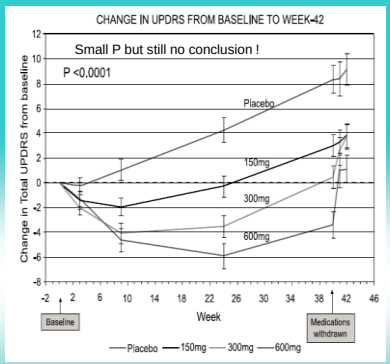
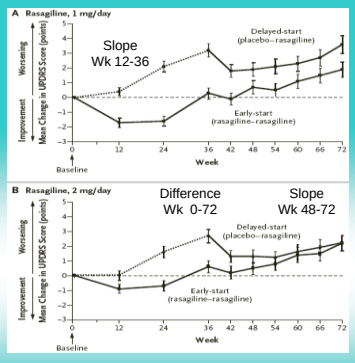
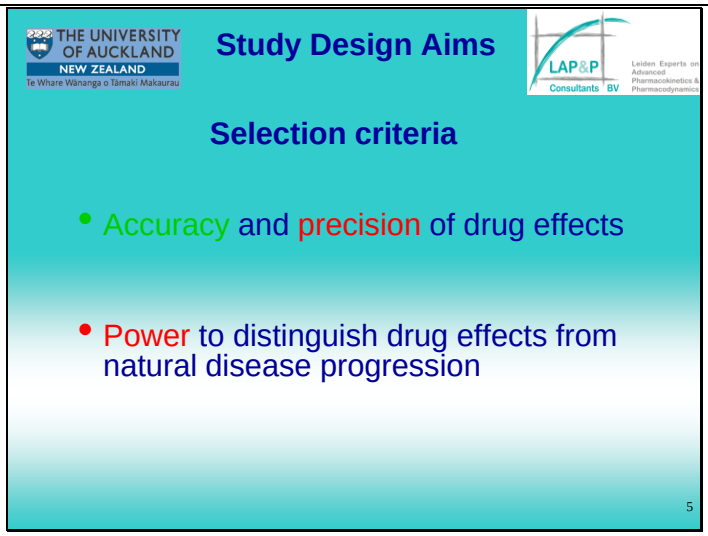
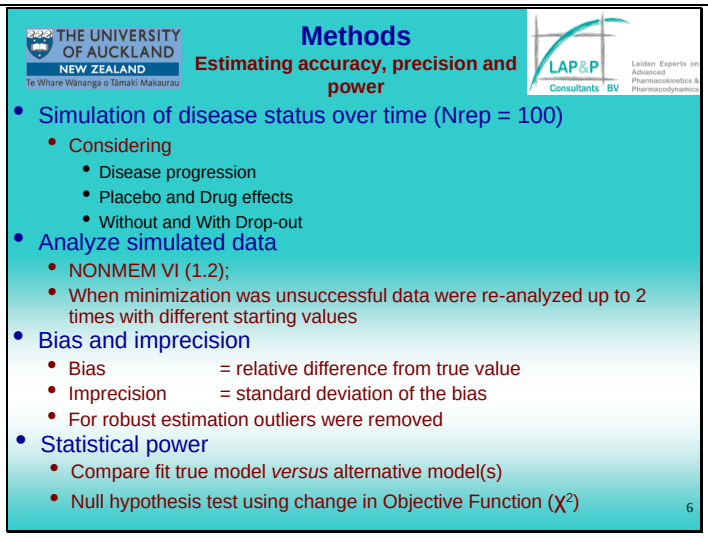
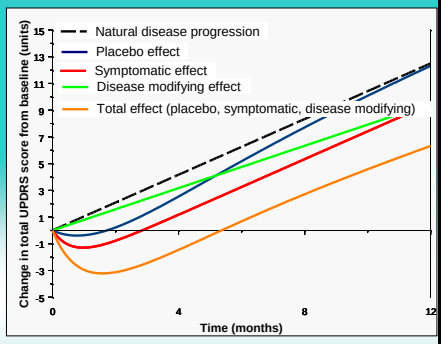
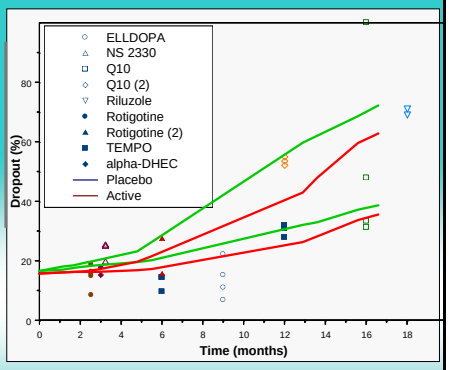
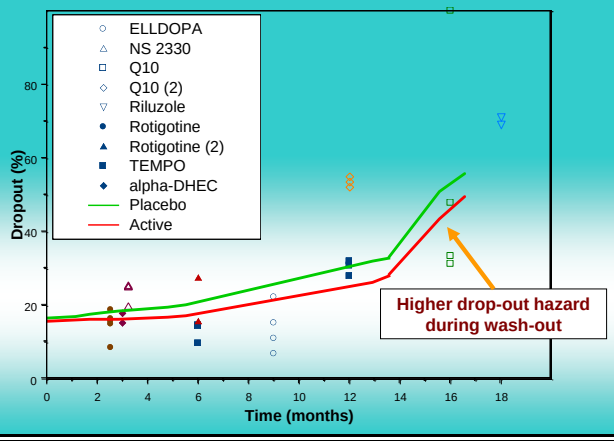
| | | |
|---|---|---|
| Slide 1 | THE UNIVERSITY OF AUCKLAND NEW ZEALAND<br>Te Whare Wānanga o Tāmaki Makaurau<br>LAP&P Consultants BV<br>Leiden Experts on Advanced Pharmacokinetics & Pharmacodynamics<br><br>**Are Wash-Out Designs Better than Delayed Start Designs?**<br><br>**Nick Holford**<br>Dept. Pharmacology and Clinical Pharmacology<br>University of Auckland, New Zealand<br><br>**Bart Ploeger**<br>LAP&P Consultants BV<br>Leiden, The Netherlands<br>1 | |
| Slide 2 | THE UNIVERSITY OF AUCKLAND NEW ZEALAND<br>Te Whare Wānanga o Tāmaki Makaurau<br>LAP&P Consultants BV<br>Leiden Experts on Advanced Pharmacokinetics & Pharmacodynamics<br><br>**ELLDOPA**<br>**Washout Design**<br><br>  <br><br>ELLDOPA<br>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. |
| Slide 3 | THE UNIVERSITY OF AUCKLAND NEW ZEALAND<br>Te Whare Wānanga o Tāmaki Makaurau<br>LAP&P Consultants BV<br>Leiden Experts on Advanced Pharmacokinetics & Pharmacodynamics<br><br>**ADAGIO**<br>**Delayed Start Design**<br><br>  <br><br>ADAGIO<br>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.<br><br>ADAGIO did break new ground for traditional statistics by considering the rate of disease progression as a co-primary endpoint. |

| | | |
|---|---|---|
| Slide 4 |  | |
| Slide 5 |  | |
| Slide 6 |  | |

| | | |
|---|---|---|
| Slide 7 | **Assumptions**<br>**Disease progression & Drug Effect**<br>• Linear disease progression in untreated patients<br>• Transient symptomatic placebo effect of -5 points based on literature data<br>• Effect size comparable to deprenyl of -6 units/year<br>**50% due to symptomatic effect**<br>***Delayed onset***<br>**50% due to disease modifying effect**<br>***Immediate onset***<br>  <br>7 | |
| Slide 8 | **Drop-Out Models**<br>**Base + Response Dependent Hazard**<br>• Hazard for drop-out proportional to change in UPDRS from baseline<br>$Hazard = \beta_0 \times e^{\beta \times \Delta UPDRS}$<br>$Risk_{t=i} = \int_0^{t=i} Hazard$<br>$Dropout_{t=i} = 1 - e^{-Risk_{t=i}}$<br>• Parameters visually optimized on reported drop-out<br>  <br>• "Average" drop-out : ±30% after 16.6 months<br>• "High" drop-out : ±60% after 16.6 months<br>8 | |
| Slide 9 | **Drop-Out Models**<br>**Higher Hazard During Wash-Out**<br>  <br>9 | |

Slide 10

## Assumptions
### Design[1]

- 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

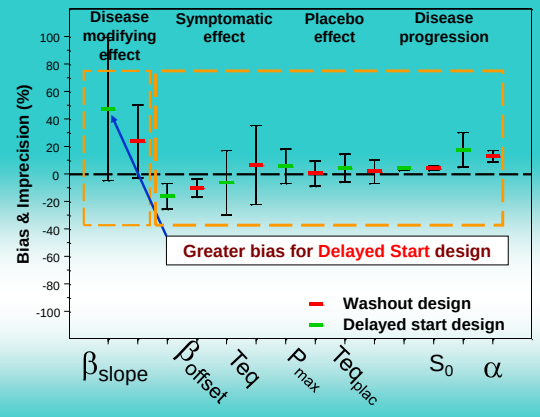
- Sampling times were optimized using WinPOPT for each scenario

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

10

Slide 11

## No Drop-Out
### Fast symptomatic onset (Teq=14 days)




11

Slide 12

## No drop-out
### Power

☒ 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

12

Slide 13

## Wash-Out + Drop-Out Power

☒ 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

13

Slide 14

## Drop-Out Power

✓ 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

14

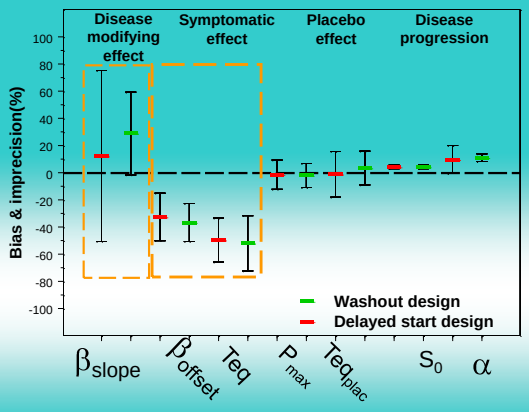
Slide 15

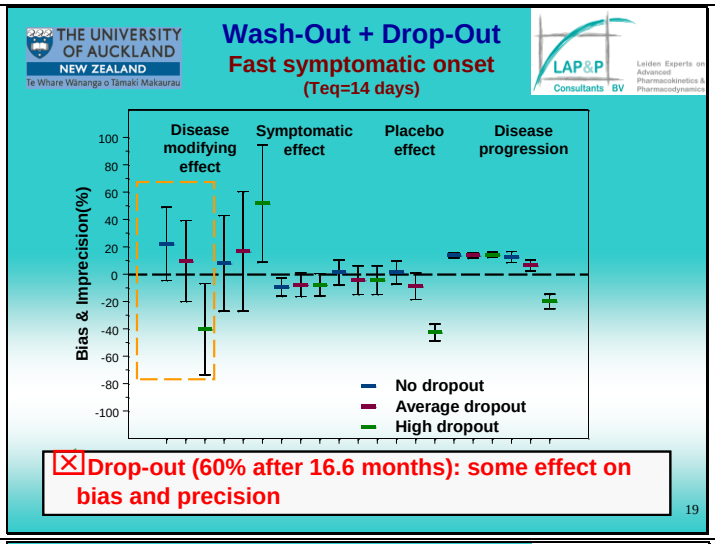
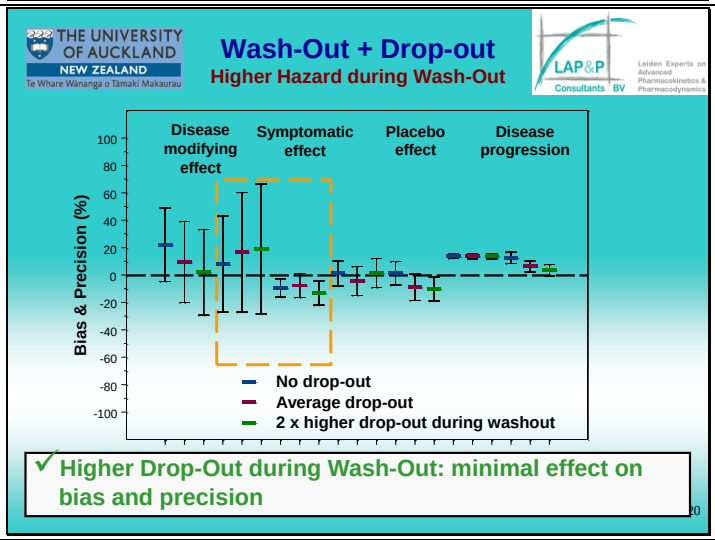
## Conclusion

- **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

15

| | | |
|---|---|---|
| Slide 16 | THE UNIVERSITY OF AUCKLAND NEW ZEALAND Te Whare Wānanga o Tāmaki Makaurau<br>**Back-up slides**<br>LAP&P Consultants BV<br>16 | |
| Slide 17 | THE UNIVERSITY OF AUCKLAND NEW ZEALAND Te Whare Wānanga o Tāmaki Makaurau<br>**Questions**<br>LAP&P Consultants BV<br>• What designs could work for slow onset symptomatic effects ?<br>  • e.g. levodopa effects keep increasing for more than a year?<br>• What would happen if wash-out speed was faster than speed of onset<br>  • e.g. levodopa seems to have fast wash-out (T½ around 7 days) ?<br>17 | |
| Slide 18 | THE UNIVERSITY OF AUCKLAND NEW ZEALAND Te Whare Wānanga o Tāmaki Makaurau<br>**No Drop-Out**<br>**Slow symptomatic onset**<br>**(Teq=90 days)**<br>LAP&P Consultants BV<br>  <br><br>18 | |

| | | |
|---|---|---|
| Slide 19 |  | |
| Slide 20 |  | |