To the U.S. Food and Drug Administration,

We are writing united on behalf of the GM2 Gangliosidosis (Tay-Sachs or Sandhoff disease) community.

We were devastated to learn that the Food and Drug Administration (FDA) issued a Complete Response Letter (CRL) for IntraBio's supplemental New Drug Application (sNDA) for AQNEURSA™ (levacetylleucine) for the treatment of GM2 Gangliosidosis.

GM2 Gangliosidosis (GM2) is a cruel, relentlessly progressive, fatal neurodegenerative disease in its infantile and juvenile forms that has no available treatments. GM2 begins early in life and robs patients of the ability to walk, talk, or perform any task of daily living. Currently, the median age of death is 4 years old for the infantile form, while those with the juvenile form succumb in adolescence. Patients and their families have endured the painful reality of watching their loved ones deteriorate without viable treatment options. The absence of any approved treatment leaves these families navigating a grim reality with no lifeline, amplifying their isolation and grief.

We were even more devastated to learn the FDA's justification for the CRL: that our patients who participated in the Phase IIb trial with NALL could have "expectation bias" that could influence their performance on tests of everyday function, namely walking and using their hands and arms (fine motor skills).

Anyone who has met or cared for a patient with GM2, or researched and studied this disease knows how scientifically baseless this claim is. GM2 patients suffer from extreme levels of physical and cognitive impairments. That patients in the trial could (1) spontaneously and collectively **improve** their neurological symptoms – e.g., regain functional abilities and skills they had lost due to disease progression – during the treatment period, and subsequently (2) rapidly lose these functional abilities during a post-treatment washout and return to their baseline status, ***simply due to expectation bias***, is so inconsistent with the nature of the disease that it is an affront to the patients and families afflicted and community who have invested their lives caring for this disorder.

It is heartbreaking that patients with GM2 are being denied access to a safe and effective treatment based on a fundamental misunderstanding of the disease's nature—specifically, the implausibility of expectation bias in individuals with such profound neurological symptoms. For years, the FDA has publicly committed to and made promises of regulatory flexibility for rare, serious, devastating disorders. You have come to our conferences, met with our physicians and families, hosted us for a listening session and an externally-led drug development meeting, and boasted to Congress and the media about your innovative, flexible approach to expediting treatments for rare diseases. You have time and time again promised that you understand the challenges our patients and families face every single day living with these rare disorders and have made promises to help us in our fight to bring new drugs—any drug—to market. Those commitments now ring hollow. Despite the absence of credible scientific basis for concern, the FDA cites "expectation bias" as justification for disregarding meaningful evidence of efficacy in this profoundly disabled population and mandating a placebo-controlled trial.

The FDA's decision to issue a CRL for AQNEURSA for the treatment of GM2 and insistence on another placebo-controlled trial be conducted negates every promise you have ever made to our, and the broader rare disease community. The FDA has already determined that AQNEURSA is safe and effective for patients with Niemann-Pick disease Type C – a closely related lysosomal storage disorder. Yet, despite the overwhelming evidence of AQNEURSA's safety and efficacy for GM2, and

despite our efforts to demonstrate that GM2 is the archetype of a serious, debilitating, rapidly progressive, ultra-rare, fatal disorder, the FDA is insisting a placebo-controlled trial be conducted.

The FDA's continued inflexibility regarding placebo-controlled trials in ultra-rare, fatal diseases is not protecting our patients – it is failing them. It is denying them a chance at treatment, all to meet an arbitrary regulatory standard that does not reflect the realities of their disease or take into account the already robust dataset available.

The burden of GM2 is staggering – physically, emotionally, and financially. An FDA-approved therapy would provide more than clinical benefit; it would bring structure, support, and a measure of stability to families living in a constant state of crisis. **Our community deserves the opportunity for the scientific disagreements underpinning the FDA's decision to be discussed openly and transparently, in a public forum.**

Given the FDA's decision reflects a fundamental misunderstanding of the science and realities of GM2 Gangliosidosis, and a complete disregard for the urgency, complexity, and suffering in this community, we demand that the FDA hold a **public advisory committee meeting** for AQNEURSA for an independent, expert review of the available scientific and clinical data.

Our children are dying. There is no time to waste. We are not asking for shortcuts. We are asking for fairness, compassion, and the regulatory flexibility rare disease families have been so long promised.

On behalf of the entire GM2 community, we urge you to conduct this public advisory committee meeting. Please give the GM2 community the opportunity we urgently need – and so deeply deserve.

Sincerely,

Kathleen M. Flynn

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Rick Karl

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On behalf of the GM2 community in the United States and Worldwide: