Collaboration between patient advocacy and industry to create a master protocol to investigate the novel therapy acetyl-L-leucine for three ultra-rare neurodegenerative diseases: Niemann-Pick type C, the GM2 gangliosides and Ataxia-telangiectasia

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INTRODUCTION

- The unique challenges of orphan drug development for serious, debilitating, progressive disorders mandate innovative approaches
- Rare disease patient communities– with their expertise and first-hand understanding of the diseases– have integral knowledge about the patient population
- Patient advocacy involvement in the design of orphan drug trials is important to help ensure the trial is feasible to recruit, tailored to the capabilities of the patients, and importantly, best positioned to detect a meaningful clinical effect

METHODS

Key Methodological Considerations [4]

1. The racemate, N-acetyl-DL-leucine, was known to be used in unlicensed settings in the patient communities. Patients and families were reluctant to participate in a placebo-controlled study where they would be required to stop the unlicensed medication and receive an inactive treatment for even 50% of the time
2. A single functional endpoint - like the 8 Meter Walk Test (8MWT) or 9 Hole Peg Test (9HPT) – would not be clinically relevant for each patient, due to the heterogeneity of these disorders
3. Traditional timed tests (e.g. 8MWT/ 9HPT-D) and broad symptom scales may not capture small, functionally relevant changes important to everyday life
4. As in all studies, there is a need to reduce bias and include a high degree of control to ensure the true treatment effect

Impact on Study Design

- Given the communities' legitimate concerns regarding placebo, to assure the feasibility of recruitment, an open-label study schema was used (Figure 1)
- Participants were assessed over three treatment periods: a baseline period, a 6-week treatment period, and a 6-week washout period, followed by a 2-year open-label extension phase

Figure 1: NALL Master Protocol Study Schema

Impact on Primary Efficacy Assessment

The Clinical Impression of Change in Severity (CI-CS) endpoint was created to address the remaining methodological considerations. The CI-CS incorporated novel elements, e.g.:

- Selecting a primary "anchor test" (either the 8MWT or 9HPT) based on each patient's unique symptoms
- Video recordings were made of the anchor tests at each visit
- Independent blinded raters assessing video pairs of each patient's anchor test (e.g. baseline video vs end-of-treatment video; end-of-treatment video vs. end-of-washout video) on a 7-point CGI-Esque likert scale

OBJECTIVES

- The orally-administered amino acid N-acetyl-L-leucine (NALL) had been shown in animal and observational clinical studies to be a novel, symptomatic and disease-modifying treatment for multiple rare and common neurological disorders [1] [2] [3]
- The industry sponsor (IntraBio Inc) set out to investigate NALL for multiple ultra-rare disorders – initially Niemann-Pick disease type C (NPC), GM2 Gangliosides (Tay-Sachs and Sandhoff, "GM2"), and Ataxia-Telangiectasia (A-T) – given their high unmet medical need
- Conscious of the unique ethical and practical challenges of conducting clinical trials for these orphan, heterogeneous patient populations, IntraBio collaborated with multinational patient advocacy organizations to design a single master protocol and novel primary endpoint to investigate NALL in three parallel trials (IB1001-201 [NCT03759639], Niemann-Pick disease type C (NPC); IB1001-202 [NCT03759665], GM2 Gangliosides (Tay-Sachs & Sandhoff, "GM2"); IB1001-203 [NCT03759678] Ataxia-Telangiectasia (A-T)) [4]
- The principal aims were:
  - Develop an innovative protocol that took into consideration the unique demographics of these ultra-rare disorders and was thus feasible to recruit and complete
  - Develop a novel primary endpoint which (i) ensured the primary outcome measure was clinically relevant for each patient; (ii) captured small, meaningful functional changes; (iii) introduced a high degree of control/ reduce bias.

RESULTS

Via the early and frequent collaboration, the IB1001 master protocol achieved the following:

1. Patients with serious, rapidly progressive, debilitating disorders were not required to be on a placebo
2. The novel primary CI-CS endpoint (assessed by blinded, independent raters), reduced detection and performance bias and allowed the post-treatment washout period to serve as a control arm
3. The novel CI-CS endpoint accounted for the heterogeneity of patients' symptoms, and ensured the assessment was clinically relevant for each patient – substantially increasing the probability of detecting a statistically significant, meaningful affect
4. Video review enabled raters to assess all functional aspects of a patient's performance as it relates to their everyday ability to complete a task

Two of the clinical trials (IB1001-201 for NPC and IB1001-202 for GM2) have been completed [5] [6]. In both studies, NALL met its primary CI-CS (Figure 2A &B) and secondary endpoints, demonstrating a statistically significant, and clinically meaningful treatment effect. NALL was well-tolerated, with no serious adverse reactions reported.

REFERENCES

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Figure 2: Clinical Impression of Change in Severity Results

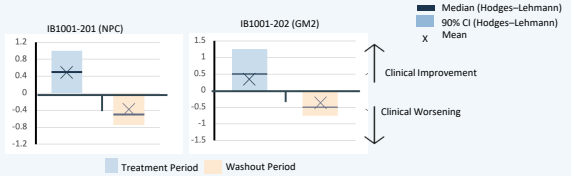

Figure 2: (A) Results from IB1001-201, NPC (B) Results from IB1001-202, GM2. In each Figure, the left-hand, blue panel compares the score for the end of treatment period versus end of baseline. The right-hand, orange panel compares the score for the end of washout period versus end of treatment. The vertical length of each column represents the 90% Hodges-Lehmann (HL) Confidence Interval of the CI-CS. Solid lines are used to denote the Hodges-Lehmann Median Estimator and cross symbols are used to denote the Mean response.

CONCLUSION

- Too frequently, rare disease clinical trials fail due to an inadequate study design that was not compatible with what can be reasonably asked of or achieved within the target rare disease patient population
- The lack of approved orphan drugs reflects this, and is evidence that traditional drug development – wherein Sponsors and Regulators design protocols with limited input from the target patient community –is failing rare disease patients (Figure 3A)
- By involving Patient Advocacy representatives as equal stakeholders in the development process, theses pitfalls can be navigated, and innovative clinical trial founded on a strong scientific rationale, and which take into account the demographics of the heterogenous, rare populations, can be developed (Figure 3B)
- The collaboration represents a model for orphan development, enabling trials to be conducted as efficiently as possible, and better ensuring a successful outcome
- These approaches are required to maximize the chance effective treatments can be made available to patients before the window of therapeutic opportunity is lost

Figure 3A - Traditional Approach

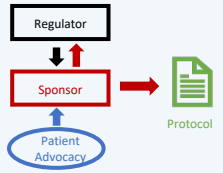

Figure 3B - Novel Approach