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An open-label, multicenter, randomized, parallel, single-dose, comparative bioavailability study of two triamcinolone hexacetonide injectable suspensions in patients with knee osteoarthritis

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ABSTRACT

Background: Triamcinolone hexacetonide (THA), a synthetic glucocorticoid with low solubility, can provide sustained pain relief and less systemic side effects in patients with knee osteoarthritis. This study aimed to characterize pharmacokinetic profile of THA-test product containing 20 mg/ml injectable suspension and compare its bioavailability with the standard reference in Indian patients with knee osteoarthritis.
Methods: In this open-label, randomized, multicenter study, 44 adult patients were randomized (1:1; test n=23, reference n=21) to receive a single dose of test or reference products. The primary objective was to characterize the pharmacokinetic profile and compare bioavailability of both products via serum triamcinolone acetonide (TCA) concentration. Secondary objectives included safety and tolerability evaluation, impact on hypothalamic-pituitary-adrenal axis, and efficacy of test and reference products in reducing index knee pain.
Results: Both products were absorbed with a median T_{max} of 23.9 hours. Comparative bioavailability analysis demonstrated no statistically significant formulation effect for ln-transformed C_{max} (1098.052 pg/ml for test, 1333.850 pg/ml for reference) and AUC_{0-t} (159112.561 pg×h/ml for test, 211531.035 pg×h/ml for reference) for TCA. T/R ratio for C_{max} was 82.3% and T/R ratio for AUC_{0-t} was 75.2%, with >100% inter-subject variability for both C_{max} and AUC_{0-t}. Additionally, recovery time of cortisol levels of test and reference arms was 96 hours and 456 hours, respectively. Both products significantly reduced knee pain ($p<0.0001$).
Conclusions: The test product provided lower systemic exposure and faster recovery of serum cortisol levels than the reference, while still providing similar beneficial effect in sustained index knee pain reduction.

Keywords: Knee osteoarthritis, Pain, Systemic exposure, Triamcinolone acetonide, Triamcinolone hexacetonide

INTRODUCTION

Osteoarthritis is the second most common rheumatologic disorder, and its prevalence ranges from 22% to 39% in India.[1,2] Knee osteoarthritis is the most common type of osteoarthritis in India. Disability-adjusted life year due to osteoarthritis has increased from 0.79 million (95% uncertainty interval [UI]: 0.40–1.55) to 2.12 million (95% UI:1.07–4.23).[3] Osteoarthritis is more prevalent in women than in men, and its incidence in women rises significantly

with age. Although ~45% of women aged >65 years show symptoms of osteoarthritis, radiological evidence can be found in ~70% of patients in this age group.[4]

Pain is one of the primary clinical signs of osteoarthritis; it especially occurs after heavy weight bearing and prolonged exertion and can worsen and become more debilitating as the disease progresses, ultimately leading to total knee arthroplasty.[4] Hence, the primary goals of osteoarthritis treatment are pain relief and functional improvements.

In routine clinical practice, patients with knee osteoarthritis are frequently prescribed intraarticular corticosteroids (IACS) such as intraarticular glucocorticoid injections for pain relief.[1] Recent guidelines suggest using IACS for short-term acute pain relief in patients who are not responsive to oral or topical pain medications.[5,6] However, the effectiveness of an IACS depends on the pharmacological properties of its formulations, in particular, drug solubility.[8] A compound with low solubility has a long mean residence time (MRT) within joints and prolonged duration of action and can thus maintain synovial levels for a long period with sustained effect and less systemic side effects.[9,10]

Triamcinolone hexacetonide (THA), a 21-t-butyl acetate of triamcinolone acetonide (TCA), is an IACS. THA helps in slower release of its active metabolite TCA, thereby providing enhanced efficacy.[11] Although TCA has shown noticeable pain reduction in patients with knee osteoarthritis, it rapidly effluxes from the joint delimiting pain relief duration.[12,13] THA 20 mg/ml is approved globally for treating joint pain, swelling and stiffness in subacute and chronic inflammatory joint diseases including rheumatoid arthritis.[14] Moreover, THA has shown better efficacy and faster pain relief than the current standards of care – methyl prednisolone (MPA) and TCA.[15]

THA has low solubility inside the joint cavity (0.0002% wt/vol), a prolonged MRT of 6.1 days, and a duration of action of 21 days.[14,16,17] In addition, it does not undergo in situ hydrolysis after intraarticular administration.[18] The aim of the current study was to characterize the pharmacokinetic profile of a test product containing 20 mg/ml injectable suspension of THA and compare its bioavailability with that of a reference product in Indian patients with knee osteoarthritis.

METHODS

Study design

This was an open-label, randomized, multicenter, single-period, single-dose, parallel-group comparative bioavailability study conducted at four sites in India (B. J. Medical College and Civil Hospital, Ahmedabad, Gujarat; GSVM Medical College, Kanpur, Uttar Pradesh; KLE's Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi, Karnataka; and Medical College Baroda and SSG Hospital, Vadodara, Gujarat) from 23 December 2020 to 25 March 2021.

The study protocol was approved and supervised by the institutional ethics committee of all four sites involved. The study was conducted in compliance with the Declaration of Helsinki consistent with good clinical practices and applicable regulatory requirements. Written informed consent was obtained from all participating patients before enrollment. This clinical trial was registered in www.ctri.nic.in /CTRI/2020/12/029771. The manuscript followed the consolidated standards of reporting trials statement.

Following an initial 7-day screening period, all eligible patients were randomized (1:1) to receive 1 ml of either test product (injectable THA suspension USP 20 mg/ml by Abbott Healthcare Private Limited, India) or reference product (injectable THA 20 mg/ml suspension by Intrapharm Laboratories Ltd., United Kingdom) via intraarticular route on day 1. Follow-up visits were scheduled on days 5±1, 13±2, and 20±2. End-of-study (EOS) visit was on day 27±2. Thus, the total study duration was 34 days including screening period.

Eligibility criteria

Adult patients aged ≥40 years of either sex with body mass index (BMI) ≤40 kg/m^2 having a ≥6-month history of symptoms associated with knee osteoarthritis, documented radiographic evidence of grade 3 osteoarthritis of the target knee as determined by Kellgren Lawrence criteria (which demonstrates definite narrowing of joint space, moderate osteophyte formation, some sclerosis, and possible deformity of bony ends) within 3 months prior to screening, with index knee pain for >15 days over the past month, higher pain in the index knee than the contralateral knee in case of bilateral osteoarthritis, and requiring IACS for acute management of symptoms as confirmed by the investigator were enrolled in the study.[19]

Patients with ipsilateral hip osteoarthritis, gout, radicular low back pain and hip pain, pain in any other area of the lower extremities or back, fibromyalgia, Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or arthritis associated with inflammatory bowel disease, patients with history of infection in the index knee, clinical signs and symptoms of active knee infection or crystal disease of the index knee within 1 month of screening, unstable joint (such as a torn anterior cruciate ligament) within 12 months of screening, or uncontrolled diabetes (hemoglobin A1c >7.5%) and/or having known hypersensitivity to any form of triamcinolone or its excipients were excluded from the study. Pregnant and lactating women were also excluded from the study.

Patients were allowed to continue physical therapy, bracing, or any treatment for a pre-existing condition or for

an adverse event, including the study indication (e.g., analgesic medications). However, patients were instructed to avoid, if possible, intake of any short-acting analgesic or anti-inflammatory drugs from the night before the scheduled site visits for pain assessments.

Study endpoints

The primary endpoint of the study was to characterize the pharmacokinetic profile and compare the bioavailability of test and reference products. Secondary endpoints included: evaluation and comparison the safety and tolerability of test and reference products, evaluation of effect of test and reference products on the hypothalamic-pituitary-adrenal (HPA) axis, and determination of the effect of both products on index knee pain using the visual analog scale [VAS]) from baseline (prior to dosing) to days 2, 5, 13, 20 and 27.

Study assessments

Pharmacokinetic measurements

Venous blood samples (4 ml each) were collected from all patients at pre-dose (0 hour) and at 1, 2, 6, 12, 18, 24, 96 (day 5), 288 (day 13), 456 (day 20) and 624 (day 27) hours post-dose. The blood samples were centrifuged at 4300±100 rpm for 5 minutes below 10°C to separate plasma. Plasma samples were processed for pharmacokinetic assessments at Lambda Therapeutic Research Ltd., Ahmedabad, India. Samples were analyzed using a validated, selective, and sensitive liquid chromatography–mass spectrometry (LC-MS/MS) method. The calibration curves using an 8-point calibration curve standard, with concentrations ranging from 30.178 pg/ml to 3994.727 pg/ml, were used to measure the concentrations of TCA, the active metabolite of THA, in all samples.

All pharmacokinetic analyses were conducted using Phoenix® WinNonlin® version 8.1 (Certara L.P.) software. Pharmacokinetic parameters studied included the area under the plasma concentration–time curve from 0 to last measurable concentration (AUC_{0-t}), time to reach peak concentration (T_{max}), area under plasma concentration versus time curve from 0 to infinity ($AUC_{0-\infty}$), maximum measured plasma concentration (C_{max}), terminal rate constant (λ_z), and terminal half-life ($t_{1/2}$).

Serum cortisol measurements

Approximately 3.5 ml of venous blood samples were collected from each patient at baseline (day 1 pre-dose) and 24, 96, (day 5), 288 (day 13), 456 (day 20) and 624 (day 27) hours post-dose and processed for serum cortisol measurements.

The blood samples were centrifuged at 3000-3500 rpm for 10-15 minutes at room temperature. The separated serum was transferred to pre-labelled plain aliquot vials. The samples were stored at −20°C until shipment to Metropolis for analysis.

Assessment of index knee pain

The reduction in pain intensity in the index knee was assessed using VAS from baseline (prior to dosing) to day 2, day 5, day 13, day 20 and day 27 within the test and reference groups.

Safety assessments

Safety evaluations included monitoring of adverse events (AEs), clinical laboratory testing, vital signs, physical examinations, electrocardiograms, chest X-ray, index knee assessments and injection site assessments. All AEs were classified using MedDRA version 24.0.

Statistical analyses

As this was an exploratory study to assess pharmacokinetic parameters and individual bioavailability of test and reference products, a sample size of 22 patients per arm was considered sufficient for this two-treatment, single-period, parallel, single-dose study.

All pharmacokinetic parameters were analyzed descriptively. The log-transformed pharmacokinetic parameters C_{max} and AUC_{0-t} were analyzed using analysis of variance (ANOVA) for TCA. Ratio of geometric least squares means (LSMs), 90% confidence interval, and inter-patient variability were calculated for C_{max} and AUC_{0-t} of both treatments. An F-test was performed to determine the statistical significance of the effects involved in the model at a significance level of 5%.

The mean percentage change from baseline to each time point for serum cortisol concentration was reported descriptively. Reduction in pain intensity in the index knee using the VAS from baseline to each time point was evaluated using Wilcoxon sign rank test, and the Wilcoxon rank sum test was used to compare test and reference products. Safety was analyzed descriptively. Continuous variables were evaluated by treatment group using summary statistics and presented as mean (standard deviation [SD] median (range) as applicable. Categorical values were evaluated by the treatment group using frequencies and percentages.

All efficacy and safety analyses were performed using safety analysis set (all randomized patients who received at least one dose of study medication) while all pharmacokinetic analyses were performed using the pharmacokinetic (PK) analysis set (all randomized patients who completed the study and had no major protocol deviations that could have significantly influenced estimation of pharmacokinetic parameters). All statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc., USA).

RESULTS

Baseline characteristics and demographics

A total of 58 patients were screened; of these, 44 patients were randomized to test or reference treatment groups (safety analysis set: n=23 [test product] and n=21 [reference product]). All patients completed the study (Figure 1).

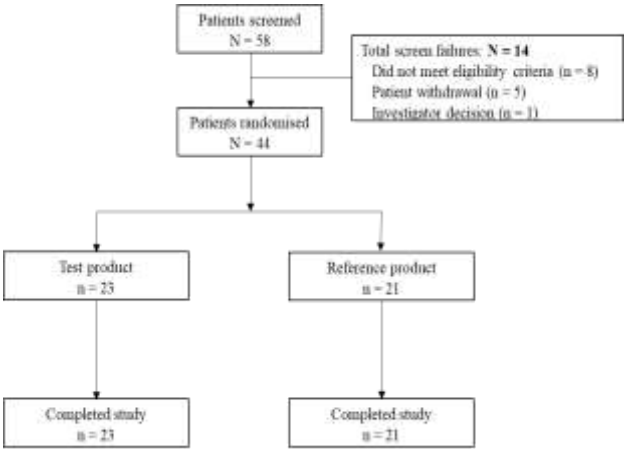

Figure 1: Study design and patient disposition.

The mean (SD) age for all patients (19 men and 25 women) was 55.9 (9.44) years with mean (SD) BMI of 25.2 (3.96) kg/m^2. The demographic and baseline characteristics of patients comparable in both treatment groups were comparable (Table 1).

Pharmacokinetic profiles of test and reference products

Both products were absorbed with a median T_{max} of 23.917 hours. The systemic exposure (C_{max} and AUC_{0-t}) of test product was slightly lower than that of reference product (C_{max} [pg/ml]: 1643.21 [1151.389] versus 2067.51 [1374.133] pg/ml and AUC_{0-t} [pg×h/ml]: 273410.69 [200038.174] versus 288349.25 [182489.384] (Table 2). Mean (SD) elimination half-life for the test product was 207.1 (158.42) hours and for the reference product was 365.6 (371.51) hours.

The comparative TCA bioavailability analysis after excluding patients with pre-dose concentration >5% of C_{max} (n=38) demonstrated no statistically significant formulation effect for ln-transformed PK parameters C_{max} and AUC_{0-t} (Table 3). T/R ratio for C_{max} was 82.3% (90% CI:51.01%-132.85%), whereas the T/R ratio for AUC_{0-t} was 75.2% (90% CI: 42.89-131.91%). Moreover, inter-subject variability for both C_{max} and AUC_{0-t} was >100%, indicating that TCA exhibits large variability in systemic circulation.

Efficacy of test and reference products

Both test and reference treatments were effective in reducing the pain intensity in the index knee as evaluated using VAS at all visits in the study, with statistically significant differences observed between baseline and post baseline visits for both treatments (p<0.0001) (Figure 2). Between-group differences in pain intensity reduction were not statistically significant.

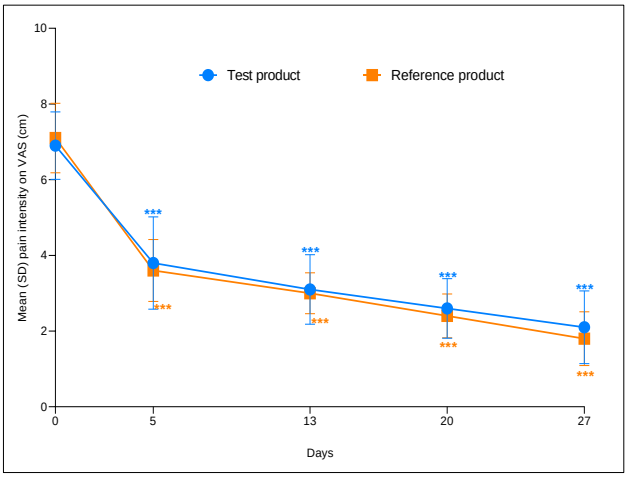

Figure 2: Pain intensity in index knee using VAS (safety analysis set).

***P value for within-group comparison from baseline to post-baseline visits by Wilcoxon signed rank test. Between-group comparisons at each visit were by Wilcoxon rank sum test were not statistically significant (p>0.05); SD: standard deviation VAS: visual analog scale

Serum cortisol evaluation

Figure 3 shows the concentration time profile of TCA and serum cortisol at each post-baseline visit. TCA and serum cortisol concentration profiles were inversely proportional in both the test and reference arms. The serum cortisol levels at baseline were relatively comparable between test and reference groups. At peak TCA plasma concentration, highest inhibition of serum cortisol level was observed for both test and reference products; however, patients receiving test product demonstrated a more rapid (at 96 hours) recovery of cortisol levels towards the baseline than patients receiving reference product (at 456 hours).

Safety findings

Only one patient receiving the test product reported contusion during the study. This was classified as a mild AE and judged as unlikely to be related to the treatment; the patient recovered without any sequalae. There were no other AEs, serious AEs or deaths reported during the study. No clinically significant changes in vital sign evaluations, ECG recordings, or laboratory tests were observed for any of the patients receiving either treatment.

Table 1: Baseline characteristics and demographics (safety analysis set).

Characteristics	Test product (N=23)	Reference product (N=21)	Total (N=44)
Age (years), mean (SD)	54.5 (8.9)	57.4 (9.9)	55.9 (9.4)
Female sex, n (%)	12 (52.2)	13 (61.9)	25 (56.8)
BMI (kg/m^2), mean (SD)	24.8 (3.6)	25.8 (4.3)	25.2 (3.9)

BMI: body mass index; SD: standard deviation; THA: triamcinolone hexacetonide

Table 2: Summary of pharmacokinetic evaluation.

Parameters	Test product (n=19)*	Reference product (n=19)*
T_{max} (hours), median (range)	23.9 (1.92–240.500)	23.9 (6.00–600.500)
C_{max} (pg/mL), mean (SD),	1643.216 (1151.388)	2067.507 (1374.133)
AUC_{0-t} (pg×h/mL), mean (SD)	273410.687 (200038.173)	288349.245 (182489.384)
$AUC_{0-\infty}$ (pg×h/mL), mean (SD)	354792.865 (180762.464) ^	339759.106 (187802.079) $
λ_z (1/hour), mean (SD)	0.006 (0.006) ^	0.003 (0.002) $
t ½ (hour), mean (SD)	207.070 (158.415) ^	365.590 (371.505) $

*Excludes patients having pre-dose concentration >5% of C_{max}; ^n=16 and $N=17. Terminal rate constant (λ_z) could be estimated based on obtained concentration data for 3 patients in the THA-test arm and 2 patients in the reference arm. Hence, $AUC_{0-\infty}$ and other elimination phase-dependent parameters could not be calculated; AUC_{0-t}: area under the plasma concentration–time curve from 0 to last measurable concentration; C_{max}: maximum measured plasma concentration; SD: standard deviation; T_{max}: time to reach peak concentration; $t_{1/2}$: terminal half-life

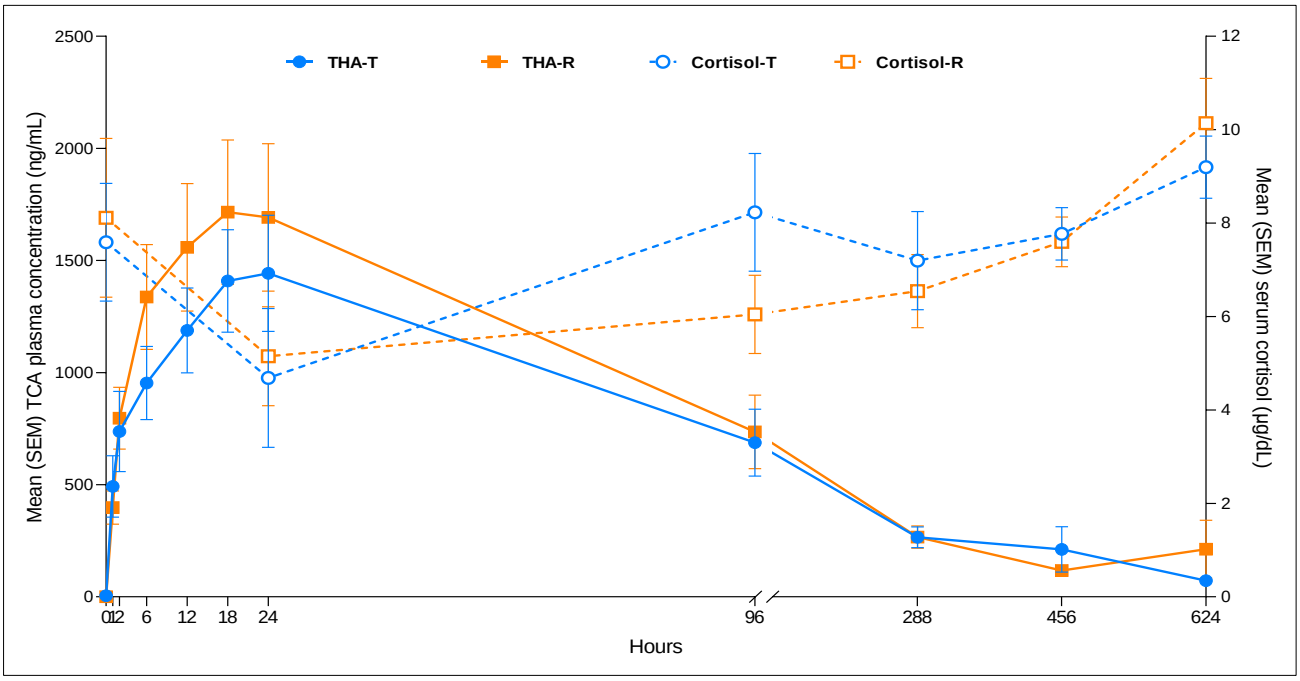

Figure 3: Pharmacokinetic profile of TCA and serum cortisol levels in THA-test and THA-reference groups (safety analysis set).

R: reference product; SEM: standard error of mean; T: test product; TCA: triamcinolone acetonide

Table 3: Comparative bioavailability for TCA.

Parameters	Test product (T), N=19	Reference product (R), N=19	T/R (90% CI)	P value*
C_{max} (pg/ml)				
Geometric mean	1024.178	1365.883	-	0.4965
Ln-transformed geometric LSM	1098.052	1333.850	82.3 (51.01-132.85)	
Ln-transformed inter-patient variability (%)	-	-	106.4	

Continued.

Parameters	Test product (T), N=19	Reference product (R), N=19	T/R (90% CI)	P value*
AUC_{0-t} (pg×h/ml)				
Geometric mean	148103.994	216031.621	-	0.3973
Ln-transformed geometric LSM	159112.561	211531.035	75.2 (42.89-131.91)	
Ln-transformed inter-patient variability (%)	-	-	135.6	

*P value by ANOVA; ANOVA: analysis of variance; AUC_{0-t}: area under the plasma concentration–time curve from 0 to last measurable concentration; CI: confidence interval; C_{max}: maximum measured plasma concentration; LSM: least square mean; TCA: triamcinolone acetonide

DISCUSSION

One of the prominent characteristics of osteoarthritis is synovial membrane inflammation resulting in chronic pain in the affected joint and decreased mobility. Hence, the key treatment strategy involves reduction of synovial inflammation in patients with OA.[20] IACS are effective in managing inflammatory joint conditions.[5-7] Various formulations are available in clinical practice. THA has low solubility; hence, it provides longer action than TCA.[17] The current study characterized the pharmacokinetic profiles and compared the bioavailability of two THA injectable suspension formulations - in patients with knee osteoarthritis based on systemic exposure of TCA.

In the current study, the pharmacokinetic profiles of test and reference THA formulations were similar, except that the test formulation had slightly lower systemic exposure in comparison with the reference formulation, and inter subject variability for both C_{max} and AUC_{0-t} was >100%. Thus, the results showed that there is a large variability in systemic circulation of TCA. Due to this reduced release of TCA into systemic circulation, the intra-synovial concentration appears to have been maintained for efficacy. This is corroborated by significant reduction in pain intensity from baseline to all post baseline visits.

Consistent with our efficacy findings, previous studies have shown that THA holds prolonged duration of action and a superior efficacy compared with TCA.[21] Studies have shown that THA is effective in reducing pain and improvement of function in patients with knee osteoarthritis for up to 24 weeks and even 24 months in some cases.[21,22] Moreover, this extended pain relief period is evident even at lower THA doses.[8,17,21] It can thus be interpreted from the above findings that THA, which differs from TCA with only an extra side chain, can block its hydrolysis in the synovial fluid more effectively than TCA.[8,23] This delay in release of TCA provides prolonged pain relief with less systemic exposure.

In the present study, serum cortisol level showed an inverse relation with TCA concentration in both test and reference groups; however, recovery to baseline cortisol levels was faster in the test group indicating lower systemic exposure, thereby reduced HPA axis suppression. Reduced systemic exposure is beneficial from a safety perspective as demonstrated by the data on HPA axis suppression. Consistent with this, Dickson et al found that in patients with lower back or lumbar pain treated with THA, the serum cortisol levels were suppressed for an average of 4.4 days.[24] The peak plasma THA concentration was achieved at 24 hours post dose administration.[24] Studies with THA have also supported the advantages of reduced systemic exposure from a safety standpoint.[25] Studies have demonstrated that the chances of any infection are also lowered as reduced HPA suppression by THA leads to adequate host defense action as serum-cortisol levels are reduced for a longer period.[26, 27] Only one patient in the THA-test group reported contusion. There were no other adverse events observed for either formulation. No new safety concerns emerged from the study.

This study is the first head-to-head study in India to directly compare the bioavailability and safety of two different THA formulations (THA-test and reference) in patients with knee OA and confirm that functional improvement and pain relief can be achieved with a single dose of injection.

Considering the exploratory comparative bioavailability design, it was not possible to evaluate long-term efficacy and safety outcomes of the test product in a large patient population. Therefore, long-term studies evaluating efficacy and safety are warranted.

CONCLUSION

Overall, a lower systemic exposure of THA-test formulation in comparison to the reference formulation was noted. Both test and reference formulations significantly reduced pain intensity in the index knee from baseline to EOS. Consistent with the lower systemic bioavailability of the test product compared with reference product, recovery to baseline cortisol levels was faster with the test product than the reference product, thereby indicating a reduced suppression of HPA axis, which could be beneficial for patients in the long-term. The study findings thus indicated that the test product had comparable bioavailability with reference product, was effective in reducing pain intensity in the index knee and was well tolerated in patients with knee osteoarthritis.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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