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Firsekibart in Reducing High-Sensitivity C-reactive Protein Levels of Gout

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Abstract: *Background*: Gout remains a challenging condition with rising global prevalence. The IL-1β drives disease pathogenesis, and high-sensitivity C-reactive protein (hsCRP) correlates with gout activity. Firsekibart, a novel fully human anti-IL-1β monoclonal antibody, has proven its efficacy on gout, while the data on reducing hsCRP remains limited. *Methods*: This multicenter, randomized, double-blind phase III trial compared Firsekibart (200 mg subcutaneous) with compound betamethasone (7 mg intramuscular) in acute gout patients who were contraindicated to, intolerant of, or unresponsive to NSAIDs and/or colchicine. Serum hsCRP levels were measured at 72 hours, 7 days post-dose, and 4 weeks post-dose. *Results*: Both groups achieved comparable hsCRP reduction at 72 hours (Firsekibart: −14.68 mg/L [95% CI: −15.75, −13.61] vs. compound betamethasone: −14.58 mg/L [−15.66, −13.50]; P=0.898). Firsekibart demonstrated better sustained suppression at 7 days post-dose (−18.63 vs. −9.28 mg/L, P<0.001) and 4 weeks (−18.37 vs. −12.65 mg/L, P<0.001). *Conclusion*: Compared with compound betamethasone, Firsekibart showed a longer-lasting anti-inflammatory effect on gout patients. This result may provide significant clinical value in the management of gout and its associated complications.

Keywords: Gout; Anti-IL-1β monoclonal antibody; Firsekibart; hsCRP; Inflammation

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1. Introduction

The incidence of gout has steadily increased over the past decades, yet its management remains suboptimal [1]. The prevalence of gout is higher in developed countries and is closely associated with genetic factors, high-purine diet, metabolic syndrome, alcohol consumption, and renal dysfunction. Gout patients often present with comorbidities, including diabetes, hypertension, and cardiovascular diseases, with elevated serum urate levels being the core pathogenic factor. Urate crystal deposition not only triggers joint inflammation but also directly contributes to hypertension and atherosclerosis development through activation of the renin-angiotensin system and induction of endothelial dysfunction [2–4].

The inflammatory cascade triggered by monosodium urate (MSU) crystals represents the cornerstone of gout pathophysiology. MSU crystals activate the NLRP3 inflammasome, leading to caspase-1-mediated processing and secretion of interleukin-1β (IL-1β) [5–6]. As the principal inflammatory mediator in gout, IL-1β initiates downstream signaling through Nuclear Factor-κB (NF-κB) and Mitogen-Activated Protein Kinase (MAPK) pathways, resulting in transcriptional upregulation of proinflammatory cytokines (including TNF-α and IL-6) and chemokines [7]. These molecular mediators recruit and activate neutrophils, which release reactive oxygen species and proteolytic enzymes that cause tissue damage and amplify the inflammatory response [8]. This process establishes a self-perpetuating cycle wherein sustained NLRP3 inflammasome activation maintains IL-1β production, thereby reinforcing the inflammatory cascade and contributing to disease progression [7].

High-sensitivity C-reactive protein (hsCRP) serves as an established biomarker for low-grade systemic inflammation and cardiovascular risk assessment [8]. In patients with gout, reductions in serum urate levels correlate with decreased hsCRP concentrations, suggesting its potential utility as a therapeutic response marker [9]. Elevated hsCRP levels may help identify patients with inflammatory phenotypes who could benefit from targeted anti-inflammatory therapies [10].

Clinical evidence demonstrates that canakinumab, an anti-IL-1β monoclonal antibody, provides rapid pain relief and reduces recurrence risk in refractory gout arthritis [11]. The CANTOS trial revealed that IL-1β inhibition with canakinumab significantly lowered cardiovascular event rates, particularly in patients achieving hsCRP levels below 2 mg/L after initial treatment [12]. Rilonacept and Anakinra, IL-1 receptor antagonist, showed efficacy in CRP reduction while relieving symptoms of gout patients [13–15]. HsCRP is widely acknowledged as a marker to evaluate the efficacy of anti-inflammatory drugs.

Targeted inhibition of IL-1β has demonstrated therapeutic efficacy in gout management [6, 16]. Current clinical guidelines recommend anti-IL-1β therapy for acute gouty arthritis patients with contraindications, intolerance, or inadequate response to NSAIDs and/or colchicine [17]. Firsekibart (previously called Genakumab), a novel fully human monoclonal antibody against IL-1β, represents a promising therapeutic alternative for gout patients [18]. However, existing evidence regarding Firsekibart's effects on hsCRP modulation in gout remains limited and requires further investigation.

This post-hoc analysis evaluated the efficacy of Firsekibart versus compound betamethasone (CB) in reducing hsCRP levels at 72 hours, 7 days post-dose, and 4 weeks post-treatment, presenting more details for the anti-inflammatory effects of Firsekibart.

2. Materials and methods

2.1. Study design

This was a multicenter, randomized, double-blind, active-controlled phase III trial conducted from January 2023 to June 2024 across 51 centers in China. The trial protocol was approved by the Ethics Review Committee of Huashan Hospital Affiliated to Fudan University (Ethics Number: 2022 (976)) and conformed to the principles of the Declaration of Helsinki. All participants provided written informed consent before enrollment.

2.2. Participants

Patients who met the 2015 American College of Rheumatology (ACR) preliminary criteria for the classification of acute primary gouty arthritis (GA) were screened for eligibility. Key inclusion criteria included patients who:

1) Aged 18 to 75 years. 2) Contraindicated for, intolerant of, or unresponsive to NSAIDs and/or colchicine. 3) Experienced ≥2 gout flares in the preceding year. Key exclusion criteria were: 1) Secondary gout (such as rheumatoid arthritis, psoriatic arthritis). 2) Severe organ dysfunction (including hepatic cirrhosis, New York Heart Association class III–IV heart failure, or estimated glomerular filtration rate <30 mL/min/1.73 m2). 3) Active systemic infection or history of recurrent infections. 4) Pregnant or breastfeeding women. 5) Participation in another interventional clinical trial within 30 days before enrollment. 6) History of malignancy within the past 5 years.

2.3. Randomization

A total of 313 patients were randomized with a ratio of 1:1 to receive a single subcutaneous dose of Firsekibart (200 mg) or intramuscular CB (7 mg), with VAS (visual analog scale) scores at screening (50 ≤VAS < 70 mm vs. 70 ≤VAS < 100 mm) as the stratification factor. Randomization was conducted through an Interactive Web Response System.

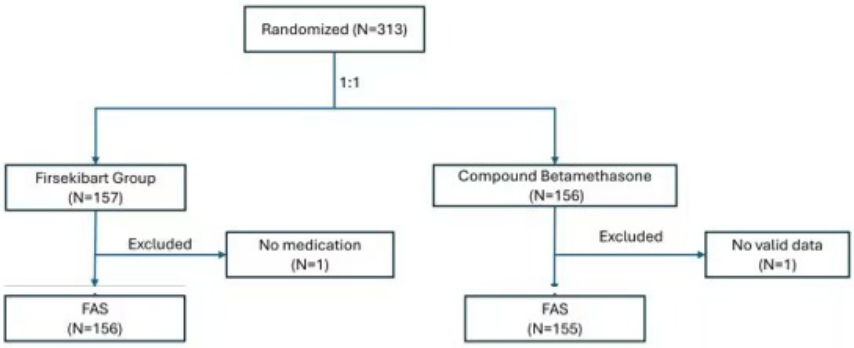


Figure 1. Flowchart for this post-hoc analysis of hsCRP

2.4. Procedure

Measuring hsCRP levels was one of the exploratory endpoints in this phase III trial. A 2 mL serum sample from venous blood was collected to measure hsCRP levels. Serum hsCRP levels were measured at baseline, 72 hours, 7 days, and 4 weeks post-dose using immunoturbidimetry with a hsCRP kit.

2.5. Statistical analysis

Continuous variables were reported as mean ± SD, and categorical variables as counts (%). HsCRP differences were analyzed using an ANCOVA (Analysis of Covariance) model, adjusting for baseline hsCRP values and VAS scores. A two-sided $P < 0.05$ was considered significant. The statistical analyses were conducted using SAS (9.4).

3. Results

3.1. Baseline characteristics

313 patients were randomized , and 311 were included in FAS (**Figure 1**). The mean ages of 45.7 ± 13.73 years and 44.1 ± 12.16 years in Firsekibart and the CB groups, respectively. A majority of patients in both groups had a history of ≥ 3 gout flares in the previous year. The presence of tophi was noted in 39.1% of the Firsekibart group and 41.9% of the CB group. The baseline characteristics of the patients were well-balanced between the two groups (**Table 1**).

Table 1. Baseline characteristics and efficacy of Firsekibart/Compound betamethasone-treated patients (FAS)

	Firsekibart (N = 156)	Compound betamethasone (N = 155)
Male (%)	100	97.4
Age (years), mean ±SD	45.7 ± 13.73	44.1 ± 12.16
BMI (kg/m^2), mean ±SD	27.45 ± 3.89	27.55 ± 3.79
≥ 3 flares reported during the prior one year N (%)	143 (91.7)	135 (87.1)
Percentage of patients with tophus N (%)	61 (39.1)	65 (41.9)

BMI: Body Mass Index; FAS: Full Analysis Set

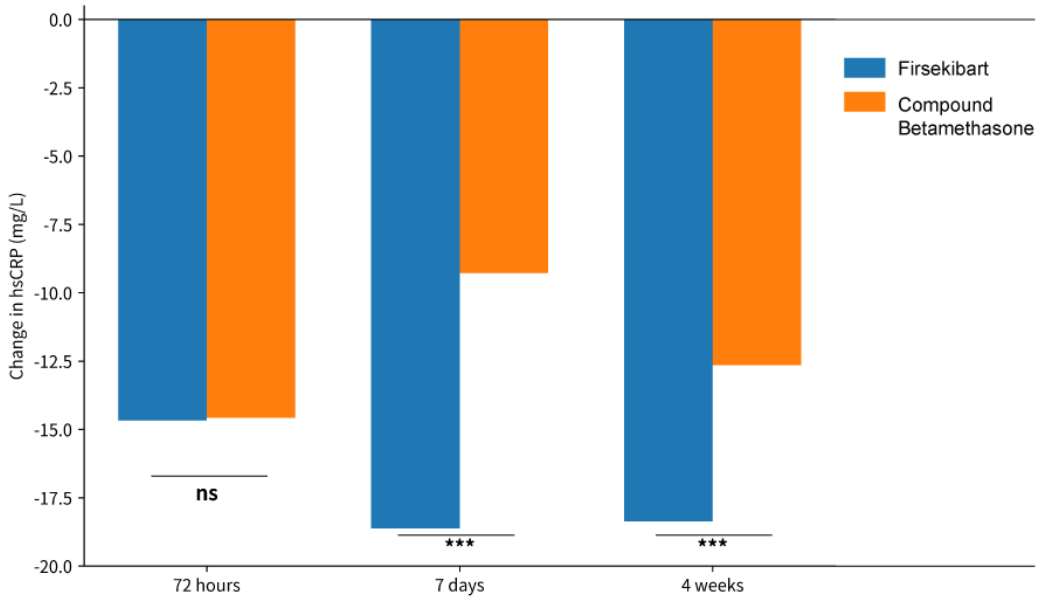
3.2. Serum HsCRP levels over time

At 72 hours, both groups showed comparable reductions in hsCRP, and the reduction was -14.68 mg/L (95% confidence interval [CI]: -15.75, -13.61) in the Firsekibart group versus -14.58 mg/L (95% CI: -15.66, -13.50) in the CB group (P = 0.8980), respectively. While both treatments showed rapid initial declines in hsCRP, the Firsekibart group maintained lower hsCRP levels at day 8 (7 days post-dose) (-18.63 mg/L [95% CI: -21.96, -15.30] versus -9.28 mg/L [95% CI: -12.64, -5.92] in the CB group, P < 0.001). This superiority also persisted at 4 weeks (-18.37 mg/L [95% CI: -20.24, -16.50] versus -12.65 mg/L [95% CI: -14.73, -10.57] in the CB group, P < 0.001). The change of hsCRP suggested a prolonged anti-inflammatory efficacy in the Firsekibart group. (**Table 2**, **Figure 2**)

Table 2. Comparison of hs-CRP levels and changes between treatment groups

Time point/interval	Firsekibart	Compound betamethasone	*P*-value
Absolute values (mg/L), mean ± SD			
Baseline	19.35 ± 36.15	23.05 ± 37.50	-
72 hours	6.01 ± 7.61	6.42 ± 9.82	-
7 days	1.91 ± 2.74	11.53 ± 30.17	-
4 weeks	2.52 ± 11.29	8.35 ± 12.42	-
Change from baseline (mg/L),LSM (95 CI%)			
72 hours	-14.68 (-15.75, -13.61)	-14.58 (-15.66, -13.50)	0.898
7 days	-18.63 (-21.96, -15.30)	-9.28 (-12.64, -5.92)	<0.001
4 weeks	-18.37 (-20.24, -16.50)	-12.65 (-14.73, -10.57)	<0.001

SD: Standard Deviation; LSM: Least Squares Mean; CI: Confidence Interval



ns: Not significant; "***" indicates $P < 0.001$.

Figure 2. Comparison of hsCRP reduction between treatment groups

At 72 hours, no significant difference was revealed between the groups; however, Firsekibart achieved a more substantial hsCRP reduction than compound betamethasone at 7 days and 4 weeks.

4. Discussion

Firsekibart demonstrated a obvious effect in reducing hsCRP levels. Within 72 hours, Firsekibart's ability to lower hsCRP was comparable to that of CB, indicating that both drugs can quickly respond to acute gout inflammation. However, at 7 days and 4 weeks, Firsekibart showed a more pronounced advantage in inhibiting hsCRP.

The core pathological mechanism of gout is the chronic inflammatory response induced by MSU crystals. MSU crystals interact with macrophages and activate the NLRP3 inflammasome through the TLR2/4 signaling pathway or mitochondrial ROS production. This activation leads to caspase-1 activation, which subsequently cleaves pro-IL-1β into its active form [6, 11]. IL-1β, which is a key proinflammatory cytokine that triggers gout flares and drives downstream inflammatory cascades, activates NF-κB through the IL-1R receptor, further amplifying the inflammatory response and promoting the infiltration of neutrophils and the release of chemokines (such as IL-6 and CXCL8) [19]. IL-1β also upregulates adhesion molecules on endothelial cells (such as selectins), exacerbating the recruitment of inflammatory cells [6]. IL-1β also induces neutrophils to release neutrophil extracellular traps (NETs), which further release oxidative stress substances (such as myeloperoxidase), thereby exacerbating tissue damage [20–22].

Therapeutic strategies targeting IL-1β have been proven effective. Canakinumab effectively alleviates acute pain in refractory gout patients and reduces the risk of recurrent flare-ups. However, an increased risk of infection is a safety concern that needs to be carefully considered in the clinical use of canakinumab [11, 16]. Firsekibart, as a novel IL-1β monoclonal antibody, exerts its effects through sustained blockade of IL-1β. By the process, the hepatic synthesis of hsCRP could also be inhibited [23]. Its prolonged half-life is similar to other IL-1β monoclonal antibodies, such as canakinumab, which has shown long-term efficacy in related autoinflammatory disorders and

thereby enables persistent inhibition of the IL-1β pathway while maintaining sustained suppression of hsCRP [24–28]. This mechanistic distinction explains why the anti-inflammatory effects of Firsekibart are sustained beyond the initial 72 hours, whereas the hsCRP-lowering effect of CB diminishes over time. Study confirmed that, in comparison to etoricoxib, Firsekibart showed better pain relief by 72 hours, faster onset of 50% pain reduction (2.0 days vs. 4.0 days), and a dramatically lower 12-week recurrence rate (6.6% vs. 66.1%) in gout patients experiencing frequent flares [29]. These benefits supported our findings that Firsekibart delivered both rapid and sustained anti-inflammatory effects on hsCRP from a clinical perspective. This sustained hsCRP inhibition likely underpins the drug's ability to prevent flare recurrence, as reduced hsCRP levels correlate with diminished inflammatory activity that triggers gout exacerbations.

Firsekibart introduces a novel dimension to gout therapy, particularly for patients who were contraindicated to, intolerant of, or unresponsive to NSAIDs and/or colchicine [25]. A stable and sustained inhibition of hsCRP hints at a more durable inflammatory control, which addresses both acute and chronic gout in pathophysiology. Colchicine significantly reduces inflammatory markers such as CRP during acute attacks by inhibiting the activation of the neutrophil NLRP3 inflammasome, blocking IL-1β release, and disrupting microtubule assembly [30]. As an anti-IL-1β monoclonal antibody, Firsekibart has a more stable hsCRP inhibitory effect that breaks the "inflammation-damage" vicious cycle in gout patients, especially for those with frequent flare-ups or concomitant metabolic syndrome. IL-1 inhibitors, including the anti-IL-1β monoclonal antibody, have been acknowledged as an effective option for gout, rheumatoid arthritis, and cardiovascular diseases [11, 31]. Firsekibart may have both anti-inflammatory and cardiovascular protective effects, and this will be further investigated in future studies.

This study contains several limitations. First, the relatively short observation period precludes assessment of the long-term impact of sustained hsCRP suppression on joint structural repair and recurrence rates. Second, the absence of in-depth analysis correlating hsCRP reduction with functional joint improvement limits the clinical utility of hsCRP as a therapeutic biomarker. Third, exclusive focus on treatment-refractory populations may introduce selection bias, restricting generalizability to the broader gout population. Future large-scale, longitudinal studies incorporating diverse cohorts and clinical outcome measures are warranted to further validate the therapeutic potential of Firsekibart.

5. Conclusion

Compared with the compound betamethasone, Firsekibart maintained hsCRP suppression over a longer follow-up period. This result may provide significant clinical value in the management of gout and its associated complications.

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Disclosure statement

The authors declare no conflict of interest.

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