Discussion

Ph 2/3 Trial for Selepressin

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Design Considerations

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- Trial design combining dose-finding and confirmation in an **adaptive phase II / III clinical trial.**
- Early stopping of non-promising treatment arms and response adaptive randomization allow one to collect more information on target dose
- Combination of learning of confirming part may increase the trial efficiency
- **Advanced approaches** to investigate a target dose range in exploratory trials **can be more efficient** to generate information on dose response than fixed sample trials and pairwise comparisons of dose groups.

Confirmatory Demonstration of Dose-Response Relationship?

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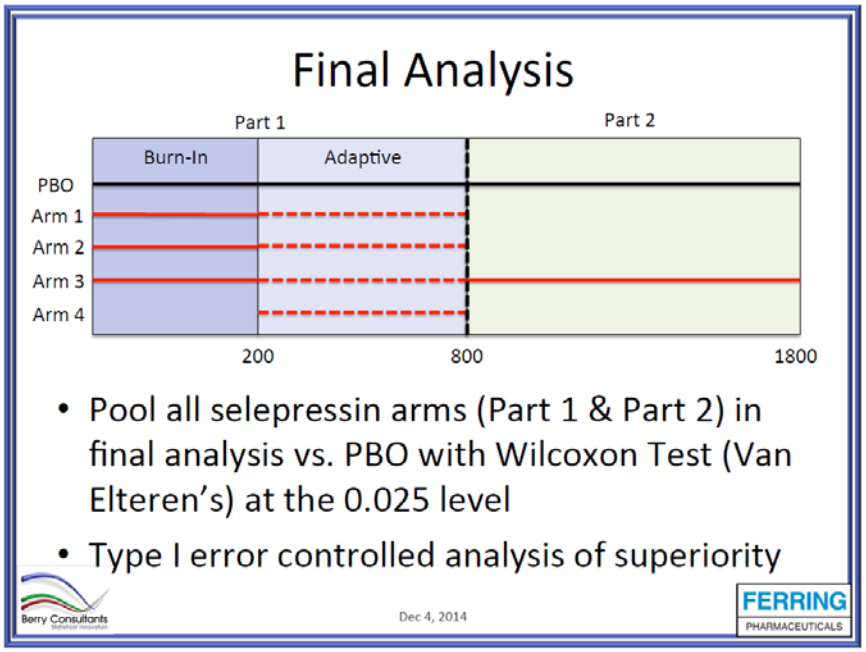
- Response adaptive patient allocation designs can be useful to generate **evidence for a dose-response relationship.**

- Type I error control of the proposed Wilcoxon Test?
  - Adaptive change of allocation fractions can lead to substantial type I error rate inflations of unadjusted tests.

    Graf et al. Maximum inflation of the type 1 error rate when sample size and allocation rate are adapted in a pre-planned interim look. Stat Med (2011):1637-47
  - Furthermore, in the presence of **time trends** (e.g., if the patient population changes over calendar time) response adaptive tests may be biased

    R Simon et al. Using randomization tests to preserve type I error with response adaptive and covariate adaptive randomization. Statistics & Probability Letters (2011):767-72
  - Demonstration of Type I error control by simulations is controversial
- Which null hypothesis is tested by the Wilcoxon test?



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- The proposed test tests only the global null hypothesis of no treatment effect in any of the arms **but does not test for efficacy in the selected dose.**

- However, it is important that the efficacy of the finally chosen dose regimen can be assessed in a confirmatory way, i.e. sufficient stand-alone evidence (testing and estimation) for the proposed dose regimen is required.

- Furthermore, for a comparison of dose 4 to control, the first stage control patients would constitute a historic control.

Conclusion

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- The proposed adaptive II/III design can be efficient to demonstrate efficacy of the test drug if robust type I error control can be demonstrated.
- However, confirmatory evidence for the finally proposed dose regimen is an open issue.
- EMA RP on adaptive designs recommends to justify the use of adaptive designs by comparison of the operating characteristics to alternative designs, (e.g., less interim analysis and adaptive features).
- Simulation studies are a very efficient tool to investigate different design options and understand their properties in various scenarios. Robust demonstration of type I error rate control remains controversial.