I AM ALS Patient-Centric Trial Design (PaCTD) Rating for Denali Therapeutics' Healey Platform Regimen G

Manufacturer: Denali Therapeutics	**NCT05842941**	
Therapy: DNL343	**Healey Platform Regimen G**	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.	Committed to a 52 week minimum OLE (aka Active Treatment Extension)	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.	Following Healey Platform protocol ratio of 3:1 active to placebo	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	Awaiting additional safety and efficacy data before launching an Expanded Access (NOTE: if an Expanded Access Program is implemented this rating will be updated.)	0
Part 1 Total		2
Part 1 Rating-Seats at the Table		0.4
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	The Healey Platform trial design has several innovative aspects including: - Broad inclusion criteria including no upper age limit, symptoms onset of less than 36 mo, 3:1 placebo ratio - Looking at several biomarkers - NfL, ISR, TDP-43, GFAP	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 to allow for evaulation and testing	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.	Some visits are virtual, use of smart phone apps, remote lab tests	1
Part 3 Total		2
Part 3 Rating-Patient-Friendly		0.1
Total Rating		0.8
x 5		4
I AM ALS PaCTD 5-Star Rating:		**4-Star**

I AM ALS Patient Centric Trial Design (PaCTD)	Brainstorm NurOwn[1]	
Open Label Extension	No	0
Minimize placebo usage - 33% or less	No (50%)	0
A side by side Expanded Access Program	No	0
Part 1 Total		**0**
Part 1 Rating-Seats at the Table		**0**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Yes	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)	24 months from onset, no older than 60 years of age. Some were scientifically justified.	0.5
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of "efficacy" emerges before end of trial	No	0
Part 2 Total		**2.5**
Part 2 Rating-Advancing Science Quickly		**0.1875**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	Yes (3 months)	0
Use of novel methods: wearables, telemedicine visits, financial burden	Telemedicine visits through COVID-19.	0.5
Part 3 Total		**0.5**
Part 3 Rating-Patient-Friendly		**0**
Total Rating		**0.1875**
x5		**1.0625**
I AM ALS PaCTD 5-Star Rating:		**1-Star**

[1] Brainstorm's clinical trial design was created before the FDA updated its ALS clinical trial guidance in the Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry in September 2019.

I AM ALS Patient Centric Trial Design (PaCTD)	Orphazyme Arimoclomol[2]	
Open Label Extension	Yes-18 months	1
Minimize placebo usage - 33% or less	Yes (33%)	1
A side by side Expanded Access Program	No	0
Part 1 Total		**2**
Part 1 Rating-Seats at the Table		**0.4**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Yes	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)		1
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of "efficacy" emerges before end of trial	No	0
Part 2 Total		**3**
Part 2 Rating-Advancing Science Quickly		**0.225**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	No	1
Use of novel methods: wearables, telemedicine visits, financial burden	telemedicine visits, travel reimbursement, drug shipped to home, home nursing visits	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**0.725**
x5		**3.625**
I AM ALS PaCTD 5-Star Rating:		**4-Star**

[2] Orphazyme's clinical trial design was created before the FDA updated its ALS clinical trial guidance in the Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry in September 2019.

I AM ALS Patient Centric Trial Design (PaCTD)	Alexion Ultomiris	
Open Label Extension	Yes - 2 years	1
Minimize placebo usage - 33% or less	Yes (33%)	1
A side by side Expanded Access Program	No	0
Part 1 Total		**2**
Part 1 Rating-Seats at the Table		**0.4**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Subset Analysis & NFL	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)	No age restriction, symptom onset 36 months, Riluzole and Radicava fine	1
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of “efficacy” emerges before end of trial	No	0
Part 2 Total		**3**
Part 2 Rating-Advancing Science Quickly		**0.225**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	No	1
Use of novel methods: wearables, telemedicine visits, financial burden	telemedicine visits, travel reimbursement	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**0.725**
x5		**3.625**
I AM ALS PaCTD 5-Star Rating:		**4-Star**

I AM ALS Patient Centric Trial Design (PaCTD)	Biogen BIIB067 (SOD1)[3]	
Open Label Extension	Yes	1
Minimize placebo usage - 33% or less	Yes (33%)	1
A side by side Expanded Access Program	No	0
Part 1 Total		**2**
Part 1 Rating-Seats at the Table		**0.4**
Consideration of disease heterogeneity: e.g., Cross-Over design or Delayed Start Design	SOD1	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)		1
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of "efficacy" emerges before end of trial	No	0
Part 2 Total		**3**
Part 2 Rating-Advancing Science Quickly		**0.225**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	No	1
Use of novel methods: wearables, telemedicine visits, financial burden	telemedicine visits, state travel reimbursement	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**0.725**
x5		**3.625**
I AM ALS PaCTD 5-Star Rating:		**4-Star**

[3] Biogen's clinical trial design was created before the FDA updated its ALS clinical trial guidance in the Amyotrophic Lateral Sclerosis: Developing Drugs for Treatment Guidance for Industry in September 2019.

I AM ALS Patient Centric Trial Design (PaCTD) The HEALEY ALS Platform Trial tests multiple treatments in one trial. This listing will be updated if additional drugs are added to the trial.	**Platform Trial** **Clene Nanomedicine CNM-Au8** **Biohaven Pharmaceutical Holding Co Verdiperstat** **Ra Pharmaceuticals Zilucoplan**	
Open Label Extension	Yes - up to 1 year +	1
Minimize placebo usage - 33% or less	Yes (25%)	1
A side by side Expanded Access Program	CNM-Au8 - Yes Verdiperstat - Yes Zilucoplan - Pending[4]	1[5]
Part 1 Total	**3**	**3[6]**
Part 1 Rating-Seats at the Table	**0.6**	**0.6[7]**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Yes	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)	Yes (36 months from symptoms). No upper age limit.	1
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of “efficacy” emerges before end of trial	No	0
Part 2 Total	**3**	**3**
Part 2 Rating-Advancing Science Quickly	**0.225**	**0.225**
Use of Run-In Observation Period - 3 months not	No	1

[4] Ra Pharmaceuticals’ Zilucoplan Expanded Access Program is pending.
[5] Ra Pharmaceuticals’ Zilucoplan rating is 0 until the Expanded Access Program begins.
[6] Ra Pharmaceuticals’ Zilucoplan receives a 2 until the Expanded Access Program begins.
[7] Ra Pharmaceuticals’ Zilucoplan receives a 0.4 until the Expanded Access Program begins.

acceptable -1 month ideally		
Use of novel methods: wearables, telemedicine visits, financial reimbursement	Yes	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**0.925**[8]
x 5		**4.625**[9]
I AM ALS PaCTD 5-Star Rating:		**5-Star**[10]

[8] Ra Pharmaceuticals' Zilucoplan receives a 0.725 until the Expanded Access Program begins.
[9] Ra Pharmaceuticals' Zilucoplan receives a 3.625 until the Expanded Access Program begins.
[10] Ra Pharmaceuticals' Zilucoplan receives a 4-Star rating until the Expanded Access Program begins. A 5-Star rating is an average of the three drugs in the trial.

I AM ALS Patient-Centric Trial Design (PaCTD)	Duke University Theracurmin	
Open Label Extension	Yes - the whole trial is OLE	1
Minimize placebo usage - 33% or less	No placebo	1
A side by side Expanded Access Program		1
Part 1 Total		**3**
Part 1 Rating-Seats at the Table		**0.6**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Yes	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)	Yes	1
Investigation of biomarker	Yes - microbiome compared to healthy controls	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of “efficacy” emerges before end of trial		1
Part 2 Total		**4**
Part 2 Rating-Advancing Science Quickly		**0.3**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	No	1
Use of novel methods: wearables, telemedicine visits, financial burden	Yes	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**1**
x5		**5**
I AM ALS PaCTD 5-Star Rating:		**5-Star**

I AM ALS Patient-Centric Trial Design (PaCTD)	Apellis Pegcetacoplan	
Open Label Extension	Yes	1
Minimize placebo usage - 33% or less	33% placebo	1
A side by side Expanded Access Program	No	0
Part 1 Total		**2**
Part 1 Rating-Seats at the Table		**0.4**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Yes	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)	Yes	1
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of “efficacy” emerges before end of trial	No	0
Part 2 Total		**3**
Part 2 Rating-Advancing Science Quickly		**0.225**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	No	1
Use of novel methods: wearables, telemedicine visits, financial burden	Yes	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**0.725**
x5		**3.625**
I AM ALS PaCTD 5-Star Rating:		**4-Star**

I AM ALS Patient-Centric Trial Design (PaCTD)	Cytokinetics Courage Reldesemtiv	
Open Label Extension	Yes	1
Minimize placebo usage - 33% or less	33% placebo	1
A side by side Expanded Access Program	Enrolling 550 in COURAGE. All eligible for OLE + EAP participants in prior trials	1
Part 1 Total		**3**
Part 1 Rating-Seats at the Table		**0.6**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design	Yes; cross over	1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)	Yes; Two years from symptom onset. Vital capacity of 65%. ALS-FRS-R of 44 or less. Riluzole and Radicava are allowed	1
Investigation of biomarker	Yes; serum (blood), DNA, DME, muscle strength, PROs	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of “efficacy” emerges before end of trial	Yes; In the second interim analysis	1
Part 2 Total		**4**
Part 2 Rating-Advancing Science Quickly		**0.3**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	No	1
Use of novel methods: wearables, telemedicine visits, financial burden	Yes; Novel methods; telemedicine visits, mobile phone apps, home nursing visit: remote labs, spirometry	1
Part 3 Total		**2**
Part 3 Rating-Patient-Friendly		**0.1**
Total Rating		**1**
x5		**5**
I AM ALS PaCTD 5-Star Rating:		**5-Star**

I AM ALS Patient-Centric Trial Design (PaCTD)	AB Science Mastinib	
Open Label Extension		1
Minimize placebo usage - 33% or less	33% placebo	1
A side by side Expanded Access Program	No	0
Part 1 Total		**2**
Part 1 Rating-Seats at the Table		**0.4**
Consideration of disease heterogeneity: e.g., Cross-Over Design or Delayed Start Design		1
Use of scientifically supportable inclusion criteria, pre-defined subset analysis, re-randomization at trial conclusion to equalize outlier progressors between trial arms, or alternative controls (historical, algorithmic etc.)		1
Investigation of biomarker	Yes	1
Independent Unblinded Review Panel that can communicate with FDA where substantial proof of “efficacy” emerges before end of trial	No	0
Part 2 Total		**3**
Part 2 Rating-Advancing Science Quickly		**0.225**
Use of Run-In Observation Period - 3 months not acceptable -1 month ideally	12 week run-in	0
Use of novel methods: wearables, telemedicine visits, financial burden	Taxi reimbursement	0
Part 3 Total		**0**
Part 3 Rating-Patient-Friendly		**0**
Total Rating		**0.625**
x5		**3.125**
I AM ALS PaCTD 5-Star Rating:		**3-Star**