

Phase II/III Adaptive Design with Treatment Selection: A case study

Frank Bretz, David Lawrence, Peter Thomas -- Novartis

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Phase II/III Adaptive Design with Treatment Selection: A case study *Outline*

- Introduction
- Trial Design
- Adaptive Statistical Methodology
- Interim Analysis Decision Making
- Experience with the FDA
- Conclusions

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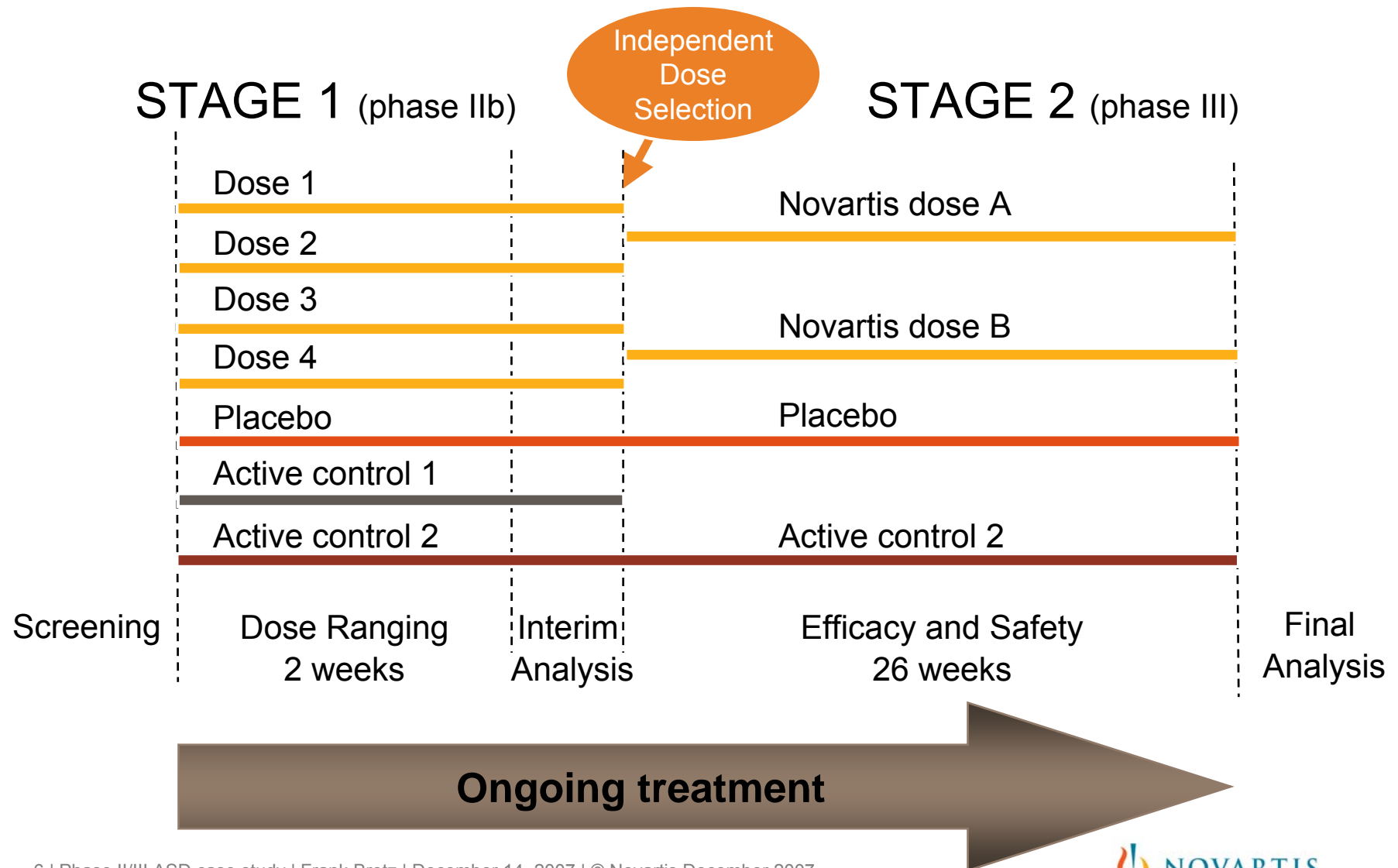
Introduction

- In a chronic disease
- Adaptive seamless design (ASD) to confirm dose selection
- To support registration and label claims
- Trial to provide pivotal confirmation of efficacy, safety, and tolerability of the selected doses
- Plus a second pivotal study of 'standard' design

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Phase II/III Adaptive Design with Treatment Selection: A case study *Trial Design*



Phase II/III Adaptive Design with Treatment Selection: A case study *Trial Design*

- Primary endpoint
 - Continuous variable – objective measurement after 12 weeks
 - Comparison with placebo for superiority
- Key secondary endpoint
 - Continuous variable – objective measurement after 12 weeks
 - Comparison with active control 2 for non-inferiority
- Important secondary
 - Continuous variable – subjective patient reported quality of life
 - Comparison with placebo for superiority
- Multiple additional secondary endpoints

Phase II/III Adaptive Design with Treatment Selection: A case study *Trial Design*

- Objectives interim analysis
- To investigate four doses of new treatment versus placebo and active controls with respect to the primary endpoint after **2** weeks of treatment
- To investigate four doses of new treatment versus placebo and active controls with respect to cumulative selected safety data e.g. AEs, parameters specific to the class of drug
- Independent external DMC to select 2 adjacent doses based on pre-defined guidelines

Phase II/III Adaptive Design with Treatment Selection: A case study *Trial Design*

- Sample size for stages 1 and 2 based on simulation work
- Requirements for simulation
 - Minimum Clinically Important Difference (MCID), Standard Deviation (SD), power required and alpha* (as usual)
 - Correlation between 2 and 12 week data
 - Estimated treatment effect
 - Interim analysis decision guidelines
- Output from simulation
 - Probability of picking specific dose pairs
 - Power for primary and key secondary endpoints
- Each simulation run 100000 times

Phase II/III Adaptive Design with Treatment Selection: A case study *Trial Design*

■ Sample size estimations

- stage 1 (7 arms) 115 pts per arm (805 total)
- stage 2 (4 arms) 285 additional pts per arm (1140 total)

■ Based on:

- Probability of dose selection at interim under various dose response scenarios. Simulations indicate that 115 pts per arm in stage 1 will **select two appropriate doses** to take forward with at least **75%** probability
- Requiring **90%** power to detect a significant difference in the **primary endpoint** (superiority of an individual dose versus placebo)
- Requiring at least **85%** power to detect a significant difference in the **key secondary endpoint** (non-inferiority of an individual dose versus active control 2)

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Adaptive Statistical Methodology

- A multiplicity correction of $\alpha/4$ will be used for the final analysis. This is a conservative adjustment, i.e., only 2 treatment arms will be tested at the final analysis
- The simple **Bonferroni adjustment** will be used in conjunction with sequential testing of the important hypotheses, independently for each selected dose:
 - First, primary: superiority versus placebo
 - Second, key secondary: non-inferiority versus active control
 - Third, important secondary: superiority versus placebo
- This procedure will control the family-wise type I error rate at level alpha for the primary, key and important secondary hypotheses

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Interim analysis decision making

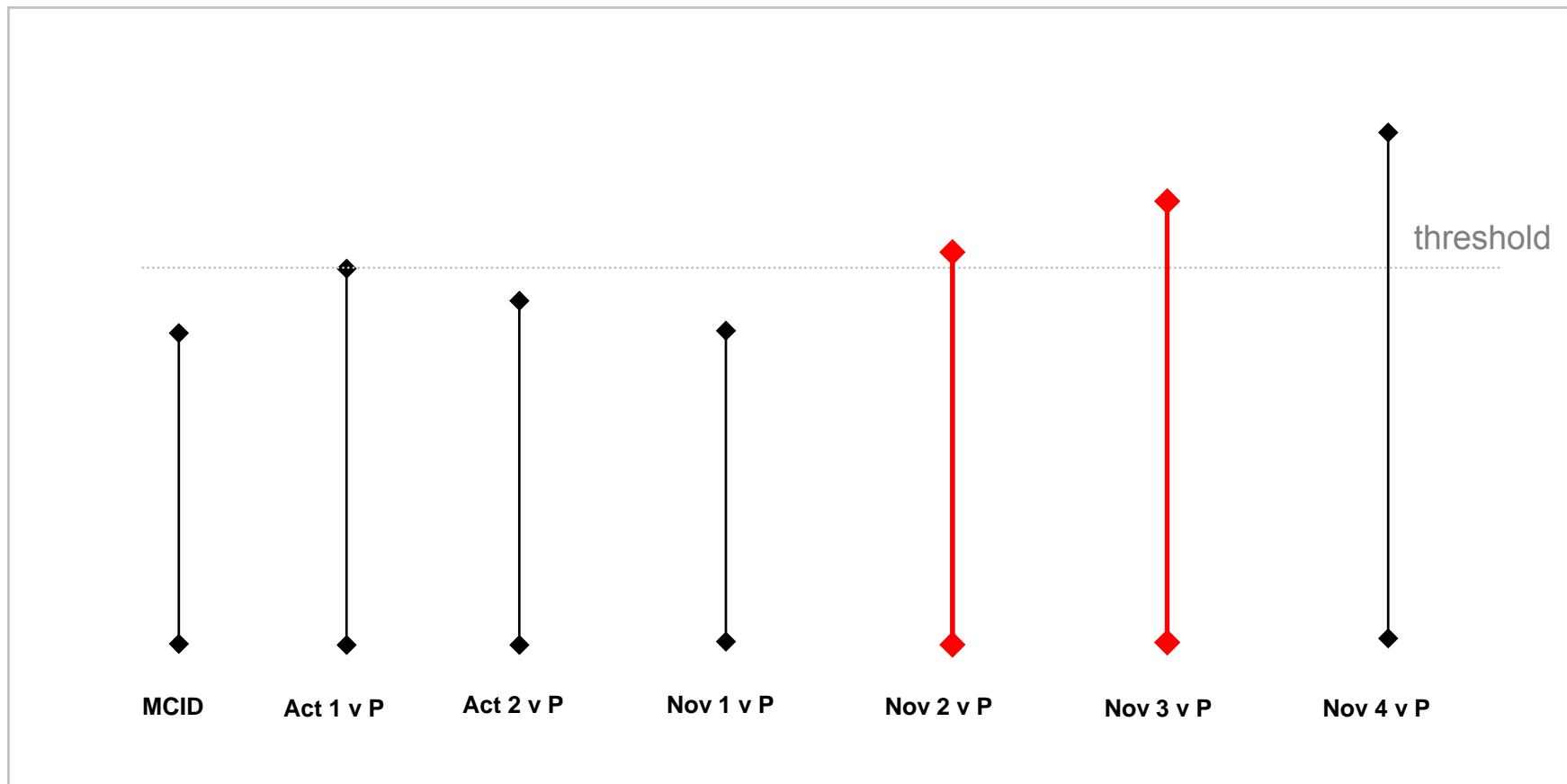
DMC dose selection guidelines

- Numerical i.e. no p-values, comparison of primary endpoint (versus placebo) of each dose with a threshold value.
- Threshold value is the maximum of:
 - Minimum Clinically Important Difference (MCID)
 - Primary endpoint active control 1 versus placebo
 - Primary endpoint active control 2 versus placebo
- The doses selected to continue to Stage 2 will be the lowest dose with an effect greater than the threshold value (or the closest to that value if no dose exceeds) and the next highest dose. In case the first dose chosen is dose 4 (the maximum), the next lower dose will be used in Stage 2. **See next slide for examples**
- If a safety signal is seen for any dose the DMC will weigh this information against the efficacy data in selecting doses
- *In the case of unexpected results e.g. no dose response or lack of efficacy for the active controls, the DMC have discretion to deviate appropriately from the guidelines*

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Interim analysis decision making

Scenario 1

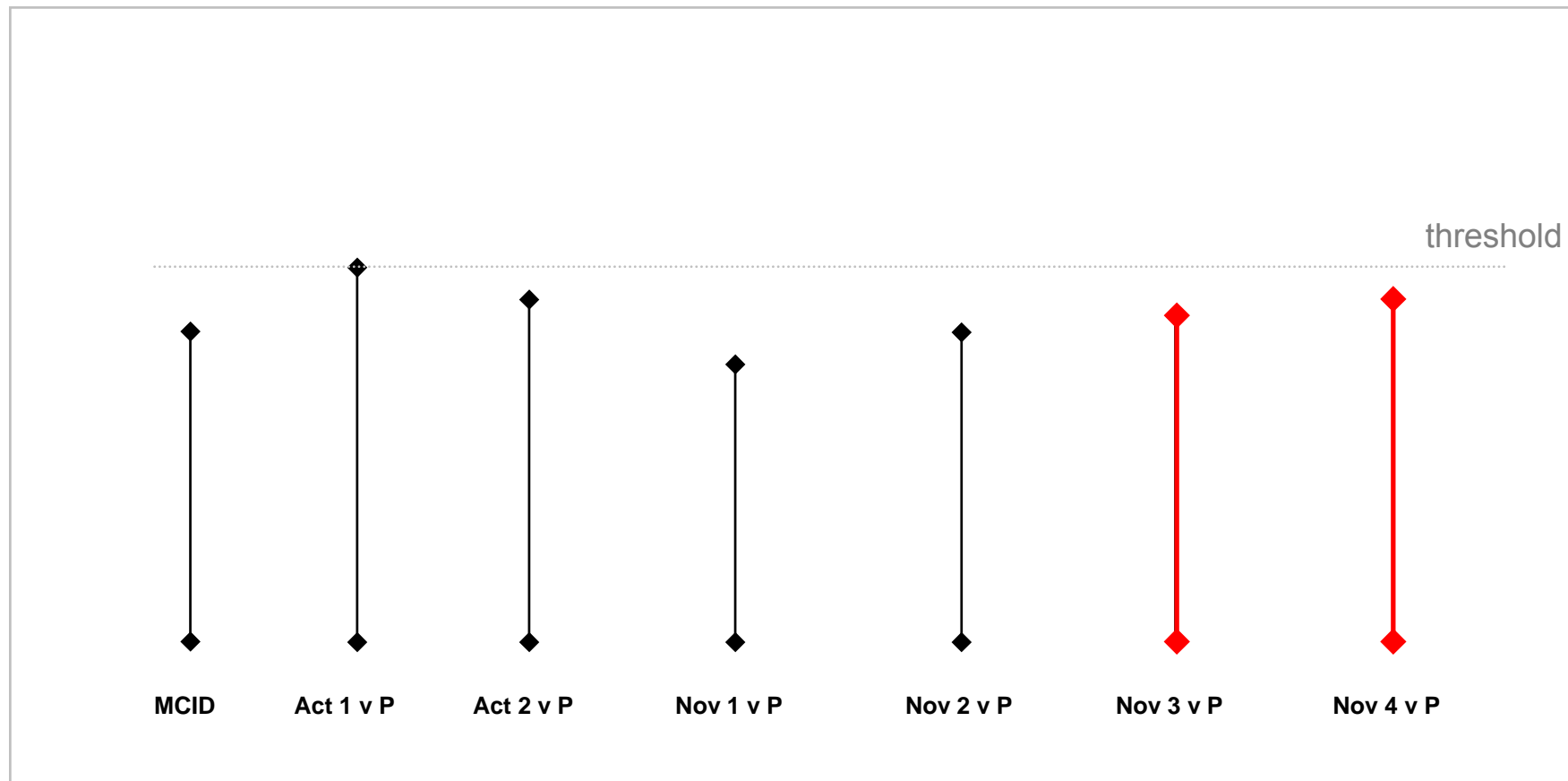


Doses selected: 2 and 3

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Interim analysis decision making

Scenario 2

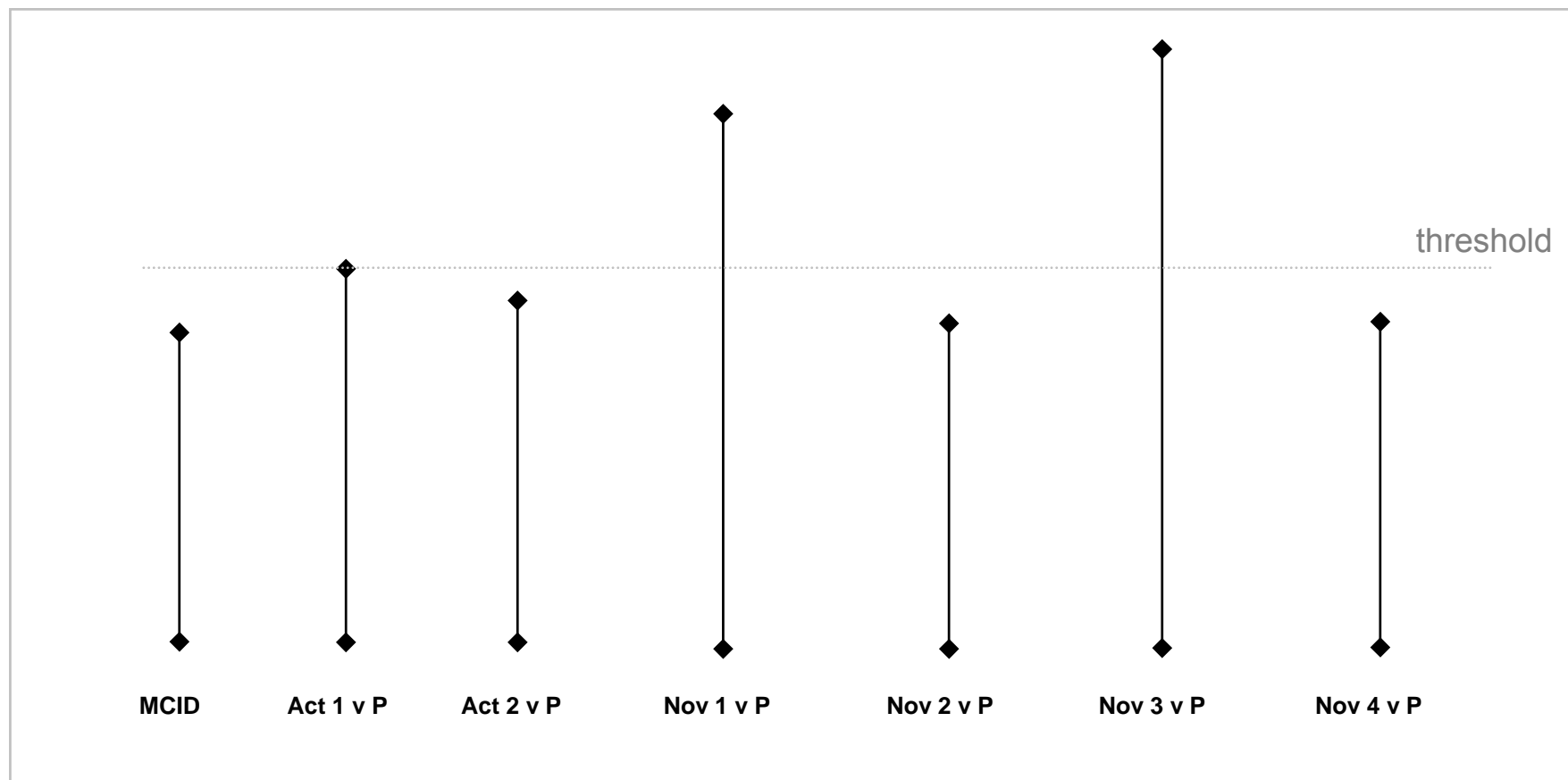


Doses selected: 3 and 4

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Interim analysis decision making

Scenario 3



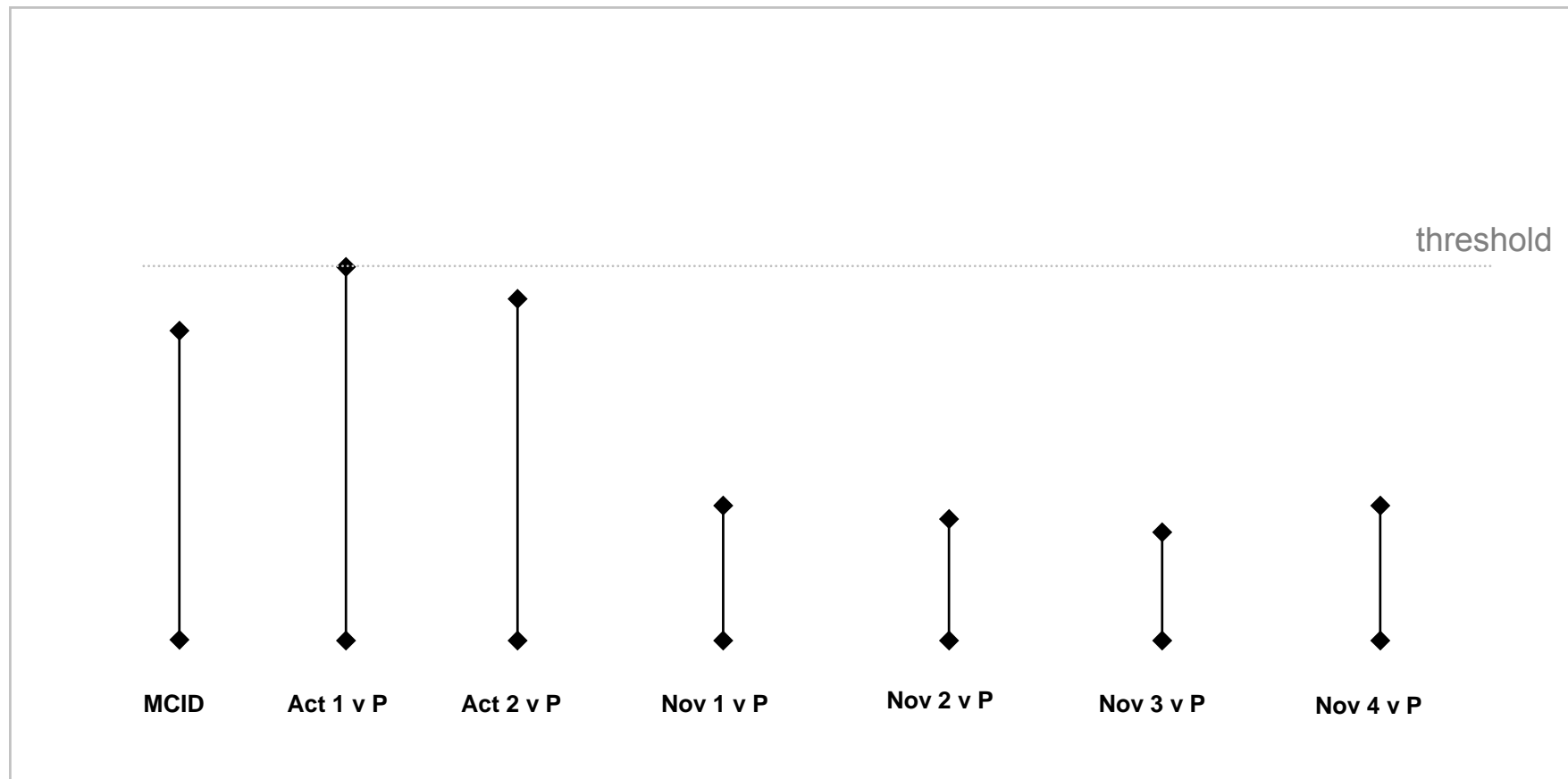
Complex data, DMC may deviate from guidelines.

Doses selected by DMC after consultation with Sr. Novartis representative(s).

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Interim analysis decision making

Scenario 4



Lack of response and possible futility, DMC may deviate from guidelines.

Consultation with Sr. Novartis representative(s).

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Phase II/III Adaptive Design with Treatment Selection: A case study *Experience with the FDA*

- “Special Protocol Assessment”
 - briefing book including protocol
- Face-to-face meeting to discuss ASD as well as other project issues. Issues raised:
 - Related to ASD
 - Protecting trial integrity i.e. who produces the interim analysis report
 - Not related to ASD
 - Basis for dose selection
 - Choice of non-inferiority margin for key secondary endpoint
 - Methods to handle missing data for important secondary endpoint

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Phase II/III Adaptive Design with Treatment Selection: A case study

Conclusions

- Conducting adaptive trials present a number of challenges
- Adaptive trials require a great deal of upfront planning especially in the confirmatory setting
- Protection of trial integrity is paramount