Over the years it had been recognized that patients treated with levodopa often progressed to states of serious disability. It was hypothesised that this was due to a toxic effect of levodopa. The ELLDOPA (Early vs Late Levodopa) study was intended to determine if treatment changed progression and to decide if treatment should be started early or delayed as long as possible (if progression was accelerated). The analysis was based on the incorrect assumption that all levodopa symptomatic effects would washout within 2 weeks of stopping treatment. The authors ended up with no firm conclusions and clinicians still had no clear guidance on when to start levodopa.

Rasagiline is very similar to selegiline and might be expected to have similar effects. Two delayed start design studies (TEMPO (Hauser 2009), ADAGIO (Olanow 2009)) have tried to demonstrate disease modifying effects. The ADAGIO study assumed all symptomatic effects would be completed by 12 weeks. Like ELLDOPA this was not a robust assumption about the time course of symptomatic effects as shown for both the immediate treatment and delayed treatment arms.

ADAGIO did break new ground for traditional statistics by considering the rate of disease progression as a co-primary endpoint.
Objective

Compare Wash-Out and Delayed Start designs for describing and distinguishing symptomatic and disease modifying effects in slowly progressing diseases.

Study Design Aims

Selection criteria

- Accuracy and precision of drug effects
- Power to distinguish drug effects from natural disease progression

Methods

Estimating accuracy, precision and power

- Simulation of disease status over time (Nrep = 100)
  - Considering
    - Disease progression
    - Placebo and Drug effects
    - Without and With Drop-out
  - Analyze simulated data
    - NONMEM VI (1.2);
    - When minimization was unsuccessful data were re-analyzed up to 2 times with different starting values
  - Bias and imprecision
    - Bias = relative difference from true value
    - Imprecision = standard deviation of the bias
    - For robust estimation outliers were removed
  - Statistical power
    - Compare fit true model versus alternative model(s)
    - Null hypothesis test using change in Objective Function ($\chi^2$)
Assumptions
Disease progression & Drug Effect

- Linear disease progression in untreated patients
- Transient symptomatic placebo effect of -5 points based on literature data
- Effect size comparable to deprenyl of -6 units/year
- Transient symptomatic placebo effect of -5 points based on literature data

50% due to symptomatic effect
Delayed onset

50% due to disease modifying effect
Immediate onset

Drop-Out Models
Base + Response Dependent Hazard

- Hazard for drop-out proportional to change in UPDRS from baseline
  \[ \text{Hazard} = \beta_0 \times e^{\beta_1 \times \text{UPDRS}} \]
  \[ \text{Risk}_\text{out} = \text{Hazard} \]
  \[ \text{Dropout}_\text{out} = 1 - e^{-\text{Risk}_\text{out}} \]
  - Parameters visually optimized on reported drop-out

* "Average" drop-out: ±30% after 16.6 months
* "High" drop-out: ±60% after 16.6 months

Drop-Out Models
Higher Hazard During Wash-Out

- Higher drop-out hazard during wash-out
### Assumptions

**Design**

- Treatment arms: placebo and active (1:1)
- Sample size: 500 per group
- Observations: 11 per subject
- Trial duration: 16.6 months
- Delayed start: 6 months
- Washout: 13.6 months

- Sampling times were optimized using WinPOPT for each scenario

---

**Slide 11**

**No Drop-Out**

**Fast symptomatic onset**

(Teq=14 days)

- Greater bias for Delayed Start design

---

**Slide 12**

**No drop-out**

**Power**

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Combined = 50% slope + 50% offset effect at end of study
**Slide 13**

**Wash-Out + Drop-Out
Power**

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Combined = 50% slope + 50% offset effect at end of study

**Slide 14**

**Drop-Out
Power**

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Combined = 50% slope + 50% offset effect at end of study

**Slide 15**

**Conclusion**

- **Delayed Start & Wash-Out designs:**
  - Treatment effect parameters estimated with acceptable accuracy and precision
  - Minimal influence of drop-out

- **Delayed Start design:**
  - Combined effect cannot be separated from symptomatic model
  - Independent of speed of symptomatic onset

- **Wash-Out design:**
  - Combined effect can be separated from symptomatic model if:
    - Fast symptomatic onset (Teq=14 days)
    - Drop-out is around 30% after 16.6 months
  - Higher drop-out during wash-out has minimal influence on power

- **Wash-Out Design essential for distinguishing symptomatic from disease modifying effects**
Questions

- What designs could work for slow onset symptomatic effects?
  - e.g. levodopa effects keep increasing for more than a year?

- What would happen if wash-out speed was faster than speed of onset
  - e.g. levodopa seems to have fast wash-out ($T_{1/2}$ around 7 days)?

No Drop-Out
Slow symptomatic onset
($T_{eq}=90$ days)
**Slide 19**

**Wash-Out + Drop-Out**

Fast symptomatic onset (Teq=14 days)

- **No dropout**
- **Average dropout**
- **High dropout**

- **Bias & Imprecision (%):**
  - No drop-out
  - Average drop-out
  - High dropout

- **Drop-out (60% after 16.6 months):** some effect on bias and precision

**Slide 20**

**Wash-Out + Drop-out**

Higher Hazard during Wash-Out

- **Disease modifying effect**
- **Symptomatic effect**
- **Placebo effect**
- **Disease progression**

- **Bias & Precision (%):**
  - No drop-out
  - Average drop-out
  - 2 x higher drop-out during washout

- **Higher Drop-Out during Wash-Out: minimal effect on bias and precision**