DIFFERENT TYPES OF TRIALS FOR DIFFERENT OBJECTIVES: EXAMPLES FOR MOVEMENT DISORDERS (Parkinson disease)

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Conflicts of interest

Pr Rascol has received scientific grants from the French Ministry of Health (Programme Hospitalier de Recherche Clinique), the French Ministry of Research (Agence Nationale de la Recherche), France-Parkinson and has served as a scientic advisor or a consultant to drug companies developping and marketing medications for the treatment of PD including Addex, Boehringer-Ingelheim, Chelsea, GSK, Lundbek, Merck, Merz, Osmotica, Oxford Biomedica, Novartis, Orion, TEVA, UCB …

Learning Objectives:

- To acknowledge the importance of defining clear objective(s) for clinical trials in PD

- To identify the main outcome measurements available to assess efficacy in PD

- To understand the main trial designs used to show efficacy in PD

Different clinical trials in PD have different objectives. Such objectives strongly impact on trial design and outcome measurements.

1- Primary objective: Efficacy (or Safety) **?**

2- Short-term symptomatic efficacy or **long-term efficacy on PD progression ?**

. Symptoms: Motor or **Non-motor ones?**

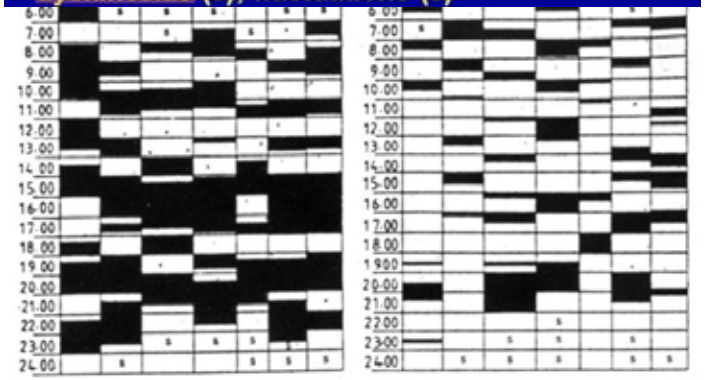
. Disease progression: Prevention of motor complications, « Neuroprotection », « Disease-modification »?…

3- "Pathophysiological" academic objectives or **"Regulatory" industrial objectives?**

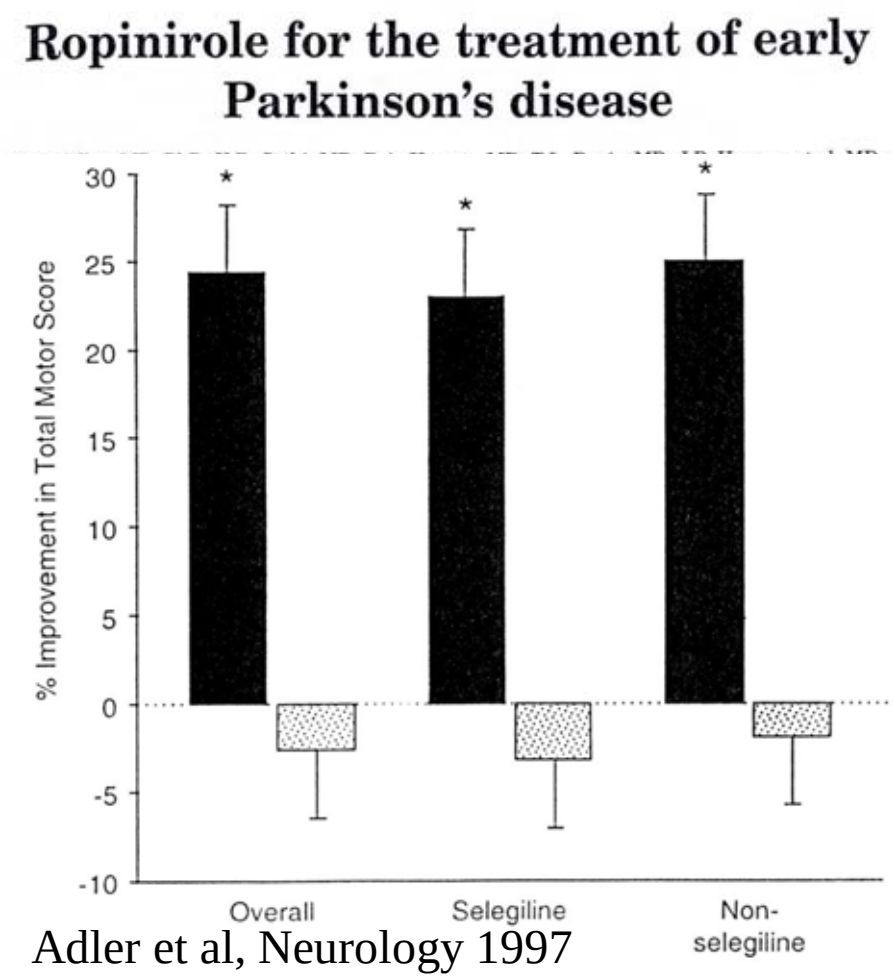
Main *outcomes*: (1) Outcomes to assess efficacy in trials aiming at evaluating motor symptoms in PD

- Parkinsonism: **MDS-UPDRS**
(Goetz et al, 2008)
- Motor Fluctuations: **Diaries**
(Hauser et al, 2004)
- Dyskinesia: **UDysRS**
(Goetz et al, 2008)
- Other motor outcomes?
(gait, balance, falls,speach…)

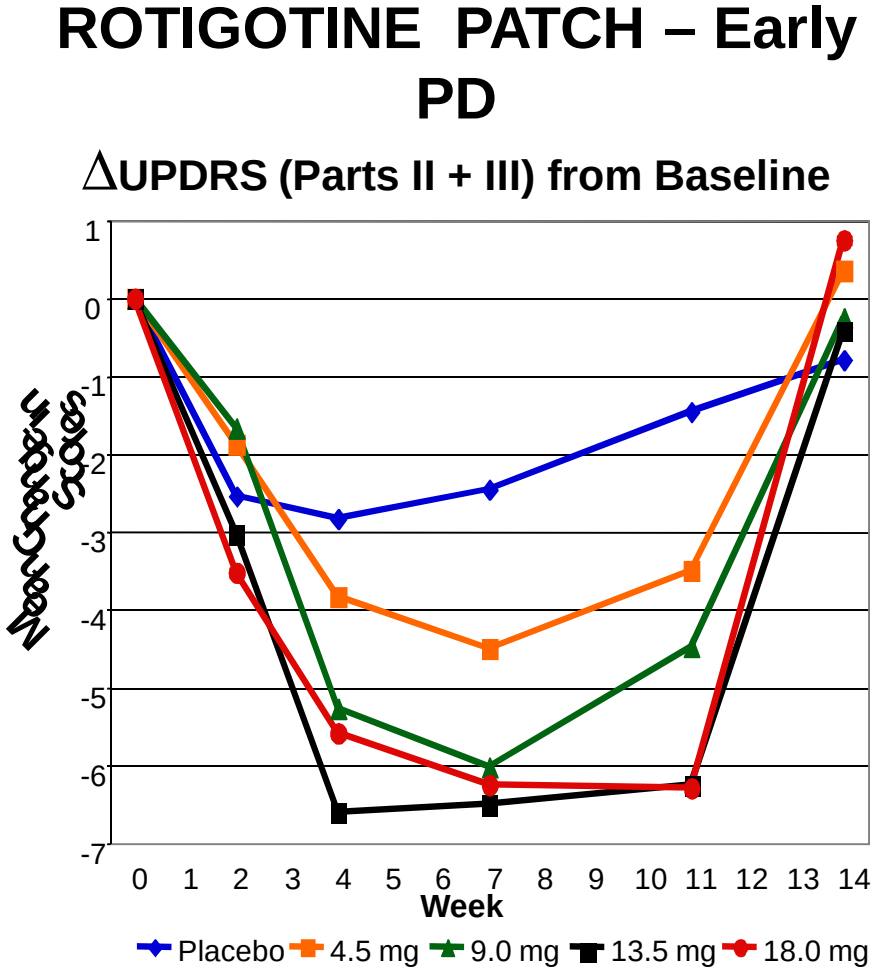
4 Parts – **50 Items**
I: Non-Motor Experiences of Daily Living **13 items:** Interview (6) Questionnaire (7)
II: Motor Experiences of Daily Living
13 items (all patient questionnaire)
III: Motor Section - **18 items** by examiner
IV: Motor Complications **6 items:** Interview: **dyskinesias (3); fluctuations (3)**



Exemple: using UPDRS to assess the symptomatic efficacy of dopamine agonists on parkinsonian symptoms



Adler et al, Neurology 1997



Main *outcomes*: (2) Outcomes to assess efficacy on Non Motor symptoms in PD

- Depression
- Anxiety
- Cognition
- Sleep
- Daytime somnolence
- Impulse Control Behaviors
- Psychosis
- Pain
- Autonomic dysfunction (HO, incontinence, constipation, salivation….)
-...

The *Movement* Disorder Society

MDS-Rating Scales taskforce

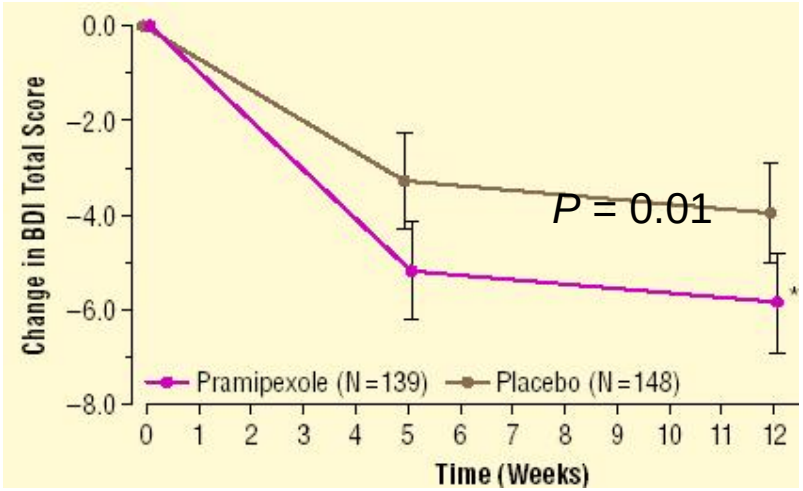
Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial

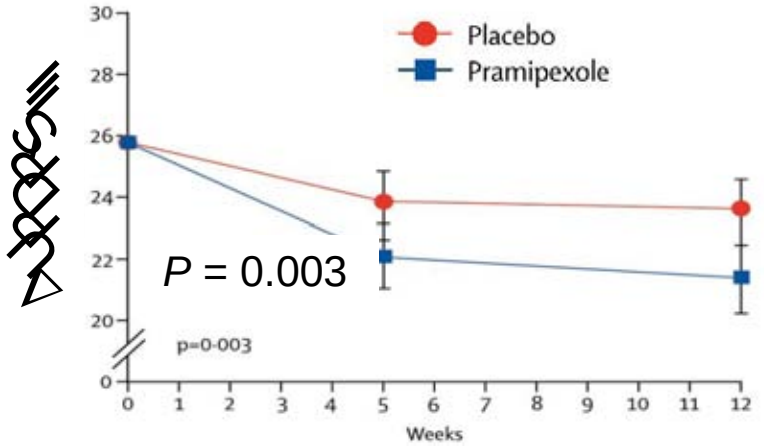
Lancet Neurol. 2010

Paolo Barone, Werner Poewe, Stefan Albrecht, Catherine Debieuvre, Dan Massey, Olivier Rascol, Eduardo Tolosa, Daniel Weintraub

- **12-week, Parallel group, PBO-Controlled RCT**
- **296 non fluctuating "optimized" PD patients with depressive symptoms (GDS>=5)**
- **Primary enpoint: Δ Beck Depressive Inventory**
- **Results (treatment effect):**
  ΔBDI: -1.9 [-0.5/-3.4] p=0.01
  ΔUPDRSIII: -2.2 [-0.7/-3.7] p=0.003

Path analysis showed that the direct effect of parmipexole on depressive symptoms accounted for 80% of total treatment effect (p=0.04)





A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease

I.H. Richard, MD

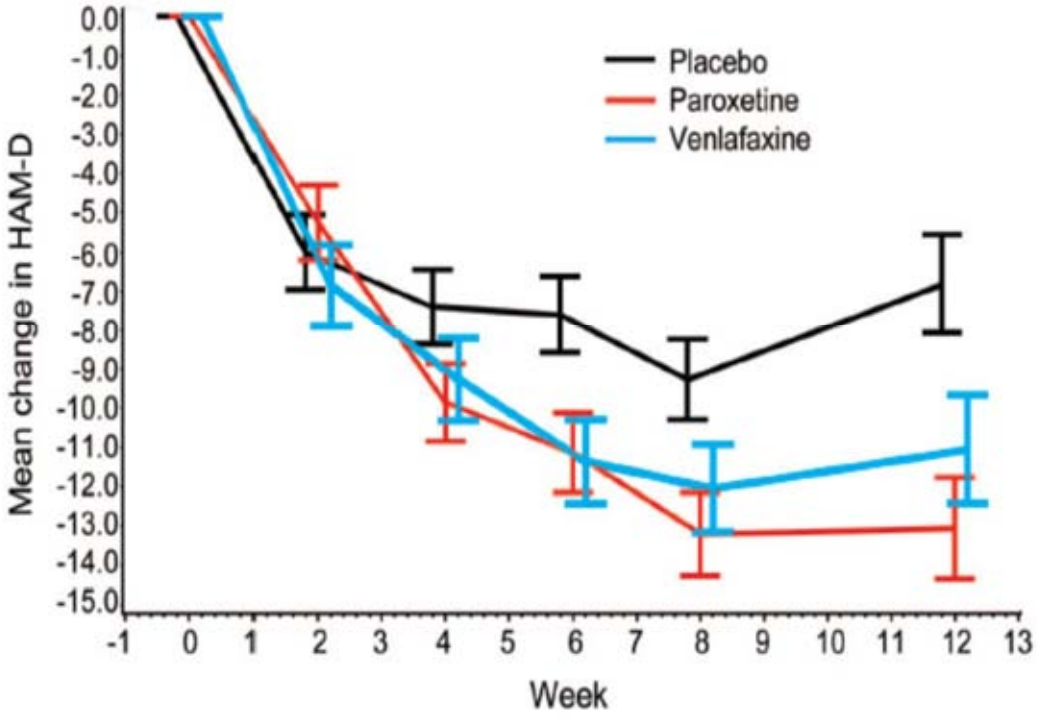
Neurology© 2012;78:1229-1236

- **12-week, 3-arm, parallel group, DB, PBO-controlled RCT**

- **115 PD patients with depression or operationally sub-syndromal syndrome**
  - **Paroxetine (n=42)**
  - **Venlafaxine XR (n=34)**
  - **Placebo (n=39)**

- **Primary endpoint:**
  ∆ HAM-D

Figure 2 Adjusted mean change in Hamilton Rating Scale for Depression (HAM-D) score over time by treatment group

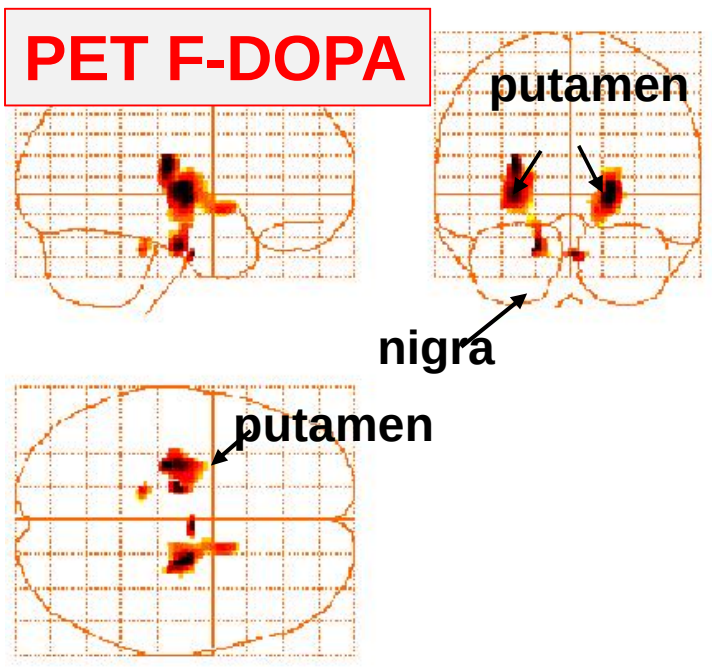


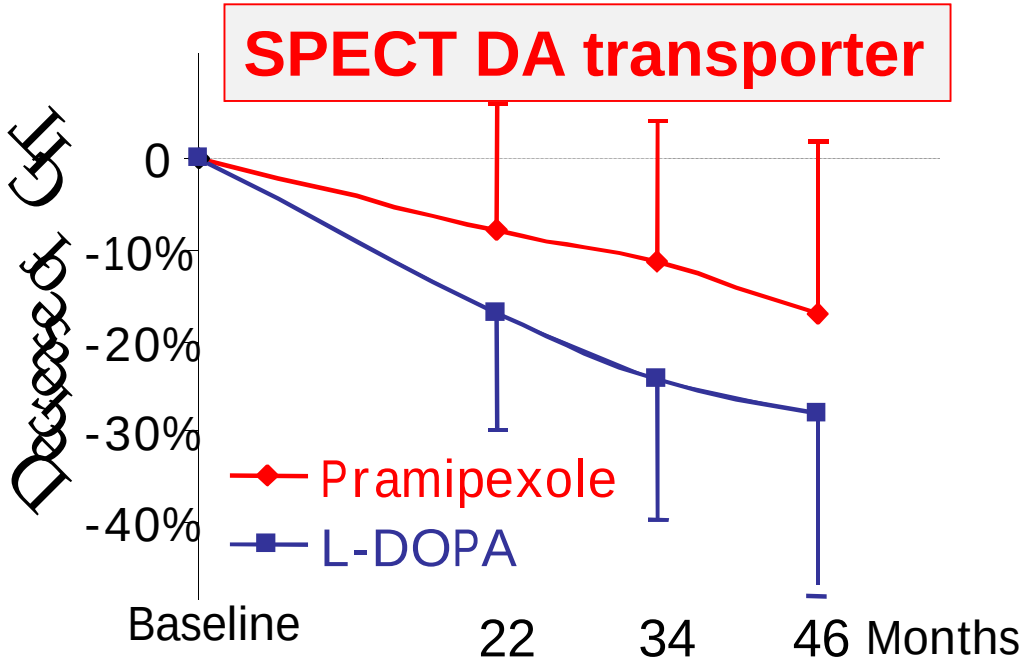
Mean changes are adjusted for center and the baseline HAM-D score using a repeated-measures analysis of covariance model. Error bars represent 1 SEM.

Main *outcomes*: (3) Outcomes to measure disease progression in PD

- Biomarkers ?
- Time to endpoint ?
- Rate of progression of symptoms or disability?

The current failure of dopaminergic neuro-imaging biomarkers to assess disease-modification in PD





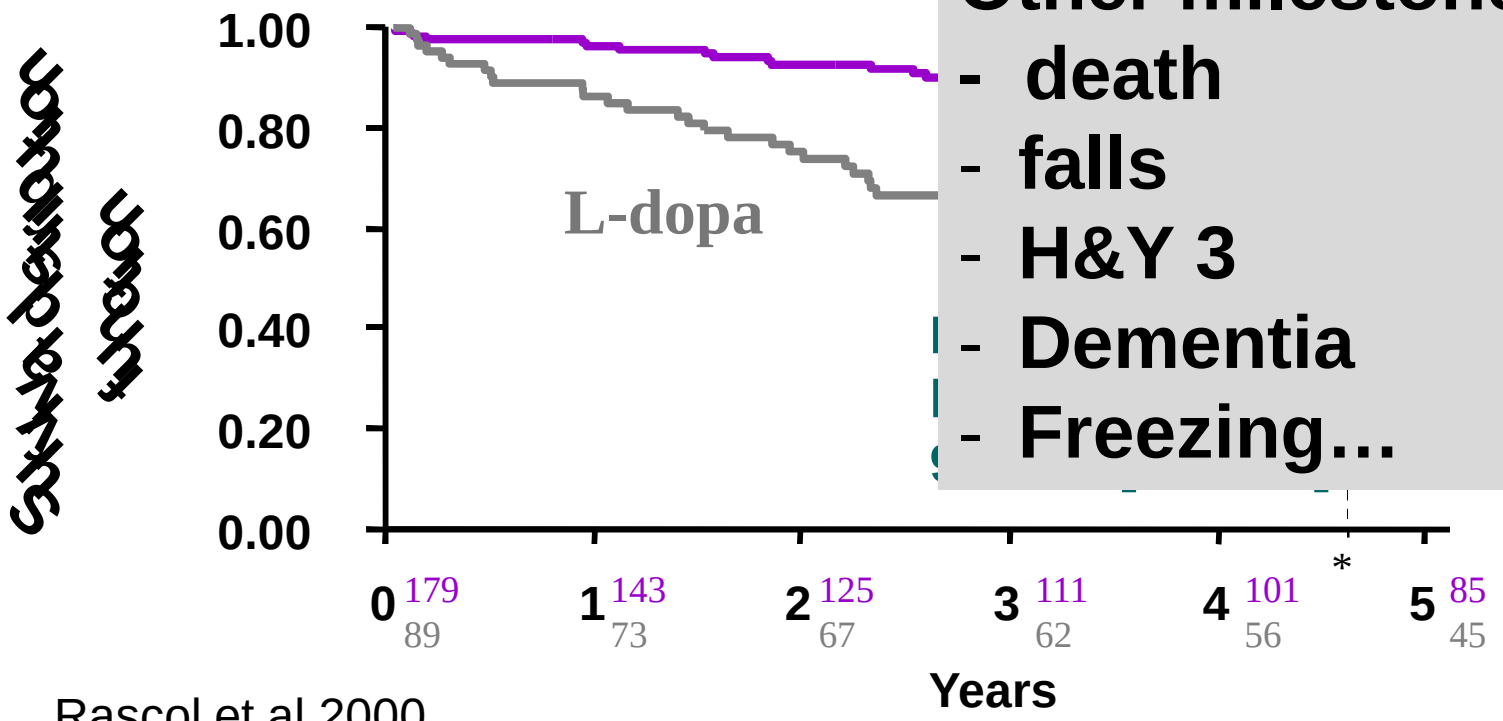
Ropinirole (REAL-PET, Whone et al, 2002)

Pramipexole (CALM-PD, PSG 2002)

- **Comparison versus levodopa (and not placebo)**
- **Confounding pharmacodynamic effects (desensitization)?**

Time to endpoint to capture PD progression: Time to dyskinesia (UPDRS item 33) to assess the risk of dyskinesia over time

Time to onset of dyskinesia:
Kaplan-Meier plot



Other milestones:
- **death**
- **falls**
- **H&Y 3**
- **Dementia**
- **Freezing…**

Rascol et al 2000

* Low denominator beyond this time point

Measuring the rate of progression of PD using UPDRS scores over time ?

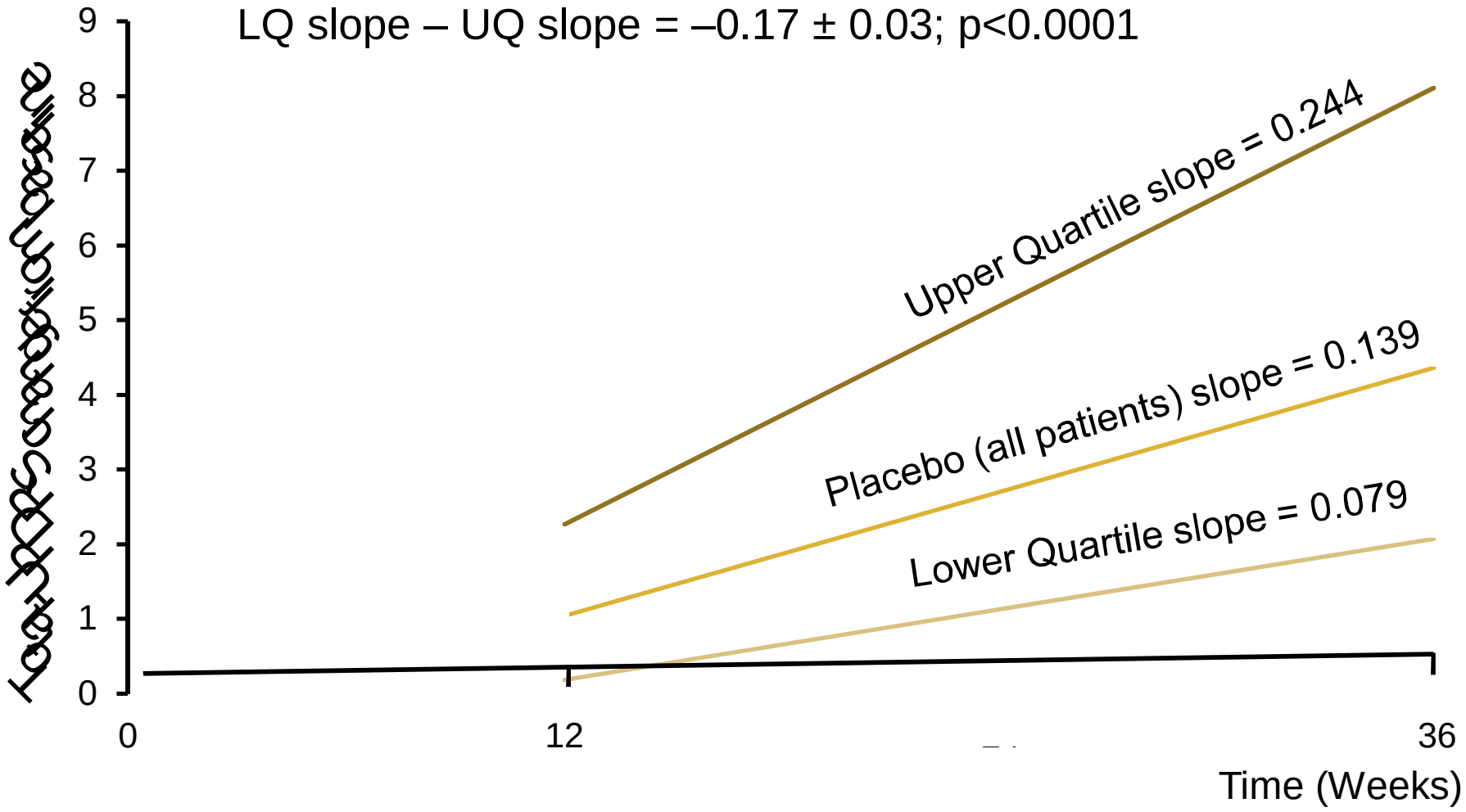
- Early (untreated) PD patients : + 8-12 UPDRS/year

(placebo arm of clinical trials)

		Baseline Total-UPDRS score	Age at baseline		
DATATOP[1,2]	Deprenyl/ tocopherol			12/year	12/year
ROADS[3]	Lazabemide			8/year	8/year
QE2[4]	Coenzyme Q10			12/16 months	9/year
TEMPO[5]	Rasagiline			4.1/6 months	8.2/year
ELLDOPA[6]	Levodopa			8.4/9.5 months	10.6/year

[1]PSG. N Engl J Med. 1993; 328:176; [2]PSG. Arch Neurol. 1989; 46:1052; [3]PSG. Ann Neurol. 1996; 40:99; [4]Shults et al. Arch Neurol. 2002; 59:1541
[5]PSG. Arch Neurol. 2004; 61:561; [6]Fahn et al. N Engl J Med. 2004; 351:2498.

Rate of UPDRS progression on placebo in the ADAGIO study



Rascol et al. Lancet Neurology 2011

Choosing the most appropriate *population* to assess efficacy in PD

- **«Early» PD patients** (untreated, «de novo»)

- **« Advanced » PD patients** (on levodopa with motor fluctuations)

- **Others** (dyskinetic, stable on levodopa, « late PD» with dementia, psychosis, falls…)

Choosing the most appropriate *duration* of follow-up to assess efficacy in PD

From a single acute challenge to >5-year follow-up

EMEA and FDA recommandations:

- Monotherapy in «Early PD » = minimum of 6 months
- Adjunct to L-DOPA in « Advanced PD » = minimum of 3 months

DESIGNS **TO ASSESS SHORT-TERM EFFICACY IN CLINICAL TRIALS IN PD**

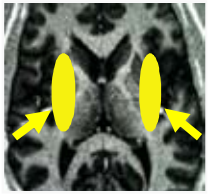
- **Uncontrolled** versus **Randomized** Controlled trials (RCTs)
- **Open** versus **Double-blind** RCTs
    . Placebo effect in PD
    . Active comparator
- **Cross-over** versus **Parallel groups**

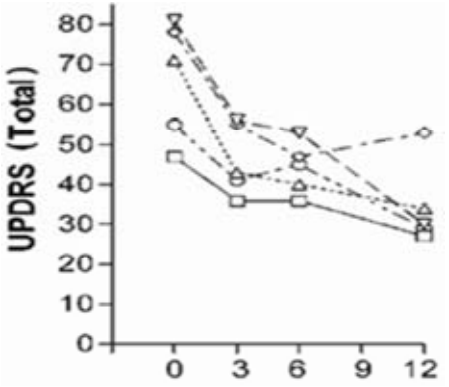
Open-label trials and the placebo effect in PD

- GDNF intracerebral infusion

  Open-label trial (Gill et al, Nat Med 2003)

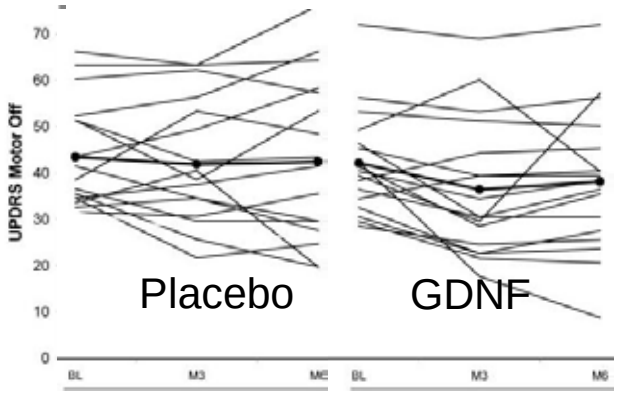
  5 advanced PD patients
  Primary outcome = UPDRS
  1year follow-up
  - **39% UPDRS III and - 61% UPDRS II**





- GDNF infusion Placebo-controlled RCT (Lang et al, 2006)

  34 advanced PD patients
  Placebo-controlled RCT
  6 month follow-up
  Primary outcome = UPDRS
  -10% (GDNF) versus -5% (placebo) UPDRS score



- Similar findings with many other interventions:

Mesencephalic embryonic cell grafts (Freed et al, 2001);
Spheramine° (Gross et al, 2011)…

The placebo response rate is high in PD (16% patients have >50% reduction in UPDRS score,range 0-55% on placebo) (Goetz et al, 2008)

Placebo diplaces [11C] raclopride binding in the brain of patients with PD (De la Fuente-Fernandez et al, 2001)

- DA release : 17% reduction in [11C]raclopride binding corresponding to a >200% increase in extracellular DA concentration
- Equivalent to amphetamine effect in normal subjects

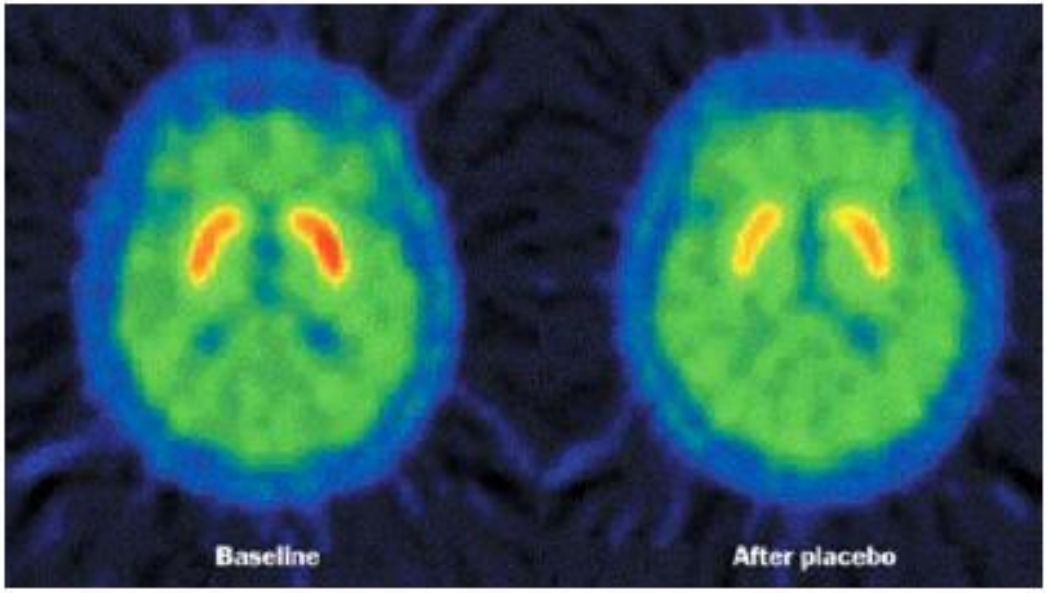
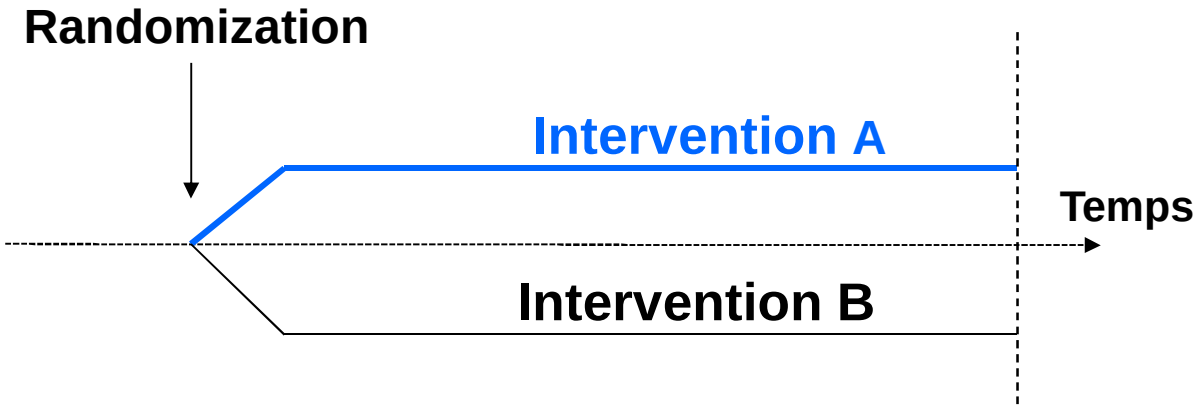


Fig. 1. [^{11}C]raclopride PET scans of a patient with PD at baseline and following injection of saline (placebo). Decreased [^{11}C]raclopride binding to D2 receptors in the striatum after placebo in the *After placebo* image indicates tracer displacement by placebo-induced endogenous dopamine release.

=> *Comparative designs* are “mandatory” to prove efficacy in PD

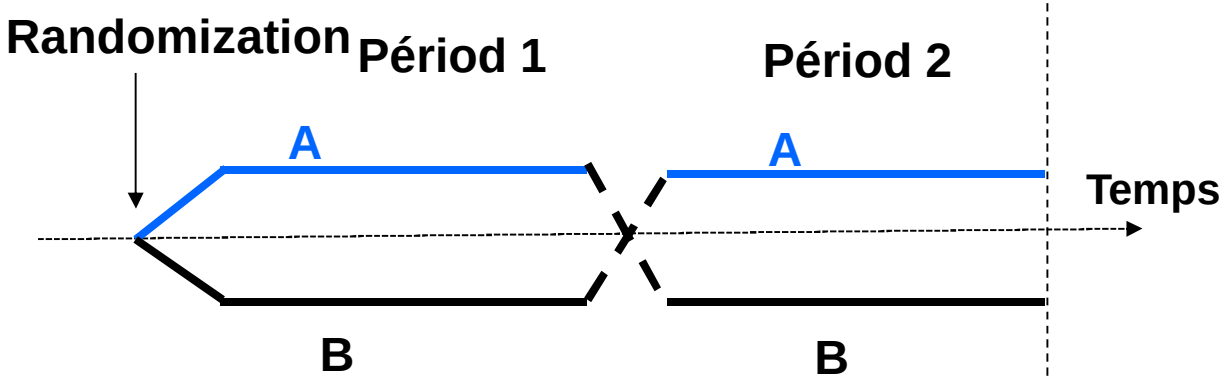
Ø PARALLEL GROUPS



Advantages :
- simple
- easy to analyze
- “long” follow-up

Disadvantages:
- variability (inter-individual)
- Larger number of subjects

Ø CROSS-OVER

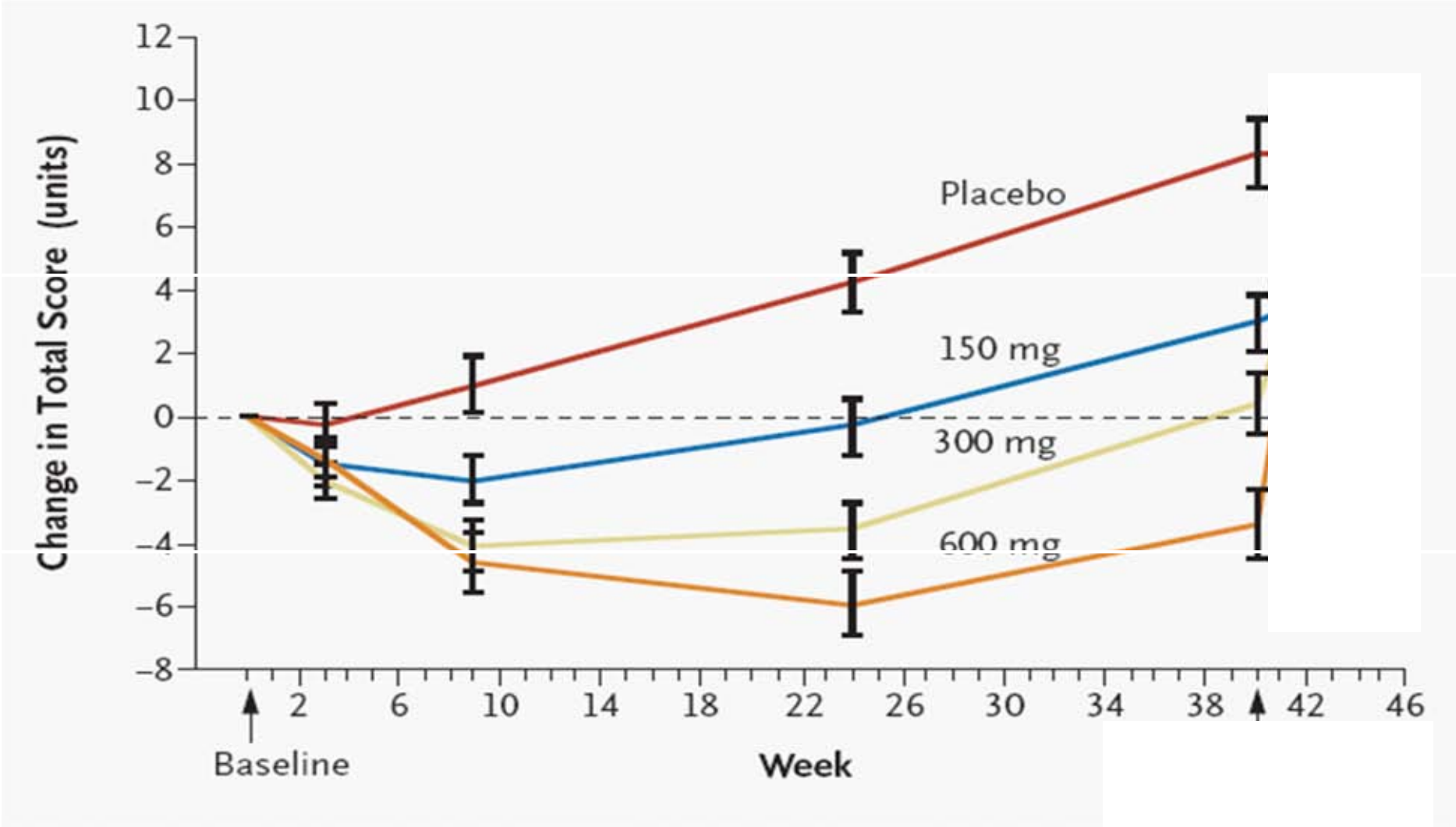


Advantages :
- lower variability (intra-individual)
- smaller numbers

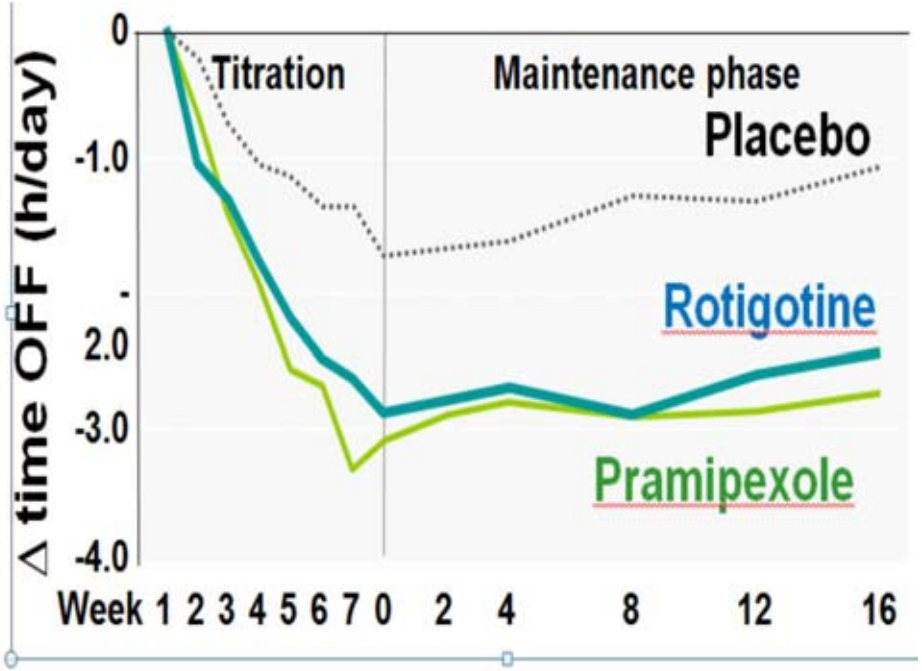
Disadvantages:
- disease progression
- carry-over effect
- short follow-up

Example of a *Placebo-controlled* parallel group RCT in PD

ELLDOPA STUDY (Fahn et al, 2004)



Examples of RCT with *active comparator*



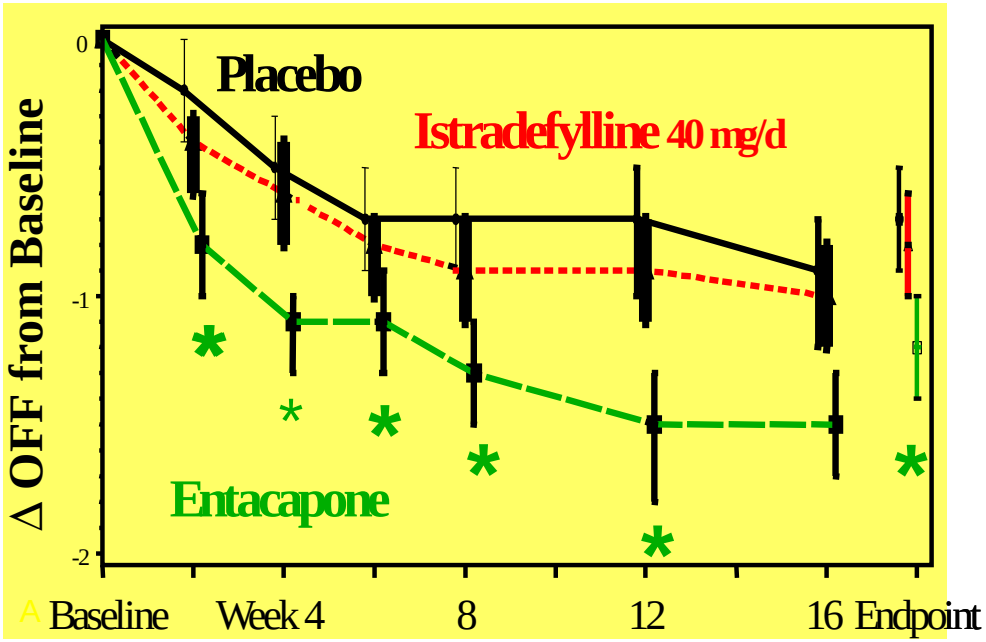
Cleopatra, Poewe et al, 2007:

3-arms RCT 4-month: Rotigotine / Pramipexole / Placebo

506 PD patients with fluctuations.

Primary outcome: Δ time spent OFF on diaries

Both active arms > placebo



NCT00199394 6002-EU-007

3-arms RCT 16-week: istradefylline 40 mg / placebo / entacapone,

405 advanced PD,

Primary outcome: Δ time spent OFF on diaries

Entacapone but not Istradefylline > placebo

Early development ("Experimental" / Proof-of-Concept / Phase II type) trials

=> *to confirm an hypothesis and translate to humans*

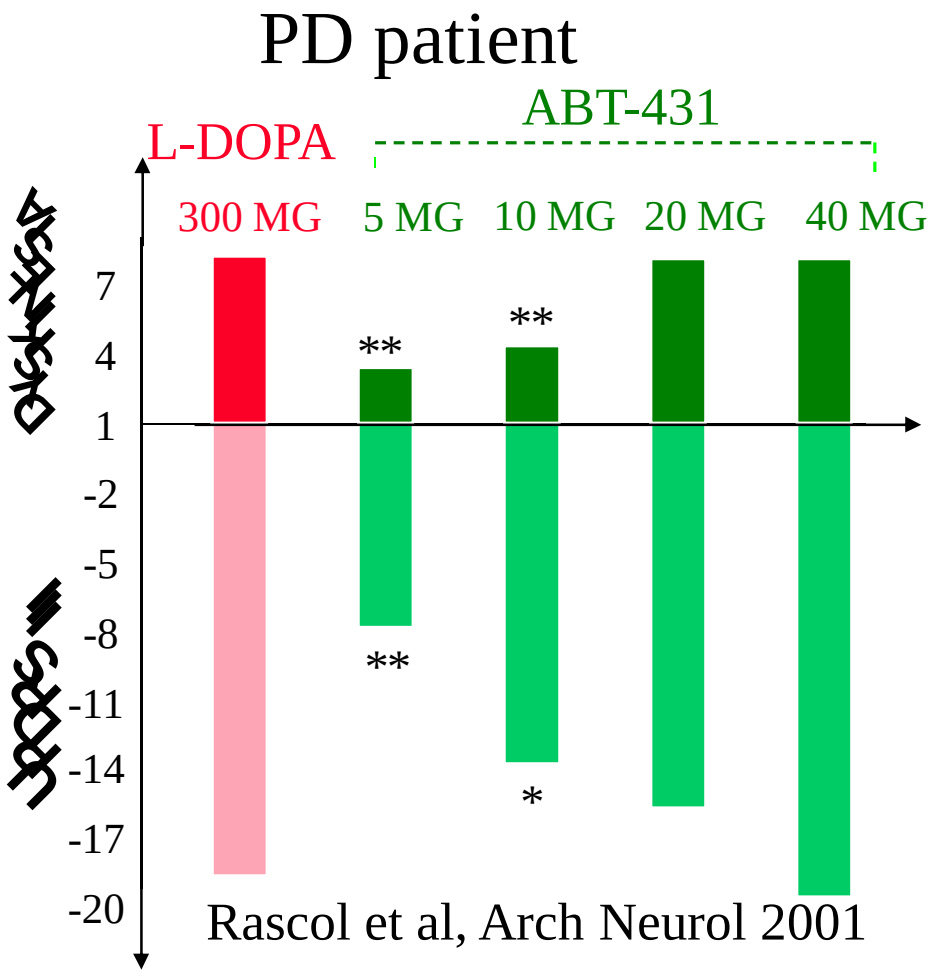
as opposed to

Pragmatic Regulatory (Phase III-type) trials

=> *to be generalized to clinical practice*

An example of an early POC (Phase IIa) trial in PD

- Objective: to assess the antiparkinsonian + dyskinetic effects of the D1 agonist ABT 431
- Methods:
  - Single acute challenge
  - Cross-over Design
  - L-DOPA as comparator
  - 4 different doses
  - 8 “advanced” PD patients assessed in the practically defined OFF state
  - Outcomes: UPDRS + AIMS



An example of a Phase IIb ("Go-no-Go") trial in PD

Preladenant in patients with Parkinson's disease and motor fluctuations: a phase 2, double-blind, randomised trial

Lancet Neurol 2011; 10: 221–29

Robert A Hauser, Marc Cantillon, Emmanuelle Pourcher, Federico Micheli, Vincent Mok, Marco Onofrj, Susan Huyck, Kenneth Wolski

- **12-week, dose-finding, Phase IIb, 5-arm (1/2/5/10mgbid), parallel group, DB, PBO-controlled RCT**
- **253 PD patients with OFF episodes**
- **Primary endpoint:**
  Δ in time spent OFF from baseline
- **Results:**
  -1 hour OFF (5 and 10 mg dose)
- **Safety:**
  BP: slight increase
  Dyskinesia severity and ESS: no change

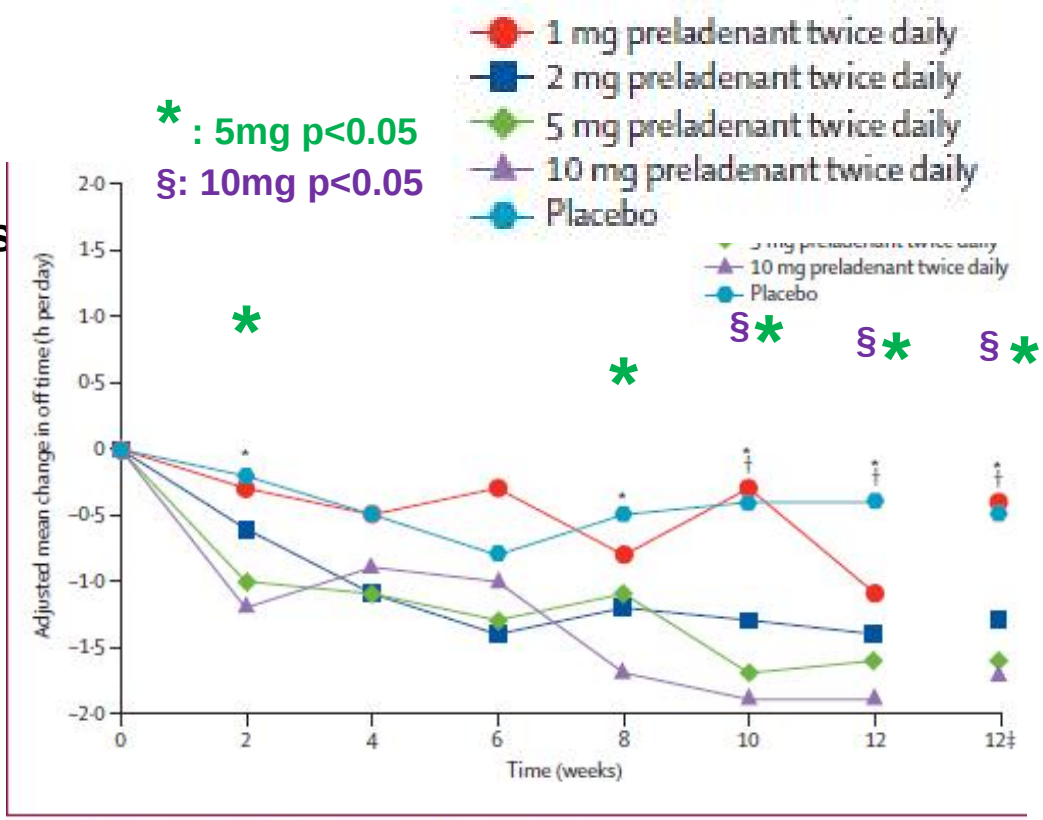
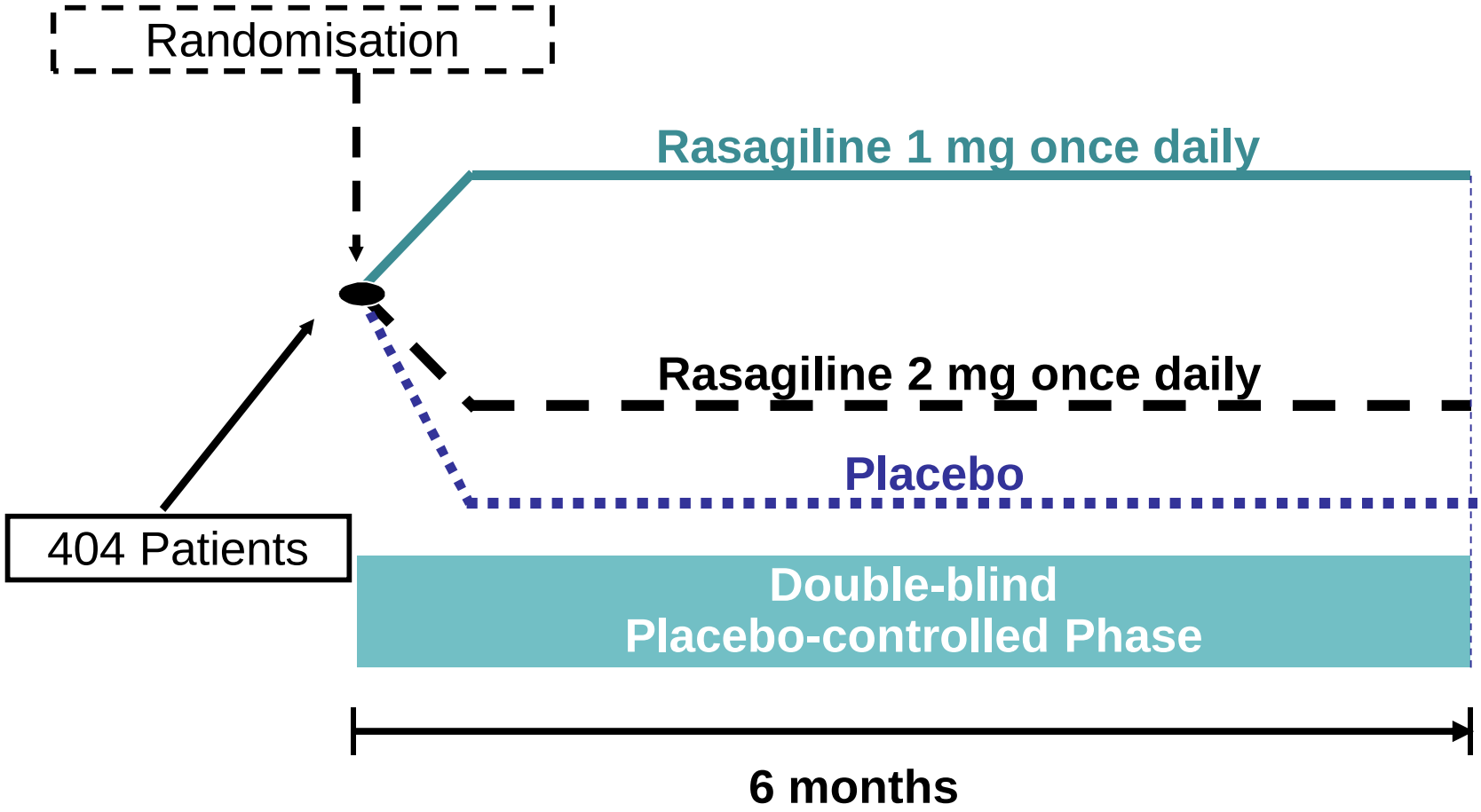


Figure 3: Mean change in off time from baseline to each visit

An example of Phase III trial

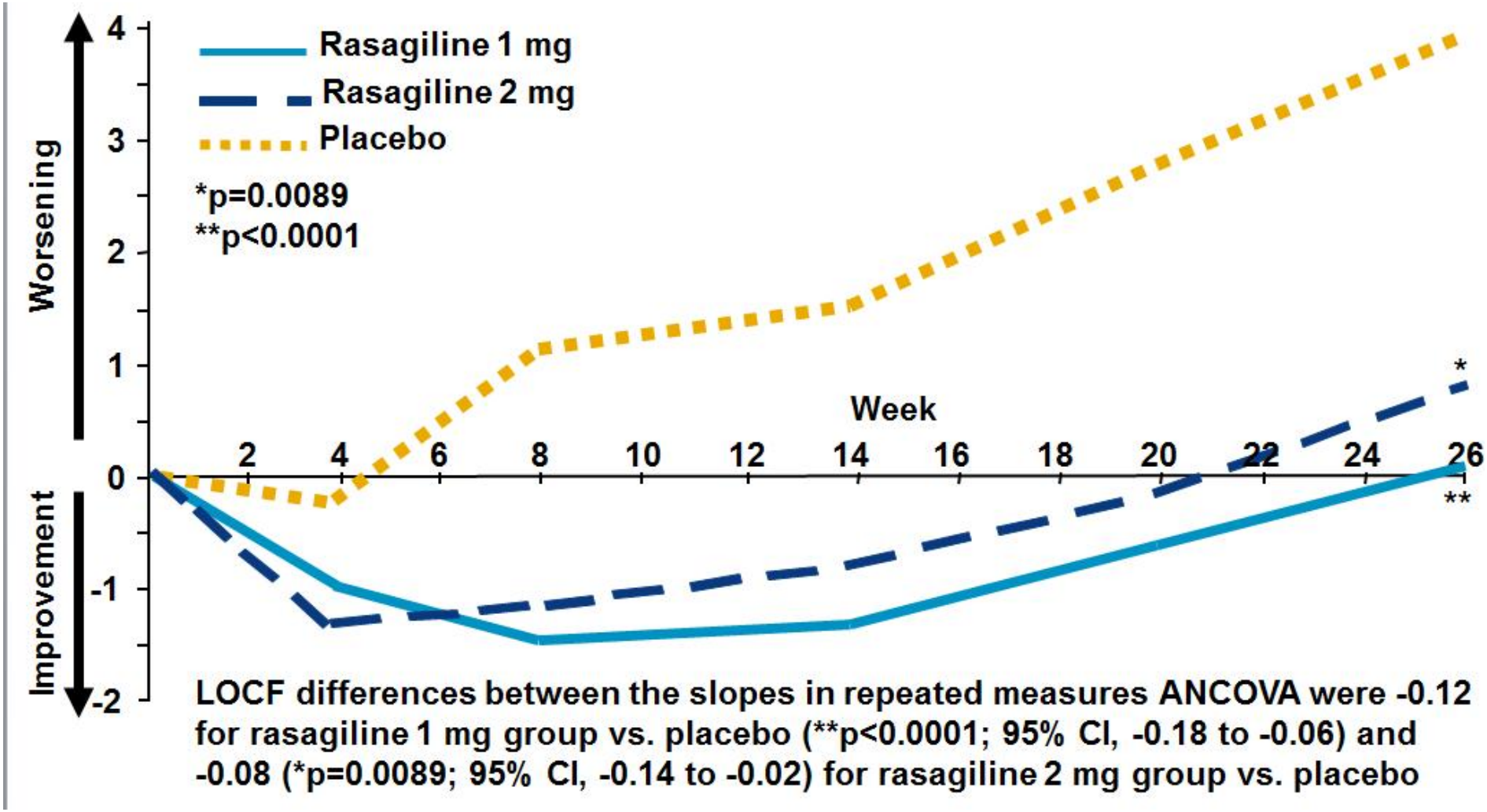
TEMPO trial (PSG, 2002)

Double-Blind Placebo-controlled RCT, 404 early PD patients, 6-month follow-up, 2 doses, Primary endpoint: Δ UPDRS endpoint vs baseline



An example of Phase III trial

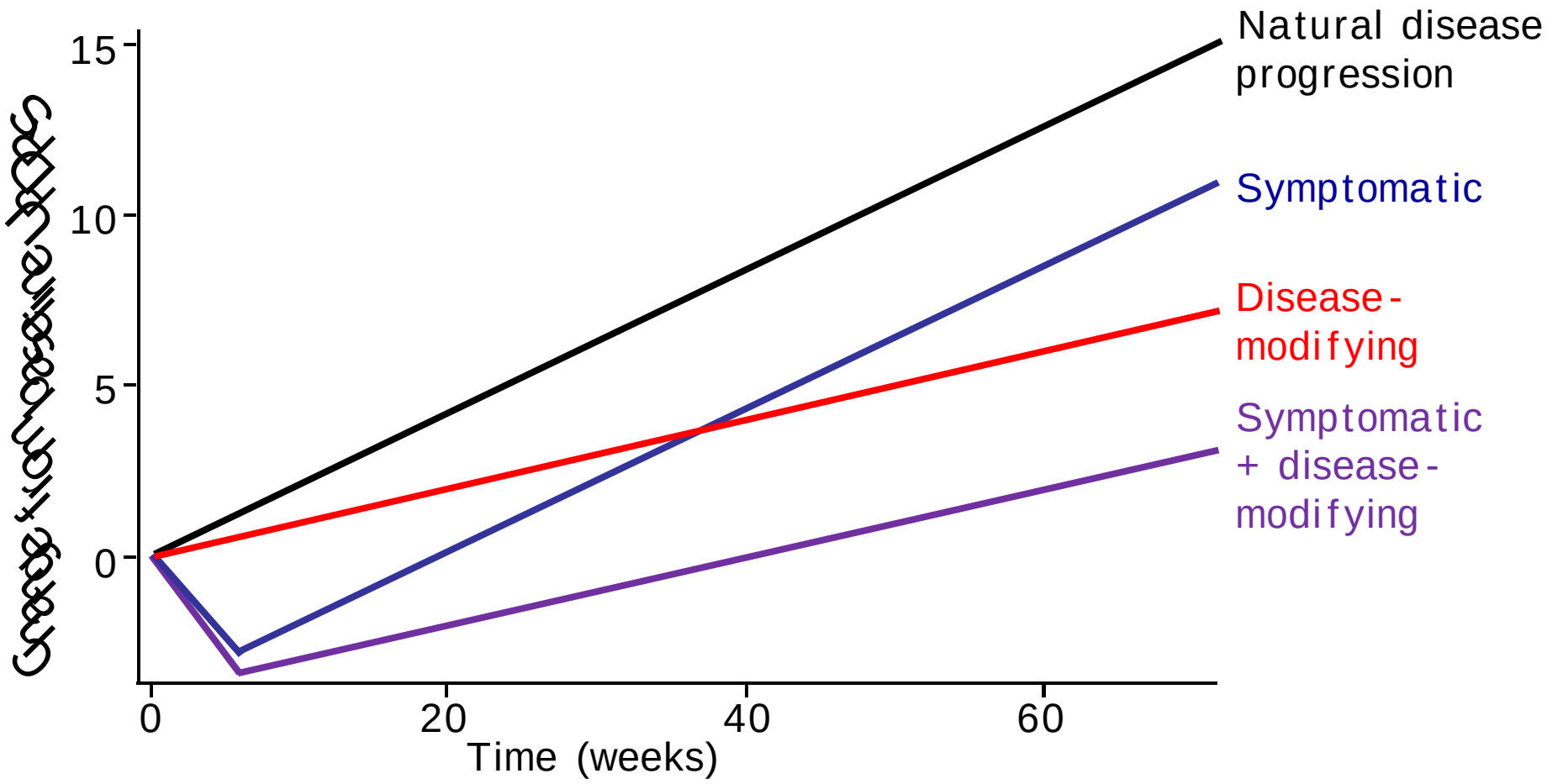
TEMPO trial (PSG, 2002)



DESIGNS OF CLINICAL TRIALS TO ASSESS LONG-TERM EFFICACY ON DISEASE PROGRESSION IN PD

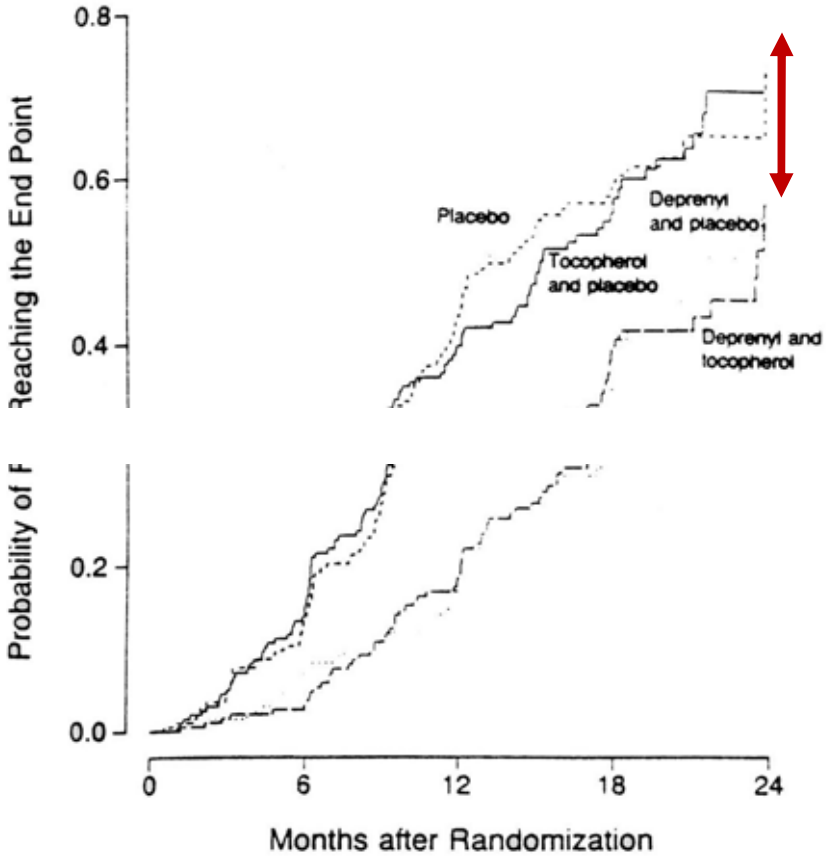
- Time to event
- Wash-out
- Delayed-start

UNTANGLING DRUGS WITH DIFFERENT EFFECTS ?



Bhattaram et al. AAPS J 2009; 11 (3): 456

Time to event: the example of the DATATOP study (PSG, 1993)

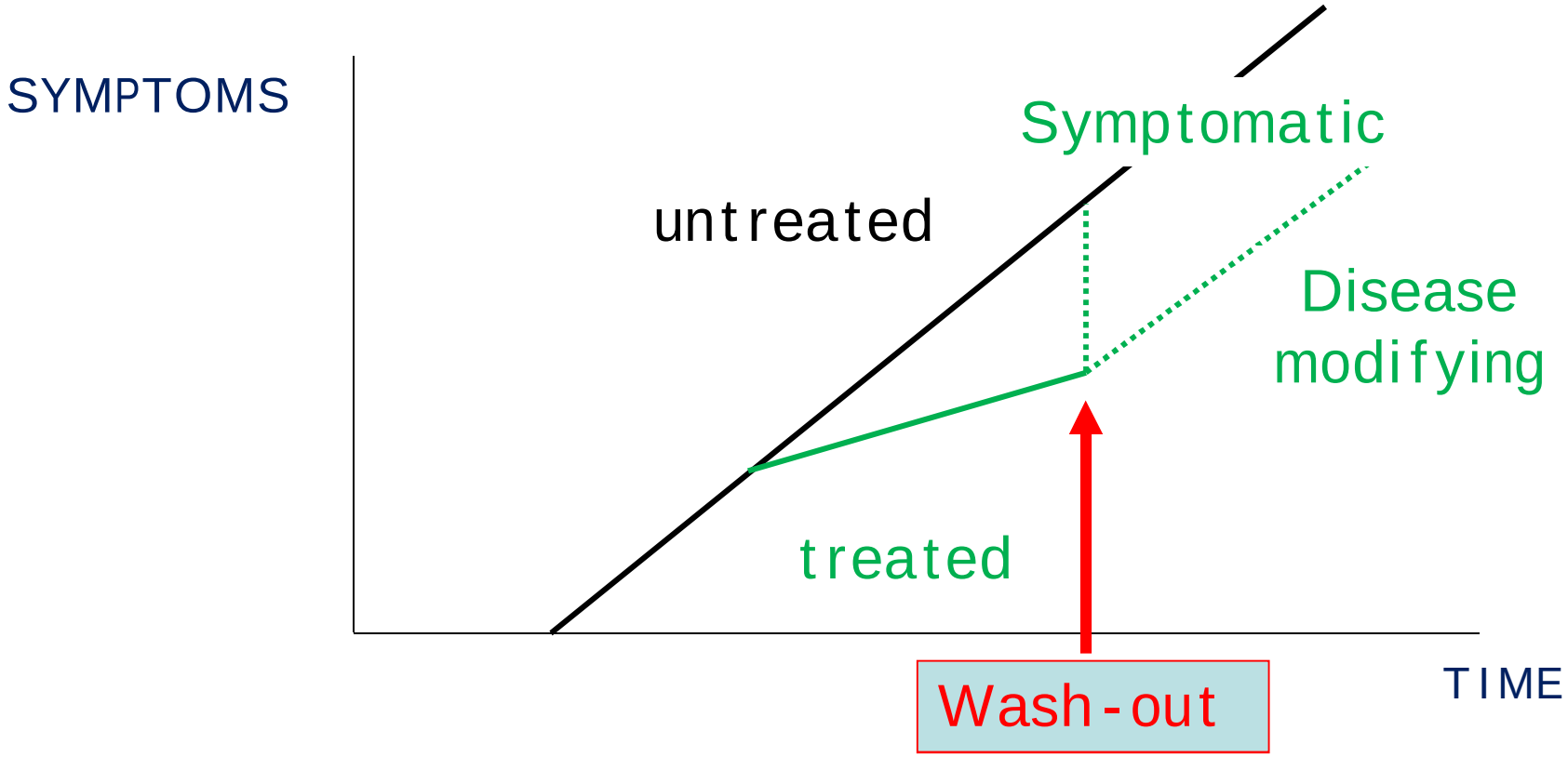


Time to L-DOPA delayed over the first 12 months of follow-up

Inconclusive finding because *the symptomatic effect of deprenyl* may account for the delay in L-DOPA without influencing the underlying pathological process...

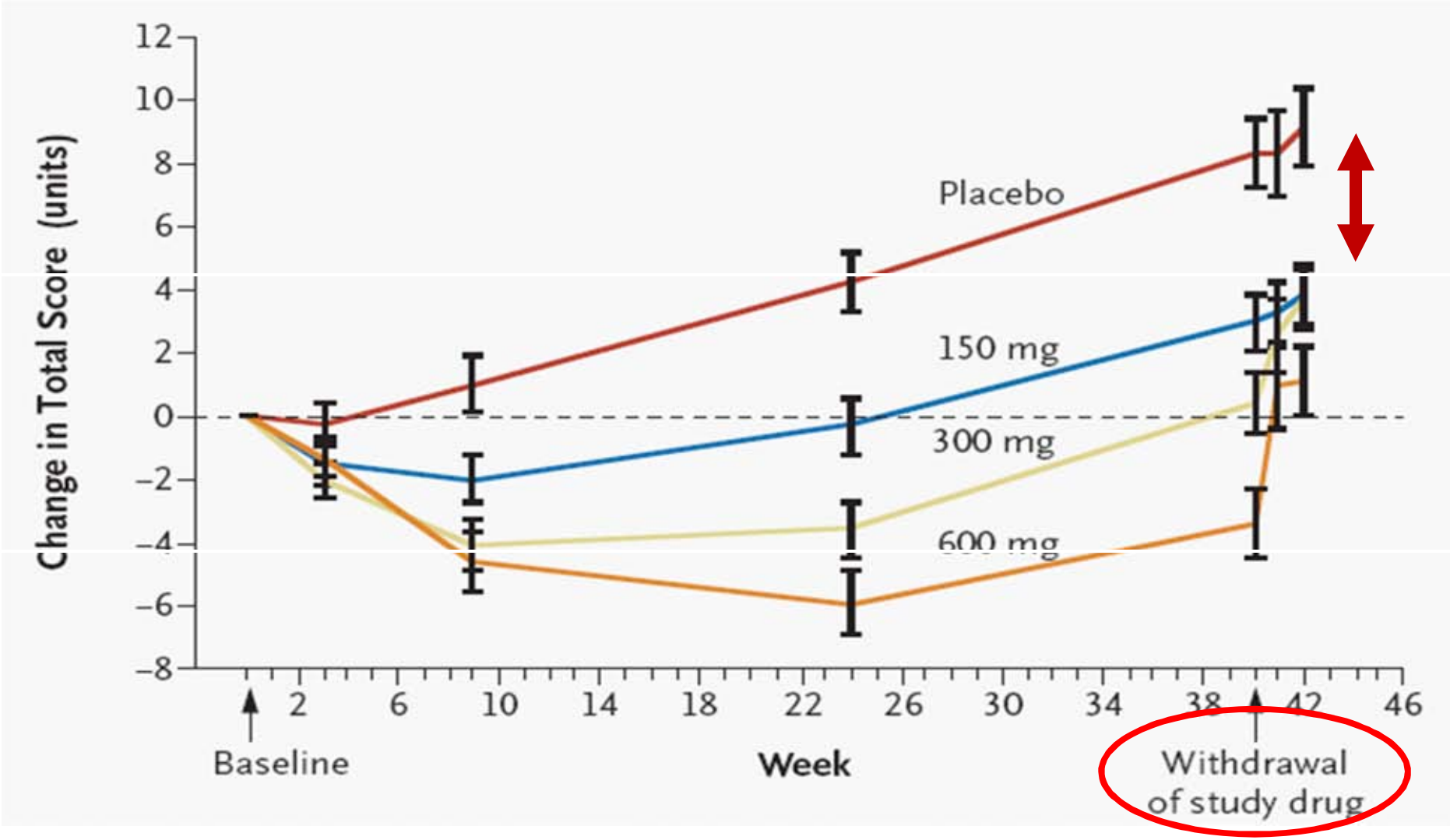
=> Separating a “confounding” symptomatic effect from a “disease-modifying” effect ?

WASHING-OUT DESIGN



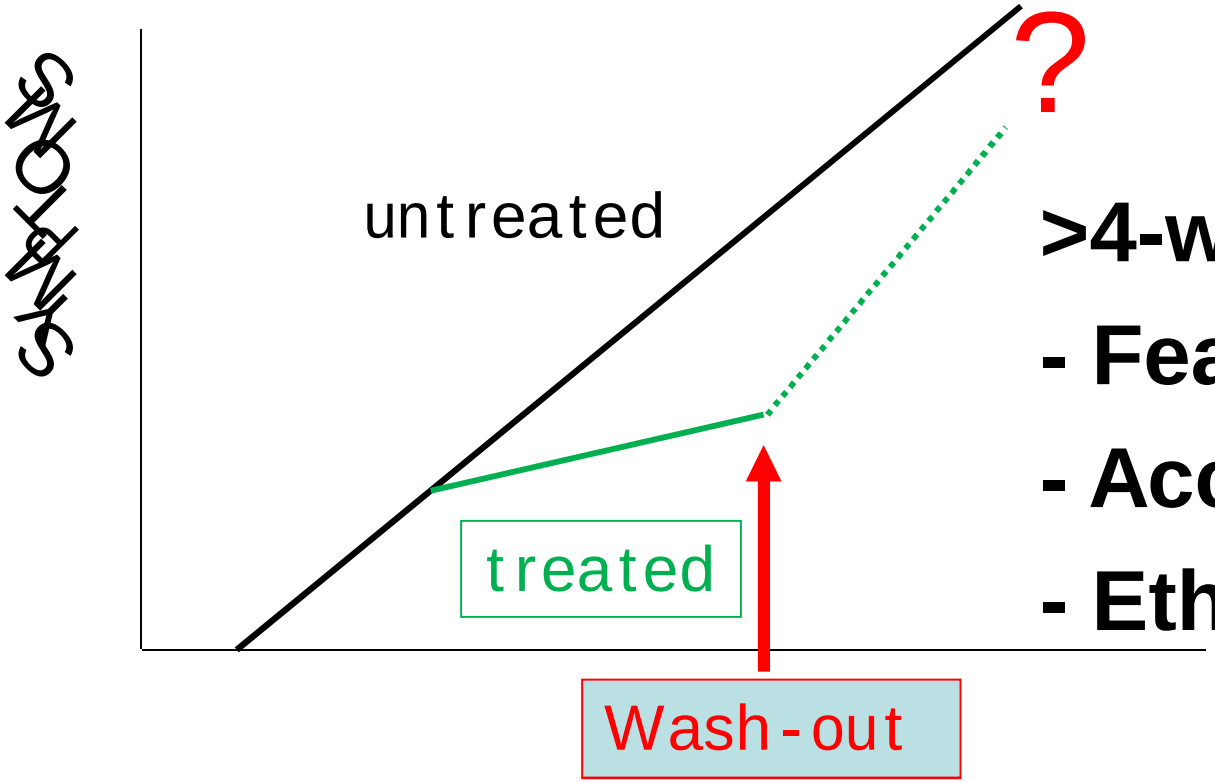
WASH-OUT DESIGN

ELLDOPA STUDY (Fahn et al, 2004)



WASHING-OUT LIMITATIONS

How long a medication should be withdrawn to eliminate 100% of its symptomatic benefit (*long duration response*) ?



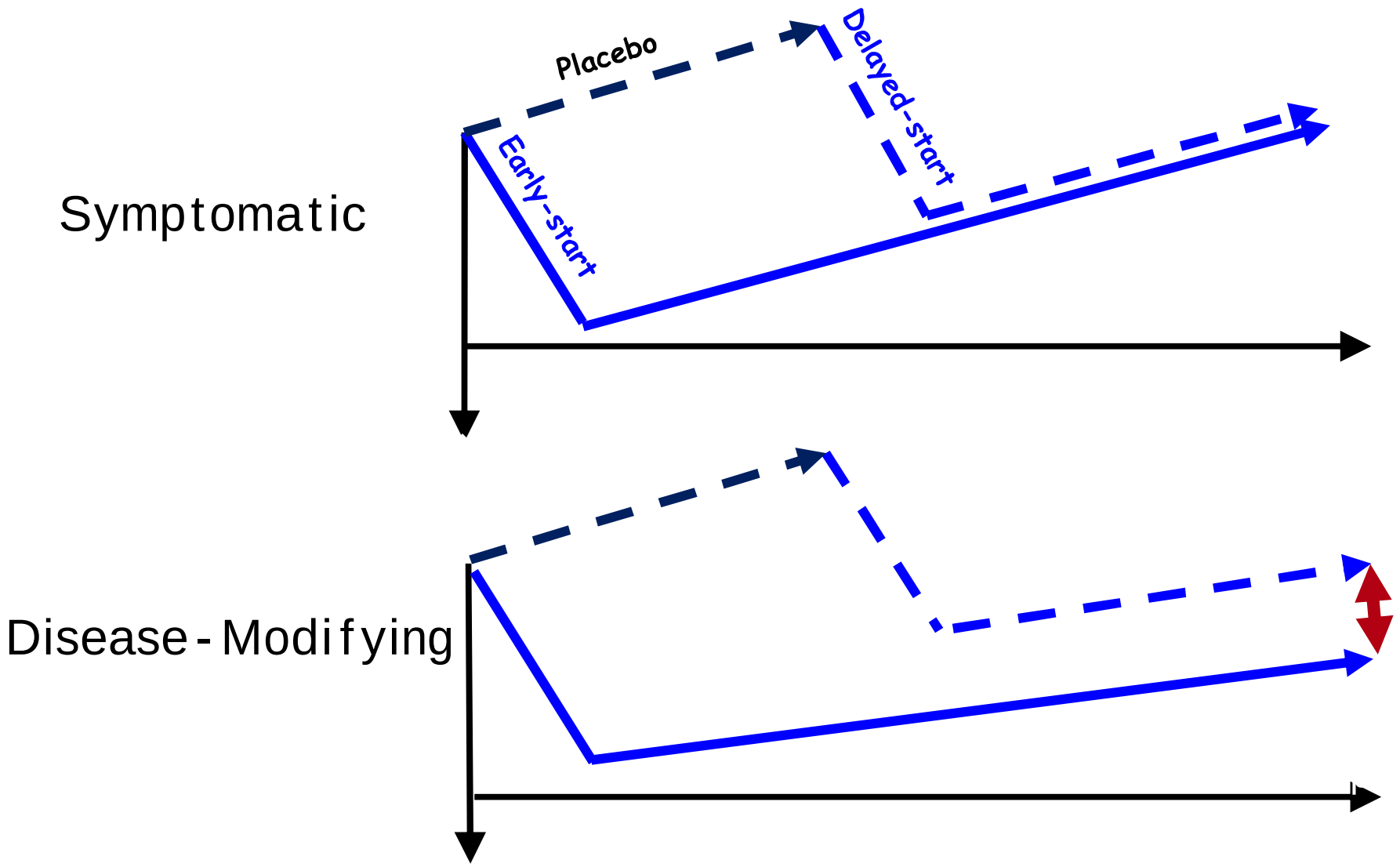
>4-weeks wash-out:

- Feasible ?

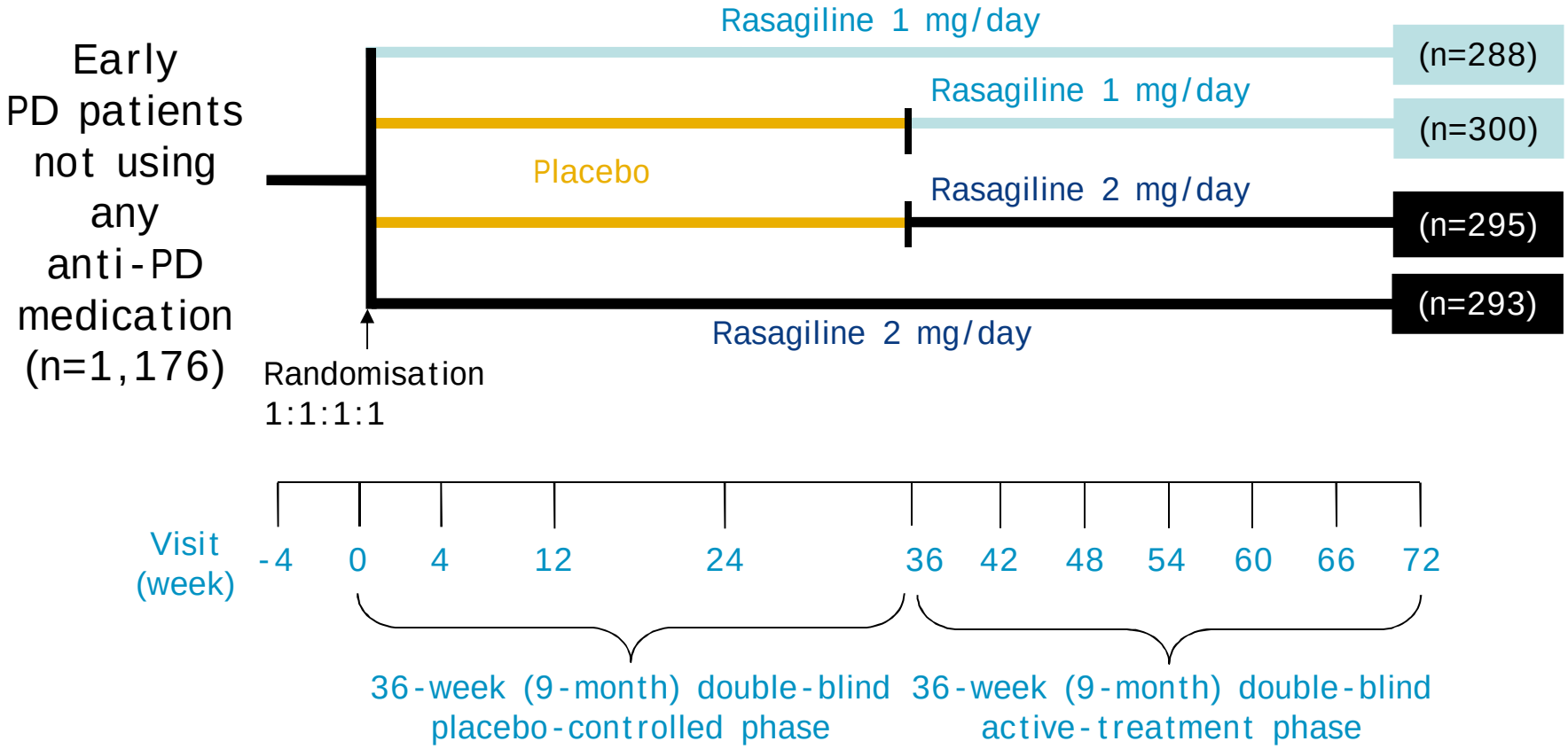
- Acceptable ?

- Ethical ?

THE DELAYED START DESIGN:

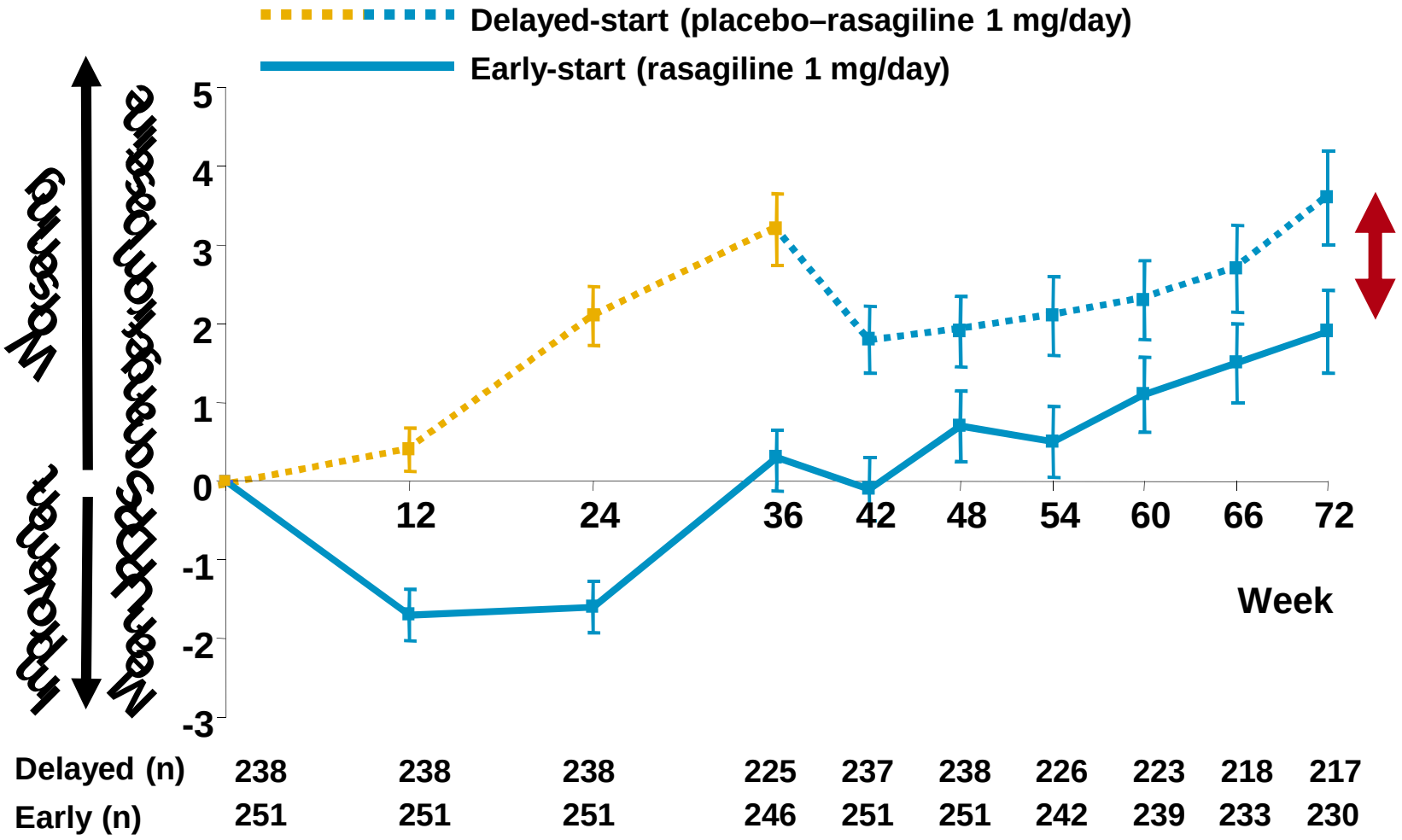


ADAGIO DELAYED START STUDY



Olanow et al. Mov Disord 2008; 23: 2194; Olanow, Rascol et al. N Engl J Med 2009; 361: 1268

ADAGIO: mean UPDRS change from baseline, rasagiline 1 mg/day
(ACTE data analysis set)

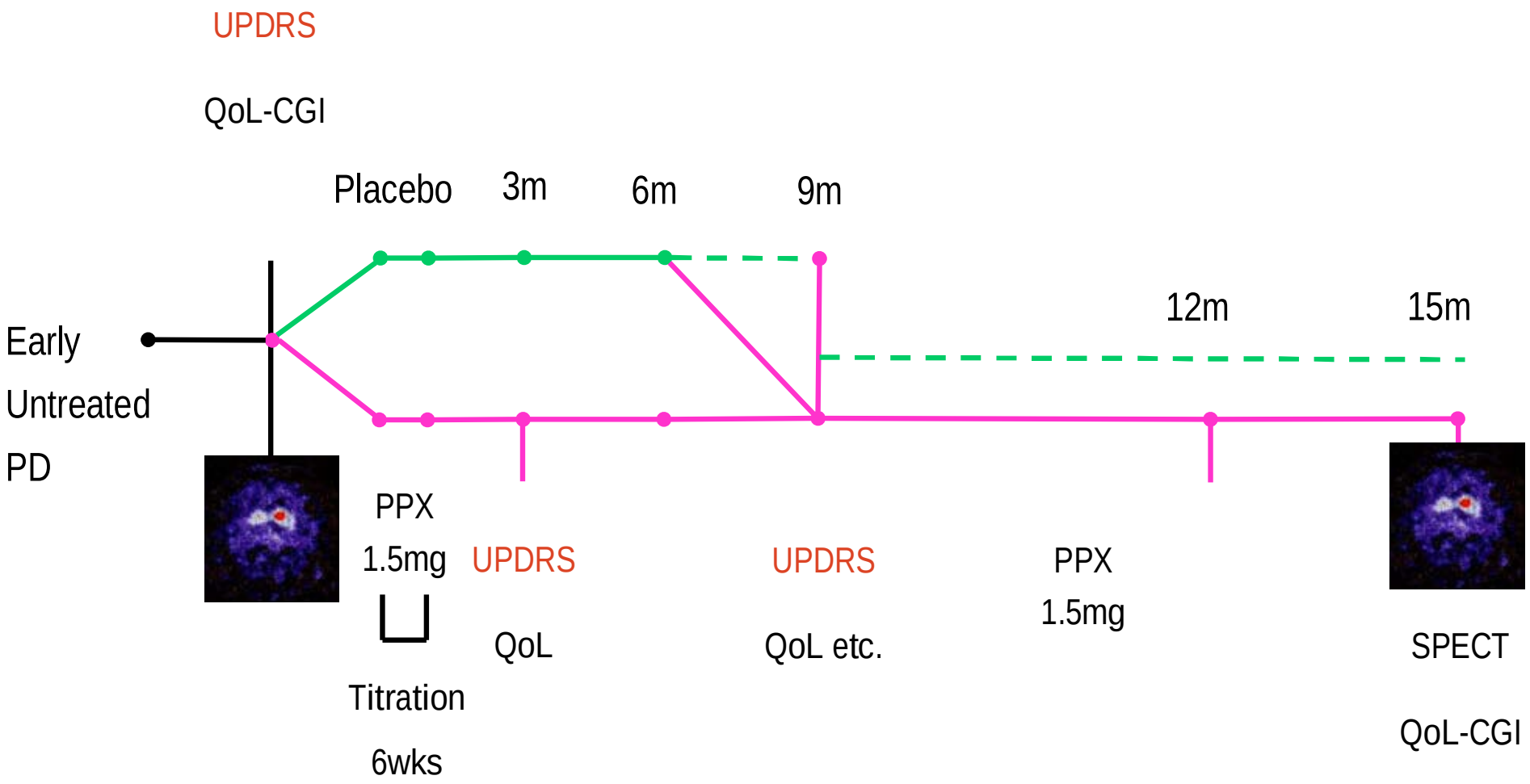


ACTE data analysis set

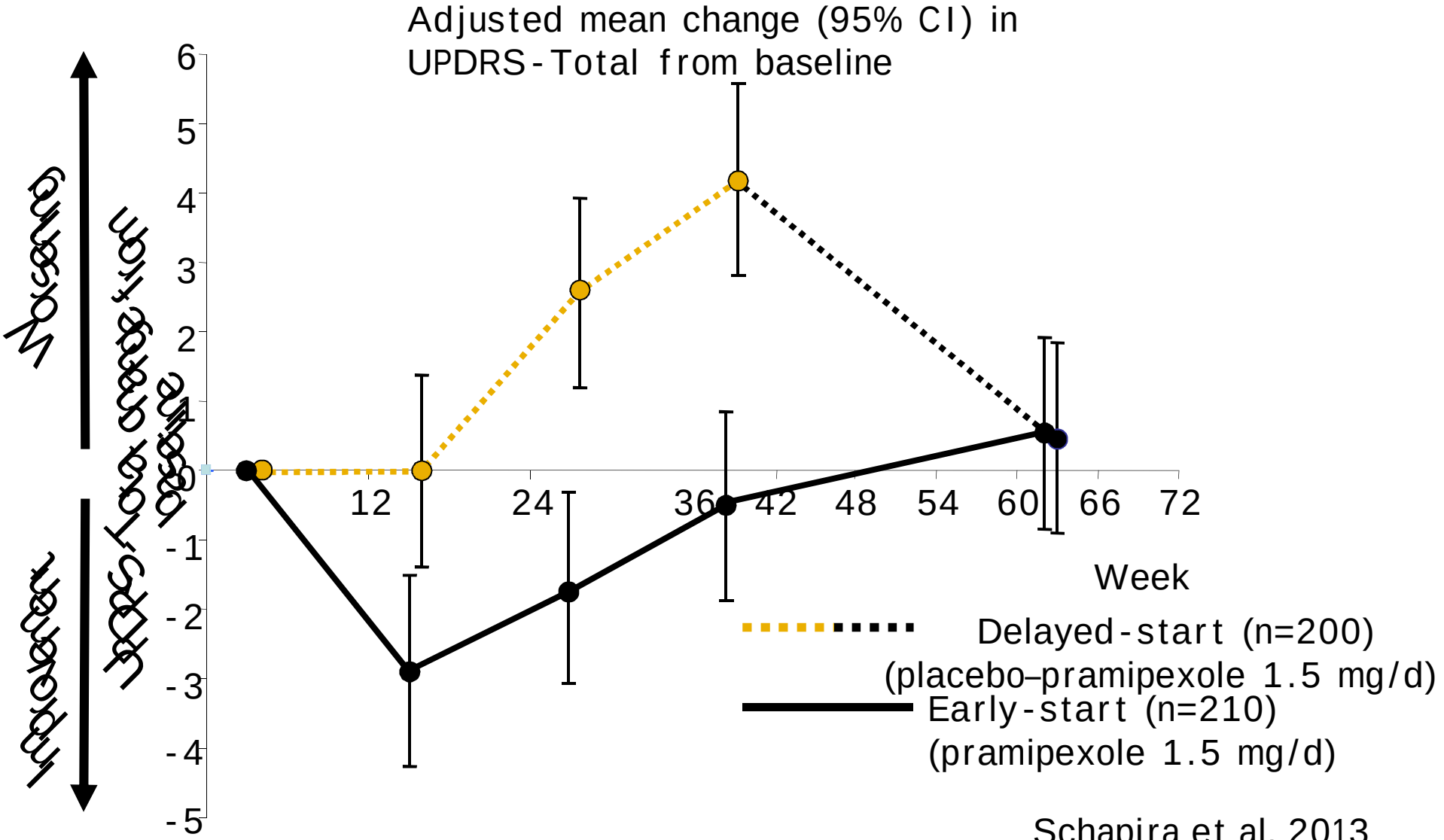
Olanow, Rascol et al. N Engl J Med 2009; 361: 1268

DELAYED START DESIGN:A GENERIC CUMULATIVE SYMPTOMATIC BENEFIT ?

PROUD STUDY: a delayed-start trial with the DA agonist pramipexole (Schapira et al, 2013)



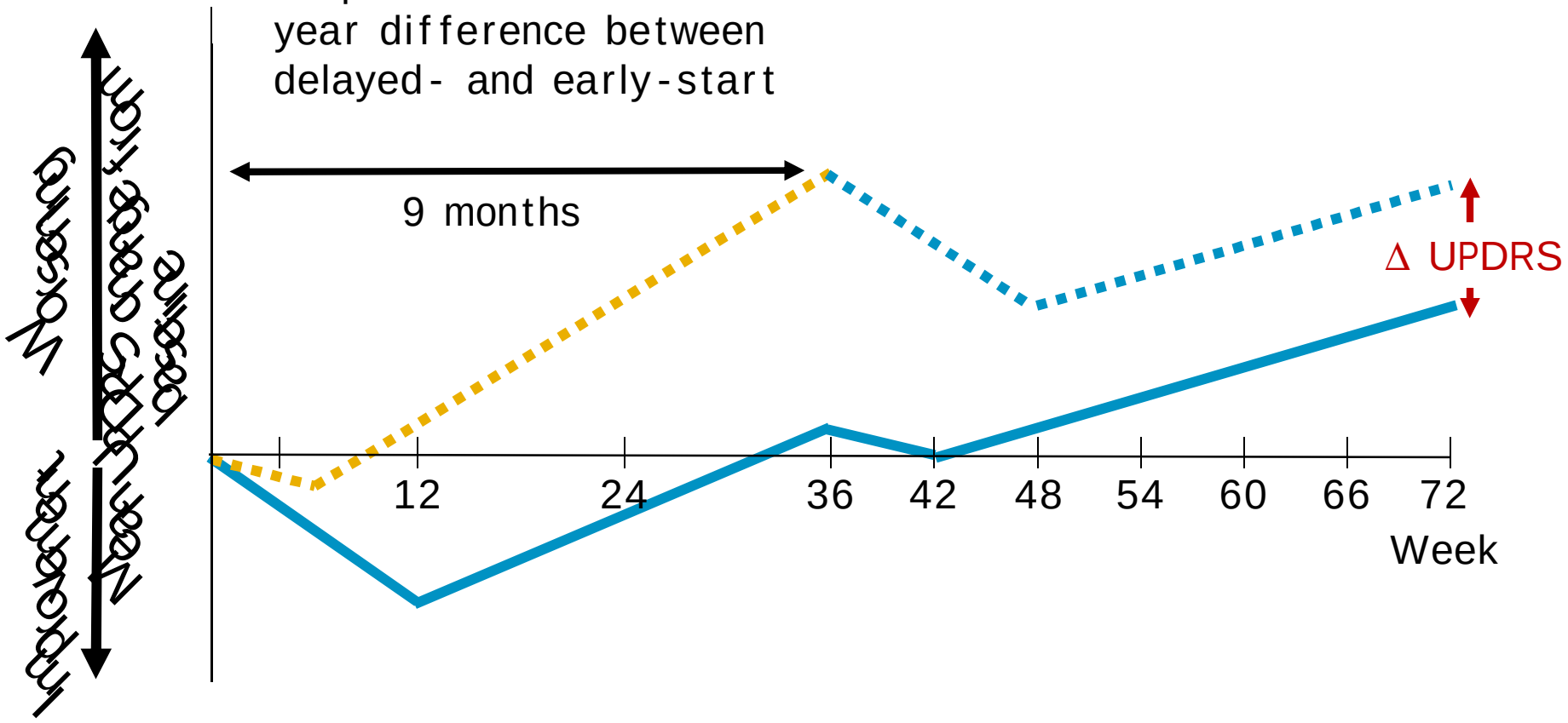
PROUD study: No difference between early- and delayed-start on UPDRS progression at endpoint



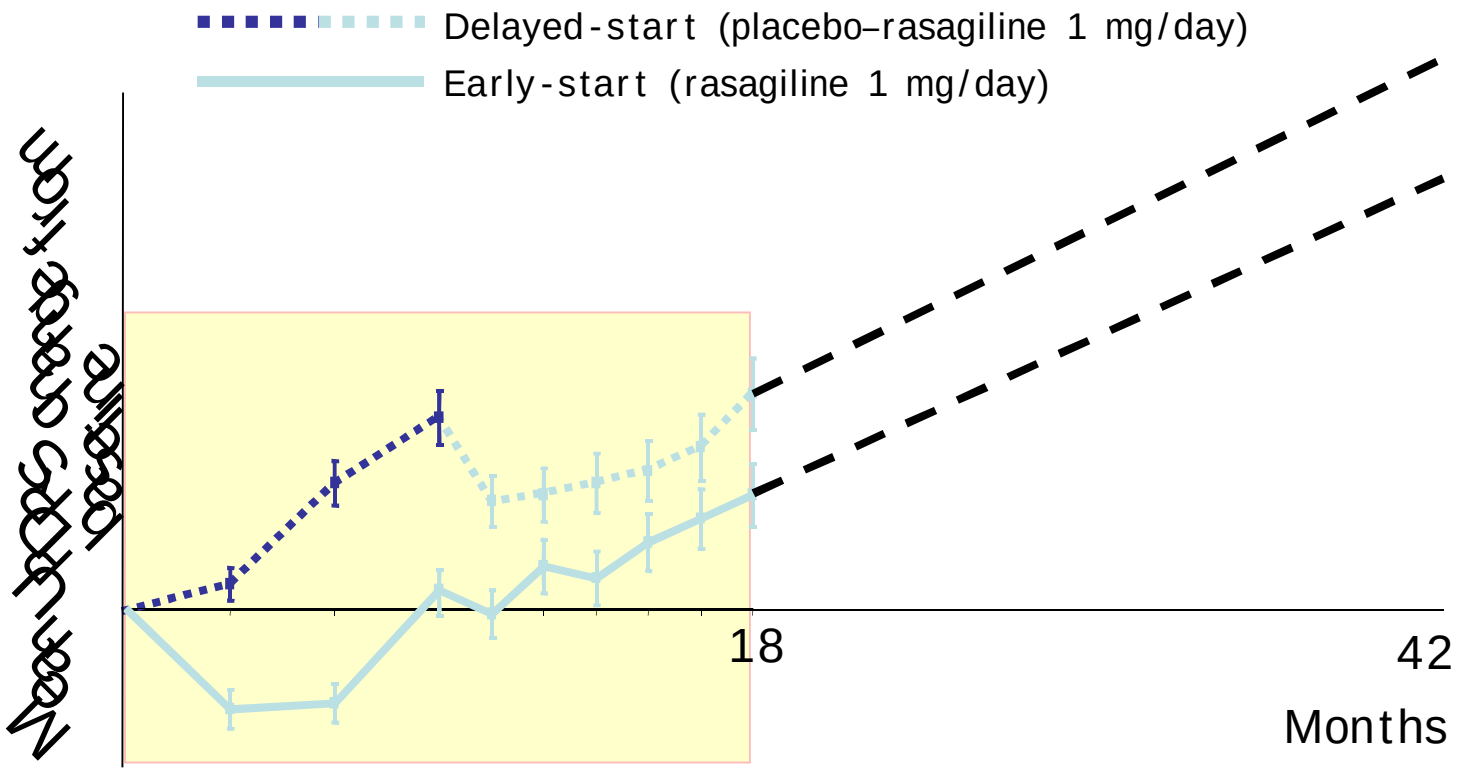
Schapira et al. 2013

THE DELAYED-START DESIGN IS A DESIGN FOR EXPLANATORY AND NOT PRAGMATIC STUDIES

- The difference at endpoint is a result of <1 year difference between delayed- and early-start

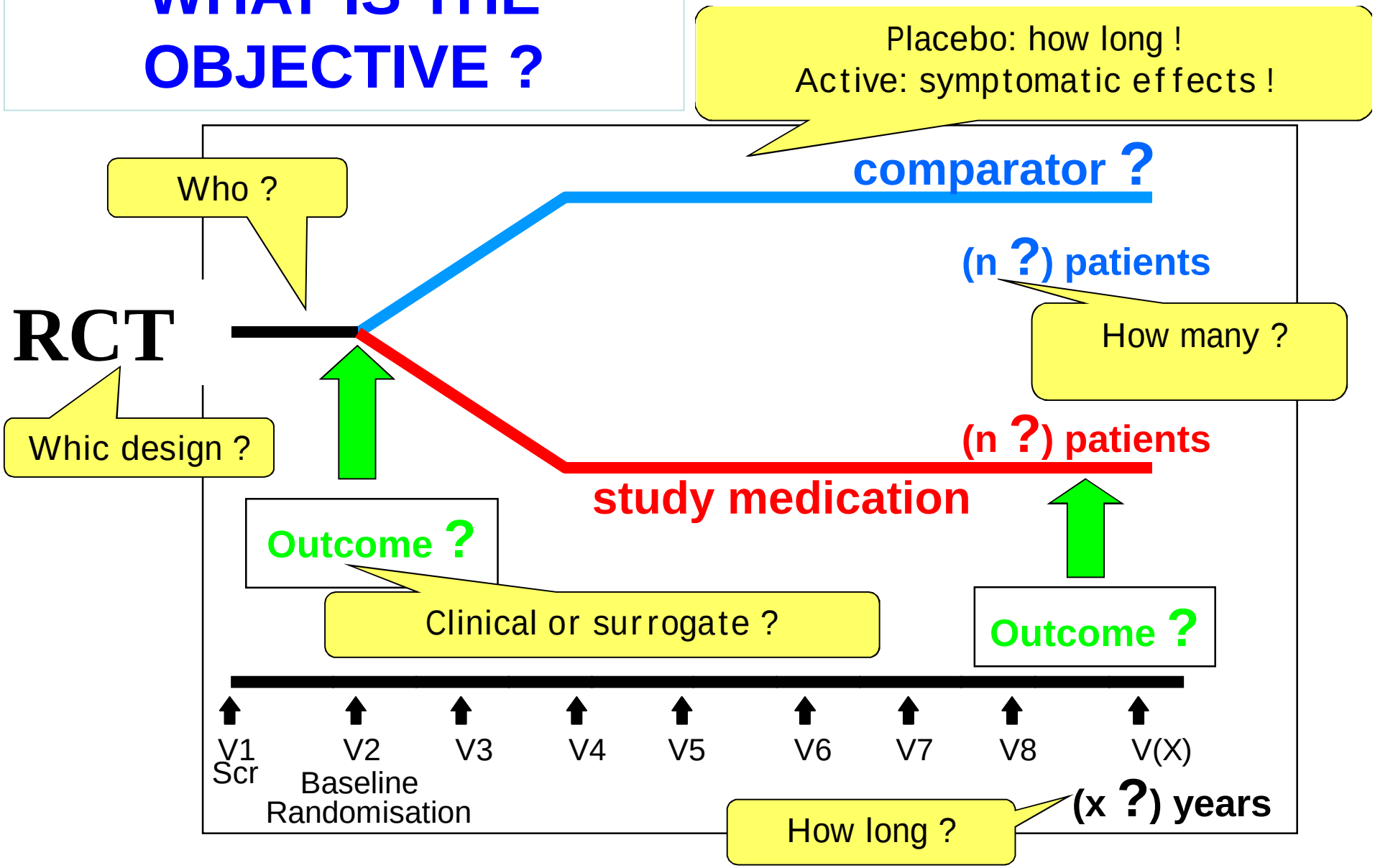


THE DELAYED-START DESIGN IS A DESIGN FOR EXPLANATORY AND NOT PRAGMATIC STUDIES



STUDY DESIGN

WHAT IS THE OBJECTIVE ?



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