

## Case Study

# Harnessing Biostatistics and Real-World Evidence to Advance cALD Treatment

Cerebral adrenoleukodystrophy (cALD) is a rare, rapidly progressive neurodegenerative condition that affects young boys and adult males with ALD. For Minoryx Therapeutics, a Spain-based biotechnology company focused on rare central nervous system diseases, developing leriglitazone, known as Nezglyal, for cALD required an evidence strategy suited to both the severity and rarity of the disease.

The pivotal NEXUS study was an open-label, single-arm study involving 23 boys aged 2 to 12 years. Because a placebo arm was considered unethical, the program needed a credible estimate of how comparable patients would be expected to progress without treatment. MMS biostatistics and biometrics experts strengthened the evidence around the natural-history benchmark in this population, carried out appropriate comparative analyses using external control arm patient-level real-world data, and supported the statistical case throughout the European Medicines Agency review.

## The Challenge

Without a randomized placebo group, demonstrating a treatment effect depended on establishing a defensible understanding of the disease's natural course. The program's benchmark assumed that approximately 10% of untreated patients would experience clinically and radiologically arrested disease, based on published natural-history evidence.

In addition, regulators needed confidence that other well established and clinically relevant endpoints measured in NEXUS would also deviate from natural history in the same population, including its disease severity, age range, eligibility criteria and baseline prognostic profile.

A simple comparison with published historical summaries would not sufficiently account for potential differences between the study population and the patients described in the literature. The analysis therefore needed to account for any differences in important prognostic factors, manage the limitations of a very small rare-disease dataset and withstand detailed scrutiny during the marketing authorization review.

## The Solution

MMS conducted a deeper literature review and extracted patient-level data from relevant natural-history publications. The team restricted and interrogated the available evidence to identify patients who more closely resembled those enrolled in NEXUS, confirming that the approximately 10% natural-history benchmark was reasonable for the planned comparison.

MMS then developed a pre-specified statistical analysis plan for an external control arm to examine the other endpoints. Working cross-functionally across biostatistics and biometrics, the team used propensity score-based weighting to balance the NEXUS participants and external-control patients according to age and other prognostic variables.

This created a more comparable basis for determining whether the observed differences in population represented a treatment effect rather than differences in the patients' baseline risk of progression.

Weighted analyses were included in the marketing authorization application from day zero. MMS continued to support Minoryx Therapeutics through successive rounds of questions and objections from the European Medicines Agency, providing statistical responses and helping communicate the totality of the evidence.

During the CHMP oral explanation, MMS directly addressed statistical questions from the committee and helped clarify the robustness and clinical relevance of the external-control analysis.

## The Result

The Committee for Medicinal Products for Human Use issued a positive opinion recommending marketing authorization under exceptional circumstances for Nezglyal (leriglitazone) in a defined population of boys with cALD.

In the open-label study, seven of 20 evaluable boys (35%) showed arrested disease remaining clinically stable and without meaningful radiological worsening after up to 96 weeks of treatment or until transplantation. Of nine boys with gadolinium-negative lesions at baseline, six (66.7%) showed arrested disease.

The positive CHMP opinion was a key milestone for Minoryx Therapeutics and showed how a rigorously designed external control arm, using patient-level real-world evidence and pre-specified modelling, can support regulatory decisions when a randomized placebo-controlled trial is unethical or unfeasible.

From evidence generation and statistical modelling through regulatory questions and the CHMP oral explanation, MMS helped Minoryx Therapeutics present a robust case for the treatment's effect in this rare, rapidly progressing disease.

## Key Success Factors

- Patient-level real-world data used as an external control arm to carry out additional analyses supporting a true treatment effect
- A pre-specified statistical analysis plan designed to withstand regulatory scrutiny
- Propensity score-based weighting to balance important prognostic factors
- Cross-functional biostatistics and biometrics support from analysis through regulatory review
- Direct statistical support during European Medicines Agency questions and the CHMP oral explanation
- A positive CHMP opinion for a defined gadolinium-negative cALD population

## Let's Talk!

If you'd like to discuss this case study further or learn more on how our technology enabled services can support your development project, please visit [mmsholdings.com](https://mmsholdings.com) or get in touch [info@mmsholdings.com](mailto:info@mmsholdings.com)