Osteoarthritis and Cartilage 25 (2017) 1942–1951

Osteoarthritis and Cartilage

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

A new lipid formulation of low dose ibuprofen shows non-inferiority to high dose standard ibuprofen: the FLARE study (flaring arthralgia relief evaluation in episodic flaring knee pain) – a randomised double-blind study

S.M.A. Bierma-Zeinstra † ‡ *, J. Brew §, K. Stoner §, R. Wilson ‖, A. Kilbourn §, P.G. Conaghan ¶

† *Department of General Practice, Erasmus MC – University Medical Centre, Rotterdam, The Netherlands*
‡ *Department of Orthopedics, Erasmus MC – University Medical Centre, Rotterdam, The Netherlands*
§ *Infirst Healthcare Ltd, 45 Beech Street, London, UK*
‖ *Spica Consultants Ltd, Marlborough, UK*
¶ *Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds & NIHR Leeds Musculoskeletal Biomedical Research Centre, Leeds, UK*

ARTICLE INFO

Article history:
Received 4 April 2017
Accepted 1 September 2017

Keywords:
Arthralgia
Ibuprofen
Joint pain
Knee
Osteoarthritis
Symptom flare-up

SUMMARY

Objective: To investigate short-term efficacy and safety of a novel lipid ibuprofen formulation 1200 mg/day compared with standard ibuprofen 1200 mg/day and 2400 mg/day in episodic knee arthralgia/flaring pain.

Design: Multicentre, randomised, double-blind, 3-arm, non-inferiority trial conducted at 27 primary care centres. Adults with ≥1 knee flare episode within 12 months were recruited within 24 h of new flare with pain severity ≥5 on a 0–10 numerical rating scale (NRS). Primary outcome was change from baseline in WOMAC pain subscale over 5 days. Main secondary outcome was Gastrointestinal Symptom Rating Scale (GSRS) change from baseline. Other endpoints included assessment of WOMAC total subscale scores and self-reported NRS for pain, subject nominated activity, stiffness and swelling.

Results: 462 patients were enrolled (58.9% males; mean age 52.2 years). Treatment allocation comprised 148 lipid 1200 mg, 155 soft-gel 1200 mg, 159 soft-gel 2400 mg. WOMAC pain subscale scores decreased in all groups, with lipid 1200 mg being non-inferior to soft-gel 1200 mg (adjusted mean difference −0.26 [95% confidence interval [CI] −0.69, 0.17]) and to soft-gel 2400 mg (difference 0.19 [95% CI −0.24, 0.62]). No differences were seen in mean GSRS total scores. NRS secondary endpoints suggested greater improvements in the lipid 1200 mg group compared to soft-gel 1200 mg, with similar results to soft-gel 2400 mg. The most frequent drug-related adverse events (AEs) were gastrointestinal (GI) disorders, with statistically fewer events for lipid 1200 mg vs soft-gel 2400 mg ($P = 0.01$, post-hoc analysis).

Conclusions: Ibuprofen 1200 mg/day lipid formulation was non-inferior to standard ibuprofen soft-gel capsules 1200 mg and 2400 mg/day in relieving flaring knee pain. NRS endpoints showed lipid 1200 mg was numerically similar to soft-gel 2400 mg.

Trial registration number: EudraCT number: 2014-004254-33.

Introduction

Frequent knee pain affects approximately 25% of adults >55 years,[1,2] limiting function and mobility, and results in reduced quality of life.[3] The aetiology is often unknown, although osteoarthritis (OA) is the most common joint disease, particularly in older adults.

* Address correspondence and reprint requests to: S.M.A. Bierma-Zeinstra, Department of General Practice, Department of Orthopedics, Erasmus University Medical Centre, Rotterdam, The Netherlands.

E-mail addresses: s.bierma-zeinstra@erasmusmc.nl (S.M.A. Bierma-Zeinstra), John.Brew@seekacure.com (J. Brew), Karen.Stoner@infirst.co.uk (K. Stoner), rosamund@spicaconsultants.com (R. Wilson), Tony.Kilbourn@infirst.co.uk (A. Kilbourn), p.conaghan@leeds.ac.uk (P.G. Conaghan).

http://dx.doi.org/10.1016/j.joca.2017.09.002

Intermittent, disabling pain episodes,[4] or flare-ups[5] are part of the natural history of knee OA[6] and may occur in early and advanced disease.[4] Symptoms may be characterised by abrupt changes and short-term fluctuations.[7] Early stage OA is characterised by such flare-ups usually brought on by a trigger, e.g., an unusual activity or movement, but has limited impact.[4] The pathological process underlying these episodic flares is unclear, although association with physician-assessed effusion, patient self-reported swelling, and changes in synovial fluid composition imply an inflammatory component.[5,8] Fluctuating pain is also associated with change in effusion or synovitis scores assessed on magnetic resonance imaging (MRI).[9]

Pharmacological OA treatments include analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), intra-articular corticosteroids, and opioids, all of which have been shown to provide effective pain relief compared to placebo[10] and NSAIDs offer similar pain relief to opioids in OA patients.[11] However, few studies have addressed management of knee pain flare. Given the predominance of pharmacological management for OA,[12,13] it is likely that similar agents are commonly used for acute episodes of knee pain. NSAIDs are the commonest OA therapy, with ibuprofen being the most commonly prescribed.[14,15] It is well-tolerated with a well-established safety profile; the most common adverse effects (AEs) are gastrointestinal (GI) (estimated incidence of 12.1%).[16] Ibuprofen shows the lowest rate of GI side-effects compared to other NSAIDs, with these being dose-related.[17] A recent review of the cardiovascular risks associated with use of NSAIDs by regulatory authorities has shown these to be dose- and time-dependent.[18] Unlike the lower doses (1200 mg/day), high daily doses of ibuprofen (2400 mg/day) are associated with increased risk of cardiovascular events (myocardial infarction [MI] and stroke).[19] These findings are supported by a recent white paper in OA[20] and a meta-analysis on the risk of acute MI with NSAIDs.[21] Thus, the lowest possible ibuprofen dose should be given, whilst maintaining suitable efficacy.

The FLaring Arthralgia Relief Evaluation in episodic flaring knee pain (FLARE) study investigated the efficacy, safety and tolerability of a new lipid formulation of ibuprofen (Flarin®, Infirst Healthcare) 1200 mg/day, and compared its effects with standard soft-gel capsules (1200 mg or 2400 mg/day) over 5 days in patients suffering episodic knee flare pain. The lipid formulation fully dissolves ibuprofen within a lipid matrix (hard fat and glycerol monolinoleate), which is anticipated to reduce the gastric effects which are associated with conventional ibuprofen formulations, and may reduce gastric irritation associated with high local ibuprofen concentrations. The 5-day treatment course is consistent with the approved short-term over-the-counter treatment period before patients are advised to seek medical advice (typically 5–10 days). However, to ensure this study represented 'real world' usage, patients could receive a second 5-day treatment course if requested.

Method

The study comprised a multicentre, randomised, double-blind, 3-arm design to test for non-inferiority by comparing ibuprofen 1200 mg/day lipid formulation with standard ibuprofen soft-gel capsules at a dose of 1200 mg/day or 2400 mg/day. It was conducted at 27 centres, comprising general practitioner surgeries in the UK and The Netherlands. Patients with a history of knee flares were identified by a variety of methods, including medical record review and local advertising whereupon potential patients were then referred to a local study site. Patients were screened to determine study eligibility and were instructed to return to the study site within 24 h if they experienced another knee flare. The study was approved by the central independent ethics committee of each country (UK: NRES Committee East Midlands – Northampton; Netherlands: Independent Review Board Nijmegen). All patients provided written informed consent.

Study population

Males or females aged 18–70 years with a history of ≥1 knee flare pain episodes in the previous 12 months (with or without treatment), who experienced a new knee flare episode with pain severity ≥5 on a 0–10 numerical rating scale (NRS) and who attended a baseline evaluation within 24 h of experiencing the new knee flare episode, were eligible for participation. Key exclusion criteria were recent serious illness, fracture, significant injury or surgery to the knee, recent intra-articular treatment or systemic corticosteroids, and use of any pain medication within 7 days of study baseline.

Randomisation

Treatment was determined by a central 1:1:1 randomisation schedule prepared using standard computer software with a random seed number and a block size of six. This software incorporates a reproducible standard procedure for generating random numbers. Medication was distributed to centres using complete block numbers.

Treatment groups

Patients were randomised to one of three treatment arms:

- 5-day treatment with 2 × 200 mg lipid ibuprofen capsules three times daily (total daily dose 1200 mg)
- 5-day treatment with 1 × 400 mg soft-gel ibuprofen capsule plus 1 × placebo capsule three times daily (total daily dose 1200 mg)
- 5-day treatment with 2 × 400 mg soft-gel capsule ibuprofen capsules three times daily (total daily dose 2400 mg)

All study drugs were produced by the same manufacturer on behalf of Infirst Healthcare and were presented as identical soft white oval gelatin capsules to preserve blinding. Treatments were taken every 6 h (i.e., morning, afternoon and evening) with half a glass of water (2 h pre- or post-food). The study treatment dose was taken after completing the baseline assessments. After 5 days' treatment (Course 1), patients returned to the study centre to assess whether their knee flare had been adequately controlled (based on a pre-defined 4-point scale). Eligible patients who wanted further treatment after completing Course 1 could receive a further 5-day treatment period (Course 2).

Outcomes

Primary study outcome was change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (normalised to 0–10 range) after 5 days' treatment. This is a widely used and validated instrument for evaluating OA.[22] The pain subscale is the most studied and reliable endpoint within the WOMAC[23,24] and the clinical experts involved in the study design and authors considered the pain subscale to be the most appropriate endpoint.

The main secondary outcome was change from baseline after 5 days in the Gastrointestinal Symptom Rating Scale (GSRS) based on 7-point Likert scale of 15 items.[25] Other secondary endpoints included assessment of WOMAC total score and subscale scores for function and stiffness; average daily self-reported NRS scores (0–10

scale) for pain, subject-nominated activity, stiffness and self-reported swelling; patient's global assessment of the overall knee flare episode using a NRS (0–10 scale); and the proportion of patients achieving an OMERACT-OARSI response.[26]

Statistical analysis

Sample size: This was based on assessing non-inferiority of the lipid 1200 mg capsule to the 1200 mg and 2400 mg soft-gel capsules for change from baseline after 5 days' treatment in the WOMAC pain score. The number of evaluable patients required to test for non-inferiority was 146 per treatment group, assuming the true treatment difference was 0, the non-inferiority margin was 0.8, and the SD was 2.1, using a 1-sided 2.5% alpha-level with 90% power. The choice of non-inferiority margin was based on the WOMAC 0–10 NRS, translated from a score of 8 if based on a 0–100 visual analogue scale (VAS). An observed clinically important difference of 10–20 has been reported,[27–29] and a meta-analysis of randomised controlled NSAID clinical trials for OA knee pain[30] showed the lower confidence interval [CI] for the effect size was 7.4. A slightly higher value than the lower bound of this interval (i.e., 8.0) was chosen due to the short duration of the trials included in the meta-analysis.

Efficacy parameters: All analyses were performed on the Full Analysis Set (FAS), where treated patients without any post-baseline data were excluded. No imputation was used for missing data. An analysis of covariance (ANCOVA) was used to test the effect of lipid 1200 mg on the change from baseline after 5 days' treatment in the WOMAC pain scale score compared to the standard formulations. The model included fixed effects for treatment group and centre (pooled where necessary) and baseline WOMAC pain score as a linear covariate. Centres contributing <6 subjects to the primary endpoint analysis were pooled based on geographical location for analysis purposes, with small centres pooled with their nearest neighbour and only occurred within each country. A sensitivity analysis assessed the robustness of the primary endpoint results to the method of handling missing data. This analysis was performed on the randomised set including patients excluded from the FAS, using a baseline observation carried forward (BOCF) approach for patients with no on-treatment data.

Changes from baseline after 5 days' treatment in the GSRS total score; WOMAC total, stiffness scale and function scale scores; GSRS dimension scores; and patient's global assessment of outcome were analysed using the same methodology as the primary endpoint. Daily NRS scores (scale of 0–10) were analysed using a mixed model for repeated measures (MMRM) approach, with the analysis including effects for treatment group, day, pooled centre, baseline score and the treatment-by-day and baseline score-by-day interaction terms. The adjusted treatment group difference at each day with the corresponding 95% CI was presented along with the *P*-value. The proportion of patients achieving an OMERACT-OARSI response,[20] and proportion of patients in each of the knee flare categories after 5 days' treatment were analysed using a stratified (by pooled centre) Cochran-Mantel-Haenszel (CMH) test. Time to knee flare resolution was compared using a Cox proportional hazards model, stratified by centre (pooled where necessary). Time-to-event analysis using a Cox proportional hazards model stratified by pooled centre was used to estimate a hazard ratio. A stratified log-rank test and Kaplan–Meier estimates were used to support the analyses.

Safety parameters: Planned safety analyses were descriptive. Post-hoc statistical analyses formally tested for the difference between groups for all GI AEs and treatment-related GI AEs using the CMH test.

Results

464 patients were randomised: 462 (99.6%) received treatment between 17-Mar-2015 and 10-Aug-2016 (148 lipid 1200 mg, 155 soft-gel 1200 mg, 159 soft-gel 2400 mg). 58.9% of patients were male and mean age was 52.2 years (79.7% aged <65). The left knee was index in 53.5% of patients (Table I). Treatment groups were broadly balanced at baseline regarding medical history. Overall, 256 patients (55.4%) were taking concomitant medications, particularly for cardiovascular indications and diabetes; only a small number of patients were taking paracetamol (0.4%), other analgesic agents (<2.5%), or other agents that could cause GI upsets (<10%).

Average patient compliance was >97% in all groups. Twenty-three patients (5.0%) prematurely discontinued the study, with similar numbers across the treatment groups. Two patients were randomised but not treated (both lipid 1200 mg group). The most common reason for premature discontinuation was 'Other' (10 patients [2.2%]) most frequently due to patients attending the clinic early for their follow-up appointment (primarily due to symptom resolution). Eight patients (1.7%) withdrew due to AEs, two patients (0.4%) due to protocol deviation, and one patient (0.2%) because knee flare was resolved. Note: patients who

Table I
Patient demographic characteristics (Treated Set)

	Lipid 1200 mg	Soft-gel 1200 mg	Soft-gel 2400 mg	Total
Number of patients [N (%)]	148 (100.0)	155 (100.0)	159 (100.0)	462 (100.0)
Gender [N (%)]				
Male	87 (58.8)	91 (58.7)	94 (59.1)	272 (58.9)
Female	61 (41.2)	64 (41.3)	65 (40.9)	190 (41.1)
Ethnicity [N (%)]				
Asian	5 (3.4)	5 (3.2)	3 (1.9)	13 (2.8)
Black	6 (4.1)	5 (3.2)	2 (1.3)	13 (2.8)
White	131 (88.5)	142 (91.6)	152 (95.6)	425 (92.0)
Other	6 (4.1)	3 (1.9)	2 (1.3)	11 (2.4)
Age (years)				
Mean (SD)	51.6 (13.6)	51.7 (13.0)	53.3 (12.6)	52.2 (13.1)
Median (range)	53.5 (18, 70)	55.0 (18, 69)	56.0 (19, 69)	55.0 (18, 70)
Age group [N (%)]				
<65 years	114 (77.0)	130 (83.9)	124 (78.0)	368 (79.7)
≥65 years	34 (23.0)	25 (16.1)	35 (22.0)	94 (20.3)
Index knee [N (%)]				
Left	75 (50.7)	84 (54.2)	88 (55.3)	247 (53.5)
Right	73 (49.3)	71 (45.8)	71 (44.7)	215 (46.5)

discontinued were included in the primary FAS analyses unless they did not have WOMAC at baseline and at least one on-treatment (during the first 5-day treatment course) assessment of WOMAC pain score (or an important protocol violation for the per protocol analysis). A total of 130 patients received a second treatment course (44 lipid 1200 mg, 46 soft-gel 1200 mg, 40 soft-gel 2400 mg) (Fig. 1).

Efficacy results

After 5 days' treatment (completion of Course 1), mean WOMAC pain subscale scores in the FAS were lower, indicating improvement, in all three treatment groups: lipid 1200 mg change from 5.72 to 3.05, soft-gel 1200 mg from 5.60 to 3.26, and soft-gel 2400 mg from 5.61 to 2.82 (Table II). Differences in the adjusted means between the lipid 1200 mg and soft-gel groups regarding changes from baseline to the end of Course 1 were −0.26 (95% CI: −0.69, 0.17) for the comparison lipid 1200 mg vs soft-gel 1200 mg, and 0.19 (95% CI: −0.24, 0.62) for the comparison lipid 1200 mg vs soft-gel 2400 mg. Since the whole of the 95% CIs lay below the pre-defined non-inferiority margin of 0.8 (but above the superiority margin of 0), lipid 1200 mg was concluded to be non-inferior both to soft-gel 1200 mg and 2400 mg (Table II, Fig. 2). These FAS results were confirmed by the supportive analysis in the per protocol population, and by the sensitivity analysis using BOCF for missing data (see online appendix). Comparison of thetwo soft-gel groups showed that the non-inferiority criteria was not met between the soft gel 1200 mg and 2400 mg groups. Furthermore,

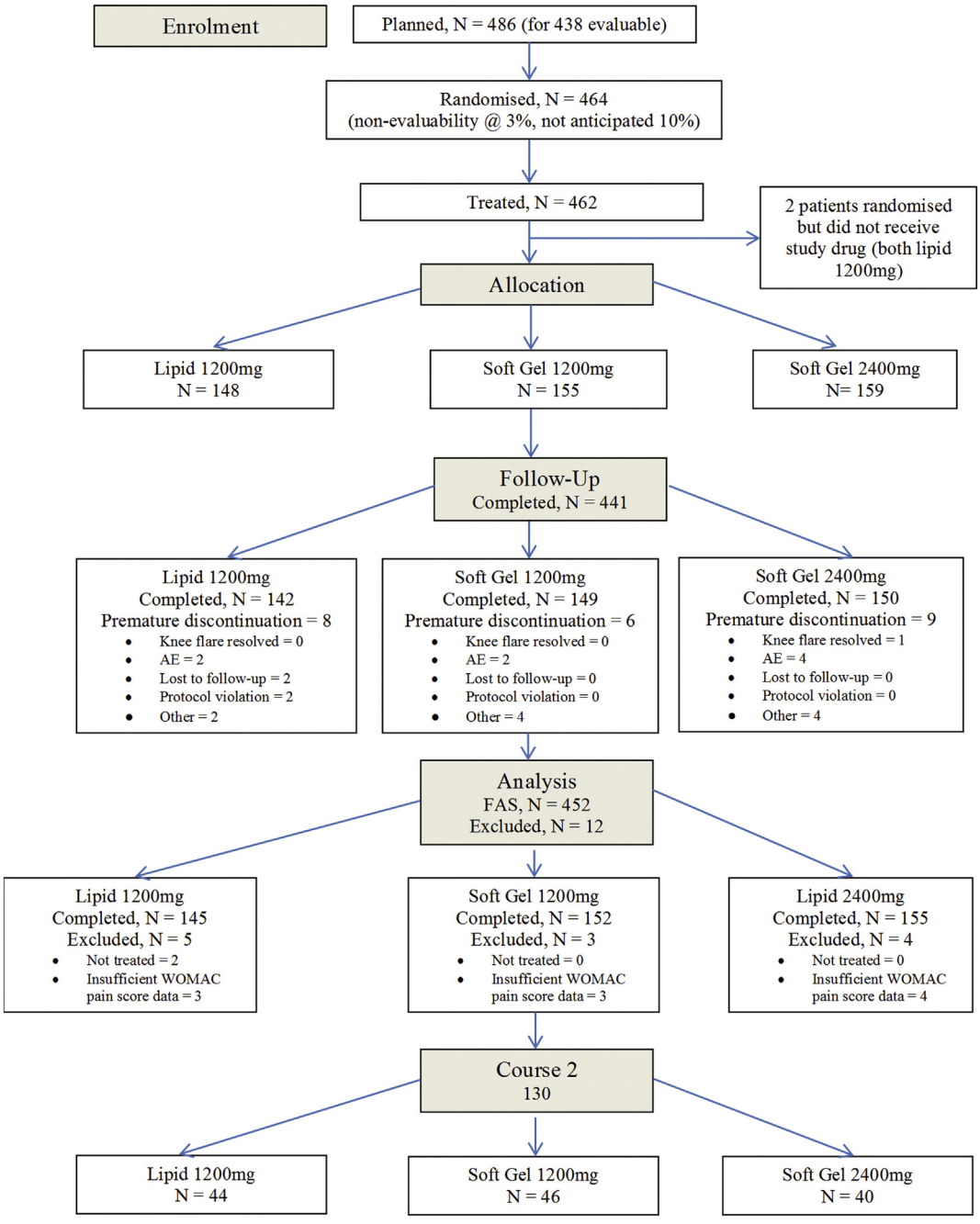

Fig. 1. CONSORT diagram.

Table II
WOMAC scores after 5 days of treatment (Full Analysis Set)

	Lipid 1200 mg	Soft-gel 1200 mg	Soft-gel 2400 mg
Number of patients in analysis set	145	152	155
Pain Scale score, n in analysis	145	152	155
Baseline score, mean (SD)	5.72 (1.64)	5.60 (1.69)	5.61 (1.64)
End of Course 1 (5 days) (mean [SD])	3.05 (2.11)	3.26 (2.14)	2.82 (2.25)
Change from baseline to end of Course 1:			
Adjusted mean (SE)*	−2.42 (0.17)	−2.16 (0.17)	−2.61 (0.17)
95% confidence interval*	(−2.76, −2.09)	(−2.49, −1.84)	(−2.94, −2.29)
Difference (lipid 1200 − soft-gel)			
Adjusted mean (SE)*		−0.26 (0.22)	0.19 (0.22)
(95% CI)*, P-value (superiority)*†		(−0.69, 0.17), 0.2327	(−0.24, 0.62), 0.3799
Total score, n in analysis	144	149	154
Baseline score, mean (SD)	5.44 (1.74)	5.49 (1.62)	5.45 (1.70)
End of Course 1 (5 days) (mean [SD])	2.94 (2.04)	3.13 (2.05)	2.77 (2.16)
Change from baseline to end of Course 1:			
Adjusted mean (SE)*	−2.32 (0.16)	−2.18 (0.16)	−2.53 (0.15)
95% confidence interval*	(−2.63, −2.01)	(−2.49, −1.87)	(−2.84, −2.23)
Difference (lipid 1200 − soft-gel)			
Adjusted mean (SE)*		−0.14 (0.21)	0.21 (0.20)
(95% CI)*, P-value*†		(−0.54, 0.26), 0.4908	(−0.19, 0.61), 0.3012
Stiffness score, n in analysis	144	152	154
Baseline score, mean (SD)	6.38 (1.91)	6.06 (1.96)	6.15 (2.03)
End of Course 1 (5 days) (mean [SD])	3.29 (2.36)	3.57 (2.40)	3.18 (2.38)
Change from baseline to end of Course 1:			
Adjusted mean (SE)*	−2.78 (0.19)	−2.38 (0.19)	−2.80 (0.19)
95% confidence interval*	(−3.16, −2.40)	(−2.75, −2.02)	(−3.17, −2.43)
Difference (lipid 1200 − soft-gel)			
Adjusted mean (SE)*		−0.40 (0.25)	0.02 (0.25)
(95% CI)*, P-value*†		(−0.88, 0.09), 0.1098	(−0.47, 0.50), 0.9434
Function score, n in analysis	145	149	155
Baseline score, mean (SD)	5.25 (1.92)	5.39 (1.71)	5.32 (1.82)
End of Course 1 (5 days) (mean [SD])	2.86 (2.05)	3.06 (2.09)	2.72 (2.17)
Change from baseline to end of Course 1:			
Adjusted mean (SE)*	−2.26 (0.16)	−2.14 (0.16)	−2.46 (0.15)
95% confidence interval*	(−2.57, −1.95)	(−2.44, −1.83)	(−2.77, −2.16)
Difference (lipid 1200 − soft-gel)			
Adjusted mean (SE)*		−0.12 (0.20)	0.21 (0.20)
(95% CI)*, P-value*†		(−0.52, 0.28), 0.5598	(−0.19, 0.60), 0.3056

WOMAC scores range from 0 (best outcome) to 10 (worst outcome).
Negative values indicate an improvement from baseline.
* ANCOVA on observed data including treatment, pooled centre and baseline WOMAC total score terms.
† Standard 2-sided 5% significance level for superiority.

the 95% CI for this comparison did not include zero, suggesting soft-gel 1200 mg is less effective than soft-gel 2400 mg, consistent with expected dose-dependent benefits. It is noteworthy that this comparison was not formally pre-planned but was produced with the statistical model output.

Mean GSRS total scores (main secondary efficacy endpoint) were low at baseline and only small changes were seen during the study (adjusted mean changes: 0.08 for lipid 1200 mg, 0.05 for soft-gel 1200 mg, 0.13 for soft-gel 2400 mg). Differences in the adjusted means for the comparison lipid 1200 mg vs soft-gel groups were 0.03 (95% CI: −0.08, 0.13) for soft-gel 1200 mg, and −0.05 (95% CI: −0.16, 0.05) for soft-gel 2400 mg (Table III). Mean GSRS dimension scores over time (i.e., other secondary endpoints) were generally marginally higher or unchanged at the end of Course 1 compared with baseline, and none were statistically significant.

For the additional secondary endpoints, mean WOMAC subscale scores (total, stiffness and function scores) were all lower, indicating improvement, at the end of Course 1 compared to baseline in all three treatment groups. No statistically significant differences emerged between treatment groups regarding changes from baseline to the end of Course 1 in any of the WOMAC subscale scores analysed (Table II).

NRS scores for pain, stiffness, patient-nominated activity, and swelling decreased each day from baseline until the end of Course 1 in all treatment groups, with patients reporting increased benefits each day over the 5-day treatment period. Results in the lipid 1200 mg group tended to be numerically closer to those in the soft-gel 2400 mg group and higher than the soft-gel 1200 mg group (not statistically significant). However, the difference between lipid 1200 mg and soft-gel 1200 mg for swelling reached nominal statistical significance after treatment completion (adjusted mean difference −0.4, 95% CI: −0.8, −0.0, $P = 0.04$) (Fig. 3).

Mean global NRS assessment scores were similar for all treatment groups at baseline, being approximately 50% lower (indicating improvement) in each group after Course 1. Greatest improvement was seen in the soft-gel 2400 mg group, followed by the lipid 1200 mg group (−3.1 in the soft-gel 2400 mg group, −2.8 in the lipid 1200 mg group, and −2.6 in the soft-gel 1200 mg group). Differences in the adjusted means between the lipid 1200 mg and soft-gel groups in the changes from baseline to the end of Course 1 were −0.2 (95% CI: −0.7, 0.3, $P = 0.43$) for the comparison lipid 1200 mg vs soft-gel 1200 mg, and 0.3 (95% CI: −0.2, 0.7, $P = 0.30$) for the comparison lipid 1200 mg vs soft-gel 2400 mg.

The percentage of responders according to OMERACT-OARSI criteria was lowest in the soft-gel 1200 mg group (69.7%), followed by 73.1% in the lipid 1200 mg group and 76.1% in the soft-gel 2400 mg group. Similarly, most patients assessed their knee flare as controlled (i.e., fully controlled/under control) at the end of Course 1: 81 patients (55.9%) in the lipid 1200 mg group, 75 patients (49.3%) in the soft-gel 1200 mg group, 92 patients (59.4%) in the soft-gel 2400 mg group. The odds ratio for responders (i.e., fully

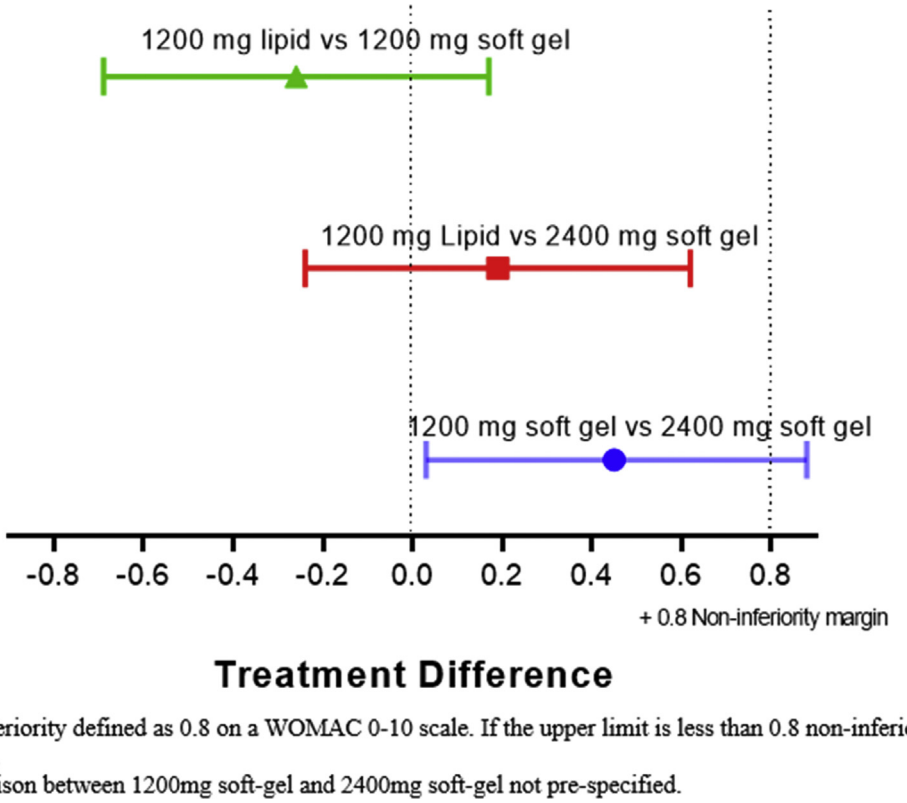

Fig. 2. Effect of treatment on WOMAC pain subscale scores.

controlled/under control) at the end of Course 1 for the comparison lipid 1200 mg vs soft-gel 1200 mg was 1.25 (95% CI: 0.76, 2.06), indicating higher odds of response in the lipid 1200 mg group. The odds ratio was below one for the comparison lipid 1200 mg vs soft-gel 2400 mg (0.82, 95% CI: 0.50, 1.34) (Table IV).

Of the 130 patients who opted for a second course (total treatment duration 10 days), knee flare was fully controlled/under control in 58 patients (44.6%): 22 patients (50.0%) in the lipid 1200 mg group, 12 patients (26.1%) in the soft-gel 1200 mg group, and 24 patients (60.0%) in the soft-gel 2400 mg group.

Safety results

The number of patients with at least 1 AE was 54 (36.5%) in the lipid 1200 mg group, 53 (34.2%) in the soft-gel 1200 mg group, and 65 (40.9%) in the soft-gel 2400 mg group. Most AEs were mild or moderate in severity, with two patients per group experiencing severe AEs. Overall, GI AEs were most frequently reported: 26.4% in the lipid 1200 mg group, 30.3% in the soft-gel 1200 mg group, and 33.3% in the soft-gel 2400 mg group. The odds ratio for GI AEs in the soft-gel 2400 mg group compared to the lipid 1200 mg group was 1.40 (95% CI: 0.85, 2.29), $P = 0.18$ (post-hoc analysis).

The percentage of patients with drug-related AEs based on Investigator blinded assessment was lower in the lipid 1200 mg group (18.9% compared to 23.9% in the soft-gel 1200 mg group and 31.4% in the soft-gel 2400 mg group). The most frequently reported drug-related AEs were GI disorders (16.2% for lipid 1200 mg, 22.6% for soft-gel 1200 mg, 28.3% for soft-gel 2400 mg) (Table V). The odds ratio in the soft-gel 2400 mg group compared to the lipid 1200 mg group for drug-related GI AEs was statistically significant: 2.04 (95% CI: 1.17, 3.56, $P = 0.01$) (post-hoc analysis).

Nine patients discontinued study drug due to AEs, the most common being diarrhoea (three patients), abdominal discomfort (two patients), and dyspepsia (two patients). Five discontinuations were in the soft-gel 2400 mg group. One patient in the soft-gel 2400 mg group experienced a serious, severe AE of worsening endometriosis and led to study drug discontinuation, although this was considered unrelated to treatment.

Table III
Gastrointestinal Symptom Rating Scale (GSRS) scores after 5 days of treatment (Full Analysis Set)

	Lipid 1200 mg N = 145	Soft-gel 1200 mg N = 152	Soft-gel 2400 mg N = 155
Total score, n in analysis	145	149	154
Change from baseline to end of Course 1:			
Adjusted mean (SE)*	0.08 (0.04)	0.05 (0.04)	0.13 (0.04)
95% confidence interval*	(−0.00, 0.16)	(−0.03, 0.14)	(0.05, 0.21)
Difference (lipid 1200 − soft-gel)			
Adjusted mean (SE)*		0.03 (0.05)	−0.05 (0.05)
95% confidence interval*, P-value*†		(−0.08, 0.13), 0.6331	(−0.16, 0.05), 0.3373

GSRS scores range from 1 (best outcome) to 7 (worst outcome).
Positive changes from baseline indicate deterioration in GSRS outcome.
* ANCOVA on observed data including treatment, pooled centre and baseline GSRS total score terms.
† Standard 2-sided 5% significance level for superiority.

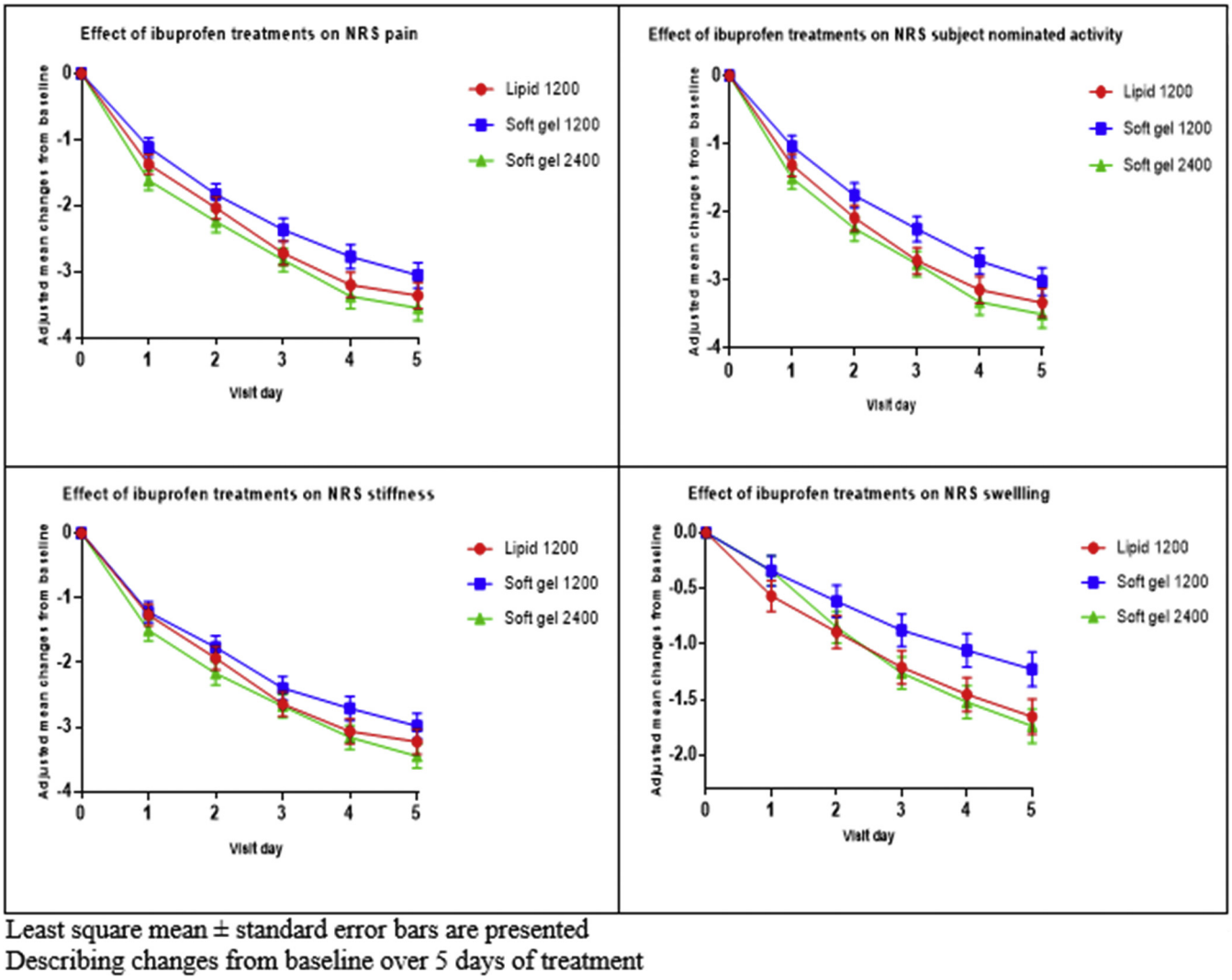

Fig. 3. Change from baseline in self-reported symptoms (NRS evaluation).

Table IV
Responses after 5 days, as assessed by OMERACT-OARSI criteria and knee flare response Categories

	Lipid 1200 mg N = 145	Soft-gel 1200 mg N = 152	Soft-gel 2400 mg N = 155
OMERACT-OARSI Response, *n in analysis*	145	152	155
Number (%) of responders	106 (73.1)	106 (69.7)	118 (76.1)
95% confidence interval (%)*	(65.1, 80.1)	(61.8, 76.9)	(68.6, 82.6)
Difference (lipid 1200 − soft-gel)†			
Odds ratio		1.135	0.833
95% confidence interval		(0.674, 1.914)	(0.488, 1.422)
P-value		0.6349	0.5056
Knee Flare Response Categories, *n in analysis*	145	152	155
End of Course 1 (5 days) score [N (%)]:			
• Fully controlled	19 (13.1)	17 (11.2)	27 (17.4)
• Under control	62 (42.8)	58 (38.2)	65 (41.9)
• Partially controlled	44 (30.3)	51 (33.6)	48 (31.0)
• Not under control	20 (13.8)	26 (17.1)	15 (9.7)
Number (%) of responders at the end of Course 1 (5 days):	81 (55.9)	75 (49.3)	92 (59.4)
95% confidence interval (%)*	(47.4, 64.1)	(41.1, 57.6)	(51.2, 67.2)
Difference (lipid 1200 − soft-gel)†			
Odds ratio		1.251	0.820
95% confidence interval		(0.759, 2.062)	(0.501, 1.341)
P-value		0.3763	0.4204

OMERACT-OARSI response: Response defined as improvement in WOMAC pain or function of ≥50% with change of ≥2, or improvement in at least two of: 1) pain ≥20% with change of ≥1, 2) function ≥20% with change of ≥1, 3) global assessment ≥20% with change of ≥1.
Knee flare response categories: Response defined as knee flare category of 'Fully controlled' or 'Under control'.
Odds ratios >1 indicate higher odds of response in lipid 1200.
* Exact (Clopper-Pearson) confidence interval for a binomial proportion.
† CMH statistics controlling for pooled centre.

Table V
Drug-related adverse events reported for >1% of patients in any treatment group (Treated Set)

System Organ Class Preferred term	Lipid 1200 mg N (%)	Soft-gel 1200 mg N (%)	Soft-gel 2400 mg N (%)
Number of patients	148 (100.0)	155 (100.0)	159 (100.0)
Number of patients with at least one drug-related AE	28 (18.9)	37 (23.9)	50 (31.4)
Gastrointestinal disorders	24 (16.2)	35 (22.6)	45 (28.3)
Diarrhoea	5 (3.4)	8 (5.2)	8 (5.0)
Nausea	7 (4.7)	7 (4.5)	8 (5.0)
Abdominal distension	4 (2.7)	4 (2.6)	12 (7.5)
Abdominal discomfort	7 (4.7)	3 (1.9)	9 (5.7)
Dyspepsia	3 (2.0)	7 (4.5)	11 (6.9)
Constipation	4 (2.7)	2 (1.3)	6 (3.8)
Flatulence	2 (1.4)	5 (3.2)	5 (3.1)
Abdominal pain upper	2 (1.4)	8 (5.2)	5 (3.1)
Gastro-oesophageal reflux disease	1 (0.7)	5 (3.2)	7 (4.4)
Eructation	3 (2.0)	4 (2.6)	5 (3.1)
Gastrointestinal motility disorder	1 (0.7)	3 (1.9)	2 (1.3)
Abdominal pain	2 (1.4)	3 (1.9)	6 (3.8)
Gastrointestinal sounds abnormal	3 (2.0)	4 (2.6)	4 (2.5)
Defaecation urgency	1 (0.7)	1 (0.6)	2 (1.3)
Faeces hard	0 (0.0)	1 (0.6)	3 (1.9)
Abdominal tenderness	1 (0.7)	0 (0.0)	2 (1.3)
General disorders and administration site conditions	1 (0.7)	1 (0.6)	4 (2.5)
Nervous system disorders	3 (2.0)	2 (1.3)	1 (0.6)
Headache	2 (1.4)	2 (1.3)	0 (0.0)
Vascular disorders	2 (1.4)	0 (0.0)	0 (0.0)
Hypertension	2 (1.4)	0 (0.0)	0 (0.0)

Discussion

We believe this is the first large-scale study to investigate episodic knee pain flares in primary care patients. The FLARE study was designed to address the need for effective, short-term treatment for relief of flaring knee pain. The primary study endpoint was change from baseline after 5 days' treatment in the WOMAC pain scale score, and the primary analysis was the test for non-inferiority between treatments. The outcome of the primary analysis was that improvements in WOMAC pain scale score were observed in all three treatment groups and lipid 1200 mg treatment was non-inferior to soft-gel 1200 mg and 2400 mg. This finding was confirmed by the outcome of the supportive analyses. For NRS endpoints, results for lipid 1200 mg were remarkably consistent with the soft-gel 2400 mg group.

Knee OA is a leading cause of knee pain and is associated with disability and functional limitations in adults.[31] It has been ranked alongside heart disease, depressive symptomatology and stroke for resulting levels of disability.[32] Up to one-third of older adults (>55 years) show radiological evidence of knee OA, indicating an annual prevalence of 25%.[2,33] The study patient cohort is younger than normally found in typical OA trials and was recruited from primary care settings, suggesting representation of early clinical phase OA.

NSAIDs are commonly used to treat knee pain and OA, most frequently ibuprofen[14,15] which is typically administered at a daily dose of 1200 mg.[34] The higher 2400 mg dose has shown additional anti-inflammatory properties and may be used for conditions such as rheumatoid arthritis and ankylosing spondylitis. A meta-analysis assessed the effectiveness of different preparations and doses of NSAIDs on OA pain and showed all preparations, irrespective of dose, improved point estimates of pain symptoms compared with placebo, with higher NSAID dosages being most effective.[35]

The GSRS total score was the key secondary study endpoint because most common AEs associated with ibuprofen are GI-related. However, mean GSRS total scores were low at baseline and only small changes were seen during the study. Mean GSRS dimension scores (abdominal pain, constipation, diarrhoea, indigestion, reflux) also showed only small changes, with no statistically significant differences between the treatment groups, suggesting the GSRS may not be an appropriate tool to detect changes in GI symptoms in this patient population, or may be unsuitable for short-term studies.

Pain, stiffness, patient-nominated activity, and swelling NRS scores decreased daily from baseline until the end of Course 1 in all treatment groups, with patients reporting increased benefits each day throughout the 5-day treatment period. Although differences between treatment groups did not reach statistical significance, there was a trend for the results in the lipid 1200 mg group to be numerically closer to those in the soft-gel 2400 mg group, and higher than those in the soft-gel 1200 mg group. It is noteworthy that the difference between lipid 1200 mg and soft-gel 1200 mg groups for swelling reached nominal statistical significance after treatment, and the WOMAC stiffness score also showed a closer result to the soft-gel 2400 mg group. This could indicate an anti-inflammatory effect of the lipid 1200 mg treatment that was closer to the soft-gel 2400 mg group. However, these findings require further investigation.

Responder analyses also supported the primary and secondary efficacy analyses, with responder rates according to OMERACT-OARSI criteria being lowest in the soft-gel 1200 mg group (69.7%), followed by the lipid 1200 mg group (73.1%) and the soft-gel 2400 mg group (76.1%). The percentage of responders per group was relatively high compared with published data from OA trials where a responder rate of approximately 60% has been reported.[36] This probably reflects the patient population in the current study that comprised patients with short-term, self-limiting knee pain compared to usual OA populations.

Although the mechanism of action for the lipid formulation has yet to be fully defined, lipid drug delivery systems appear to target the lymphatic part of the immune system rather than reaching the systemic circulation via the portal vein and liver from the small intestine as is commonly the case with oral treatments.[37] This means there is a reduction in first-pass metabolism and potential for higher lymphatic-mediated ibuprofen lipoprotein fraction drug exposure.[37] Theoretically, the trend of enhanced efficacy seen in the lipid 1200 mg group compared with the soft-gel 1200 mg group may be due to lipid-mediated lymphatic targeting of the

immune system.[37] Further research is needed to evaluate this hypothesis.

The study treatments were well-tolerated and no new safety issues emerged. AEs occurred with lowest frequency in the lipid 1200 mg group and at highest frequency in the soft-gel 2400 mg group. The most common AEs/drug-related AEs were GI disorders, a known ibuprofen adverse effect. A post-hoc analysis revealed significantly more drug-related GI AEs in the soft-gel 2400 mg group compared to the lipid 1200 mg group ($P = 0.01$), indicating as expected that the lipid 1200 mg formulation is likely to be gastro-sparing. No drug-related cardiovascular events were noted which was unsurprising given the short treatment duration. However, given that the cardiovascular effects of ibuprofen are dose and time-related,[18,19] this new lipid ibuprofen formulation may be advantageous in reducing dose-related AEs in patients with cardiovascular risk factors. Further long-term studies are needed to substantiate this hypothesis.

This was a ground-breaking study as patients were recruited from the community setting and treated within 24 h of developing spontaneous flaring knee pain. However, limitations to the study design included the lack of a placebo arm, although ibuprofen has been unequivocally shown to have a dose response for pain reduction and we intended to detect treatment differences rather than confirming previously proven efficacy. Patients were only followed-up for a short time; future studies may incorporate a longer follow-up period to assess duration of post-knee flare resolution. However, patients with other clear causes of knee flares were excluded, which narrows the study population towards the early stage OA population.

In conclusion, a new low-dose lipid formulation of ibuprofen 1200 mg/day was non-inferior to standard soft-gel ibuprofen capsules 1200 mg/day and 2400 mg/day in relieving flaring knee pain. The outcome of the primary efficacy analysis was robust and supported by secondary efficacy analyses. The response in the soft-gel groups appeared to be dose-related, with the soft-gel 1200 mg group being inferior to the soft-gel 2400 mg group. For the NRS assessments, the lipid 1200 mg group was more closely aligned with the soft-gel 2400 mg group than the soft-gel 1200 mg group. The lipid 1200 mg treatment also showed numerically greater improvements in other secondary endpoints, such as swelling and stiffness, compared to soft-gel 1200 mg and comparable results to the 2400 mg group. This is the first time over such a short duration that a lipid formulation of ibuprofen 1200 mg/day has been shown to be as effective as ibuprofen 2400 mg/day in relieving flaring joint pain and may provide information for patient self-management together with guidance for clinicians on treatment of early stage OA.

Author contributions

Professor Sita MA Bierma-Zeinstra (SBZ)
John Brew (JB)
Rosamund Wilson (RW)
Karen Stoner (KS)
Anthony Kilbourn (AK)
Professor Philip G Conaghan (PGC)

- Involved in the conception and design of the study, or acquisition of data, or analysis and interpretation of data: SBZ, JB, KS, RW, AK, PGC.
- Drafting the article or revising it critically for important intellectual content: SBZ, JB, KS, RW, AK, PGC.
- Final approval of the version to be submitted: SBZ, JB, KS, RW, AK, PGC.
- All authors take responsibility for the integrity of the work as a whole, from inception to finished article.

Competing interest statement

PGC has been a consultant for Abbvie, Flexion Therapeutics, Infirst, Medivir and Merck Serono. PGC is supported in part by the National Institute for Health Research (NIHR) Leeds Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

JB, KS and AK are employees of Infirst Healthcare Ltd. RW is a statistical consultant to Infirst Healthcare.

SBZ declares that her institution received consultancy fees from Infirst Healthcare with respect to this study.

Role of the funding source

This study was funded by infirst Healthcare, manufacturers of the new lipid formulation of ibuprofen (Flarin®). This funding includedinvolvement in the design of the study, the statistical analysis, andthe drafting of this manuscript.

Acknowledgments

Medical writing support was provided by Debbie Jordan Ltd, with funding from infirst Healthcare.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.joca.2017.09.002.

References

1. McAlindon TE, Cooper C, Kirwan JR, Dieppe PA. Knee pain and disability in the community. Br J Rheumatol 1992;31:189–92.
2. O'Reilly SC, Muir KR, Doherty M. Screening for pain in knee osteoarthritis: Which question? Ann Rheum Dis 1996;55:931–3.
3. Favero M, Ramonda R, Goldring MB, Goldring SR, Punzi L. Early knee osteoarthritis. RMD Open 2015;1(Suppl 1):e000062.
4. Hawker GA, Stewart L, French MR, Cibere J, Jordan JM, March L. Understanding the pain experience in hip and knee osteoarthritis – an OARSI/OMERACT initiative. Osteoarthr Cartil 2008;16:415–22.
5. Marty M, Hilliquin P, Rozenberg S, Valat JP, Vignon E, Coste P, *et al*. Validation of the KOFUS (Knee Osteoarthritis Flare-Ups Score). Jt Bone Spine 2009;76(3):268–72.
6. Osteoarthritis: Care and Management Clinical Guideline [CG177] Published date: February 2014. Accessed 10-Feb-2017, at https://www.nice.org.uk/guidance/cg177.
7. Leffondré K, Abrahamowicz M, Regeasse A, Hawker GA, Badley EM, McCusker J, *et al*. Statistical measures were proposed for identifying longitudinal patterns of change in quantitative health indicators. J Clin Epidemiol 2004;57(10):1049–62.
8. Conrozier T, Mathieu P, Vignon E, Piperno M, Rinaduo M. Differences in the osteoarthritic synovial fluid composition and rheology between patients with or without flare: a pilot study. Clin Exp Rheumatol 2012;30:729–34.
9. Zhang Y, Nevitt M, Niu J, Lewis C, Torner J, Guermazi A, *et al*. Fluctuation of knee pain and changes in bone marrow lesions, effusions, and synovitis on magnetic resonance imaging. Arthritis Rheum 2011;63(3):691–9.
10. Bannuru R, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med 2015;162:46–54.

11. Smith SR, Deshpande BR, Collins JE, Katz JN, Losina E. Comparative pain reduction of oral non-steroidal anti-inflammatory drugs and opioids for knee osteoarthritis: systematic analytic review. Osteoarthr Cartil 2016;24:962–72.
12. Kennedy S, Moran M. Pharmacological treatment of osteoarthritis of the hip and knee. BCMJ 2010;52(8):404–9.
13. Machado GC, Maher CG, Ferreira PH, Pinheiro MB, Lin C-WC, Day RO, *et al*. Efficacy and safety of paracetamol for spinal pain and osteoarthritis: systematic review and meta-analysis of randomised placebo controlled trials. BMJ 2014;350:h1225.
14. Bushra R, Aslam N. An overview of clinical pharmacology of ibuprofen. Oman Med J 2010;25(3):155–1661.
15. Rainsford KD. History and development of ibuprofen. In: Rainsford KD, Ed. Ibuprofen. A Critical Bibliographic Review. London: Taylor and Francis; 1999:1–24.
16. Kellstein DE, Waksman JA, Furey SA, Binstok G, Cooper SA. The safety profile of non prescription ibuprofen in multiple-dose use: a meta-analysis. J Clin Pharmacol 1999;39:520–32.
17. Moore N, Pollack C, Butkerait P. Adverse drug reactions and drug-drug interactions with over-the-counter NSAIDs. Ther Clin Risk Manag 2015;11:1061–75.
18. FDA Safety Announcement, http://www.fda.gov/Drugs/DrugSafety/ucm451800.htm.
19. EMA/H/A-31/140, EMA/PRAC/182074/2015 Pharmacovigilance Risk Assessment Committee. Recommendation of the Pharmacovigilance Risk Assessment Committee Pursuant to Article 31 of Directive 2001/83/EC Resulting from Pharmacovigilance Data, for Medicinal Products Containing Ibuprofen and Dexibuprofen (Systemic Formulations) 2015.
20. Submitted to U.S FDAOARSI: Osteoarthritis – a Serious Disease December 1, 2016.
21. Bally M, Dendukuri N, Rich B, Nadeau L, Helin-Salmivaara A, Garbe E, *et al*. Risk of acute myocardial infarction with NSAIDs in real world use: bayesian meta-analysis of individual patient data. BMJ 2017;357:j1909.
22. Bellamy N, Buchanan WW, Goldsmith CH, Stitt L. 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.
23. Woolacott NF, Corbett MS, Rice SJC. The use and reporting of WOMAC in the assessment of the benefit of physical therapies for the pain of osteoarthritis of the knee: findings from a systematic review of clinical trials. Rheumatology 2012;51:1440–6.
24. Zhang W, Nuki G, Moskowitz RW, Abramson S, Altman RD, Arden NK, *et al*. OARSI recommendations for the management of hip and knee osteoarthritis Part III: changes in evidence following systematic cumulative update of research published through January 2009. Osteoarthr Cartil 2010;18:476–99.
25. Svedlund J, Sjödin I, Dotevall G. GSRS - a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci 1988;33(2):129–34.
26. 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. Osteoarthr Cartil 2004;12:389–99.
27. Angst F, Aeschlimann A, Michel BA, Stucki G. Minimal clinically important rehabilitation effects in patients with osteoarthritis of the lower extremities. J Rheumatol 2002;29(1):131–8.
28. Bijlsma JW. Patient centred outcomes in osteoarthritis. Ann Rheum Dis 2005;64(1):1–2.
29. Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, *et al*. Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis 2005;64(1):29–33.
30. Bjordal JM, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ 2004;329(7478):1317.
31. Zeni Jr JA, Axe MJ, Snyder-Mackler L. Clinical predictors of elective total joint replacement in persons with end-stage knee osteoarthritis. BMC Musculoskelet Disord 2010;11:86.
32. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, Wilson PWF, *et al*. The effects of specific medical conditions on the functional limitations of elders in the Framingham Study. Am J Public Health 1994;84:351–8.
33. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis 2001;60:91–7.
34. Schiff M, Minic M. Comparison of the analgesic efficacy and safety of nonprescription doses of naproxen sodium and ibuprofen in the treatment of osteoarthritis of the knee. J Rheumatol 2004;31(7):1373–83.
35. Da Costa BR, Reichenbach S, Keller N, Nartey L, Wandel S, Jüni P, *et al*. Effectiveness of non-steroidal anti-inflammatory drugs for the treatment of pain in knee and hip osteoarthritis: a network meta-analysis. Lancet 2016;387(10033):2093–105.
36. Bingham III CO, Smugar SS, Wang H, Peloso PM, Gammaitoni A. Predictors of response to cyclo-oxygenase-2 inhibitors in osteoarthritis: pooled results from two identical trials comparing Etoricoxib, Celecoxib, and placebo. Pain Med 2011;12:352–61.
37. Trevaskis NL, Charman WN, Porter CJH. Lipid-based delivery systems and intestinal lymphatic drug transport: a mechanistic update. Adv Drug Deliv Rev 2008;60(6):702–16.