A Planned Phase 3, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of Pridopidine in Participants with ALS

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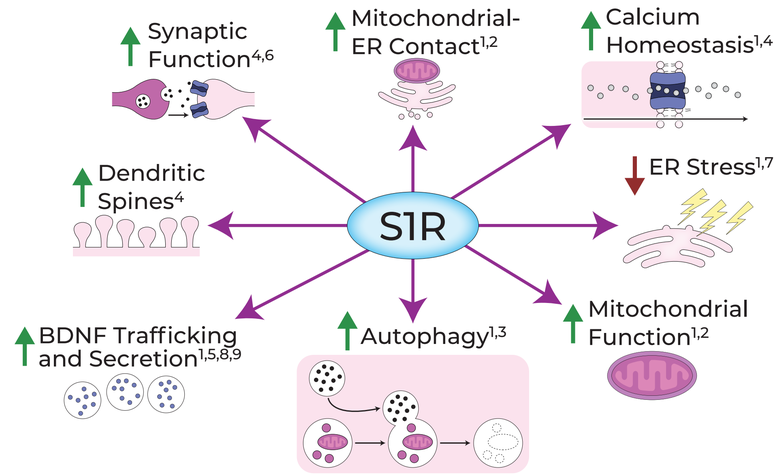
Introduction

- Pridopidine is an investigational small molecule in clinical development for ALS and Huntington's Disease (HD)
  - It is a selective and potent sigma-1 receptor (S1R) agonist
- Compelling preclinical evidence demonstrates S1R-mediated neuroprotective effects of pridopidine in *in vitro* and in *in vivo* models of neurodegeneration
- Orally-administered pridopidine 45 mg bid was evaluated in the HEALEY ALS Platform Trial
  - Within the full study population, no benefit was observed in primary and secondary endpoints as compared to placebo
  - In a subgroup of patients with more rapidly progressing disease, definite or probable ALS by El Escorial Criteria (EEC) and <18 months from symptom onset, pridopidine showed benefits versus placebo in multiple clinical endpoints
- The safety and tolerability profile of pridopidine was comparable to placebo
- These data inform the design of an upcoming global phase 3 trial which will further evaluate pridopidine's efficacy and safety in this patient population

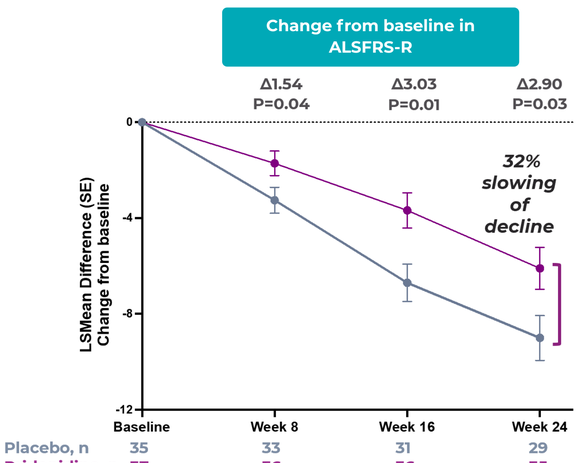
Activation of the S1R by pridopidine positively influences multiple neuroprotective pathways

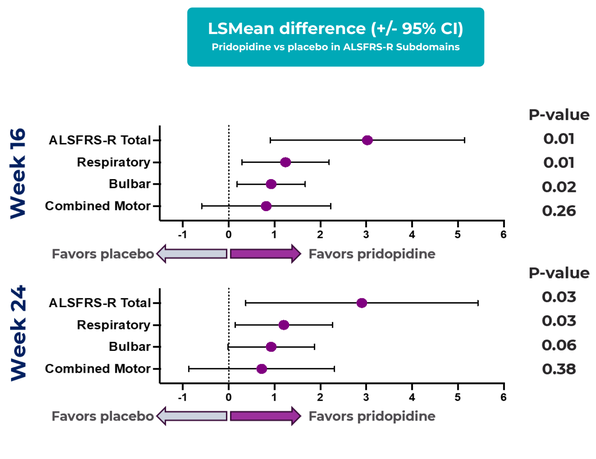


1. Adapted from Aishwarya et al., Front Physiol. 2021; 12:705575, 2. Naia et al, 2021 Neurotherapeutics 18(2):1017-1038, 3. Wang et al., Autophagy. 2022 4:1-26, 4. Ryskamp et al., Neurobiol Dis. 2017; 97:46-59, 5. Geva et al., Hum Mol Genet. 2016 25(18):3975-3987, 6. Francardo et al., Neurotherapeutics. 2019 Apr; 16(2): 465–479 7. Shenkman et al., J Neurochem 2021 Jul;158(2):467-481; 8. Lenoir et al., Neurobiol Dis. 2022 Oct 15:173:105857; 9. Ionescu et al., Cell Death Dis. 2019 Mar 1;10(3):210

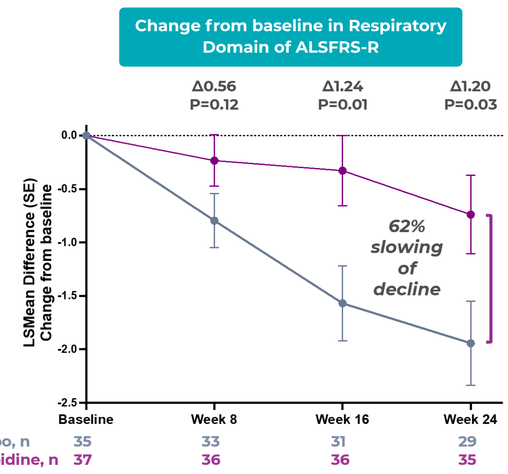
Post hoc analysis of definite, probable & early (<18 months) subgroup

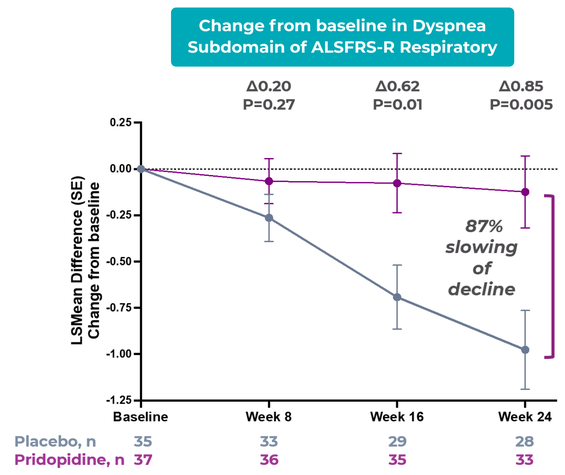
Pridopidine slows disease progression as measured by ALSFRS-R by 32% at week 24; all domains contribute





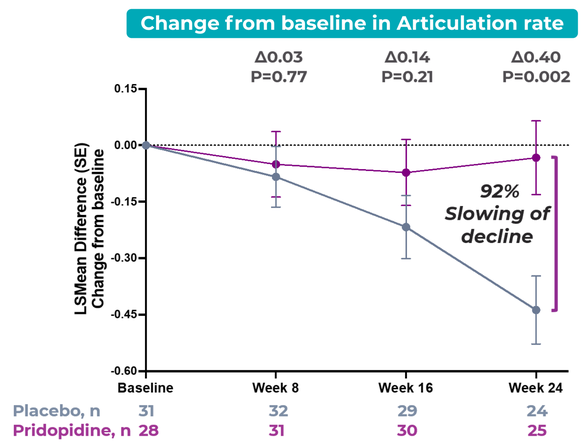
Pridopidine slows decline in Respiration and Dyspnea as measured by ALSFRS-R domains through 24 weeks

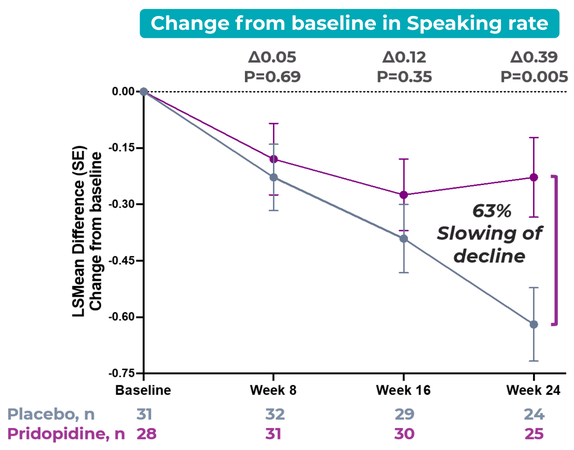




ALSFRS-R: Revised Amyotrophic Lateral Sclerosis Functional Rating Scale

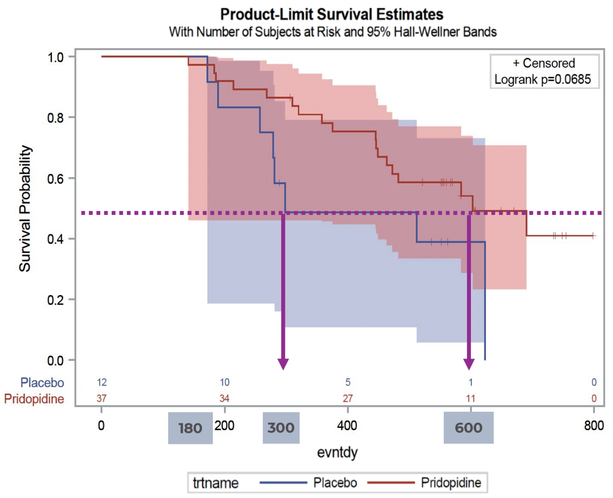
Pridopidine demonstrates robust slowing of decline in Articulation and Speaking rate through 24 weeks





Analysis includes only patients who had recorded speech data (available data only)

Survival analysis shows potential survival benefit with pridopidine



- Kaplan-Meier curves show separation starting from ~6 months (180 days), (log rank test: p=0.069)
- ~At approximately 300 days (~10 months) post first dose, pridopidine showed a survival probability of ~85% compared to ~50% survival probability for placebo
- Time to 50% survival probability was substantially longer in pridopidine group (~300 vs 600 days)

Time-to-event outcomes
Log-rank test
Focal regimen: RGD, Analysis set: Definite or Probable, <18mo Since Symptom Onset
Outcome measure: Death alone (OmniTrace 06/2023)

Placebo=12, pridopidine=37 (placebo from Healey RGD)

All p-values are nominal; Cudkowicz, M. AAN Annual meeting, April 6-9, 2025, San Diego, CA

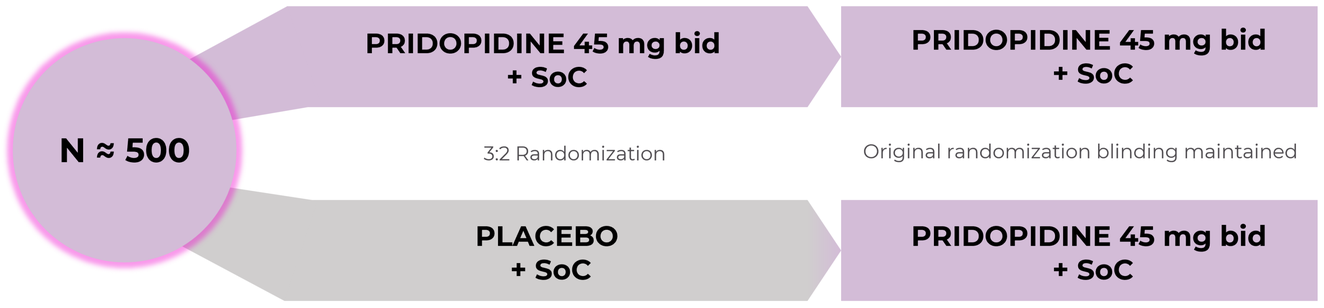
A Phase 3 Global, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Pridopidine in Participants with ALS

Key Inclusion Criteria

- Age 18 to 80
- Definite or Probable ALS by EEC
- <18 months from symptom onset
- TRICALS Risk Profile -6 < to < -2
- Able to swallow a capsule
- On stable dose of SoC (>4 weeks)

Key Exclusion Criteria

- Presence of tracheostomy or permanent assisted ventilation
- Slow Vital Capacity (SVC) < 60%
- Nuedexta or DM/Q at doses above 20 mg DXM + 10 mg quinidine bid
- Clinically significant unstable medical condition



Primary objective: To evaluate the effect of pridopidine on disease progression in patients with ALS

Primary endpoint
- Change from baseline in ALSFRS-R, adjusted for mortality

Safety

Plasma biomarkers

Secondary endpoints
- Survival
- Motor features & composite measures of speech
- Respiratory function (SVC)
- Bulbar function as assessed by the bulbar subdomain of the ALSFRS-R
- Quality of Life (ALSAQ-40)

Exploratory
- Patient-reported outcome measures (Communicative Participation Item Bank [CPIB], Center for Neurologic Study Lability Scale [CNS-LS], EQ-5D-5L)

TRICALS The highway towards a cure

NEALS

DM/Q: dextromethorphan/quinidine; DXM: dextromethorphan; SoC - Standard of Care, may include riluzole, edaravone and other ALS medications

Conclusions

- The HEALEY ALS Platform Trial demonstrated potential benefit of pridopidine on ALS progression in a subgroup of rapidly progressing patients early in the disease [Definite or Probable by EEC and Early (< 18 months from symptom onset)] :
  - *Post hoc* analyses show significant benefits for ALSFRS-R total score, ALSFRS-R respiratory, bulbar and quantitative speech characteristics
  - *Post hoc* survival analysis shows potential survival benefit
- No new safety signals were identified
- A homogenous, rapidly progressing population is planned to be enrolled in a global, multi-center Phase 3 trial to determine a therapeutic effect within the limited timeframe of clinical trial
- Based on pridopidine's mechanism of action, it is anticipated that trial results could be extrapolatable to the broader population of people living with ALS

FERRER & PRILENIA are partners in co-development and commercialization of pridopidine for Europe and other select markets*
* Middle East and North African Region, the Southern African Region, the Central and South American Region, and the Commonwealth of Independent States Region

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