Send Orders of Reprints at reprints@benthamscience.net

32 *The Open Rheumatology Journal,* **2013**, *7*, 32-37

Open Access

The Efficacy of Continuous Versus Intermittent Celecoxib Treatment in Osteoarthritis Patients with Body Mass Index ≥30 and <30 kg/m^2

George H. Sands*, Pritha Bhadra Brown and Margaret Noyes Essex

Pfizer Inc., New York, NY, USA

Abstract: *Objective*: Characterize the effect of body mass index (BMI) on the efficacy of continuous daily celecoxib treatment compared with intermittent celecoxib treatment.

Methods: Prespecified exploratory analysis of a 24-week, double-blind, parallel-group, randomized, multicenter international study. 858 patients with knee or hip osteoarthritis (OA) were randomized to receive celecoxib 200 mg daily either as continuous or intermittent treatment. Efficacy was measured by Western Ontario and McMaster Universities Arthritis Index (WOMAC) total and subscale scores and the number of flare events.

Results: Least squares mean increases (worsening) in WOMAC total scores were significantly less in the continuous treatment group than in the intermittent treatment group in patients with a BMI <30 kg/m^2 (1.33 *vs* 4.85; p=0.016) and in patients with a BMI ≥30 kg/m^2 (1.84 *vs* 5.12; p=0.019). There was a greater worsening in patients with a BMI ≥30 kg/m^2 than in those with a BMI <30 kg/m^2 in both the continuous and intermittent groups. Fewer flares were reported in the continuous treatment group than in the intermittent group in patients with a BMI <30 kg/m^2 (0.55 *vs* 0.88; p<0.0001) and ≥30 kg/m^2 (0.54 *vs* 0.97; p<0.0001). There were no differences in adverse events in the two BMI groups.

Conclusions: Continuous celecoxib treatment was significantly more efficacious than intermittent use in patients with a BMI <30 kg/m^2 compared with obese patients (≥30 kg/m^2) as assessed by WOMAC total scores and the number of flares. These data suggest that including weight loss as part of a treatment regimen for obese OA patients could be important.

Keywords: NSAIDs, osteoarthritis, BMI, flare, WOMAC, continuous, intermittent.

INTRODUCTION

Weight is an important factor in osteoarthritis (OA) as obese subjects are at a higher risk of developing knee and hip OA [1]. Obese patients have a higher risk of developing knee and hip pain, with increasing body weight resulting in more pain [2]. As there is a rising obesity epidemic worldwide, it is expected the number of obese patients with knee OA will increase [3].

In subjects with or at higher risk for knee OA, both a high body mass index (BMI) and a large waist circumference were associated with poorer outcomes in Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores, and 20-meter walk and chair stand outcomes [4]. In addition, African American women with either a high BMI or a large waist circumference were at greater risk for poorer outcomes than white women with a high BMI or a large waist circumference [4]. Obesity is therefore an important preventable and treatable risk factor in patients with OA [5, 6]. Current guidelines for the management of OA recommend weight loss for overweight patients with knee and hip OA [7, 8]. A reduction in body weight has been reported to decrease the odds for developing symptomatic knee OA in women [9], and in a meta-analysis, an association was found between weight reduction in patients with knee OA and improvement in physical disability [3]. In a recent explorative study, it was found that a high BMI is detrimental to joint health among subjects exposed to high levels of activity [10]. However, subjects with a low BMI and high levels of activity were at lower risk of knee OA than those who were less active [10].

Some OA patients may experience asymptomatic periods alternating with OA flares while others may have continuous OA symptoms. Intermittent treatment with nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) selective inhibitors is often perceived as a safer option due to concerns regarding the gastrointestinal and cardiovascular adverse effects thought to be associated with these therapies [11]. Intermittent therapy leads to less exposure to the drugs, a longer time to develop adequate serum levels of the drug, and potentially fewer adverse outcomes. In patients with symptomatic OA who were successfully treated for an OA flare with open-label celecoxib, continuous celecoxib treatment was compared with intermittent celecoxib treatment in a double-blind, randomized, multicenter international trial to investigate the efficacy and safety of these regimens. Continuous treatment with celecoxib 200 mg/d was significantly more efficacious than intermittent celecoxib treatment in preventing OA flares of the hip and knee, without an increase in overall adverse events (AEs), which included aggravated and new-onset hypertension [11]. However, the effect of BMI on the

*Address correspondence to this author at the Pfizer Inc., 235 East 42nd Street, New York, NY, USA; Tel: +1 212 733 6358; Fax: +1 212 309 4481; E-mail: george.sands@pfizer.com

1874-3129/13

efficacy of continuous versus intermittent NSAID treatment has not been previously investigated.

An exploratory analysis was performed to characterize the effect of BMI on the efficacy of continuous daily celecoxib treatment compared with intermittent celecoxib treatment, as measured by WOMAC total and subscale scores and by the number of flares.

MATERIALS AND METHODS

A prespecified exploratory analysis of a double-blind, parallel-group, randomized, multicenter international study [11] was conducted to determine WOMAC total scores (including pain, stiffness, and physical function) and the number of OA flares, during the blinded postrandomization period, in patient groups according to BMI (≥30 kg/m^2 and <30 kg/m^2). A detailed description of the study design has been previously published [11] and is briefly described below.

Study Design

A total of 858 patients, originating from 106 investigational centers across North and South America and Europe, aged 18-80 years with knee or hip OA, determined by American College of Rheumatology criteria, were randomized (1:1 ratio stratified by site) to receive celecoxib 200 mg qd either as continuous (daily) or intermittent (celecoxib 200 mg qd when needed to treat OA flare meeting predefined criteria).

The trial consisted of three periods. Period I (up to 14±2 days) included the screening (Visit 1) and washout period. During this period, patients with an OA flare within 14 days following discontinuation of NSAID treatment were identified and allowed to enter Period II. Period II (up to 14±2 days) included the flare visit (Visit 2) and the open-label run-in treatment period with 200 mg celecoxib daily. During this period, only patients in whom treatment with celecoxib resulted in a successful treatment of an OA flare, without additional flares, were eligible to enter Period III. Period III (22 weeks) included randomization (Visit 3) followed by a double-blind treatment period during which the efficacy of continuous *vs* intermittent celecoxib treatment was investigated (Visit 3 or randomization visit).

The occurrence and resolution of an OA flare were defined objectively based on patient scores on the Patient's Assessment of Arthritis Pain Numeric Rating Scale and the Patient's Global Assessment of Arthritis, and were confirmed based on the outcome of the Physician's Global Assessment of Arthritis administered by the investigator.

Efficacy Analysis

Efficacy assessments were conducted during the double-blind treatment period (Period III). The efficacy assessment measurements included WOMAC index scores (total, pain, stiffness, and physical function), and the number of flare events experienced by patients per time of exposure (mean number of flares per month). Safety was monitored from Period II to the end of Period III. Only AEs occurring during the blinded treatment period (Period III) were reported.

Statistical Analysis

Analyses were performed on the intent-to-treat (ITT) population (patients who received ≥1 dose of study medication postrandomization) and flare-modified ITT (FmITT) population (all patients meeting criteria for the ITT population plus having flare durations of ≤ 14+2 days), using a two-sided type 1 error of 0.05. WOMAC scores were analyzed as change in WOMAC total, and pain, stiffness, and physical function subscores from randomization to final visit.

RESULTS

Patient Characteristics

Baseline demographics and clinical characteristics were similar in both treatment groups. In the continuous treatment group, the mean age of patients with a BMI <30 kg/m^2 was 59.2 years, and the mean age of patients with a BMI ≥30 kg/m^2 was 57.8 years. In the intermittent treatment group, the mean ages were 58.9 years and 58.6 years, respectively (Table **1**). The duration of OA was 6.1 years and 6.5 years in

Table 1. Patient Demographics and Characteristics at Randomization Visit

	Continuous Use Celecoxib 200 mg qd		Intermittent Use Celecoxib 200 mg qd	
	BMI <30 kg/m^2 n=209	BMI ≥30 kg/m^2 n=222	BMI <30 kg/m^2 n=205	BMI ≥30 kg/m^2 n=222
Female, n (%)	145 (69.4)	172 (77.5)	149 (72.7)	154 (69.4)
Age, years, mean (SD)	59.2 (10.2)	57.8 (9.8)	58.9 (10.3)	58.6 (9.0)
Race, white, n (%)	156 (74.6)	182 (82.0)	151 (73.7)	182 (82.0)
BMI, mean (SD)	25.8 (2.6)	34.9 (4.6)	25.7 (2.6)	35.0 (4.4)
Duration of OA, years, mean (SD)	6.1 (6.3)	6.5 (6.5)	6.6 (6.8)	7.0 (6.8)
Total WOMAC score, mean (SD)	24.3 (14.0)	26.2 (14.1)	26.0 (14.8)	26.5 (13.3)
WOMAC Subscale Scores, Mean (SD)				
Pain	4.8 (3.0)	5.0 (2.9)	5.2 (3.1)	5.0 (2.9)
Stiffness	2.2 (1.4)	2.4 (1.4)	2.3 (1.4)	2.5 (1.2)
Physical function	17.3 (10.3)	18.8 (10.5)	18.4 (10.9)	19.1 (9.9)

BMI, body mass index; OA, osteoarthritis; qd, daily; SD, standard deviation; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

patients with a BMI <30 kg/m^2 and a BMI ≥30 kg/m^2, respectively, in the continuous treatment group. In the intermittent group, the duration of OA was 6.6 years and 7.0 years in patients with a BMI <30 kg/m^2 and a BMI ≥30 kg/m^2, respectively (Table **1**).

At baseline, BMI was <30 kg/m^2 in 48.5% (209/431) of patients in the continuous treatment group and 48.0% (205/427) of patients in the intermittent group. BMI was ≥30 kg/m^2 in 51.5% (222/431) of patients in the continuous treatment group and 52.0% (222/427) in the intermittent treatment group.

WOMAC Index Scores

WOMAC total and subscores were comparable at randomization in both BMI groups in the ITT population (both p>0.05, Table **1**). Following the 22 weeks of blinded treatment, the least squares mean increases (worsening) were significantly less in the continuous treatment group than in the intermittent treatment group in patients with a BMI <30 kg/m^2 (1.33 *vs* 4.85, respectively; p=0.016) and in patients with a BMI ≥30 kg/m^2 (1.84 *vs* 5.12, respectively; p=0.019) (Table **2**). A greater worsening in patients with a BMI ≥30 kg/m^2 was observed in both the continuous and intermittent treatment groups than patients with a BMI <30 kg/m^2.

Increases in pain, stiffness, and physical function WOMAC subscale scores were significantly less in the continuous than intermittent treatment group in patients with a BMI <30 kg/m^2 and a BMI ≥30 kg/m^2 (p<0.05), with the exception of the WOMAC stiffness subscale in patients with a BMI ≥30 kg/m^2. The WOMAC stiffness subscale score was not significantly different between continuous and intermittent use in patients with a BMI ≥30 kg/m^2 (p=0.075).

In the FmITT population, increases in total, pain and physical function WOMAC subscale scores from baseline to final visit were significantly less in the continuous than intermittent treatment group in patients with a BMI ≥30 kg/m^2 (p<0.05), except for the WOMAC stiffness subscale (p=0.162). WOMAC total and subscale scores were not significantly different between continuous and intermittent use in patients with a BMI <30 kg/m^2 (p>0.05).

Number of Flares

In the subset of patients with a BMI <30 kg/m^2, the continuous treatment group experienced fewer flares per month than the intermittent treatment group (0.55 *vs* 0.88, respectively; p<0.0001; ITT population); the same was true in the patients with a BMI ≥30 kg/m^2 (0.54 *vs* 0.97, respectively; p<0.0001; ITT population) (Table **3**). Fewer flares per month were also reported in the continuous than intermittent treatment group in the FmITT population in patients with a BMI <30 kg/m^2 (FmITT: 0.51 *vs* 0.91; p=0.0008) and in patients with a BMI ≥30 kg/m^2 (FmITT: 0.47 *vs* 0.98; p<0.0001).

Table 2. Least Squares Mean Changes (LSM) from Randomization Visit to Final Visit in WOMAC Pain, Stiffness, Physical Function, and Total Scores for the Double-Blind Treatment Period

	BMI <30 kg/m^2			BMI ≥30 kg/m^2		
	Continuous Use Celecoxib 200 mg qd n=209	Intermittent Use Celecoxib 200 mg qd n=205	p Value	Continuous Use Celecoxib 200 mg qd n=222	Intermittent Use Celecoxib 200 mg qd n=222	p Value
ITT Population						
Total WOMAC score, LSM (SE)	1.33 (1.03)	4.85 (1.03)	0.016	1.84 (0.98)	5.12 (0.99)	0.019
95% CI	(-0.69 to 3.35)	(2.83 to 6.87)		(-0.08 to 3.77)	(3.18 to 7.06)	
WOMAC pain subscale, LSM (SE)	0.32 (0.23)	1.05 (0.23)	0.024	0.40 (0.21)	1.31 (0.21)	0.002
95% CI	(-0.13 to 0.77)	(0.60 to 1.50)		(-0.01 to 0.81)	(0.90 to 1.73)	
WOMAC stiffness subscale, LSM (SE)	0.10 (0.10)	0.42 (0.10)	0.019	0.13 (0.10)	0.38 (0.10)	0.075
95% CI	(-0.10 to 0.29)	(0.23 to 0.62)		(-0.06 to 0.32)	(0.19 to 0.57)	
WOMAC physical function subscale, LSM (SE)	0.89 (0.74)	3.40 (0.74)	0.017	1.36 (0.71)	3.45 (0.71)	0.038
95% CI	(-0.57 to 2.34)	(1.95 to 4.86)		(-0.04 to 2.75)	(2.05 to 4.85)	
FmITT						
Total WOMAC score, LSM (SE)	-0.15 (1.18)	2.40 (1.28)	0.145	-0.13 (1.15)	3.89 (1.17)	0.015
95% CI	(-2.47 to 2.17)	(-0.12 to 4.91)		(-2.38 to 2.13)	(1.59 to 6.18)	
WOMAC pain subscale, LSM (SE)	0.07 (0.26)	0.48 (0.29)	0.292	-0.00 (0.24)	1.12 (0.25)	0.001
95% CI	(-0.45 to 0.58)	(-0.09 to 1.04)		(-0.48 to 0.48)	(0.63 to 1.61)	
WOMAC stiffness subscale, LSM (SE)	0.01 (0.11)	0.24 (0.12)	0.164	-0.00 (0.11)	0.23 (0.12)	0.162
95% CI	(-0.20 to 0.23)	(0.00 to 0.47)		(-0.22 to 0.23)	(0.01 to 0.46)	
WOMAC physical function subscale, LSM (SE)	-0.25 (0.85)	1.71 (0.92)	0.117	-0.09 (0.83)	2.55 (0.84)	0.026
95% CI	(-1.92 to 1.41)	(-0.10 to 3.52)		(-1.71 to 1.54)	(0.90 to 4.21)	

BMI, body mass index; CI, confidence interval; ITT, intent-to-treat; FmITT: flare-modified ITT; qd, daily; SE, standard error; WOMAC, Western Ontario and McMaster Universities Arthritis Index.

Table 3. Number of Flare Events Per Time of Exposure to Study Medication[a]

	BMI <30 kg/m^2			BMI ≥30 kg/m^2		
	Continuous Use Celecoxib 200 mg qd	Intermittent Use Celecoxib 200 mg qd	p Value	Continuous Use Celecoxib 200 mg qd	Intermittent Use Celecoxib 200 mg qd	p Value
ITT population, n	209	205		222	222	
No. of flare events per month, mean (SD)	0.55 (0.78)	0.88 (0.86)	<0.0001	0.54 (0.69)	0.97 (1.13)	<0.0001
Median	0.38	0.63		0.36	0.71	
Range	0.00-7.50	0.00-4.29		0.00-4.29	0.00-9.40	
FmITT population, n	146	121		153	151	
No. of flare events per month, mean (SD)	0.51 (0.88)	0.91 (1.01)	0.0008	0.47 (0.74)	0.98 (1.32)	<0.0001
Median	0.20	0.57		0.19	0.55	
Range	0.00-7.50	0.00-4.29		0.00-4.29	0.00-9.40	

[a]Time of exposure is the time in months from the first dose of double-blind study medication at the beginning of Period III to the last dose of study medication. Patients may have more than one flare.
ITT, intent-to-treat; FmITT: flare-modified ITT.

Safety Results

Sixteen patients experienced serious AEs; six were in the continuous treatment group (four in the BMI <30 kg/m^2 and two in the BMI ≥30 kg/m^2) and ten were in the intermittent treatment group (four in the BMI <30 kg/m^2 and six in the BMI ≥30 kg/m^2). Serious AEs in the continuous treatment group included nephrolithiasis, metastases to central nervous system, melena, rectal hemorrhage, and coronary artery disease in patients with a BMI <30 kg/m^2 and chest pain, atrial fibrillation, acute respiratory failure, and pulmonary edema in patients with a BMI ≥30 kg/m^2. Serious AEs in the intermittent treatment group included skin laceration, OA, gastritis, chest pain, and abdominal pain in patients with a BMI <30 kg/m^2 and knee arthroplasty, squamous cell carcinoma, non-cardiac chest pain, pancreatitis, OA, bipolar I disorder, hypertension crisis, and transient ischemic attack in patients with a BMI ≥30 kg/m^2.

In the BMI <30 kg/m^2 group, discontinuations due to AEs occurred in 5.3% and 4.4% of subjects receiving celecoxib continuous treatment and celecoxib intermittent treatment, respectively. In the BMI ≥30 kg/m^2 group, discontinuations due to AEs occurred in 5.0% and 6.8% of subjects, respectively. No deaths were reported. Numerically fewer AEs were reported in the celecoxib continuous treatment group than the celecoxib intermittent treatment group in patients with a BMI <30 kg/m^2 (54.5% *vs* 59.0%) while the frequency of AEs was similar in the BMI ≥30 kg/m^2 celecoxib continuous and intermittent treatment groups (59.0% *vs* 58.6%). Headache was the most frequently reported AE in all groups (Table **4**).

DISCUSSION

In this study of patients with OA, lower WOMAC least squares mean change scores (less worsening) were observed in the continuous celecoxib treatment group than in the intermittent celecoxib treatment group for patients with a BMI <30 kg/m^2 and for those with a BMI ≥30 kg/m^2. Patients with a BMI <30 kg/m^2 and those with a BMI ≥30 kg/m^2 who were in the continuous celecoxib treatment reported fewer flares than patients receiving intermittent treatment. There was more symptomatic worsening, as defined by WOMAC total scores (greater least squares mean change scores), in patients with a BMI ≥30 kg/m^2 than in those with a BMI <30 kg/m^2 for both the continuous and intermittent celecoxib treatment groups.

The results of this exploratory analysis are consistent with published findings. An association between obesity (BMI ≥30 kg/m^2) and arthritis was reported in previous cross-sectional studies [12, 13], cohort studies [14-16], and case-control studies [17-19]. The odds ratio, or relative risk of arthritis, in these studies was 1.6-6.8 among subjects who were obese. Lower WOMAC scores and fewer flares were reported in nonobese patients (BMI <30 kg/m^2) in this study.

While fewer patients experienced severe AEs in the continuous treatment group compared with the intermittent treatment group, the number of serious AEs reported did not differ by BMI status in this analysis. This finding contrasts with those from an analysis from the Celecoxib *vs* Omeprazole and Diclofenac for At-Risk Osteoarthritis and Rheumatoid Arthritis Patients (CONDOR) trial where BMI was shown to be one of the risk factors associated with clinically significant blood loss (≥2 g/dL decrease in hemoglobin and/or a ≥10% decrease in hematocrit) in patients treated with celecoxib and diclofenac slow release plus omeprazole [20]. This was the first time BMI was reported as a predictive factor for clinically significant blood loss in patients with arthritis and NSAID users [20].

The current guidelines for the management of OA recommend weight loss in overweight patients with knee and hip OA [7, 8]. A reduction in body weight has been reported to decrease the odds for developing symptomatic knee OA in women [3, 9] and to help alleviate OA symptoms [3, 21]. Continuous reinforcement of a weight loss program over 1 year has been shown to be successful in reducing pain in obese patients with knee OA, although not necessarily improving function [22]. Although physicians often fail to advise obese adults with arthritis to lose weight, adults who report receiving such advice were more likely to report weight-loss efforts [23, 24]. This analysis suggests that

Table 4. Summary of Treatment-Emergent Adverse Events (AE), Safety Population

	BMI <30 kg/m^2		BMI ≥30 kg/m^2	
	Continuous Use Celecoxib 200 mg qd n=209 n (%)	**Intermittent Use Celecoxib 200 mg qd n=205 n (%)**	**Continuous Use Celecoxib 200 mg qd n=222 n (%)**	**Intermittent Use Celecoxib 200 mg qd n=222 n (%)**
Total no. patients with AE	114 (54.5)	121 (59.0)	131 (59.0)	130 (58.6)
AE ≥2% Patients in Either Treatment Group by Preferred Term				
Headache	33 (15.8)	32 (15.6)	32 (14.4)	36 (16.2)
Back pain	10 (4.8)	20 (9.8)	10 (4.5)	11 (5.0)
Arthralgia	9 (4.3)	14 (6.8)	8 (3.6)	11 (5.0)
Nasopharyngitis	7 (3.3)	8 (3.9)	12 (5.4)	12 (5.4)
Diarrhea	1 (0.5)	11 (5.4)	6 (2.7)	6 (2.7)
Pain in extremity	9 (4.3)	10 (4.9)	9 (4.1)	11 (5.0)
Dyspepsia	6 (2.9)	3 (1.5)	11 (5.0)	3 (1.4)
Upper respiratory tract infection	7 (3.3)	9 (4.4)	7 (3.2)	10 (4.5)
Hypertension	2 (1.0)	9 (4.4)	7 (3.2)	4 (1.8)
Upper abdominal pain	3 (1.4)	9 (4.4)	4 (1.8)	1 (0.5)
Sinusitis	5 (2.4)	1 (0.5)	6 (2.7)	9 (4.1)
Musculoskeletal pain	4 (1.9)	3 (1.5)	3 (1.4)	9 (4.1)
Insomnia	3 (1.4)	6 (2.9)	8 (3.6)	2 (0.9)
Edema peripheral	3 (1.4)	5 (2.4)	1 (0.5)	7 (3.2)
Bronchitis	2 (1.0)	2 (1.0)	1 (0.5)	7 (3.2)
Muscle spasms	7 (3.3)	1 (0.5)	3 (1.4)	4 (1.8)
Dizziness	6 (2.9)	6 (2.9)	2 (0.9)	2 (0.9)
Nausea	2 (1.0)	6 (2.9)	3 (1.4)	3 (1.4)
Abdominal pain	4 (1.9)	2 (1.0)	6 (2.7)	2 (0.9)
Contusion	1 (0.5)	1 (0.5)	2 (0.9)	6 (2.7)
Myalgia	4 (1.9)	4 (2.0)	6 (2.7)	5 (2.3)
Toothache	1 (0.5)	4 (2.0)	2 (0.9)	2 (0.9)
Fatigue	0 (0)	6 (2.9)	6 (2.7)	3 (1.4)
Pain	4 (1.9)	6 (2.9)	2 (0.9)	3 (1.4)
Influenza	5 (2.4)	4 (2.0)	5 (2.3)	5 (2.3)
Vomiting	1 (0.5)	4 (2.0)	4 (1.8)	2 (0.9)
Viral infection	0 (0)	4 (2.0)	3 (1.4)	0 (0)
Rash	0 (0)	4 (2.0)	1 (0.5)	3 (1.4)

weight reduction in patients with OA might lead to decreased numbers of OA flares and significantly less worsening in patient functioning, as described by the WOMAC total score and subscales for pain, functioning, and stiffness. Improved awareness of the relationship between OA and weight might help motivate patients to lose weight.

CONCLUSIONS

Daily celecoxib treatment was significantly more efficacious than intermittent use, and more so in patients with a BMI <30 kg/m^2 compared with obese patients (BMI ≥30 kg/m^2) as assessed by WOMAC total scores and the number of flares per month. These data support the importance of including weight loss as part of the treatment regimen for obese and perhaps overweight patients with OA and suggest weight loss could help reduce the burden of illness experienced by these OA patients.

AUTHOR'S CONTRIBUTIONS

G.H. Sands – conduct of study, analysis and interpretation of data, critical revision/drafting of the manuscript, final approval to submit.

P. Bhadra Brown – statistical analysis and interpretation, critical revision/drafting of the manuscript, final approval to submit.

M. Noyes Essex – analysis and interpretation of data, critical revision/drafting of the manuscript, final approval to submit.

CONFLICT OF INTEREST

G.H. Sands – Pfizer Inc. full-time employee and shareholder.

P. Bhadra Brown – Pfizer Inc. full-time employee and shareholder.

M. Noyes Essex – Pfizer Inc. full-time employee and shareholder.

ACKNOWLEDGEMENTS

The study was sponsored by Pfizer Inc, New York, NY, USA. Editorial support was provided by C. Campbell, PhD, of PAREXEL, UK and was funded by Pfizer Inc.

REFERENCES

[1] Baum T, Joseph GB, Nardo L, *et al.* Correlation of magnetic resonance imaging-based knee cartilage T2 measurements and focal knee lesions with body mass index: thirty-six-month followup data from a longitudinal, observational multicenter study. Arthritis Care Res (Hoboken) 2013; 65: 23-33.

[2] Hitt HC, McMillen RC, Thornton-Neaves T, Koch K, Cosby AG. Comorbidity of obesity and pain in a general population: results from the Southern Pain Prevalence Study. J Pain 2007; 8: 430-6.

[3] Christensen R, Bartels EM, Astrup A, Bliddal H. Effect of weight reduction in obese patients diagnosed with knee osteoarthritis: a systematic review and meta-analysis. Ann Rheum Dis 2007; 66: 433-9.

[4] Colbert CJ, Almagor O, Chmiel JS, *et al.* Excess body weight and four-year function outcomes: comparison of African Americans and whites in a prospective study of osteoarthritis. Arthritis Care Res (Hoboken) 2013; 65: 5-14.

[5] Powell A, Teichtahl AJ, Wluka AE, Cicuttini FM. Obesity: a preventable risk factor for large joint osteoarthritis which may act through biomechanical factors. Br J Sports Med 2005; 39: 4-5.

[6] Teichtahl AJ, Wang Y, Wluka AE, Cicuttini FM. Obesity and knee osteoarthritis: new insights provided by body composition studies. Obesity (Silver Spring) 2008; 16: 232-40.

[7] Hochberg MC, Altman RD, Toupin April K, *et al.* American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2012; 64: 465-74.

[8] Zhang W, Moskowitz RW, Nuki G, *et al.* OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. Osteoarthr Cartil 2008; 16: 137-62.

[9] Felson DT, Zhang Y, Anthony JM, Naimark A, Anderson JJ. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. Ann Intern Med 1992; 116: 535-9.

[10] Remmes Martin K, Kuh D, Harris TB, Guralnik JM, Coggon D, Wills AK. BMI, occupational activity, and leisure-time physical activity: an exploration of risk factors and modifiers for knee osteoarthritis. Arthritis Rheum 2012; 64: S348

[11] Strand V, Simon LS, Dougados M, *et al.* Treatment of osteoarthritis with continuous versus intermittent celecoxib. J Rheumatol 2011; 38: 2625-34.

[12] Zakkak JM, Wilson DB, Lanier JO. The association between body mass index and arthritis among US adults: CDC's surveillance case definition. Prev Chronic Dis 2009; 6: A56.

[13] Tukker A, Visscher TL, Picavet HS. Overweight and health problems of the lower extremities: osteoarthritis, pain and disability. Public Health Nutr 2009; 12: 359-68.

[14] Felson DT, Anderson JJ, Naimark A, Walker AM, Meenan RF. Obesity and knee osteoarthritis. The Framingham Study. Ann Intern Med 1988; 109: 18-24.

[15] Manninen P, Riihimaki H, Heliovaara M, Makela P. Overweight, gender and knee osteoarthritis. Int J Obes Relat Metab Disord 1996; 20: 595-7.

[16] Gelber AC, Hochberg MC, Mead LA, Wang NY, Wigley FM, Klag MJ. Body mass index in young men and the risk of subsequent knee and hip osteoarthritis. Am J Med 1999; 107: 542-8.

[17] Coggon D, Reading I, Croft P, McLaren M, Barrett D, Cooper C. Knee osteoarthritis and obesity. Int J Obes Relat Metab Disord 2001; 25: 622-7.

[18] Oliveria SA, Felson DT, Cirillo PA, Reed JI, Walker AM. Body weight, body mass index, and incident symptomatic osteoarthritis of the hand, hip, and knee. Epidemiology 1999; 10: 161-6.

[19] Holmberg S, Thelin A, Thelin N. Knee osteoarthritis and body mass index: a population-based case-control study. Scand J Rheumatol 2005; 34: 59-64.

[20] Lanas A, Goldstein JL, Chan FKL, *et al.* Risk factors associated with a decrease ≥2 g/dL in haemoglobin and/or ≥10% haematocrit in osteoarthritis patients taking celecoxib or a nonselective NSAID plus a PPI in a large randomised controlled trial (CONDOR). Aliment Pharmacol Ther 2012; 36: 485-92.

[21] Christensen R, Astrup A, Bliddal H. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. Osteoarthr Cartil 2005; 13: 20-7.

[22] Bliddal H, Leeds AR, Stigsgaard L, Astrup A, Christensen R. Weight loss as treatment for knee osteoarthritis symptoms in obese patients: 1-year results from a randomised controlled trial. Ann Rheum Dis 2011; 70: 1798-803.

[23] Mehrotra C, Naimi TS, Serdula M, Bolen J, Pearson K. Arthritis, body mass index, and professional advice to lose weight: implications for clinical medicine and public health. Am J Prev Med 2004; 27: 16-21.

[24] Fontaine KR, Haaz S, Bartlett SJ. Are overweight and obese adults with arthritis being advised to lose weight? J Clin Rheumatol 2007; 13: 12-5.

Received: February 27, 2013 Revised: May 15, 2013 Accepted: May 16, 2013