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THE EFFICACY AND SAFETY OF A FIXED-DOSE COMBINATION OF APOCYNIN AND PAEONOL IN SYMPTOMATIC KNEE OA: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL

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Abstract:
Purpose: There is a great unmet need for the development of effective treatments to treat the symptoms of OA. Low-grade inflammation in OA has been highlighted as a major driver for disease. The Nuclear-Factor Kappa-B (NF-κB) pathway mediates an array of inflammatory and tissue degrading processes with increased release of extra-cellular matrix fragments activating additional inflammatory cascades and is involved in OA pathogenesis. Nrf2 is a nuclear transcription factor that plays a key role in response to oxidative stress and has also been demonstrated to play a role in OA pathogenesis. A fixed-dose combination of apocynin and paenol in a ratio of 2:7 (APPA) has been shown to inhibit activation of NF-κB cascade, reducing inflammation and upregulating Nrf2, and reducing damage caused by reactive oxygen species. We report the results of a phase 2a study evaluating the efficacy and safety of APPA in patients with symptomatic knee OA.
Methods: The trial was a 28-day randomized, placebo-controlled, double-blind study comparing 800 mg of APPA twice daily with matched placebo capsules. Patients with radiographic knee OA KL-grade 2 or 3, and a WOMAC pain score ≥40 and ≤90/100 of target knee at screening and baseline were randomized 1:1 to APPA or placebo. Main exclusion criteria included recent intraarticular surgery or injection therapy, hip pain greater than the target knee, and BMI ≥40 kg/m^2. The primary endpoint was change from baseline to Day 28 in the WOMAC pain score. Key secondary endpoints included WOMAC Function, Stiffness and Total scores. Safety outcomes included reported adverse events (AE), clinical laboratory parameters, ECG, and vital signs. A pre-defined subgroup analysis in subjects with a baseline PainDETECT score >12 indicated a positive effect. Accordingly, post-hoc analyses were undertaken to

further assess the effects of APPA in subgroups of participants with higher disease severity.
Results: 152 participants were randomized, and 149 (98%) completed the trial. The mean age (SD) was 61.6 (8.4) years, 49.3 % were female, mean BMI of 30.3 (4.5) kg/m^2. 49.3 % had KL-grade 2 in target knee, and the target knee mean WOMAC pain score at baseline was 55.3 (10.2). The two groups were comparable at baseline with respect to KL-score, WOMAC pain score, gender, age, and BMI. The primary endpoint of change in WOMAC pain from baseline to Day 28 was not met, mean difference between APPA and placebo was -0.89 (95 % CI: -5.62, 3.84, p=0.71, Figure 1A). Similarly, no significant differences were found on other key secondary endpoints (WOMAC Function and WOMAC total **Figures 1B and C**, respectively.) APPA was well tolerated and no differences in frequencies of reported AEs were noted, apart from a higher proportion of subjects reporting mild to moderate gastrointestinal discomfort reported with APPA compared to placebo (12% vs. 6.5 %, transient diarrhea 4% APPA vs. 0 % placebo). No clinically relevant changes were found on clinical biochemistry or hematology parameters, urine dipstick, vital signs nor ECG parameters. In the pre-defined subgroup of participants with baseline PainDETECT ≥ 13 (N=45), the difference in mean change in pain from baseline favored the APPA-group (mean difference: -11.20, 95 % CI: -20.29 to -2.11, p=0.02). **Figure 2** shows that analysis of participants > 50 WOMAC pain at baseline (Group 1, N=95), and a KL-grade of the non-target knee >2 (Group 2, N=105), and a combination of these two criteria (Group 3, N=64) found a positive effect of APPA compared to placebo (Group 1 mean difference: -2.61, 95 % CI: -8.98 to 3.76, p=0.42, Group 2 mean difference: -4.01, 95 % CI: -9.35 to 1.33, p=0.14, and Group 3 mean difference -8.32, 95 % CI: -15.48 to -1.16, p=0.02).
Conclusions: Treatment with APPA 800 mg twice daily for 28 days in patients with symptomatic knee OA was not overall associated with significantly improved outcomes compared to placebo. The treatment was well-tolerated and safe. Exploratory subgroup analyses, however, showed a significant effect of APPA in patients with moderate to severe OA, with predominantly nociceptive pain, indicating that further research in the effects of APPA in appropriate patients is warranted.

Figure 1:

LS Mean change in WOMAC pain (A), WOMAC Function (B), and WOMAC Total (C) during the trial in the modified Intention-to-treat population (N=152). Error bars are 95 % CI.

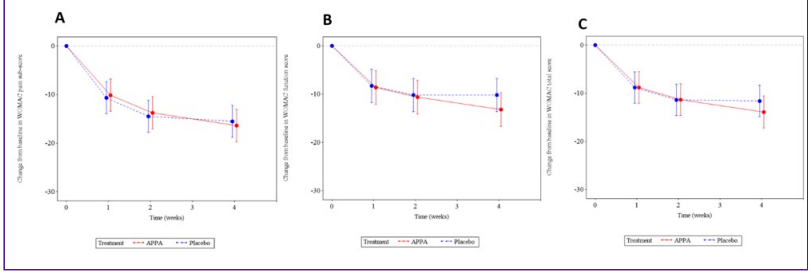

Figure 2

LS Mean change in WOMAC pain in subgroups with WOMAC pain > 50 out of 100 at baseline in the target knee, N=95 (A), with KL-grade 2-4 in the contralateral knee, N=105 (B), and the combined subgroup, N=64 (C) during the trial. Error bars are 95 % CI.