

Adaptive Seamless Designs for Phase IIb/III Clinical Trials

Jeff Maca, Ph.D.

Assoc. Director, Biostatistics

Novartis Pharmaceuticals

Outline

- Introduction and motivation of adaptive seamless designs (ASD)
- Statistical methodology for seamless designs
- Simulations and comparisons of statistical methods
- Considerations for adaptive design implementation

Introduction and Motivation

Reducing time to market is/has/will be a top priority in pharmaceutical development

- Brings valuable medicines to patients sooner
- Increases the value of the drug to the parent company

Adaptive seamless designs can help reduce this development time

Definitions

Seamless design

- A clinical trial design which combines into a single trial objectives which are traditionally addressed in separate trials

Adaptive Seamless design

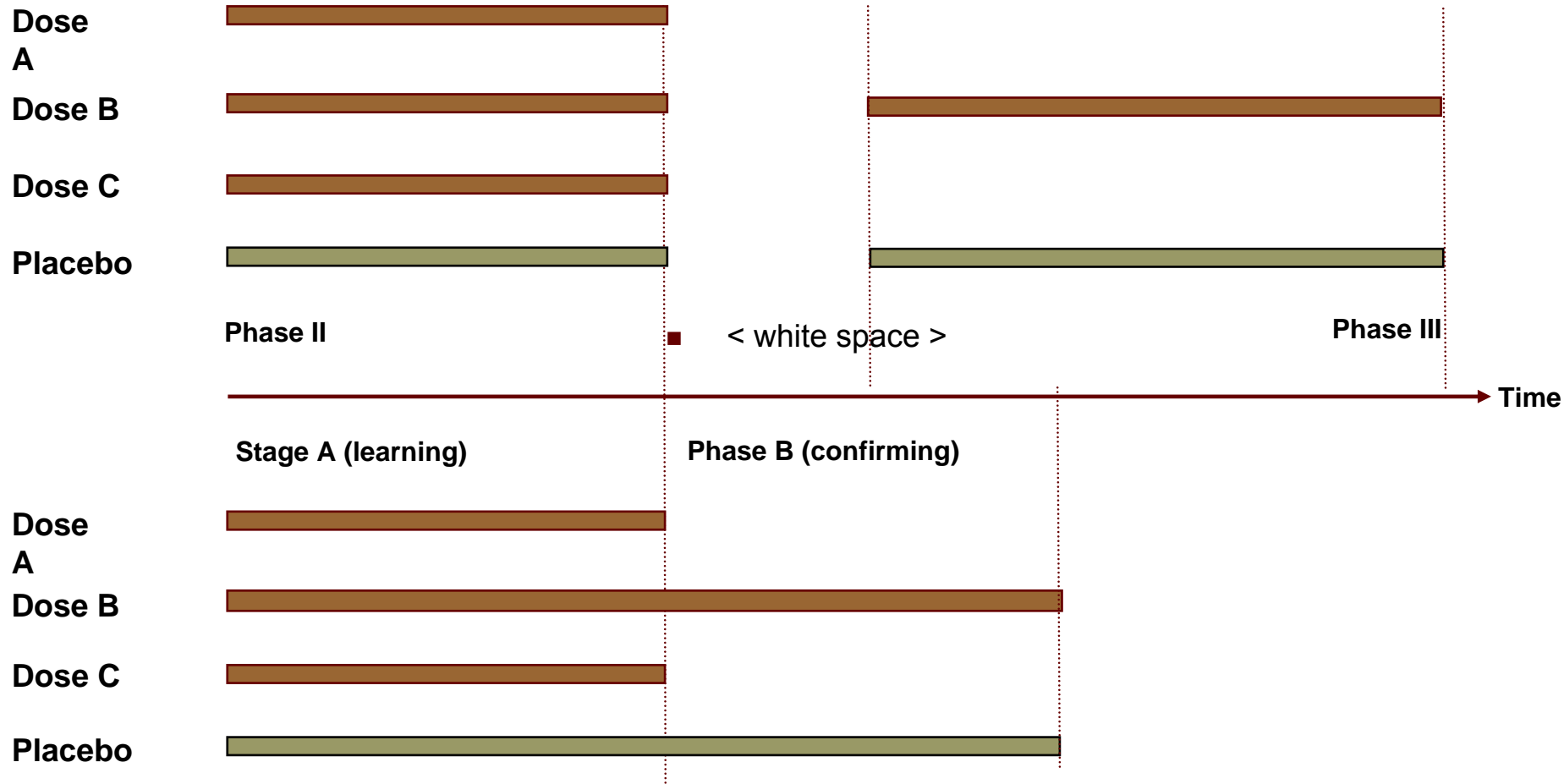
- A seamless trial in which the final analysis will use data from patients enrolled before and after the adaptation (*inferentially* seamless)

Adaptive Seamless Designs

Primary objective – combine “dose selection” and “confirmation” into one trial

- Although dose is most common phase IIb objective, other choices could be made, e.g. population
- After dose selection, only change is to new enrollments (patients are generally not re-randomized)
- Patients on terminated treatment groups could be followed
- All data from the chosen group and comparator is used in the final analysis. Appropriate statistical methods must be used

Adaptive Seamless Designs



Statistical methodology

Statistical methodology for Adaptive Seamless Designs must account for potential biases and statistical issues

- Selection bias (multiplicity)
- Multiple looks at the data (interim analysis)
- Combination of data from independent stages

Statistical methodology - Bonferroni

Simple Bonferonni adjustment

Test final hypothesis at $\alpha / \# \text{ trt}$

- Accounts for selection bias: multiplicity adjustment
- Multiple looks at the data: not considered
- Combination of data from stages by simple pooling
 - In some sense, ignores that there was an interim analysis at all
- Most conservative approach, simple to implement
- No other adjustments (i.e., sample size) can be made

Statistical Methodology – Closed Testing

And alternative and more powerful approach is a closed testing approach, and combination of p-values with inverse normal method

Methodology combines:

- Closed testing of hypothesis
- Simes adjustment of p-values for multiplicity
- Combines data (p-values) from stages via the inverse normal method (or Fisher's combination)

Statistical Methodology – Sample sizes

Choosing sample sizes

- There are two sample sizes to consider for a seamless design, n_1 , n_2
- If t is the number of treatments, the total sample size N is:

$$N = t \cdot n_1 + 2 \cdot n_2$$

- The larger n_1 , the better job of choosing the “right” dose. However, this makes the total much larger.
- Power can be determined by simulation, and is also a function of the (unknown) dose response

Statistical Methodology – Power

Simulation for power comparison

To compare the two methods for analyzing an adaptive seamless designs, the following parameters were used:

- Sample sizes were $n_1 = n_2 = 75$
- Primary endpoint is normal, with $\sigma = 12$
- One dose was selected for continuation
- Various dose responses were assumed
- 20,000 reps used for simulations (error = $\pm 0.5\%$)

Statistical Methodology – Power

Simulation for power comparison

Selecting 1 treatment group from 2 possible treatments

Dose Response (Δ placebo)	Power Bonferroni	Power Closed Test
0 , 4.5	83.1%	83.2%
4.5, 4.5	91.0%	92.2%

Statistical Methodology – Power

Simulation for power comparison

Selecting 1 treatment group from 3 possible treatments

Dose Response (Δ placebo)	Power Bonferroni	Power Closed Test
0 ,0, 4.5	79.4%	78.9%
4.5, 4.5, 4.5	90.8%	92.7%

Considerations for Seamless Designs

With the added flexibility of seamless designs, comes added complexity.

- Careful consideration should be given to the feasibility for a seamless design for the project.
- Not all projects can use seamless development
- Even if two programs can use seamless development, one might be better suited than the other
- Many characteristics add or subtract to the feasibility

Considerations for Seamless Designs

Enrollment vs. Endpoint

- The length of time needed to make a decision relative to the time of enrollment must be small
 - Otherwise enrollment must be paused
- Endpoint must be well known and accepted
 - If the goal of Phase II is to determine the endpoint for registration, seamless development would be difficult
- If surrogate marker will be used for dose selection, it must be accepted, validated and well understood

Considerations for Seamless Designs

Clinical Development Time

- There will usually be two pivotal trials for registration
- Entire program must be completed in shorter timelines, not just the adaptive trial

Considerations for Seamless Designs

Logistical considerations

- Helpful if final product is available for adaptive trial (otherwise bioequivalence study is needed)
- Decision process, and personnel must be carefully planned and pre-specified

Considerations for Seamless Designs

Novel drug or indication

- Decision process which will be overly complicated could be an issue with an external board
- If there are a lot of unknown issues with the indication or drug, a separate phase II trial would be better
- However, getting a novel drug to patients sooner increases the benefit of seamless development

Conclusions

- Adaptive seamless designs have an ability to improve the development process by reducing timelines for approval
- Statistical methods are available to account for adaptive trial designs
- Extra planning is necessary to implement an adaptive seamless design protocol
- Benefits should be carefully weighed against the challenges of such designs before implementation

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