Urology Research, 2025, Volume 3, Issue 3
https://ojs.bbwpublisher.com/index.php/UR
Online ISSN: 2981-8230
Print ISSN: 3083-4910

Efficacy and Safety of Firsekibart in Gout Patients with Different Estimated Glomerular Filtration Rates

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Abstract: *Objective*: To compare the efficacy and safety of Firsekibart versus compound betamethasone in gout patients with different estimated glomerular filtration rate (eGFR) levels. *Methods*: Patients were randomized 1:1 to receive a single dose of Firsekibart (200 mg) or Compound betamethasone (7mg). Patients were divided into three subgroups according to baseline eGFR: ≥90, 60-89, and 30-59 ml/min/1.73 m^2 to evaluate 72-hour pain relief, 12/24-week recurrence rate, renal function changes, and safety events. *Results*: Of 311 patients in full analysis set (FAS), 113 (36.3%) had baseline eGFR 60-89 ml/min/1.73 m^2, and 42 (13.5%) had baseline eGFR 30-59 ml/min/1.73 m^2. Similar reduction in visual analogue scale (VAS) scores at 72-hour was observed in each eGFR subgroup betwteen Firsekibart and compound betamethasone group (P>0.05). Compared with Compound betamethasone, Firsekibart reduced the risk of recurrence at 12/24 weeks in patients with different eGFR subgroups (all P<0.0001). In safety evalution, no obvious changes of creatinine and eGFR were observed in each subgroup during 24-week follow up. Treatment emergent adverse events (TEAEs) incidence was comparable in each eGFR subgroup analysis. In total, 1(0.6%) treatment-emergent serious adverse events (TESAE) and 0 treatment-related adverse events(TRSAE) occurred in the Firsekibart group compared to 6 (3.8%) and 3 (1.9%) in the Compound betamethasone group, respectively. *Conclusion*: Overall, Firsekibart demonstrated non-inferior short-term pain relief while offering better prevention of new flares, with a lower incidence of serious adverse events compared to compound betamethasone ,and results were consistent across eGFR subgroups. Both Firsekibart and compound betamethasone showed little effect on renal function.

Keywords: Acute gouty arthritis; Chronic kidney disease; Inflammation; Firsekibart; Compound betamethasone

Online publication: Oct 17, 2025

1. Introduction

When the concentration of uric acid in the blood exceeds its dissolution limit, monosodium urate crystals are formed and deposited in the joints and surrounding tissues, inducing acute inflammatory reactions, resulting in gout attacks[1]. Acute gouty arthritis (AGA) is the core clinical manifestation of gout. According to statistics, the global incidence of gout increased from 93.10/100,000 to 109.08/100,000 from 1990 to 2021, and the incidence rate in China increased from 122.52/100,000 to 151.61/100,000 during the same period[2]. Hyperuricemia is

an important factor in the development and prognosis of chronic kidney disease (CKD)[1]. Kidney disease is common in gout patients, about 71% of adult gout patients accompany with glomerular filtration rate (eGFR) <60 mL/min/1.73 m2)[3], and 20% with eGFR <30 mL/min/1.73 m2). Hyperuricemia in patients with gout can accelerate kidney damage, and decreased renal function can aggravate uric acid accumulation, leading to recurrent gout and significantly increasing the difficulty of treatment[4].

Glucocorticoids are routinely administered during acute gout attacks, especially when patients present with systemic symptoms or when colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs) are ineffective, contraindicated, or renal insufficiency[5]. Despite the powerful anti-inflammatory and immunosuppressive effects of glucocorticoids, they are widely used to treat a variety of immune-mediated inflammatory diseases. However, glucocorticoids have serious side effects, and long-term use can increase the risk of infection in patients, leading to complications such as insulin resistance and osteoporosis[6].

Interleukin-1β (IL-1β) is a pro-inflammatory factor produced and released by a variety of cells in response to inflammatory signals, participating in a variety of autoimmune inflammatory responses, and is also an important target of anti-inflammatory therapy. In the gout inflammatory response, IL-1β drives gout attacks by activating endothelial cells, releasing inflammatory factors, and recruiting neutrophils[7-10]. IL-1β acts as a key effector protein in the NLR family pyrin domain containing protein 3 (NLRP3) pathway, mediating renal fibrosis in CKD[11, 12]. IL-1β inhibitors are more selective than glucocorticoids and have fewer expected side effects while effective. Targeted inhibition of IL-1β can not only control the gout inflammatory response, but may also provide renal protection for patients with CKD.

Firsekibart is a new fully human monoclonal antibody independently developed in China, and has a high affinity for IL-1β[13],and showed great efficacy and safety in treating gout[13]. However, the effect of Firsekibart in gout patients with CKD has not been reported. Therefore, we made an post-hoc subgourp analysis of Firsekibart in patients with different baseline eGFRs.

2. Methods

2.1.Study design and patient population

This study was a multicenter, randomized, double-blind, double-dummy, positive-controlled phase III clinical trial conducted in 51 centers in China, including patients with contraindications, intolerance, insufficient efficacy of NSAIDs and/or colchicine, and recurrent attacks of acute gout from January 2023 to June 2024. Key inclusion criteria included: age 18 to 75 years; body mass index (BMI)≤40 kg/m^2, meeting the American College of Rheumatology 2015 classification criteria for gout[14]; ≥2 episodes of acute gout in the prior 1 year; contraindications, intolerance, or poor efficacy to NSAIDs and/or colchicine. Key exclusion criteria included: allergy to the study drug or similar drugs; use of prohibited medications within a specific time prior to screening (such as NSAIDs, and colchicine); eGFR ＜ 30mL/min/1.73m^2, diseases that may interfere with joint assessment (such as rheumatoid arthritis); history of severe immunodeficiencyand severe comorbidities.

The study was approved by the ethical review committees of all participating centers. All patients signed an informed consent form prior to enrollment. Study registration numbers: NCT05983445 and CTR20223136.

2.2. Data collection

Demographic data, clinical manifestations, and laboratory examination data were collected by electronic data acquisition system. In this post-hoc article, patients were divided into three groups based on baseline eGFR,:

eGFR ≥90 mL/min/1.73 m^2; eGFR 60-89 mL/min/1.73 m^2; and eGFR 30-59 mL/min/1.73 m^2[15]. Key follow-up index included: the change in pain intensity from baseline to 72 hours， recurrence time within 12/24 weeks, and renal function measurements at Day8, 4 and 24 weeks after drug administration.

2.3. Treatment regimen

Patients were randomized in a 1:1 ratio to receive a single dose Firsekibart (200m) or compound betamethasone(7mg) using a stratified block randomization method, with pain intensity at screening (50 ≤VAS < 70 mm vs. 70 ≤VAS < 100 mm) as the stratification factor. The study was designed by a 24-week of double-blind core studies treatment followed by another 24-week open-label extension, and a 12-week safety follow-up since last dose. During the double-blind period, patients who experienced a subsequent flare would require re-treatment with the same study drug with a time interval of >14 days between doses.

2.4. Efficacy and safety evaluation

Change in the VAS pain score of the target joint, time to first new flare within 12/24 weeks, proportion of patients experiencing at least 1 new flare and the mean number of flares per patient over 12/24 weeks were measured to evaluate the efficacy.Besides ,we used change in creatinine and eGFR to evaluate the influence on the renal function and the incidence of adverse events to evaluate the overall safety. Safety assessments were classified according to the common terminology Criteria for Adverse Events, version 5.0.The occurrence of adverse events in each subgroup during the study period was recorded.

2.5. Statistical analysis

Categorical data were presented as numbers and percentages. Continuous variables are presented as means with standard deviations or medians with quartiles (quartile 1 [Q1], quartile 3 [Q3]). The full analysis set (FAS) ,which included all randomized patients who received at least 1 dose of the study drug and had at least 1 post-treatment efficacy assessment, was used for the analysis of VAS scores and recurrence. The safety set (SS) ,which included all randomized patients who received at least 1 dose of the study drug and had safety assessments, was use for the analysis of renal function and

For the change in pain intensity at 72 h post-dose, a non-inferiority test was conducted using a mixed-effects model for repeated measures. The model included baseline VAS score as a covariate, treatment group, assessment time points, and the interaction between treatment group and time points as fixed effects. For the time to first new flare within 12 weeks after treatment, HR of the Firsekibart versus Compound betamethasone group was estimated with stratified Cox proportional hazards model using the prespecified stratification factors at randomization. The median time to flare and corresponding 95% CI for each group were estimated with the Kaplan-Meier method.

3. Outcomes

3.1. Baseline characteristics

A total of 311 patients (156 in the Firsekibart group and 155 in the Compound betamethasone group) were included in full analysis set (FAS). Baseline demographics and disease characteristics were generally comparable between groups (**Table 1**).

Table 1. Baseline data

	Firsekibart group(N = 156)				Compound betamethasone group(N = 155)			
	≥ 90 mL/ min/1.73 m^2 (N = 76)	60–89 mL/ min/1.73 m^2 (N = 59)	30–59 mL/ min/1.73 m^2 (N = 21)	Total (N = 156)	≥ 90 mL/ min/1.73 m^2 (N = 80)	60–89 mL/ min/1.73 m^2 (N = 54)	30–59 mL/ min/1.73 m^2 (N = 21)	Total (N = 155)
Male, n (%)	76 (100)	59 (100)	21 (100)	156 (100)	79 (98.8)	52 (96.3)	20 (95.2)	151 (97.4)
Age, Years, Mean (SD)	39.0 (11.87)	49.6 (12.36)	58.8 (9.58)	45.7 (13.73)	39.0 (9.99)	47.3 (12.84)	55.4 (6.66)	44.1 (12.16)
BMI (kg/m^2), mean (SD)	28.00 (4.013)	27.19 (3.960)	26.17 (2.831)	27.45 (3.885)	28.20 (4.290)	26.84 (3.197)	26.91 (2.692)	27.55 (3.788)
Number of flares in prior 1 year, n (%)								
2 flares	7 (9.2)	5 (8.5)	1 (4.8)	13 (8.3)	14 (17.5)	5 (9.3)	1 (4.8)	20 (12.9)
3–5 flares	38 (50.0)	28 (47.5)	7 (33.3)	73 (46.8)	35 (43.8)	25 (46.3)	9 (42.9)	69 (44.5)
6–12 flares	24 (31.6)	23 (39.0)	9 (42.9)	56 (35.9)	25 (31.3)	15 (27.8)	7 (33.3)	47 (30.3)
> 12 flares	7 (9.2)	3 (5.1)	4 (19.0)	14 (9.0)	6 (7.5)	9 (16.7)	4 (19.0)	19 (12.3)
Presence of gouty tophi, n (%)	22 (28.9)	28 (47.5)	11 (52.4)	61 (39.1)	30 (37.5)	25 (46.3)	10 (47.6)	65 (41.9)

eGFR: estimated glomerular filtration rate; BMI: body mass index

3.2.VAS scores analysis of patients with different baseline eGFRs

In total, VAS scores changes from baseline to 72h post-dose in Firsekibart and Compound betamethasone groups were -57.09 mm and -53.77 mm, respectively, with a difference of -3.32mm

(95%CI:-7.561 to 0.914).In patients with baseline eGFR ≥90 ml/min/1.73 m^2, the VAS scores changes from baseline to 72h post-dose in Firsekibart and Compound betamethasone groups were -56.42 mm and -53.74 mm, respectively, with a difference of -2.68 mm (95% CI: -8.949 to 3.594). In the patients with baseline eGFR of 60-89 ml/min/1.73 m^2, the VAS scores changes from baseline to 72h post-dose in Firsekibart and Compound betamethasone groups were -57.72 mm and -51.82 mm, with a difference of -5.90mm (95% CI: -12.401 to 0.602). In patients with a baseline eGFR of 30-59 ml/min/1.73 m^2, the VAS scores changes from baseline to 72h post-dose in Firsekibart and Compound betamethasone groups were -58.22mm and -58.33mm, respectively, with a difference of 0.11 mm (95% CI: -13.115 to 13.329) (**Table 2**). As the upper bound of the 95% CI was below the 10 mm, Firsekibart showed non-inferiority on pain relief, and consistent trend was seen in different eGFR subgroup.

3.3. Recurrence analysis of patients with different baseline eGFR

The median time to first new flare was not reached within 12 weeks in the Firsekibart group within different baseline eGFRs, while in compound betamethasone group, it was 82 days in patients with baseline eGFR of ≥90 ml/min/1.73 m^2， 30.5 days in the patients with baseline eGFR of ≥60-89 ml/min/1.73 m^2, and 21.0 days in patients with a baseline eGFR of 30-59 ml/min/1.73 m^2.

Compared with compound betamethasone, lower recurrence rate was seen in Firsekibart group . By week 12, in patients with baseline eGFR of ≥90 ml/min/1.73 m^2,10.64% patients in the Firsekibart group experienced ≥1 acute flare compared with 51.59% patients in the compound betamethasone group. Consistent results were shown in patients with baseline eGFR of ≥60-89 and 30-59 ml/min/1.73 m^2 (13.56% vs 77.78%, 4.76% vs 95.24%).

Compared with the compound betamethasone, Firsekibart reduced the 12-week risk of new flare in patients with different baseline eGFRs (≥90 mL/min/1.73 m^2: hazard ratio (HR)=0.15, 95% CI: 0.072 to 0.329, *P<0.0001*; 60-89 mL/min/1.73 m^2: HR=0.09, 95% CI: 0.042 to 0.194, *P<0.0001*; 30-59 mL/min/1.73 m^2: HR=0.02, 95% CI: 0.003 to 0.158, *P=0.0002*). Consistent results were seen within 24 weeks(**Table 3**, **Figure**

1).These results indicated that compared with compound betamethasone, Firsekibart reduced the risk of acute gout recurrence within 12 and 24 weeks in different renal function situation

Table 2. VAS scores changes from baseline to 72 h in the full analysis set

Baseline eGFR	Variables	Fiesekibart group(N = 156)	CB group(N = 155)
Total	Change from baseline (mm), LSM (95% CI)	-57.09 （-60. 082, -54. 098）	-53.77 (-56.767, -50.765)
	Treatment difference (mm) LSM (95% CI)	-3.32 (95%CI:-7.561, 0.914)	
≥ 90 mL/min/1.73 m^2	Change from baseline (mm), LSM (95% CI)	-56.42 (-60.911, -51.928)	-53.74 (-58.118, -49.366)
	Treatment difference (mm) LSM (95% CI)	-2.68 (-8.949, 3.594)	
60–89 mL/min/1.73 m^2	Change from baseline (mm), LSM (95% CI)	-57.72 (-62.209, -53.227)	-51.82 (-56.515, -47.122)
	Treatment difference (mm) LSM (95% CI)	-5.90 (-12.401, 0.602)	
30–59 mL/min/1.73 m^2	Change from baseline (mm), LSM (95% CI)	-58.22 (-67.516, -48.927)	-58.33 (-67.635, -49.022)
	Treatment difference (mm) LSM (95% CI)	0.11 (-13.115, 13.329)	

CB: Compound betamethasone, eGFR: estimated glomerular filtration rate; CI: confidence interval, LSM: least squares mean

Table 3. Recurrence analysis in in the full analysis set

Baseline eGFR	Variables	Fiesekibart group (N = 156)	CB group (N = 155)	HR (95% CI) compared to CB group	*p*-value
≥ 90 mL/min/1.73 m^2	Time to first acute gout flare within 12 weeks (days) Median (95% CI)	NR (NE, NE)	82.0 (48.00, -)	0.15 (0.072 0.329)	< 0.0001
	Recurrence rate (%) (95% CI)	10.64 (5.466, 20.151)	51.59 (41.153,62.930)		
	Time to first acute gout flare within 24 weeks (days) Median (95% CI)	NR (NE, NE)	82.0 (48.00, -)	0.21 (0.113, 0.408)	< 0.0001
	Recurrence rate (%) (95% CI)	24.23 (10.675,49.448)	54.75 (44.063, 66.113)		
60–89 mL/min/1.73 m^2	Time to first acute gout flare within 12 weeks (days) Median (95% CI)	NR (NE, NE)	30.5 (24.00,55.00)	0.09 (0.042, 0.194)	< 0.0001
	Recurrence rate (%) (95% CI)	13.56 (7.024, 25.289)	77.78 (66.021, 87.703)		
	Time to first acute gout flare within 24 weeks (days) Median (95% CI)	NR (NE, NE)	30.5 (24.00,55.00)	0.11 (0.051, 0.220)	< 0.0001
	Recurrence rate (%) (95% CI)	15.25 (8.246, 27.265)	75.93 (63.980, 86.275)		
30–59 mL/min/1.73 m^2	Time to first acute gout flare within 12 weeks (days) Median (95% CI)	NR (NE, NE)	21.0 (15.00,29.00)	0.02 (0.003, 0.158)	0.0002
	Recurrence rate (%) (95% CI)	4.76 (0.685, 29.279)	95.24 (80.296, 99.668)		
	Time to first acute gout flare within 24 weeks (days) Median (95% CI)	NR (NE, NE)	21.5 (15.00, 29.00)	0.04 (0.008, 0.167)	< 0.0001
	Recurrence rate (%) (95% CI)	9.52 (2.471, 32.995)	95.00 (79.470, 99.655)		

CB: Compound betamethasone, eGFR: estimated glomerular filtration rate; HR: risk ratio; 95% CI: 95% confidence interval

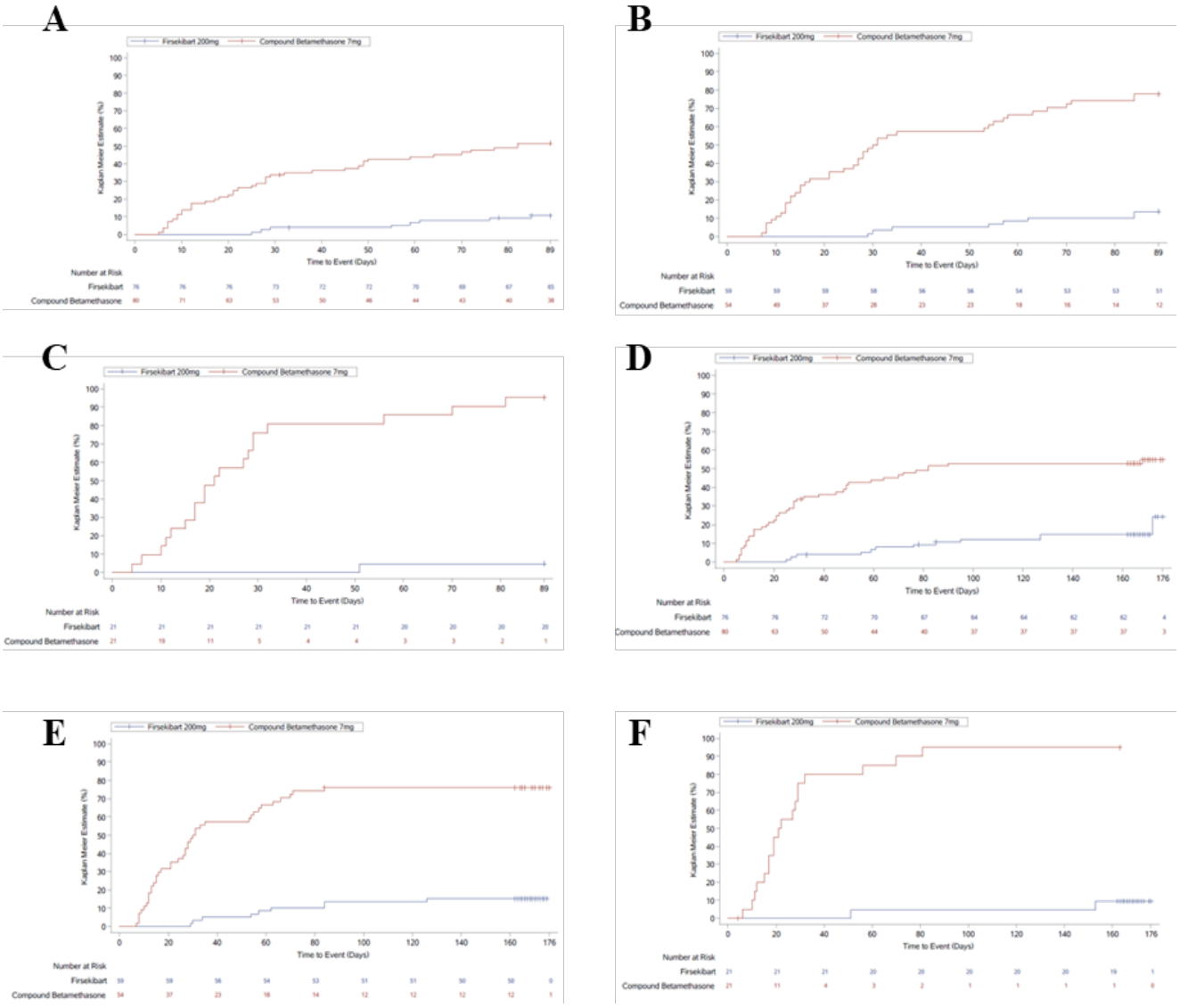

Figure 1. Kaplan-Meier curve of time to first acute gout flare within 12/24 weeks with different eGFR groups in the full analysis set A-C: Kaplan-Meier curve of time to first acute gout flare within 12weeks in eGFR: ≥90, 60-89, and 30-59 mL/min/1.73 m². D-F：Kaplan-Meier curve of time to first acute gout flare within 24 weeks in eGFR: ≥90, 60-89, and 30-59 mL/min/1.73 m².

3.4. Renal function analysis of patients with different baseline eGFR

A total of 312 patients (156 in the Firsekibart group and 156 in the Compound betamethasone group) were included in safety set (SS).The creatinine and eGFR were stable during 24-week observation in Firsekibart group（**Figure 2**）. The changes in eGFR was -6.407~3.520 ml/min/1.73 m^2 (least squares mean) in the Firsekibart group with different eGFR stratification at multiple time observation points within 24 weeks(**Table 4**). Progression to stage 4 kidney disease (eGFR <30 ml/min/1.73 m^2) was rare and just occurred in 1 (0.64%) patient of Firsekibart group.

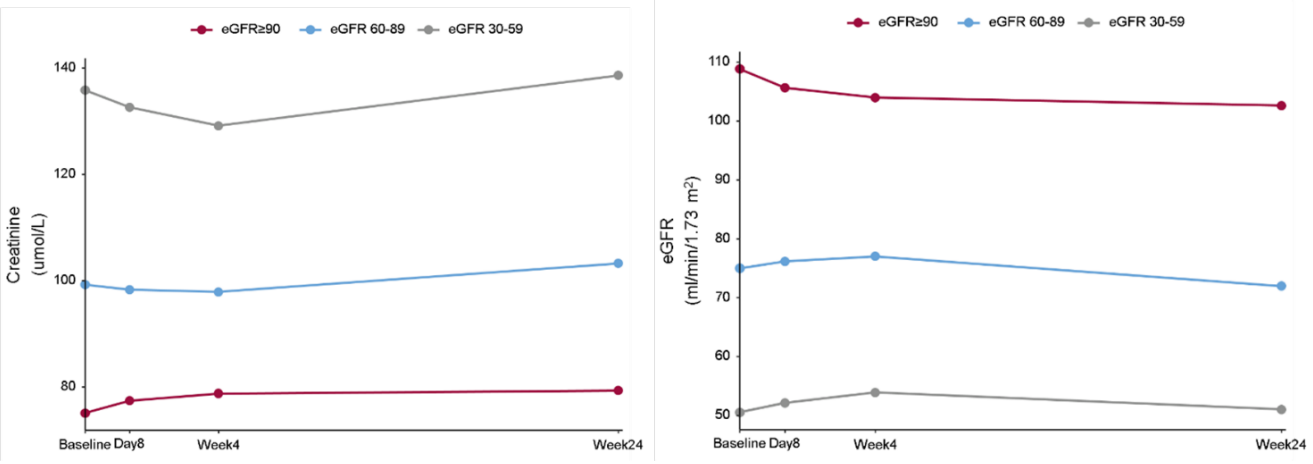

Figure 2. Effects of Firsekibart on creatinine and eGFR in safety set.

Table 4. Changes in creatinine and eGFR in safety set

Baseline eGFR	Variables	Fiesekibart group (N = 156)	CB group (N = 156)	Difference
≥ 90 mL/min/1.73 m^2		Day 8 - baseline		
	Creatinine (umol/L) LSM (95% CI)	2.483 (0.717, 4.248)	1.612 (-0.109, 3.333)	0.870 (-1.599, 3.340)
	eGFR (mL/min/1.73 m^2) LSM (95% CI)	-3.486 (-6.273, -0.699)	-2.184 (-4.900, 0.532)	-1.302 (-5.199, 2.595)
		Week 4 - baseline		
	Creatinine (umol/L) LSM (95% CI)	3.844 (1.842, 5.846)	1.169 (-0.902, 3.241)	2.675 (-0.212, 5.562)
	eGFR (mL/min/1.73 m^2) LSM (95% CI)	-5.059 (-8.322, -1.796)	-0.850 (-4.227, 2.526)	-4.209 (-8.912, 0.494)
		Week 24 - baseline		
	Creatinine (umol/L) LSM (95% CI)	4.525 (2.478, 6.573)	2.400 (0.381, 4.419)	2.125 (-0.758, 5.008)
	eGFR (mL/min/1.73 m^2) LSM (95% CI)	-6.407 (-9.621, -3.193)	-3.382 (-6.552, -0.212)	-3.025 (-7.551, 1.501)
60–89 mL/min/1.73 m^2		Day 8 - baseline		
	Creatinine (umol/L) LSM (95% CI)	-0.629 (-2.891, 1.633)	-1.785 (-4.150, 0.580)	1.156 (-2.126, 4.439)
	eGFR (mL/min/1.73 m^2) LSM (95% CI)	1.073 (-1.115, 3.260)	1.989 (-0.298, 4.275)	-0.916 (-4.091, 2.259)
		Week 4 - baseline		
	Creatinine (umol/L) LSM (95% CI)	-1.035 (-4.061, 1.990)	1.513 (-1.996, 5.022)	-2.548 (-7.207, 2.111)
	eGFR (mL/min/1.73 m^2) LSM (95% CI)	2.003 (-0.692, 4.698)	-0.508 (-3.634, 2.619)	2.510 (-1.642, 6.663)
		Week 24 - baseline		
	Creatinine (umol/L) LSM (95% CI)	4.407 (1.421, 7.393)	-3.664 (-6.909, -0.419)	8.071 (3.652, 12.490)
	eGFR (mL/min/1.73 m^2) LSM (95% CI)	-3.350 (-5.987, -0.713)	4.414 (1.548, 7.280)	-7.764 (-11.672, -3.856)

Table 4 (Continued)

Baseline eGFR	Variables	Fiesekibart group (N = 156)	CB group (N = 156)	Difference
30–59 mL/min/1.73 m^2		Day 8 - baseline		
	Creatinine (umol/L) LSM (95% CI)	-3.555 (-9.949, 2.839)	-3.125 (-9.678, 3.429)	-0.430 (-9.642, 8.782)
	eGFR (mL/min/1.73 m^2) LSM (95% CI)	1.546 (-1.180, 4.272)	2.411 (-0.382, 5.205)	-0.865 (-4.794, 3.064)
		Week 4 - baseline		
	Creatinine(umol/L) LSM (95% CI)	-7.177 (-15.600, 1.246)	-10.063 (-20.786, 0.660)	2.886 (-10.795, 16.568)
	eGFR (mL/min/1.73 m^2) LSM (95% CI)	3.520 (-0.670, 7.710)	6.164 (0.821, 11.507)	-2.645 (-9.479, 4.190)
		Week 24 - baseline		
	Creatinine(umol/L) LSM (95% CI)	2.124 (-9.513, 13.760)	-11.024 (-22.951, 0.903)	13.148 (-3.617, 29.913)
	eGFR (mL/min/1.73 m^2) LSM (95% CI)	0.569 (-3.627, 4.764)	6.112 (1.811, 10.412)	-5.543 (-11.592, 0.505)

CB: Compound betamethasone, eGFR: estimated glomerular filtration rate; CI: confidence interval, LSM: Least squares mean

3.5. Adverse events analysis of patients with different baseline eGFR

The overall incidence of treatment-emergent adverse events (TEAEs) was comparable between groups, occurring in 111 patients (71.2%; grade ≥ 3, 12.2%) in the Firsekibart group and 109 patients (69.9%; grade ≥ 3, 10.9%) in the compound betamethasone group. Treatment-related adverse events (TRAEs) were reported in 79 patients (50.6%; grade ≥ 3, 10.9%) receiving Firsekibart and 80 patients (51.3%; grade ≥ 3, 5.1%) receiving compound betamethasone. Compared with compound betamethasone, Patients in Firsekibart group experienced less treatment-emergent serious adverse events (TESAE) (1(0.6%) vs 6 (3.8%)). All 3 treatment-related serious adverse events (TRSAE) cases occurred in the Compound betamethasone group. The adverse events in different eGFR stratification were shown in **Table 5**.

Table 5. Adverse events in safety set

	Fiesekibart group (N = 156)				CB group (N = 156)			
	≥ 90 mL/ min/1.73 m^2 (N = 76)	60–89 mL/ min/1.73 m^2 (N = 59)	30–59 mL/ min/1.73 m^2 (N = 21)	Total (N = 156)	≥ 90 mL/ min/1.73 m^2 (N = 80)	60–89 mL/ min/1.73 m^2 (N = 55)	30–59 mL/ min/1.73 m^2 (N = 21)	Total (N = 156)
TEAE (%)	59 (77.6)	42 (71.2)	10 (47.6)	111 (71.2)	60 (75.0)	38 (69.1)	11 (52.4)	109 (69.9)
TRAE (%)	46 (60.5)	26 (44.1)	7 (33.3)	79 (50.6)	45 (56.3)	29 (52.7)	6 (28.6)	80 (51.3)
Grade ≥ 3 of TEAE (%)	12 (15.8)	6 (10.2)	1 (4.8)	19 (12.2)	12 (15.0)	3 (5.5)	2 (9.5)	17 (10.9)
Grade ≥ 3 of TRAE (%)	12 (15.8)	4 (6.8)	1 (4.8)	17 (10.9)	5 (6.3)	3 (5.5)	0	8 (5.1)
TESAE (%)	0	1 (1.7)	0	1 (0.6)	3 (3.8)	3 (5.5)	0	6 (3.8)
TRSAE (%)	0	0	0	0	0	3 (5.5)	0	3 (1.9)

CB: Compound betamethasone, eGFR: estimated glomerular filtration rate; TEAE: treatment-emergent adverse events; TRAE: treatment-related adverse events; TESAE: treatment-emergent serious adverse events; TRSAE: treatment-related serious adverse events

4. Discussion

In this study, the pain relief efficacy of Firsekibart was comparable to that of compound betamethasone at 72 hours in patients with different baseline eGFRs. Besides,compared with compound betamethasone , Firsekibart reduced the recurrence risk of gout over 12/24 weeks. In the evalution of renal function, creatinine and eGFR were stable during 24-week observation in Firsekibart group. In the evalution of adverse events, there was no obvious difference in the overall incidence of TEAEs between Firsekibart and Compound betamethasone, and patients in Firsekibart group experienced less TESAE and TRSAEs, indicating that Firsekibart had a favorable safety profile.These results support that Firsekibart has better efficacy than Compound betamethasone in gout patients with CKD without worsening renal function, and its long-term use may offer a higher safety profile than compound betamethasone.

Recurrent gout flare can lead to multisystem damage through persistent inflammatory responses and monosodium urate crystal deposition, including irreversible joint destruction, secondary tophi infection, and increased risk of acute cardiovascular events[16]. Studies have shown enhanced renal medullary echogenicity in patients with severe gout, possibly due to sodium urate crystallization and the formation of stones within the renal medulla[17], suggesting that sodium urate crystal-driven inflammation may directly affect kidney structure and function in patients with gout[18]. An prospective study including 0.5 million adults showed frequent gout flares (≥2) greater elevated risks for CKD（HR compared to no gout=10.95）than single gout flare(HR compared to no gout=3.01)[19]. Therefore, preventing recurrent gout attacks is crucial for the treatment of patients with gout and CKD. The current study confirmed that Firsekibart reduced the risk of gout recurrence , and this advantage was consistent in patients with different stages of CKD. These results suggest that the efficacy of Firsekibart in preventing gout flare can also befinet kidney.

According to the 2024 edition of the “Clinical Practice Guidelines for the Assessment and Management of Chronic Kidney Disease” released by KDIGO, a global kidney disease prognosis organization, when conducting risk assessment for CKD patients, if the eGFR changes in CKD patients occur in follow-up testing > 20% exceeding expectations, further attention and evaluation are needed[20]. In the present study, patients with different baseline eGFRs in both groups experienced small fluctuations in eGFR at different times after treatment. The changes in eGFR from the baseline was -6.407~3.520 ml/min/1.73 m^2 in the Firsekibart group and -3.382~6.164 ml/min/1.73 m^2 the Compound betamethasone group, which did not meet the criteria indicating a significant change in CKD patient.Therefore, neither compound betamethasone nor Firsekibart showed any adverse effects on kidney function in this study..

Colchicine and NSAIDs are the first-line drugs for treating gout attacks, and glucocorticoid can also be considered when there are contraindications or poor treatment effect for colchicine/ NSAIDs [5]. However, these drugs need to be used with greater caution in patients with CKD. Colchicine treatment may cause gastrointestinal adverse reactions, liver and kidney damage, and bone marrow suppression, and regular monitoring of liver and kidney function and routine blood tests are required[5]. NSAIDs may have adverse effects on the kidneys, including acute and chronic renal failure, nephrotic syndrome with interstitial nephritis, papillary necrosis, and decreased potassium and sodium excretion[21]. Glucocorticoids are commonly used for gout patients with CKD, but long-term use can cause significant side effects such as glucolipid metabolism disorders, increased risk of infection, and osteoporosis[6]. Firsekibart is a novel, fully human anti-interleukin-1β monoclonal antibody, which dot not excrete through the kidneys in its original form, making it a potentially better choice for gout patients with CKD.

Anti-inflammatory therapy is vital to reducing gout attacks and kidney damage. Sodium urate crystals formed during hyperuricemia initiate gout by activating monocytes and macrophages. IL-1β released after macrophage activation can cause infiltration and activation of joint neutrophils, leading to other local and systemic inflammatory responses[22]. There is a bidirectional relationship between IL-1β and monocytes/macrophages, which are the main source of IL-1β, which in turn activates macrophages. IL-1β also stimulates the release of other inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin-6 (IL-6) by activating the nuclear factor κB (NF-κB) pathway, causing local inflammation and kidney damage[23]. In addition, uric acid itself activates the immune system, and uric acid from nucleosides released in dead cells has been shown to have a significant promoting effect on inflammatory responses in the body[24]. In the kidney, urate-induced activation of NLRP3 inflammasomes and release of IL-1β promote chemokine signaling in proximal tubular cells, leading to tubular damage and proteinuria, which in turn promotes intrarenal inflammation, interstitial fibrosis, and the development of chronic kidney disease[25]. Therefore, anti-inflammatory therapy, especially targeting IL-1β as a key effector in the inflammatory response, can alleviate tissue damage caused by hyperuricemia and urate crystallization at the pathological level. This also provides the theoretical foundation for the treatment effects of Firsekibart in gout patients with CKD.

The safety analysis in this study showed the overall incidence of TEAEs between Firsekibart and compound betamethasone group were comparable, and it remains consistent in the each eGFR subgroup analysis.

5. Conclusion

In summary, IL-1β inhibitors have both theoretical and clinical research support for treating gout and reducing the progression of CKD. In this study, Firsekibart demonstrated non-inferior short-term pain relief while offering better prevention of new flares, with a lower incidence of serious adverse events compared to compound betamethasone, and results was consistent across eGFR subgroups. Both Firsekibart and compound betamethasone showed little effect on renal function.

This trial has several limitations. Firstly,it is a post-hoc subgroup analysis based on existing data, the sample size of each subgroup is small and the follow-up time is not long enough to comfirm the observation of renal outcomes. Nevertheless, the results still provide a preliminary reference for clinical practice, and more researches with larger samples are needed to verify the above conclusions in the future.

Disclosure statement

The authors declare no conflict of interest.

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