Pridopidine in Huntington Disease

Pridopidine is currently in development for Huntington disease (HD). Multiple clinical studies have been conducted providing important understanding about safety, mechanism of action, and efficacy. HD is a rare, inherited, chronically progressive and ultimately fatal brain disease. The disease typically starts between the ages of 30 to 50, and causes loss of physical, mental, and emotional abilities. Key symptoms of HD include:

- Personality changes, mood swings, and depression (including increased suicidal ideation),
- Forgetfulness and impaired judgment,
- Unsteady gait and involuntary movements (chorea), and
- Slurred speech, difficulty in swallowing, and significant weight loss

Originally, pridopidine was thought to exert its effects by modifying dopamine signaling through dopamine receptors. Dopamine is a chemical (neurotransmitter) produced in the brain important for regulating movement. Therefore, prior trials with pridopidine in HD were designed to assess primarily the effect of pridopidine on motor symptoms (like slow and/or abnormal movements).

The PRIDE-HD study was originally designed as a 26-week, phase 2, randomized, placebo-controlled clinical trial evaluating four different doses (between 45.0–112.5 mg twice a day) of pridopidine for the treatment of Huntington disease. The four different and increasing doses were planned because for dopamine modulators, higher doses were expected to be more efficacious. While the PRIDE-HD trial was ongoing, new research showed that the effect of pridopidine was not mediated by the dopamine receptor but rather via activation of the Sigma-1 receptor (S1R).

The S1R is a protein expressed at high levels in the brain and in motor neurons of the spinal cord. Activation of S1R upregulates numerous cellular functions that are important for cell health and survival. The understanding that the primary target of pridopidine was the S1R suggested the original design of the PRIDE-HD clinical trial might not have been optimal. With the understanding that pridopidine was activating the S1R (and not dopamine), the trial was extended from 26 weeks to 52 weeks, because the investigators wanted to evaluate pridopidine's effect on loss of functional capacity with progressive disease. In HD, a minimum of 52 weeks is needed to evaluate an effect on progressive loss of function.

In PRIDE-HD, participants on pridopidine did show improvement in their motor symptoms compared to baseline. However, the study did not meet its primary composite endpoint at 26 weeks (as assessed by comparing the active drug and placebo groups) due to an unprecedented strong and sustained placebo effect.

Upon completion of the extended PRIDE-HD study, investigators performed additional analyses and showed that a dose of 45mg of pridopidine twice a day (the dose currently being tested in the ALS study) had a significant beneficial effect after 52 weeks on the Total Functional Capacity (TFC) scale (McGarry et al, JHD 2020). The 13-point TFC scale is widely used and accepted as a clinically meaningful outcome measure in HD assessing the global level of function (i.e. the additive effects of all symptoms [e.g. motor, cognitive and behavioral] on the performance of subjects in everyday life settings). The TFC scale assesses an individual's capacity to work, handle finances, and perform domestic chores and self-care tasks.

To date, there has been no other treatment besides pridopidine that has shown a positive effect on TFC in HD. Perhaps even more impressively, additional analysis showed that the beneficial effects of 45mg pridopidine twice a day on TFC were maintained over 5 years in PRIDE-HD

participants followed in an Open-Label study (Open-HART, McGarry et al, JHD 2020). Participants who received pridopidine showed significantly slower decline in the TFC scale over 5 years compared with historical controls.

Importantly, extensive safety data in >1300 patients accumulating more than 1000 patient-years of drug exposure showed the pridopidine dose of 45mg twice-a-day to be safe and tolerable, with a side effect profile comparable to that of placebo. The most common treatment-related side effects reported across all pridopidine clinical studies were insomnia, diarrhea, nausea, and dizziness. Serious Adverse Events (SAEs) were analyzed in an integrated safety database of 22 clinical trials with pridopidine. The only "commonly reported" SAE (i.e. seen in at least 1 participant out of 200) in the pridopidine group that was considered possibly related to study drug, was bleeding in the protective layers surrounding the brain (seen in 6/981 participants of which 1 case was considered possibly related to study drug). This event was associated with a patient falling and hitting their head. The overall occurrence of any SAEs in pridopidine studies is low, and most are characteristic of patients with HD.

Pridopidine was selected for inclusion in the Healey Master Platform trial given the genetic link to disease, compelling preclinical data in models of ALS and HD, demonstration of potential clinical efficacy in HD patients, and the strong safety profile of the drug. Since that time, the pridopidine ALS trial design has been reviewed and approved by the FDA, the central Institutional Review Board for the Healey platform, and leading ALS clinicians. In addition, a global Phase III study in Huntington disease is currently ongoing testing the effect of pridopidine on functional progression. This study is testing the same dose as will be used in the ALS clinical trial.