THU0441

RISK-BENEFIT OF CO-ADMINISTERED TRAUMEEL® (TR14) AND ZEEL® (ZE14) INTRA-ARTICULAR (IA) INJECTIONS IN PATIENTS WITH MODERATE-TO-SEVERE PAIN ASSOCIATED WITH OA OF THE KNEE (OAK)

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Background: Data for Tr14&Ze14, a combination of dilute biological and mineral components was recently reported to be effective in treatment of OAK.[3] In a recent meta-analysis of OAK pain from 129 studies/32129 patients (Pt)[1], IA placebos (Pb) were significantly superior to oral Pb. Statistically normalized (Hedges g)[2] effect sizes (ES) at 3 months compared to IA-Pb were: IA-hyaluronates (HA) 0.34, IA-corticosteroids (C) 0.32, diclofenac 0.23, ibuprofen 0.15, naproxen 0.09, celecoxib 0.04, acetaminophen (indeterminable).

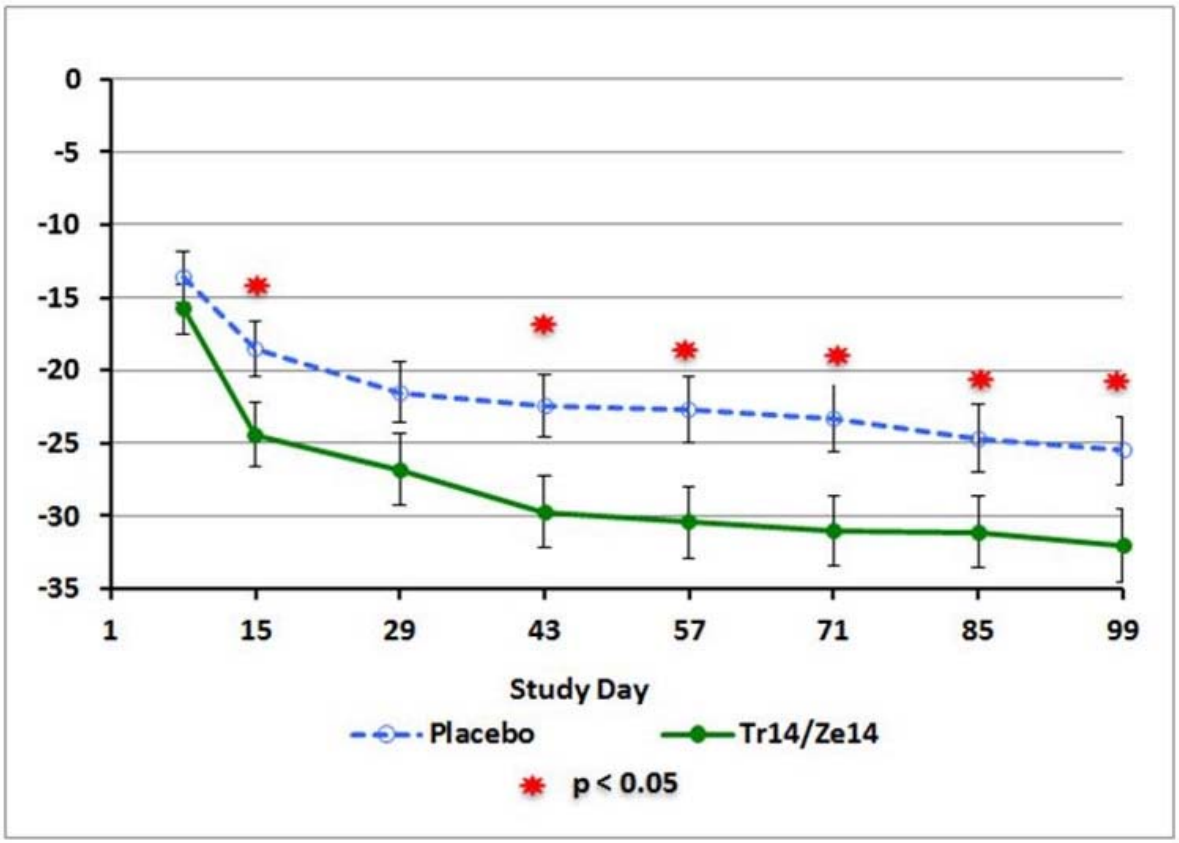
Objectives: To qualitatively assess risk-benefit; guide clinical utility of Tr14&Ze14 relative to other treatments (Tx).

Methods: Patients (Pt) with OAK randomized to 3 weekly IA injections of either Tr14&Ze14 or saline.[3] Primary efficacy variable was change in knee pain from Baseline to End-of-Study (Week 17) measured by WOMAC OA Pain Subscale (Section A, 1-5) 100 mm VAS (WOP). ES were calculated for comparison to meta-analysis data.[2] Safety was assessed by monitoring vital signs, target-knee physical examinations, adverse events, concomitant medications, and regulatory databases (PSURs/DSURs).

Results: 232 Pt (All Tr14&Ze14, n=119, All Pb, n=113; Intention-to-Treat Tr14&Ze14, n=117, Pb, n= 111). As expected, Tr14&Ze14 did not discriminate for WOP after only 1 of 3 injections on Day 8 ($p=0.371$), but subsequently was significantly superior to Pb ($p<0.05$) on Days 15, 43, 57, 71, 85 and 99 (primary endpoint); approached significance on Day 29 ($p=0.0686$, Figure 1). ES compared to IA-Pb were 0.26, 0.22, 0.30, 0.31, 0.30, 0.25 and 0.25 for Days 15, 29, 43, 57, 71, 85 and 99, respectively, indicating persistent efficacy over time with values comparable or superior to independently reported IA and oral Tx. Also, for 50'walk pain, Tr14&Ze14 was significantly superior to Pb ($p<0.05$) on all Days post-Day 8 except Day 29 ($p=0.0501$). There were no related SAEs; other AEs were generally mild and mostly unrelated to treatment. PSURs/DSURs confirmed a favorable safety profile; Tr14 exposure was at least 117,333,284 ampoules or 2,257,043 Pt-years with cumulative 7 serious and 39 non-serious possibly-related ADRs; Ze14 was at least 30,168,795 ampoules or 580,169 Pt-years with a cumulative 0 serious and 9 non-serious ADRs.

Figure 1: Mean (±SE) WOMAC A Changes from Baseline (ITT Population, N=228)

Image/graph:



Conclusions: Tr14&Ze14 provided statistically significant and clinically relevant pain relief on days 15 to 99 in comparison to Pb in a double-blind, randomized, controlled trial.[3] Efficacy ES were consistent with those observed for IA-HA, IA-C and oral NSAIDs. Unlike oral NSAIDs, the safety profile was benign with no signals of cardiovascular, gastrointestinal or other concerning risks. From a qualitative perspective, the risk-benefit relationship for Tr14&Ze14 appears favorable, particularly compared to oral NSAIDs.

References: 1) Bannuru et al. Ann Intern Med; 162: 1/6/15:p46-54. 2) Cooper & Hedges. The Handbook of Research Synthesis. New York: Russell Safe Foundation; 1994. 3) Lozada, C., del Rio, E., Reitberg, DP., Smith, R., Kahn, C., and Moskowitz, RW. Arth Rheumat 66 (10) Suppl.: S1266 (Abstr 2896).

Disclosure of Interest: C. Lozada Consultant for: Rio Pharmaceutical Services, LLC; HEEL USA, E. del Rio Consultant for: Biologische Heilmittel Heel GmbH, D. Reitberg Consultant for: Rio Pharmaceutical Services, LLC, R. Smith Consultant for: Rio Pharmaceutical Services, LLC, R. Moskowitz Consultant for: Rio Pharmaceutical Services, LLC; HEEL USA

DOI: 10.1136/annrheumdis-2015-eular.4268

Source: https://b-com.mci-group.com/Abstract/Statistics/AbstractStatisticsViewPage.aspx?AbstractID=255797