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## Are Wash-Out Designs Better than Delayed Start Designs?

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## ELLDOPA Washout Design

CHANGE IN UPDRS FROM BASELINE TO WEEK 42

Small P but still no conclusion!  
 $P < 0.0001$

Week: -2, 2, 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46

Legend: Placebo, 150mg, 300mg, 600mg

Medications withdrawn at Week 42

ELLDOPA  
Fahn 2006

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.

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## ADAGIO Delayed Start Design

**A Rasagiline, 1 mg/day**

Improvement (Worsening) Mean Change in UPDRS Score (points)

Slope Wk 12-36

Week: 0, 12, 24, 36, 48, 60, 72

**B Rasagiline, 2 mg/day**

Improvement (Worsening) Mean Change in UPDRS Score (points)






Difference Wk 0-72 Slope Wk 48-72

Week: 0, 12, 24, 36, 48, 60, 72


ADAGIO  
Olanow et al 2009

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.

<p>Slide 4</p>	  <h2 style="text-align: center;">Objective</h2> <p style="text-align: center;">Compare <b>Wash-Out</b> and <b>Delayed Start</b> designs for describing and distinguishing <b>symptomatic</b> and <b>disease modifying</b> effects in slowly progressing diseases</p> <p style="text-align: right;">4</p>	
<p>Slide 5</p>	  <h2 style="text-align: center;">Study Design Aims</h2> <h3 style="text-align: center;">Selection criteria</h3> <ul style="list-style-type: none"> <li>• <b>Accuracy</b> and <b>precision</b> of drug effects</li> <li>• <b>Power</b> to distinguish drug effects from natural disease progression</li> </ul> <p style="text-align: right;">5</p>	
<p>Slide 6</p>	  <h2 style="text-align: center;">Methods</h2> <h3 style="text-align: center;">Estimating accuracy, precision and power</h3> <ul style="list-style-type: none"> <li>• Simulation of disease status over time (Nrep = 100) <ul style="list-style-type: none"> <li>• Considering <ul style="list-style-type: none"> <li>• Disease progression</li> <li>• Placebo and Drug effects</li> <li>• Without and With Drop-out</li> </ul> </li> </ul> </li> <li>• Analyze simulated data <ul style="list-style-type: none"> <li>• NONMEM VI (1.2);</li> <li>• When minimization was unsuccessful data were re-analyzed up to 2 times with different starting values</li> </ul> </li> <li>• Bias and imprecision <ul style="list-style-type: none"> <li>• Bias = relative difference from true value</li> <li>• Imprecision = standard deviation of the bias</li> <li>• For robust estimation outliers were removed</li> </ul> </li> <li>• Statistical power <ul style="list-style-type: none"> <li>• Compare fit true model <i>versus</i> alternative model(s)</li> <li>• Null hypothesis test using change in Objective Function (<math>\chi^2</math>)</li> </ul> </li> </ul> <p style="text-align: right;">6</p>	


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## Assumptions

### Disease progression & Drug Effect



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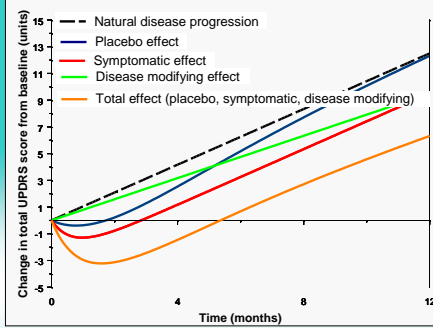
- Linear disease progression in untreated patients
- Transient symptomatic placebo effect of -5 points based on literature data
- Effect size comparable to deprenyl of -6 units/year

50% due to symptomatic effect


Delayed onset

50% due to disease modifying effect

Immediate onset




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## Drop-Out Models

### Base + Response Dependent Hazard



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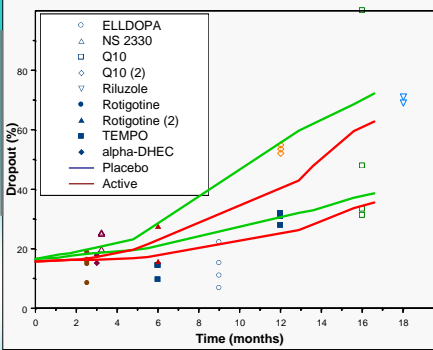
- Hazard for drop-out proportional to change in UPDRS from baseline

$$\text{Hazard} = \beta_0 \times e^{\beta \times \Delta \text{UPDRS}}$$

$$\text{Risk}_{t=i} = \int_0^{t=i} \text{Hazard}$$

$$\text{Dropout}_{t=i} = 1 - e^{-\text{Risk}_{t=i}}$$


- Parameters visually optimized on reported drop-out



• "Average" drop-out : ±30% after 16.6 months

• "High" drop-out : ±60% after 16.6 months


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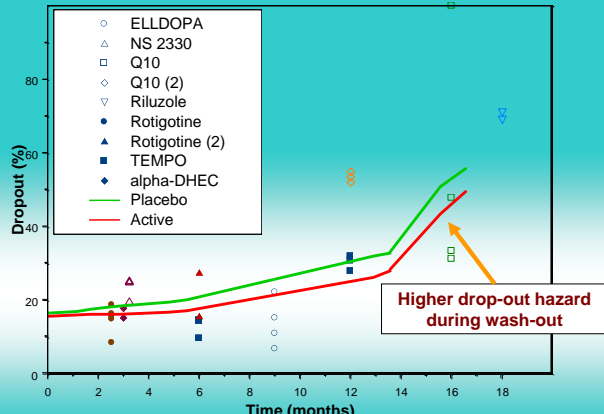
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## Drop-Out Models


### Higher Hazard During Wash-Out



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## Assumptions Design<sup>1</sup>



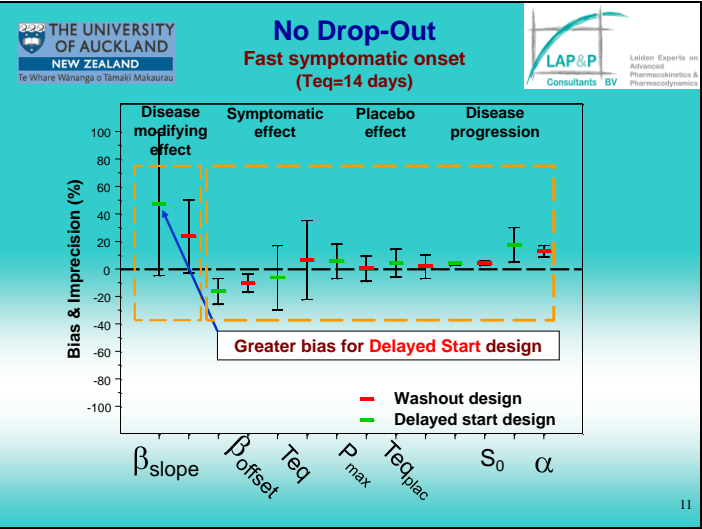
Leiden Experts in Advanced Pharmacokinetics & Pharmacodynamics

- 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

<sup>1</sup>www.fda.gov/ohrms/dockets/ac/06/slides/2006-4248s2-4-FDABhattaram&Siddiqui.ppt

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## No drop-out Power




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⊠ Not possible to distinguish between treatment effects for slow equilibrium half-life

		True	Alternative	DS	WO	DS	WO
Drop-out				None	None	None	None
	Teq (days)			14	14	90	90
	Washout			No	Yes	No	Yes
Power	Combined	Slope	100	100	100	100	
	Combined	Offset	54	97	50	56	


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

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## Wash-Out + Drop-Out Power



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**✗ Drop-out (60% after 16.6 months): High effect on power**

		True	Alternative	DS_14	WO_14	WO_14	WO_14
Drop-out				None	None	Average	High
	Teq (days)			14	14	14	14
	Washout			No	Yes	Yes	Yes
Power	Combined	Slope	100	100	100	100	
	Combined	Offset	54	97	87	51	

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


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## Drop-Out Power



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**✓ Higher drop-out during wash-out: minimal effect on power**

		True	Alternative	DS	WO	WO	WO
Drop-out				None	None	Average	Avg+2x
	Teq (days)			14	14	14	14
	Washout			No	Yes	Yes	Yes
Power	Combined	Slope	100	100	100	100	
	Combined	Offset	54	97	87	86	

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


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## Conclusion



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- **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**

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## Back-up slides

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## Questions

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- 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) ?

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## No Drop-Out

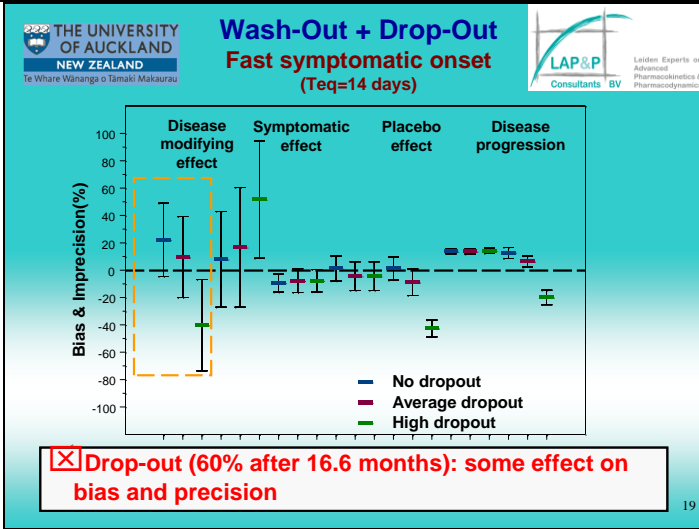
Slow symptomatic onset  
( $T_{eq}=90$  days)

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Parameter	Washout design (Bias & imprecision %)	Delayed start design (Bias & imprecision %)
$\beta_{slope}$	~30	~15
$\beta_{offset}$	~-30	~-35
$T_{eq}$	~-40	~-50
$P_{max}$	~0	~0
$T_{eq,plac}$	~0	~0
$S_0$	~0	~0
$\alpha$	~0	~0

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