



Phenotypic Factors and Celecoxib Efficacy in Knee OA: A Post-hoc Pooled Analysis of Two Randomized, Double-Blind, Placebo-Controlled Trials

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ABSTRACT

Introduction: Knee osteoarthritis (OA) is a major cause of disability worldwide and disproportionately affects women and individuals with obesity. Treatment response might vary by sex and body mass index (BMI). This study assessed whether celecoxib pain reduction differs across sex (male versus female) or BMI (obese ≥ 30 kg/m² versus nonobese < 30 kg/m²) in knee OA patients, using change from baseline in Visual Analog Scale (VAS) pain at Week 6 as primary endpoint.

Methods: This post hoc pooled analysis included two randomized, double-blind,

placebo-controlled trials (NH49-96-02-060; NH49-98-02-087). Adults with knee OA flare and baseline VAS pain ≥ 40 mm received placebo, 100 mg of celecoxib twice daily (BID), or 200 mg once daily (OD) for 6 weeks. Mild baseline pain was excluded to align with original trial criteria. The full analysis set (FAS) included patients with ≥ 1 dose and ≥ 1 post-baseline assessment. Primary subgroups were assessed using analysis of covariance (ANCOVA) with last observation carried forward (LOCF) for missing data, with longitudinal evaluation at Week 2 and 6 using mixed model for repeated measures (MMRM). Sensitivity analyses using alternative imputation methods were also performed.

Results: A total of 1360 participants (427 men, 933 women) were included. Baseline VAS pain score was higher in women and patients with obesity (both $p < 0.0001$), who also showed

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greater placebo response. At Week 6, both celecoxib regimens significantly reduced pain versus placebo across sex and BMI subgroups. Women had greater observed pain reductions with similar efficacy between sexes, and obese participants showed comparable benefit with both doses. Similar findings were observed in MMRM analyses. Celecoxib provided rapid, sustained OA pain relief across the two subpopulations.

Conclusions: 100 mg of celecoxib BID and 200 mg OD showed consistent analgesic efficacy across sex and BMI subgroups, despite higher baseline pain and stronger placebo response in women and obese participants. These findings support the use of either regimen across diverse OA patient profiles and suggest that baseline pain differences do not necessarily reduce response to cyclooxygenase (COX)-2 inhibition.

Keywords: Knee osteoarthritis (OA); Celecoxib; Sex differences; Body mass index (BMI); Obesity; Visual analog scale (VAS); Pain reduction; Post hoc pooled analysis

Key Summary Points

Why carry out this study?

Knee osteoarthritis (OA) is a heterogeneous condition with higher pain burden in women and individuals with obesity; yet treatment effects are rarely evaluated across these clinically relevant subgroups, highlighting the need for phenotype-aware approaches to better evaluate treatment response.

This post hoc analysis aimed to assess whether the analgesic efficacy of celecoxib is consistent across subgroups defined by sex and body mass index (BMI).

What was learned from the study?

100 mg of Celecoxib twice a day and 200 mg once a day produced rapid and clinically meaningful pain reduction versus placebo across sex and BMI subgroups, with rapid onset at Week 2 and sustained effect through Week 6.

Despite differences in baseline pain and placebo response in women and patients with obesity, treatment effects were generally consistent across subgroups, and sensitivity analyses using alternative missing data assumptions supported the robustness of these findings.

Taken together, these findings reinforce the broad applicability of either celecoxib dosing regimen across diverse knee OA patient profiles, while informing future personalized, phenotype-guided, pain-management strategies.

INTRODUCTION

Knee osteoarthritis (OA) is a leading cause of disability worldwide, affecting over 500 million individuals, with a disproportionate burden borne by women (60%) and individuals who are obese. As the global population ages and obesity rates continue to rise, the prevalence and impact of OA are expected to escalate [1, 2]. Traditionally viewed as a degenerative joint disease primarily linked to aging, OA is now increasingly recognized as a multifactorial condition influenced by genetic, hormonal, metabolic, and psychosocial factors [3, 4].

Emerging evidence underscores the importance of phenotypic characterization in OA, particularly with respect to sex and obesity. Women not only exhibit a higher prevalence of

OA, especially post-menopause, but also literature suggests that they experience greater pain sensitivity and more severe clinical symptoms compared with men [5–7]. These differences are not fully explained but are partially attributed to complex interactions among sex hormones, pain perception mechanisms, gender roles and psychosocial influences [7]. Specifically, sex-related variations in pain expression are often explained by socially constructed roles and expectations. Yet, biological factors such as hormones and neurobiological mechanisms are also intertwined with these roles, influencing how pain signals are processed and perceived [7, 8]. Despite this growing understanding that OA is phenotypically heterogeneous, most trials do not incorporate sex-specific analyses for pharmacological interventions, limiting the ability to determine whether therapeutic responses differ across patient subgroups [9]. Consequently, current OA management remains largely uniform, even though evidence suggests that tailored therapeutic strategies may be clinically warranted in certain circumstances.

Obesity, another critical risk factor, contributes to OA through both mechanical and metabolic pathways. Excess body weight increases joint loading, particularly in weight-bearing joints, such as knees and hips, accelerating cartilage degradation [4, 10]. Concurrently, obesity-induced metabolic inflammation, characterized by the release of pro-inflammatory adipokines (such as leptin and adiponectin) exacerbates joint damage even in nonweight-bearing joints [4]. This has led to the identification of a distinct metabolic syndrome-associated OA (MetS-OA) phenotype, which may respond differently to treatment [4]. This post hoc pooled analysis explores two trials focusing on knee OA patients to evaluate the effect of sex and body mass index (BMI) for the first time on the observed level of pain relief experienced by the studied clinical trial populations. Metabolic syndrome was not explored in this analysis because data on its individual components were not collected in the original trials.

Given that family physician appointment time is typically limited to less than 10 minutes, there is often insufficient opportunity to use detailed OA questionnaires (e.g., Western

Ontario and McMaster Universities Osteoarthritis Index - WOMAC) that are commonly used in clinical research and therefore only evaluation of pain using a visual analog scale (VAS) is considered here. Elderly patients typically affected by OA also commonly have multiple comorbidities and therefore a consultation must focus on the complexity of a patient, not just a single condition at any one time. It is, however, important for clinicians to consider at least a simple evaluation of the patients' pain to track improvement or deterioration. Long term deterioration can lead to disability, which is often associated with increased mortality as well as morbidity [11, 12]. Additionally, there is a growing imperative to consider personalized treatment approaches in knee OA. Recognizing and targeting phenotypic variations, especially those related to age, sex, body composition and metabolic health, could help understanding differences in drug response enhancing therapeutic efficacy, reducing disease burden, and improving quality of life for affected individuals [13].

The aim of this post hoc pooled analysis was to evaluate the applicability of two commonly prescribed celecoxib dosing regimens [100 mg twice daily (BID) and 200 mg once daily (OD)] across diverse knee OA patient profiles, on the basis of biological sex and BMI. By assessing the consistency of treatment effects across these clinically relevant subgroups, this study also seeks to inform future personalized, phenotype-guided approaches to pain management in OA.

METHODS

Data Set

This post hoc pooled analysis is based on the same two closely comparable randomized, double-blind, placebo-controlled studies (NH49-96-02-060 and NH49-98-02-087) [14, 15], which have also been presented in a previous analysis [16] focusing on pain severity at baseline. In both the current analysis and our previously published work [16], the decision to pool the two Williams's trials was based on their strong

methodological and clinical similarity. These substantial commonalities support the appropriateness of pooling the datasets, enabling increased statistical power and a more robust evaluation of treatment effects across dosing strategies while maintaining internal consistency. Participants were randomized to receive placebo or celecoxib (100 mg BID or 200 mg OD) for 6 weeks. The analgesic efficacy of different celecoxib dosing regimens was evaluated in patients with knee OA, according to American College of Rheumatology criteria, using VAS pain scores measured at baseline, Week 2 and 6. Only efficacy data from patients whose baseline pain was moderate (VAS 40–69 mm) or severe (VAS ≥ 70 mm) were considered. To remain consistent with the approach adopted in the original trials and previous pooled analysis [16], patients with mild pain score at baseline ($n = 44$; 3%), were not included. Table 1 presents demographic data of the full analysis set (FAS) study population.

Objective and Outcome Measure

The main objective of our pooled analyses was to evaluate the efficacy of celecoxib in sex-based subgroups (male versus female) and in BMI-based subgroups, comparing obese (BMI ≥ 30 kg/m²) and nonobese (BMI < 30 kg/m²). As for the previous pooled analysis based on pain severity, the primary efficacy endpoint was the change from baseline in VAS pain score at Week 6.

Statistical Analysis

All efficacy analyses were conducted using the FAS, consistent with the original trials analyses. The FAS was defined as all randomized patients who received at least one dose of the study drug, had at least one post-baseline efficacy assessment, and had a baseline VAS pain score of ≥ 40 mm, in alignment with the original trial inclusion criteria. The primary efficacy endpoint was analyzed per subgroup using analysis of covariance (ANCOVA) with study and treatment as fixed effects and baseline VAS pain score as a covariate, using the last observation carried forward (LOCF) approach to deal with

missing post-baseline scores. Least-squares (LS) mean changes from baseline were calculated, and treatment differences were reported with 95% confidence intervals (CIs) and unadjusted *p*-values. A mixed-effects model for repeated measures (MMRM) with study, treatment, treatment-by-visit interaction, and baseline VAS pain score as covariate, was used to analyze the Week 2 and 6 data. A treatment-by-subgroup interaction term was incorporated into the overall ANCOVA and MMRM model to assess the homogeneity of treatment effects. After results were available, a *t*-test was performed to check for baseline differences in pain scores between the subgroups and an interaction term of baseline pain score by subgroup was added in the model to verify the contribution of subgroup specific baseline pain score on the change from baseline. Statistical significance was set at $p < 0.05$ (two-sided) and no correction for multiplicity has been applied, given the exploratory nature of post hoc subgroup analyses. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). To assess the robustness of results to missing data assumptions, sensitivity analyses were conducted within the MMRM framework using reference-based imputation methods, including copy-reference (CR) and jump-to-reference (J2R). The CR approach assumes that, following dropout, subjects in the active treatment arms have outcomes that progressively converge toward those observed in the placebo arm, resulting in a gradual attenuation of the treatment effect. By contrast, the J2R approach assumes that, following dropout, subjects immediately switch to the outcome trajectory of the placebo group, such that any treatment effect is lost from that point onward. Consequently, J2R represents a more extreme assumption, as missing post-dropout data are imputed based solely on placebo outcomes without incorporating previous on-treatment information [17].

Ethics Compliance

No primary human or animal data were collected for this post hoc analysis. The study represents a pooled evaluation of previously published

Table 1 Demographic characteristics of FAS population

Demographics	Placebo (<i>n</i> = 464)	100 mg BID (<i>n</i> = 460)	200 mg OD (<i>n</i> = 436)
Sex, <i>n</i> (%)			
Female	327 (70.47)	312 (67.83)	294 (67.43)
Male	137 (29.53)	148 (32.17)	142 (32.57)
Moderate pain, <i>n</i> (%)			
Female	156 (33.62)	138 (30)	136 (31.2)
Male	70 (15.08)	94 (20.43)	81 (18.57)
Severe pain, <i>n</i> (%)			
Female	171 (36.85)	174 (37.82)	158 (36.23)
Male	67 (14.43)	54 (11.74)	61 (13.99)
Age (years), mean $\pm$ SD	62.0 $\pm$ 11.5	62.5 $\pm$ 11.2	61.9 $\pm$ 11.7
OA duration (years), mean $\pm$ SD	9.01 $\pm$ 8.5	9.23 $\pm$ 8.8	9.02 $\pm$ 8.0
Height (cm), mean $\pm$ SD	167.2 $\pm$ 9.9	167.5 $\pm$ 9.7	167.5 $\pm$ 10.4
Weight (kg), mean $\pm$ SD	89.52 $\pm$ 19.9	90.18 $\pm$ 21.8	91.64 $\pm$ 21.5
BMI (kg/m ²), mean $\pm$ SD	32.08 $\pm$ 7.1	32.12 $\pm$ 7.3	32.67 $\pm$ 7.4
BMI, <i>n</i> (%)			
< 30 kg/m ²	207 (44.61)	199 (43.26)	170 (38.99)
$\geq$ 30 kg/m ²	254 (54.74)	255 (55.43)	263 (60.32)
Missing data (weight and/or height)	3 (0.65)	6 (1.31)	3 (0.69)
BMI moderate pain, <i>n</i> (%)			
< 30 kg/m ²	116 (25)	109 (23.7)	92 (21.1)
$\geq$ 30 kg/m ²	108 (23.27)	118 (25.65)	124 (28.44)
BMI severe pain, <i>n</i> (%)			
< 30 kg/m ²	91 (19.6)	90 (19.56)	78 (17.88)
$\geq$ 30 kg/m ²	146 (31.46)	137 (29.79)	139 (31.88)
BMI (kg/m ²), mean $\pm$ SD			
< 30 kg/m ²	26.43 $\pm$ 2.6	26.02 $\pm$ 2.7	25.90 $\pm$ 2.8
$\geq$ 30 kg/m ²	36.69 $\pm$ 6.2	36.88 $\pm$ 6.1	37.05 $\pm$ 6.0
VAS (mm), mean $\pm$ SD			
Female	69.67 $\pm$ 14.56	70.02 $\pm$ 15.50	69.62 $\pm$ 15.59
Male	68.09 $\pm$ 14.86	66.13 $\pm$ 14.79	64.79 $\pm$ 13.78
BMI < 30 kg/m ²	66.78 $\pm$ 13.89	67.22 $\pm$ 15.19	66.46 $\pm$ 14.93

Table 1 continued

Demographics	Placebo (<i>n</i> = 464)	100 mg BID (<i>n</i> = 460)	200 mg OD (<i>n</i> = 436)
BMI $\geq$ 30 kg/m ²	71.28 $\pm$ 14.91	70.20 $\pm$ 15.36	69.11 $\pm$ 15.27

Values are expressed as either numbers (%) of patients or mean $\pm$ standard deviation (SD)

VAS visual analog scale, BID twice a day, OD once a day, BMI body mass index, OA osteoarthritis

randomized controlled trials (Williams 2000; Williams 2001). No additional data collection was undertaken; only anonymized secondary datasets were analyzed. This post hoc pooled analysis was conducted using anonymized data from two previously completed randomized controlled trials. The original studies received approval from the relevant institutional review boards or ethics committees, all participants provided written informed consent prior to study participation, and the studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

RESULTS

Patients

FAS included 1360 male and female participants ($\geq$ 18 years) meeting inclusion criteria in OA flare state (VAS $\geq$ 40 mm). The treatment groups were comparable for age, race, BMI and sex. Out of 1360 patients, 427 were males and 933 females. The female subgroup also included a relatively greater number of obese individuals compared with the male group (*n* = 562, ~60.2% versus *n* = 210, ~49.2% respectively). Notably, sex-based subgroups, BMI based subgroups, and the previously reported subgroups based on pain severity [14] represent different cross-sections of the same overall patient population from these two similar analyses. Indeed, looking at cross tabulation data for sex and BMI subgroups, 46% (54%) of females, and 57% (43%) of males are in the moderate (severe) group while 55% (45%) of the nonobese, and 45% (55%) of the obese are in the moderate (severe) group, confirming that these represent different subgroups selection.

Efficacy: VAS Pain Score Analysis by Sex

Both treatment arms demonstrated a statistically significant reduction in VAS pain scores compared with placebo at Week 6 in both subgroups, as illustrated in Table 2 by the Least-Squares mean difference (LSMeans), confirming the efficacy of celecoxib in reducing OA pain in both males and females. Notably, baseline VAS pain scores were significantly higher ($p < 0.0001$, *t*-test) in female compared with males (Table 1). Additionally, the female subgroup presented greater absolute pain reduction across both celecoxib dosage regimens at Week 6. However, this effect, together with a larger placebo response, led to numerically smaller treatment differences versus placebo.

MMRM subgroup analyses confirmed clinically meaningful reductions in VAS scores in both women and men, consistent with ANCOVA findings (Table 2). At both Week 2 and 6, celecoxib demonstrated greater pain reduction than placebo in both sex subgroups, supporting a rapid onset and sustained treatment effect, with similar magnitudes across dosing regimens and minor sex-specific nuances (Fig. 1). Sensitivity analyses (Supplementary Tables 1 and 2) using CR and J2R imputation methods yielded results broadly consistent with the primary MMRM analysis. At Week 6, efficacy results in females were stable across all methods, with comparable effect sizes and maintained statistical significance. By contrast, in males, treatment effect estimates remained numerically similar across imputation methods, but statistical significance was sensitive to the imputation approach and was attenuated under the more conservative J2R assumption.

Table 2 ANCOVA and MMRM results for change from baseline in VAS pain scores for males and females with moderate and severe pain at baseline—FAS population

ANCOVA analysis: results at week 6					
Subgroup	Treatment	LS means (95% CI)		LS means difference (95% CI)	<i>p</i> -Value*
Female	Placebo (<i>n</i> = 239)	−24.38	(−27.64, −21.12)	–	–
	Celecoxib 100 mg BID (<i>n</i> = 271)	−30.39	(−33.45, −27.34)	−6.01 (−10.48, −1.54)	0.0084
	Celecoxib 200 mg OD (<i>n</i> = 264)	−30.21	(−33.31, −27.12)	−5.83 (−10.32, −1.34)	0.0111
Male	Placebo (<i>n</i> = 103)	−18.03	(−22.69, −13.37)	–	–
	Celecoxib 100 mg BID (<i>n</i> = 133)	−25.25	(−29.34, −21.15)	−7.22 (−13.43, −1.01)	0.0228
	Celecoxib 200 mg OD (<i>n</i> = 127)	−27.04	(−31.23, −22.84)	−9.01 (−15.29, −2.73)	0.0050
MMRM analysis: results at week 2 and 6					
		Subgroup	Placebo <i>n</i> [†] = 327; <i>n</i> [‡] = 137	Celecoxib 100 mg BID <i>n</i> [†] = 312; <i>n</i> [‡] = 148	Celecoxib 200 mg OD <i>n</i> [†] = 294; <i>n</i> [‡] = 142
Observed mean ± SD	Baseline	Female	69.67 ± 14.56	70.02 ± 15.50	69.62 ± 15.59
		Male	68.09 ± 14.86	66.13 ± 14.79	64.79 ± 13.78
LS Mean change from baseline (SE) by visit	Week 2	Female	−20.58 (1.49)	−28.83 (1.40)	−28.40 (1.42)
		Male	−17.30 (2.12)	−26.60 (1.86)	−25.24 (1.91)
	LS mean difference (95% CI)	Female	–	−8.25 (−12.26, −4.24)	−7.81 (−11.85, −3.78)
		Male	–	−9.30 (−14.85, −3.74)	−7.93 (−13.55, −2.32)
	<i>p</i> -Value**	Female	–	< 0.0001	0.0002
		Male	–	0.0011	0.0058
	Week 6	Female	−24.88 (1.74)	−30.57 (1.60)	−30.64 (1.64)
		Male	−18.69 (2.52)	−25.14 (2.15)	−26.89 (2.19)
	LS mean difference (95% CI)	Female	–	−5.70 (−10.34, −1.06)	−5.76 (−10.45, −1.07)
		Male	–	−6.45 (−12.96, 0.06)	−8.20 (−14.78, −1.63)
	<i>p</i> -Value**	Female	–	0.0162	0.0161
		Male	–	0.0522	0.0146

SD Standard deviation, *SE* Standard error, *CI* Confidence interval, *BID* Twice a day, *OD* Once a day, *LS* Least-squares.

p*-Value derived from analysis of covariance (ANCOVA) model including terms for study, treatment, and baseline score, and using last observation carried forward (LOCF). *p*-Value derived from MMRM (mixed-effects model for repeated measures) including terms for study, treatment, visit, treatment-by-visit, and baseline VAS pain score. *n*[†]: number of female subjects. *n*[‡]: number of male subjects

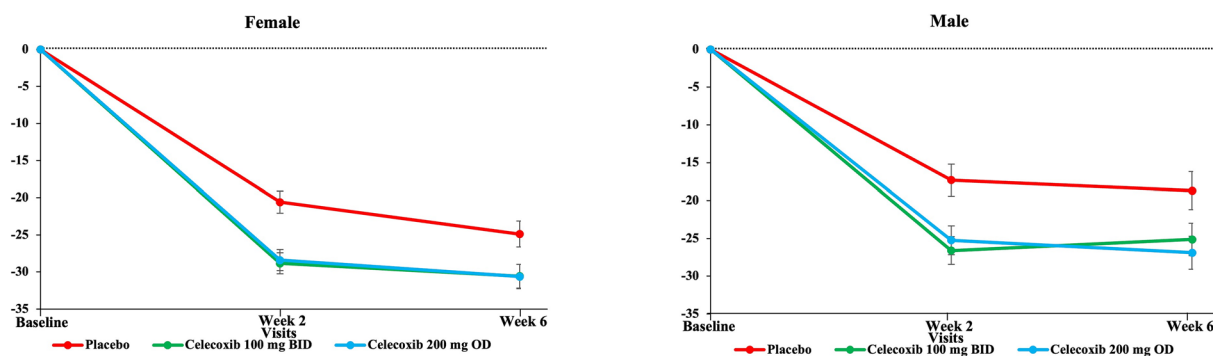


Fig. 1 LSMeans (SE) Change from baseline in VAS pain score at week 2 and 6 in the FAS population, by sex over time; VAS: visual analog scale; SE: standard error; CFB: change from baseline; BID: twice a day; OD: once a day

Efficacy: VAS Pain Score Analysis by BMI

As expected, patients with obesity (BMI ≥ 30 kg/m²) presented significantly higher ($p < 0.0001$, t -test) baseline VAS pain score (Table 1) than nonobese patients (BMI < 30 kg/m²), consistent with a marked separation between groups defined by an average BMI difference of ~ 10 kg/m² (36.88 versus 26.13).

In the ANCOVA analysis, both treatment arms demonstrated statistically relevant reduction in VAS pain scores at Week 6, compared with placebo in both BMI subgroups (Table 3). Notably, the placebo group showed greater improvement in obese (approximately 24.0 VAS points) than non-obese (20.6 VAS points) subgroup, contributing to a smaller treatment–placebo difference despite comparable absolute pain reductions. In the obese subgroup both dosage regimens provided statistically significant and almost equal LS Means differences at Week 6 compared with placebo. The nonobese subgroup presented also statistically significant results with numerically larger treatment–placebo difference compared with the obese subgroup.

The MMRM analysis was largely confirmatory, demonstrating that both celecoxib regimens achieved clinically meaningful reductions in VAS pain scores at Week 2 and 6 across BMI subgroups (Table 3, Fig. 2).

An early benefit was clear in obese subgroup for both regimens, and in nonobese for 100 mg BID. Among nonobese patients, both regimens showed statistically significant reductions versus

placebo at Week 6. Interestingly, the 200 mg OD regimen became statistically significant only at Week 6 (LS mean difference -7.97 ; 95% CI -13.73 to -2.21 ; $p = 0.0068$), despite a smaller and non-significant difference at Week 2 (LS mean difference -3.97 ; 95% CI -9.00 to 1.06 ; $p = 0.1220$; Fig. 2). By contrast, in the obese subgroup, although both celecoxib dosage regimens produced substantial and comparable reductions in VAS pain score at Weeks 2 (LS mean change -28.54 for 100 mg BID and -29.59 for 200 mg OD) and Week 6 (LS mean changes: -29.23 for 100 mg BID and -29.44 for 200 mg OD), the treatment–placebo differences were smaller at Week 6 (< 5 points) and did not reach statistical significance ($p = 0.0721$ for 100 mg BID and $p = 0.0600$ for 200 mg OD) as shown in Table 2 and Fig. 2. Sensitivity analyses (Supplementary Tables 3 and 4) using CR and J2R, were consistent with the primary MMRM findings. In patients with obesity, although absolute pain reductions were comparable to those in non-obese patients, treatment–placebo differences (approximately -4 to -5 mm) remained reduced and did not reach statistical significance across imputation methods.

Overall, treatment effects were consistent across analytical approaches, with some sensitivity of statistical significance to subgroup size and imputation method. (Supplementary Tables 5 and 6). No statistically significant treatment-by-subgroup interactions were observed for sex ($p = 0.9353$) or BMI ($p = 0.3919$), indicating no evidence of heterogeneity of treatment effect across subgroups.

Table 3 ANCOVA and MMRM results for change from baseline in VAS pain scores for obese (BMI ≥ 30 kg/m²) and non-obese (BMI < 30 kg/m²) participants with moderate and severe pain at baseline—FAS population**ANCOVA analysis: results at Week 6**

Subgroup	Treatment	LS means (95% CI)	LS means difference (95% CI)	<i>p</i> -Value*
Nonobese	Placebo (<i>n</i> = 151)	−20.61 (−24.50, −16.71)	–	–
	Celecoxib 100 mg BID (<i>n</i> = 170)	−27.84 (−31.51, −24.17)	−7.24 (−12.58, −1.89)	0.0081
	Celecoxib 200 mg OD (<i>n</i> = 148)	−28.93 (−32.86, −24.99)	−8.32 (−13.85, −2.79)	0.0033
Obese	Placebo (<i>n</i> = 189)	−24.01 (−27.70, −20.33)	–	–
	Celecoxib 100 mg BID (<i>n</i> = 228)	−29.32 (−32.68, −25.96)	−5.31 (−10.29, −0.32)	0.0370
	Celecoxib 200 mg OD (<i>n</i> = 240)	−29.47 (−32.74, −26.20)	−5.46 (−10.39, −0.52)	0.0302

MMRM analysis: results at week 2 and 6

		Subgroup	Placebo <i>n</i> [†] = 207; <i>n</i> [‡] = 254	Celecoxib 100 mg BID <i>n</i> [†] = 199; <i>n</i> [‡] = 255	Celecoxib 200 mg OD <i>n</i> [†] = 170; <i>n</i> [‡] = 263
Observed mean $\pm$ SD	Baseline	Nonobese	66.78 $\pm$ 13.89	67.22 $\pm$ 15.19	66.46 $\pm$ 14.93
		Obese	71.28 $\pm$ 14.91	70.20 $\pm$ 15.36	69.11 $\pm$ 15.27
LS mean change from baseline (SE) by visit	Week 2	Nonobese	−19.97 (1.80)	−27.80 (1.70)	−23.93 (1.82)
		Obese	−19.21 (1.66)	−28.54 (1.51)	−29.59 (1.47)
	LS mean difference (95% CI)	Nonobese	–	−7.83 (−12.69, −2.97)	−3.97 (−9.00, 1.06)
		Obese	–	−9.33 (−13.74, −4.92)	−10.38 (−14.74, −6.02)
	<i>p</i> -value*	Nonobese	–	0.0016	0.1220
		Obese	–	< 0.0001	< 0.0001
	Week 6	Nonobese	−21.41 (2.12)	−28.15 (1.93)	−29.38 (2.03)
		Obese	−24.51 (1.95)	−29.23 (1.75)	−29.44 (1.74)
	LS mean difference (95% CI)	Nonobese	–	−6.75 (−12.37, −1.12)	−7.97 (−13.73, −2.21)
		Obese	–	−4.72 (−9.88, 0.43)	−4.93 (−10.07, 0.21)
	<i>p</i> -Value*	Nonobese	–	0.0188	0.0068
		Obese	–	0.0721	0.0600

n[†]: number of nonobese subjects. *n*[‡]: number of obese subjects. *BMI* body mass index, *LS* least-squares, *SD* standard deviation, *SE* standard error, *CI* confidence interval, *BID* twice a day, *OD* once a day. **p*-Value derived from ANCOVA (analysis of covariance) model including terms for study, treatment, and baseline score, and using last observation carried forward (LOCF). ***p*-Value derived from mixed-effects model for repeated measures (MMRM) including terms for study, treatment, visit, treatment-by-visit, and baseline VAS pain score. Obese subjects classified as body mass index (BMI) ≥ 30 kg/m²; non-obese subjects classified as BMI < 30 kg/m²

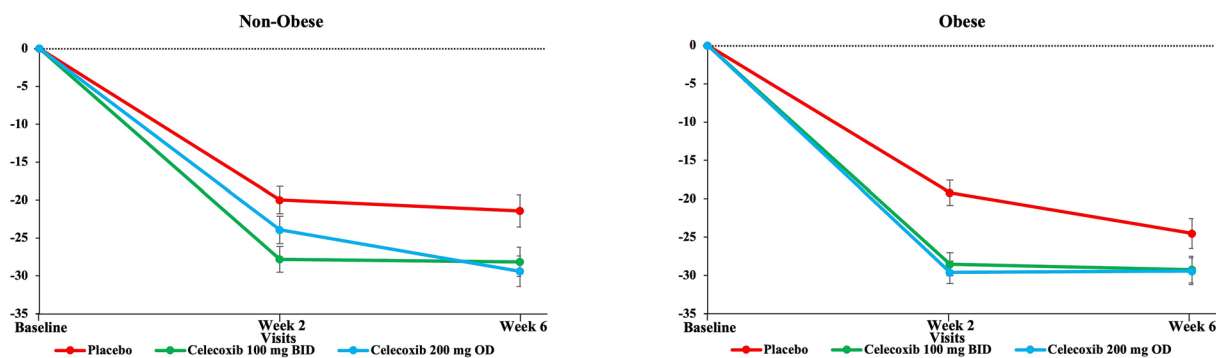


Fig. 2 LSMeans (SE) Change from baseline in VAS pain score at week 2 and 6 in the FAS population, by BMI over time; VAS: visual analog scale; SE: standard error; CFB:

change from baseline; BID: twice a day; OD: once a day; BMI: body mass index

DISCUSSION

To our knowledge, this is the first pooled analysis of randomized controlled trials evaluating the influence of biological sex and BMI on celecoxib efficacy in the treatment of OA-related pain. Overall, the findings demonstrate that both celecoxib dosage regimens are equally effective in reducing pain across male and female participants, as well as in obese and non-obese participants. In the prespecified ANCOVA primary analysis, celecoxib showed statistically significant improvements versus placebo in both sexes, with comparable magnitudes of pain reduction. MMRM analyses were largely concordant with these results, with the only divergence observed in male patients receiving 100 mg BID where statistical significance was narrowly missed at Week 6 ($p = 0.0522$). This finding is most plausibly explained owing to the smaller size of the male subgroup (approximately half the number of female participants), rather than a consistent sex-specific difference in treatment. To assess robustness to missing data assumptions, sensitivity analyses using CR and J2R approaches were conducted. As expected, J2R attenuated statistical significance owing to more extreme imputation. Overall, results support the robustness of the treatment effect. Importantly, absolute reductions in pain remained consistent across methods, reinforcing the robustness of the treatment effect. However, subgroup results should be interpreted with caution, as

they remain exploratory, and not powered for definitive comparisons. The results based on biological sex are noteworthy when considered alongside the evidence reported by Mogil [18], which highlights that women generally report higher baseline pain levels than men in OA and other musculoskeletal conditions. This disparity is probably attributable to both biological, hormonal and psychosocial factors influencing pain perception and modulation. In the current dataset, women exhibited higher baseline VAS pain scores, and a stronger placebo response compared with men, suggesting that there are subtle differences which may influence the observed treatment–placebo gap between sexes, particularly in analysis sensitive to placebo dynamics.

Similarly, BMI-based subgroup analyses warrant cautious interpretation. As expected, obese participants presented with higher baseline pain scores, consistent with the established association between obesity, increased mechanical joint load, systemic inflammation, and heightened pain perception in OA. In ANCOVA analysis, both celecoxib dosage regimens produced statistically significant pain reductions versus placebo in obese and nonobese subgroups, with broadly comparable absolute reductions from baseline. However, MMRM analyses revealed a smaller treatment–placebo difference at Week 6 in the obese subgroup, resulting in borderline statistical significance despite similar absolute pain reductions. Consistent with the sensitivity analyses, these patterns were not materially influenced by the choice of imputation method.

In addition, it remains possible that long-term treatment responses may differ modestly across phenotypically distinct patient subgroups. Given the elevated baseline BMI ($\sim 36\text{--}37\text{ kg/m}^2$) in the obese subgroup, clinicians should consider a structured weight-loss intervention, alongside analgesic pharmacotherapy, since weight reduction is a core nonpharmacological component of OA related symptoms management. These findings should be interpreted within a multimodal management framework. In patients with obesity, pharmacological treatment alone is unlikely to provide sufficient pain relief and should be complemented by structured weight-loss and lifestyle interventions in line with EULAR, OARSI and ESCEO [19–22] recommendations. Such combined approaches may address both symptomatic and underlying metabolic contributors to OA.

An important potential source of bias in this analysis relates to differential withdrawals rates between treatment groups. The markedly higher rate of treatment-failure discontinuations [approximately 2.5-fold higher in the placebo group (23.3%)] compared with 100 mg of celecoxib BID (9.1%) and 200 mg OD (9.4%), corresponding to an absolute difference of approximately 14% (data not shown) may have enriched the remaining placebo population with responders over time, thereby narrowing the observed treatment–placebo differences at Week 6. This effect might have been particularly relevant in the obese subgroup, where placebo responses were more pronounced. The sensitivity analyses, CR and J2R address these issues to a certain extent. Despite these limitations, celecoxib consistently demonstrated clinically meaningful pain reduction (approximately 29 VAS points) irrespective of BMI subgroup, supporting its use in OA pain management, including patients with obesity.

This analysis has several limitations. First, it is post hoc in nature and therefore exploratory. The original trials were not designed or powered to detect differences within sex- or BMI-defined subgroups, increasing the risk of type II error, particularly in smaller groups such as males. Another potential limitation of this analysis is clearly the

marked ratiometric imbalance between subgroups, with some categories having sample sizes that are two- to three-fold smaller than their corresponding counterparts. The male subgroup ($n = 427$) was under-represented compared with females ($n = 933$) and similar disproportions were observed between nonobese ($n = 576$) and obese ($n = 772$) participants. These imbalances may have reduced statistical sensitivity in smaller subgroups and consequently limited the generalizability of subgroup findings. Future research using larger OA datasets and potentially extending to other rheumatological conditions, such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS) could provide further insights into phenotypic factors influencing analgesic efficacy, helping to resolve remaining ambiguity around subgroup-related variability in response. Such analyses would also allow exploration of sex-related differences across rheumatic diseases with distinct epidemiological profiles, given that RA is predominantly female while AS is principally a condition affecting males. Although safety outcomes were not specifically assessed here, they were reported in the primary publications of the two clinical studies [14, 15] and were consistent with the recognized safety profile of COX-2 selective NSAIDs in patients with relatively few comorbidities. Celecoxib's safety profile has also been well established in large-scale trials, including the PRECISION study [23], which provided important information on the relative long-term safety of celecoxib in patients at increased cardiovascular risk compared with ibuprofen and naproxen at prescription-strength doses.

CONCLUSIONS

This pooled post hoc analysis demonstrates that celecoxib provides consistent and clinically meaningful pain reduction in knee OA across diverse patient subgroups defined by sex and BMI. Larger prospective studies and retrospective analyses are warranted to further clarify potential phenotypic influences on treatment response.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Jean-Yves Reginster has received support and/or a paid consultant and/or received payment or honoraria and/or received support for attending meetings and/or travel and/or Participation on Advisory Board of Viatris. Nicholas Fuggle received payment or honoraria from Viatris, Amgen, and UCB. Egbert Biesheuvel and Chris Walker are employees and own stocks in Viatris. Srinivasan Venugopal, Sagar Suresh Kumbhar, and Raffaella Maria Rita Chiaese are employees of Viatris. Ernest Choy has received support and/or received grants and/or a paid consultant and/or received payment or honoraria and/or is an editor of and/or owns stocks and/or recipient of miscellaneous services from Viatris, Pfizer, BioCancer, Sanofi, Abbvie, Biogen, Fresenius Kabi, Editor of Rheumatology (Oxford), and Inmedix

Ethical Approval. No primary human or animal data were collected for this post hoc

analysis. The study represents a pooled evaluation of previously published randomized controlled trials (Williams 2000; Williams 2001). No additional data collection was undertaken; only anonymized secondary datasets were analyzed. This post hoc pooled analysis was conducted using anonymized data from two previously completed randomized controlled trials. The original studies received approval from the relevant institutional review boards or ethics committees, all participants provided written informed consent prior to study participation, and the studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

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