Poster ID
135

Perseverance Is Key for Regulatory Success in Ultra-Rare Diseases – Key Learnings from Arimoclomol's Regulatory Journey

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21st Annual WORLD*Symposium*, February 3-7, 2025, San Diego, CA, USA

Niemann-Pick Disease Type C

- Ultra-rare, progressive neurodegenerative disease with an incidence of 1:100,000 (estimated 600-900 patients in the US).[1]
- Caused by mutations in the *NPC1* (95% of cases) or the *NPC2* gene.
- Defects in the NPC1 and NPC2 proteins causes lysosomal dysfunction, leading to cytotoxic accumulation of unesterified cholesterol and glycosphingolipids in lysosomes, which drives neurodegeneration and peripheral organ dysfunction.
- Median age at death is 13 years.[2]

Arimoclomol

- Arimoclomol is the first FDA-approved treatment for NPC when used in combination with miglustat.
- Arimoclomol is indicated for the treatment of adult and pediatric patients (≥ 2 years) with Niemann-Pick disease type C (NPC).
- Small molecule.
- Crosses the blood-brain barrier.
- Formulated as oral capsule that can be swallowed whole, or mixed with either soft food or liquid and dosed through a feeding tube.

The Arimoclomol Journey: First-in-Indication Medicine for an Ultra-Rare Disease

Clinical Studies

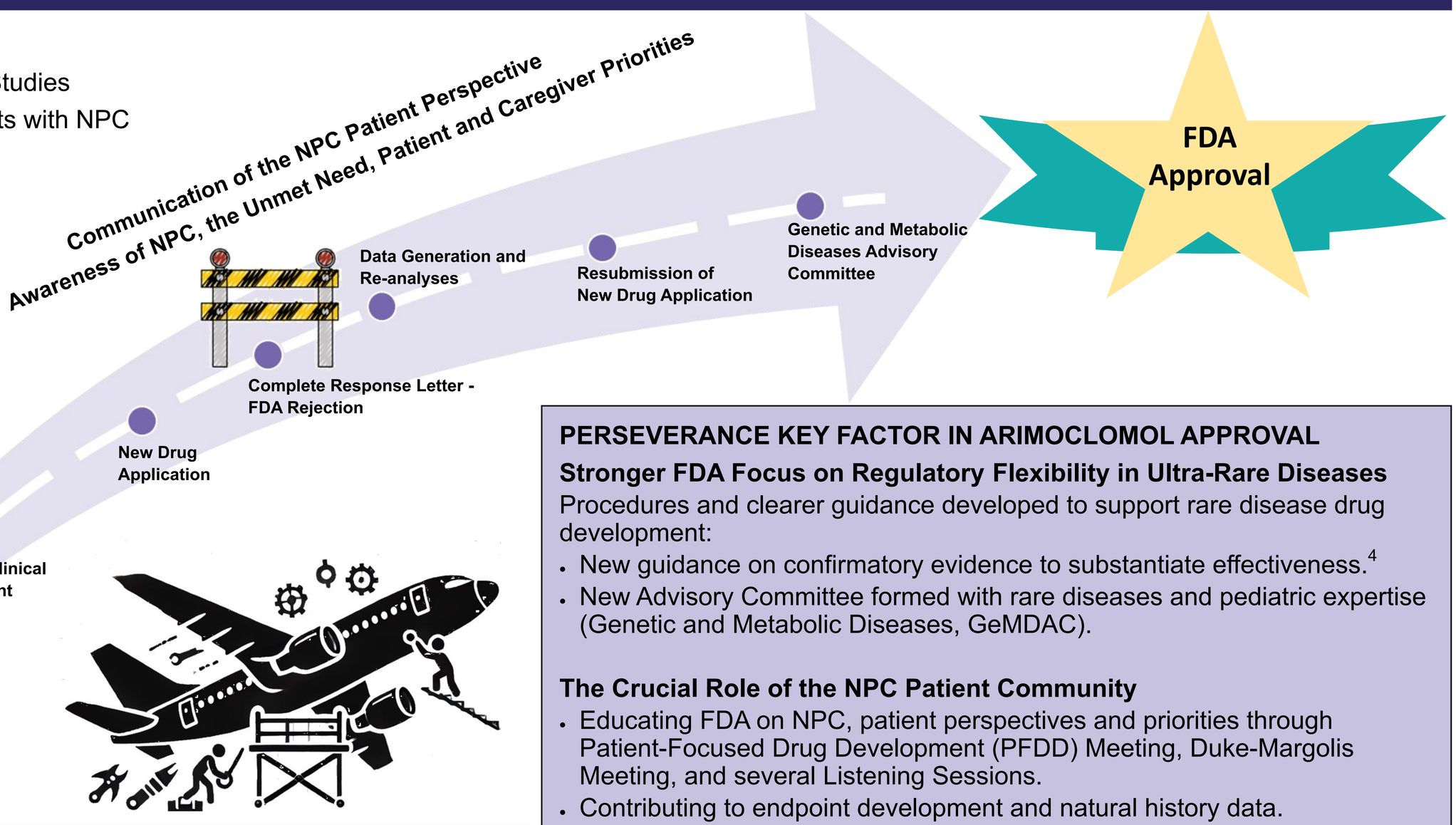
- 11 Clinical Pharmacology Studies
- 2 Clinical Studies in Patients with NPC

Regulatory Interactions

- 12 FDA Meetings

Designations:

- Breakthrough Therapy
- Rare Pediatric Disease
- Orphan Drug
- Fast Track



PERSEVERANCE KEY FACTOR IN ARIMOCLOMOL APPROVAL

Stronger FDA Focus on Regulatory Flexibility in Ultra-Rare Diseases

Procedures and clearer guidance developed to support rare disease drug development:

- New guidance on confirmatory evidence to substantiate effectiveness.[4]
- New Advisory Committee formed with rare diseases and pediatric expertise (Genetic and Metabolic Diseases, GeMDAC).

The Crucial Role of the NPC Patient Community

- Educating FDA on NPC, patient perspectives and priorities through Patient-Focused Drug Development (PFDD) Meeting, Duke-Margolis Meeting, and several Listening Sessions.
- Contributing to endpoint development and natural history data.
- Participation in clinical trials, and numerous surveys to validate the NPC Clinical Severity Scale.
- Participation in Sponsor's FDA Meetings.

Continuous Data Generation and Endpoint Development

- Bolstered nonclinical data package.
- Further validation of clinical endpoint (NPC Clinical Severity Scale).
- 5 years of long-term clinical data.
- 3.5 years of real-world data from Expanded Access Program.

BUILDING THE PLANE WHILE FLYING

Regulatory Challenges in Ultra-Rare Diseases

Ultra-Rare Diseases Characterized by:

- Limited patient populations that challenges clinical trial conduct, the likelihood of statistical significance, and impact of missing data.
- Complex etiologies, limited understanding of natural history and heterogenous disease progression.
- Lack of established biomarkers and validated endpoints.
- Approximately 2/3 of all lysosomal diseases lack approved therapies.[3]

First-in-indication

- No regulatory roadmap to follow.
- Regulators have limited knowledge about the disease.
- Limited natural history data available.

Regulatory Aspects

- Orphan drugs requires regulatory flexibility – unpredictable as guidance documents have been sparse.
- Long development leads to changes in the regulatory environment.
  - Evolving regulatory guidance.
  - Change in staff and management at the FDA.
- Misalignment between agencies and within FDA divisions.
- Reluctance to accept real-world data or uncontrolled long-term data as evidence
- Risk of type 2 error in regulatory decisions (rejecting an effective drug).

Key Messages

- Strong and persistent patient advocacy is critical.
- Recognition of the patients, caregivers, and clinicians being the experts.
- Essential to consider confirmatory evidence early in drug development, preferably already in the preclinical phase.
- FDA to re-calibrate the benefit-risk ratio for ultra-rare diseases, as defining a regulatory roadmap through drug approval nurture future investments and drug development.
- Despite recent FDA initiatives for supporting rare diseases there is still a need for regulatory flexibility tailored to ultra-rare diseases with truly unmet need, complicated etiologies and limited research on biomarkers.

Literature References:

[1]Burton BK, Ellis AG, Orr B et al. *Mol Genet Metab*. 2021;134(1-2):182-7
[2]Bianconi SE, Hammond DI, Farhat NY et al. *Mol Genet Metab*. 2019;126(4):466-9
[3]Mechler K, Mountford WK, Hoffmann GF, Ries M. *Orphanet J Rare Dis*. 2015;10:46
[4]FDA Draft Guidance for Industry. Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence, September 2023.

Acknowledgements: This work was sponsored by Zevra Denmark A/S.

Disclosures: LH and AA are employees of Zevra Denmark A/S.