EFFICACY OF BIO-OPTIMIZED CURCUMA EXTRACT (Flexofytol®) FOR PAINFUL KNEE OSTEOARTHRITIS : data from COPRA, a multicenter randomized controlled study

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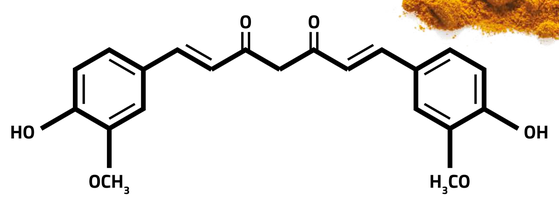
Flexofytol® is a ***Curcuma Longa* extract** with an increased bioavailibility (bio-optimized) by mixing curcuma extract with polysorbate in a well-defined ratio.



Population and study design

150 patients with symptomatic knee OA were randomized in a prospective double blinded, 3 parallel groups, comparative and multicenter study. Patients received 3 months continuous treatment with either high dose Flexofytol® (n=49, 140.01 mg Curcuma longa L. extract /treatment), low dose Flexofytol® (n=47, 93.34 mg *Curcuma longa* L. extract/treatment) or placebo (n=45, Sunflower seed oil fill ingredient). Each treatment corresponded to 3 oral capsules two times a day to respect the blinding. Study populations were described in TABLE 1.

TABLE 1

Study population

	Placebo	Low dose	High dose	Total
Randomized subject (ITT population)	47	49	54	**150**
Subjects who have one efficacy basal measure and at least one corresponding post-baseline efficacy measurement (FAS population)	45	47	49	**141**
All treated subjects who had not suffered any major protocol deviation (PP population)	25	27	26	**78**

Table1 : Detailed experimental population of the study. Full Analysis Set population (FAS), Intention To Treat (ITT) ; Per-Protocol Population (PP).

At inclusion, all patients took pain killers or anti-inflammatory drugs which were authorized during the study.

Efficacy and Safety Outcomes

The co-primary outcome measures were the variation of serum levels of sColl2-1 biomarker, a specific peptide of type II collagen molecule, between T0 and T3 (3 months) and the variation of Patient Global Assessment of Disease Activity (PGADA) using a Visual Analog Scale (VAS) between T0 and T3. TABLE 2.

TABLE 2

Co-primary endpoints-outcomes

- The variation of serum levels of sColl2-1 biomarker between T0 and T3.
- The variation of global assessment of disease activity using a VAS between T0 and T3.

Secondary endpoints-outcomes

- The variation of serum levels of sColl2-1 (biomarker of cartilage degradation) and ultrasensitive CRP biomarkers between T0 and the different time points (1 and 3 months).
- The variation of pain and function between T0 and the different time points :
  - Mean knee pain over the last 24 hours using a visual analogue scale (VAS)
  - Global assessment of disease activity using a VAS
  - Knee Injury and Osteoarthritis Outcome Score (KOOS) index and its subscale scores using a self-administered questionnaire
- The tolerance as the incidence of adverse events and as the incidence of drop-outs.
- The compliance assessed by counting the capsules within the investigation kits brought back by the patient at each follow-up visit and by curcumin level monitoring in serum samples.
- The patients' satisfaction with treatment evaluated by the investigator at each follow-up visit by a five-category scale i.e. better, little better, same, little lower or far lower.
- The use of rescue treatments i.e. Paracetamol and oral NSAIDs during the month prior to each visit was recorded at each visit.

RESULTS

DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

In the FAS population, the mean age of patients was 61.8 years with a majority of women (80.1%) having a diagnosed OA for a mean (SD) of 7.20 (7.269) years concerning the right knee (52.2%). The mean (SD) KL grading was 2.4 (0.5) and the mean (SD) BMI was 29.7 (5.09) kg/m². 99.3% of patients had an history of mean knee pain ≥ 40 in the last 3 months before inclusion and all of them suffered at inclusion of a mean (SD) knee pain in the last 24 hours of 62.09 (14.072). All these baseline characteristics were not significantly different between groups (TABLE 2).

TABLE 3

Demographic and baseline characteristics of patients

		Flexofytol® high dose N=49	Flexofytol® low dose N=47	Placebo N=45
Age (years)	Mean (SD)	60.9 (9.78)	61.4 (7.49)	63.3 (7.69)
Sex, n (%)	Female	39 (79.6)	40 (85.1)	34 (75.6)
BMI (kg/m2)	Mean (SD)	29.4 (4.87)	30.4 (5.23)	29.4 (5.2)
Time from diagnosis of knee OA (years)	Mean (SD)	7.41 (7.294)	6.6 (4.671)	7.6 (9.3)
KL grade, n (%)	Grade I	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Grade II	31 (63.3%)	27 (57.4%)	29 (64.4%)
	Grade III	18 (36.7%)	19 (40.4%)	16 (35.6%)
	Grade IV	0 (0.0%)	1 (2.0%)	0 (0.0%)
Target knee (the most symptomatic), n (%)	Right	27 (55.1%)	22 (46.8%)	25 (55.6%)
Target knee pain (VAS, mm)	Mean (SD)	62.9 (13.8)	63.3 (15.8)	59.9 (12.3)
Coll2-1 (nM)	Mean (SD)	384.2 (141.3)	373.8 (133.5)	384.7 (122.0)

FLEXOFYTOL® DECREASED SERUM COLL2-1 LEVELS, A BIOMARKER OF CARTILAGE DEGRADATION

Comparison of time evolution curves showed that sColl2-1 levels were lower in the treated groups but differences were not significant (Figure 1). Looking at absolute difference, complementary analyses of sColl2-1 performed on PP population, revealed a significant difference between treated (pooled low and high dose groups) and placebo groups at T3 values (Figure 2).

FLEXOFYTOL® DECREASED PATIENT GLOBAL ASSESSMENT OF DISEASE ACTIVITY

The decrease in PGADA overtime was higher in Flexofytol® groups after one and three months than in placebo but difference between groups was not significant (Figure 3). Using pooled values for treated groups (Flexofytol® high plus low dose), PGADA was significantly reduced in Flexofytol® group compared to placebo at T1 and T3 (Figure 4).

FLEXOFYTOL® DECREASED QUICKLY AND SIGNIFICANTLY OA PAIN

Knee pain over the last 24 hours significantly decreased in the three groups with time. Interestingly, pain decrease was already significant after 1 and 3 months in the Flexofytol® groups, while significance was only reach after 6 months in the placebo group (Figure 5). Using complementary analyses in the ITT population and after three months of treatment, pain relief was significantly higher in the Flexofytol® groups than in the placebo (p=0.032). After one month of treatment, the VAS value was only significantly decreased in the low dose Flexofytol® group (p=0.043). The improvement in pain observed in the Flexofytol low dose group corresponds to an effect size (ES) of 0.35 for pain at T1 and 0.43 at T3. Flexofytol treated goups had a higher improvement of global KOOS and KOOS subscores than placebo group but differences between groups were not significant (Table 4).

FIGURE 1

Evolution of sCOLL2-1 in the three groups (Mean ± SE)

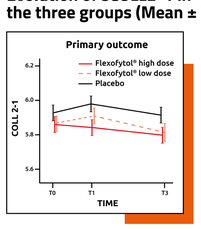


FIGURE 2

Absolute difference (from baseline) for sCOLL2-1

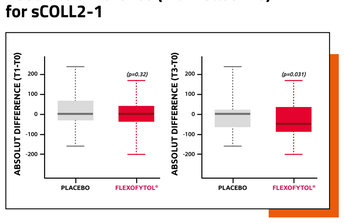


FIGURE 3

Evolution of PGADA in the three groups (Mean ± SE)

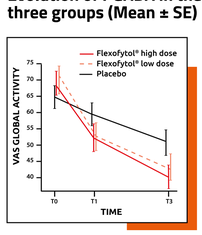


FIGURE 4

Absolute difference (from baseline) for PGADA

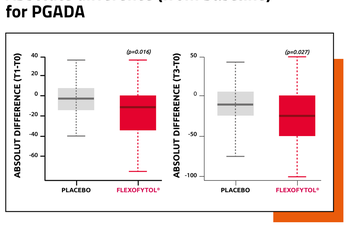
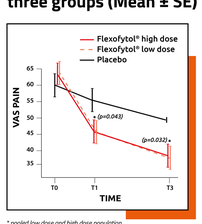


FIGURE 5

Evolution of VAS pain in the three groups (Mean ± SE)



* pooled low dose and high dose population.

FLEXOFYTOL® REDUCED NSAIDS CONSUMPTION

The mean paracetamol or NSAIDS intake decreased with time in all groups but no significant difference was observed between groups at the different time points. While global analyses did not reveal any significant difference between groups at the different time points, complementary analyses on FAS population, covering within groups difference revealed that only subjects of the Flexofytol® high dose group showed a significant decrease in the intake frequency of paracetamol at the different time points (p=0.031 at T1, p=0.0016 at T3) while no variation with time was observed in low dose and placebo group. For NSAIDS, a significant decrease of intake frequency was observed only in the low dose group (p=0.038 at T1, p=0.029 at T3).

EFFECTS OF FLEXOFYTOL ON KOOS SCORES

KOOS global score and subscales were significantly improved overtime in all groups (p<0.001) and the evolution was found comparable within the three groups in the FAS population (table 2). Although KOOS global score and subscales changes to T1 and T3 tended to be more important in the BCL groups, no significant difference between groups was found.

TABLE 4 KOOS changes between the follow-up visits (T3 and T1) and baseline - FAS population

		BCL high dose Mean+/-SD	BCL low dose Mean+/- SD	Placebo Mean+/-SD
	N	**49**	**46**	**45**
KOOS change at T1 (Difference between T1 and baseline)	Global score	35.2 ± 67.5	18.0 ± 57.6	7.9 ± 60.2
	Pain	7.1 ± 17.5	4.8 ± 16.7	3.1 ± 13.9
	Symptoms	6.7 ± 15.2	2.9 ± 13.6	1.7 ± 14.6
	Function in daily living (ADL)	5.9 ± 19.6	4.0 ± 16.5	1.4 ± 13.2
	Function in sport and recreation (Sport/Rec)	10.5 ± 18.0	4.2 ± 16.7	2.3 ± 15.4
	Knee related Quality of life (QOL)	5.6 ± 14.8	3.1 ± 14.9	-0.2 ± 16.2
	N	**47**	**38**	**40**
KOOS change at T3 (Difference between T3 and baseline)	Global score	56.3 ± 82.6	48. ± 73.1	42.1 ± 66.2
	Pain	12.3 ± 19.4	12.8 ± 18.4	10.8 ± 16.5
	Symptoms	10.0 ± 16.6	7.4 ± 16.0	7.5 ± 14.7
	Function in daily living (ADL)	9.2 ± 19.5	10.3 ± 20.9	7.3 ± 14,6
	Function in sport and recreation (Sport/Rec)	11.1 ± 20.5	9.6 ± 15.3	9.7 ± 17. 8
	Knee related Quality of life (QOL)	12.4 ± 20.3	9.2 ± 19.3	6.6 ± 16.8

CONCLUSION

Flexofytol®, at a low dose, induced a rapid symptomatic relief of knee pain and a beneficial effect on the patient assessment of disease. Further, at low dose Flexofytol® reduced NSAIDs consumption and showed an excellent safety. This study suggests some beneficial effects of Flexofytol® in symptomatic knee OA over 1 and 3 months, and provides information on the dose to use and the design of a larger phase III clinical trial.