External Control Arms Driving Regulatory Decision Making: Industry Examples and Learnings

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Some settings where external control arms can add value

- Establish primary proof of efficacy
- Establish long-term efficacy and/or safety
- Support label expansion
- Answer HTA questions
- Inform design of an upcoming trial
- Derive a ‘suitable’ threshold for a single arm trial (SAT)
- Establish a non-inferiority margin

Case study 1: Abatacept (Orencia) - external controls from registry data support approval for aGVHD prophylaxis

Clinical objective

- aGvHD risk is as high as 40% and transplant associated mortality is similarly high
- PhII RCT comparing ABA+SOC vs SOC for prevention of aGvHD

Use of external controls

- Inclusion of a placebo-controlled arm was not feasible for the mismatch unrelated donor cohort due to investigator's concerns over more severe outcomes expected based on prior observations in this patient population using SOC; hence, an external control arm was added.
- A registry study using patients from the CIBMTR database was conducted to confirm results from the Ph2.

Key outcomes/lessons learned

- ABA vs SOC: d180 OS 98% vs 75%; GFS 65% vs 35%
- Approved in US; Canada & Israel via Project Orbis; withdrawn from Switzerland/EU.

Kean LS, Burns LJ, Kou TD, et al. Abatacept for acute graft-versus-host disease prophylaxis after unrelated donor hematopoietic cell transplantation. *Blood*. 2024;144(17):1834-1845. doi:10.1182/blood.2023023660

Case study 2: Atidarsagene autotemcel (Lenmeldy) for metachromatic leukodystrophy (MLD)

Clinical objective

- MLD clinical manifestations include progressive motor dysfunction and neurocognitive decline, eventually leading multiorgan system failure, or death
- The safety and efficacy of LENMELDY was assessed in children across two single-arm, open-label clinical trials

Use of external controls

- External control data from a longitudinal cohort of children with MLD
- Matched on age, genotype and disease sub-type

Key outcomes/lessons learned

- 100% had preserved neurodevelopmental skills at 5 years vs 0% in untreated historical controls
- The EU and US labels include reference to the ECA data

Gangji RN, Ali QA, Dhamija R, Corado AM, Kharbanda S; ACMG Therapeutics Committee. Lenmeldy (atidarsagene autotemcel) for individuals with early metachromatic leukodystrophy (MLD): A therapeutics bulletin of the American College of Medical Genetics and Genomics (ACMG). Genet Med Open. 2025 Jun 24;3:103432.

Case study 3: Liso-cel (Breyanzi) relapsed/refractory large B-cell lymphoma

Clinical objective

- Relapsed or refractory (R/R) large B-cell lymphoma patients have few treatment options and poor outcomes
- No appropriate active comparator for 3L+ and ethical concerns randomizing patients with rapidly progressive disease

Use of external controls

- Liso-cel pivotal study in LBCL was a single arm phase III
- External control arm data were derived from multiple RWD sources to create a harmonized common data model to facilitate comparative analyses

Key outcomes/lessons learned

- Overall response rate 74% vs 39%; median overall survival 23.5 vs 6.8 months
- Analysts were blinded to control patient outcomes
- Day zero sensitivity analyses

Van Le H, Van Naarden Braun K, Nowakowski GS, et al. Use of a real-world synthetic control arm for direct comparison of lisocabtagene maraleucel and conventional therapy in relapsed/refractory large B-cell lymphoma. Leuk Lymphoma. 2023;64(3):573-585. doi:10.1080/10428194.2022.2160200

Case study 4: Risdiplam (Evrysdi) Spinal Muscular Atrophy (SMA)

Clinical objective

- Spinal muscular atrophy (SMA) is a neuromuscular disorder resulting in severe weakness of the limbs, trunk and respiratory muscles
- A leading genetic cause of mortality in children, with an estimated incidence of 1 in 6,000 live births

Use of external controls

- The development of risdiplam consisted of two seamless pivotal studies
- External control study was undertaken to allow conclusions on the benefit of risdiplam in a single arm trial
- External control data came from a natural history study and the control arm of a historical clinical trial.

Key outcomes/lessons learned

- There was a significant and clinically relevant difference in patients' motor function after 24 months between the interventional arm and the external control arm
- The initial filing timelines were sped up for some markets, including the US and certain International markets, ultimately allowing earlier access in an area of high unmet need

Mercuri E, Baranello G, Boespflug-Tanguy O, et al. Risdiplam in types 2 and 3 spinal muscular atrophy: A randomised, placebo-controlled, dose-finding trial followed by 24 months of treatment. Eur J Neurol. 2023 Jul;30(7):1945-1956. doi: 10.1111/ene.15499. Epub 2022 Aug 1. PMID: 35837793.

Case study 5: Ritlecitinib 50 mg and 100 mg for Alopecia Areata - External and Synthetic Placebo-Controlled Study

Clinical objective

- Phase 3 clinical trial to evaluate the benefit and risk of a higher dose than previously evaluated in clinical trials
- High dose trial including both 50mg and 100mg has no internal randomized placebo group
- Endpoint is objective

Use of external controls

- External control (patient level placebo data through Week 24/Week 48 from completed trials)
- Synthetic control (Bayesian longitudinal data modelling to generate synthetic placebo data through week 36)
- Principled statistical analyses adjusted for potential baseline covariate imbalances

Key outcomes/lessons learned

- Trial is ongoing, but its design will eliminate the need to assign patients to placebo
- Successful example of a project included in the FDAs complex and innovative trail design (CID) program
- Modelling and simulation played a key role in understanding the operating characteristics and informing the trial design

King, B., McMichael, A., Sinclair, R. et al. Rationale and Design of a Novel, Phase 3, External and Synthetic Placebo-Controlled Clinical Trial of Ritlecitinib 50 mg and 100 mg for Alopecia Areata. Dermatol Ther (Heidelb) (2025). https://doi.org/10.1007/s13555-025-01543-7

Conclusions and key learnings

- **Multiple successful examples of ECA use in a range of settings**
- **Early and consistent engagement with health authorities is critical**
- **Data availability and quality are key to:**
  - Effectively replicate trial inclusion/exclusion criteria
  - Adequately control confounding
  - Endpoint reproducibility
- **Assignment of day zero – consider target trial emulation**
- **Generalisability of data across geographies**
- **Alignment across guidance globally**