Quel traitement de comparaison ?

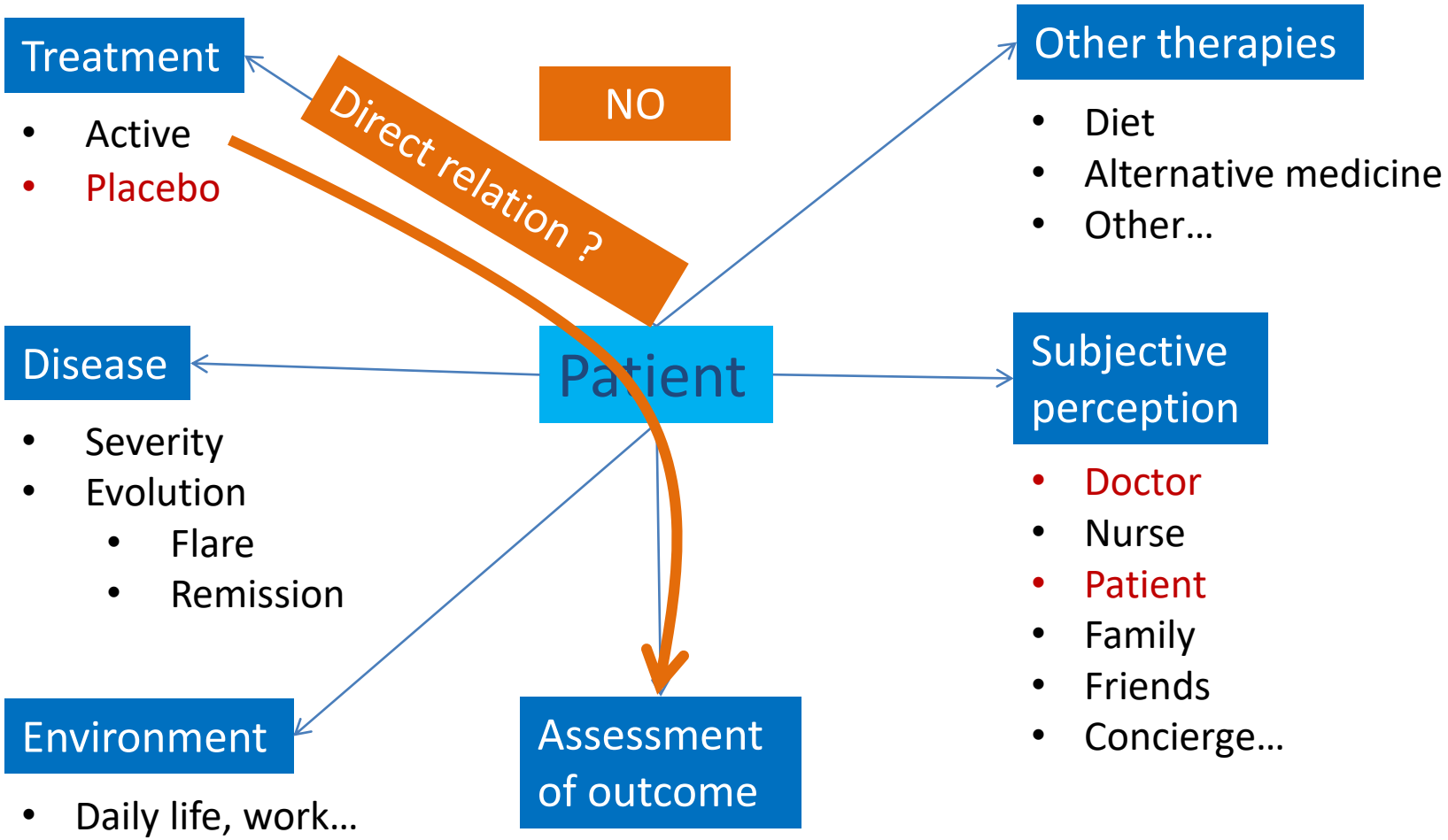
La comparaison à un placebo est-elle toujours éthique ?

- **Placebo**
- **Traitement de référence**

VUE INTÉRIEURE DE L'HOTEL-DIEU.

Pr Olivier CHASSANY
EA 7334, Patient-Centered Outcomes, Université Paris-Diderot
URC-ECO (Economie de la Santé), Hôpital Hôtel-Dieu

Factors influencing the outcome of the disease ?



Apply to most diseases: HTA, diabetes, pain, acne, osetoarthritis…

Placebo response in clinical trials

Pain	Outcome	%
Migraine	sedation	25%
Acute nephritic colic	partial or complete sedation 30 min after infusion	30%
Cancer pain	short term improvement in patients suffering from bone metastatic pain or other cancers	30-40%
IBS	pain improvement	40-70%

Chassany O, Duracinsky M. Clinical trials of pharmaceuticals; ethical aspects.
In Pharmaceutical Ethics. Salek S, Edgar A (ed), Wiley, 2002.

Placebo response in clinical trials

Conditions	Outcome	%
Hypertension	**Diastolic blood pressure < 90 mm Hg**	**30%**
Duodenal ulcer	Healing at 4 weeks	40-50%
GERD	Partial or complete resolution of pyrosis	9-69%
Dyspepsia	Symptom improvement	13-73%

Chassany O, Duracinsky M. Clinical trials of pharmaceuticals; ethical aspects.
In Pharmaceutical Ethics. Salek S, Edgar A (ed), Wiley, 2002.

Placebo response in clinical trials

Severe conditions	Outcome	%
Schizophrenia	Improvement	6-43%
Depression	**Improvement > 50% in Hamilton score**	**30-40%**
Ulcerative colitis	Clinical benefit	39%
Chronic arterial disease	Improvement of claudication distance	60%

Chassany O, Duracinsky M. Clinical trials of pharmaceuticals; ethical aspects.
In Pharmaceutical Ethics. Salek S, Edgar A (ed), Wiley, 2002.

Revestive (teduglutide) in short-bowel syndrome (syndrome de l'intestin court)

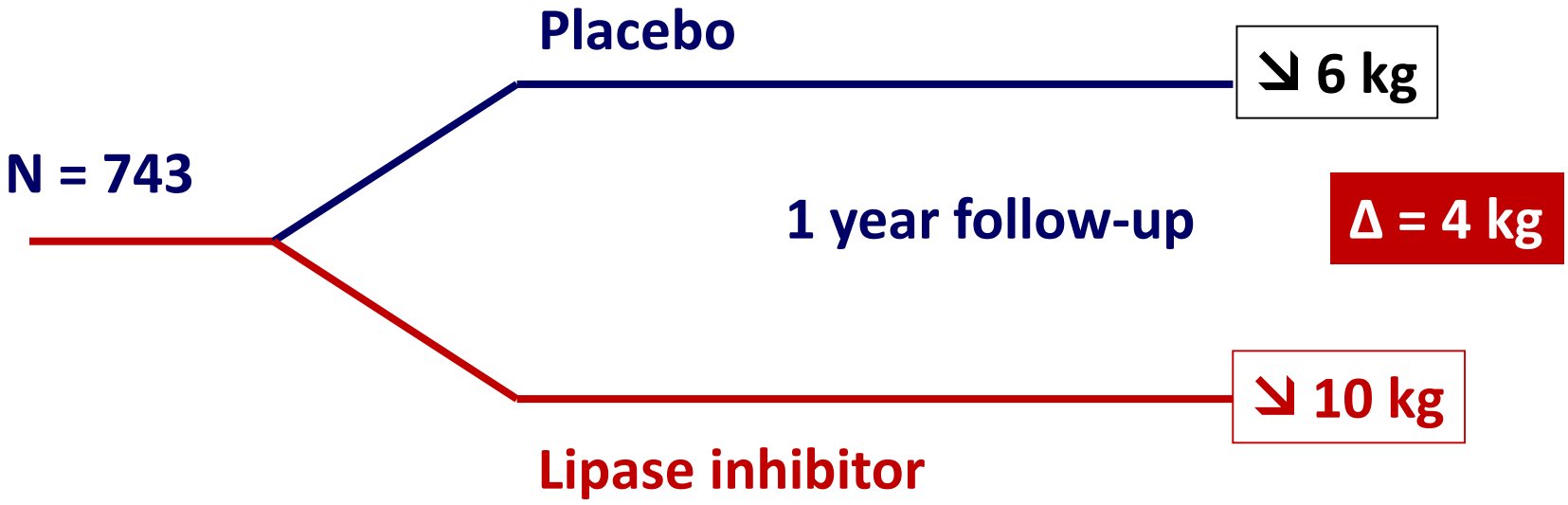
	Revestive	Placebo	p
Proportion of subjects achieving a 20% to 100% reduction of parenteral nutrition at Week 20 and 24	62.8%	**30.2%**	p=0.002
reduction in parenteral nutrition requirements at 24 weeks	4.4l/week	2.3l/week	
Proportion of subjects achieved at least a one day reduction in parenteral nutrition administration	48.8%	**20.9%**	p=0.008

EMA Marketing Authorisation 2012
Source http://www.ema.europa.eu/
Summary of Products Characteristics

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

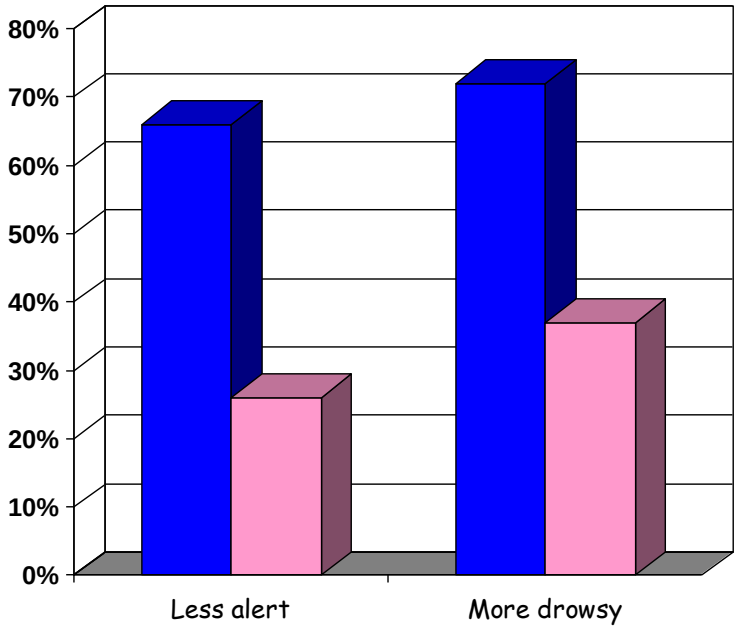
Placebo response in clinical trials

Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group



Sjöström L, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. Lancet 1998;352:167-72.

Demonstration to medical students of placebo responses and non-drug factors



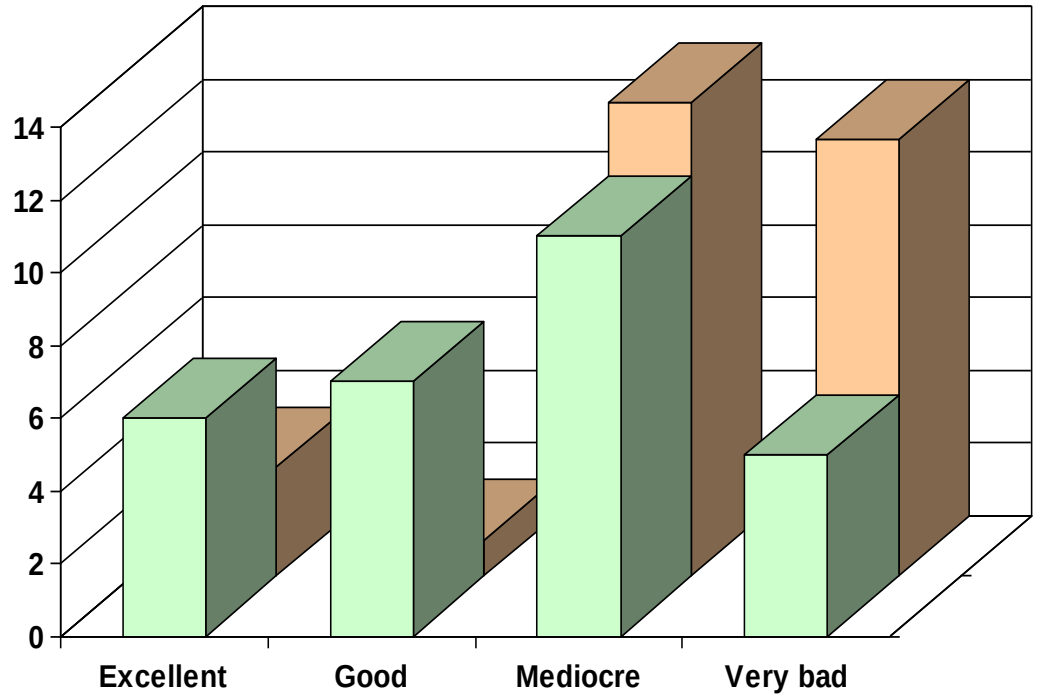
- 56 medical students
- Were told they would receive either a sedative or stimulant drug

- In fact : all received a **blue** or **pink** placebo

NOCEBO effect : 18 subjects (32%) noted side-effects, the commonest was headache (n=9). Other complaints included difficulty in concentrating & dizzy feelings (2 subjects each), and hyperactivity, abdominal discomfort, tingling or watery eyes, and ataxia (1 subject each). Later in the day, 2 subjects felt sufficiently concerned about these effects to seek reassurance from faculty members.

Blackwell B. Demonstration to medical students of placebo responses and non-drug factors. Lancet 1972

Does informed consent influence therapeutic outcome ?



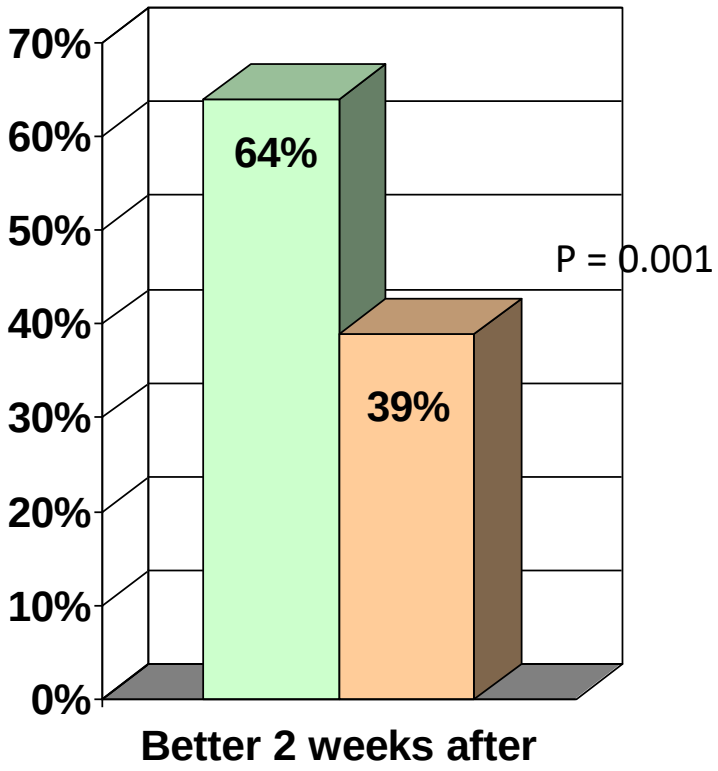
$P < 0.05$
Wilcoxon's
signed rank test

Informed consent (n=30)

Control group (n=30)

Dahan R, et al. A clinical trial of the hypnotic activity of placebo in patients admitted to hospital. BMJ 1986.

General practice consultation : is there any point being positive ?



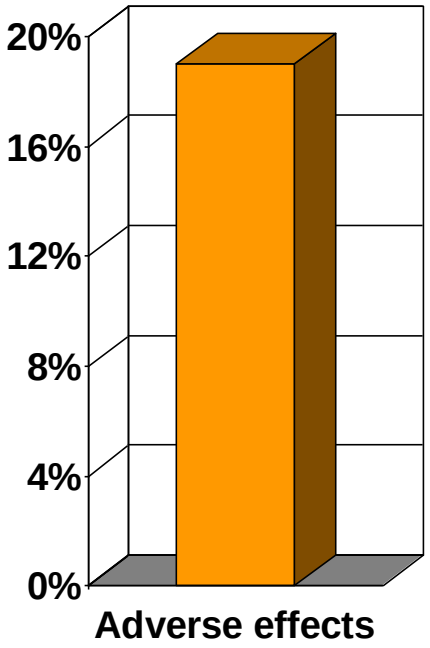
- Patients with minor illness
- Randomly assigned to the information :

“You will be better in a few days”

“I am not certain what is the matter with you”

Thomas KB et al. General practice consultation : is there any point being positive ? BMJ 1987.

The nocebo effect in healthy volunteers



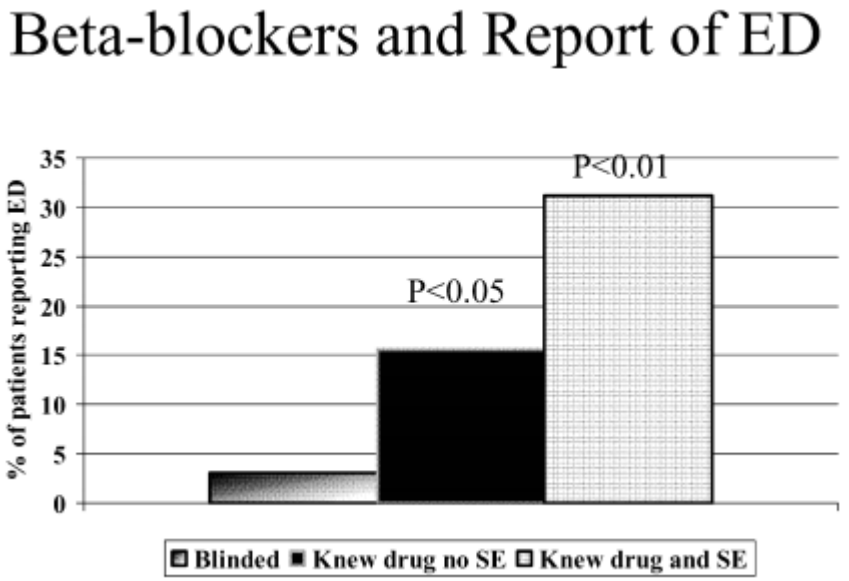
- 109 double-blind trials
- Healthy volunteers
- Overall incidence of adverse effects during placebo administration

Rosenzweig P et al. The placebo effect in healthy volunteers. Influence of experimental conditions on the adverse effects profiles during phase I studies. Clin Pharmacol Ther 1993.

Effect nocebo
Exemple dysfonction sexuelle

- 96 patients hypertendus, répartis en 3 groupes et traités par aténolol 50 mg/jr, et évalués à 3 mois sur d'éventuels effets indésirables sexuels

Groupe	Information donnée	% d'EI sexuels
1 (n = 32)	Pas d'information sur le médicament reçu	**3%**
2 (n = 32)	Information sur la nature du médicament mais pas sur les potentiels EI sexuels	**16%**
3 (n = 32)	Information sur le médicament et les EI sexuels	**31%**



Silvestri A, et al. Report of erectile dysfunction after therapy with beta-blockers is related to patient knowledge of side effects and is reversed by placebo. Eur Heart J 2003; 24: 1928-32.

Placebo-associated blood pressure response and adverse effects in the treatment of hypertension

Symptom	Active treatment	
Sleepiness	11.8	
Fatigue	9.2	
Vivid dreams	2.4	
Joint pain	10.9	

Preston RA et al. Placebo-associated blood pressure response and adverse effects in the treatment of hypertension. Arch Intern Med 2000.

Barsky AJ. Nonspecific medication side effects and the nocebo phenomenon. JAMA 2002.

Placebo-associated blood pressure response and adverse effects (NOCEBO) in the treatment of hypertension

- Placebo control aids in properly assigning adverse-effect profiles to medications. High rates of adverse events would have been incorrectly assigned to active drug treatment if a placebo control was not included

Symptom	Active treatment	Placebo group
Sleepiness	11.8	**6.6**
Fatigue	9.2	**7.5**
Vivid dreams	2.4	**4.8**
Joint pain	10.9	**16.6**

Preston RA et al. Placebo-associated blood pressure response and adverse effects in the treatment of hypertension. Arch Intern Med 2000.

Barsky AJ. Nonspecific medication side effects and the nocebo phenomenon. JAMA 2002.

Placebo-controlled trials in depression : increased risk of suicide ?

- Concern about the possibility of risk for **suicide** in placebo-group
- Suicide is a rare event in clinical trials because patients at high risk for suicide are **excluded** from outpatient trials of new antidepressants and trial participants are closely monitored for suicidal thoughts
- Evaluation of 2500 patients in placebo-controlled and active-control studies of fluoxetine : **no increase in suicides or suicide attempts among placebo-treated patients**
- Review of controlled trials of antidepressants approved for marketing (1981-1997) in almost 20 000 patients : **no difference between placebo-treated and drug-treated groups**

Beasley CM. Fluoxetine and suicide: a meta-analysis of controlled trials in depression. BMJ 1991.
Khan A, et al. Symptom reduction and suicide risk in patients treated with placebo in antidepressant clinical trials: an analysis of the FDA database. Arch Gen Psychiatry 2000

Placebo-controlled trials in diabetes

- Placebo-controlled trials are **necessary** to get relevant information on the hypoglycemic effect of the investigational drug
- However, placebo-controlled trials may be viewed as unethical in certain circumstances
- Placebo-controlled studies of **3 to 6 months duration** should therefore be reserved for patients at an **early** stage of the disease, who are not already on treatment…
- Candidates for this trial should have a relatively **low HbA1C** (e.g. less than 8.5%)
- Protocols will need to stipulate that patients will be **withdrawn** from the study if their glucose control consistently deteriorates
- For trials of less than 3 months duration, patients with higher HbA1C (e.g. less than 10%) may be enrolled

Note for guidance - On clinical investigation of medicinal products in the treatment of diabetes mellitus (type 2). CPMP, 26 july 2001.

Quel traitement de comparaison ?

- Toujours s'assurer d'une supériorité du nouveau médicament au placebo, sauf :

- **Pathologies sévères ou fatales pour lesquelles des médicaments efficaces sont disponibles**
  - **Embolie pulmonaire**
  - **Infections (méningite, pneumonie…)**
  - **Infarctus du myocarde**

- Placebo seul non éthique dans ces situations :

→ essai en add-on: tous les patients doivent recevoir le traitement de référence efficace, un groupe reçoit en plus le nouveau médicament et l'autre groupe son placebo

Supériorité versus non-infériorité ou équivalence

- **Supériorité** versus placebo ou traitement de référence : démontrer que le nouveau médicament est supérieur du comparateur d'une certaine valeur **(différence minimale importante)**

- **Non-infériorité (ou équivalence)** : démontrer que le nouveau médicament n'est pas inférieur (ou ne diffère pas) d'un traitement de comparaison d'une certaine valeur **(différence maximale)**
  - **Quand ?**
    - Impossible (et non pertinent) de pouvoir démontrer une supériorité par rapport à un traitement de référence déjà très efficace
    - Non éthique de se comparer au placebo (VIH, anticoagulants)

Quel traitement de comparaison ?

Randomisation → Nouveau traitement
Randomisation → Placebo

Essai de supériorité

Randomisation → Nouveau traitement
Randomisation → Traitement de référence

Essai de supériorité ou de non-infériorité

Randomisation → Nouveau traitement
Randomisation → Traitement de référence
Randomisation → Placebo

Essai de supériorité ou non-infériorité vs référence

Et supériorité vs placebo

Randomisation → Traitement de référence + Nouveau traitement
Randomisation → Traitement de référence + Placebo

Add-on

Essai de supériorité

Placebo – est-il encore éthique ? exemple dans le psoriasis

N = 671 (full analysis set)	Dimethyl fumarate (DMF) N = 267	Fumaderm N = 276	Placebo N = 131
Randomization	2	2	1
PASI – 16-wk	**38%**	**40%**	**15%**
Clear or almost clear (Physician Global Assessment, PGA) 16wk	**33%**	**37%**	**13%**

Mrowietz U, et al. Efficacy and safety of LAS41008 (dimethyl fumarate) in adults with moderate-to-severe chronic plaque psoriasis: A randomised, double-blind, Fumaderm(®) and placebo-controlled trial (BRIDGE). Br J Dermatol. 2016 Aug 12. doi: 10.1111/bjd.14947