A target trial emulation framework for externally controlled survival analyses in infantile-onset Niemann-Pick disease type C

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Lixia Jiao,[1] Laurence H. Keller,[1] John P. Winnike,[1] Alexander M. Gold,[1] Jessica R. Marden,[2] Andres Gomez-Lievano,[2] James Signorovitch,[2] Forbes D. Porter,[3] Elizabeth Berry-Kravis[4]

[1]Beren Therapeutics P.B.C., Thousand Oaks, CA, USA; [2]Analysis Group, Boston, MA, USA; [3]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD, USA; [4]Rush University Medical Center, Chicago, IL, USA

BACKGROUND

- Niemann-pick disease type C (NPC) is a rare genetic disorder characterized by impaired intracellular cholesterol trafficking, progressive neurological decline and premature death.[1] Infantile-onset NPC (I-NPC; neurological symptom onset <6 years of age) is associated with rapid disease progression and high mortality.[1,2]
- Adrabetadex is an investigational intrathecal therapy that re-establishes impaired intracellular cholesterol trafficking in the central nervous system.[3]
- Evaluation of therapeutic efficacy in rare diseases may require external controls when data from randomized controlled trials are not available.[4,5] However, externally controlled analyses are susceptible to bias from differences in baseline prognosis, treatment initiation at different ages, calendar time and standards of care, and post-baseline therapies.[4,6]
- Target trial emulation provides a structured framework for defining the causal question, aligning treatment and control index dates, identifying potential sources of bias, and prespecifying analyses to evaluate the robustness of treatment-effect estimates.[6]

OBJECTIVE

To apply a target trial emulation framework to identify and address potential sources of bias in an externally controlled survival analysis of adrabetadex in I-NPC.

METHODS

- Analysis included matched adrabetadex-treated participants from an expanded access program, Phase 1/2a, and Phase 2b/3 studies (n=72) and unique external control participants from prospectively and retrospectively collected natural history cohorts (n=119).
- Matching factors included disease subtype, age at neurological onset, age at index, and miglustat use at index.
- For the primary overall survival analysis, external controls were selected based on fitness-for-purpose evaluation and analysed using variable-ratio many-to-one matching with replacement, robust (sandwich) variance with clustering on unique control identifiers, and a frequency-based weight equal to the inverse of the number of controls matched to each treated participant.
- The treatment effect was estimated from a weight-adjusted Cox proportional hazards regression model with fixed effects for treatment and baseline miglustat history.
- Potential sources of bias were identified using a target trial emulation framework and addressed through study design, matching and statistical adjustment. Prespecified subgroup and sensitivity analyses evaluated the robustness of the treatment-effect estimate to alternative assumptions regarding baseline prognostic factors, external-control data source, matching methodology, intercurrent events, outcome ascertainment, censoring, and calendar time.

RESULTS

The target trial emulation framework identified four principal challenges to causal inference:

1 Prognostic Factor Confounding
Known/suspected factors including disease subtype, age at neurological symptom onset, age, miglustat use, disease severity, and genetic severity

Addressed by matching on disease subtype, age at onset (±3 months), index age, and baseline miglustat use, with sensitivity analyses on disease/genetic severity

2 Post-baseline treatment confounding
Potential differences in use of miglustat, other NPC-specific medications, supportive care

Addressed by prioritizing data sources with participant-level miglustat data and by censoring at initiation of other NPC therapies

3 Immortal time bias
Control index ages could otherwise fall at ages where survival was already assured

Addressed by setting each control's index age to the matched treated participant's age at adrabetadex initiation, with controls required to be alive and already enrolled in their prospective study at that age

4 Temporal bias
Data sources spanned different calendar periods, with changing standards of care over time

Addressed by matching and adjusting for baseline miglustat use, with birth-year and data-source subgroup/sensitivity analyses.

- Each identified potential source of bias was addressed through defined design features or evaluated through specified subgroup (Figure 1) and sensitivity analyses (Figure 2).
- Hazard ratio (HR) estimates remained consistent with the primary analysis and supportive of a clinically meaningful survival benefit in I-NPC (HR:0.289, 95% CI:0.141-0.593, p<0.0001).

Figure 1. Summary of Subgroup Analyses

SUBGROUP ANALYSES

	1 Baseline miglustat use	2 Age of neurological onset	3 Source of external control data	4 NPC SOC therapy over time
	Participants with and without baseline miglustat use	Early and late I-NPC subgroups considered separately	NIH, YODA, and French cohorts considered separately	Participants born before 2010 and born in 2010 or later
Study design challenge or potential bias assessed	Whether survival findings were consistent among participants with and without baseline miglustat use, given that miglustat use could differ across cohorts and may be associated with increased survival	Whether findings were consistent across early and late I-NPC, given that average survival is longer for individuals with late I-NPC as compared to early I-NPC	Whether findings depended on a specific external control source, given differences in calendar period, geography, study design, and available variables across cohorts	Whether findings were robust to calendar-era differences that could reflect changes in diagnosis, supportive care, SOC, or access to concomitant medications

I-NPC, Infantile-onset NPC; NIH, National Institutes of Health; NPC, Niemann-Pick disease type C; SOC, standard of care; YODA, Yale Open Data Access.

Figure 2. Summary of Sensitivity Analyses

SENSITIVITY ANALYSES

Category	Analysis	Description	Bias assessed
Baseline disease & genetic information	1 Baseline R4DNPCCSS	Incorporation of baseline score into the matching algorithm instead of age at neurological onset	Whether findings were robust to matching on measured baseline neurological severity among participants with available R4DNPCCSS data, using NIH cohort data
	2 Baseline disease severity by data source	Source-specific baseline severity measures used in matching (YODA and Freihuber, separately)	Whether findings were robust to matching on disease severity for YODA and Freihuber, separately
	3 NPC genotype	Incorporation of genotype category or genetic severity score instead of age at neurological onset	Whether findings were robust to matching on genotype-based disease severity among participants with available genotype data
	4 Baseline miglustat use assumed "no"	All Vanier participants assumed to have no miglustat use at baseline	Whether findings were robust to assuming no baseline miglustat use, given uncertainty in miglustat exposure for Vanier control participants
Matching procedures	5 One-to-one matching	One-to-one matching in place of variable-ratio many-to-one matching	Whether findings were robust to use of a simpler matching structure rather than the primary variable-ratio many-to-one matching approach
	6 Many-to-one matching without re-use	Each external control participant used only once, rather than re-used across matched sets	Whether findings were robust when each external control participant was used only once, rather than allowing re-use across matched sets
	7 Percentile-based selection of controls	Selection of controls using the 50th and 100th percentile methods	Whether findings were robust to alternative selection rules among eligible matched controls, including selection of controls with longer observed survival
Intercurrent events	8 Other NPC therapy	Censoring participants at initiation of other NPC therapy	Whether findings were robust to censoring at initiation of postbaseline NPC therapies that potentially could affect OS independently of initial treatment assignment
	9 Respiratory therapy	Censoring at first use of respiratory therapy	Whether findings were robust to censoring of respiratory therapy initiation, a postbaseline supportive-care intervention associated with disease severity and mortality risk
	10 Concomitant IV adrabetadex use	Participants receiving concomitant IV adrabetadex excluded	Whether findings persisted after excluding participants with concomitant IV adrabetadex, to reduce potential influence of non-intrathecal adrabetadex exposure
Outcome ascertainment & censoring	11 Censoring external control follow-up time	Based on matched treated participants' follow-up with one-to-one matching	Whether findings were robust to aligning follow-up duration between matched treated and external control participants
	12 Tipping-point analysis	Impute censored adrabetadex-treated participants as deaths	How many censored adrabetadex-treated participants would need to be imputed as deaths to reverse the survival conclusion
	13 One year after the last dose	Censoring at 1 year after the last dose for participants treated with adrabetadex	Whether findings were robust to limiting survival follow-up after treatment discontinuation among adrabetadex-treated participants

IV, intravenous; NIH, National Institutes of Health; NPC, Niemann-Pick disease type C; OS, overall survival; R4DNPCCSS, Rescored 4-Domain NPC Clinical Severity Scale; YODA, Yale Open Data Access.

CONCLUSIONS

Target trial emulation made the causal design explicit and identified four principal threats to inference in an externally controlled survival analysis: prognostic factor confounding, post-baseline treatment confounding, immortal time bias, and temporal bias.

These potential biases were addressed through primary design features via aligning time zero/index age and matching key prognostic factors and challenged through targeted subgroup and sensitivity analyses across alternative matching approaches, external-control sources, intercurrent events, censoring assumptions, and calendar eras.

The consistency of treatment-effect estimates across these multiple analyses from this target trial emulation-based externally controlled study supports a robust assessment of the prolonged survival benefit of adrabetadex treatment in I-NPC.

References
1. Vanier MT. *Orphanet J Rare Dis*. 2010;5:1. 2. Imrie J, et al. *BMC Neurology*. 2015;15(1). 3. Abi-Mosleh L, et al. *Proc Natl Acad Sci USA*. 2009;106(46):19316-21. 4. FDA. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Guidance for Industry (Draft Guidance). 2023. 5. European Medicines Agency. Guideline on Clinical Trials in Small Populations. 2006. 6. Hernán MA, et al. *Am J Epidemiol*. 2016;183(8):758-64.

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