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The Design and Analysis of Alzheimer's Disease Trials with a Delayed Start Period

Gopalan Sethuraman, Ph.D.
Eric Siemers, M.D.
Roy Tamura, Ph.D.
Walt Offen, Ph.D.
Richard Mohs, Ph.D.
Eli Lilly & Company

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Background

- Single period designs vs. dual period designs for treatment of AD
- Statistical analysis of dual period designs challenging

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Designs Overview

- Single period designs to show treatment effect
  - Patients randomized to treatment or placebo
  - 12 to 18 months in duration to show treatment effect
- Dual period designs
  - Delayed start designs
  - Delayed withdrawal designs
  - Complete designs (combination of delayed start, delayed withdrawal)

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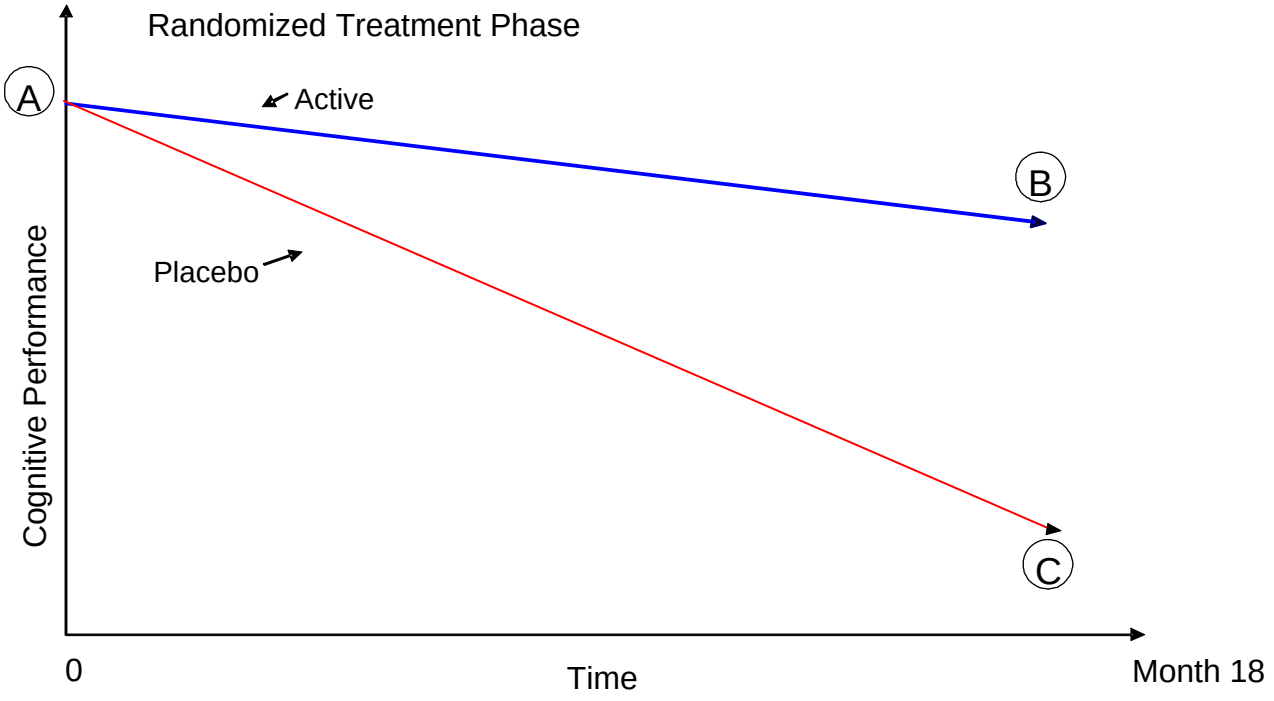
Single Period Designs

Expected outcome of separation between treatment (A to B) and placebo in cognitive decline (A to C)

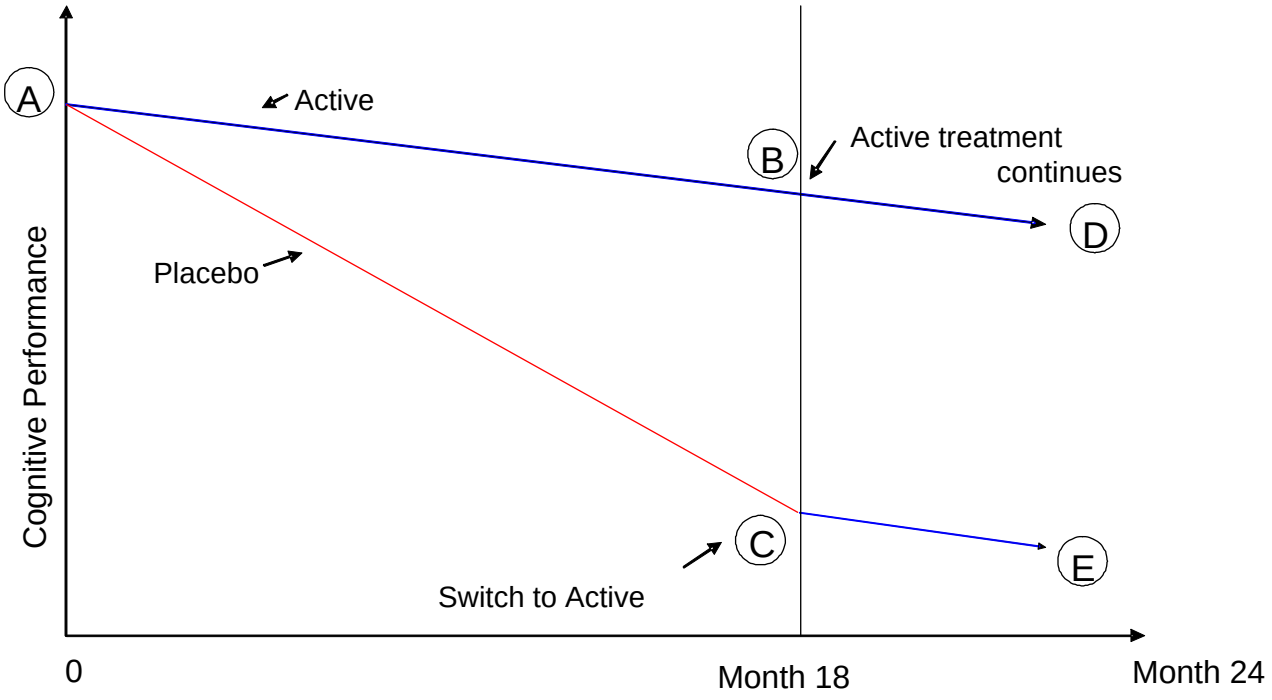


Single Period Designs

- Advantages
  - Simple and traditional
  - One analysis: Treatment effect at end of study period
- Disadvantages
  - Difficult to enroll and/or retain patients if no chance of getting active treatment at some point

Dual Period Designs - Delayed Start Design

Patients on Placebo switch to active treatment several months after start of study



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Delayed Start Design

- Advantages
  - All patients get active treatment for a period of time
  - May improve patient recruitment and retention
  - Maybe more appropriate design to show cumulative effects
- Disadvantages
  - Lack of blinding in delayed start period

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Delayed Start Design

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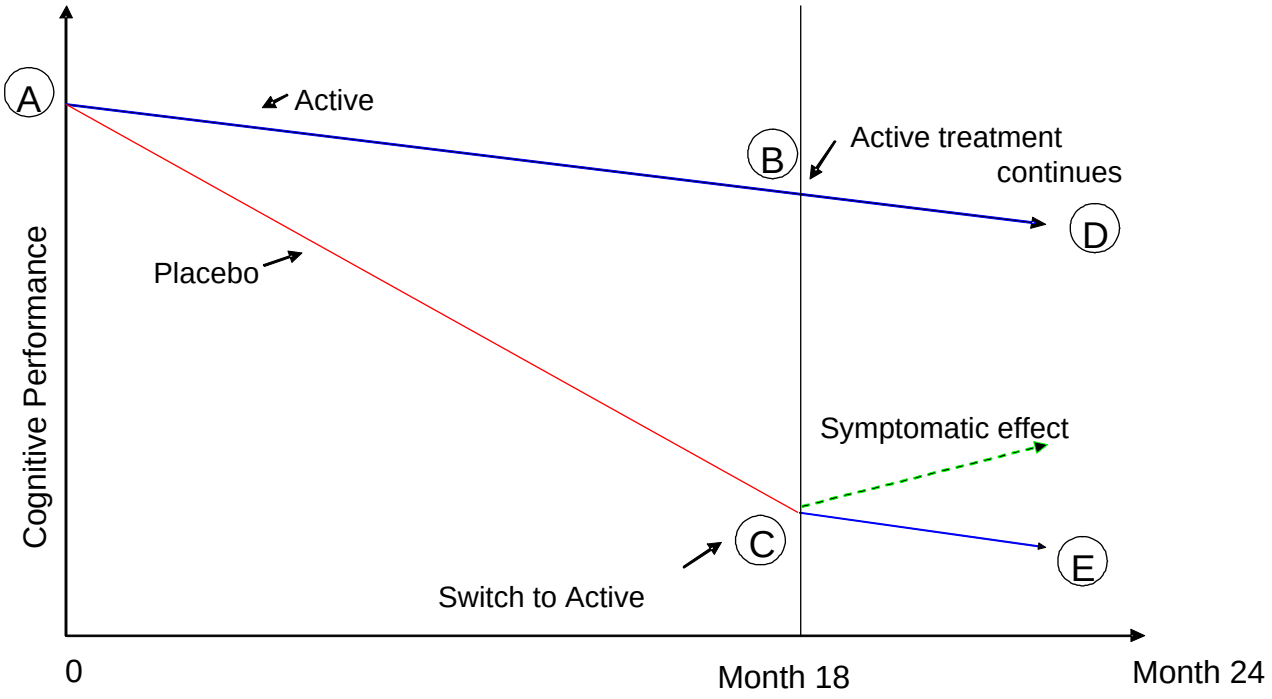

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Delayed Start Design

- Analysis includes 3 parts
  - Analysis of initial treatment period (randomized phase) only
  - Analysis of data from both periods
  - Analysis of data from delayed start period only

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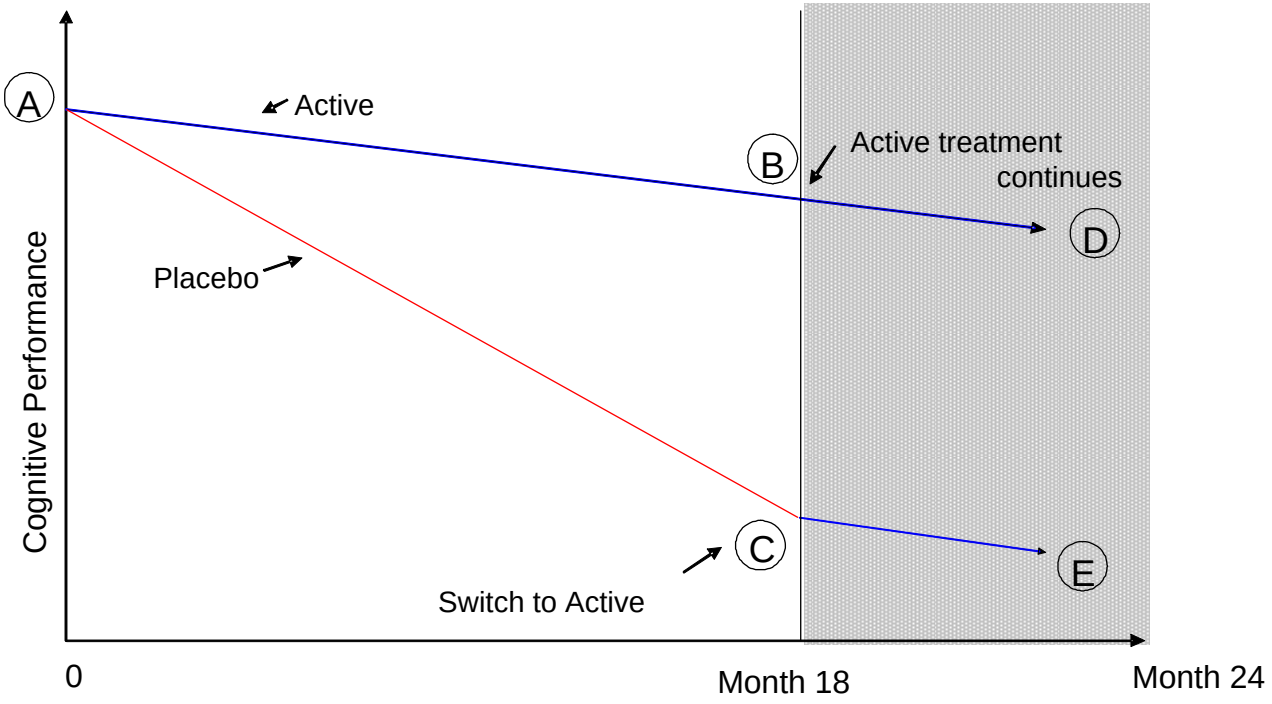
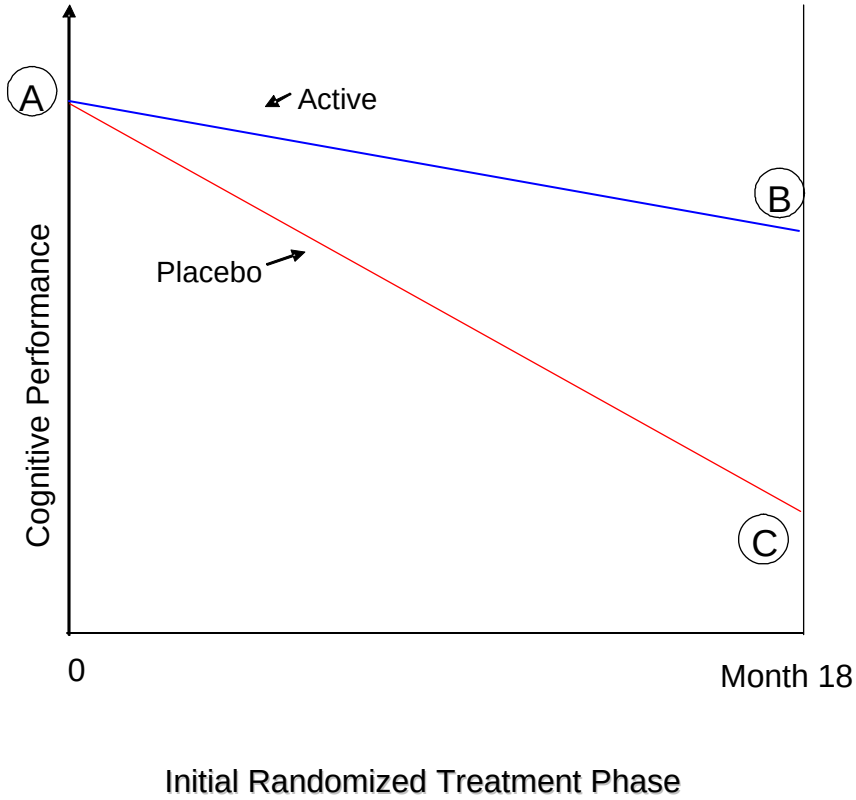
Delayed Start Design: Randomized Phase



Delayed Start Design: Randomized Phase

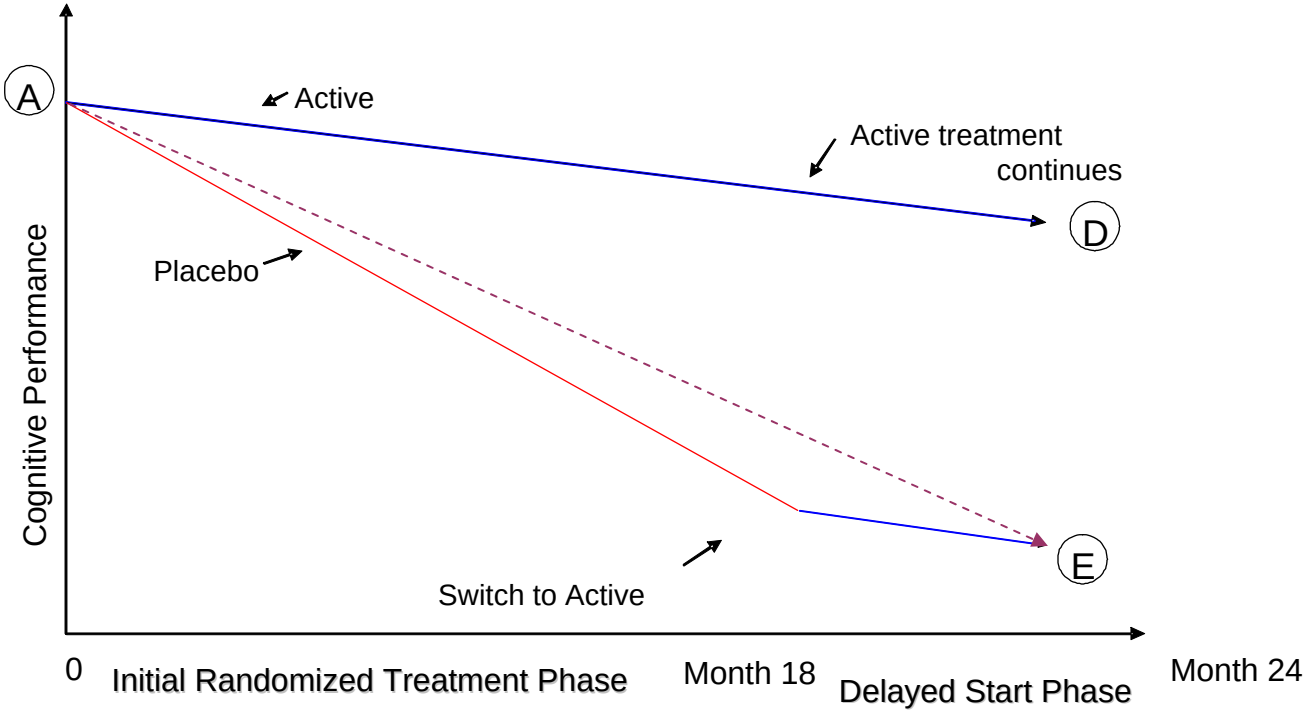
Analysis of change from A to B compared to change from A to C

- LOCF not appropriate
- Analyze only completers?
- Analysis of slopes?
  - Need to test and confirm data is linear
- Analyze using some other imputation method?
- Mixed Model Repeated Measures
  - Regulatory agencies coming around to accepting MMRM
  - Require sensitivity analysis



Delayed Start Design

- Analysis of entire study period (both periods combined)
  - Is there any value in comparing change from A to D with change from A to E?
  - What method to use? (MMRM, completers only or some other imputation method)



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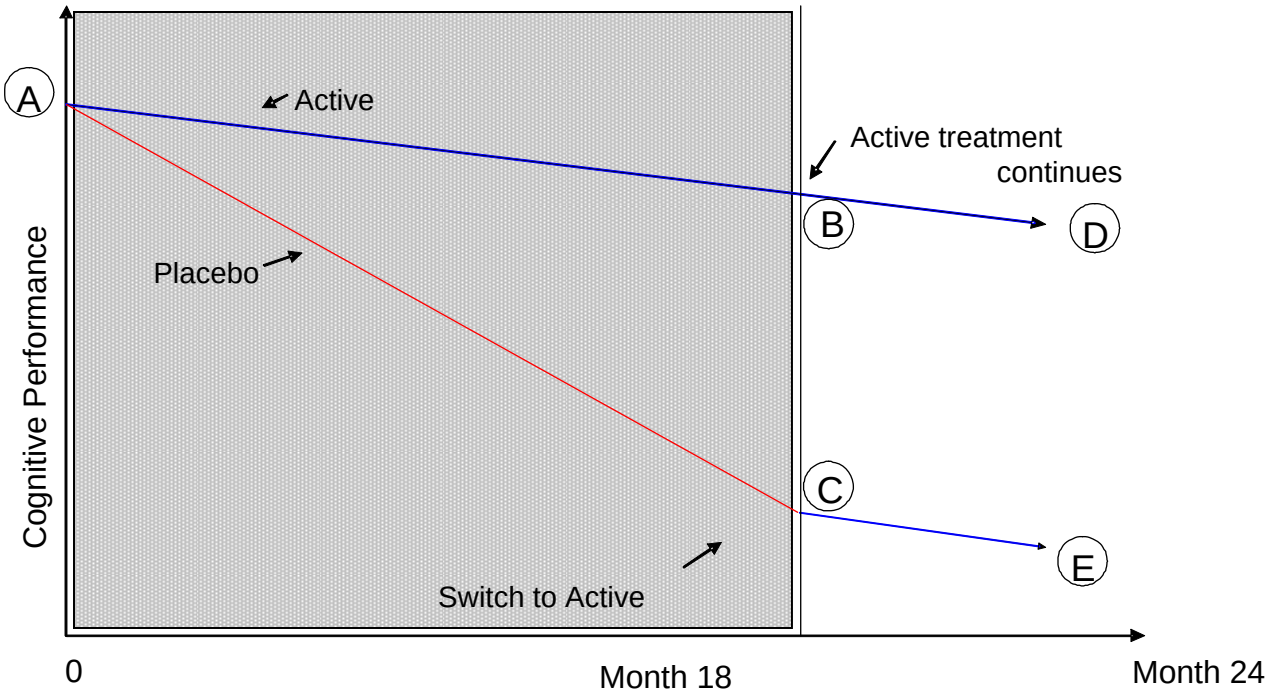
Delayed Start Phase



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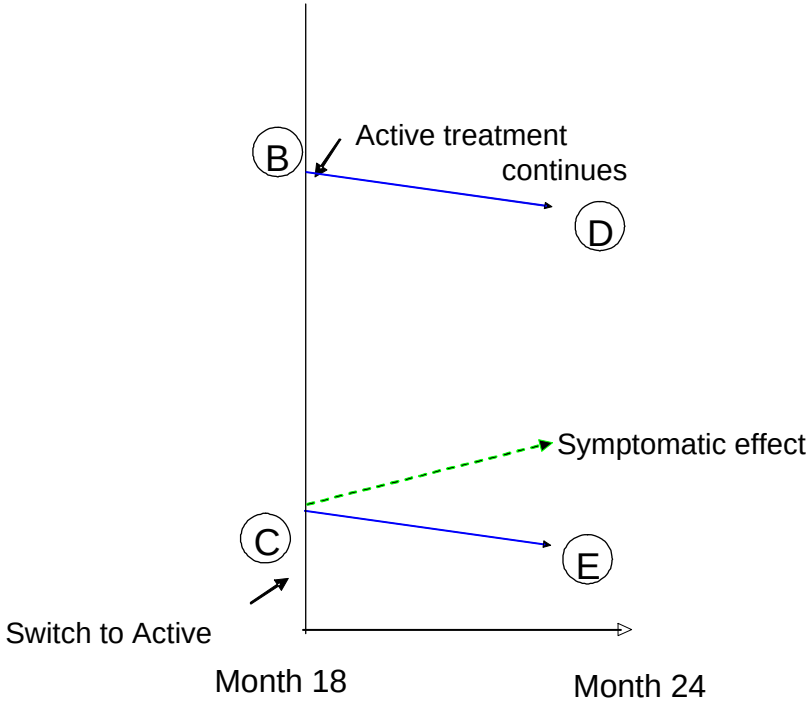
Delayed Start Phase

Analysis of change from B to D compared to change from C to E

- Comparison of slopes
  - Slope from C to E versus slope from B to D
  - Show slopes are parallel
  - Need to verify data is linear
- Test for non-inferiority to show parallelism?
- Non-inferiority margin
  - X% of difference between B and D maintained when comparing E and D



Delayed Start Phase

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Delayed Start Design – Additional Considerations

- Duration of Initial Randomized Treatment Period
  - Sufficiently long to show treatment separation and potentially cumulative effects of treatment to emerge
- Duration of Delayed-Start Period
  - Sufficiently long to show no “catching-up” by patients switched to active treatment
- Sample size ↑ for a delayed start design
- Dropouts during first phase will impact results from delayed start phase

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Conclusions

- Dual period delayed start design provides unique features
- Analysis of data is challenging
- The analysis of the different periods provides separate but complementary information
- Results of all analyses must be considered to show symptomatic or cumulative effects