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EMA Multiplicity Workshop Case study: a phase 3 study with 2 doses and secondary endpoints

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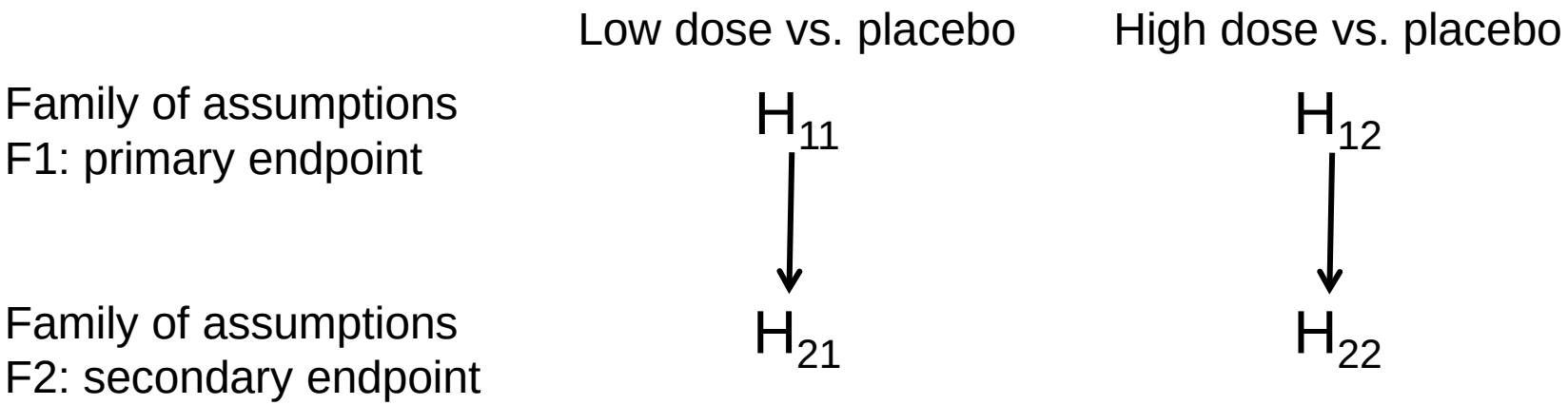
Agenda

- Context
- Challenge: maximising power vs. control type 1-error
- Separable Multitest Procedures
- Different possible strategies for our case study
- Our proposal

Context:
Study Design and Testing Strategy

- 3 treatment arms: low dose, high dose and placebo
- Primary endpoint: OS, secondary endpoint: PFS
- Familywise Error Rate ≤ α (2.5% 1-sided)
- Hierarchical logical restriction



Controling Type 1 Error vs. Maximising Power

- For each level of endpoints (family F1 and F2), we want to ensure:

  FWER=*P(Reject at least one true null hypothesis)*≤ α

- We also want to maximise the statistical power
- Problem:
  - Closed procedures such as Holm, Hochberg, Fallback and Dunnett cannot hierarchically open the gate to the testing of the secondary endpoints
  - Only “separable” multiple test procedures can be used as gate keepers.

    (Cf. Dmitrienko & Tamhane)

Separable Multitest Procedures

- Explain briefly what it is
- Bonferroni or separable mixtures of well-known procedures have been proposed by Dmitrienko & Tamhane

Hochberg vs. Bonferroni in our phase 3

- The minimum effect size for the low and high dose vs placebo comparison that can be determined to be statistically significant using Bonferroni is a hazard ratio of 0.82 and 0.79 or absolute median OS increases of approximately 1.3 and 1.5 months.
- If none p-value are >0.025, Hochberg allows declaring significant p-value up to 0.025 (instead of 0.0125 for Bonferroni).
- This is translated in term of minimum effect size as a hazard ratio of 0.84 and 0.81 or absolute median OS increases of approximately 1.1 and 1.3 months for low and high dose respectively.

$\Rightarrow$ Our clinicians did not want to lose that.

Different strategies for our phase 3

	Pros	Cons
Hochberg only	Maximise power for primary endpoint	Does not properly open the gate for the secondary endpoints
Bonferroni	Open the gate for the secondary endpoints	Does not maximise power
Separable mixture of procedures	Better power than Bonferroni Open the gate for the secondary endpoints	Not well recognised. Complexity and freedom in defining the mixture.
Hochberg for primary endpoint testing Bonferroni as gate keeper	Maximise power for primary endpoint Open the gate for the secondary endpoints if small enough p-values	May lead to an apparent contradiction: Successful primary endpoint while no secondary endpoint testing is allowed

Our proposal

- We use the Hochberg procedure to test the individual dose groups vs. placebo for the primary endpoint. Then we use the Bonferroni procedure to test the primary endpoint as gate keeper leading to the secondary endpoint testing.
- It may lead to a situation with a significant p-value using the Hochberg but not allowing a subsequent test because the Bonferroni procedure may not be significant. In this scenario, the study will be declared successful regarding its primary endpoint while no secondary endpoint formal testing will be performed.
- What the EMA would recommend?