NPC Advocacy Action Alert! Sign-on letter for FDA in support of Arimoclomol

Background: Arimoclomol, an experimental drug being developed by Zevra Therapeutics (previously by Orphazyme), completed a Phase 2/3 clinical trial in 2019. The primary endpoint assessing benefit on the 5-domain NPC Clinical Severity Scale (NPCCSS) was met, forming the basis of a New Drug Application (NDA) submitted to FDA for review. FDA concerns with the NPCCSS scoring, statistical methods, and extent of confirmatory evidence led to a Complete Response Letter (CRL) being issued by FDA in 2021, denying approval of the drug. More details about this history can be found at nnpdf.org/research/zevra/. Since the CRL, Zevra has been working diligently to develop the additional data, information, and analyses needed to address the issues raised in the CRL, including through meetings with FDA, to form the basis of a resubmission of the NDA. With Zevra's plans to complete this resubmission in the coming weeks, it is important that our community's voice is heard.

NNPDF, along with other advocacy organizations and leaders, including Ara Parseghian Medical Research Fund, Dana's Angels Research Trust, Firefly Fund, Hope for Marian, Hide and Seek Foundation, and Support of Accelerated Research (SOAR), have engaged with both Zevra and FDA over the past years to ensure that they understood the significant unmet medical needs faced by those living with NPC, and to advocate for reasonable and appropriate flexible clinical trial and regulatory approaches for all drugs for this ultra-rare disease. While our hope is that these activities have helped to shape the future for how FDA and other decision makers consider available data for new drugs to treat Niemann-Pick type C, we believe there is still an important need to ensure the patient and caregiver voice is at the center of FDA's review of the NDA resubmission for arimoclomol.

We are taking action and we need your support and input!

Sign on at

t.ly/TakeActionArimoclomol-SignOn

Learn more about our position and read the statement we will be sending to the FDA below.

NATIONAL NIEMANN-PICK DISEASE FOUNDATION, INC.
PO Box 49 | Fort Atkinson, WI 53538-0049 | 877-287-3672 | nnpdf@nnpdf.org | nnpdf.org

NPC Community Statement on the Upcoming Arimoclomol NDA Resubmission

Since the founding of the National Niemann-Pick Disease Foundation (NNPDF) in 1993, a core part of our mission has been to work to improve the lives of those living with Niemann-Pick disease by supporting and empowering patients and families affected by this condition. In the past several years, implementing this mission, in concert with our partner organizations and advocates, has focused on accelerating the development of treatments and a cure for this devastating disease.

We have now come to a seminal moment for many in our community who suffer from Niemann-Pick disease. It has now been nearly 110 years since this condition was first described by Albert Niemann and its etiology characterized by Ludwick Pick, and over six decades since the genetic disease subtypes were elucidated, yet our community continues to wait for the first treatment to be available for Niemann-Pick type C (NPC) in the United States. The hallmark hypotonia, delayed fine and gross motor development, speech impairment, and dysphagia deprive patients of the capacity to carry out everyday activities. However, NPC continues to take a toll, with often rapid neurodegeneration and progression of the disease, causing patients to lose what function and abilities they do have. Eventually NPC takes their lives prematurely. The stark reality is that, without treatment, the prognosis for patients with NPC is dismal today, particularly for those with early-onset disease. People with NPC simply cannot wait any longer.

People with NPC need a treatment – anything that has even a reasonable chance to even incrementally improve the known and relentless course of this disease. *This was clearly heard by participants in the discussion at the March 2019 Externally Led Patient-Focused Drug Development Meeting on NPC, and subsequent Listening Sessions, as we have many times before and since these meetings.*

We ask that FDA consider these perspectives from those who have the most to lose by having a potentially effective treatment be sidelined yet again. Consider their serious unmet needs. Consider the irreversible progression that they will experience if the current data is deemed inadequate and if Zevra Therapeutics is asked to identify and gather additional new data. Consider that people with NPC live with absolute certainty about their future, and so are willing to accept greater uncertainty and even risk when it comes to new drugs treatments.

People with NPC deserve to have the existing data on arimoclomol reviewed, and with this patient input in mind. ***NNPDF and its partners hope that the collective and iterative patient input we and others in our community have provided in recent years provide a framework for maximum regulatory flexibility, minimizing the chance that patients will not gain access to a drug that works due to any possibility of false negative conclusion.***

We believe that FDA regulations and policies, as well as previous approvals of other drugs for rare diseases, support applying maximum regulatory flexibility when reviewing the arimoclomol NDA resubmission. This is supported by Congress, where the 2023 Agriculture Appropriations Bill, Senate

Appropriations Committee Report "encourages FDA to use its existing authorities and pathways to meet the urgent unmet medical need of the current generation of NPC patients…" (S. REP. NO. 118-44, at 127 (2023).

NPC is an ultra-rare condition with approximately 300 people known in the United States. It is well-established in FDA regulation and policy that rare diseases face unique challenges in drug development that make it harder to design and conduct clinical trials that definitively confirm a drug benefit. The presence of these challenges demands a more flexible approach. Rare diseases must be considered differently than more prevalent conditions, and ultra-rare and highly heterogenetic diseases even more so.

Especially when combined with the serious unmet medical needs (as discussed above), ***diseases like NPC deserve the maximum regulatory flexibility in the review of data from clinical trials and accompanying confirmatory evidence.***

FDA's own policies say so. FDA's 2019 Substantial Evidence of Effectiveness Draft Guidance says that "certain situations, such as when a disease is rare ***or*** *the disease is life threatening* ***or*** *severely debilitating with an unmet medical need, may warrant additional flexibility." NPC certainly meets* ***all three*** *of these criteria.*

There is ample precedent set by FDA for approving applications for drugs that have a wide range of efficacy data, everything from pivotal studies not meeting their primary endpoint or not even having a randomized, placebo-controlled arm (or sometimes even a prespecified protocol). Recently, in April of this year, FDA approved a drug, Qalsody, for a type of amyotrophic lateral sclerosis (ALS), even though the primary endpoint did not come close to being achieved. Yet, in its review, FDA chose to approve the NDA, during which they considered other analyses that ultimately supported approval. We believe that any new analyses of the NPCCSS results should be considered even if not deemed a "perfect solution" to concerns that FDA had raised, as perfect should not be the enemy of good. The same goes for any new confirmatory evidence provided by Zevra Therapeutics.

We are asking for the same consideration in regulatory flexibility that has been given to other rare and ultra-rare, progressive, and genetic conditions, such as ALS, Duchenne muscular dystrophy, Batten disease, and MPS.

The NPC community calls on the FDA to apply appropriate and maximal regulatory flexibility in its review of the NDA resubmission for arimoclomol.

We have the utmost respect for FDA's role in ensuring that drugs approved in the United States are both safe and effective, including that the benefits outweigh the potential risks. We share this goal with the FDA. The ultimate approval decision on arimoclomol should be considered in the context of this serious and life-threatening unmet medical need that is ultra-rare. The NPC community's need for a treatment is both urgent and great, so careful consideration of the totality of the data, taking into account patient experiences and preferences, is deserved.

Call to Action: Request for Comments Regarding Regulatory Flexibility for NPC and Why Full Consideration of Clinical Trial Data is Important to You

We plan to deliver this statement to FDA in the near future. As part of this, **we also would like to represent your voice to the FDA!** We want to ensure the FDA hears from families living with NPC and other care partners, clinicians, and more, since any decision FDA makes will impact you and your loved ones. FDA needs to hear from the members of this community on key issues and concerns that may help FDA understand why applying regulatory flexibility is warranted for all drugs in development for NPC.

Make your voice heard!

Sign on to this statement by adding your name and any comments by January 5, 2024 at **t.ly/TakeActionArimoclomol-SignOn**. Your input will be included in our outreach to the FDA. We will release the package publicly after it has been submitted to the FDA.

Sign on at

t.ly/TakeActionArimoclomol-SignOn

Deadline is Friday, January 5, 2024

For questions contact nnpdf@nnpdf.org

Supporting One Another. Supporting Our Community.