

Meta-Analysis of Randomized Clinical Trials Investigating the Effect of TDT 064, a Gel-Based Formulation Containing Ultra-Deformable Phospholipid Vesicles, in Patients with Knee Osteoarthritis

Matthias Rother^{1*}, Johannes Vester², Wolfgang W Bolten³, Werner Kneer⁴ and Philip G Conaghan⁵

¹International Medical Research (IMR) Partner GmbH, Department of Clinical Research, Graefelfing, Germany

²idv Data Analysis & Study Planning, Department of Biometry and Clinical Research, Krailling, Germany

³Klaus-Miehlke-Klinik, Abtl. Rheumatologie, Wiesbaden, Germany

⁴Orthopaedic Outpatient Centre, Stockach, Germany

⁵Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds, UK

Abstract

Background: Ketoprofen-containing ultra-deformable phospholipid vesicles (IDEA-033) have been compared with drug-free vehicle (TDT 064) in randomized, controlled trials in knee osteoarthritis (OA). A pronounced treatment effect was reported for TDT 064, with an effect size (ES) comparable with celecoxib in one trial. Our meta-analysis determined whether these TDT 064 effects are beyond any expected placebo effect.

Methods: Five randomized, placebo-controlled studies of IDEA-033 in knee OA using TDT 064 as a control were included. Change from baseline in Western Ontario and McMaster Universities (WOMAC) OA Index pain and function subscale scores from each study were standardized and the ES calculated at various times. We compared our results with previously reported data on placebo response using similar methodology in a meta-analysis of 198 randomized OA trials.

Results: ES for pain relief at Week 6 was markedly higher for TDT 064 studies (ES: 1.04 [95% confidence interval (CI): 0.98–1.09]) than that previously reported for placebos in knee OA (ES: 0.54 [95% CI: 0.49–0.60]), as was the ES for function improvement (ES: 0.93 [95% CI: 0.87–0.98] vs ES: 0.49 [95% CI: 0.44–0.54], respectively). Higher ES for pain relief for TDT 064 studies was also reported with prior oral nonsteroidal anti-inflammatory drugs (NSAIDs) exposure (ES: 1.00 [95% CI: 0.93–1.07]), and in patients with high (ES: 1.08 [95% CI: 1.00–1.17]) or low baseline pain (ES: 1.03 [95% CI: 0.95–1.11]).

Conclusions: The magnitude of the effect with TDT 064 indicates this is unlikely to be solely a result of a placebo response.

Keywords: IDEA-033; Osteoarthritis; Placebo response; Sequeosome; TDT 064; Transfersome

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed for osteoarthritis (OA)-associated pain, but these agents are not without limitations. Oral NSAIDs carry a risk of significant, age-related, systemic adverse effects on the cardiovascular, renal, hepatic, and gastrointestinal systems [1-3]. Furthermore, oral NSAIDs can only be used with caution, or are contraindicated, in substantial numbers of patients due to comorbidities or concomitant medication [4]. With topical application, the risk of side effects is reduced [1], but pharmacokinetic absorption of topically applied NSAIDs varies depending on the individual agent, the underlying disease, and the site of application [5].

Ultra-deformable phospholipid Transfersome[®] vesicles (IDEA AG, Germany) were originally developed to deliver high concentrations of drugs to subdermal tissue. The excipients of Transfersome[®] vesicles and the drug-free Sequeosome[™] vesicles (TDT 064; Pro Bono Bio Entrepreneur Ltd, UK) are used in a variety of pharmaceutical, food, and cosmetic products approved across Europe. Ketoprofen-containing Transfersome[®] vesicles (IDEA-033) have been compared with TDT 064 in a number of randomized, controlled, clinical trials in patients with OA of the knee [6-10]. Conflicting results were obtained for IDEA-033 in these studies compared with the vehicle, but a pronounced treatment effect was reported for TDT 064 throughout all of the studies, with a size comparable to IDEA-033. In one of these studies, the effects of TDT 064 were statistically significantly superior to oral placebo and statistically non-inferior to 100 mg twice daily (b.i.d.) celecoxib, the

registered dose for the treatment of OA [6]. The comparison with celecoxib was selected due to its improved gastrointestinal tolerability compared with non-selective NSAIDs [11-13]; recently 200 mg b.i.d. celecoxib demonstrated equivalent efficacy to 75 mg b.i.d. diclofenac in the treatment of patients with arthritis at high risk of gastrointestinal complications [14]. In another of these studies, IDEA-033 was statistically inferior to TDT 064 in relieving pain associated with OA [8]. Based on these findings, TDT 064 has been registered in Europe as a medical device for the treatment of pain associated with OA.

The concept of a placebo or contextual response is widely recognized in OA trials, although debate exists regarding the size of the effect and the factors that contribute to it [15,16]. We conducted a meta-analysis to determine whether the treatment effects seen with TDT 064 in clinical trials compare with published placebo effects, as well as topical NSAID effects. Specifically, we compared the treatment effects seen with TDT 064 with the placebo effect size (ES) reported

***Corresponding author:** Matthias Rother, MD, International Medical Research (IMR) Partner GmbH, Department of Clinical Research, Graefelfing, Germany, Tel: + 49 (0)89 85 83 609 25; Fax: +49 (0)89 85 83 609 26; E-mail: m.rother@imr-partner.de.

Received May 20, 2013; Accepted June 28, 2014; Published June 30, 2014

Citation: Rother M, Vester J, Bolten WW, Kneer W, Conaghan PG (2014) Meta-Analysis of Randomized Clinical Trials Investigating the Effect of TDT 064, a Gel-Based Formulation Containing Ultra-Deformable Phospholipid Vesicles, in Patients with Knee Osteoarthritis. *Rheumatology (Sunnyvale)* 4: 137. doi:10.4172/2161-1149.1000138

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in a large meta-analysis of interventional studies [16] using the same methodology. In addition, factors known to influence the placebo response in OA trials, such as baseline pain or use of a flare design, were investigated.

Methods

TDT 064 studies included in the meta-analysis

Efficacy data on TDT 064 were analyzed in a meta-analysis of all randomized, placebo-controlled, Phase II/III studies of IDEA-033 in OA of the knee conducted with TDT 064 as a drug-free vehicle control: four 12-week, Phase III studies of topically applied TDT 064 (CL-033-III-02, CL-033-III-03, CL-033-III-04, and CL-033-III-06) and one 6-week Phase II study (CL-033-II-03) conducted across Europe and America in patients with OA of the knee (Table 1). The intent-to-treat (ITT) population of each of the studies was used as the patient population for the meta-analysis. Data from study CL-033-II-03 were not included in the Week 12 analysis, as this study was only of 6 weeks' duration.

Statistical methods

A formal parametric meta-analysis was performed to investigate the overall pre-post effect of TDT 064 across all studies. All studies utilized the Western Ontario and McMaster Universities (WOMAC) OA Index, but as different versions were used between studies, the changes from baseline in WOMAC pain and function subscales (Visual Analog Scale [VAS] or Numerical Rating Scale [NRS]) from each of the studies were standardized to a 0–100 scale. Within-group standardized mean differences were calculated as pre-post ES for all studies using the Hedges method, based on change from baseline of the WOMAC pain and function subscale scores at Weeks 2, 6, and 12. ESs of 0.2, 0.5, and 0.8 represent small, medium, and large ESs, respectively [17]. Missing values were replaced using the last observation carried forward (LOCF) approach and missing follow-up values were replaced by baseline values. In some studies, the baseline observation carried forward (BOCF) approach was also used (Table 1). Results are presented as two-sided tests with two-sided 95% confidence intervals (CIs). The meta-analysis was performed both with a fixed effects model (FEM) and a random effects model (REM) [18]. Patterns of homogeneity were assessed by means of the Gail and Simon test with $p < 0.02$ representing qualitative interactions [19]. Formal meta-analysis procedures were performed by means of the validated software package MetaSub (version 4.1) by idv/Gauting, Germany [20], and forest plots were constructed using the validated software package ForestPlot (version 4.1) also by idv/Gauting. Statistical significance was determined using the CI approach: if the lower bound of the two-sided 95% CI is lying above the benchmark for equality, or the upper bound is lying below the benchmark for equality, statistical significance is shown.

Subgroup analyses were conducted to assess the effect of baseline characteristics on the TDT 064 ES according to washout of previous analgesic treatment at screening (yes vs. no), including patients from studies using a 'flare design' and patients with NSAID exposure at screening from 'nonflare' studies, where the NSAID was washed out between screening and baseline. Further subgroup analyses assessed the effect of low versus high baseline pain severity on TDT 064 ES. Data were dichotomized by the median baseline pain values of all patients.

Literature reference

We compared the results of our meta-analysis with those of Zhang and colleagues, who published a systematic review and meta-analysis examining the placebo response and its determinants in

198 randomized OA trials, including 193 placebo groups [16]. The methodology was designed to be as close as possible to that reported to have been used for the Zhang analyses, in order to make comparisons as robust as possible. The placebo ES for pain in the Zhang meta-analysis, defined as the standard mean difference between baseline and endpoint, was 0.51 (95% CI: 0.46–0.55) for all placebo-controlled trials, 0.03 (95% CI: –0.13 to 0.18) for all untreated controls, 0.54 for trials of knee OA (95% CI: 0.49–0.60), and 0.63 for trials of topical NSAIDs (95% CI: 0.47–0.80).

Results

Pain relief

The ES for pain relief, based on the change from baseline at Week 6 on the WOMAC pain subscale, was higher for the combined TDT 064 studies (ES FEM: 1.04 [95% CI: 0.98–1.09]; ES REM: 1.01 [95% CI: 0.84–1.19]) than that reported in the Zhang meta-analysis for trials of knee OA (ES: 0.54 [95% CI: 0.49–0.60]), and trials using topical NSAIDs (ES: 0.63 [95% CI: 0.47–0.80]) (Figure 1). When comparing data from the five individual TDT 064 studies with the Zhang data, pain reduction was again substantially higher with TDT 064, except in study CL-033-II-03 (ES: 0.60 [95% CI: 0.42–0.77]) (Figure 1). As expected, larger ESs were reported with longer treatment duration, but all ESs seen with TDT 064 were larger than for the placebo arms of the studies reported by Zhang et al. The ES (FEM) for pain relief was 0.85 (95% CI: 0.79–0.90) at Week 2 and 1.15 (95% CI: 1.09–1.21) at Week 12. The ES for pain relief was greater in the individual TDT 064 studies included in the Week 12 analysis than that reported for knee OA trials and trials of topical NSAIDs in the Zhang meta-analysis (Figure 2).

Improvement in function

Based on the change from baseline at Week 6 on the WOMAC function subscale, the ES for improvement in function was higher for the combined TDT 064 studies (ES FEM: 0.93 [95% CI: 0.87–0.98]; ES REM: 0.90 [95% CI: 0.79–1.01]) than for 80 studies reporting WOMAC function data in the Zhang meta-analysis (ES: 0.49 [95% CI: 0.44–0.54]) (Figure 3). Improvements in function were higher with TDT 064 than with the Zhang data in each of the five studies, but the magnitude of the effect was smallest in study CL-033-II-03 (ES: 0.64 [95% CI: 0.46–0.82]). Assessing the impact of treatment duration on improvement in function revealed similar findings as for pain, with an ES (FEM) of 0.70 (95% CI: 0.64–0.76) at Week 2 and 1.03 (95% CI: 0.97–1.09) at Week 12 for the combined TDT 064 studies. Data from study CL-033-II-03 were not included in the Week 12 analysis.

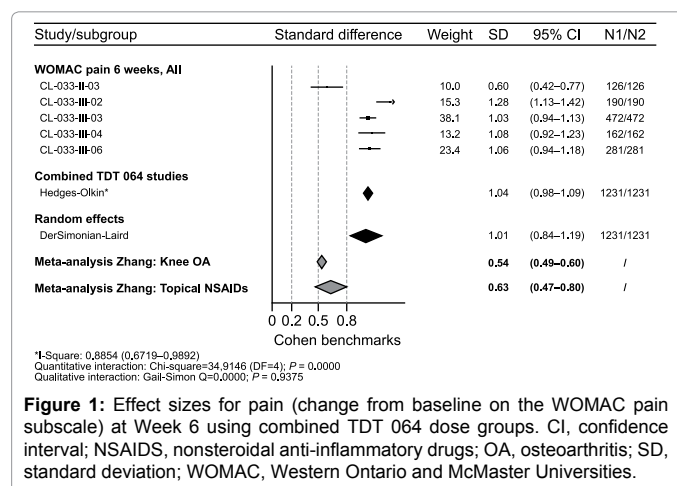


Figure 1: Effect sizes for pain (change from baseline on the WOMAC pain subscale) at Week 6 using combined TDT 064 dose groups. CI, confidence interval; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities.

Study no.	Regimen	Volume (dose) of TDT 064 applied	Key inclusion criteria	Treatment duration and imputation method	ITT patients, n	ITT patients receiving TDT 064, n
CL-033-II-03	IDEA-033 vs TDT 064+celecoxib vs TDT 064+placebo	4.8 g b.i.d.	<ul style="list-style-type: none"> 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 WOMAC at baseline ≥ 40 mm and >15 mm at screening Median baseline WOMAC pain score (VAS): 53.0–57.1 mm 	6 weeks LOCF	397	132 (+celecoxib) 127 (+placebo)
CL-033-III-02	Three doses of IDEA-033 vs TDT 064	1.1, 2.2, and 4.4 g b.i.d.	<ul style="list-style-type: none"> 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 WOMAC at baseline ≥ 40 mm and >15 mm at screening Mean baseline WOMAC pain score (VAS): 64.1–65.7 mm 	12 weeks LOCF	828	190 (all TDT 064 doses combined)
CL-033-III-03	Two doses of IDEA-033 vs two doses of TDT 064 vs oral celecoxib vs oral placebo	2.2, and 4.4 g b.i.d.	<ul style="list-style-type: none"> OA of the index knee with/without concurrent analgesic medication Age >45 years (if aged 18–45, radiologic evidence of knee OA) Median baseline WOMAC pain score: 4.6–4.9 	12 weeks LOCF and BOCF	1395	238 (2.2 g TDT 064) 234 (4.4 g TDT 064)
CL-033-III-04	Three doses of IDEA-033 vs TDT 064+oral naproxen vs TDT 064+oral placebo	1.1, 2.2, and 4.4 g b.i.d.	<ul style="list-style-type: none"> 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) WOMAC at baseline ≥ 40 mm and >15 mm at screening Median baseline WOMAC pain score (VAS): 74.0–79.4 mm 	12 weeks LOCF	837	164 (+naproxen; combined dose) 162 (+placebo)
CL-033-III-06	IDEA-033 vs TDT 064	4.4 g b.i.d.	<ul style="list-style-type: none"> OA of the index knee with/without concurrent analgesic medication Age >45 years (if aged 18–45, radiologic evidence of knee OA) Median baseline WOMAC pain score: 5.2–5.4 	12 weeks LOCF and BOCF	555	281 (4.4 g TDT 064)
					Total=4012	Total=1320

b.i.d., twice daily; BOCF, baseline observation carried forward; ITT, intent-to-treat; LOCF, last observation carried forward; NSAIDs, nonsteroidal anti-inflammatory drugs; OA, osteoarthritis; VAS, Visual Analog Scale; WOMAC, Western Ontario and McMaster Universities.

Table 1: Summary of the randomized OA trials of TDT 064 included in the meta-analysis.

Subgroup analyses

Subgroup analyses assessing the effect of baseline characteristics on the TDT 064 ES revealed substantially higher ESs for pain relief for the combined TDT 064 studies than those reported by Zhang et al., irrespective of prior oral NSAID exposure (ES FEM: 1.00 [95% CI: 0.93–1.07]; ES REM: 0.97 [95% CI: 0.76–1.19]) (Figure 4a), high baseline pain severity (ES FEM: 1.08 [95% CI: 1.00–1.17]; ES REM: 1.05 [95% CI: 0.87–1.23]) (Figure 4b), or low baseline pain severity (ES FEM: 1.03 [95% CI: 0.95–1.11]; ES REM: 1.03 [95% CI: 0.81–1.26]) (Figure 4c).

Discussion

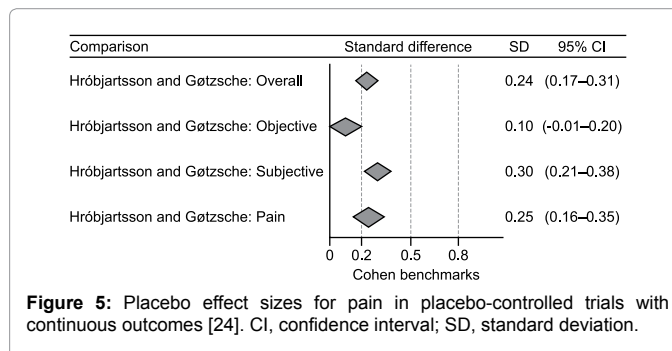
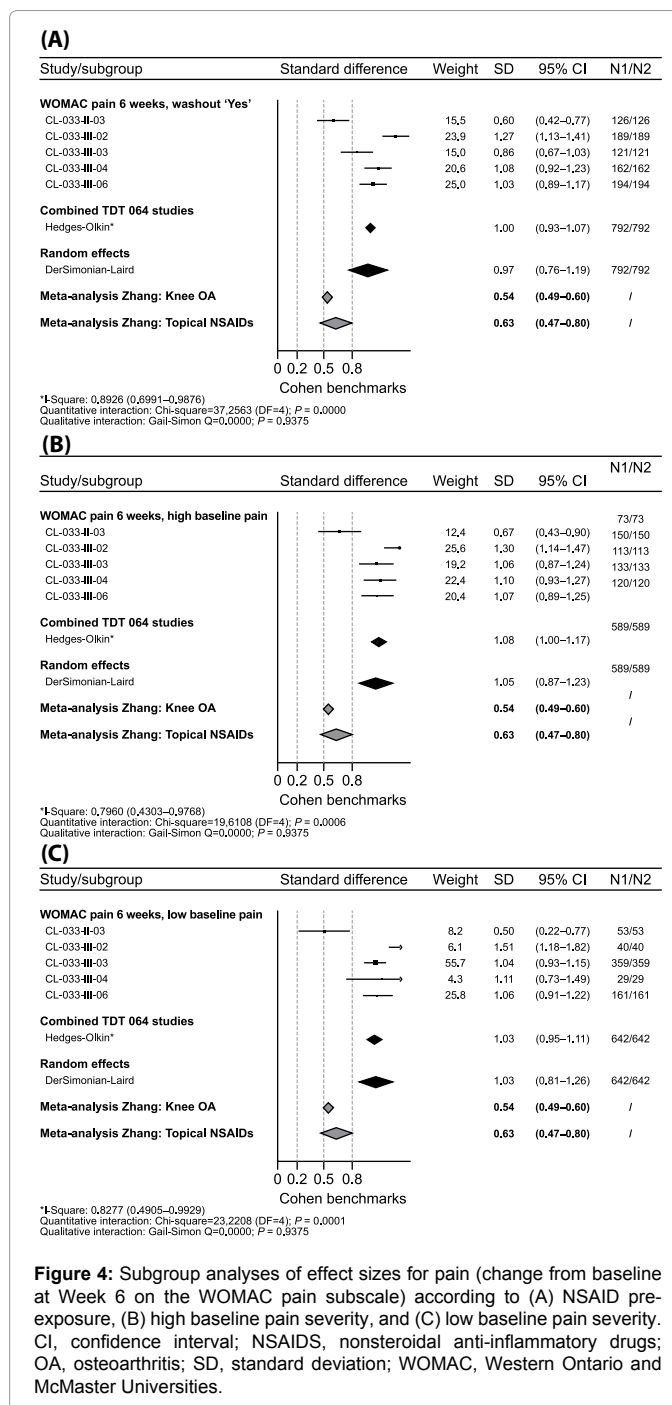
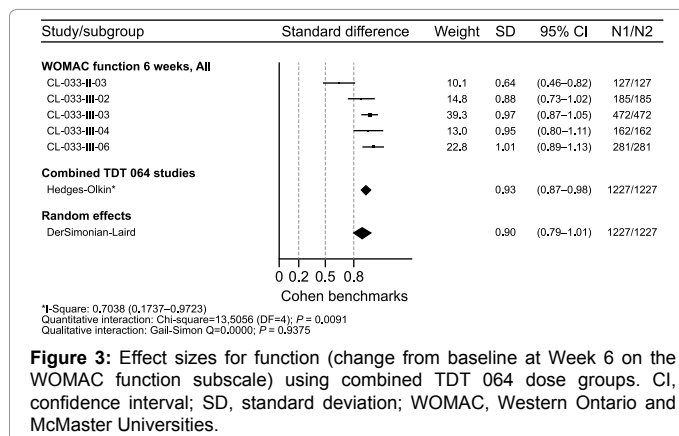
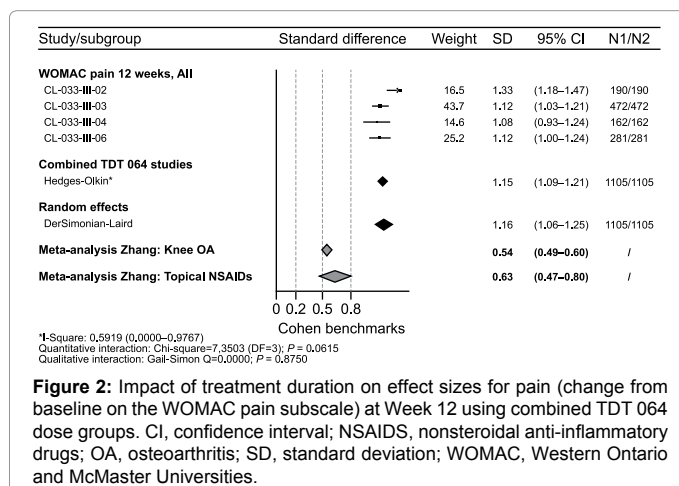
Using a formal meta-analysis procedure, we combined the results of the WOMAC pain and function subscales across five randomized,

Phase II/III studies to determine whether TDT 064, a topical formulation containing ultra-deformable drug-free Sequeosome™ vesicles, has an effect beyond that expected for a placebo in patients with knee OA. We employed a well-established and robust statistical method to calculate within-group standardized differences for all studies, based on the change from baseline of the WOMAC pain and function subscale scores at various timepoints. As data from all controlled studies of IDEA-033 in which TDT 064 was used as a drug-free vehicle control were included, there was no inherent selection bias in the meta-analysis. The WOMAC subscale was chosen as the efficacy outcome measure since this is the most commonly used clinical assessment tool validated for each of the countries participating in trials in this meta-analysis. Although the original studies were conducted some time ago, they did include other outcome measures, such as 50% responder rates, but for this analysis, the parameters selected were the ones that reflected the methodology used in the literature reference and those that were

common to all studies. Compared with the literature reference, pain reduction and improvement in function were substantially higher with TDT 064, irrespective of the treatment duration, baseline pain severity, or flare design. The magnitude of the effect was lowest in the Phase II study and consistently high in the four Phase III studies.

There is an ongoing debate about the most appropriate model to be used for meta-analyses. Simulations show that the fixed effect test for the REM produces a Type I error that is too liberal, whereas the random effect test for the FEM gives a Type I error that is too conservative [21]. We therefore decided to report the results of both models, which importantly produced consistent results. Furthermore, the use of the LOCF approach has been reported to introduce bias in clinical trials [22]; however, we chose to utilize the LOCF approach to mirror the methodology used in the literature reference. Notably, some of the studies included in our meta-analysis used both BOCF and LOCF imputation methods, and outcomes were consistent with the two approaches.

TDT 064 has been registered in Europe as a medical device for the treatment of pain associated with OA, based on the results of the studies included in this meta-analysis [6,8-10] (Table 1). In study CL-033-II-03, pain relief was reported with both IDEA-033 and TDT 064, but superiority of IDEA-033 to TDT 064 in improving physical function was not shown [7]. Marked clinical improvements in pain were also reported in study CL-033-III-02 with both IDEA-033 and TDT 064; pain relief was greater with IDEA-033 than TDT 064, but not improvements in physical function [10]. In CL-033-III-03, pain relief



with IDEA-033 was not superior to TDT 064, and both formulations were superior to oral placebo and non-inferior to celecoxib [6]. Furthermore, in study CL-033-III-06, IDEA-033 was shown to be statistically inferior to TDT 064 in relieving OA knee pain [8].

Multiple regression analyses of the data reported by Zhang et al. [16] identified significant increases in the size of the placebo effect with an increase in the effect of the active treatment, possibly due to a higher patient expectation of benefit [15]; an increase in baseline pain/disease severity; a larger sample size; and an invasive route of administration [15,16]. Placebo response rates were reported for trials using a wide range of active therapies, most commonly Cox II inhibitors (30 trials, n=4755), NSAIDs (27 trials, n=1957), intra-articular hyaluronan (15 trials, n=937), and topical NSAIDs (13 trials, n=896) [16]. The ES for topical NSAIDs was 0.63, which was higher than all other active treatments including oral NSAIDs (ES: 0.49), with the exception of intra-articular hyaluronan (ES: 0.73). However, trials involving multiple treatment injections were associated with the highest placebo ES, as expected [15,16]. Results of our meta-analysis showed that the effects of TDT 064 did not appear to be influenced by factors known to affect the placebo response, such as prior use of oral NSAIDs, or low or high baseline pain severity.

The number of randomized patients included in the studies in our meta-analysis is smaller than that in the meta-analysis reported by Zhang and colleagues, thus it might be premature to compare the magnitude of the absolute ES data for TDT 064 with other OA treatments. However, we can conclude that the response to TDT 064 is substantially larger than that seen across a range of placebos from other studies. Of note, in a systematic review and meta-analysis examining placebo response, the authors concluded that a possible effect on patient-reported continuous outcomes, especially pain, could not be clearly distinguished from bias [23,24]. The meta-analysis included 114 randomized trials comparing placebo with no treatment, subsequently updated to include a total of 156 trials investigating 46 clinical conditions [24]. A beneficial effect of placebo was noted overall in trials with continuous outcomes (ES: 0.24 [95% CI: 0.17–0.31]) (Figure 5). Ten clinical conditions were investigated in ≥ 3 trials with continuous outcomes (pain, obesity, asthma, hypertension, insomnia, nausea, depression, anxiety, phobia, and smoking), but placebo only had a statistically significant pooled effect on pain (ES: 0.25 [95% CI: 0.16–0.35]; 44 trials involving 2833 patients), and phobia (three trials involving 57 patients). The ES was statistically significantly different for trials with patient-reported outcomes (ES: 0.30 [95% CI: 0.21–0.38]) versus those with observer-reported outcomes (ES: 0.10 [95% CI: –0.01 to 0.20]; p=0.002).

Taken together, these findings demonstrate that the magnitude of the effect observed with TDT 064 in this meta-analysis, both with regards to pain relief and improvement in function, is unlikely to be solely a result of a placebo response. In particular, looking at study CL-033-III-03, which demonstrated statistically non-inferior pain relief with TDT 064 to oral celecoxib, the ES for pain relief with TDT 064 was 1.12 (95% CI: 1.03–1.21) at Week 12 and calculation of the ES for oral celecoxib using the same methodology gave a value of 1.21 (95% CI: 1.07–1.36). The comparable effect with an established treatment for pain associated with OA further supports the clinical significance of the response to TDT 064. Work is ongoing to better understand the efficacy mechanism of TDT 064.

Role of the Funding Source

Funding for the original study was provided by IDEA AG, Munich, Germany. Funding for the meta-analysis was provided by Pro Bono Bio Entrepreneur Ltd, UK.

Conflicts of Interest

MR was an employee of IDEA AG at the time the meta-analysis was conducted and is a paid consultant of Pro Bono Bio Entrepreneur Ltd; JV has received honoraria for expert advice provided to IDEA AG, Mucos, Heel, E. Merck, Steigerwald, EVER Pharma, Storz, and EMS; WWB has received honoraria for expert advice provided to Abbott, AstraZeneca, IDEA AG, and Merck Sharp & Dohme; WK has received investigator grants from IDEA AG; PGC has participated in speaker meetings or advisory boards for Janssen, Merck, Pfizer, Pro Bono Bio Entrepreneur Ltd, and Servier.

Acknowledgments

Financial support for medical writing of this manuscript, provided by Bollin Strategies, was supplied by Pro Bono Bio Entrepreneur Ltd, UK.

Author Contributions

JV contributed to statistical analysis; WWB provided advice about the design of the study; PGC contributed to the interpretation of the analysis; all authors discussed the results, contributed to the development of the manuscript, and approved the final version for submission.

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