BORROWING EXTERNAL CONTROLS FOR AN EVENT-DRIVEN PEDIATRIC TRIAL IN PAH: A CASE STUDY

Adele Morganti, Matthieu Villeneuve  Actelion JNJ Biostatistics
Cristina Sotto, An Vandebosch  JNJ SDS-SMM
OUTLINE

- Pediatric PAH - Background
- Case study: borrowing external controls for an event-driven pediatric trial in PAH
- Conclusions
PEDIATRIC PAH – BACKGROUND

Rare disease affecting the vessels of pulmonary circulation

- Adult efficacy proven by time to disease progression or exercise capacity.

Partial extrapolation accepted by HAs

- No PD/intermediate endpoint that can be defined across pediatric subsets
  - Effect on pulmonary vascular resistance requires invasive approach, unacceptable in children (nowadays)
  - Exercise capacity can only be assessed in developmentally able children
As of today, **time to disease worsening** represents the only clinically meaningful efficacy endpoint to study PAH in the pediatric patients (Gomberg-Maitland 2013)

Conducting event driven study is challenging due to:

- the rarity of the disease
- increasing off-label use in the pediatric patients
STANDARD SUPERIORITY EVENT-DRIVEN DESIGN

Standard TTE Design
- accrual rate=5/months
- max study duration=60 months
- 50% survival @18 mos. for CONTROL
- HR=0.6 (from adult study)
- 1-sided significance level=2.5%
- 1:1 randomization

N=205
- power >80%
- events: 129

Based on HA interactions:
Strict control of type I at 0.025 (1-sided)

Sponsor concern:
Power > 80% (linked to conclusiveness for FDA discussion for written request)

Study duration needs to meet regulatory timelines
A POSSIBLE SOLUTION: BORROWING CONTROLS

Decrease sample size by borrowing **external controls** from an ongoing pediatric PAH trial with a different drug and same primary endpoint

Fit with Pocock criteria (1976) external control

1. same SoC treatments
2. contemporary with same eligibility criteria
3. same endpoint: time to disease progression (with adjudication)
4. WHO group 1, same etiology
5. similar geographical landscape
6. patient selection and accrual expected to be similar

**Only one contemporary data source for external controls!**
ROBUST PRIOR

- Bayesian methods for incorporating external control information for a new trial → exchangeability assumption
  - always a possibility of prior-data conflict

- Robust approach
  - combines an informative and a vague prior, appropriately weighted
    \[ p(\theta) = w_1 p_1(\theta) + (1 - w_1) p_2(\theta) \]
    mixture prior informative part vague part

  - updated (posterior) weights shift to the corresponding component depending on the degree of (dis)similarity

Schmidli et al. (2014) Biometrics 70: 1023-1032.
BAYESIAN INFORMATIVE PRIOR

PRIOR for
\[ \log(\text{HR}) = \log(\lambda_a) - \log(\lambda_c) \]

Asymptotic Normal distribution approximation of \( \log(\text{HR}) \) is used.

We applied robust prior and power prior approaches for \( \log(\lambda_c) \) and compared the operating characteristics in this context.
PAH EVENT-DRIVEN TRIAL: BAYESIAN APPROACH

Simulations were performed to explore operational characteristics

**PRIOR:**

**ONGOING TRIAL FOR CONTROL**

**Robust Prior Approach**
- weight of informative part: 0.7, 0.9
- vague/informative variance ratio: 1000
- no. of events for CONTROL in parallel trial: 20, 40
- 10,000 simulated trials
- varying control event rate

**Power Prior Approach**
- full borrowing (alpha=1)
- static

**ACCUMULATED DATA:**

**TRIAL ON NEW DRUG VS. CONTROL**

**Standard TTE Design**
- accrual rate=5/mo.
- 50% survival @18 mos. for CONTROL
- HR=0.6 (from GRIPHON adult study)
- 1-sided significance level=2.5%
- 1:1 randomization

**Sample size/events reduced to N=150 / 89**
BORROWING WINDOW

Simulations were performed to identify an efficient borrowing window:

An efficient borrowing window was defined as:

- type I < 0.025 (1-sided)
- power > 80%
Operational Characteristics: Type I Error and Power Varying the Event Rate of the External Control Group
40 Events Borrowed; Accumulated Data: N=150 / e=89; Weight of informative Prior: 0.7

HR=0.60
- robust prior
- power prior

HR=1
- robust prior
- power prior

% of trust with a posterior probability of (HR=1) strictly greater than 0.975

Prior cumulative incidence at 18 months
Operational Characteristics: Type I Error and Power Varying the Event Rate of the External Control Group

40 Events Borrowed; Accumulated Data: N=150/e=89; Weight of informative Prior: 0.7

HR=0.60
- robust prior
- power prior

HR=1
- robust prior
- power prior

% of trials with a posterior probability of (HR=1) strictly greater than 0.025

Prior cumulative incidence at 18 months
Operational Characteristics: Type I Error and Power Varying the Event Rate of the External Control Group
40 Events Borrowed; Accumulated Data: N=150 /e=89; Weight of informative Prior: 0.9

HR=0.60
- robust prior
- power prior

HR=1
- robust prior
- power prior

% of trials with a posterior probability of (HR-1) strictly greater than 0.95
Prior cumulative incidence at 18 months
Operational Characteristics: Type I Error and Power Varying the Event Rate of the External Control Group
40 Events Borrowed; Accumulated Data: N=150 /e=89; Weight of informative Prior: 0.9

HR=0.60
- robust prior
- power prior

HR=1
- robust prior
- power prior
CONCLUSIONS

- When strict type I and II error control is required, robust and power prior approaches require strict homogeneity between internal and external controls (low probability of success).

- The borrowing window is similar when comparing robust prior and power prior approach.
  - Varying the prior weight does not address departure from homogeneity in our case (only one source).
THANK YOU.
REFERENCES


[Schmidli 2014] Schmidli et al. “Robust Meta-Analytic-Predictive Priors in Clinical Trials with Historical Control Information“, Biometrics 2014; 70 1023-1032
BACK-UP
Operational Characteristics: Type I Error and Power Varying the Event Rate of the External Control Group

20 Events Borrowed; Accumulated Data: N=150 /e=89; Weight of informative Prior: 0.7

HR=0.60
- robust prior (solid green line)
- power prior (dashed green line)

HR=1
- robust prior (solid red line)
- power prior (dashed red line)
Operational Characteristics: Type I Error and Power Varying the Event Rate of the External Control Group
20 Events Borrowed; Accumulated Data: N=150 /e=89; Weight of informative Prior: 0.9

HR=0.60
- robust prior

HR=1
- robust prior

Priors and their impact on the cumulative incidence at 18 months.