I AM ALS Patient-Centric Trial Design (PaCTD) Rating for Ionis' Ulefnersen

Research discoveries about ALS have been coming at a more rapid pace the last several years and at times these discoveries and advances require rethinking of clinical trial design. Our committee truly wants to encourage drug developers to leverage these discoveries and innovate trial design to move therapies through a quicker and more efficient approval process.

The Ionis trial, rated below, involving a drug that targets the FUS gene mutation is a case in point. Because the FUS mutation being targeted is very rare but also causes a particularly fast moving form of the disease, they have designed their trial differently. First inclusion criteria are particularly broad - almost no exclusions other than needing to have the mutation. Second, they offer free genetic testing so a person living with ALS can find out quickly whether they have the mutation. Finally they are running a combined Phase 1, 2, and 3 trial to move the treatment quickly towards approval.

By combining the three trial phases Ionis has the potential to accelerate the drug's development and thus benefit the whole ALS community. However this makes it extraordinarily difficult to offer an Expanded Access Program as they are just beginning to collect safety data. Our team, rather than reducing their rating for not having an EAP, has taken all of the above factors into account and after much debate we have removed Expanded Access as criteria when reviewing this trial.

Again we feel it is important in assigning ratings that we retain some ability to vary methodology to take into account scientific and trial design innovation as knowledge of the disease advances.

I AM ALS Patient-Centric Trial Design (PaCTD) **The meaning of patient centric is a combination of maximizing seats on the bus, making it easier for patients to participate and promoting trials that are likely to produce clear results allowing the approval process to start as opposed to just needing another trial.**		
Manufacturer: Ionis	NCT04768972	
Therapy: Ulefnersen		Rating
Open Label Extension Rating: 0 if not offered, .5 or 1 depending on if announced/implemented, how the OLE is structured, looking at length of time, amount of patient data collected that can help in the approval process, etc.	Offers OLE to all participants beginning in Phase 2 of the study for a period of between 2-5 years	1
Minimize placebo usage Rating: 0, .5 or 1 depending on how progressive design is. Are the odds of receiving placebo less than 50%? For example the Healy Platform trial only randomizes 25% of participants into the shared placebo control and received a score of 1. Traditional 50/50 randomization gets a 0 score.	2:1 placebo ratio	1

Expanded Access Program A side by side Intermediate (or larger) Rating: 0 if not offered, .25 proposed, .5 filed with FDA, .75 approved by FDA, 1 implemented. Other considerations: number of slots, time length and amount of patient data collected that can help in the approval process, or, once drug is approved, to help convince payors to cover all, policy posted on co. website	The novelty of this trial design takes away the ability to offer a "traditional" EAP and therefore a rating is not applicable at this time. Yet this innovative trial design, a combined Phase 1, 2 and 3 trial, potentially compresses the time frame needed for answers and maximizes access to active drug. The trial is currently only in the Phase 1 stage so safety data needs to be gathered and evaluated before an EAP can be offered.	N/A
Part 1 Total		2
Part 1 Rating-Seats at the Table		0.6
A trial is awarded a rating of 0-1.0 depending on whether it incorporates design elements that may increase the chance of producing definitive trial results and advance the science of clinical trials in ALS. The following list provides examples but is not exhaustive. - Consideration of disease heterogeneity such as using a predictive algorithm for trial inclusion or a crossover design - Investigation of potentially regulatory grade biomarkers such as neurofilament light or digital biomarkers such as accelerometers. - Independent unblinded review panel for interim efficacy check-ins if warranted	- Novel trial design - one study covering all Phases - 1, 2, 3 - Looking at biomarkers in serum & SVC - Free genetic testing available - Rescue option for fast progressors	1
Part 2 Total		1
Part 2 Rating-Advancing Science Quickly		0.3
Minimize Use of Run-In Observation Period and Washout Period – Rating: 0. .5, 1 depending how accommodative the trial with patient friendly features like no run in period	Minimal run-in period - 4 weeks	1
Use of novel methods: wearables, telemedicine visits, financial reimbursement Rating: 0, .5, 1 depending how accommodative the trial design is to patient participation such as use of patient friendly features like travel reimbursement for patient and caregiver, home collection of patient data during the trial.	- Broad eligibility criteria - Allows SOC therapy use - Travel assistance and reimbursement	1

Part 3 Total		2
Part 3 Rating-Patient-Friendly		0.1
Total Rating		1
x 5		5
I AM ALS PaCTD 5-Star Rating:		**5-Star**