

SUPPLEMENTARY MATERIALS

Title:

Pridopidine does not significantly prolong the QTc interval at the clinically relevant therapeutic dose

Authors

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Table S1: ECG and Cardiac-related Exclusion Criteria in HART, MermaiHD and PRIDE-HD

Exclusion criteria	HART	MermaiHD	PRIDE-HD
Prolonged QT interval at screening	QTc interval of > 450 msec for males or > 470 msec for females	QTc interval of > 450 msec for males or > 470 msec for females	QTcF of >450 msec for males or females
Patients with clinically significant heart disease at the screening visit	Clinically significant heart conditions as judged by the investigator	Clinically significant heart conditions as judged by the investigator	Significant cardiac event (eg, myocardial infarction), angina pectoris, or episode of congestive heart failure or presence of cardiac disease that in the opinion of the investigator increased the risk of ventricular arrhythmia, History of arrhythmia that was symptomatic or required treatment, symptomatic or uncontrolled atrial fibrillation despite treatment, or asymptomatic sustained ventricular tachycardia, Presence of left bundle branch block. Known history of long QT syndrome or a first degree relative with this condition.
Co-medications with proven to prolong QT interval	Prohibited	Prohibited	Prohibited

msec=milliseconds.

Table S2: Changes from Baseline in Heart Rate (Δ HR, bpm) (PRIDE-HD)

Treatment/Dose	Visit	Time	N	Mean	SD	90% Confidence Interval	
Placebo	Baseline	Post-Dose	82	1.6	8.63	0.0	3.2
	Week 2	Pre-Dose	78	1.9	7.85	0.4	3.4
		Post-Dose	81	0.6	9.99	-1.2	2.5
	Week 4	Pre-Dose	81	0.3	7.47	-1.0	1.7
		Post-Dose	81	0.3	9.00	-1.4	1.9
	Week 6	Pre-Dose	80	1.2	9.43	-0.5	3.0
		Post-Dose	80	0.9	9.39	-0.8	2.7
	Week 12	Pre-Dose	77	-0.7	8.43	-2.3	0.9
		Post-Dose	75	-0.1	9.66	-1.9	1.8
	Week 16	Pre-Dose	72	1.3	9.74	-0.7	3.2
		Post-Dose	72	0.5	9.49	-1.4	2.4
	Week 20	Pre-Dose	71	0.3	8.98	-1.4	2.1
		Post-Dose	71	1.2	9.47	-0.6	3.1
	Week 26	Pre-Dose	70	0.9	9.01	-0.9	2.7
	Week 39	Pre-Dose	55	2.5	7.96	0.7	4.3
	Week 52	Pre-Dose	52	1.7	10.05	-0.7	4.0
Pridopidine 45 mg bid	Baseline	Post-Dose	81	3.7	8.27	2.1	5.2
	Week 2	Pre-Dose	76	2.6	7.58	1.2	4.1
		Post-Dose	76	2.5	9.69	0.7	4.4
	Week 4	Pre-Dose	73	-0.2	8.31	-1.8	1.5
		Post-Dose	73	3.0	8.35	1.4	4.7
	Week 6	Pre-Dose	71	2.2	6.89	0.8	3.6
		Post-Dose	69	3.7	8.34	2.0	5.3
	Week 12	Pre-Dose	68	2.2	7.55	0.6	3.7
		Post-Dose	65	3.5	7.97	1.9	5.2
	Week 16	Pre-Dose	65	2.5	7.89	0.9	4.2
		Post-Dose	63	3.3	8.37	1.6	5.1
	Week 20	Pre-Dose	63	2.6	8.79	0.7	4.4
		Post-Dose	63	4.3	9.60	2.2	6.3
	Week 26	Pre-Dose	62	1.3	8.33	-0.5	3.1
	Week 39	Pre-Dose	49	2.4	8.97	0.2	4.5
	Week 52	Pre-Dose	44	1.0	7.07	-0.8	2.8

Treatment/Dose	Visit	Time	N	Mean	SD	90% Confidence Interval	
Pridopidine 67.5 mg bid	Baseline	Post-Dose	77	3.3	7.35	1.9	4.7
	Week 2	Pre-Dose	71	2.8	9.18	0.9	4.6
		Post-Dose	74	3.4	8.08	1.8	5.0
	Week 4	Pre-Dose	73	3.1	7.33	1.6	4.5
		Post-Dose	72	5.9	8.95	4.2	7.7
	Week 6	Pre-Dose	69	5.5	9.54	3.6	7.4
		Post-Dose	67	5.4	11.61	3.0	7.7
	Week 12	Pre-Dose	65	4.3	9.92	2.3	6.4
		Post-Dose	64	5.1	9.52	3.1	7.1
	Week 16	Pre-Dose	63	6.5	8.57	4.7	8.3
		Post-Dose	63	8.0	9.57	6.0	10.0
	Week 20	Pre-Dose	62	6.1	9.25	4.1	8.1
		Post-Dose	62	7.2	9.65	5.1	9.2
Pridopidine 90 mg bid	Week 26	Pre-Dose	62	4.4	8.67	2.5	6.2
	Week 39	Pre-Dose	46	5.2	10.88	2.5	7.9
	Week 52	Pre-Dose	41	4.1	11.21	1.1	7.0
	Baseline	Post-Dose	80	1.7	8.32	0.1	3.2
	Week 2	Pre-Dose	73	3.7	7.12	2.3	5.1
		Post-Dose	77	4.1	8.05	2.6	5.7
	Week 4	Pre-Dose	78	2.8	7.32	1.5	4.2
		Post-Dose	78	4.7	8.39	3.1	6.2
	Week 6	Pre-Dose	77	4.5	7.03	3.1	5.8
		Post-Dose	77	6.1	8.80	4.4	7.8
	Week 12	Pre-Dose	71	2.6	7.67	1.1	4.1
		Post-Dose	71	4.2	9.41	2.3	6.1
	Week 16	Pre-Dose	68	3.6	7.39	2.1	5.1
		Post-Dose	69	5.4	8.39	3.7	7.0
	Week 20	Pre-Dose	67	6.0	8.13	4.3	7.7
		Post-Dose	67	5.8	8.50	4.1	7.5
	Week 26	Pre-Dose	64	4.4	8.10	2.7	6.1
	Week 39	Pre-Dose	54	4.4	8.71	2.4	6.4
	Week 52	Pre-Dose	53	3.6	9.99	1.3	5.9
	Baseline	Post-Dose	79	5.1	8.63	3.5	6.7

Treatment/Dose	Visit	Time	N	Mean	SD	90% Confidence Interval	
Pridopidine 112.5 mg bid	Week 2	Pre-Dose	72	6.6	8.54	5.0	8.3
		Post-Dose	77	7.2	9.41	5.4	9.0
	Week 4	Pre-Dose	77	6.0	8.55	4.4	7.6
		Post-Dose	77	9.9	10.66	7.9	11.9
	Week 6	Pre-Dose	73	7.7	9.36	5.9	9.6
		Post-Dose	70	8.6	10.10	6.6	10.6
	Week 12	Pre-Dose	67	6.3	9.79	4.4	8.3
		Post-Dose	66	8.4	11.05	6.2	10.7
	Week 16	Pre-Dose	66	7.5	9.07	5.6	9.4
		Post-Dose	66	9.5	9.54	7.5	11.5
	Week 20	Pre-Dose	64	6.7	9.40	4.7	8.6
		Post-Dose	64	9.6	10.38	7.5	11.8
	Week 26	Pre-Dose	62	5.2	9.56	3.2	7.2
	Week 39	Pre-Dose	44	5.4	9.73	3.0	7.9
	Week 52	Pre-Dose	43	2.3	9.95	-0.2	4.9

Based on descriptive statistics

bid=twice-daily; bpm=beats per minute; LOV=last observed value; SD=standard deviation.

Table S3: PRIDE-HD – Pridopidine Plasma Concentrations by Dose Group and Visit

Treatment/Dose	Time	Visit	N	Mean	SD	90% Confidence Interval	
Pridopidine 45 mg bid	Pre-Dose	Baseline	79	0	0	0	0
		Week 4	51	237	120	209	265
		Week 6	60	554	235	504	605
		Week 16	48	524	231	468	580
		Week 26	45	506	231	449	564
		Week 52	30	432	219	364	500
	Post-Dose	Baseline	75	87	61	75	99
		Week 2	76	304	142	276	331
		Week 4	66	382	167	348	417
		Week 6	61	666	287	604	727
		Week 12	60	699	250	645	753
		Week 16	59	637	258	581	693
		Week 20	57	653	279	591	715
Pridopidine 67.5 mg bid	Pre-Dose	Baseline	78	0	0	0	0
		Week 4	54	604	215	555	653
		Week 6	62	852	267	795	908
		Week 16	53	892	338	814	970
		Week 26	46	794	420	690	898
		Week 52	26	639	285	543	734
	Post-Dose	Baseline	74	110	65	98	123
		Week 2	73	405	160	374	437
		Week 4	67	866	283	809	924
		Week 6	66	1091	316	1026	1156
		Week 12	64	1061	366	985	1137
		Week 16	61	1130	410	1042	1218
		Week 20	60	1020	328	949	1091
Pridopidine 90 mg bid	Pre-Dose	Baseline	80	0	0	0	0
		Week 4	55	821	337	745	897
		Week 6	68	1057	414	973	1140
		Week 16	57	1166	497	1056	1276
		Week 26	52	1093	468	984	1202
		Week 52	44	920	423	813	1027

	Post-Dose	Baseline	77	103	52	94	113
		Week 2	75	806	308	746	865
		Week 4	74	1085	411	1005	1164
		Week 6	75	1377	418	1297	1458
		Week 12	69	1364	492	1265	1463
		Week 16	65	1435	536	1324	1546
		Week 20	63	1461	514	1353	1569
Pridopidine 112.5 mg bid	Pre-Dose	Baseline	78	0	0	0	0
		Week 4	51	1273	506	1155	1392
		Week 6	62	1416	569	1295	1537
		Week 16	55	1495	576	1365	1625
		Week 26	46	1366	609	1215	1517
		Week 52	33	1195	633	1008	1382
	Post-Dose	Baseline	75	94	62	82	106
		Week 2	72	773	399	695	851
		Week 4	72	1553	537	1448	1659
		Week 6	66	1715	665	1578	1851
		Week 12	62	1636	664	1495	1776
		Week 16	64	1760	674	1620	1901
		Week 20	60	1757	719	1602	1912

Values are presented as ng/mL; mean $\pm$ standard deviation (SD).

Table S4: QTc Interval (msec) by Dose Group and Timepoint (PRIDE-HD)

Treatment/Dose	Visit	Time	N	Mean	SD	90% Confidence Interval	
Placebo	Baseline	Pre-Dose	82	408.1	13.41	405.7	410.6
		Post- Dose	82	408.4	14.67	405.7	411.1
	Week 2	Pre-Dose	78	406.4	13.35	403.8	408.9
		Post- Dose	81	409	14.5	406.3	411.6
	Week 4	Pre-Dose	81	408	13.88	405.4	410.6
		Post- Dose	81	406.9	13.93	404.3	409.4
	Week 6	Pre-Dose	80	406.3	14.95	403.5	409.1
		Post- Dose	80	408.6	14.66	405.9	411.3
	Week 12	Pre-Dose	77	408.3	13.41	405.8	410.9
		Post- Dose	75	409.6	12.25	407.2	411.9
	Week 16	Pre-Dose	72	407.5	12.34	405.1	410
		Post- Dose	72	408.5	14.16	405.7	411.3
	Week 20	Pre-Dose	71	407.8	14.2	405	410.6
		Post- Dose	71	409.7	13.65	407	412.4
Pridopidine 45 mg bid	Baseline	Pre-Dose	81	410.6	16.66	407.5	413.7
		Post- Dose	81	412.4	18.03	409	415.7
	Week 2	Pre-Dose	76	409.8	16.76	406.6	413
		Post- Dose	76	411.1	17.47	407.7	414.4
	Week 4	Pre-Dose	73	409.4	16.48	406.2	412.6
		Post- Dose	73	415.3	19.41	411.6	419.1
	Week 6	Pre-Dose	71	412.5	18.93	408.8	416.3
		Post- Dose	69	415.4	17.89	411.8	419
	Week 12	Pre-Dose	68	413.2	16.9	409.8	416.6
		Post- Dose	65	416.7	18.17	413	420.5
	Week 16	Pre-Dose	65	412.2	16.84	408.7	415.7
		Post- Dose	63	415.2	16.97	411.7	418.8
	Week 20	Pre-Dose	63	413.8	18.54	409.9	417.7
		Post-	63	416.5	17.34	412.9	420.2
Pridopidine 67.5 mg bid	Baseline	Pre-Dose	79	409.7	15.73	406.8	412.6
		Post- Dose	77	411.6	14.96	408.8	414.5
	Week 2	Pre-Dose	71	408.4	16.98	405	411.8
		Post- Dose	74	412.9	15.21	409.9	415.8

	Week 4	Pre-Dose	73	414.1	15.99	411	417.2
		Post- Dose	72	420.2	17.68	416.7	423.6
	Week 6	Pre-Dose	69	415.5	14.43	412.6	418.4
		Post- Dose	67	420.4	15.28	417.3	423.5
	Week 12	Pre-Dose	65	419.2	13.01	416.5	421.9
		Post- Dose	64	422.6	14.01	419.7	425.6
	Week 16	Pre-Dose	63	417.2	14.02	414.3	420.2
		Post- Dose	63	420.8	12.2	418.3	423.4
Pridopidine 90 mg bid	Baseline	Pre-Dose	80	407.8	15.62	404.9	410.7
		Post- Dose	80	410.4	16.6	407.3	413.5
	Week 2	Pre-Dose	73	412.8	17.93	409.3	416.3
		Post- Dose	77	420.7	17.34	417.4	424
	Week 4	Pre-Dose	78	414.9	16.62	411.7	418
		Post- Dose	77	419.9	18.3	416.4	423.4
	Week 6	Pre-Dose	77	416.5	18.06	413.1	420
		Post- Dose	77	424.1	17.72	420.8	427.5
	Week 12	Pre-Dose	71	416.9	16.18	413.7	420.1
		Post- Dose	71	422.5	18.24	418.9	426.1
	Week 16	Pre-Dose	68	416.6	15.42	413.5	419.7
		Post- Dose	69	420.9	16.72	417.5	424.2
	Week 20	Pre-Dose	67	418.4	15.58	415.3	421.6
		Post- Dose	67	423.7	17.21	420.2	427.2
Pridopidine 112.5 mg bid	Baseline	Pre-Dose	80	407.2	17.52	403.9	410.4
		Post- Dose	79	410.2	18.23	406.8	413.6
	Week 2	Pre-Dose	72	414.1	19.23	410.3	417.8
		Post- Dose	77	419.9	17.99	416.4	423.3
	Week 4	Pre-Dose	77	421.4	18.71	417.9	425
		Post- Dose	77	426.1	20.5	422.2	430
	Week 6	Pre-Dose	73	420.9	19.32	417.1	424.6
		Post- Dose	70	425.3	20.12	421.3	429.3
	Week 12	Pre-Dose	67	421.5	18.86	417.6	425.3
		Post- Dose	66	422.4	20.52	418.2	426.7
	Week 16	Pre-Dose	66	420	17.97	416.3	423.6

		Post- Dose	66	422.5	18.65	418.6	426.3
	Week 20	Pre-Dose	64	419.2	19.46	415.2	423.3
		Post- Dose	64	422.3	21.25	417.8	426.7

Table S5: Change from Baseline in QTcF (Δ QTcF, msec) by Dose Group and Timepoint (PRIDE-HD)

Treatment/Dose	Visit	Time	N	Mean	SD	90% Confidence Interval	
Placebo	Baseline	Post- Dose	82	0.3	9.84	-1.5	2.1
	Week 2	Pre-Dose	78	-1.7	8.56	-3.3	-0.1
		Post- Dose	81	0.7	9.75	-1.1	2.5
	Week 4	Pre-Dose	81	-0.3	9.97	-2.2	1.5
		Post- Dose	81	-1.4	12.85	-3.8	0.9
	Week 6	Pre-Dose	80	-2.1	11.11	-4.2	0.0
		Post- Dose	80	0.2	10.01	-1.7	2.1
	Week 12	Pre-Dose	77	-0.4	9.77	-2.2	1.5
		Post- Dose	75	0.5	10.61	-1.6	2.5
	Week 16	Pre-Dose	72	-1.7	11.34	-3.9	0.5
		Post- Dose	72	-0.7	12.57	-3.2	1.7
	Week 20	Pre-Dose	71	-1.8	11.94	-4.2	0.6
		Post- Dose	71	0.1	11.43	-2.2	2.4
Pridopidine 45 mg bid	Baseline	Post- Dose	81	1.8	11.00	-0.3	3.8
	Week 2	Pre-Dose	76	0.3	10.39	-1.7	2.2
		Post- Dose	76	1.6	9.78	-0.3	3.4
	Week 4	Pre-Dose	73	0.3	11.47	-2.0	2.5
		Post- Dose	73	6.2	12.60	3.8	8.7
	Week 6	Pre-Dose	71	3.3	11.35	1.1	5.6
		Post- Dose	69	5.8	12.53	3.3	8.3
	Week 12	Pre-Dose	68	4.4	10.31	2.4	6.5
		Post- Dose	65	8.1	10.91	5.8	10.3
	Week 16	Pre-Dose	65	3.5	11.25	1.2	5.9
		Post- Dose	63	7.0	13.63	4.1	9.8
		Pre-Dose	63	5.6	11.60	3.1	8.0

Treatment/Dose	Visit	Time	N	Mean	SD	90% Confidence Interval	
	Week 20	Post- Dose	63	8.3	11.78	5.8	10.8
Pridopidine 67.5 mg bid	Baseline	Post- Dose	77	1.9	10.62	-0.1	3.9
	Week 2	Pre-Dose	71	-1.0	9.81	-2.9	1.0
		Post- Dose	74	3.3	10.47	1.2	5.3
	Week 4	Pre-Dose	73	4.6	10.13	2.6	6.6
		Post- Dose	72	10.5	11.26	8.3	12.7
	Week 6	Pre-Dose	69	4.9	10.25	2.8	6.9
		Post- Dose	67	9.8	11.53	7.5	12.2
	Week 12	Pre-Dose	65	7.8	10.66	5.6	10.0
		Post- Dose	64	11.1	12.19	8.6	13.7
	Week 16	Pre-Dose	63	5.7	11.32	3.4	8.1
		Post- Dose	63	9.4	11.86	6.9	11.9
	Week 20	Pre-Dose	62	4.7	11.12	2.4	7.1
		Post- Dose	62	10.1	13.03	7.4	12.9
Pridopidine 90 mg bid	Baseline	Post- Dose	80	2.5	9.38	0.8	4.3
	Week 2	Pre-Dose	73	4.1	11.82	1.8	6.4
		Post- Dose	77	12.5	12.17	10.2	14.8
	Week 4	Pre-Dose	78	6.9	9.27	5.1	8.6
		Post- Dose	77	12.1	12.09	9.8	14.4
	Week 6	Pre-Dose	77	8.4	9.31	6.6	10.2
		Post- Dose	77	16.0	12.35	13.7	18.4
	Week 12	Pre-Dose	71	9.7	8.79	7.9	11.4
		Post- Dose	71	15.2	11.03	13.1	17.4
	Week 16	Pre-Dose	68	8.4	10.04	6.4	10.5
		Post- Dose	69	13.2	11.01	11.0	15.4
	Week 20	Pre-Dose	67	10.5	11.36	8.2	12.8
		Post-Dose	67	15.9	12.73	13.3	18.5
Pridopidine 112.5 mg bid	Baseline	Post- Dose	79	3.0	9.71	1.2	4.8
	Week 2	Pre-Dose	72	6.0	12.26	3.6	8.4
		Post- Dose	77	12.3	12.23	10.0	14.6
		Pre-Dose	77	13.8	11.29	11.7	16.0

Treatment/Dose	Visit	Time	N	Mean	SD	90% Confidence Interval	
	Week 4	Post- Dose	77	18.5	15.74	15.6	21.5
	Week 6	Pre-Dose	73	13.7	12.93	11.2	16.2
		Post- Dose	70	17.9	14.03	15.1	20.7
	Week 12	Pre-Dose	67	14.7	10.98	12.4	16.9
		Post- Dose	66	15.4	14.32	12.5	18.4
	Week 16	Pre-Dose	66	13.0	10.44	10.8	15.1
		Post- Dose	66	15.5	13.37	12.7	18.2
	Week 20	Pre-Dose	64	12.2	14.99	9.1	15.3
		Post- Dose	64	15.2	19.70	11.1	19.3