Université Paris Cité

A randomized placebo-controlled trial of oral resveratrol for patients with painful knee osteoarthritis (ARTHROL)

Prof. Christelle NGUYEN, MD, PhD
Paris, FRANCE

Université Paris Cité, Faculté de Santé, UFR de Médecine
AP-HP.Centre, Hôpital Cochin, Rééducation de l'Appareil Locomoteur et des Pathologies du Rachis,
INSERM UMR-S1124, Campus St-Germain-des-Prés

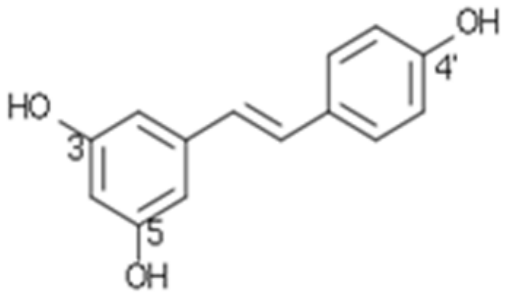
Disclosures

ARTHROL was funded by the French Ministry of Health (PHRC National 2015)

MINISTÈRE
DES SOLIDARITÉS
ET DE LA SANTÉ
Liberté
Égalité
Fraternité

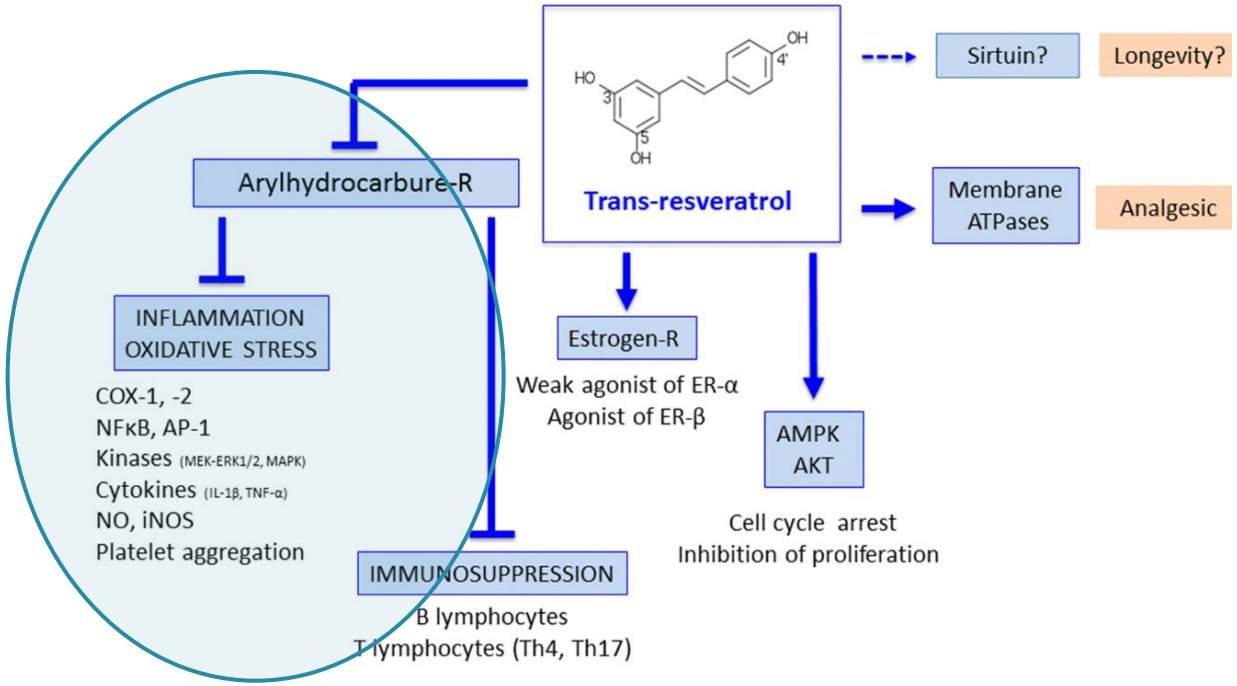
Trans-resveratrol (3,5,4’-trihydroxystilbene, t-Res)

- Parent compound of a family of **hydroxystilbenes**
- Present in spermatophyte plants: **grapevine, peanuts, pine or Chinese knotweed**



Nguyen C et al, Nutrients 2017

t-Res effects in osteoarthritis (OA) models



Available over the counter

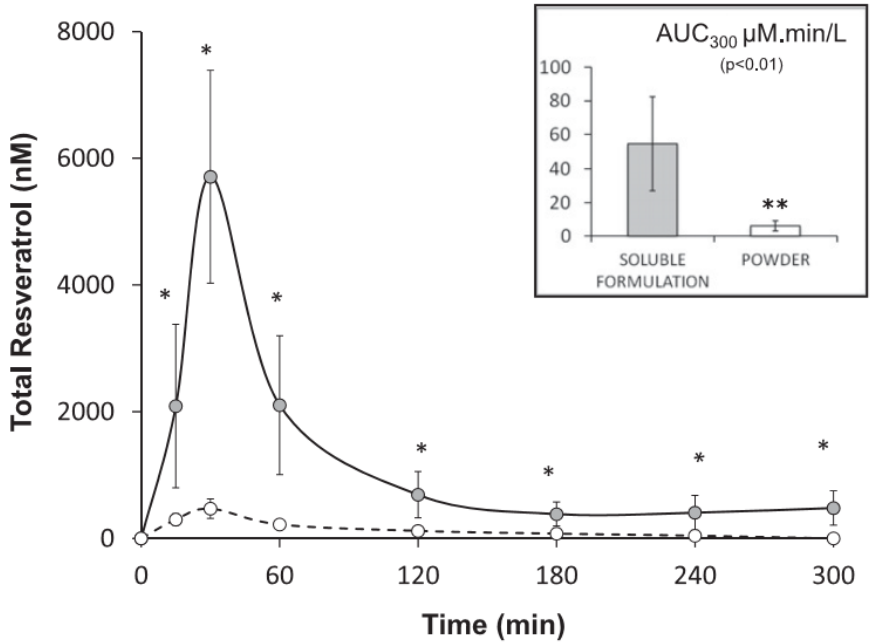
3 RCTs in knee pain / OA

- 75 mg 2/d: no effect
- 500 mg 1/d: ↘ pain at M3

Nguyen C et al, Nutrients 2017
Wong RHX et al. Menopause 2017
Thaung Zaw JJ et al. Menopause 2020
Huassain SA et al. Clin Interv Aging 2018

Low biodegradibility, a drawback to clinical translation

➔ Innovative formulation consisting in a **complex dietary oil solution** of 20 mg t-Res embedded in a caplet **(patent WO: YVERY n° 2010/007252)**



Following oral administration of 40 mg (2 caplets):

- AUC_{300} was 54.7 mM min/L versus 6.1 mM min/L for the powder
- **Total $AUC_{0-\alpha}$ values were 8.5 times higher for the soluble formulation**

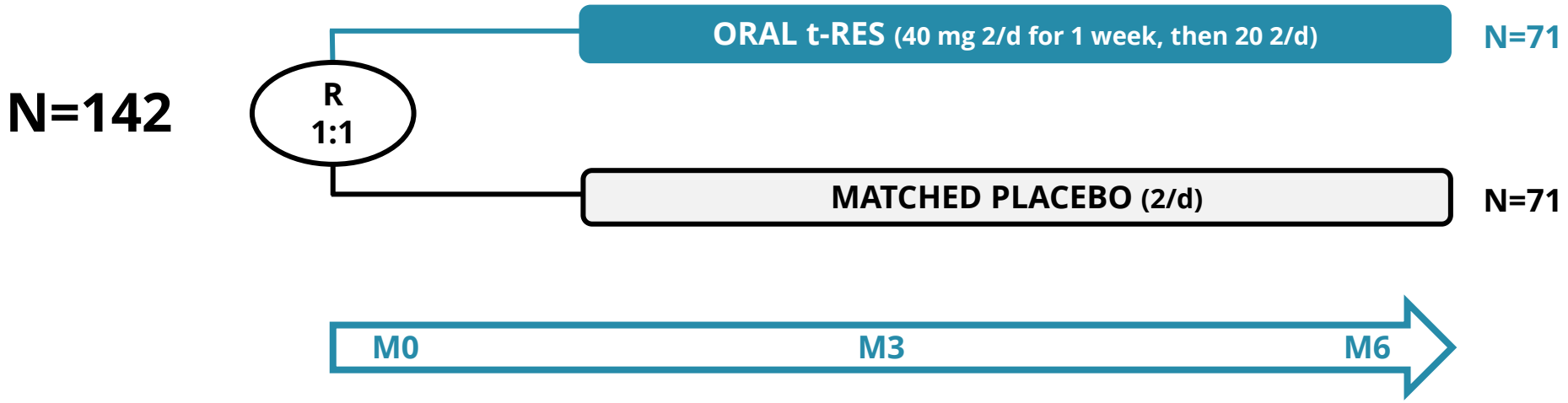
Nguyen C et al, Nutrients 2017

Primary objective of ARTHROL trial

To compare the effects of oral t-Res, in this innovative formulation, **as an add-on therapy to usual care**, with those of matched oral placebo, for individuals with painful knee OA on knee pain variations at 3 months

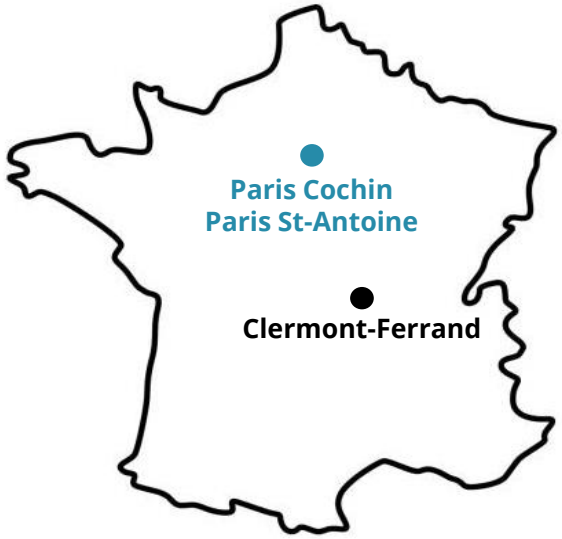
Design and interventions

Double-blind, randomized, placebo-controlled trial



Nguyen C et al, BMJ Open 2017

Participants



Recruitment

- From **November 2017 to November 2021**
- 3 tertiary care centres in FRANCE
- 6 board-certified physicians (rheumatologists and/or physiatrists), with experience as trialists
- In- and outpatients of the departments

Inclusion criteria

- ≥ 40 years old
- 1986 ACR criteria for knee OA
- Pain involving the knee
- **Duration ≥ 1 month**
- **Intensity ≥ 40/100** on the day of assessment
- **K-L 1, 2 or 3** on X-rays

Exclusion criteria

- History of inflammatory rheumatic diseases
- Neurological disorders involving the lower limbs
- Knee trauma ≤ 2 months
- Intra-articular injections ≤ 2 months
- Knee surgery ≤ 1 year
- Contraindication to resveratrol
- Current use of anticoagulants
- Current use of IM, IV and/or oral corticosteroids

Outcomes

Primary	**Mean change in knee pain**	**3 months**
Secondary	Mean change in knee pain	6 months
	Mean change in WOMAC function	3 and 6 months
	Mean change in patient global assessment	3 and 6 months
	OARSI-OMERACT response	3 and 6 months
	Intra-articular injections	3 and 6 months
	Analgesics	3 and 6 months
	NSAIDs	3 and 6 months

Analyses

Sample size calculation

- α risk of .05, power (1-β) of .90
- **Predicted mean difference in mean change in knee pain at 3 months of 15 (27) points (ES ~ .55) ➔ 69 participants in each group were needed**

Descriptive analyses

- Categorical variables were described with frequencies and percentages
- Quantitative variables were described with mean (SD)

Comparative analyses: all were conducted on an intent-to-treat basis

- Continuous outcomes: constrained longitudinal data analysis model
- Dichotomous outcomes: Poisson model with log link under regression standardization framework for estimating the marginal measure of association

All statistical tests were 2-sided: with P < .05 considered statistically significant

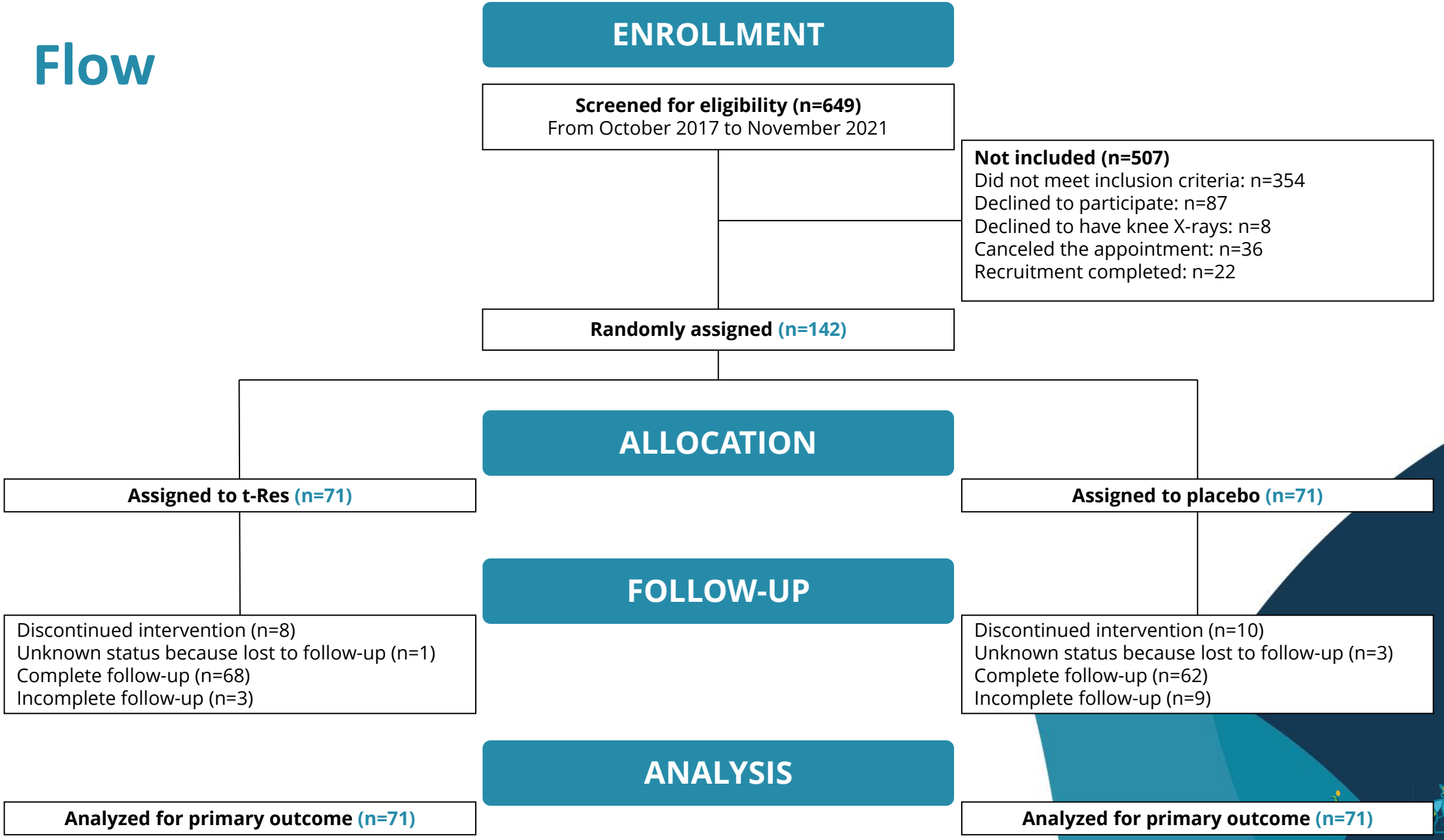
Results

Oral resveratrol in adults with knee osteoarthritis: a randomized placebo-controlled trial (ARTHROL)

Christelle Nguyen MD, PhD, Emmanuel Coudeyre MD, PhD, Isabelle Boutron MD, PhD, Gabriel Baron PhD, Camille Daste MD, MPH, Marie-Martine Lefèvre-Colau MD, PhD, Jérémie Sellam MD, PhD, Jennifer Zauderer MD, Francis Berenbaum MD, PhD, François Rannou MD, PhD

Nguyen C et al, PLOS MED, 2024 (in revision)

Flow

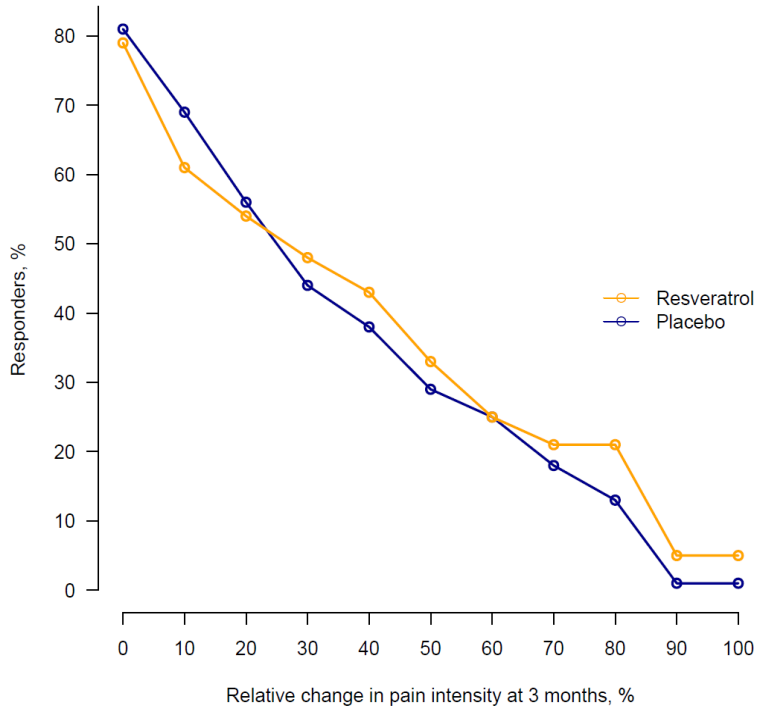

ENROLLMENT
Screened for eligibility (n=649)
From October 2017 to November 2021
Not included (n=507)
Did not meet inclusion criteria: n=354
Declined to participate: n=87
Declined to have knee X-rays: n=8
Canceled the appointment: n=36
Recruitment completed: n=22
Randomly assigned (n=142)
ALLOCATION
Assigned to t-Res (n=71)
Assigned to placebo (n=71)
FOLLOW-UP
Discontinued intervention (n=8)
Unknown status because lost to follow-up (n=1)
Complete follow-up (n=68)
Incomplete follow-up (n=3)
Discontinued intervention (n=10)
Unknown status because lost to follow-up (n=3)
Complete follow-up (n=62)
Incomplete follow-up (n=9)
ANALYSIS
Analyzed for primary outcome (n=71)
Analyzed for primary outcome (n=71)

Participants

	t-Res n=71	Placebo n=71	Total n=142
• Age (years), mean (SD)	59.8 (8.9)	63.0 (10.1)	61.4 (9.6)
• Women, n (%)	50 (70)	51 (72)	101 (71)
• Body mass index (kg/m²), mean (SD)	28.3 (6.7)	28.3 (5.6)	28.3 (6.2)
Treatments in the previous 3 months, n (%)			
• Intra-articular corticoids and/or hyaluronan	13/70 (19)	7/70 (10)	20/140 (14)
• Non-opioid oral analgesics	40/68 (59)	46/69 (67)	86/137 (63)
• Oral NSAIDs	32/70 (46)	29/70 (31)	61/140 (44)
• Home-based exercises	27 (38)	31 (44)	58 (41)
• Weight management	30 (42)	22 (31)	52 (37)
Clinical characteristics, mean (SD)			
• **Knee pain intensity (NRS, 0-100)**	56.9 (14.0)	55.5 (13.1)	**56.2 (13.5)**
• **Knee pain duration (years)**	8.2 (7.6)	8.9 (8.7)	**8.5 (8.2)**
• **WOMAC function (0-68)**	44.1 (16.0)	44.4 (16.9)	**44.2 (16.4)**
• Patient global assessment (NRS, 0-100)	69.2 (20.1)	63.0 (22.0)	66.1 (21.2)
X-ray findings in femorotibial or patellofemoral compartments, n (%)			
• Maximal KL grade 1	13 (18)	11 (16)	24 (17)
• Maximal KL grade 2	22 (31)	23 (32)	45 (32)
• **Maximal KL grade 3**	36 (51)	37 (52)	**73 (51)**

Primary outcome at 3 months

	t-Res n=71	Placebo n=71	Absolute difference (95% CI)	p
Change in knee pain (NRS, 0-100), mean (95% CI)	**-15.7** (-21.1 to -10.3)	**-15.2** (-20.5 to -9.8)	**-0.6** (-8.0 to 6.9)	0.88



~ 55% participants **had a 20% reduction in knee pain** intensity at 3 months **in both groups**

Secondary outcomes

	t-Res n=71	Placebo n=71	Absolute difference (95% CI)	Relative risk (95% CI)	p
3 months after randomization					
Change in WOMAC function (0-68), mean (95% CI)	-9.2 (-13.0 to -5.4)	-10.6 (-14.3 to -6.8)	1.4 (-3.9 to 6.7)	-	0.59
Change in PGA (NRS, 0-100), mean (95% CI)	1.4 (-3.3 to 6.2)	1.2 (-3.5 to 5.9)	0.2 (-5.9 to 6.4)	-	0.95
OARSI-OMERACT response, n (%)	34/66 (52)	**34/68 (50)**	1.5 (-15.3 to 18.3)	1.03 (0.74 to 1.43)	0.86
Intra-articular corticoids and/or hyaluronan, n (%)	5/67 (8)	6/67 (9)	-1.6 (-10.7 to 7.5)	0.82 (0.27 to 2.51)	0.73
Analgesics, n (%)	38/67 (57)	39/64 (61)	-4.5 (-21.4 to 12.4)	0.93 (0.70 to 1.24)	0.60
NSAIDs, n (%)	18/66 (27)	24/67 (36)	-8.9 (-24.4 to 6.8)	0.75 (0.46 to 1.25)	0.27
6 months after randomization					
Change in knee pain (NRS, 0-100), mean (95% CI)	-16.8 (-23.4 to -10.3)	-17.1 (-23.4 to -10.9)	0.4 (-8.4 to 9.1)	-	0.93
Change in WOMAC function (0-68), mean (95% CI)	-12.6 (-17.3 to -8.0)	-9.4 (-14.0 to -4.9)	-3.2 (-9.5 to 3.1)	-	0.32
Change in PGA (NRS, 0-100), mean (95% CI)	1.8 (-4.2 to 7.9)	1.9 (-3.9 to 7.8)	-0.2 (-7.7 to 7.5)	-	0.98
OARSI-OMERACT response, n (%)	29/60 (48)	**34/66 (52)**	-3.6 (-21.1 to 13.9)	0.93 (0.74 to 1.43)	0.68
Intra-articular corticoids and/or hyaluronan, n (%)	7/60 (12)	5/65 (8)	4.0 (-6.2 to 14.1)	1.51 (0.55 to 4.39)	0.44
Analgesics, n (%)	30/59 (51)	33/63 (52)	-2.6 (-20.2 to 15.0)	0.95 (0.68 to 1.34)	0.77
NSAIDs, n (%)	15/60 (25)	20/65 (31)	-6.5 (-22.0 to 9.0)	0.79 (0.45 to 1.39)	0.41

Discussion

Main result

- No evidence of a reduction in knee pain at 3 months with this formulation of oral t-Res

Main interpretation

- Oral t-Res may not be effective in this indication
- Oral t-Res may not have a sufficient biological effect on the pain pathways involved in OA

Other hypotheses

- Low bioavailability of t-Res in the targeted tissues?
- “Severe” population: long-lasting and high levels of pain and activity limitations?

Limitations

- No control of co-interventions ➔ reflect the use of t-Res as an add-on therapy
- Underpower (optimistic hypothesis) ➔ more conservative hypothesis (ES ~ .30)

Summary and perspectives

The absolute mean change from baseline in knee pain at 3 and 6 months did not differ between participants who received oral t-Res and those who received matched oral placebo

Our findings do not support the use of t-Res supplementation, in this formulation, for reducing knee pain in adults with painful knee OA

Ackowledgements

MINISTÈRE DES SOLIDARITÉS ET DE LA SANTÉ
Liberté
Égalité
Fraternité

URC Paris Centre CIC

Dr. Hendy Abdoul, Dr. Laëtitia Peaudecerf, Dr. Claire du Ranquet

Principal Investigator

Prof. François Rannou

Scientific Director

Prof. Christelle Nguyen

Methodologist

Prof. Isabelle Boutron

Statistician

Dr. Gabriel Baron

Investigators Paris Cochin

Dr. Camille Daste

Dr. Marie-Martine Lefèvre-Colau

Dr. Jennifer Zauderer

Investigators Paris St-Antoine

Prof. Francis Berenbaum

Prof. Jérémie Sellam

Investigator Clermont-Ferrand

Prof. Emmanuel Coudeyre

Thank you

christelle.nguyen2@aphp.fr
@cchnguyen

MÉDECINE
Santé
Université Paris Cité