Supplementary Information

Article Title:
The Safety Profile of Pridopidine, a Novel Sigma-1 Receptor Agonist for the Treatment of Huntington's Disease

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Supplementary Table 1: Overview of Related TEAEs in the Safety Population – Subgroup Analysis by Intrinsic and Extrinsic Factors

Subgroup	Subgroup Cutoffs	Number of Patients in Each Subgroup		Number of Patients with At Least One TEAE n, (%)					
		(out of total N=533 in Safety Group)	(out of total N=534 in Safety Group)	Related TEAEs		Related Serious TEAEs		Related TEAEs Leading to Discontinuation from Treatment	
		Placebo	Pridopidine 45 mg bid	Placebo	Pridopidine 45 mg bid	Placebo	Pridopidine 45 mg bid	Placebo	Pridopidine 45 mg bid
Intrinsic Factors									
Age	<54 years	n=299	n=290	106 (35.5)	94 (32.4)	6 (2.0)	1 (0.3)	17 (5.7)	15 (5.2)
	≥54 years	n=234	n=244	61 (26.1)	83 (34.0)	1 (0.4)	3 (1.2)	9 (3.8)	18 (7.4)
Sex	Female	n=276	n=264	88 (31.9)	86 (32.6)	3 (1.1)	0	11 (4.0)	15 (5.7)
	Male	n=257	n=270	79 (30.7)	91 (33.7)	4 (1.6)	4 (1.5)	15 (5.8)	18 (6.7)
Baseline TFC score	7-13	n=448	n=449	135 (30.1)	140 (31.2)	3 (0.7)	3 (0.7)	20 (4.5)	26 (5.8)
	0-6	n=85	n=85	32 (37.6)	37 (43.5)	4 (4.7)	1 (1.2)	6 (7.1)	7 (8.2)
CAG repeat length	<45 repeats	n=310	n=303	90 (29.0)	103 (34.0)	4 (1.3)	4 (1.3)	15 (4.8)	21 (6.9)
	≥45 repeats	n=172	n=189	60 (34.9)	51 (27.0)	2 (1.2)	0	9 (5.2)	7 (3.7)
Extrinsic Factors									
ADM usage	On ADMs at any time	n=238	n=243	73 (30.7)	76 (31.3)	7 (2.9)	3 (1.2)	14 (5.9)	9 (3.7)
	Off ADMs all the time	n=295	n=291	94 (31.9)	101 (34.7)	0	1 (0.3)	12 (4.1)	24 (8.2)

Subgroup	Subgroup Cutoffs	Number of Patients in Each Subgroup		Number of Patients with At Least One TEAE n, (%)					
		(out of total N=533 in Safety Group)	(out of total N=534 in Safety Group)	Related TEAEs		Related Serious TEAEs		Related TEAEs Leading to Discontinuation from Treatment	
		Placebo	Pridopidine 45 mg bid	Placebo	Pridopidine 45 mg bid	Placebo	Pridopidine 45 mg bid	Placebo	Pridopidine 45 mg bid
Region	North America	n=188	n=195	54 (23.9)	63 (32.3)	0	0	15 (5.8)	18 (6.7)
	Europe	n=344	n=336	122 (35.5)	114 (33.9)	7 (2.0)	4 (1.2)	16 (4.7)	22 (6.5)

ADM: antidopaminergic medication;
TEAE: treatment-emergent adverse event;
TFC: total functional capacity;
bid: twice daily;
CAG: cytosine-adenine-guanine.

Supplementary Table 2: Overview of HD Patients Receiving Pridopidine 45 mg bid Who Died During the Double-Blind and Open-Label Clinical Studies

Study Name and Number	Cause of death (MedDRA Preferred Term)	Study Day - Start of SAE	Study Day - Death	Relation to study drug
Double-Blind, Placebo-Controlled Studies				
PROOF-HD (PL101-HD301)	Pneumonia	494	526	Unrelated
PROOF-HD (PL101-HD301)	Death	491	491	Unrelated
PROOF-HD (PL101-HD301)	Head injury	342	342	Unrelated
MermaiHD (ACR16C008)	Subarachnoid haemorrhage	35	35	Unlikely
Open-Label Extension Studies				
Open PRIDE-HD (TV7820-CNS-20016)	Cachexia	527	527	Unrelated
Open PRIDE-HD (TV7820-CNS-20016)	Toxicity to various agents	237	237	Unrelated
Open PRIDE-HD (TV7820-CNS-20016)	Anaemia	448	467	Unrelated
MermaiHD-OLP (ACR16C008-OLP)	Completed suicide	362	362	Unlikely
Open-HART (ACR16C015)	Multiple myeloma	1568	1686	Unrelated
Open-HART (ACR16C015)	Pneumonia Aspiration; Respiratory failure	2366	2369	Unrelated
Open-HART (ACR16C015)	Arteriosclerosis coronary artery; cardiac failure congestive, myocardial infarction	342	342	Unrelated
Open-HART (ACR16C015)	Pneumonia aspiration	149	161	Unrelated
Open-HART (ACR16C015)	Starvation	240	263	Unrelated
Open-HART (ACR16C015)	Pneumonia aspiration	455	480	Unrelated

Study Name and Number	Cause of death (MedDRA Preferred Term)	Study Day - Start of SAE	Study Day - Death	Relation to study drug
Open-HART (ACR16C015)	Endocarditis	327	336	Unrelated
Open-HART (ACR16C015)	Completed suicide	1527	1527	Unrelated

In addition, in the PROOF-HD study, one patient in the pridopidine 45 mg bid group died of a cardiac arrest (deemed unrelated) 384 days after being off study drug since Day 56, following elective heart surgery for aortic insufficiency which was diagnosed on Day 2.

ADM: antidopaminergic medication
TEAE: treatment-emergent adverse event
TFC: total functional capacity
bid: twice daily
CAG: cytosine-adenine-guanine
MedDRA: Medical Dictionary for Regulatory Activities
SAE: serious adverse event
OLP: open-label phase
PROOF-HD: Pridopidine Outcome on Function in Huntington's Disease
Open-HART: Open-label extension of Huntington's Disease trials
MermaiHD: Multicenter study of Pridopidine in Huntington's Disease