HTA48

Reducing Decision Uncertainty in Ultra-Rare Paediatric Conditions: A Delphi-Based Approach to Inform HTA and Pricing & Reimbursement for Non-Dystrophic Myotonias

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Background

Robust evidence generation in ultra-rare paediatric disorders is challenging due to:

- The scarcity and geographical dispersion of patients,
- The severe nature of the disease,
- Ethical considerations regarding participation in a prolonged trial.

The opportunities for addressing evidence gaps are limited due to:

- The time needed to generate additional data pre-submission,
- A lack of robust natural history or comparative data, or registries through which it can be collected.

Thus, the evidence package may often contain uncertainties relevant to conventional health technology assessment (HTA) and clinical decision-making. However, in the context of the ultra-rare paediatric disease some uncertainties might carry a different weight or be accepted by the relevant stakeholders.

Thus, there is a need for a structured methodology to reliably characterize expected trial evidence gaps and prioritize potential methods to address uncertainties from a payer and clinician perspective.

Aims

To assess how a clinician Delphi panel, supported by proxy-payer interviews, can identify and prioritise evidence uncertainties in ultra-rare paediatric disorders trials, and to evaluate feasible evidence-generation strategies that can support HTA decision-making.

Methods

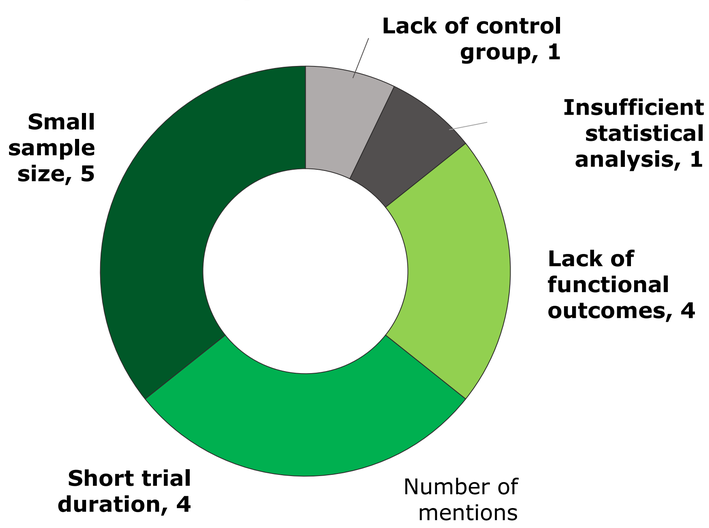
- Data from paediatric patients with non-dystrophic myotonias (NDM) enrolled in the MEX-NM-301 (NCT04624750)[1] and MEX-NM-303 (NCT04622553)[2] mexiletine trials were used as a case study.
- The study recruited 10 European proxy-payers from 5 countries who discussed HTA-relevant evidence gaps in presented clinical trials and their potential impact on pricing and reimbursement decisions.
- Subsequently, a two-round clinician Delphi panel, recruiting 12 European clinicians experienced with treating paediatric NDM, was conducted.
- Round 1: Clinicians identified evidence gaps relevant to their clinical practice and assessed the importance of the evidence gaps highlighted by proxy-payers.
- Round 2: Clinicians revised their responses based on the consolidated round 1 results to achieve consensus and rated possible approaches to address the gaps.

Results

Figure 1. Observed evidence limitations

The uncertainties identified by clinicians (1a) and payers were generally understood within the context of the ultra-rare, neuromuscular disease and would still allow for positive HTA and clinical decision-making as well as provide a significant clinical benefit to patients (1b).

1.a. Frequency of mentions of evidence gap on decision-making



1.b. Overall impression of the trial data in treating paediatric patients with NDMs

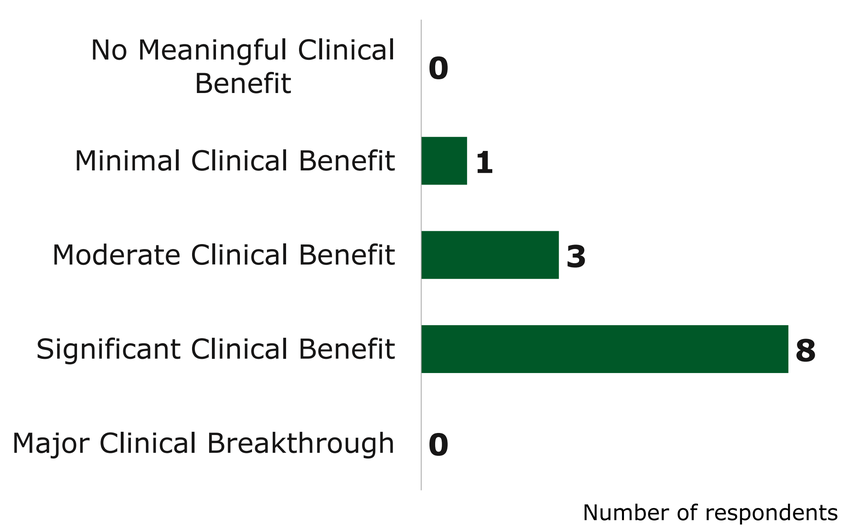


Figure 2. Further evidence generation would increase the meaningfulness of trial data

Payers and clinicians proposed broadly similar evidence generation strategies, that would increase the decision-relevance of the RCT outcomes and improve the HTA/clinical decision-making.

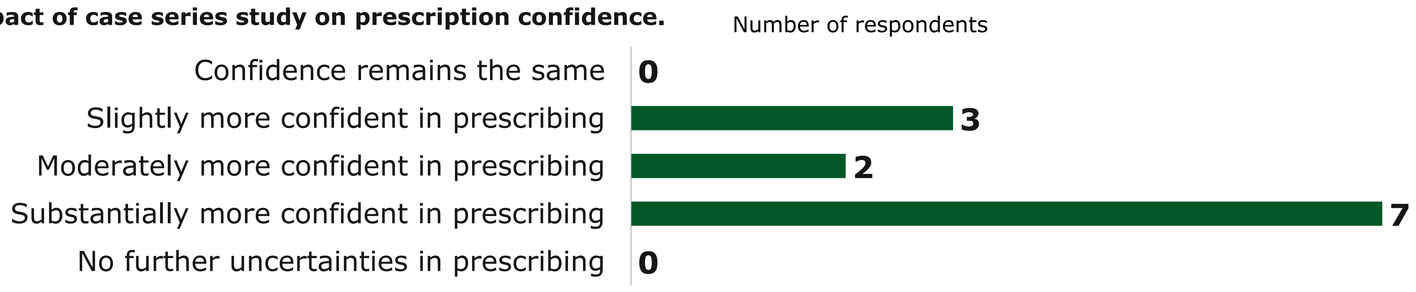
2. Suggested evidence generation strategies

Evidence generation strategy	Proposed by proxy-payers	Proposed by clinicians	Evidence gap addressed	Rationale	Limitations
Use of historical controls	Yes	Yes	Lack of comparative data, small sample size, lack of functional outcomes	Increased available safety and efficacy data	Identification of historical data
Real-world evidence data	Yes	Yes			Sufficient patient recruitment
Indirect Treatment Comparison against Standard of Care	Yes	No	Lack of comparative data	Comparison to SoC	Identification of eligible trials
Use of adult data	Yes	Yes	Short trial duration, small sample size	Extrapolation of safety and efficacy data	Not accepted by payers in some countries
Study extension	Yes	Yes	Short trial duration	Longer-term data	Time constraints
Subgroup analysis	No	Yes	Lack of comparative data	Useful for communicating safety	Non-significant results due to population size
Educational tools	No	Yes	Most gaps	Improves clinician knowledge	No new data generated

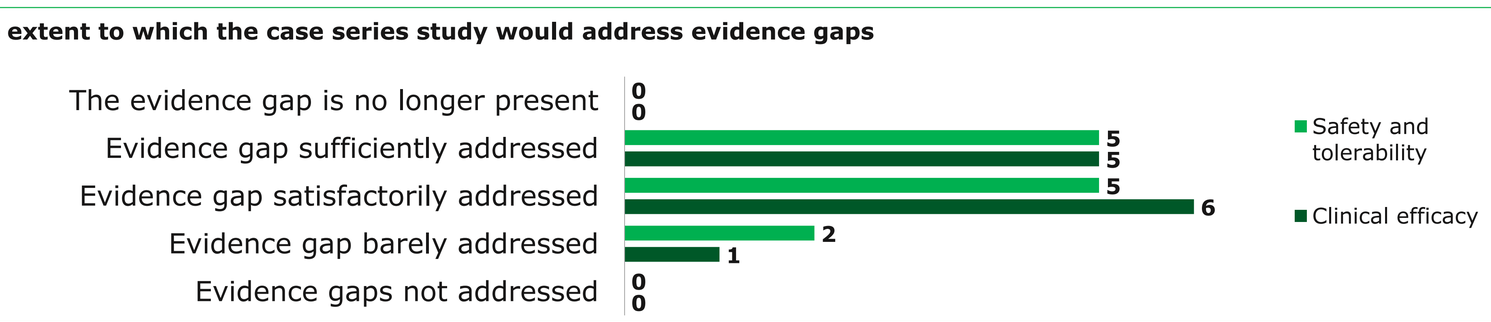
Figure 3. Case series would satisfy evidence limitations

A paediatric patient case series was suggested by proxy-payers and clinicians as a sufficient way to address evidence gaps in the absence of RCT data. Clinicians expressed that it would increase their confidence in prescribing paediatric mexiletine (3a) and that it would address identified evidence gaps (3b). This suggests its potential acceptability in HTA and clinical contexts for ultra-rare conditions.

3.a. Impact of case series study on prescription confidence.



3.b. The extent to which the case series study would address evidence gaps



Discussion and conclusions

Despite inherent limitations in ultra-rare paediatric evidence generation, this study demonstrates that targeted approaches can meaningfully reduce uncertainty, support clinician confidence, and inform HTA decision-making. For example, post-launch evidence generation strategies (e.g. case studies series) that align with managed access agreements could reduce decision uncertainty over time, enabling earlier patient access and continued evidence development. The Delphi Method can provide a viable pathway for evidence development aligned with HTA and clinical requirements.

References

1. Lupin Ltd. An Open-Label, Non-Comparative Study to Evaluate the Steady-State Pharmacokinetics, Safety, and Efficacy of Mexiletine in Adolescents and Children With Myotonic Disorders. https://clinicaltrials.gov/study/NCT04624750 (2024).
2. Lupin Ltd. Open-Label Extension Study to Evaluate the Long-Term Safety and Efficacy of Mexiletine in Paediatric Patients With Myotonic Disorders Who Have Completed the MEX-NM-301 Study. https://clinicaltrials.gov/study/NCT04622553 (2025).

Abbreviations

HTA: Health technology assessment; NDM: Non-dystrophic myotonias; P&R: Pricing and reimbursement; SoC: Standard of care

Acknowledgments

The study was conducted by Remap Consulting UK.
The study was funded by Lupin Neurosciences

Disclosures

KS, CH: Consultancy fees from Lupin Neurosciences; AB, AZ-W, RO, MvA: Employees of Lupin Neurosciences; HL: Employee of AGH Partners UK