PROGRESS TOGETHER

Inpda

International Niemann-Pick Disease Alliance

International Niemann-Pick Disease Alliance (INPDA)
Suite 2, Vermont House
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16th March 2022

Dear Dr Enzmann,

I write in my capacity as the President of the International Niemann-Pick Disease Alliance (INPDA), and on behalf of our 23 member organisations, who advocate on behalf of patients and families affected by Niemann-Pick diseases in 17 countries. We would like to request your attention in a matter of concern for our Niemann-Pick type C (NPC) patient community.

NPC is a progressive, ultra-rare and significantly life limiting neurodegenerative disorder that is pan-ethnic and affects all age groups. It is impossible to overstate the devastating consequences of this disease for affected individuals and their families. The heterogenous nature, challenging symptoms and inevitable fatal outcome of NPC impose a major burden upon patients, their families, health services and society. Confronted with a diagnosis of which most people have never heard, families face daily challenges in accessing the medical care and social support they need.

Orphazyme A/S, a Danish biopharmaceutical company, has been developing arimoclomol as a potential therapy for NPC. Through a public press release on 23rd February,[1] we learned of a negative trend vote on the MAA for arimoclomol and the likely indication that the CHMP will not approve arimoclomol when it convenes by the end of March 2022.

Since the inception of this clinical trial, expert advocates and patient representatives from the global NPC community have contributed substantial time, insight and experience as the product transitioned from

[1] Orphazyme A/S. Orphazyme announces update on regulatory review of arimoclomol in the European Union. 2022.

preclinical studies, to where it is today. Arimoclomol has been shown to be safe and effective through a robust clinical program and has received Orphan Drug and Rare Paediatric Disease Designations.[2]

Whilst there is, as yet, no prospect of a curative therapy for NPC, the EMA approval of miglustat in 2002 changed the lives of NPC patients and their families. Miglustat, a disease modifying therapy that has been shown to slow the progression of this disease, is now recommended as the standard of care for NPC patients.[3] However, miglustat is not tolerated by all patients and on its own is not enough to address the high level of unmet medical need in this patient community.

The benefits of arimoclomol alongside miglustat as standard of care, have been evidenced through the trial data and by patients who demonstrate disease stability. Disease stability, or slowing of progression, is widely seen as a meaningful and important outcome for patients. This is reflected in the opinion of expert clinicians, who recognize that whilst symptom reversal is unlikely, an achievable goal is to slow or halt progression, which has life changing impact for patients and their families, bringing better quality and quantity of life.

We would like to highlight the experience of patients affected by Cystic Fibrosis (CF) and the many, sometimes small, improvements to their medical care seen over many years, that are responsible for the improved survival and quality of life of CF patients today. The median predicted survival age for CF patients has increased from 25 years in 1985 to 46 years based on 2019 registry data, with babies who are born in 2019 or after, predicted to live to be 48 years or older. The length of survival is due to better insights into the natural course of the disease leading to treatments that target respiratory infections, inflammation, mucociliary clearance, and nutritional status. It has already been widely acknowledged that NPC will require a similar combination approach to therapies, with one solution not appropriate for all. Due to the rarity and therefore low numbers of NPC patients, plus the high degree of clinical variability, measuring efficacy of potential therapies is challenging in clinical trials; for instance, only recently has the effects of miglustat on neurological NPC manifestations been assessed, with benefits ranging from cellular changes in the brain through to visible clinical improvements and improved survival.[4]

We were integral to the creation of the International Niemann-Pick Disease Registry (INPDR), which collects global and longitudinal clinical and genetic data at an individual patient level, plus patient reported outcomes.[5] Enormous progress has been made in this work and the INPDR will have

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[2] Patterson M, Mengel E, Da Riol R, Del Toro M, Deodato F, Gautschi M et al. Persistent Effect of Arimoclomol in Patients with Niemann-Pick Disease Type C: 24-Month Results from an Open-Label Extension of a Pivotal Phase 2/3 Study. Abstracts of the 46th Annual Meeting of the Society for Neuropediatrics. 2021;.

[3] Geberhiwot T, Moro A, Dardis A, Ramaswami U, Sirrs S, Marfa M et al. Consensus clinical management guidelines for Niemann-Pick disease type C. Orphanet Journal of Rare Diseases. 2018;13(1).

[4] Pineda M, Walterfang M, Patterson M. Miglustat in Niemann-Pick disease type C patients: a review. Orphanet Journal of Rare Diseases. 2018;13(1).

[5] Bolton S, Soran V, Marfa M, Imrie J, Gissen P, Jahnova H et al. Clinical disease characteristics of patients with Niemann-Pick Disease Type C: findings from the International Niemann-Pick Disease Registry (INPDR). Orphanet Journal of Rare Diseases. 2022;17(1).

applications in pharmacovigilance, efficacy monitoring, trial control groups, natural history studies and epidemiology.

Time, however, is not on our side. There are multiple and complex issues in therapy development in NPC, including its rarity, clinical heterogeneity and a lack of accepted surrogate endpoints, which pose particular challenges in conducting clinical trials. The INPDA is supportive of innovative and collaborative research work to increase understanding and explore further treatment options. We have learnt that placebo-controlled studies are frequently neither ethically appropriate nor additionally informative for therapies in our disease and we are actively working with sponsors and other stakeholders to find innovative and safe ways to develop effective and accessible therapeutics.

We understand that these challenges will require cross-sectoral consultation, collaborative action and considered effort to find appropriate solutions. Whilst this important work takes place, we would like to respectfully urge you, as you consider the future of arimoclomol, which has a favourable risk/benefit profile and has been shown to improve the lives and prognosis of those affected by this relentlessly progressive disease, to fully take into account the potential impact of reducing the treatment options available to patients now. We invite you to learn more about the impact of NPC and the work of the INPDA via our website www.inpda.org.

Yours sincerely,

Sandra Cowie

Sandra Cowie, President, INPDA, on behalf of:

INPDA EU Organisations:

Niemann-Pick France

Vaincre Les Maladies Lysosomales

Niemann-Pick Selbsthilfegruppe

Associazione Italiana Niemann-Pick

Niemann-Pick Suisse

Niemann-Pick Foreningen I Norge

Volwassenen, Kinderen en Stofwisselingsziekten

Fundacion Niemann-Pick de España

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Asociación ASMD España

Associacion Niemann-Pick de Fuenlabrada

INPDA Global Organisations:

Associacion Niemann-Pick de Argentina

Australian NPC Disease Foundation

Associação Niemann-Pick Brasil

Niemann-Pick Canada

Niemann-Pick UK (NPUK)

National Niemann-Pick Disease Foundation

Niemann-Pick B R-S

The Hollie Foundation

The Wylder Nation Foundation

LSD Society and Niemann-Pick Community Pakistan

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Niemann-Pick Community Organisations:

Ara Parseghian Medical Research Fund

Dana's Angels Research Trust

Hide & Seek Foundation

The Firefly Fund

Hope for Hayley

Hope for Marian

Signed and Supported by members of the global NPC Community:

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