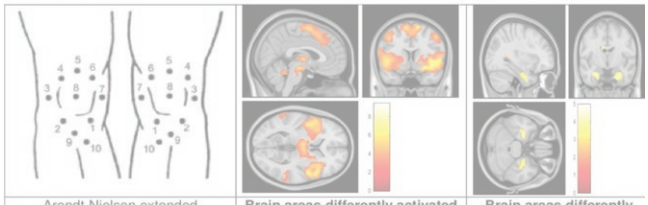
area. However, TKR group showed a higher activation that implicated the region of the amygdala and anterior hippocampus during the tibial fMRI test (point 10).

Table 1. Central sensitization Odds Ratio (OR) with 95% Confidence Interval (95%CI)

	O.R. (95% CI)	p-value
Treatment	0.69 (0.24- 1.98)	0,494
Sex	12.11 (4.32- 33.95)	$2{,}09*10^{-6}$
Age	0.72 (0.26- 1.97)	0,525
BMI	1.88 (0.69- 5.17)	0,219

Conclusion: Presenting central sensitization is not a risk for KOA patients to undergo a TKR, but the mechanism underlaying sensitization in both treatment groups might be different, with amygdala playing an important role in TKR patients. The amygdala is an important element of the brain systems that both express emotions and modulate pain. The activation of the amygdala in response to pressure stimulation on a sensitized knee site is interpreted as a failure of the descending pain inhibitory systems, and the occurrence of a major emotional response during the painful experience in patients that ultimately received TKR.



Arendt-Nielsen extended peripatellar map

Brain areas differently activated between both treatment groups during interline fMRI test (point 7)

Brain areas differently activated between both treatment groups during the tibial fMRI test (point 10). The areas activated in TKR group correspond to amygdala and anterior hippocampus

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Extended peripatellar map including the points tested for tenderness, and brain areas differently activated between both treatments groups during painful stimulation to point 7 (interline) and point 10 (tibial surface, a commonly sensitized site).

Disclosure of Interests: None declared

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POS0180 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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Background: There is a great unmet need for the development of effective treatments to treat the symptoms of OA. Nuclear-Factor Kappa-B (NF-κB) and Nrf2 play a key roles in OA pathogenesis and have been identified as potential targets. A fixed-dose combination of apocynin and paenol in a ratio of 2:7 (APPA) has been shown to inhibit activation of NF-κB and upregulate Nrf2. [1]

Objectives: 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 2-3, 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. 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 (SD) WOMAC pain score at baseline was 55.3 (10.2). The two groups were comparable in terms of baseline pain score, gender, age, and BMI.

The primary endpoint was not met, mean difference (MD) 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 Figure 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 %).

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 (MD: -11.20, 95 % CI: -20.29 to -2.11, p=0.02). Analysis of participants > 50 WOMAC pain at baseline (Group 1, N=95, Figure 1D), and a KL-grade of the non-target knee >2 (Group 2, N=105, Figure 1E), and a combination of these two criteria (Group 3, N=64, Figure 1F) found a positive effect of APPA compared to placebo (Group 1 MD: -2.61, 95 % CI: -8.98 to 3.76, p=0.42, Group 2 MD: -4.01, 95 % CI: -9.35 to 1.33, p=0.14, and Group 3 MD: -8.32, 95 % CI: -15.48 to -1.16, p=0.02).

Conclusion: Treatment with APPA 800 mg twice daily for 28 days in patients with symptomatic knee OA overall was not associated with significantly improved outcomes compared to placebo. The treatment was well-tolerated and safe. Subgroup analyses, however, showed a significant effect of APPA in patients with moderate to severe OA, indicating that further research in the effects of APPA in appropriate patients is warranted.

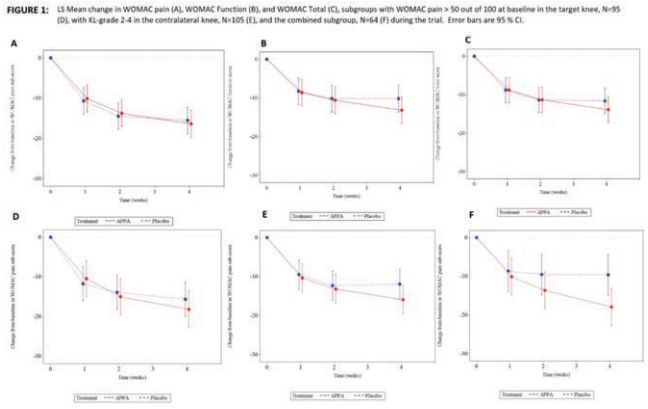

FIGURE 1: LS Mean change in WOMAC pain (A), WOMAC Function (B), and WOMAC Total (C), subgroups with WOMAC pain > 50 out of 100 at baseline in the target knee, N=95 (D), with KL-grade 2-4 in the contralateral knee, N=105 (E), and the combined subgroup, N=64 (F) during the trial. Error bars are 95 % CI.

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