# 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 & PURPOSE

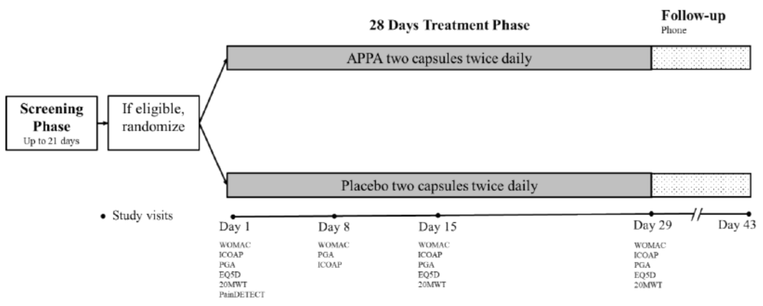
There is a great unmet need for the development of effective treatments to treat the symptoms of OA. Low-grade inflammation in OA has been highlighted as a major driver for disease. The Nuclear-Factor Kappa-B (NF-κB) pathway mediates an array of inflammatory and tissue degrading processes with increased 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(1). We report the results of a phase 2a study evaluating the efficacy and safety of APPA in patients with symptomatic knee OA.

## METHODS

### DESIGN

The trial was a 28-day randomized, placebo-controlled, double-blind study comparing 800 mg of APPA twice daily with matched placebo capsules. The trial design is illustrated below in Figure 1.

**Figure 1:** Trial design, study visits and main outcome measures




### PARTICIPANTS

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.

### STATISTICS

Treatment effect of the primary endpoint was based on a repeated measures ANOVA model including the baseline value, the treatment group, the visit, and treatment by visit as interaction. Comparison of APPA versus placebo was performed within the context of this model. The same ANOVA model used for the primary endpoint was used to assess the treatment effect of the main secondary endpoints. The significance level was set at 5 % two-sided.

## RESULTS

One-hundred and fifty-two participants were randomized, and 149 (98%) completed the trial.

The study population was well balanced between the treatment groups, as shown in Table 1.

**Table 1:** Baseline demographics of the primary analysis population; Intention-to-Treat population (ITT). BMI: Body Mass Index. SD: Standard deviation. KL: Kellgren-Lawrence. WOMAC: Western Ontario and McMaster Osteoarthritis Index

| ITT population | APPA N=75 | Placebo N=77 |
|---|---|---|
| Mean Age, yrs (SD) | 62.5 (8.1) | 60.7 (8.6) |
| Male Sex, n (%) | 45 (60.0) | 32 (41.6) |
| BMI, kg/m$^2$ (SD) | 30.79 (4.33) | 29.88 (4.72) |
| KL-grade, target knee, n (%) | | |
| 2 | 37 (49.3) | 38 (49.4) |
| 3 | 38 (50.7) | 39 (50.6) |
| Mean WOMAC pain (0-100) at baseline (SD) | 54.4 (10.1) | 56.2 (10.4) |

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 2A). Similarly, no significant differences were found on other secondary endpoints Figures 2B.

**Figure 2A:**; Primary efficacy analysis, LSmean change from baseline in WOMAC pain of the Intention-to-Treat population (ITT). Error bars are 95 % CI. WOMAC: Western Ontario and McMaster Osteoarthritis Index

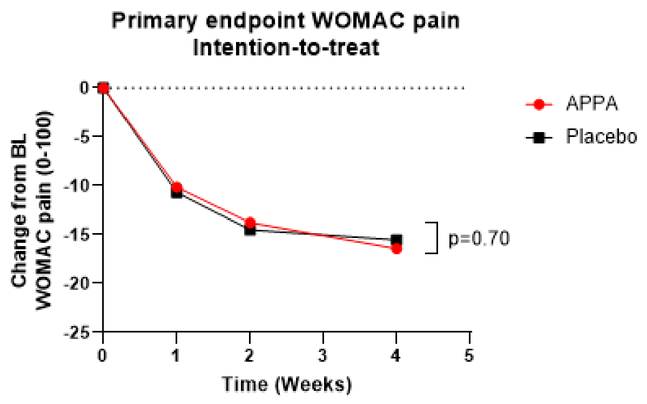
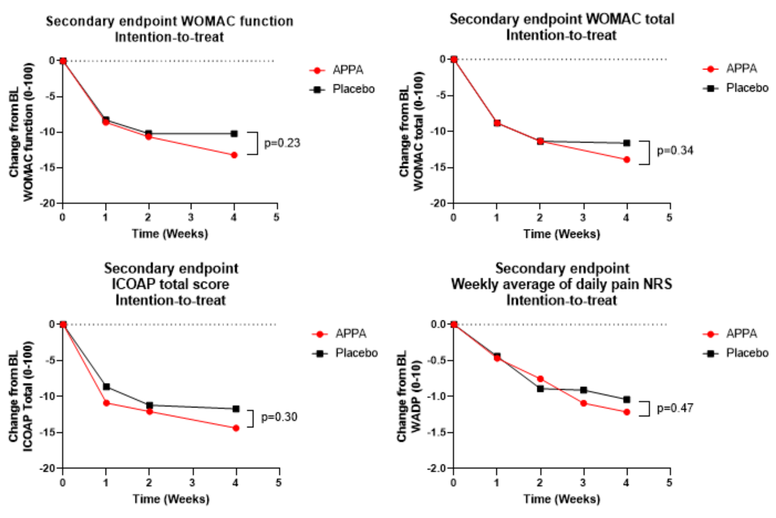


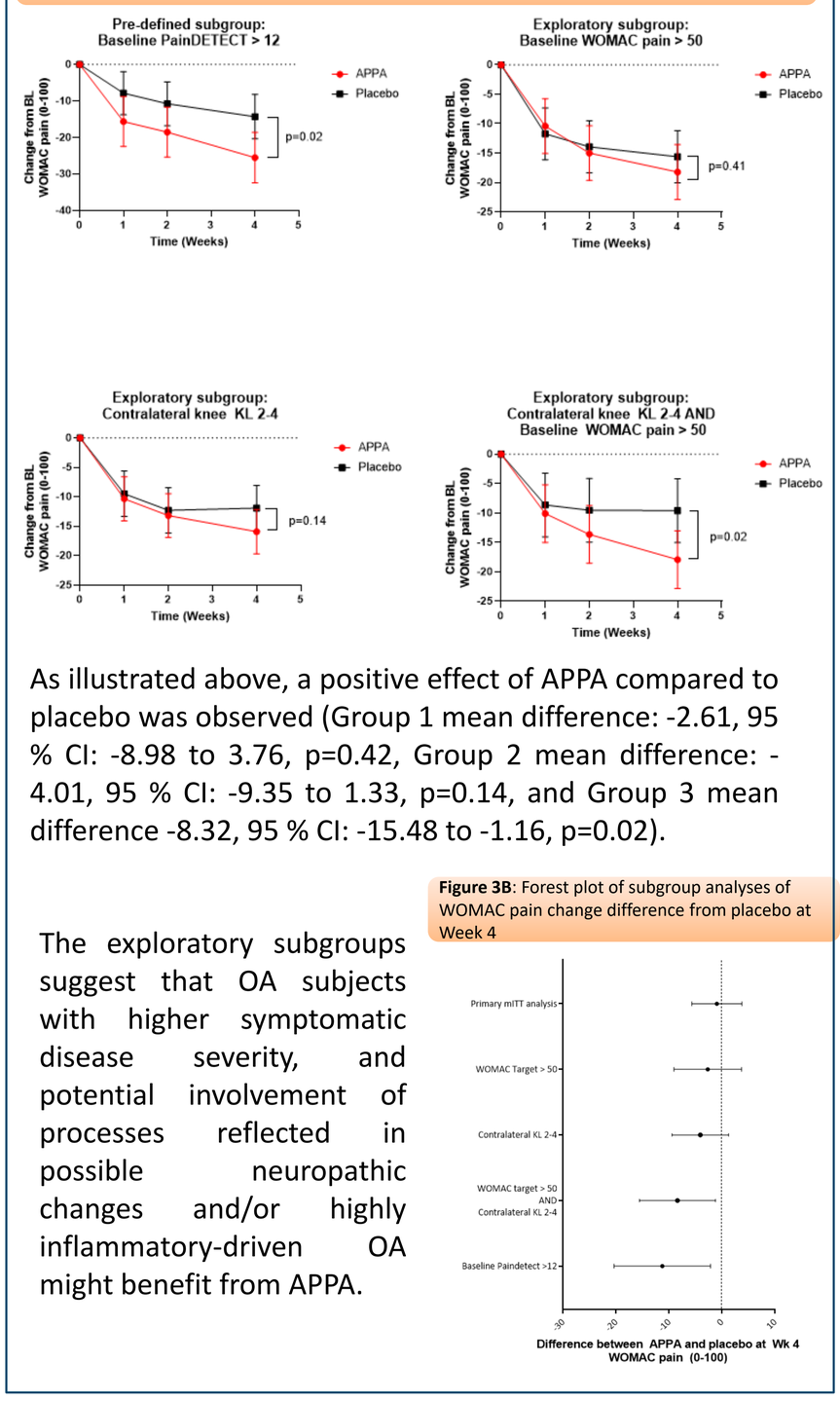

**Figure 2B:**; Primary and key secondary efficacy analyses, LSmean change from baseline in WOMAC Function, WOMAC Total, ICOAP Total score, and Weekly Average of Daily Pain NRS, of the Intention-to-Treat population (ITT). Error bars are 95 % CI. WOMAC: Western Ontario and McMaster Osteoarthritis Index




## SUBGROUP ANALYSES

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. Figure 3 shows the PainDETECT-subgroup, and the analysis of participants > 50 WOMAC pain at baseline (Group 1, N=95), and a KL-grade of the nontarget knee >2 (Group 2, N=105), and a combination of these two criteria (Group 3, N=64).

**Figure 3A**: Subgroup analyses of WOMAC pain change from baseline during the trial




As illustrated above, a positive effect of APPA compared to placebo was observed (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).

The exploratory subgroups suggest that OA subjects with higher symptomatic disease severity, and potential involvement of processes reflected in possible neuropathic changes and/or highly inflammatory-driven OA might benefit from APPA.

**Figure 3B**: Forest plot of subgroup analyses of WOMAC pain change difference from placebo at Week 4




## CONCLUSION

**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 indicating that further research in the effects of APPA in appropriate patients is warranted.**

**Table 2**: Treatment-emergent adverse events reported with a frequency of > 2 % in either treatment group.

| Safety population<br>System Organ Class<br>Preferred Term | APPA N=75 n (%), E | Placebo N=77 |
|---|---|---|
| All TEAEs | 25 (33.3) 38 | 27 (35.1) 40 |
| Gastrointestinal disorders | | |
| Diarrhoea | 3 (4.0) 4 | 0 |
| Dyspepsia | 2 (2.7) 2 | 0 |
| Gastrooesophageal reflux | 4 (5.3) 4 | 0 |
| General disorders and administration site condition | | |
| Feeling hot | 3 (4.0) 3 | 0 |
| Influenza like illness | 2 (2.7) 2 | 1 (1.3) 1 |
| Infections and infestations | | |
| Cystitis | 1 (1.3) 1 | 2 (2.6) 2 |
| Injury, poisoning and procedural complications | | |
| Contusion | 0 | 3 (3.9) 3 |
| Investigations | | |
| Red blood cells urine | 3 (4.0) 3 | 4 (5.2) 4 |
| White blood cells urine | 1 (1.3) 1 | 4 (5.2) 4 |
| Nervous system disorders | | |
| Headache | 3 (4.0) 4 | 2 (2.6) 2 |
| Rash | 2 (2.7) 2 | 1 (1.3) 1 |

## SAFETY

At least one adverse event was reported by 36.0 % and 41.6 % of study participants receiving APPA or placebo, respectively. APPA was well tolerated and as shown in Table 2, no differences in frequencies of reported AEs were noted, apart from a higher proportion of subjects reporting gastrointestinal discomfort reported with APPA compared to placebo. All but one reported AEs were mild to moderate.

In total, three participants discontinued the trial; two in the APPA group, and one receiving placebo.

One AE, “diarrhoea” in a participant receiving APPA led to discontinuation from the trial. During the trial one serious adverse event (prostate cancer) was reported, in a participant receiving placebo.

No clinically relevant changes were found on clinical biochemistry or hematology parameters, urine dipstick, vital signs nor ECG parameters.

## PERSPECTIVES

- OA patients with higher inflammatory involvement may experience higher symptom severity
- The findings that APPA may be more efficacious in OA patients with higher symptom severity may reflect anti-inflammatory effects by APPA
- Future research should evaluate the effect of APPA in OA patients with inflammatory-driven disease

## REFERENCES

1: Cross AL, Hawkes J, Wright HL, Moots RJ, Edwards SW. APPA (apocynin and paeonol) modulates pathological aspects of human neutrophil function, without supressing antimicrobial ability, and inhibits TNFα expression and signalling. Inflammopharmacology. 2020 Oct; 28(5):1223- 1235)