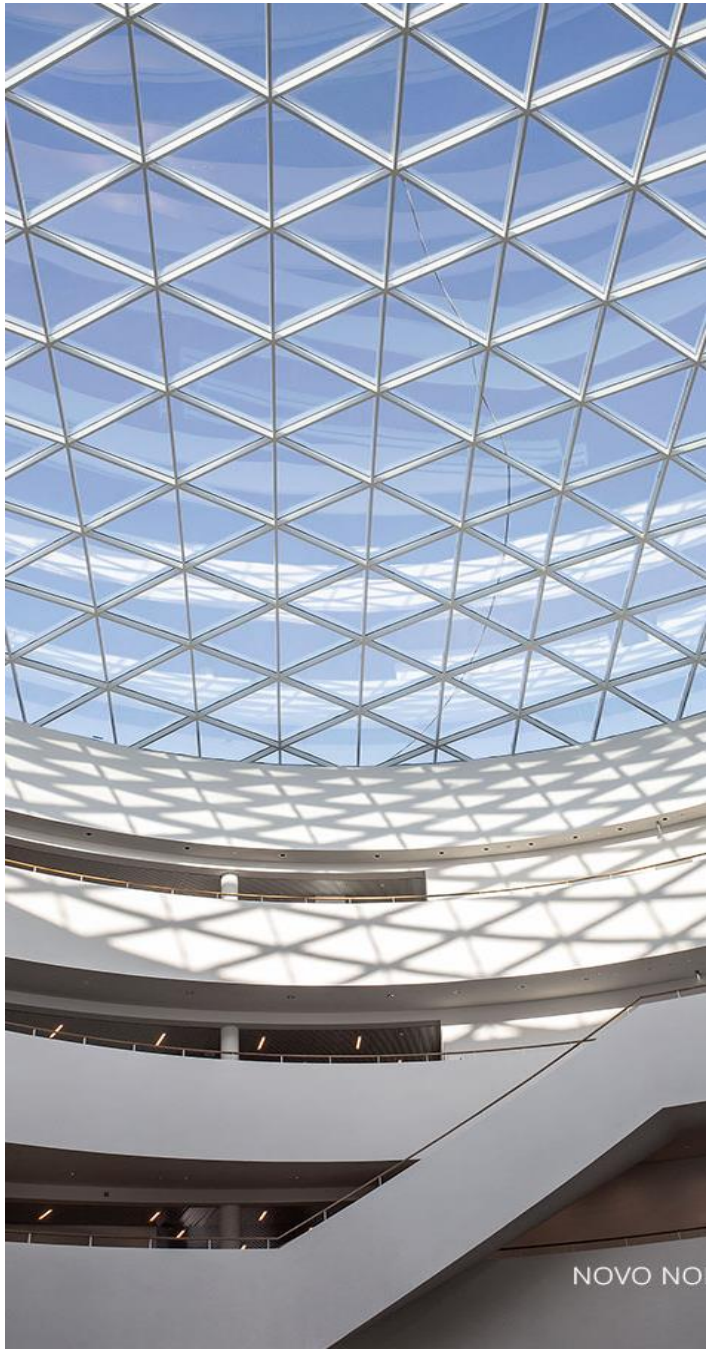

A confirmatory two-stage adaptive procedure for assessing average bioequivalence

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Agenda

Setting and problem

Features of the design

Theoretical properties

Simulation performance

Some points to be challenged by

Settings and problem as they were presented to us

- **Context:** Initiated while working at Leo Pharma A/S with collaborators Kyle Raymond and Marie Louise Østerdal (Both statisticians at Leo)
- **Project:** Comparing two different administrations of an antibody treatment in atopic dermatitis patients.
- **Goal:** To claim bioequivalence of a new ”patient friendly” injection type compared to the standard one for admininstering the antibody treatment.
- **Challenge:** Uncertainty up front about the actual dosing/uptake of the drug with the new form of adminstration. The sneaky suspicion is that there might be under-dosing but how much is anyones guess
- **One possible solution:** we want to adapt to the suspected level of underdosing once we have some information on it→2 stage adaptive design with sample size reestimation

Initial wishes for design

- Approx 80 subjects for stage 1 balancing timelines and expected precision of pk endpoints (Cmax and AUC) in a parallel arm setting
- If stage 1 estimated geometric mean ratios (test versus reference) reflect more than 25% difference we give up on bioequivalence -- BUT we still want to know as much as possible about the magnitude of underdosing (that we suspect).
- An ”ordinary” 95% CI at the end of the trial consistent with any inferential decision about average bioequivalence to gauge the ”level of potential underdosing”
- As fast as possible →optimize the number of patients it takes in stage 2 to get an informative result

Our strategy:

Simultaneous inference on Cmax and AUC+no unnecessary retesting

Proposal: An adaptive TOST procedure-stage 1

- Let $\theta^{(l)}, \mathrm{l} = 1{,}2$ denote the targeted population summaries of Cmax and AUC

- We consider the following one-sided null hypotheses of non-bioequivalence:

$$H_0^-\colon \min\left(\theta^{(1)}, \theta^{(2)}\right) < -\Delta;\ \ H_0^+\colon \max\left(\theta^{(1)}, \theta^{(2)}\right) > \Delta$$

- Stagevise p-values for H_0^- equal those obtained for the smallest stagevise estimate
- Stagevise p-values for H_0^+ equal those obtained for the largest stagevise estimate

- Stage 1 p-values are evaluated separately for each hypothesis according to an efficiacy bound α_1 and binding futility bound α_0 (we have 0.5 in mind)

- A separate decision (stop for efficacy/futility or proceed) is made for each hypothesis

Proposal: An adaptive TOST procedure-stage 2

- If we proceed sample-size reestimation is made according to the scenario based on conditional power.
- Stagevise p-values are combined at stage 2 using a combination test.
- Critical value computed to ensure type 1 error control for each separate hypothesis
- Bioequivalence declared if both hypotheses are rejected.

Note: If we have already decided on a hypothesis at stage 1 it is not evaluated further after stage 2 (despite the fact that we could do it)

Type 1 error control

- For testing bioequivalence, that is: $H_0^- \cup H_0^+$
- Is ensured if type 1 error control is enforced when testing H_0^- and H_0^+ separately
- This is, in turn, ensured (asymptotically) if stagewise p-values are p-clud (asymptotically):

$$\lim_{n\to\infty} P\left(p_j \leq \alpha\right) \leq \alpha, for\ 0 \leq \alpha \leq 1$$

- Which you can show with some effort (The situation $\theta^{(1)} = \theta^{(2)}$ is non-trivial)

Overall confidence limits: Construction

- Based on overall p-values:

$$Q(p_1, p_2, \alpha_0, \alpha_1) = p_1 I(p_1 < \alpha_1 \; or \; p_1 \geq \alpha_0) + I(\alpha_1 \leq p_1 < \alpha_0)\{\alpha_1 + \int_{\alpha_1}^{\alpha_0} \int_0^1 I(C(x,y) \leq C(p_1, p_2))dydx\}$$

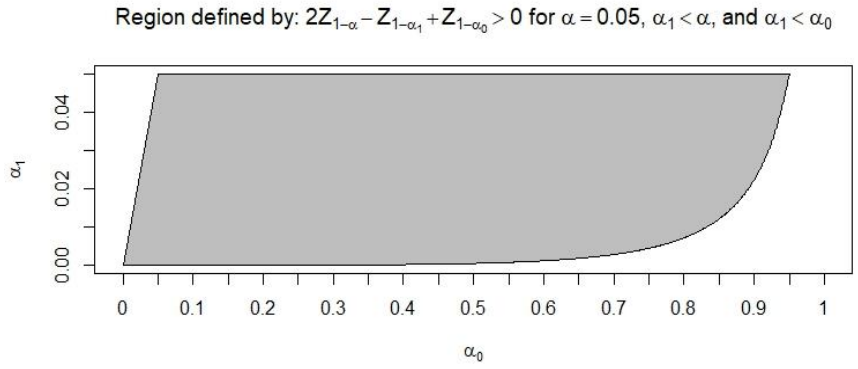
- Where *C* denotes the chosen combination function (f.i. inverse normal)

- Insert stagewise shifted p-values p_{l-} (H_0^-: $\min(\theta^{(1)}, \theta^{(2)}) \leq \delta$) and p_{l+} (H_0^+: $\max(\theta^{(1)}, \theta^{(2)}) \geq \delta$) into Q

- Solve $Q(p_{1-}, p_{2-}, \alpha_0, \alpha_1) = \alpha$ to obtain a lower 1-α lower confidence bound L for $\min(\theta^{(1)}, \theta^{(2)})$.
- Solve $Q(p_{1+}, p_{2+}, \alpha_0, \alpha_1) = \alpha$ to obtain a upper 1-α lower confidence bound U for $\max(\theta^{(1)}, \theta^{(2)})$.

Overall confidence limits: properties

- Confidence is ensured since shifted p-values are asymptotically p-clud when evaluated at the true parameter value
- Not up-front ensured that L<U←May be based on different data
- This can be ensured if loosely stated: stage 1 precision is large enough, does not vary too much between endpoints, and large values α_0 are avoided (how large depends in a complicated manner on efficacy bound and precision difference between endpoints)



One strategy for sample size reestimation

- Based on stage 1 estimates and ensuring overall power to reject:
  1. $H_0^- \cup H_0^+$
  2. H_0^-
  3. H_0^+
- Depending on the ”futility” decisions made at stage 1

- The basic focus is to minimize sample-size

- One out of many possible strategies (and maybe not the best) for sample-size re-estimation.

Simulation performance: some points learned

- Sensible confidence bounds (L<U) are not ensured per default. The restraints that are derived theoretically to ensure this do the job.
- The targeted degree of confidence is met in the simulations
- Evaluating both endpoints simultaneously gains power
- Minor gains in power are achieved by avoiding re-evaluations of decisions made at stage 1 (no re-testing of rejected/accepted null hypotheses.)

What literately not to like

- **The price of sensible confidence bounds**
  - With the outlined setup, it requires binding futility
  - And even restricts the simultaneous choice of efficacy and futility bound
  - These requirements are definitely controversial

- **Pooling of endpoint summaries**
  - If you aim for separate statements for each PK endpoint the ”win on all” approach presented here is not the way to go

Additional details

- An early version on this work is freely available on Arxiv: [2203.09182] Properties of a confirmatory two-stage adaptive procedure for assessing average bioequivalence (arxiv.org)