EP-104IAR (Long-Acting Intra-Articular Injection of Fluticasone Propionate): Results from a Phase 2 Randomized, Double-blind, Vehicle-Controlled Trial in 318 Patients with Knee Osteoarthritis

Dr. James Helliwell[1], Dr. Amanda Malone[1], Dr. Mark Kowalski[1], Christine Dobek[1], M.Sc
[1] Eupraxia Pharmaceuticals Inc. Victoria, BC Canada

Background

Knee Osteoarthritis (OA) causes pain and loss of function; however, it is extremely clinically variable and can present anywhere from an asymptomatic incidental finding to a permanently disabling disorder. Treatment guidelines are primarily aimed at symptom management. Milder patients control symptoms with weight-loss, exercise, and acetaminophen. Intra-articular (IA) corticosteroids are conditionally recommended for more moderate OA symptoms (*Kolasinski, et al., 2019*)[1], while severe patients rely on opioids or undergo knee replacement surgery.

Patients can remain in moderate pain for years; however, currently available immediate-release corticosteroids have a limited duration of efficacy, risk of systemic side-effects (*Juni, et al., 2015*)[2] and there exists debate as to their potential to damage following repeated injections. Longer IA residence time is expected to provide increased clinical benefit by extending the duration of efficacy and reducing the frequency of injections. Eupraxia Pharmaceuticals Inc. (Eupraxia) is developing EP-104IAR (long-acting fluticasone propionate (FP) for IA injection) to treat OA symptoms.

Purpose

Eupraxia previously presented results from non-clinical studies evaluating PK and local joint safety in beagle dogs (*Webb et al, 2018*)[3]. These data indicated that the prolonged local residence time of EP-104IAR had no impact on cartilage health and supported initiation of clinical development. Safety and PK data from a Phase 1 trial in 32 OA knee patients were consistent with nonclinical findings and supported the continued clinical development of EP-104IAR in Phase 2.

Here we report primary and secondary efficacy analysis results and safety findings from a Phase 2, randomized, double-blind, vehicle-controlled parallel-group trial evaluating the efficacy of EP-104IAR in 318 patients with knee OA (NCT04120402). We will discuss whether pain severity had an impact on the outcome measures based on responder analyses performed in the sub-set of subjects with moderate OA pain at baseline.

Methods

Subjects were randomized 1:1 to a single IA dose of EP-104IAR 25 mg, or vehicle and followed for 24 weeks. Males and females, ≥40 years, with a diagnosis of primary knee OA, Kellgren-Lawrence Grade 2-3 and symptoms for ≥ 6 months were enrolled.

A 2-week baseline period was used to determine baseline/qualifying pain; defined as weekly WOMAC Pain scores ≥ 4.0 to ≤9.0 (out of 10) which did not vary by >3 points. Bilateral subjects required pain to be ≤6.0 in their non-Index knee. Following dosing, subjects recorded weekly WOMAC Pain and monthly WOMAC total measurements. Safety assessments included adverse events (AEs), vital signs, laboratory evaluations (including cortisol, ACTH stimulation testing), and knee examinations.

The primary endpoint was the difference in change from baseline between treatments in WOMAC Pain at Week 12. A mixed-effects model for repeated measures (MMRM) was employed. Key secondary endpoints were analyzed using analogous methods.

Study Design and Demographics

Study Design

- Double-blind, placebo-controlled
- Target 300 patients, 1:1 randomization
  - 80% power to detect 0.8-point change
  - Assumed 20% withdrawal rate
- 25 mg vs placebo (vehicle)
- 6-month follow-up
- Moderate OA (K-L Grade 2-3)
- Moderate to severe pain (WOMAC Pain 4-9)

Demographics

	EP-104IAR 25 mg	Placebo	Total
Enrolled	163	155	318
Completed	156	148	304
Discontinued	7 (4.3%) (0 drug related)	7 (4.5%)	14 (4.4%)
Mean Dose	26.3 mg	-	-
Mean Age	64.0 years	63.2 years	63.6 years
Gender	42%M 58%F	43%M 57%F	42.5%M 57.5%F
Mean Body Mass Index	29.9	29.9	29.9
Mean K-L OA Rating	2-47.2% 3-52.8%	2-49.0% 3-50.3%	2-48.1% 3-51.6%
% Moderate / Severe	64% / 36%	71% / 29%	68% / 32%

Results

Primary Endpoints

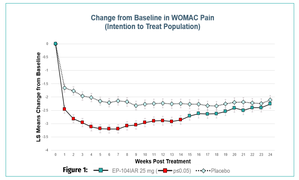

Figure 1:

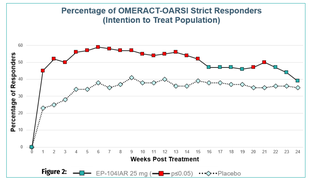

Figure 2:

Figure 1: Change in WOMAC Pain at 12 weeks (P=0.004). Significant, durable and meaningful pain relief to 14 weeks.

Figure 2: OMERACT-OARSI Strict responders (>50% improvement and an absolute change ≥2 points in WOMAC Pain) show Clinically meaningful and significant improvement in pain past 12 weeks (P=0.011). (*Pham T, D van der Heijde, Altman R.D et al.*)[4]

Secondary Endpoints

Key Secondary Endpoints met :

- **WOMAC function** was achieved at 12 weeks.
- **Area under the Curve for WOMAC pain,** which measures the average pain relief was achieved at 12 weeks and remained statistically significant till the end of the 24-week study, with a p-value less than 0.001.
- **OMERACT-OARSI strict responders**- 50% or greater improvement in their WOMAC pain score from baseline, with an absolute change of at least two points on the WOMAC scale was met with significance to at least 15 weeks.

Pre-Specified analyses of Moderate OA Patients

(Moderate patients: 3.5 – 6.5 on Baseline WOMAC Pain Score. N=214 (68%)

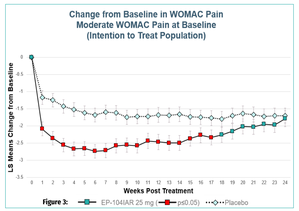

Figure 3:

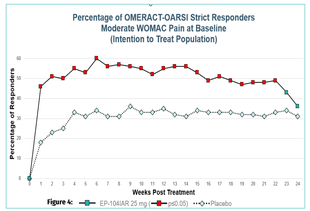

Figure 4:

Figure 3: Moderate OA patients show significant (P≤0.05), durable and meaningful pain relief to 17 weeks.

Figure 4: OMERACT-OARSI Strict responders (>50% improvement and an absolute change ≥2 points in WOMAC Pain) show clinically meaningful and significant improvement in pain to 22 weeks (P ≤0.05).

Results

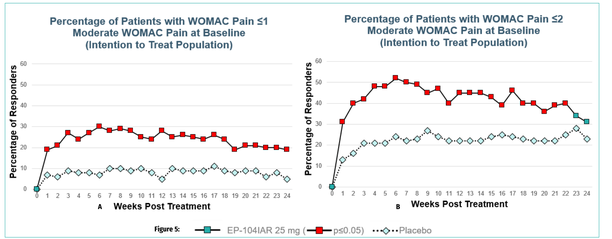

Figure 5:

Figure 5: Near complete pain relief observed in a significant portion of patients (P≤0.05). These patient maintained minimal pain (WOMAC pain score of less than 1 (A) and WOMAC pain score of less than 2 (B) for 24 weeks .

Safety

Adverse Events by Treatment Group (Safety Population)

	EP-104IAR 25 mg n=163	Placebo n=155	Overall N=318
Subjects with at least 1 TEAE*	106 (65.0%)	89 (57.4%)	195 (61.3%)
Mild	47 (28.8%)	33 (21.3%)	
Moderate	57 (35.0%)	55 (35.5%)	
Severe	2 (1.2%)	1 (0.6%)	
0 Drug related			
Subjects with at least 1 Serious TEAE	4 (2.5%)	1 (0.6%)	5 (1.6%)
0 Drug related			
Subjects with study medication-related TEAE	15 (9.2%)	11 (7.1%)	26 (8.2%)
Subjects with at least 1 TEAE leading to withdrawal	2 (1.2%)	0	2 (0.6%)
0 Drug related			

Table 1

Adverse Events by Treatment Group (Safety Population)

Adverse Events with Incidence ≥5%	EP-104IAR 25 mg n=163	Placebo n=155	Overall N=318
Arthralgia	38 (23.3%)	23 (14.8%)	61 (19.2%)
Index knee,	24 (14.7%)	16 (10.3%)	40 (12.6%)
Index knee, treatment-related*	9 (5.5%)	9 (5.8%)	18 (5.3%)
Covid-19	14 (8.6%)	14 (9.0%)	28 (8.8%)
Nasopharyngitis	14 (8.6%)	12 (7.7%)	26 (8.2%)
Influenza	6 (3.7%)	9 (5.8%)	15 (4.7%)
Influenza like illness	4 (2.5%)	10 (6.5%)	14 (4.4%)

Table 2

Table 1: EP-104IAR is well tolerated . No serious or severe drug-related treatment-emergent adverse events. Adverse events were similar between EP-104IAR and Placebo.

Table 2: Adverse events which occurred in at least a 5% rate and similar to Placebo suggesting EP-104IAR is well tolerated.

Pharmacokinetics

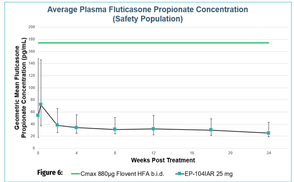

Figure 6:

Serum Cortisol

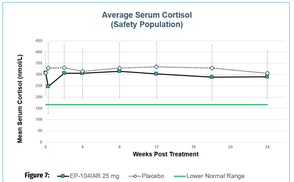

Figure 7:

Figure 6: Extended release to over 24+ weeks observed. This indicates large systemic safety as plasma concentrations of fluticasone is well below the systemic exposure experienced by patients who take Flovent on a daily basis.

Figure 7: EP-104IAR has minimal and transient effects on serum cortisol which is normalized by 2 weeks. The cortisol levels are also comparable between treatment arms throughout monitoring period.

Results

Serum Glucose

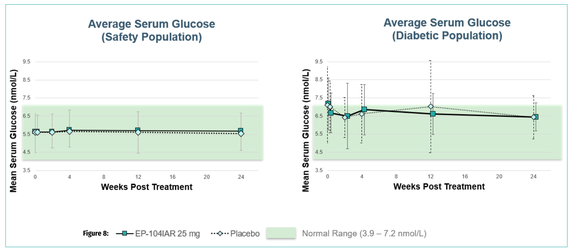

Figure 8:

Figure 8: No significant effects seen on serum glucose levels, including in non-insulin dependent diabetic patients (n-26)

Conclusions

In the overall study population, a single dose of EP-104IAR provided clinically and statistically significant reduction in WOMAC Pain for 14 weeks compared to vehicle — longer than all currently approved pharmacologic including immediate and extended-release corticosteroids.

Furthermore, in subjects with moderate OA pain, the duration of significant pain-relief persisted for 17 weeks. Responder analyses in moderate OA subjects demonstrated that clinically meaningful differences persisted for the majority of the study (the percentage of OMERACT-OARSI strict responders was statistically different until Week 22 and the percentage of subjects who dropped to WOMAC Pain ≤1 was statistically different until Week 24). This suggests EP-104IAR could offer clinically meaningful benefit for a substantially longer period than any other currently marketed corticosteroids, providing a promising treatment for the currently under-served moderate knee OA patient population.

Regardless of baseline OA pain, EP-104IAR was well-tolerated in all subjects and resulted in low but sustained plasma levels for the entire 24-week study period. These results demonstrate that Eupraxia's delivery technology offers stable drug delivery over an extended period, with the potential for a reduced systemic side-effect profile compared to other IA corticosteroids. These data also support the potential for EP-104IAR to be used for repeat and bilateral dosing of knee OA.

The safety and efficacy of EP-104IAR will be further evaluated in Phase 3 trials.

References

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Disclosures & Contact Information

All listed authors are paid employees of Eupraxia Pharmaceuticals Inc.

Eupraxia Pharmaceuticals Inc., 201-2067 Cadboro Bay Road, Victoria, BC. Canada V8R 5G4
www.eupraxiapharma.com or info@eupraxiapharma.com