

Efficacy of Celecoxib in Treating Symptoms of Viral Pharyngitis: a Double-blind, Randomized Study of Celecoxib versus Diclofenac

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This study compared the efficacy and safety of the cyclooxygenase-2 specific inhibitor celecoxib with the conventional non-steroidal anti-inflammatory drug diclofenac in the symptomatic treatment of viral pharyngitis. Adult patients from 27 study centers in Latin America were treated with oral doses of celecoxib 200 mg once daily or 200 mg twice daily, or diclofenac 75 mg twice daily for 5 days in a double-blind, randomized study. The primary efficacy assessment was 'Throat Pain on Swallowing' on day 3. In addition, secondary quality-of-life assessments were performed on days 3 and 5. All adverse events and treatment-emergent signs and symptoms were recorded. Data from 313 patients were evaluable for efficacy (105 celecoxib 200 mg once daily, 107 celecoxib 200 mg twice daily, 101 diclofenac 75 mg twice daily). The upper 95% confidence limits for the visual analog scale of 'Throat Pain on Swallowing' on day 3 for celecoxib 200 mg once daily relative to diclofenac

75 mg twice daily, and celecoxib 200 mg twice daily relative to diclofenac 75 mg twice daily were 9.26 and 7.83, respectively. All secondary efficacy and quality-of-life measures were clinically similar for the three treatment groups, and no statistically significant differences were detected. The incidences of treatment-emergent adverse events and withdrawals due to adverse events were similar for all groups, but numerically higher among patients taking diclofenac than celecoxib. More patients in the diclofenac group reported gastrointestinal complaints (7.3%) compared with those in the celecoxib groups (4.3% in the celecoxib 200 mg once-daily group and 3.4% in the celecoxib 200 mg twice-daily group). In conclusion, 5 days of treatment with celecoxib 200 mg once daily is as effective as diclofenac 75 mg twice daily in the symptomatic treatment of viral pharyngitis. Celecoxib 200 mg once daily is also as effective as celecoxib 200 mg twice daily in this condition.

KEY WORDS: CELECOXIB; CYCLOOXYGENASE (COX)-2 SPECIFIC INHIBITORS; VIRAL PHARYNGITIS; SYMPTOMATIC TREATMENT; THROAT PAIN ON SWALLOWING

Introduction

The symptoms of viral pharyngitis are painful and often impact on patients' quality of life. Non-steroidal anti-inflammatory drugs (NSAIDs) have been the primary treatment option for relief from the symptoms associated with this condition.^{1,2} Many of the clinical studies conducted with NSAIDs have demonstrated effective reduction in the symptoms of fever, pain, and inflammation.^{1 - 7} The conventional NSAID, diclofenac, is routinely used for the symptomatic treatment of viral pharyngitis in Latin America.

Conventional NSAIDs are associated with gastrointestinal adverse events.^{8 - 10} These events can occur even with short-term use and include inhibition of platelet function and serious gastrointestinal events such as ulceration, perforation, and bleeding. The clinical benefits of NSAIDs are due to the inhibition of cyclooxygenase (COX)-2, whereas many of the adverse events are likely to result from non-specific COX inhibition.^{11 - 13} Thus, specific inhibition of COX-2 provides the therapeutic benefits of conventional NSAIDs but avoids the adverse events associated with COX-1 inhibition. Cyclooxygenase-2 specific inhibitors, such as celecoxib, are as effective as conventional NSAIDs in alleviating symptoms of pain and inflammation,^{14 - 16} and have improved safety profiles.^{17,18} Arthritis studies have shown that a once-daily regimen is as effective as a twice-daily regimen in treating pain and inflammation.^{19,20}

This study tested the hypotheses that celecoxib 200 mg once daily is as effective as diclofenac 75 mg twice daily as a symptomatic treatment in viral pharyngitis, and that celecoxib 200 mg once daily is as effective as celecoxib 200 mg twice daily.

Patients and methods

STUDY DESIGN

This multicenter, double-blind, randomized study was conducted in 27 centers in Brazil, Colombia, and Mexico. Adult patients with presumed viral pharyngitis were assigned to receive either celecoxib 200 mg once daily, celecoxib 200 mg twice daily, or diclofenac 75 mg twice daily for 5 days. All treatments were administered orally. Randomization was achieved using a computer-generated randomization schedule and the randomization was stratified to achieve balance within each center.

PATIENTS

The major inclusion criteria for this trial were:

- (i) Male and female patients of at least 18 years of age with presumed acute viral pharyngitis who were otherwise healthy were eligible for inclusion. Viral pharyngitis was presumed based on pharyngeal hyperemia and odynophagia, defined as pain scores of ≥ 66 mm out of 100 mm on a Visual Analog Scale (VAS), with an onset of symptoms of less than 48 hours prior to randomization and which had worsened by ≥ 15 mm from the day before enrollment to the first day of the trial;
- (ii) Patients needed to have a rating of 'fair', 'poor', or 'very poor' on the patient's global assessment of disease activity that had worsened by at least one grade before the first day of the trial.

Other criteria were a negative throat swab for Group A β -hemolytic streptococci, and female patients were required to be either post-menopausal or surgically sterilized, or to have a negative urine pregnancy test result prior to randomization, and to be using

adequate contraception during the study, and not to be breast-feeding or lactating.

Patients were excluded from the study if they had temperatures $> 38.5^{\circ}\text{C}$ (oral temperature) or $> 39.0^{\circ}\text{C}$ (axillary temperature). Patients were also excluded if their pharyngitis was exudative and/or ulcerative, or if they had active gastrointestinal ulcers, gastrointestinal disease, or presumed infectious mononucleosis. Other exclusion criteria were: hypersensitivity to the study drugs, sulfonamides, urticaria or allergic-type reactions after taking aspirin or other NSAIDs; and use of antibiotics, antihistamines, NSAIDs, or COX-2 specific inhibitors < 24 hours, or analgesics < 6 hours, before the baseline visit, or any investigational drug < 30 days before the first dose or during the trial.

All patients gave written, informed consent for their participation, and the protocol was approved by the appropriate Independent Ethics Committee at each center, according to principles based on the Declaration of Helsinki.

EFFICACY MEASUREMENTS

The primary efficacy end-point was 'Throat Pain on Swallowing' on day 3, which was measured by patients completing a diary card with a 100-mm VAS where 0 mm indicates 'No pain' and 100 mm denotes 'The worst pain'.

As secondary efficacy end-points, patient's VAS 'Throat Pain on Swallowing' on day 5, patient's VAS 'Throat Pain at Rest', and physician's assessment of disease activity (categorical) on day 3 and day 5 were determined. Other secondary end-points were performed to determine quality-of-life outcomes:

- (i) Patient's global assessment of disease activity at baseline, day 3, and day 5,

measured on a categorical scale ranging from 1 (very good: asymptomatic and no limitation of normal activities) to 5 (very poor: very severe symptoms which are intolerable, and inability to carry out normal activities);

- (ii) Patient's functional activity at baseline, day 3, and day 5, rated on a categorical scale ranging from 0 (able to work and function normally in all activities) to 3 (working, studying, or housekeeping activities severely impaired/unable to perform; and requiring bed rest);
- (iii) Patient's and physician's satisfaction with treatment at day 3 and day 5, measured on a 7-point scale from very satisfied to very dissatisfied.

SAFETY AND TOLERABILITY

All adverse events were recorded on the case report form. Drug safety was assessed on the basis of spontaneously reported treatment-emergent signs and symptoms, and drug tolerability on the basis of the incidences of adverse events, serious adverse events, and adverse events causing withdrawal.

STATISTICAL ANALYSIS

A sample size of 100 patients per treatment arm was calculated to provide at least 80% power to declare non-inferiority of celecoxib as compared with diclofenac. The maximum clinically acceptable difference for declaring non-inferiority between the treatment groups was 15 mm on a 100-mm VAS. The sample size calculations were based on non-inferiority margins and statistically evaluated as the upper limit of the 95% confidence interval for the treatment difference not exceeding 15 mm.

Efficacy and quality-of-life analyses were conducted with data from the evaluable cohort, defined as all eligible patients who took at least one dose of study medication

and who provided baseline and day 3 VAS pain scores. Patient disposition and safety analyses were conducted with data from the intent-to-treat (ITT) population, defined as all patients who took at least one dose of study medication.

Continuous outcomes were analysed using analysis of covariance (ANCOVA), with baseline as the covariate; the analysis of the continuous data at baseline was performed using PROC MIXED analysis of variance with center as the random factor and treatment as fixed. For the analysis of the efficacy and quality-of-life outcomes, celecoxib 200 mg once daily and celecoxib 200 mg twice daily were compared with diclofenac 75 mg twice daily; these were considered to be independent tests, and there was no adjustment for multiple comparisons. Efficacy results are presented by displaying 95% confidence intervals of the least squares means treatment differences.

The ordered categorical post-baseline data were analysed using the logistic regression for polytomous responses model and results presented as odds ratios. The model included treatment with the baseline as covariate and was run overall, and then pair-wise for celecoxib 200 mg once daily versus diclofenac 75 mg twice daily, and celecoxib 200 mg twice daily versus diclofenac 75 mg twice daily. Center was not included in this model. All patients receiving at least one dose of study medication were included in the safety analysis.

Results

PATIENTS

A total of 357 patients were enrolled across the 27 study centers, of whom 303 (85%) completed the study. The most frequently cited reason for non-completion was loss to follow-up (5%); others violated entry criteria,

did not comply with the protocol, were withdrawn due to adverse events, or did not complete the study due to treatment failure (Fig. 1). All 357 patients were included in the ITT population. The baseline demographic and clinical characteristics were similar among all three treatment groups (Table 1).

A total of 44 patients were excluded from the evaluable cohort. These involved 12 patients from the celecoxib 200 mg once-daily group, 10 from the celecoxib 200 mg twice-daily group, and 22 patients from the diclofenac 75 mg twice-daily group. The reasons for patient exclusions were violation of major inclusion criteria, not having VAS assessments at baseline and at least one visit, and the clinical judgment of the blinded medical reviewer prior to database lock.

EFFICACY

The mean scores for the patient's VAS assessment of 'Throat Pain on Swallowing' at day 3 (i.e. the primary efficacy end-point) for the three treatments were: 36.3 mm for celecoxib 200 mg once daily; 35.1 mm for celecoxib 200 mg twice daily; and 32.7 mm for diclofenac twice daily (Fig. 2). The upper 95% confidence limits of celecoxib 200 mg once daily relative to diclofenac 75 mg twice daily, and celecoxib 200 mg twice daily relative to diclofenac 75 mg twice daily were 9.26 and 7.83, respectively.

For the secondary efficacy end-points, the patient's assessment of 'Throat Pain on Swallowing' at day 5, patient's assessment of 'Throat Pain at Rest' at days 3 and 5, and the physician's global assessment of disease activity at days 3 and 5, were clinically similar for the three treatment groups, and no statistically significant differences were detected (data not shown).

Regarding the secondary quality-of-life end-points of patient's global assessment of

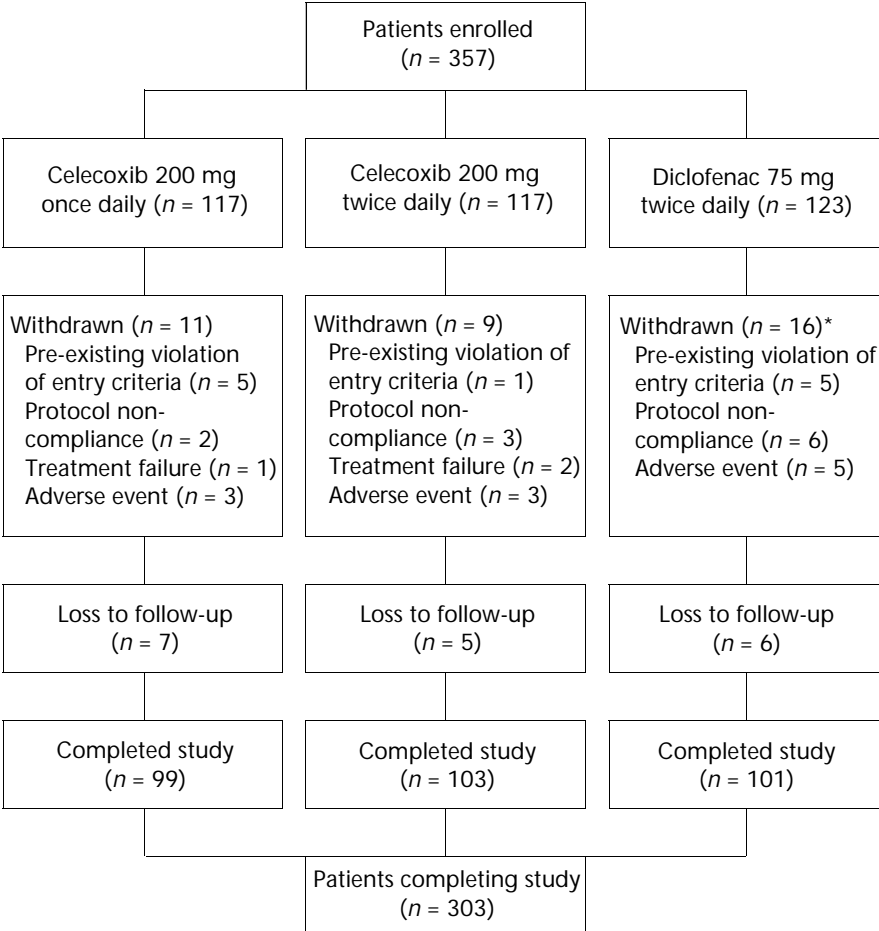


FIGURE 1: Disposition of intent-to-treat patients (≥ 18 years) with presumed viral pharyngitis. *For one patient in the diclofenac group, both entry criteria violation and adverse event were selected as reasons for withdrawal, but the former was later confirmed as primary

TABLE 1: Baseline demographic and clinical characteristics of study patients (≥ 18 years) with presumed viral pharyngitis

Evaluable cohort	Celecoxib 200 mg once daily (n = 105)	Celecoxib 200 mg twice daily (n = 107)	Diclofenac 75 mg twice daily (n = 101)
Age (years)			
Mean	32	31	32
Range	18 – 76	18 – 74	18 – 65
Gender (% female)	63.5	62.6	71.3

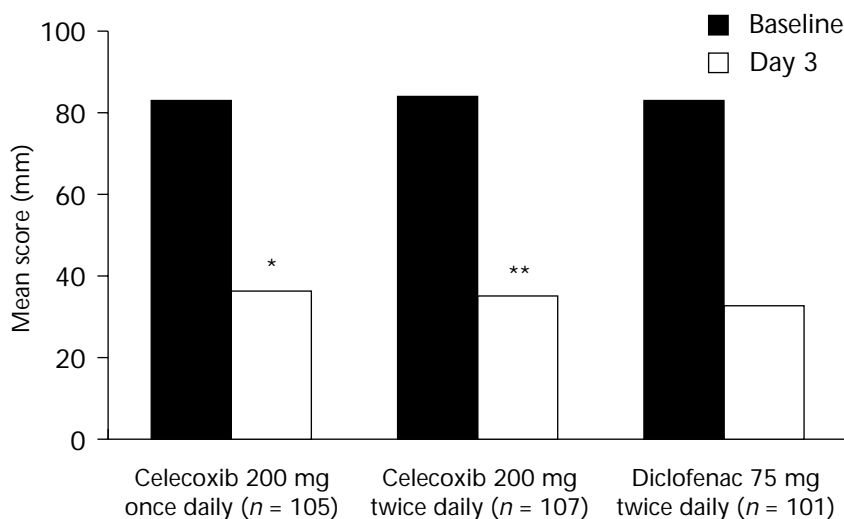


FIGURE 2: Mean 'Throat Pain on Swallowing' scores, measured on a Visual Analog Scale, at baseline and day 3 in patients (≥ 18 years) with presumed viral pharyngitis. *Upper 95% confidence limit for celecoxib 200 mg once daily relative to diclofenac 75 mg twice daily = 9.26. **Upper 95% confidence limit for celecoxib 200 mg twice daily relative to 75 mg diclofenac twice daily = 7.83

disease activity and patient's functional activity, there were no statistically significant differences observed between the three treatment groups (Table 2 and Fig. 3). At baseline, the majority of patients reported their condition to be either 'poor' (55.1 – 59.4% of patients across treatment groups) or 'very poor' (8.9 – 14.3%). In contrast, at day 3, the majority of patients reported their condition as either 'good' (47.7 – 49.5%) or 'very good' (20.5 – 24.7%). For the patient's functional activities outcome, the majority of patients reported their 'Activities reduced' (55.7% – 66.7%), whereas at day 3 the majority of patients reported that they were 'Able to work and function normally in all activities' (57.6 – 64.8%). Further improvement in symptoms of disease activity and patient's functional activity were reported at day 5. There were no significant differences between the three treatment groups for

patient's and physician's satisfaction with therapy at days 3 and 5 (Table 2).

SAFETY AND TOLERABILITY

The incidences of treatment-emergent adverse events and withdrawals due to adverse events were similar for the three treatment groups, although numerically higher among patients taking diclofenac than celecoxib. In the diclofenac group, 15.4% of patients reported a treatment-emergent adverse event, compared with 11.1% in the celecoxib 200 mg once-daily group and 9.4% in the celecoxib 200 mg twice-daily group.

Treatment-emergent adverse events were most commonly reported for the gastrointestinal system, body as a whole, and resistance mechanism disorders (Table 3). The incidence of gastrointestinal complaints from the diclofenac group (7.3%) was numerically greater than that of the

TABLE 2:
Baseline, day 3, and day 5 quality-of-life assessments in patients (≥ 18 years) with presumed viral pharyngitis

Evaluable cohort	Celecoxib 200 mg once daily (<i>n</i> = 105)	Celecoxib 200 mg twice daily (<i>n</i> = 107)	Diclofenac 75 mg twice daily (<i>n</i> = 101)
Patient's global assessment of disease activity (%)			
Baseline: poor or very poor	72.4	68.2	68.3
Day 3: good or very good	69.9	74.2	68.2
Day 5: good or very good	91.1	93.1	95.0
Patient's assessment of functional activity (%)			
Baseline: reduced/impaired activities	94.3	84.9	90.1
Day 3: normal in all activities	57.8	57.6	64.8
Day 5: normal in all activities	85.1	87.1	92.0
Patient's satisfaction with therapy (%)			
Day 3: satisfied/very satisfied	71.9	57.2	69.3
Day 5: satisfied/very satisfied	87.7	84.2	86.6
Physician's satisfaction with therapy (%)			
Day 3: satisfied/very satisfied	65.5	55.4	67.8
Day 5: satisfied/very satisfied	90.4	84.2	85.1

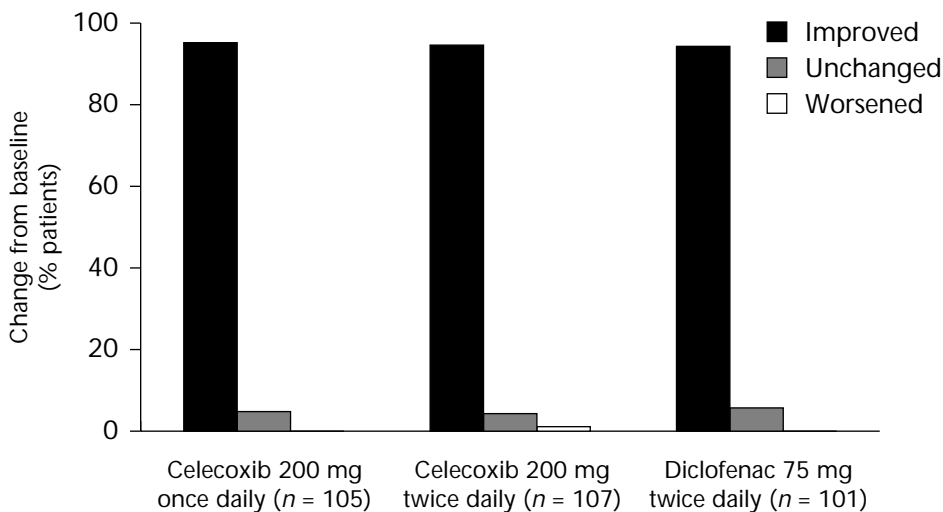


FIGURE 3: Change in patient's global assessment of disease activity on day 3 compared with baseline

TABLE 3:
Incidence of treatment-emergent adverse events ($\geq 1\%$) patients (≥ 18 years) with presumed viral pharyngitis

Intent-to-treat cohort	Celecoxib 200 mg once daily (<i>n</i> = 117)	Celecoxib 200 mg twice daily (<i>n</i> = 117)	Diclofenac 75 mg twice daily (<i>n</i> = 123)
Body as a whole	1 (0.9%)	4 (3.4%)	7 (5.7%)
Fever	0 (0%)	2 (1.7%)	5 (4.1%)
Headache	1 (0.9%)	1 (0.9%)	2 (1.6%)
Central and peripheral nervous system	1 (0.9%)	2 (1.7%)	3 (2.4%)
Dizziness	0 (0%)	2 (1.7%)	1 (0.8%)
Dysphonia	1 (0.9%)	0 (0%)	2 (1.6%)
Gastrointestinal system	5 (4.3%)	4 (3.4%)	9 (7.3%)
Upper abdominal pain	1 (0.9%)	3 (2.6%)	5 (4.1%)
Diarrhea	0 (0%)	0 (0%)	2 (1.6%)
Resistance mechanism	3 (2.6%)	3 (2.6%)	4 (3.3%)
Nose congestion	2 (1.7%)	0 (0%)	2 (1.6%)
Sinusitis	2 (1.7%)	0 (0%)	1 (0.8%)

celecoxib groups (4.3% and 3.4% for the once- and twice-daily regimens, respectively). Upper abdominal pain was reported by more patients in the diclofenac group (4.1%) than in the celecoxib once-daily (0.9%) and celecoxib twice-daily (2.6%) groups. This was also true of general body disorders, the most common of which was fever (4.1% in the diclofenac group and 0% and 1.7% for the celecoxib once- and twice-daily regimens, respectively). Resistance mechanism disorders included various manifestations of upper respiratory tract infection (nose congestion, sinusitis, tonsillitis) and were evenly distributed among the three treatment groups. The majority of adverse events were mild to moderate in severity and considered by the investigators not to be related to study medication. No serious adverse events were recorded.

A total of 12 patients withdrew from the study due to at least one adverse event, three

from each of the celecoxib groups and six from the diclofenac group. The most common adverse events leading to withdrawal were abdominal pain (four patients), fever (three patients), bacterial infection (two patients), and tonsillitis (two patients).

Discussion

Evaluation of the primary efficacy variable, patient's assessment (VAS) of 'Throat Pain on Swallowing' on day 3, indicates that celecoxib 200 mg once daily is as effective as diclofenac 75 mg twice daily as a symptomatic treatment for patients with viral pharyngitis. Although there was no placebo group in this study, the efficacy of NSAIDs versus placebo in treating the symptoms of pharyngitis has been established.^{2,3} This suggests that the

improvement observed is not simply due to natural remission.

Further, celecoxib 200 mg once daily was demonstrated to be as effective as celecoxib 200 mg twice daily in this condition. This has important implications in clinical practice since drugs that can be administered once daily may offer additional compliance advantages over drugs, such as diclofenac, that require more frequent dosing.²¹ Consistent with this finding, a higher proportion of patients were either satisfied or very satisfied with their treatment in the celecoxib 200 mg once-daily group compared with the celecoxib 200 mg twice-daily group.

These conclusions are further supported by the results of all the secondary efficacy analyses. It is of particular note that quality of life improved to the satisfaction of a large majority of patients and physicians after only 3 days of therapy in all three groups.

All regimens were well tolerated; however, despite the relatively short trial duration, there was a trend towards better tolerability for celecoxib compared with diclofenac in terms of emerging gastrointestinal complaints (upper abdominal pain and diarrhea). This finding is consistent with previous studies that have demonstrated improved gastrointestinal tolerability in patients receiving celecoxib compared with NSAIDs.^{17,18} In addition, numerically fewer

patients receiving celecoxib experienced fever compared with those receiving diclofenac. Although this observation lacks statistical significance, it is consistent with a previous study that has demonstrated an anti-pyretic effect of celecoxib in endotoxin-induced fever.²² Further research is warranted to elucidate further the potential anti-pyretic benefits of celecoxib.

The findings of the current study are consistent with previous reports involving arthritis patients, which have found celecoxib to be as effective an anti-inflammatory and analgesic agent as conventional NSAIDs, including diclofenac, but with an improved platelet and gastrointestinal safety profile.^{14 - 18,23} The analgesic efficacy shown by celecoxib in this study is also comparable to that observed by conventional NSAIDs in the symptomatic treatment of experimental rhinovirus colds and inflammatory disorders of the ear, nose, and throat.^{6,24 - 26}

In conclusion, the results of this randomized, double-blind study have shown that celecoxib 200 mg once daily is as effective as diclofenac 150 mg/day in the symptomatic treatment of viral pharyngitis. With its favorable upper gastrointestinal tolerability profile, celecoxib has the potential to offer a clinical advantage over diclofenac in this indication.

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