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The role of polmacoxib as a tissue-specific cox-2 inhibitor in the management of osteoarthritis: A comprehensive review

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Abstract
Osteoarthritis (OA) is a persistent degenerative and incapacitating condition distinguished by intricate issues affecting the entire synovial joint. NSAIDs and available COX-2 inhibitors that are useful in osteoarthritis show limitations in terms of adverse effects. They all have black box warnings as they are not cardio, renal, and GI safe. Polmacoxib, a novel nonsteroidal anti-inflammatory drug (NSAID), is the first, tissue-selective, once-a-day osteoarthritic drug with a unique mode of action that specifically targets affected joints to relieve pain and restore mobility. Its unique mechanism of action is projected to provide a meaningful enhancement of cardiovascular, renal, and gastrointestinal safety over currently available NSAID options. The pharmacological profile of this drug is characterized by its ability to inhibit COX-2 via the CYP3A4 pathway. In this review, we describe the clinical efficacy, safety, and tolerability of polmacoxib in the treatment of OA.

Keywords: Management, osteoarthritis, impingements, sprains, strains, comprehensive review

Introduction

Overview of osteoarthritis

The most frequent reason patients visit an orthopedician is typically pain. Common chronic orthopedic conditions can include arthritis, ankylosing spondylosis, osteoporosis, bursitis, neuropathy, and low back pain. Common acute orthopedic conditions Include dislocations, fractures or impingements, sprains, and strains.

Osteoarthritis (OA) stands as a prevalent form of arthritis and a persistent degenerative and incapacitating condition distinguished by intricate issues affecting the entire synovial joint. These issues encompass structural irregularities in the hyaline articular cartilage, deterioration of intact subchondral bone, tissue enlargement and heightened vascularity in the synovium, and instability of the tendons and ligaments [1].

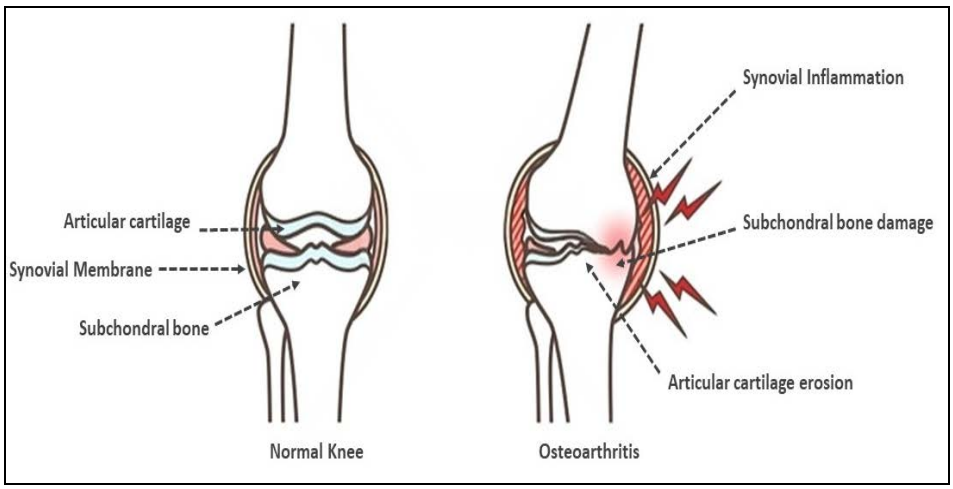

Fig 1: Phenotype of India

In 2021, more than 22% of adults aged over 40 were diagnosed with knee osteoarthritis (OA), and it is projected that globally, over 500 million individuals are presently impacted by OA. The prevalence of OA in India escalated from 23.46 million individuals in 1990 to 62.35 million in 2019, affecting approximately 22-39% of the population [1].

Pathophysiology of Oa

The pathogenesis of OA has been extensively studied over the past decades. The complex pathological mechanisms underlying the onset and development of OA remain unobserved, even though risk factors have been identified and structural changes in synovial joints are well understood [1].

Prostaglandin E2 (PGE2) mediated damage in OA

One of the initial impacts of proinflammatory cytokines is the activation of phospholipase A2 (PLA2), which cleaves cellular membranes and releases arachidonic acid [2].

During inflammation and catalysing the conversion of arachidonic acid into PGH2, COX-2 is highly up-regulated. PGE2 is a precursor of many eicosanoids, such as prostacyclin and thromboxane, but special attention will be paid to PGE2. This is a major proinflammatory prostaglandin. PGE2 is a major mediator of inflammation, contributing to several pathogenic features of arthritis such as pain, inflammation, and bone loss [2].

(a) PGE2-mediated pain pathophysiology

By reducing the activation threshold of afferent pain nerve endings to pain mediators, PGE2 mediates pain hypersensitization.

(b) PGE2-mediated cartilage degeneration

Inflammatory mediators like IL-1β and TNF-α trigger a cascade of events within chondrocytes, notably by stimulating the expression of cyclooxygenase-2 (COX-2), an enzyme crucial in the production of prostanoids. Subsequently, the prostanoid receptor EP4 undergoes upregulation via a COX-2-dependent mechanism. This heightened COX-2 activity leads to increased concentrations of prostaglandin E2 (PGE2), a potent mediator of inflammation. Consequently, the expression of disintegrin and metalloproteinase with thrombospondin repeats (ADAMTS) and matrix metalloproteinases (MMPs) is amplified. Moreover, PGE2 exerts detrimental effects on cartilage integrity by reducing proteoglycan production and promoting the release of newly synthesized proteoglycans. Furthermore, IL-1β and TNF-α activate transcription factors NF-κB and JNK, culminating in heightened expression of inducible nitric oxide synthase (iNOS) and subsequent nitric oxide (NO) production. This NO, in turn, plays a multifaceted role in cartilage degradation, inducing chondrocyte apoptosis, inhibiting proteoglycan synthesis, and enhancing MMP activity. Notably, the synergy between NO and PGE2 exacerbates the process of cartilage degradation, further exacerbating the pathophysiological cascade [3].

(c) PGE2-mediated Synovial inflammation

In osteoarthritic synovium, increased levels of IL-1β and TNF-α stimulate the expression of cyclooxygenase (COX)-2 and the ensuing production of prostaglandin E2 (PGE2). PGE2 augments the expression of proteolytic enzymes, including matrix metalloproteinases (MMPs) and urokinase-type plasminogen activator (uPA), thereby contributing to the destruction of the articular joint [3].

(d) PGE2-mediated Subchondral bone resorption

In chondrocytes and osteoblasts, IL-1β stimulates the expression of cyclooxygenase (COX)-2, which results in the synthesis of receptor activator of NF-κB ligand (RANKL). Then, RANKL promotes the development of osteoclast precursor cells into quiescent osteoclasts. Moreover, it causes quiescent osteoclasts to express COX-2 and prostaglandin E2 (PGE2), which in return stimulates osteoclasts in an autocrine and paracrine way. In these two ways, number osteoclast increases extensively and that leads to expression of Carbonic anhydrase II. Carbonic anhydrase II, which is extensively expressed on the inner surface of osteoclasts, converts CO2 and H2O into bicarbonate and H+. Acidification in the resorption pit is essential to dissolve the inorganic matrix of bone [3].

Clinical therapy for osteoarthritis

As of now, there is no definitive cure for OA. Treatment strategies for OA encompass physical interventions, pharmacological therapies, and surgical interventions [4].

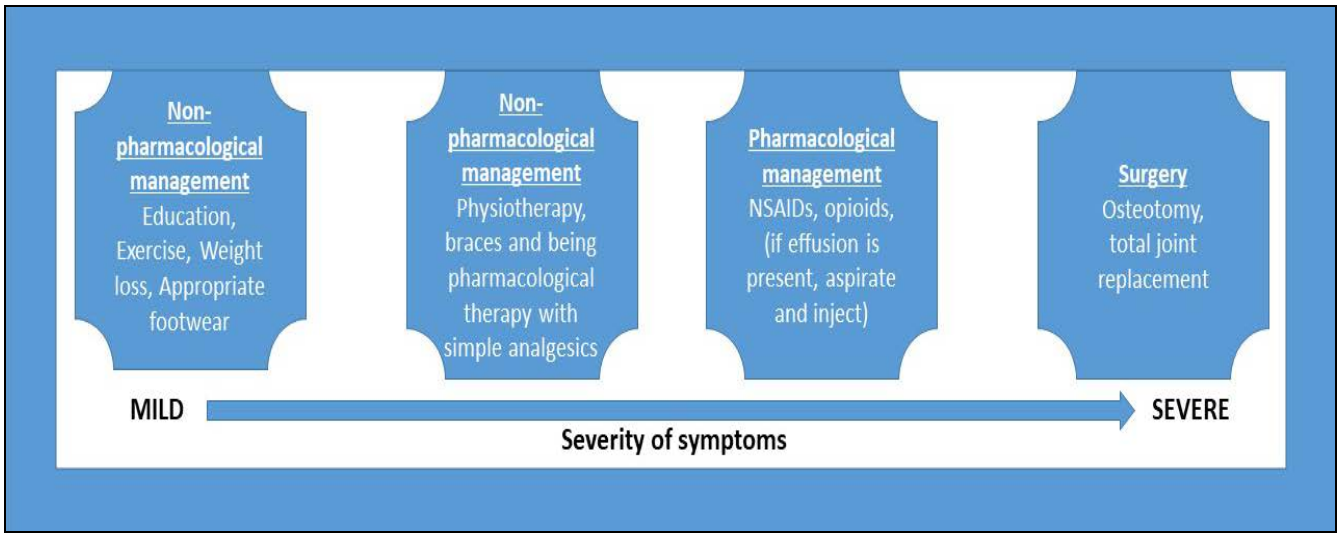

Fig 2: Clinical therapies for osteoarthritis

Table 1: Limitations of currently used treatment options [5]

Drug	Limitations
Paracetamol/ acetaminophen	In patients with comorbidities, there is an increased risk of gastrointestinal complications and multi-organ failure. With supratherapeutic doses of paracetamol ingested with a potentially increased risk of cardiovascular events at a rate similar to that with non-steroidal anti-inflammatory drugs. Meta-analysis has found a low-level effect for pain management in OA, with no benefit over placebo.
Non-steroidal anti-inflammatory drugs	Whereas NSAIDs have shown efficacy superior to paracetamol, the potential adverse effects of routine NSAIDs are well documented. Over 16,500 deaths and hospital admissions per year in the USA are due to NSAIDs-related gastrointestinal toxicity. Associated cardiovascular and renal risks exist even with a better safety profile of COX-2 inhibitors. The concomitant use of a proton pump inhibitor is recommended especially with non-selective NSAIDs, significantly reducing the relative and absolute risk of dyspepsia
Opioids	In comparison to placebo, patients exhibited a fourfold increase in the likelihood of treatment discontinuation attributable to adverse events. Additionally, opioids are associated with elevated risks of cardiovascular incidents and fractures. Despite offering a modest to moderate overall therapeutic benefit, the potential for significant harm underscores the recommendation against their prolonged utilization by the majority of clinical guidelines.
Corticosteroids (intra-articular injection)	Intra-articular corticosteroid injections offer short-term pain relief (typically lasting 1-2 weeks in randomized controlled trials) and enhanced function for osteoarthritis (OA) patients experiencing acute exacerbations accompanied by joint effusions and localized inflammation. Nevertheless, administering intra-articular injections more frequently than once every 4 months may lead to cartilage and joint deterioration, along with an elevated risk of infection.
Hyaluronic acid (intra-articular injection)	Hyaluronic acid is a critical constituent component of normal synovial fluid and a contributor to joint homeostasis. In OA, the concentration of endogenous intra-articular hyaluronic acid is decreased; thus, the viscoelasticity of synovial fluid is also reduced. The original rationale for intra-articular hyaluronic acid injection is based on this, but the effects to date suggest little benefit over a placebo from several meta-analyses
Duloxetine	Common adverse effects include nausea, constipation, fatigue, xerostomia, and decreased appetite

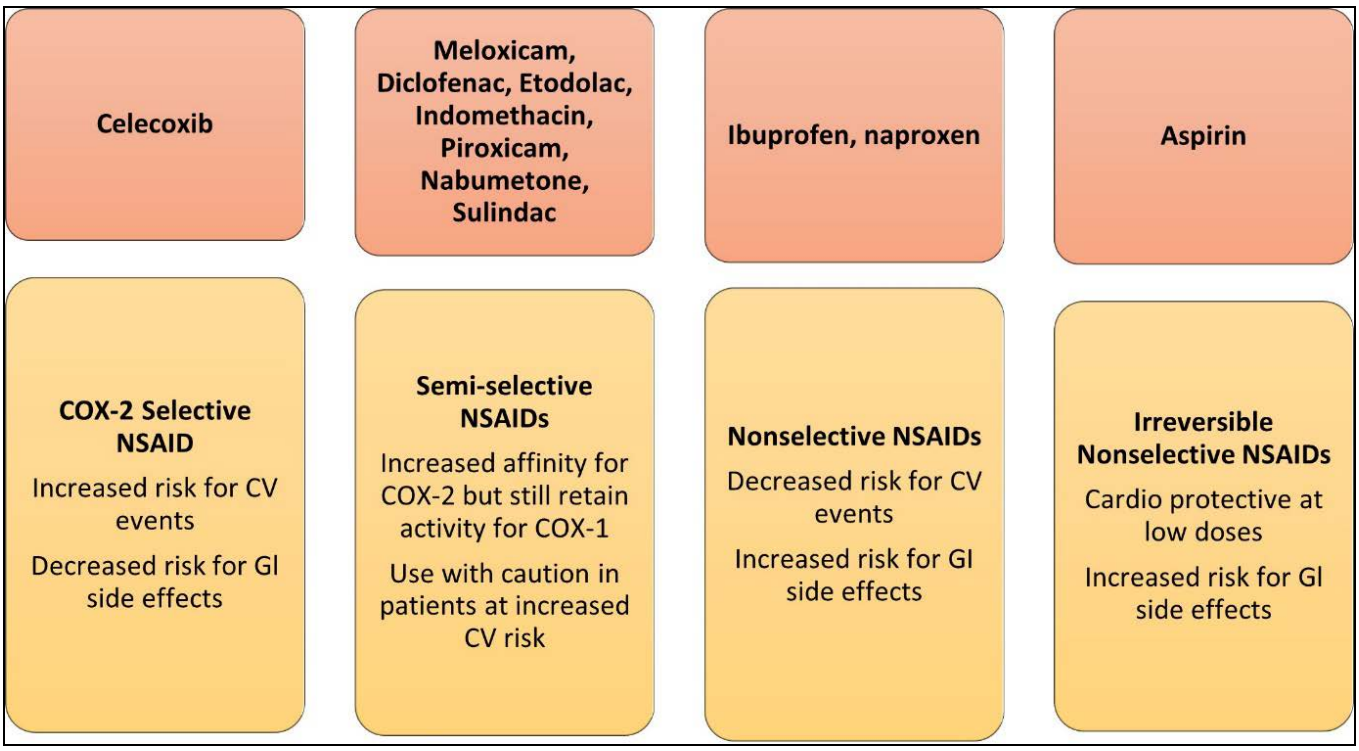

Fig 3: ADR comparison of currently available NSAIDs

Polmacoxib

Polmacoxib is the first, tissue-selective and once-a-day osteoarthritis drug with a novel mode of action that specifically targets affected joints to relieve pain and restore mobility.

Polmacoxib is a first-in-class dual preferential COX2/carbonic anhydrase I/II inhibitor.

It is approved for osteoarthritis treatment in South Korea & Turkey and the MENA region covering 19 countries and it has been recently approved in India.

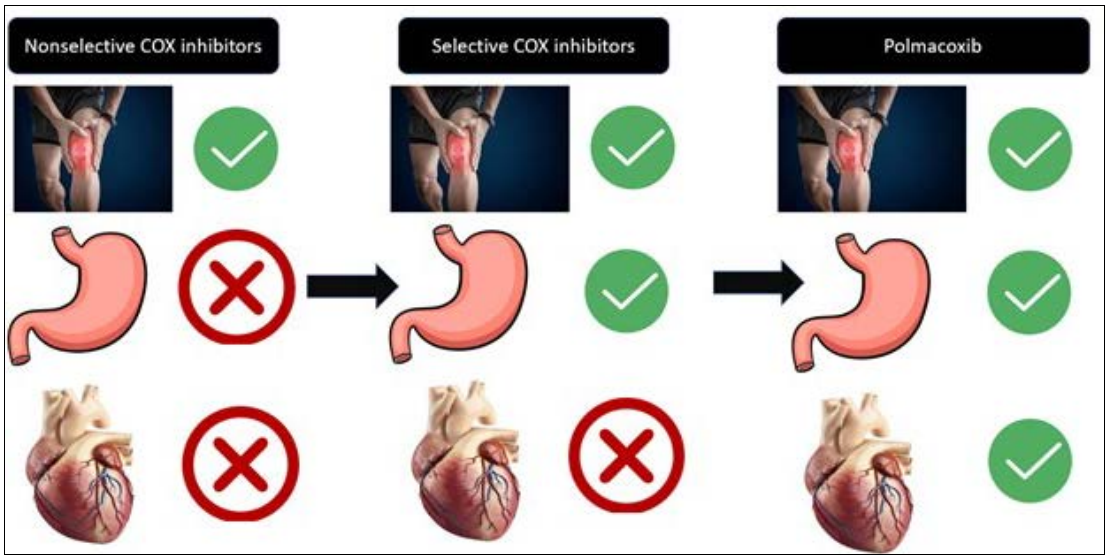

Fig 4: Evolution of NSAIDs

Mechanism of action of Polmacoxib [6]**:**

Polmacoxib, is also a selective cyclooxygenase-2 (COX-2) inhibitor, a type of non-steroidal anti-inflammatory drug, and acts as a potent inhibitor of several carbonic anhydrase isoforms, due to its aryl sulfonamide moiety inhibition of COX-2.

Unlike other NSAIDs, Polmacoxib has a dual mode of action:

- Inhibition of COX-2
- Binding to carbonic anhydrase (CA) with high affinity.

In instances where both COX-2 and CA (carbonic anhydrase) are concurrently present, the strong affinity of polmacoxib for CA diminishes its COX-2 inhibitory efficacy.

Polmacoxib does not inhibit COX-2 in CA-rich tissues (e.g. CV system), but it fully inhibits COX-2 in CA-deficient tissues (inflamed joints).

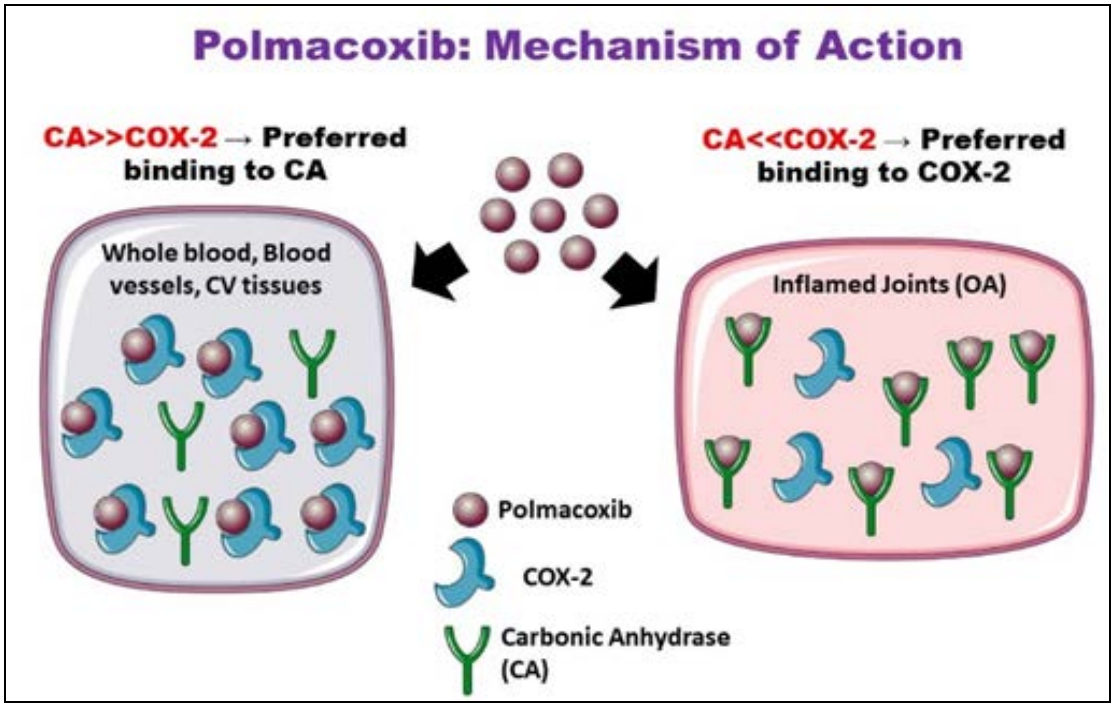

Fig 5: Polmacoxib mechanism of action

Polmacoxib has unique binding to carbonic anhydrase (CA) [4]

- Polmacoxib showed the strongest inhibitory activity against CA, compared to other coxibs like celecoxib,
- Polmacoxib inhibits CA more effectively than celecoxib and valdecoxib,
- The dual action mechanism of Polmacoxib may minimize the adverse CV effects of COX-2 inhibition,
- While polmacoxib potentially remains in a mixed state with CA, low-dose administration of polmacoxib is thought to have a minor influence on total CA function in the circulatory system,
- In the active site, the three molecules of polmacoxib organize themselves along hydrophobic interaction as "stack-on-formation", and fully occupy a cone-shaped active pocket in CA
- The inhibitory activity of polmacoxib against COX-2 is inherited by increasing the concentration of CA.

Pharmacokinetics of Polmacoxib [7]

Absorption

Table 2: Different absorption parameters and their value

Variable(unit)	Reference drug	Test drug
Cmax(ng/mL)	295.41 ± 40.79 (13.81)	321.36 ± 36.09 (11.23)
AUClast (ng·hr/mL)	68544.30 ± 15046.80 (21.95)	72423.10 ± 15241.00 (21.04)
AUCinf (ng·hr/mL)	75886.70 ± 19347.50 (25.50)	79956.30 ± 20741.10 (25.94)
t1/2(hr)	187.35 ± 39.76 (39.76)	183.29 ± 46.70 (46.70)
Tmax (hr)median(range)†	4.00 [2.000~10.000]	3.50 [1.000~24.100]
Arithmetic (mean ± SD) (CV%) † Median value [Minimum value ~ Maximum value]		

Distribution: At this time, the mean steady-state C max was 2,054 ng/mL in whole blood and 40 to 51 ng/mL in plasma
Metabolism: This drug is mainly metabolized by CYP3A4
Excretion: Mainly through feces, less through urine

Polmacoxib-associated cardiovascular safety [7]
Polmacoxib tissue-selective-COX2-inhibition mechanism is projected to provide a meaningful enhancement of cardiovascular safety over currently available NSAIDs.
Polmacoxib substantially inhibits thromboxane but does not inhibit prostacyclin in clinically recommended dose groups.
CA promotes cardiomyocyte hypertrophy while polmacoxib can prevent cardiomyocyte hypertrophy through carbonic anhydrase inhibitory function.

Polmacoxib-associated Gastrointestinal & renal safety [8]
CA is abundant in GI tract, lung, liver, gallbladder, kidney, urinary bladder, bone marrow, and brain.
The GI tract and kidney are thought to be the primary organs where NSAIDS including coxibs exhibit side effects.
Consequently, a COX-2 inhibitor with CA binding potential would show attenuated COX-2 binding in the GI tract and kidney (due to its competition by CAs), which could be translated into reduced adverse effects associated with COX-2 inhibition in those organs.
Polmacoxib demonstrated a notable enhancement in gastrointestinal safety in comparison to conventional NSAIDs that are available in the market.

Table 3: The comparative advantage with COX-2 inhibitors & Other NSAIDS [7, 8]

Parameters	Naproxen, Ibuprofen, diclofenac	Etoricoxib	Celecoxib	Polmacoxib
Classification	Non-preferential NSAID	COX-2 inhibitor	COX-2 inhibitor	Tissue selective COX-2 inhibitor
Indication	Osteoarthritis & Others	Osteoarthritis	Osteoarthritis & Others	Osteoarthritis
Amount	75-2,400 mg/day	30 mg	200 mg	2mg
Dose	2-4 times a day	Once a day	Once a day	Once a day
Half-life	6-12 hrs	22 hrs	11 hrs	5 days
Efficacy	Non-inferior to traditional NSAID & Celecoxib	Non-inferior to traditional NSAID	Non-inferior to traditional NSAID and Celecoxib	Non-inferior to Celecoxib
Gastrointestinal safety	Inferior to Traditional NSAID	Similar with Celecoxib	Superior to traditional NSAIDs	Similar with Celecoxib
CV side effects	Moderate or high	High	Moderate	None observed to date

Polmacoxib Clinical Studies

Table 4: Summary of Polmacoxib studies

Clinical Studies	Summary
Phase 1 study[9]	• Whole blood concentrations were 50 to 70 times higher than plasma concentrations in all dose cohorts in both male and female subjects. • There were no clinically significant drug-related changes in blood pressure between treatment groups. • The most frequently encountered adverse events were aphthous stomatitis and dyspepsia. • It suppressed TXB2 and PGE2 at all doses, and only the highest dose suppressed the urinary excretion of the urinary prostacyclin metabolite.
Phase 2a study[10]	• The high dose group (8 mg) showed more than a 2-fold greater magnitude of improvement than the placebo group on the primary endpoint of change in the WOMAC score from baseline to Day 21. • Weekly pain relief scores showed statistically significant improvements at Days 7, 14, 21, and 28 ($p<0.05$ at all time periods) which demonstrated that Polmacoxib had an early onset of activity and provided sustained treatment benefits over the entire treatment period. • No relevant treatment group differences were noted for any other vital sign, clinical laboratory parameter, or ECG parameter. • No subject experienced gastrointestinal bleeding or other clinically relevant adverse GI side effects.
Phase 2b study[11]	• Polmacoxib doses of 2 mg and 4 mg exhibited non-inferiority to celecoxib 200 mg across all efficacy assessments. • Polmacoxib 2 mg dose produced higher efficacy than celecoxib 200 mg, though not statistically significant (the study was not powered for superiority) • There were no withdrawals from the study due to ineffectiveness. • The adverse effect profile of polmacoxib 2 mg is favorable (similar to celecoxib 200 mg) • Polmacoxib 2 mg dose selected for Phase 3 clinical studies
Phase 3 study[6]	• Efficacy (6-week study) The superiority of polmacoxib 2 mg once-daily vs. placebo Non-inferiority of polmacoxib 2 mg once-daily vs. celecoxib 200 mg once-daily • Long Term Safety (6-month study) There were no drug-related major adverse events in either the celecoxib or polmacoxib groups. Most adverse events observed were mild to moderate and were anticipated within the context of this trial

Phase 3 Study [6]
Title of study
A Double-blind, Randomized, Multicenter, Active and Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of CG100649 in Osteoarthritis Patients

The objective of the study

The 6-week Efficacy Study aimed to assess the analgesic efficacy and safety of polmacoxib 2 mg compared to celecoxib 200 mg, as well as the superiority of polmacoxib 2 mg over placebo when administered once daily to individuals with hip or knee osteoarthritis throughout the 6-week treatment period.

The Extension Study aimed to collect a total of 24 weeks of safety data from subjects who volunteered to participate in the extension.

Results

Polmacoxib showed superior efficacy over celecoxib with statistical significance (P=0.005)

71.9% of subjects taking polmacoxib experienced improvement in signs and symptoms of osteoarthritis

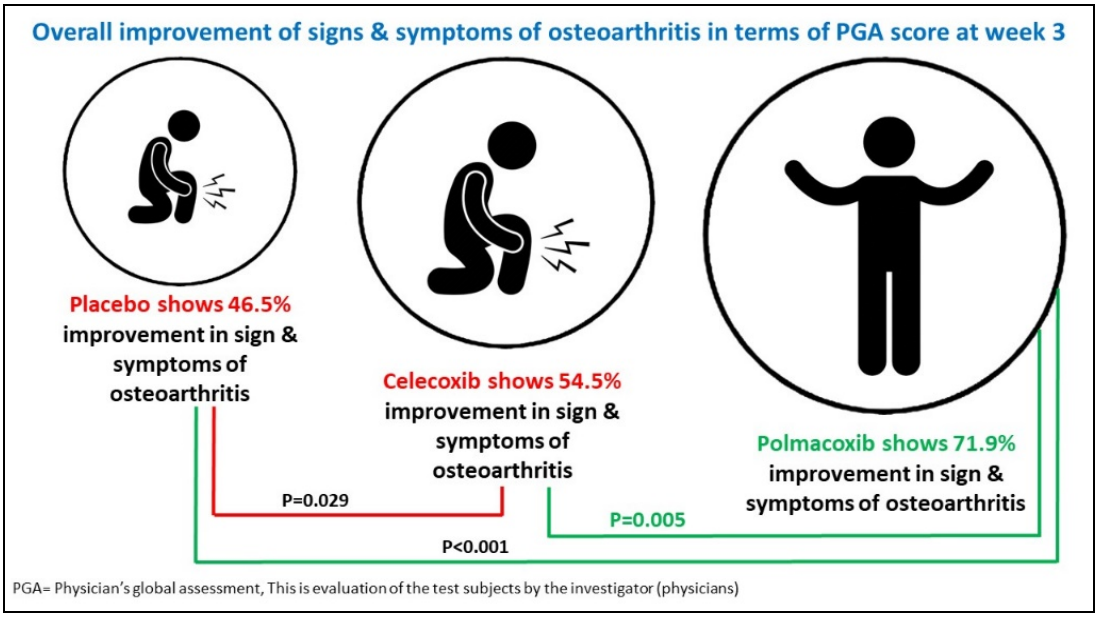

Fig 6: Polmacoxib showed superior efficacy over celecoxib

- Polmacoxib showed Quicker Onset of Relief from osteoarthritis symptoms over celecoxib
- Polmacoxib showed statistically significant superiority over placebo at Week 3 (P=0.003), but celecoxib did NOT show statistically significant differentiation from placebo at Week 3 (P=0.069).

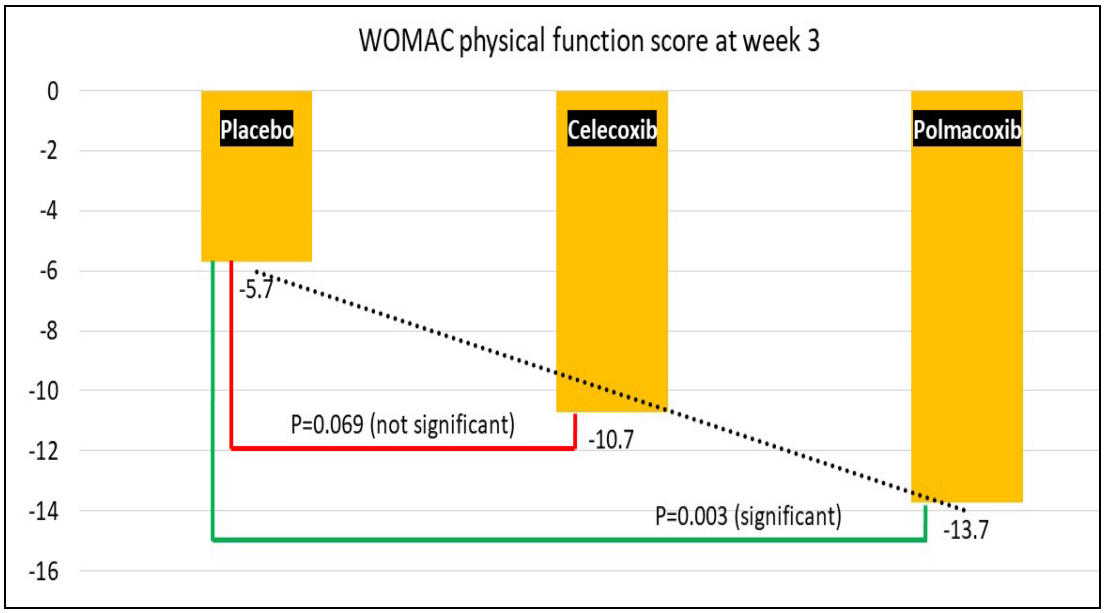

Fig 7: Polmacoxib showed a quicker onset of relief from osteoarthritis symptoms over celecoxib

Polmacoxib demonstrated non-inferior or better efficacy against celecoxib in all other efficacy endpoints including WOMAC-pain and stiffness subscales at week 3 and week 6.

Safety Results from the 6-week Efficacy Study

- No serious adverse events related to the medication occurred in either the Polmacoxib or celecoxib treatment groups.
- Most adverse events were mild to moderate and were anticipated within the scope of this trial.
- There were no notable differences of statistical significance observed among all three groups.
- Polmacoxib has successfully achieved the clinical study endpoints. The 2 mg dosage was well tolerated, and over the 6-week treatment period, demonstrated comparable analgesic efficacy and safety to celecoxib 200 mg, with

superior analgesic efficacy compared to placebo.
- Nevertheless, considering the secondary endpoints of WOMAC-Physical function and PGA at Week 3, polmacoxib exhibited a superior efficacy profile compared to celecoxib. This implies that the 2 mg dosage of polmacoxib may lead to a faster onset of relief from the manifestations of osteoarthritis when compared to celecoxib 200 mg.
- The Treatment-Emergent Adverse Events (TEAEs) documented in this study exhibited primarily mild manifestations consistent with the anticipated pharmacological profile of COX-2 inhibitor medications.
- There were not clinically significant or statistically meaningful differences in the incidence of TEAEs among the groups treated with polmacoxib 2 mg, celecoxib 200 mg, or placebo.

Safety conclusions from safety extension study (24 weeks) only polmacoxib 2mg was administered (open-label, single arm)
- No serious adverse events related to the drug were observed.
- Throughout the safety extension study, the 2mg dosage of polmacoxib was well-tolerated, with TEAEs generally presenting as mild.
- There were no notable increases in the incidence of any TEAEs during the 18-week safety extension period or the combined 24-week extended safety period.
- The study of clinical laboratory tests, vital signs, ECGs, and physical examination data yielded no clinically significant findings.

Indication [12]
Polmacoxib is indicated for the treatment of idiopathic (primary) osteoarthritis of the hip/knee.

Contraindications [12]
Polmacoxib should be used with extreme caution and avoided altogether in individuals with a history of hypersensitivity reactions to the drug or sulphonamides, as well as those who have experienced allergic reactions to aspirin, other NSAIDs, or COX-2 inhibitors, including those with asthma, acute rhinitis, nasal polyps, angioedema, or urticaria. Additionally, patients with poorly controlled hypertension despite antihypertensive therapy, edema or fluid retention, hepatic or renal impairment, active peptic ulcer or gastrointestinal bleeding, and inflammatory bowel diseases like Crohn's disease or ulcerative colitis should avoid Polmacoxib due to potential exacerbation of these conditions. Furthermore, individuals with congestive heart failure (NYHA II-IV) or established ischemic heart disease, peripheral arterial disease, or cerebrovascular disease are at increased risk of adverse cardiovascular events with Polmacoxib use. The drug is contraindicated in pregnant or nursing women due to potential harm to the foetus or infant. Polmacoxib should not be used for pain management before or after coronary artery bypass surgery (CABG) due to increased cardiovascular risks. Patients with hyperkalemia or coagulation disorders, or those receiving anticoagulants, should also avoid Polmacoxib due to potential exacerbation of these conditions and increased risk of adverse effects. Healthcare providers must carefully evaluate patients for these contraindications and closely monitor them for any adverse reactions while using Polmacoxib.

Possible drug-drug interactions of Polmacoxib [12]
Since this drug is mainly metabolized by CYP3A4 in the liver, caution should be exercised when administered concurrently with drugs that inhibit CYP3A4.

- **Interaction with ketoconazole or erythromycin**

When ketoconazole 400 mg was administered concurrently once a day, ketoconazole inhibited the metabolism of this drug through CYP3A4 and increased the AUC of this drug by 1.3 times. Therefore, when starting concomitant administration of this drug, a lower dose than the usual dose should be considered. Also, the Tmax (median) was 71.9 hours when this drug and ketoconazole were administered concurrently, which was longer than 9 hours when administered alone, so caution should be exercised that treatment response time may be delayed when administered concurrently with ketoconazole.

- **Interaction with ACE inhibitors or angiotensin II receptor blockers**

Since the antihypertensive effect of an ACE inhibitor or angiotensin II receptor blocker may be reduced by nonsteroidal anti-inflammatory drugs, including this drug, this interaction should be taken into consideration when administering this drug and an ACE inhibitor or angiotensin II receptor blocker in combination. Interaction with Diuretic:
In the case of nonsteroidal anti-inflammatory drugs, including this drug, it has been confirmed that the natriuretic effect of furosemide and thiazide diuretics may be reduced in some patients by inhibition of prostaglandin synthesis in the kidney. Therefore, during concomitant administration of these drugs and nonsteroidal anti-inflammatory drugs, including this drug, patients should be closely monitored for signs of renal failure.

- **Interaction with Aspirin**

There is no consistent evidence that administered concurrently with aspirin may reduce the risk of serious cardiovascular thrombotic reactions associated with the use of nonsteroidal anti-inflammatory drugs, including this drug. Selective COX-2 inhibitors may be administered concurrently with low-dose aspirin (not more than 325 mg per day), but it has been reported that the incidence of gastrointestinal adverse events (gastrointestinal ulcers) or other gastrointestinal complications is higher than when this drug alone is administered. Since this drug has not been studied for its effect on platelets, it cannot be used as a substitute for aspirin as a preventive therapy for the cardiovascular system.

Conclusion
In conclusion, Polmacoxib, a novel NSAID, exhibits remarkable efficacy in treating osteoarthritis (OA), surpassing the performance of Celecoxib by demonstrating faster relief onset and achieving superior Physician Global Assessment (PGA) scores with statistical significance. Its potency as the most potent NSAID and COX-2 inhibitor underscores its effectiveness in inhibiting key enzymes implicated in OA progression. Notably, Polmacoxib exerts disease-modifying effects by inhibiting carbonic anhydrase (CA) and prostaglandin E2 (PGE2), potentially altering the course of the disease. Remarkably, therapeutic efficacy in OA can be attained with just a 2 mg/day dose, the lowest among all known NSAIDs, coupled with the convenience of once-a-day dosing. Its improved gastrointestinal safety profile eliminates the need for adjunctive GI protective agents, while its unique mode of action promises enhanced cardiovascular safety

compared to existing NSAID options. Polmacoxib stands as a promising advancement in OA management, offering unparalleled efficacy, safety, and convenience.

References

1. Yao Q, Wu X, Tao C, Zhang X, Hu J, Zhou Y. Osteoarthritis: Pathogenic signaling pathways and therapeutic targets. Signal Transduct Target Ther. 2023;8(1):56. DOI: 10.1038/s41392-023-01008-7.
2. Or BD, Rael LT, Thomas GW, Brody EN. Inflammatory pathways in knee osteoarthritis: Potential targets for treatment. Curr Rheumatol Rev. 2015;11(1):50-58. DOI: 10.2174/1573397111666141024114065.
3. Zweers MC, Boer DTN, Roon VJ, Bijlsma JW, Lafeber FP, Mastbergen SC. Celecoxib: Considerations regarding its potential disease-modifying properties in osteoarthritis. Arthritis Res Ther. 2011;13(5):239. DOI: 10.1186/ar3458.
4. Hunter DJ, Lo GH. The management of osteoarthritis: An overview and call to appropriate conservative treatment. Rheum Dis Clin North Am. 2008;34(3):689-712. DOI: 10.1016/j.rdc.2008.06.002.
5. Yu SP, Hunter DJ. Emerging drugs for the treatment of knee osteoarthritis. Expert Opin Emerg Drugs. 2015;20(3):361-78. DOI: 10.1517/14728214.2015.1044641.
6. Lee M, Yoo J, Kim JG, Kim YC, Kim YS, Kim HY, *et al*. A randomized, multicenter, phase III trial to evaluate the efficacy and safety of polmacoxib compared with celecoxib and placebo for patients with osteoarthritis. Clin Orthop Surg. 2017;9(4):439-57. DOI: 10.4055/cios.2017.9.4.439.
7. Kim HT, Cha H, Hwang KY. Structural insight into the inhibition of carbonic anhydrase by the COX-2-selective inhibitor polmacoxib (CG100649). Biochem Biophys Res Commun. 2016;478(1):1-6. DOI: 10.1016/j.bbrc.2016.07.074.
8. Hunter DJ, Lo GH. The management of osteoarthritis: an overview and call to appropriate conservative treatment. Rheum Dis Clin North Am. 2008;34(3):689-712. DOI: 10.1016/j.rdc.2008.06.002.
9. Kim MJ, Lim HS, Jin S, Kim Y, Kim H, Lee Y, *et al*. Pharmacokinetic, pharmacodynamic, and safety/ tolerability profiles of CG100649, a novel COX-2 inhibitor: results of a phase I, randomized, multiple-dose study in healthy Korean men and women. Clin Ther. 2015;37(1):197-210. DOI: 10.1016/j.clinthera.2014.12.007.
10. Szombati I. CG100649, a tissue-specific dual inhibitor of COX-2 and carbonic anhydrase: Phase 2A clinical trial in hip & knee osteoarthritis. Osteoarthritis Cartilage. 2009;17(S1). Available from: https://www.academia.edu/77919738/324_CG100649_a_Tissue_Specific_Dual_Inhibitor_of_COX_2_and_Carbonic_Anhydrase_Phase_2A_Clinical_Trial_in_Hip_and_Knee_Osteoarthritis.
11. Easwaran R, Mistry UK, Bhole M, Peethambaran K, Easwaran R, Mistry UK, *et al*. Polmacoxib: A review of the newer non-steroidal anti-inflammatory drug in osteoarthritis. Cureus. 2024;16(4). Available from: https://www.cureus.com/articles/229040-polmacoxib-a-review-of-the-newer-non-steroidal-anti-inflammatory-drug-in-osteoarthritis.
12. Acelex.co.kr. Polmacoxib prescribing information. Available from: http://acelex.co.kr/acelex-side/prescribing-information-and-warnings/?ckattempt=2. Accessed July 5, 2024.

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