Confirmatory testing of secondary hypotheses on combined data from multiple trials

Case studies and reflections

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Outline

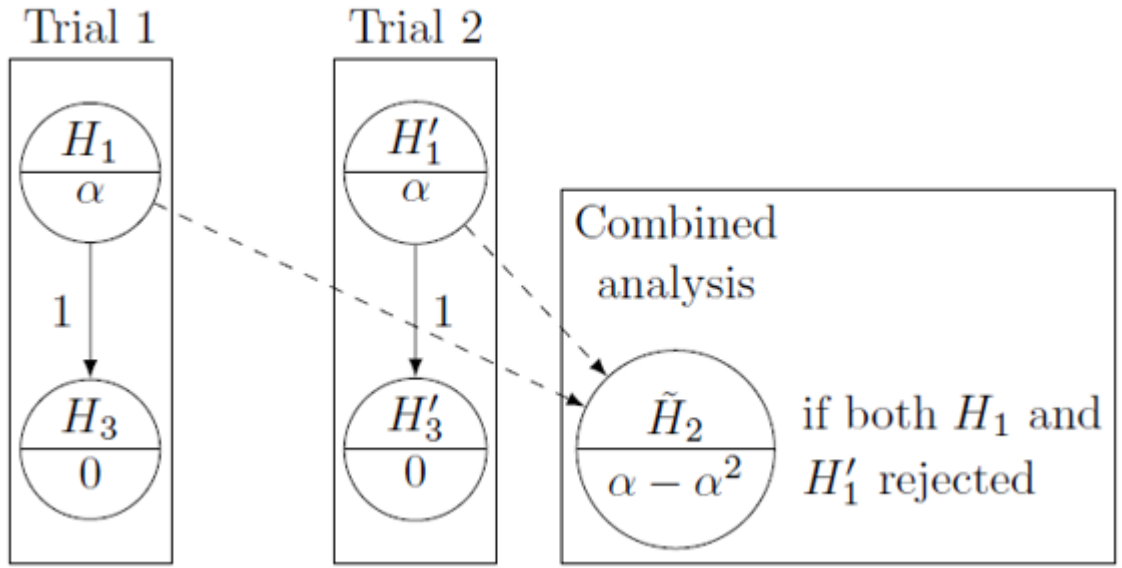
- Motivation & methods (recap from Dong)
- Case Study 1: Ofatumumab in Multiple Sclerosis (MS)
- Case Study 2: Secukinumab in Hidradenitis Suppurativa (HS)
- Case Study 3: Ligelizumab in Chronic Spontaneous Urticaria (CSU)
- Discussion

Motivation & methods

- The two-trials convention asks for two separate trials that independently provide convincing and mutually corroborating evidence of efficacy
  - “Substantial evidence”, from “adequate and well-controlled investigations, including clinical investigations” (Kefauver-Harris Amendments of the Food, Drug and Cosmetic Act, 1962)
  - Evolved by FDA Modernization Act (1997), FDA Guidance (1998), FDA Draft guidance (2019)
- What about secondary objectives?
  - What are the regulatory requirements?
  - What if a secondary objective requires a much larger sample size than the primary?

Motivation & methods

- We propose to test important but sample-size intense secondary objectives on combined data across trials, controlling the submission-wise error rate (SWER) at a prespecified level
  - See Dong's talk for details on methodology and significance levels

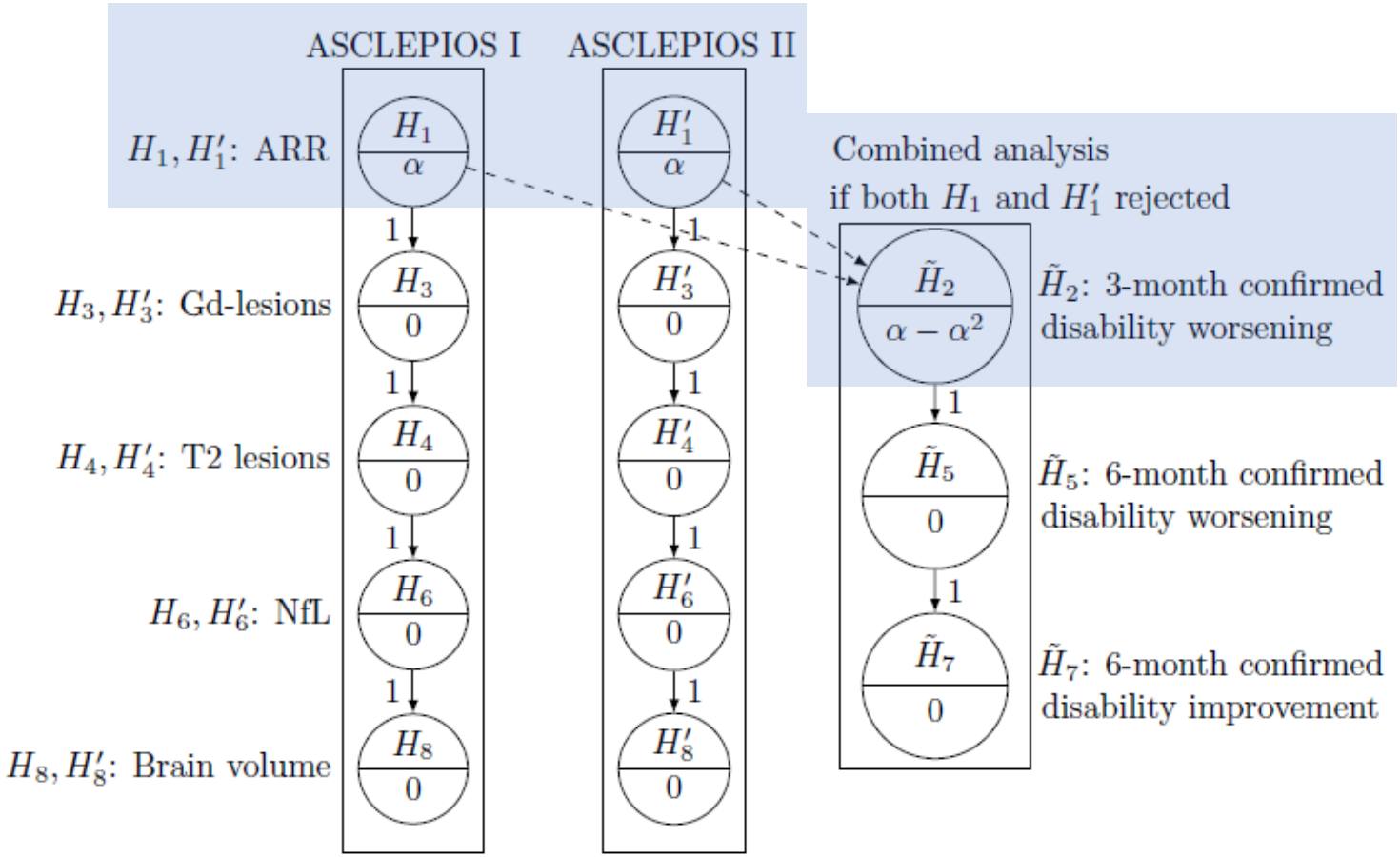


Case Study 1: Ofatumumab in MS

- ASCLEPIOS I and II trials
  - Identical in trial population and design, conducted concurrently
  - Primary endpoint: Annualized Relapse Rate (ARR, neg bin regression)
  - Important secondary endpoint: Disability worsening (time to event)
    - Requires twice the sample size of a similarly powered analysis of ARR

Case Study 1: Ofatumumab in MS

- Statistical strategy



Case Study 1: Ofatumumab in MS

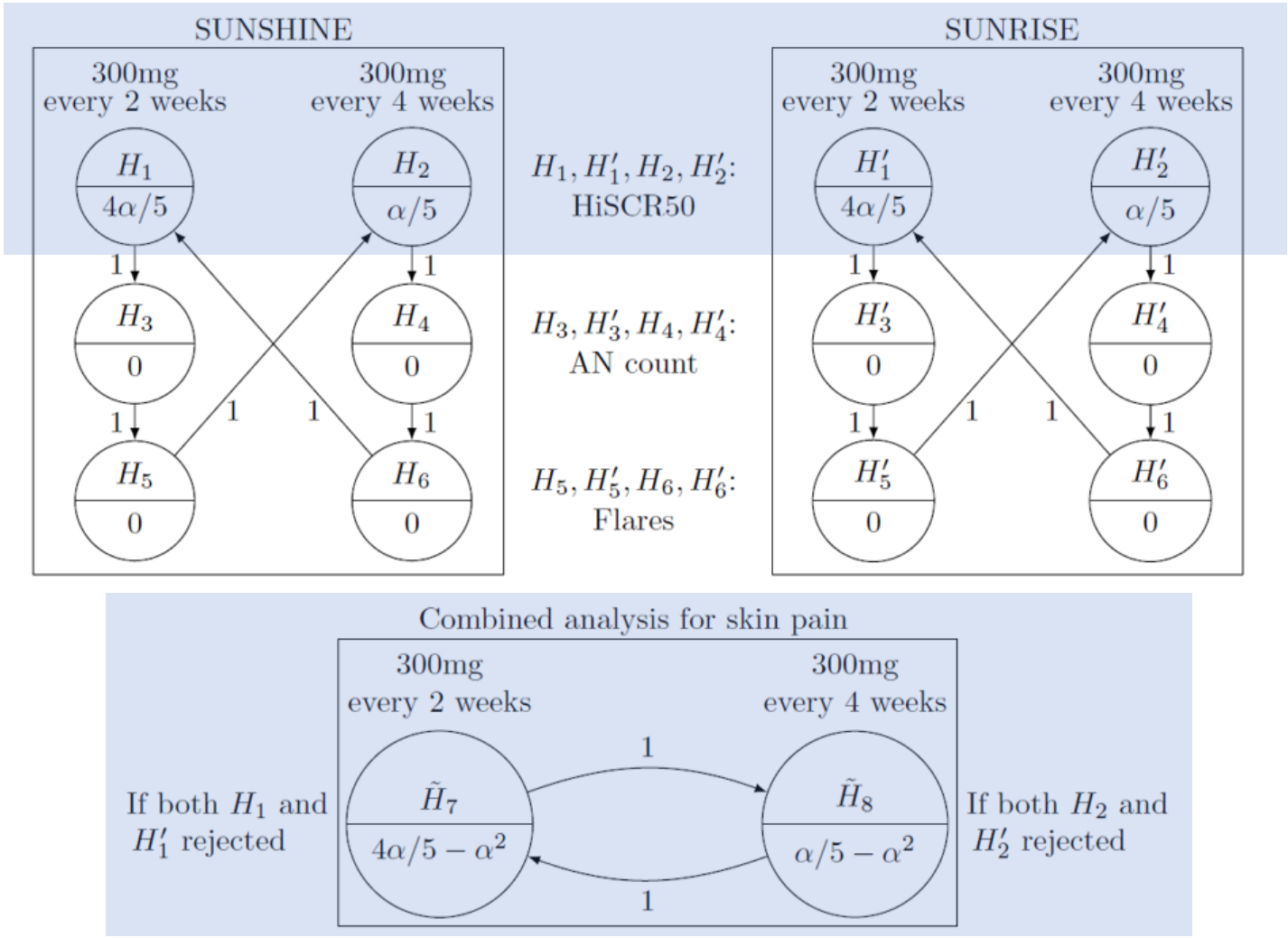
- Results
  - Approval in US, EU & more, including claim on disability worsening
- Alternatives
  - Test disability worsening in only one of the pivotal trials (Avonex®, Mavenclad®, Tysabri®, Mayzent®)
    - Claim based on single trial (which may need to be large)
    - FWER and SWER controlled, but available data from other trial(s) ignored → less efficient
  - Derive claim on disability worsening from one of several trials in which it is tested (Betaferon®, Gilenya®, Lemtrada®, Rebif®, and Tecfidera®)
    - Claim based on single trial (out of several)
    - FWER controlled within each trial, but SWER may be inflated
  - In contrast, ofatumumab's approach achieved high power while controlling SWER

Case Study 2: Secukinumab in HS

- SUNSHINE and SUNRISE trials
  - Identical design, conducted concurrently
  - Two dose regimens
  - Primary endpoint: HiSCR50, i.e. 50% reduction in abscesses and nodules, with no increase in abscesses and/or draining fistulae
  - Important secondary endpoint: Skin Pain
    - Requires twice the sample size of HiSCR50, due to greater subjectivity / variability

Case Study 2: Secukinumab in HS

- Statistical strategy (EMA)



Case Study 2: Secukinumab in HS

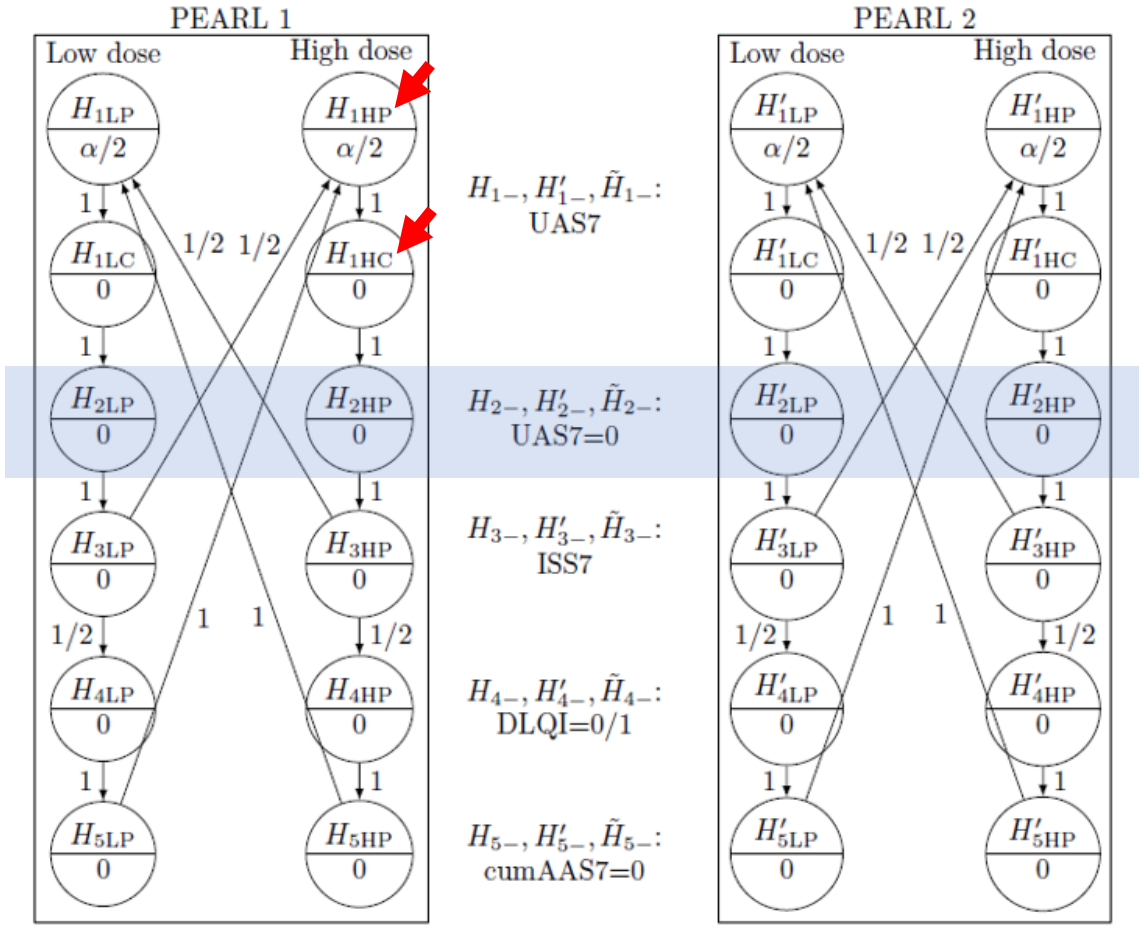
- Results (EMA)
  - Approval, including claim on Skin Pain with the higher regimen
- US strategy
  - FDA asked for all analyses to be at the trial level, for replication purposes
  - Hence, Skin Pain was tested separately per trial (and regimen)
  - Neither regimen demonstrated efficacy in Skin Pain in both trials

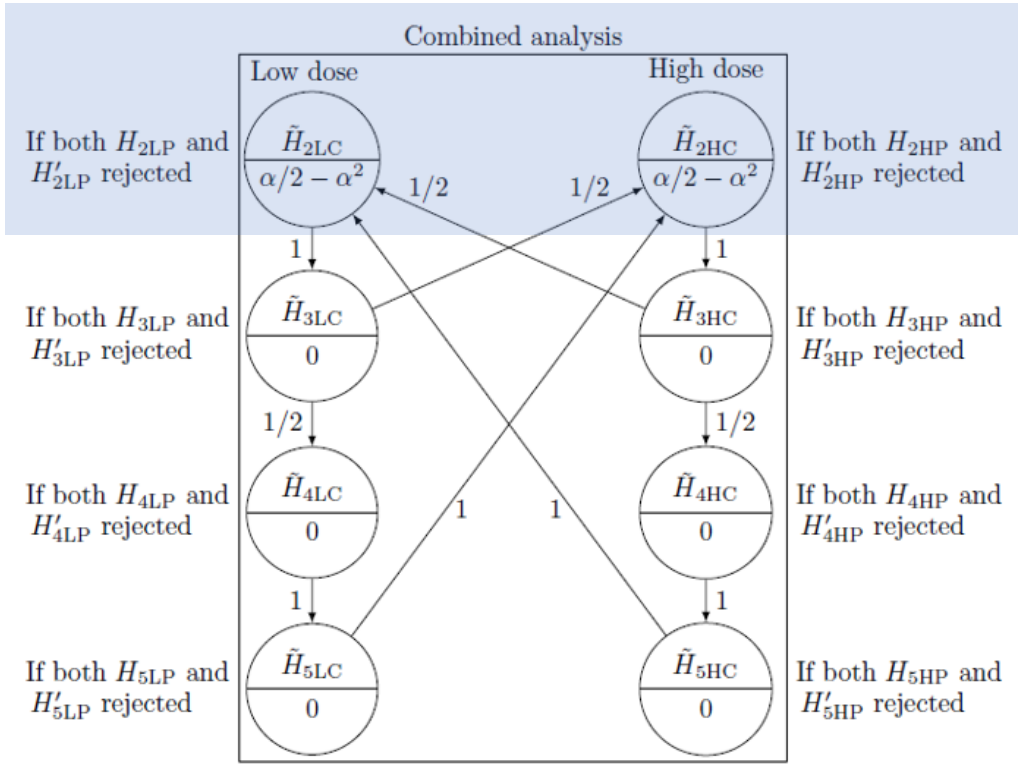
Case Study 3: Ligelizumab in CSU

- PEARL 1 and 2 trials
  - Identical design, conducted concurrently
  - Two doses
  - Primary endpoint: Urticaria Activity Score; four secondary endpoints
  - Two comparators
    - vs placebo
    - vs omalizumab → requiring larger sample size for adequate power
  - Trials initially planned to provide pivotal evidence for all objectives independently of each other (fully adhering to the two-trials convention)
  - COVID-19 interrupted the running trials and caused concern about the achievable sample size and increased variability of the data
  - Statistical strategy was modified before unblinding, to mitigate these risks

Case Study 3: Ligelizumab in CSU

- Statistical strategy





Case Study 3: Ligelizumab in CSU

- Nota bene
  - Only the secondary endpoints were tested vs omalizumab on combined data; the primary endpoint was tested separately in both trials vs both comparators
- Results
  - Superiority vs placebo (both doses, both trials), but not vs omalizumab
  - Formally, secondary endpoints could not be tested vs either comparator
  - Nominally, they were significant vs placebo but not omalizumab

Discussion

- These case studies show that important but sample-size intense secondary objectives can be tested on combined data across trials
  - Most efficient use of all data → high power
  - Replication & independent substantiation can still be checked by trial-specific analyses of the same objectives (in trend, not necessarily significant)
  - Primary objective still tested separately, following the two-trials convention
- The overarching testing strategy across trials allows keeping control of the submission-wise error rate (SWER)
  - Combination strategy requires trials to be «similar» and concurrent
- Implementation must be prespecified and aligned with regulatory stakeholders
  - Opinions differ, discussion welcome

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