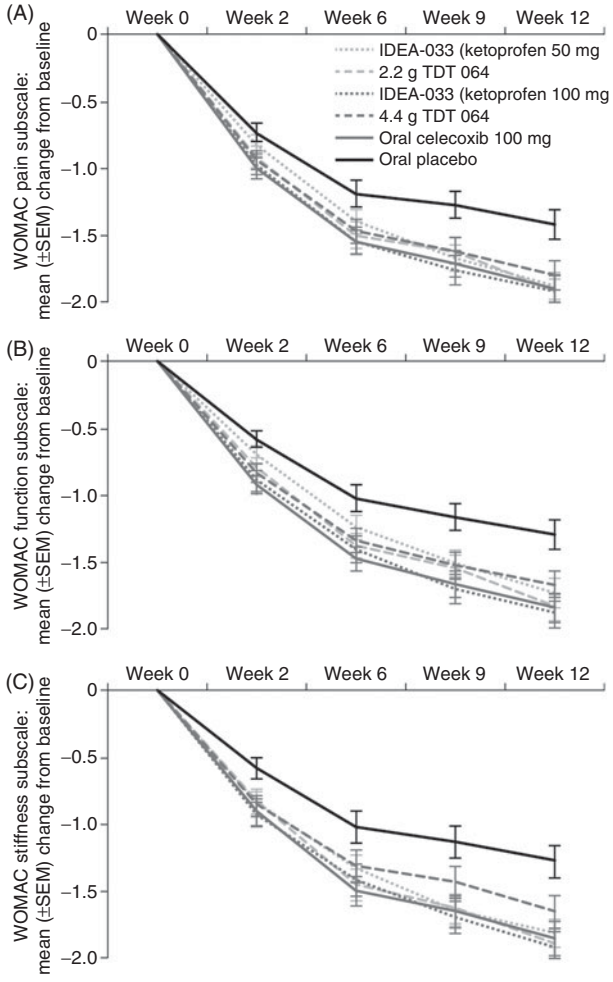

Figure 3. Change from baseline in the WOMAC (NRS Version 3.1) (A) pain, (B) function, and (C) stiffness subscales in the phase III, randomized study CL-033-III-03 (ITT analysis with adjustment for analgesic use; baseline observation carried forward)[33]. ITT, intent-to-treat; NRS, numerical rating scale; SEM, standard error of mean; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. Reproduced from Conaghan *et al.* Rheumatology (Oxford) 2013;52:1303-12 with permission from Oxford University Press on behalf of the British Society of Rheumatology.

study designs have been widely used in studies of COX-II inhibitors[62], and have been associated with a treatment effect of higher magnitude than nonenrichment designs[62,63]. The selection of patients likely to respond to NSAIDs in this study may therefore have contributed to the statistical superiority of the ketoprofen groups compared with TDT 064.

Meta-analysis of the treatment effect of TDT 064 in osteoarthritis studies

The treatment effect of TDT 064 observed in the IDEA-033 clinical studies was unexpected, given its lack of pharmacologically active substance. An effect of placebo on continuous subjective outcomes such as pain has been reported[64], and a placebo effect on pain, function, and stiffness, has been documented in intervention trials in OA[65]. In order to confirm that the effect of TDT 064 in these randomized trials was beyond that expected for placebo, a formal meta-analysis of the ES on pain from four of the trials was conducted[66] and compared with the ES calculated for placebo by similar methodology in a meta-analysis of 198 interventional trials in OA[65]. Using standardized data from studies CL-033-III-02, CL-033-III-03, CL-033-III-04, and CL-033-III-06, ES was calculated for the change from baseline to endpoint in WOMAC pain. The combined ES for TDT 064 was 1.15 (95% confidence interval [CI]: 1.09–1.21), which was higher than the values reported by Zhang *et al.*[65] for knee OA studies (ES: 0.54 [95% CI: 0.49–0.60]), and for the placebo arms reported from topical NSAID studies (ES: 0.63 [95% CI: 0.47–0.80]; Figure 4). The ES for the individual TDT 064 studies were of greater magnitude than the ES reported by Zhang *et al.*[65] (Figure 4).

Collectively, these findings argue that TDT 064 has an effect on pain and function, which cannot be solely accounted for by a placebo response. This is supported by the demonstration of statistical noninferiority to oral celecoxib in study CL-033-III-03. Additionally, patients' expectation of benefit in study CL-033-III-03 was unlikely to have been influenced by the use of oral celecoxib as an active control, as patients in the study were not blinded to topical or oral treatment.

Tolerability of TDT 064 in clinical studies

Topical administration of TDT 064 alone

TDT 064 was administered epicutaneously twice daily for up to 12 weeks to 952 patients in studies CL-033-III-02, CL-033-III-03, and CL-033-III-06[30,33,34]. A low proportion of patients in these studies discontinued treatment due to AEs (Table 3). No patients experienced serious AEs related to TDT 064, and treatment-related AEs (TRAEs) that were reported were mild-to-moderate in severity in almost all cases. The organ systems most frequently affected by TRAEs across the three studies in the TDT 064 treatment arms were skin and subcutaneous tissue (6–18% of patients), GI system (3% of patients in study CL-033-III-03 treated with the 4.4 g dose), nervous system (1–2% of patients), and musculoskeletal system/connective tissue (1% in study CL-033-III-06). Systemic TRAEs were rare, with <1% of patients experiencing vascular events (hypertension, varicose veins), and no TRAEs affecting the cardiac or renal systems. This supports the use of TDT 064 for a wide range of patients with OA, as many patients with OA are elderly and have comorbid conditions affecting the cardiac, renal, vascular, and GI systems[17]. However, rare adverse events are unlikely to be

Table 2. Efficacy outcomes in studies CL-033-III-02, CL-033-III-03, and CL-033-III-06 of TDT 064 in OA-associated knee pain (ITT analysis[a]).

Study	Treatment regimens (no. of patients in ITT population)	Mean (SD) change from baseline to week 12 in WOMAC pain (%)	Mean (SD) change from baseline to week 12 in WOMAC function (%)	Mean (SD) change from baseline to week 12 in WOMAC stiffness (%)	Responders (%)[b]	PGA of response to therapy rating of good or excellent (% patients)
CL-033-III-02[30] 2(NCT00316784)	IDEA-033 (25 mg ketoprofen) bid ($n=214$)	−53.4 (31.1)	−37.1 (35.2)	NR	88.6	49.8
	IDEA-033 (50 mg ketoprofen) bid ($n=213$)	−57.1 (31.7)	−44.7 (39.3)	NR	86.8	57.4
	IDEA-033 (100 mg ketoprofen) bid ($n=211$)	−57.4 (29.3)	−42.0 (35.7)	NR	88.6	49.3
	TDT 064 1.1 g, 2.2 g, or 4.4 g bid ($n=190$)	−49.5 (34.1)	−36.1 (39.0)	NR	77.5	43.2
CL-033-III-03[33] (NCT00716547)	IDEA-033 (100 mg ketoprofen) bid ($n=230$)	−40.9 (35.6)	−38.7 (35.8)	−39.7 (46.7)	43.5	46.5
	IDEA-033 (50 mg ketoprofen) bid ($n=233$)	−40.8 (33.1)	−36.6 (33.3)	−39.4 (36.3)	45.1	51.1
		−39.8 (33.4)	−37.0 (32.0)	−35.9 (45.4)	40.8	45.0
	TDT 064 2.2 g bid ($n=238$)	−37.8 (37.0)	−35.3 (35.5)	−24.2 (158.4)	40.6	45.3
	TDT 064 4.4 g bid ($n=234$)	−40.4 (35.0)	−38.2 (33.8)	−37.9 (47.6)	42.9	48.5
	Oral celecoxib 100 mg bid ($n=233$)	−29.3 (34.1)	−26.1 (35.0)	−25.6 (40.3)	29.5	33.5
	Oral placebo bid ($n=227$)					
CL-033-III-06[34] (NCT00722852)	IDEA-033 (100 mg ketoprofen) bid ($n=274$)	−38.6 (37.9)	−37.4 (36.4)	−38.9 (37.4)	41.2	54.8
	TDT 064 4.4 g bid ($n=281$)	−44.6 (39.0)	−42.3 (39.4)	−43.8 (38.2)	50.5	60.5

[a]With adjustment for analgesic use for Studies CL-033-III-03 and -06.
[b]Responders defined per study according to OMERACT/OARSI criteria (CL-033-III-02), or as the percentage of patients achieving ≥50% reduction in pain (CL-033-III-03 and CL-033-III-06).
bid, twice daily; ITT, intent-to-treat; NR, not reported; OA, osteoarthritis; PGA, patient's global assessment; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

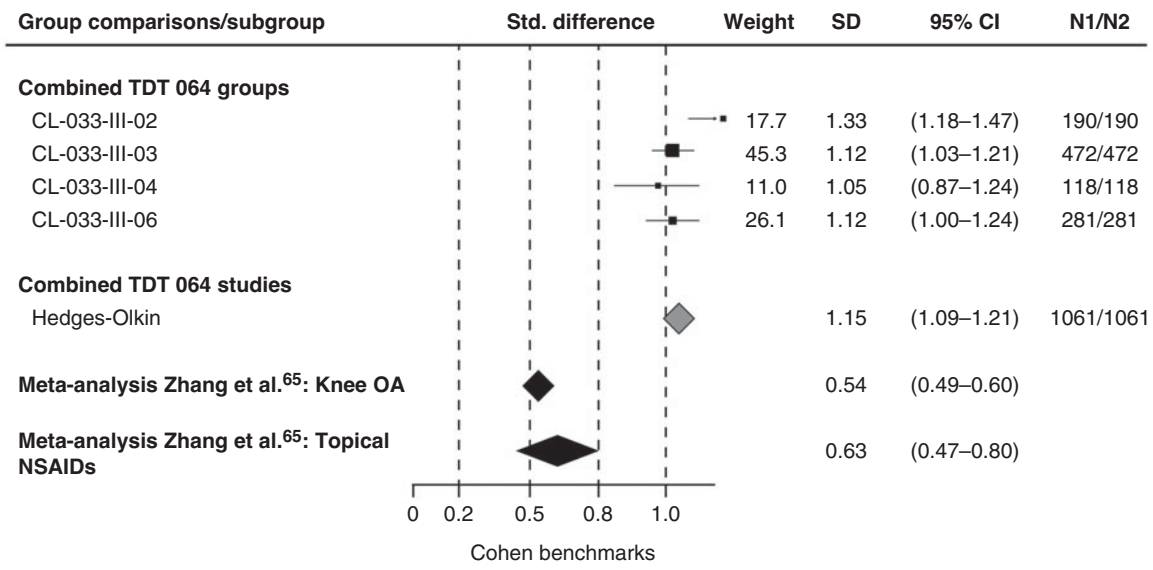

Figure 4. Meta-analysis of the ES for the change from baseline to week 12 in the WOMAC (NRS Version 3.1) pain subscale for the TDT 064 12 week studies[66]. CI, confidence interval; ES, effect size; NRS, numerical rating scale; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

detected in a clinical development program with approximately 2000 subjects.

Dermal AEs most frequently associated with use of TDT 064 include erythema, dry skin, itching, and rash (Table 3). Typically, these were of mild-to-moderate intensity[30,33,34], and transient, beginning after ~2 weeks' treatment, and resolving within a few weeks even with continued use[67]. Re-administration of TDT 064 is usually possible once any skin reaction has resolved[67].

In study CL-033-III-03, 15.9% of patients who received oral celecoxib experienced GI TRAEs (most commonly gastric pain and heartburn)[33]. In contrast, ≤3% of patients in the three key studies of TDT 064 experienced GI TRAEs. In study CL-033-III-03, this difference was reflected in the greater use of omeprazole and in the severity of dyspepsia assessment scores among patients in the celecoxib group[33]. These data suggest a more favorable GI tolerability profile for TDT 064 compared with oral celecoxib.

Use of TDT 064 in combination with oral NSAIDs and other analgesics

Given its drug-free formulation, TDT 064 would not be expected to interact with other medications. In study CL-033-II-03, patients received TDT 064 in combination with oral celecoxib, and in studies CL-033-III-04 and CL-033-III-05 it was administered in addition to oral naproxen for up to 52 weeks. The rate of treatment discontinuation due to AEs in these studies was 11.6–18.1%; no serious TRAEs were reported among patients receiving TDT 064 with oral NSAID (Table 3)[29,32,35,68]. AEs affecting the skin/administration site were consistent with those seen with TDT 064 alone, and occurred in up to 15% of patients (including erythema, dermatitis)[29,35,68,69]. GI events were reported in up to 11% of patients (including abdominal pain, dyspepsia, nausea, stomach discomfort)[29,68], consistent with the known effects of oral NSAIDs. No unexpected systemic treatment effects were noted in any of the three studies; no patients experienced cardiac or renal TRAEs, and <1% of patients experienced vascular events (in Study CL-033-II-03, one patient in the celecoxib plus TDT 064 group experienced hypertension considered to be related to study treatment, and two patients in the TDT 064 group experienced hypertension and hypertensive crisis respectively, neither of which was considered to be treatment-related)[29,68,69].

In all of the IDEA-033 clinical studies, use of acetaminophen was permitted for relief of breakthrough pain, and use of low-dose aspirin for prevention of CV events. No unexpected AEs occurred when TDT 064 was administered to patients on low-dose aspirin, and there were no cardiac, vascular, renal or GI TRAEs in these patients[30]. In study CL-033-III-06, analgesics were taken concomitantly by >80% of patients in both treatment groups; no specific safety observations were made in patients taking TDT 064 with concomitant analgesics[34].

These data support the feasibility of using TDT 064 in addition to oral analgesics, including NSAIDs. This could be of potential benefit for patients who require a reduction in oral NSAID dose due to safety concerns, as topical NSAID preparations should only be used in combination with oral NSAIDs with caution[21,22].

Table 3. AEs reported in randomized studies of TDT 064 alone or in combination with oral NSAIDs in patients with OA.

Study	TDT 064 regimens (no. of patients in safety population)	Withdrawals due to AEs (% patients)	Serious TRAEs (% patients)	Mild-to-moderate intensity (% all TRAEs)	TRAEs (% patients) by organ system (>1%)	TRAEs (% patients) by preferred term (>1% or most frequent)
TDT 064 administered alone						
CL-033-III-02 (NCT00316784)	TDT 064 1.1 g, 2.2 g, or 4.4 g bid ($n=199$)	6.0	0	97.1	SSTD (17.6)	Erythema (4.5)
CL-033-III-03 (NCT00716547)	TDT 064 2.2 g bid ($n=238$)	2.5	0	100	SSTD (5.9)	Dry skin (1.7)
						Allergic contact dermatitis (1.3)
						Localized erythema (1.3)
					Nervous system (1.3)	Headache (0.8)
	TDT 064 4.4 g bid ($n=234$)	3.8	0	100	SSTD (11.1)	Dry skin (3.0)
					GI (3.0)	Gastric pain (0.9)
CL-033-III-06 (NCT00722852)	TDT 064 4.4 g bid ($n=281$)	4.3	0	100	SSTD (11.4)	Rash (2.8)
						Dry skin (1.8)
						Localized erythema (1.4)
					Nervous system (2.1)	Localized rash/skin irritation (1.1)
					Musculoskeletal/connective tissue (1.4)	Headache (0.7)
						Muscle pain/knee pain/stiff knees/swelling of knees (0.4)
TDT 064 administered with oral NSAID						
CL-033-II-03[a] (NCT00317733)	TDT 064 4.8 g bid + 100 mg oral celecoxib bid ($n=132$)	13.6	0	82.6[b]	SSTD (15.2)	Erythema (11.4)
						Pruritus (3.0)
						Exanthem (1.5)
					GI (1.5)	Dyspepsia (0.8)
						Nausea (0.8)
CL-033-III-04 (NCT00211549)	TDT 064 1.1 g, 2.2 g, or 4.4 g bid + oral naproxen 500 mg bid ($n=164$)	11.6	0	94.3	GI (11.0)	Abdominal pain (3.0)
					General disorders/administration site (8.5)	Dermatitis (4.3)
						Dryness/erythema (1.8)
					SSTD (2.4)	
					Musculoskeletal/connective tissue (1.2)	Rash (1.8)
					Nervous system (1.2)	Joint swelling/myalgia (0.6)
						Headache (1.2)
CL-033-III-05 (NCT00265304)	TDT 064 4.4 g bid + oral naproxen 500 mg bid ($n=138$)	18.1	0	95.3[c]	General disorders/administration site (13.8)	Erythema (5.8)
						Dermatitis (4.3)
						Peripheral edema (2.2)
						Application-site irritation (2.2)
					GI (5.1)	Stomach discomfort (2.2)
					Investigations (2.9)	Decreased hemoglobin (1.4)
						Dermatitis (1.4)
					SSTDs (2.9)	Arthralgia (1.4))
					Musculoskeletal/connective tissue (1.4)	Headache (0.7
					Nervous system (1.4)	

[a]TRAEs in study CL-033-II-03 were defined as probably or definitely related.
[b]Data represent the percentage of patients with TRAES.
[c]Data represent the percentage of all AEs, regardless of relationship to treatment.
AEs, adverse events; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; SSTD, skin and subcutaneous tissue disorders; TRAE, treatment-related AEs (possibly, probably, or definitely related to treatment).

Use of TDT 064 in patients with cardiovascular risk factors

Studies CL-033-III-02 and CL-033-III-06 did not involve treatment with oral NSAIDs; hence, patients with established risk factors for NSAID use (e.g., ischemic heart disease, concomitant use of low-dose aspirin, hypertension, etc.) were eligible for inclusion. A sub-analysis of AEs and clinical laboratory data was conducted as part of study CL-033-III-02, to identify whether any of these comorbidities increased the frequency or severity of AEs or abnormal laboratory values. No influence of these factors on safety outcomes was apparent, suggesting that TDT 064 is well tolerated in patients at risk of NSAID-related AEs[30], supporting its potential use for a wide group of patients with OA.

Discussion

The response to TDT 064 observed consistently in the clinical studies reviewed here, and in particular the demonstration of non-inferiority to oral celecoxib, supports its use in the treatment of OA-associated pain. The improvements in pain, stiffness and function observed in studies of different designs (flare and non-flare) and in patients with risk factors for NSAID use suggest that it will benefit a wide group of patients. Treatment with TDT 064 was well tolerated across studies both when used alone and when co-administered with celecoxib, naproxen, or low-dose aspirin, and no serious AEs related to treatment were reported. TDT 064 is therefore a potential drug-free treatment option for patients with comorbidities that make them vulnerable to the side effects of NSAIDs and to drug interactions with other medications they may be taking.

Conclusions

TDT 064 is a novel drug-free treatment for relief of OA-associated pain and stiffness that is based on ultra-deformable phospholipid vesicles. Following topical application to the joint, targeted delivery across the skin barrier drives the vesicles deep into the synovial space from where they are seen to be deposited on the articular cartilage. TDT 064 has been evaluated in an extensive clinical study program in OA. A pronounced effect of TDT 064 was evident in all three studies in which it was used alone. In one of these studies, the effect of TDT 064 on both pain and function was demonstrated to be statistically noninferior to oral celecoxib, and superior to oral placebo. A meta-analysis of the effect of TDT 064 in four clinical studies indicated that the magnitude of the response to TDT 064 is beyond any effect that could be expected due to a placebo response. TDT 064 is well tolerated when used alone or in combination with oral NSAIDs, with typically mild-to-moderate AEs, which mainly affect the skin. These data support the use of TDT 064 as a topical treatment for patients with OA. Further experience with TDT 064 will enhance our understanding of the utility of this drug-free technology in the treatment of OA.

Transparency

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