WHITE PAPER

EXTERNAL CONTROLS (PART II): INFORMED CHOICES AMIDST A PORTFOLIO OF OPTIONS

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As discussed in Part 1 of this series (EXTERNAL CONTROLS IN CLINICAL RESEARCH (PART I): THE CLINICAL IMPERATIVE), regulatory concepts referable to the creation of an external control group have long been noted and occasionally implemented, particularly for diseases with severe morbidity, mortality, and unmet medical need. As defined in Guidance for Industry: E10 Choice of Control Group and Related Issues in Clinical Trials (2001), "an externally controlled trial is one in which the control group consists of patients who are not part of the same randomized study as the group receiving the investigational agent."[1] Though simple in definition, implementation of external controls into a development program for product registration must navigate a number of strategic options and design methods.

Given that these programs immediately become "non-traditional," positioning an external control so that it can successfully address industry and regulatory scrutiny requires informed choices at each point in the development process. The discussion below outlines the potential benefits and disadvantages of using an external control within a program and the key criteria from representative programs that have successfully passed industry and regulatory muster to use external controls in registrational programs.

BENEFITS AND LIMITATIONS OF EXTERNAL CONTROLS IN THE CONTEXT OF PROGRAM STRATEGY

Studies using external controls are pursued for numerous reasons. When successfully implemented, these studies allow most, if not all, patients enrolled in a planned prospective investigational study to receive potentially active treatment, as the externally derived data supplants or fully replaces a control group based either on placebo or standards of care. For sponsors, the successful application of external controls can increase patient/physician engagement. By removing a concurrently randomized control arm — thus reducing the number of patients required within the overall study — these designs may also present sponsors with potential opportunities to accelerate efficient clinical development while also reducing development costs. Additionally, contingent upon the mechanism of action, the proximity of an effect to treatment, and the objectivity of the proposed end point, there is precedence to suggest regulatory acceptance of this approach. This concept is illustrated in Table 1.

At the same time, attempts to incorporate external control data into a clinical development program can pose challenges to the acceptability of study designs. Studies relying on external controls lack randomization, and the inherently open-label nature of referential data could result in increased patient, observer, and analyst bias. Further, trial designs relying on external controls lack the direct comparability that would be present in concurrent randomized control versus treatment arms, and this may confound study interpretability, as variables that are also prognostically important by definition could not be randomly allocated across treatment groups.

The use of external controls may prompt increased stakeholder scrutiny of statistical methods and inferences of the externally controlled study. Additionally, though precedent exists for the use of external controls in support of pivotal investigations (as shown in Table 1), these are relatively limited in number. Criteria for the acceptability of these external controls to inform potentially pivotal/registrational studies appears to vary depending on agency, division, and indication, effectively precluding broad-based conclusions applicable to all therapeutic areas and strategies.

TABLE 1: REPRESENTATIVE EXAMPLES OF REGULATORY ACCEPTANCE FOR THE USE OF EXTERNAL CONTROLS. COMPOUNDS WITHIN SPECIFIC INDICATION AND THEIR UTILIZATION OF EXTERNAL CONTROLS.

Compound	Indication (FDA approval date)	External Control Source	Primary End Point	Purpose
Alglucosidase alfa[2]	Pompe disease (2010)	Direct comparison for noninferiority inference historical cohort of untreated infantile-onset Pompe disease patients with similar age and disease severity, identified by a retrospective review of medical charts	Proportions of alglucosidase alfa-treated patients who died or needed invasive ventilator support at 18 months of age	Pivotal international, multicenter, open-label, clinical trial of 18 infantile-onset Pompe 495 disease patients
Sebelipase alfa[3]	Lysosomal acid lipase indication (LAL) (2015)	Direct comparison by survival analysis Survival in an untreated historical cohort of 21 patients with a similar age at disease presentation and clinical characteristics	Survival of treated patients at 12 months of age vs untreated historical cohort	Pivotal, multicenter, open-label, single-arm clinical study of KANUMA conducted in 9 infants with LAL deficiency who had growth failure or other evidence of rapidly progressive disease prior to 6 months
Asfotase alfa[4]	Hypophosphatasia (2015)	Direct comparison by survival analysis In studies 1 and 2, survival and invasive ventilation-free survival compared in STRENSIQ-treated patients with historical cohort of untreated patients with similar clinical characteristics In study 3, height, weight, and radiographs to assess HPP-related rickets via 7-point RGI-C (Radiographic Global Impression of Change) scale compared with historical cohort of untreated patients with similar clinical characteristics	Survival and invasive ventilation-free survival	Study 1 (Pivotal 24-week prospective single-arm trial of severe perinatal/infantile-onset HPP) Study 2 (Pivotal prospective open-label study – patients aged 1 day to 78 months with perinatal/infantile-onset HPP) Study 3 (Pivotal prospective open-label 24-week trial 8 juvenile-onset HPP patients and 5 perinatal/infantile-onset HPP patients)
Eteplirsen[5]	Duchenne muscular dystrophy (2016)	Direct comparison across clinical and histopathological variables Patients who participated in Study 2 were compared to an external control group and two DMD patient registries, the “Italian DMD registry” and the “Leuven Neuromuscular Reference Center” registry	6MWT	Study 2: Open-label EXONDYS 51 4-year extension study

TABLE 1: REPRESENTATIVE EXAMPLES OF REGULATORY ACCEPTANCE FOR THE USE OF EXTERNAL CONTROLS. COMPOUNDS WITHIN SPECIFIC INDICATION AND THEIR UTILIZATION OF EXTERNAL CONTROLS. (CONT.)

Compound	Indication (FDA approval date)	External Control Source	Primary End Point	Purpose
Cerliponase alfa[6]	Late infantile CLN type 2 (2017)	Matched analyses with historical control data Untreated patients from a natural history cohort	Motor domain of a CLN2 Clinical Rating Scale	Pivotal 48-week, non-randomized single-arm extension study in symptomatic pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2)
Avelumab[7]	Metastatic Merkel cell carcinoma and urothelial carcinoma (2017)	Historical controls with matched enrollment criteria via healthcare record and patient registry	Confirmed Best Overall Response	Pivotal – comparison to single arm, open-label, Phase II
Blinatumomab[8]	Relapsed/refractory Philadelphia chromosome-negative acute lymphoblastic leukemia (accelerated approval (2014), full approval (2017))	Historical controls – patients who received standard of care, weighted analysis of patient level data from medical chart reviews	Complete remission or complete remission with partial hematologic recovery	Supportive-accelerated approval comparison to single-arm, open-label, phase 2
Omegaven (fish oil triglycerides)[9]	Parenteral nutrition-associated cholestasis (PNAC) (2018)	Historical control arm based on hospital records	Mean body weight adjusted for age	Pivotal – comparison to 2 pivotal investigator-initiated, open-label studies

Thus, awareness of the potential limitations regarding the acceptability associated with external controls in the context of an interventional trial is an important consideration when approaching these designs or programs. Recently, the FDA denied approval for a medication targeting pediatric acute graft-versus-host disease (aGVHD), whose Phase III trials had relied on an external control because of concerns that parents of aGVHD patients would not want to put their children at risk through randomization to a control group. The FDA, though, took issue with the single-arm, open-label nature of the study, despite the fact that the drug demonstrated a statistically significant benefit in its primary end point against the historical data rate.[10] The FDA's expressed concern was that similar efficacy might not be proven in a "gold-standard" randomized trial.[11]

Methodological rigor benefits from the depth and richness of trial datasets derived from multi-arm randomized trials and double-blind analysis. Therefore, it is crucial that all parties participating in a study involving external controls strive to minimize bias in the identification of the control dataset and increase stakeholder endorsement of conclusions preemptively by focusing on the method of generating the data and mapping it to prospective patients receiving active pharmacotherapy.

SUCCESS AT THE INTERSECTION OF MEDICAL NECESSITY AND TRIAL METHODOLOGY

Clinical programs that have incorporated external control data in support of product registrations, such as those in Table 1, often share common core features. These predominantly include a severe or rare disease (or both) and rigorous data collection strategy to ensure that the external control population is demographically similar to the treatment population and that data collected on this population (e.g., end points/assessments) are congruent to the planned investigational treatment group.

TABLE 2: CORE CHARACTERISTICS OF STUDIES THAT HAVE SUCCESSFULLY AND UNSUCCESSFULLY LEVERAGED EXTERNAL CONTROLS

WHEN EXTERNAL CONTROL/ RWE USE HAS BEEN ACCEPTABLE	WHEN EXTERNAL CONTROL/RWE USE HAS BEEN UNACCEPTABLE
• A priori planned analysis	• Post-hoc analysis
• Well-defined/robust natural history data	• Selection bias (e.g., non-congruent eligibility criteria)
• Objective/quantitative end points	• Confounder bias
• Unmet medical need with serious or life-threatening disease	• Temporal bias (age of historical versus active data)
• Acknowledged issues with placebo or comparator arm	• Data missing external/RWE data points
• Purpose-made natural history study or registry	• Small sample sizes or limited statistical power in external/ RWE
• Patient comparability	• Lack of transparency (ad hoc; insufficient data capture, “cherry-picking” data, undefined methods)
• No significant changes in SOC/management	
• Controlled, identified, measured confounders	
• Large observed effect size	
• Supported by additional randomized controlled trial	
• Used to permit a label extension	
• Support accelerated approval	

Indeed, a review of recent external control literature and published FDA correspondence provides an illustrative pattern of best strategies for acceptable external control use versus those that fall short.[10, 12-15] Table 2 lists some of the key characteristics of programs that have successfully (and unsuccessfully) incorporated external controls and/or real-world evidence (RWE) in support of a product registration.

For example, the biostatistical review of alglucosidase alfa for use in Pompe disease (Table 1) illustrates how bias minimization techniques were applied to warrant use of the external control: "a historical control subgroup of 62 untreated patients was used as a comparator group. The subjects were selected from a retrospective identified cohort of 168 patients with infantile-onset Pompe disease (AGLU-004-00). The selection of the subgroup was based on the entry criteria used for study 1602 [the pivotal registration study]." [16] This successful application of an historical control confirms some of the main attributes required for successful positioning, which included a priori planned analysis, patient comparability via entry criteria, and objective/quantitative end points (death or invasive ventilator support needed).

BEST NOT APPLIED IN ISOLATION

Note that not all criteria have to be met to successfully position external control data in support of product registration. However, significant justification and transparency of methods used to collect the data must be well presented. Additionally, where insufficiencies are possible in a program utilizing external controls, a supportive randomized controlled trial is often required. Consider the approval of sebelipase alfa (see Table 1) in infants who present with rapidly progressive LAL deficiency within the first six months of life.

In that program, a historical comparator group with similar demographics and baseline disease severity was derived from the population based upon a retrospective observational natural history study. These data complemented a multicenter randomized double-blind placebo-controlled clinical trial in pediatric and adult patients. This example illustrates the balance between clinical and analytic issues that should be struck during the review process. A comment within the product's biostatistical review expresses the sentiment that comparisons to a historical control are not considered to provide results as robust as comparisons within a randomized controlled study:

> IT SHOULD BE NOTED, HOWEVER, THE COMPARISONS TO AN HISTORICAL CONTROL GROUP WERE NOT CONSIDERED TO PROVIDE RESULTS THAT ARE AS ROBUST OR RELIABLE AS THOSE FROM COMPARISONS WITHIN A RANDOMIZED CONTROLLED STUDY. EVEN WHEN THERE IS AN OBSERVED BALANCE BETWEEN THE NON-CONCURRENT GROUPS IN REGARD TO IDENTIFIED BASELINE CHARACTERISTICS/COVARIATES, THEY MAY BE CONFOUNDING DUE TO BASELINE IMBALANCES IN LATENT VARIABLES, WHICH CAN INFLUENCE OUTCOME IN THERAPY. ... NEVERTHELESS, IT WAS ADJUDICATED THAT THE APPLICANT'S DUE DILIGENCE IN ACQUIRING ALL AVAILABLE, AND PROPERLY COMPARABLE, DATA WAS SUFFICIENT THEREBY MITIGATING THE AFOREMENTIONED POTENTIAL ISSUES.[17]

The critical takeaway lies in the due diligence in acquiring all available, properly comparable data. There must be good reason to rely on an external control, but when there is good reason, when those reasons are well-documented, and when appropriate steps have been taken to mitigate bias wherever it might occur, then there is precedent for submitting the data provided by the external control.

SUMMARY

While exploitation of external control data to minimize or obviate concurrent controls in interventional studies appears to be an efficient method of study design, especially in rare disease populations, the challenges for implementation of such a design are significant. Challenges exist in various domains, beginning with the nature of the disease, the end point most relevant to patient outcome, the rapidity of pharmacological effect, and the collage of disease-related and patient-specific variables that might be prognostically important to the outcome.

These challenges are highlighted by the relatively few approvals using this type of program design, though it is noted that when there is alignment between the constellation of variables, there is more likely to be industry and regulatory support for such a program. Furthermore, the data to be used within the external control dataset must be thoroughly vetted for congruency with the target population to be studied in the interventional study, which often entails the creation of a dedicated natural history or observational study (i.e., a bespoke study rather than one sampled from a convenient database). Sponsors seeking to employ an externally controlled study/program must proactively address issues of bias and external data validity with sophisticated program planning, study design, and regulatory engagement. When presented properly, an externally controlled study can provide data in support of a potentially pivotal investigation, adjudicating the needs of all stakeholders (patients, sponsor, regulators) and serving as an efficient method for providing and evaluating an investigational product.

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