Safety and efficacy of pridopidine in patients with Huntington's disease (PRIDE-HD): a phase 2, randomised, placebo-controlled, multicentre, dose-ranging study

Titre	Safety and efficacy of pridopidine in patients with Huntington's disease (PRIDE-HD): a phase 2, randomised, placebo-controlled, multicentre, dose-ranging study
Type de publication	Article de revue
Auteur	Reilmann, Ralf [1], McGarry, Andrew [2], Grachev, Igor D [3], Savola, Juha-Matti [4], Borowsky, Beth [5], Eyal, Eli [6], Gross, Nicholas [7], Langbehn, Douglas [8], Schubert, Robin [9], Wickenberg, Anna Teige [10], Papapetropoulos, Spyros [11], Hayden, Michael [12], Squitieri, Ferdinando [13], Kieburtz, Karl [14], Landwehrmeyer, Bernhard G [15]
Organisme	European Huntington's Disease Network, [16], Huntington Study Group investigators [17]
Editeur	Elsevier
Type	Article scientifique dans une revue à comité de lecture
Année	2019
Langue	Anglais
Date	Février 2019
Pagination	165-176
Volume	18
Titre de la revue	Lancet Neurology
ISSN	1474-4465

Résumé en anglais	BACKGROUND: Previous trials have shown that pridopidine might reduce motor impairment in patients with Huntington's disease. The aim of this study was to ascertain whether higher doses of pridopidine than previously tested reduce motor symptoms in a dose-dependent manner while maintaining acceptable safety and tolerability. METHODS: PRIDE-HD was a randomised, placebo-controlled, phase 2, dose-ranging study in adults (aged ≥21 years) with Huntington's disease at outpatient clinics in 53 sites across 12 countries (Australia, Austria, Canada, Denmark, France, Germany, Italy, Poland, Russia, the Netherlands, the UK, and the USA). Eligible patients had clinical onset after age 18 years, 36 or more cytosine-adenine-guanine repeats in the huntingtin gene, motor symptoms (Unified Huntington's Disease Rating Scale total motor score [UHDRS-TMS] ≥25 points), and reduced independence (UHDRS independence score ≤90%). Patients were randomly assigned (1:1:1:1:1) with centralised interactive-response technology to receive one of four doses of pridopidine (45, 67·5, 90, or 112·5 mg) or placebo orally twice a day for 52 weeks. Randomisation was stratified within centres by neuroleptic drug use. The primary efficacy endpoint was change in the UHDRS-TMS from baseline to 26 weeks, which was assessed in all randomised patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment (full analysis set). Participants and investigators were masked to treatment assignment. This trial is registered with EudraCT (2013-001888-23) and ClinicalTrials.gov (NCT02006472). FINDINGS: Between Feb 13, 2014, and July 5, 2016, 408 patients were enrolled and randomly assigned to receive placebo (n=82) or pridopidine 45 mg (n=81), 67·5 mg (n=82), 90 mg (n=81), or 112·5 mg (n=82) twice daily for 26 weeks. The full analysis set included 397 patients (81 in the placebo group, 75 in the 45 mg group, 79 in the 67·5 mg group, 81 in the 90 mg group, and 81 in the 112·5 mg group). Pridopidine did not significantly change the UHDRS-TMS at 26 weeks compared with placebo at any dose. The most frequent adverse events across all groups were diarrhoea, vomiting, nasopharyngitis, falls, headache, insomnia, and anxiety. The most common treatment-related adverse events were insomnia, diarrhoea, nausea, and dizziness. Serious adverse events occurred in the pridopidine groups only and were most frequently falls (n=5), suicide attempt (n=4), suicidal ideation (n=3), head injury (n=3), and aspiration pneumonia (n=3). No new safety or tolerability concerns emerged in this study. One death in the pridopidine 112·5 mg group due to aspiration pneumonia was considered to be possibly related to the study drug. INTERPRETATION: Pridopidine did not improve the UHDRS-TMS at week 26 compared with placebo and, thus, the results of secondary or tertiary analyses in previous trials were not replicated. A potentially strong placebo effect needs to be ruled out in future studies. FUNDING: Teva Pharmaceutical Industries.
URL de la notice	http://okina.univ-angers.fr/publications/ua18983 [18]
DOI	10.1016/S1474-4422(18)30391-0 [19]
Lien vers le document	https://www.thelancet.com/journals/laneur/article/PIIS1474-4422[20](18)30391-0/fulltext
Titre abrégé	Lancet Neurol
Identifiant (ID) PubMed	30563778 [21]

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