

Supplementary document

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Safety and pharmacokinetics of HTL0018318, a novel M₁ receptor agonist, given in combination with donepezil at steady state: a randomized trial in healthy elderly subjects

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Table S1 Visit and Assessment Schedule

Period 1: Donepezil run-in period	Screening	Pre-DPZ	DPZ 5mg	DPZ 10mg	DPZ 10mg	Steady State DPZ
	Day -28 to -2	Day 0	Day 1 to 4	Day 5	Day 6 to 18	Day 19
Admission	X	X		X	X ¹	
Informed consent	X					
In- & exclusion criteria, Demography	X					
Medical- and con-med. history	X					
Virology	X					
Cotinine test	X					
Physical examination, Temperature	X	X				X
BsHaem, BsChem, Urinalysis	X	X ²				
Urine Drug, Pregnancy ³ , Breath Alc.	X	X		X	X	
Height ⁴ and weight	X	X				
ECG 12 lead & Vital Signs (HR, BP)	X	X		X		X
ECG 24h Holter	X					X
Donepezil administration		X ⁵	X ⁵	X ⁵	X ⁶	X
Salivary flow rate		X				X
Respiratory function		X ⁷				X
VAS Bond & Lader, nausea, LSEQ	X	X		X		X
Blood PK sample donepezil				X	X ⁸	X ⁸
iPod rating of nausea and sleep quality		← X →				
(S)AE/Con-med monitoring and compliance, General symptoms	X ⁹	X ¹⁰	← X →			

Br(eath). Alc = Breath alcohol test; BsChem = Blood Sample Chemistry; BsHaem = Blood Sample Hematology; Con-med = Concomitant Medications; DPZ = Donepezil; ECG = Electrocardiogram; LSEQ=Leeds Sleep Evaluation Questionnaire; PK = Pharmacokinetics, (S)AE = (Serious) Adverse Event; VAS=visual analog scale. AE=Adverse Event; Vital signs = heart rate and blood pressure

¹ Stay overnight at the clinical research unit from the evening of Day 18 until the morning of Day 25.

² Includes pharmacogenetic sample

³ Serum pregnancy test at screening, urine pregnancy test on other visits.

⁴ Height measured only at screening.

⁵ Donepezil 5mg treatment (5 days) dispensed with instructions. Self-administration each evening before retiring.

⁶ Donepezil 10mg treatment (13 days) dispensed with instructions. Self-administration each evening before retiring. Administration at clinical research unit on Day 18

⁷ Performed twice

⁸ Donepezil PK samples on Day 18 pre-dose, 4h post dose, on Day 19 at 15h and 24h post Day 18 dose (=pre-Day 19 dose), and 4h post Day 19 dose.

⁹ Baseline conditions at screening until pre-dose Day 0; continuous monitoring from Day 0.

¹⁰ A clinical research unit physician will review subject eligibility before dosing

Period 2 (HTL0018318/placebo in combination with donepezil) and Period 3 (HTL0018318/placebo alone)										
	Pre-dose Day 20 & 45	Day 20 Day 45	Day 21 Day 46	Day 22 Day 47	Day 23 Day 48	Day 24 Day 49	Day 25 Day 50	Day 26 Day 51	Day 27 Day 52	Follow -Up Day 56-63
Stay overnight at CHDR	X ¹¹	X	X	X	X	X				
Weight	X						X			X
Physical Examination										X
BsHaem, BsChem, Urinalysis	X			X ¹²			X ¹²			X
Temperature	X		X ¹²	X ²	X ²	X ²	X			X
Urine drug, pregnancy, Br. alc.	X ¹³									
ECG 12 lead & Vital Signs	X	X ⁴	X ¹⁴	X ⁴	X ⁴	X ⁴	X			X
ECG 24h Holter		X		X		X				
HTL0018318 / placebo		X	X	X	X	X				
Administration Donepezil		X ¹⁵	X ⁵	X ⁵	X ⁵					
Salivary flow rate	X	X ¹⁶		X ⁶		X ⁶				
Respiratory function ¹⁷	X	X		X		X	X			
VAS Bond & Lader, nausea ¹⁸	X	X	X	X	X	X	X			
LSEQ	X		X ²	X ²	X ²	X ²	X			
Blood PK donepezil ¹⁹	X	X	X	X	X	X	X	X	X	X
Blood PK HTL0018318 ²⁰	X	X	X	X	X	X	X	X	X	X
Urine PK collection ²¹	X	X	X	X	X	X	X	X	X	X
(S)AE/Con-meds monitoring, general symptoms	← X →									

¹¹ Stay overnight on Day 19 and Day 44

¹² Pre-dose (all 'pre-dose' references concern HTL0018318)

¹³ Day 44 only

¹⁴ Pre-dose, 0.5h, 1h, 2h, 3h and 6h post dose

¹⁵ Donepezil 10 mg administered on Days 20 to 23 in the evening

¹⁶ Before breakfast, 2h, 4h, 6h post dose (pre-meals)

¹⁷ Pre-dose, 2h and 6h post dose on Days, 20/45, 22/47 and 24/49

¹⁸ Pre-dose, 2h, 4h, 8h post dose on Days 20/45; Pre-dose, 2h and 8h post dose on Days 21 to 24 and 46 to 49.

¹⁹ Donepezil PK: Day 20 at 15h post (Day 19) dose, pre-dose Day 20, 4h post dose. Day 21, 22, 23: 15h post previous day's dose. Day 23 pre-dose, 4h, 15h, 27h, 39h, 63h, 87h, 7-14 days post dose (14 samples in total).

²⁰ HTL0018318 PK: Day 20/45 pre-dose. Day 20/45 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 8h, 9h (Day 20 only), 12h, 13h (Day 20 only) post-dose. Day 21,22,23/46,47,48 pre-dose. Day 24/49 pre-dose, 0.25h, 0.5h, 1h, 1.5h, 2h, 3h, 4h, 8h, 12h, 24h, 48h, 72h, 7-14 days post-dose.

²¹ Day 20/45 pre-dose (spot). Day 20/45 and 24/49: 0-4h (complete), 4-8h (c), 8-12h (c), 12-24h (c). Day 25/50 (24-48h) (c). Day 26/51 (48-72h) (c). Follow-up (spot)

Table S2 Results of the statistical analysis of safety and tolerability measurements

		Contrasts						
Parameter	Treatment P-value	15 mg HTL0018318 + donepezil vs Placebo	25 mg HTL0018318 + donepezil vs Placebo	15 mg HTL0018318 alone vs Placebo	25 mg HTL0018318 alone vs Placebo	Placebo alone vs placebo + donepezil	15 mg HTL0018318 alone vs 15 mg HTL0018318 donepezil	25 mg HTL0018318 alone vs 25 mg HTL0018318 donepezil
Saliva (g)	0.0930	0.707 (-0.280, 1.694) p=0.1532	0.910 (0.066, 1.754) p=0.0355*	0.498 (-0.503, 1.499) p=0.3169	0.906 (0.057, 1.756) p=0.0373*	-0.345 (-0.703, 0.013) p=0.0579	-0.554 (-0.982, -0.125) p=0.0144*	-0.349 (-0.712, 0.015) p=0.0591
FEV 1 second (L)	0.1341	0.043 (-0.089, 0.175) p=0.5204	0.085 (-0.030, 0.201) p=0.1455	0.153 (0.012, 0.295) p=0.0340*	0.077 (-0.047, 0.200) p=0.2197	0.016 (-0.096, 0.129) p=0.7705	0.127 (-0.008, 0.262) p=0.0642	0.008 (-0.095, 0.110) p=0.8785
FVC (L)	0.2037	0.03719 (-.18178, 0.25616) p=0.7350	0.17837 (-.01162, 0.36836) p=0.0652	0.20348 (-.03215, 0.43911) p=0.0891	0.06192 (-.14530, 0.26915) p=0.5518	0.00389 (-.20241, 0.21019) p=0.9695	0.17019 (-.07662, 0.41699) p=0.1688	-.11255 (-.29932, 0.07421) p=0.2275
FEV1/FVC (%)	0.7598	1.052 (-1.237, 3.341) p=0.3606	-0.399 (-2.388, 1.590) p=0.6894	-0.327 (-2.754, 2.101) p=0.7883	1.600 (-0.537, 3.736) p=0.1389	0.492 (-1.481, 2.466) p=0.6108	-0.886 (-3.201, 1.429) p=0.4359	2.491 (0.727, 4.255) p=0.0078**
PEF (L/sec)	0.0856	0.339 (-0.280, 0.958) p=0.2771	0.273 (-0.265, 0.811) p=0.3144	0.282 (-0.377, 0.942) p=0.3947	0.606 (0.033, 1.179) p=0.0385*	-0.286 (-0.868, 0.296) p=0.3291	-0.343 (-1.036, 0.350) p=0.3253	0.047 (-0.481, 0.575) p=0.8591
VAS Alertness (mm)	0.1296	-0.70 (-2.71, 1.30) p=0.4843	-1.49 (-3.22, 0.25) p=0.0908	-1.96 (-4.04, 0.12) p=0.0637	-1.63 (-3.43, 0.18) p=0.0759	0.80 (-0.48, 2.08) p=0.2086	-0.46 (-1.91, 0.99) p=0.5217	0.66 (-0.43, 1.76) p=0.2221
VAS Calmness (mm)	0.1369	-2.37 (-5.39, 0.65) p=0.1193	-1.67 (-4.23, 0.89) p=0.1940	-3.17 (-6.21, -0.13) p=0.0418*	-2.34 (-4.92, 0.25) p=0.0748	0.59 (-0.20, 1.38) p=0.1406	-0.20 (-1.08, 0.68) p=0.6535	-0.07 (-0.75, 0.60) p=0.8264
VAS Mood (mm)	0.0908	-0.24 (-2.38, 1.90) p=0.8214	-0.38 (-2.22, 1.45) p=0.6763	-2.93 (-5.23, -0.63) p=0.0135*	-2.49 (-4.49, -0.48) p=0.0158*	2.66 (0.54, 4.77) p=0.0167*	-0.03 (-2.55, 2.49) p=0.9796	0.55 (-1.32, 2.43) p=0.5414
VAS Nausea (log(mm))	0.5595	-0.08 (-0.23, 0.06) p=0.2569	-0.04 (-0.16, 0.08) p=0.4963	-0.06 (-0.21, 0.08) p=0.3780	-0.05 (-0.17, 0.07) p=0.4239	-0.02 (-0.06, 0.01) p=0.2017	-0.01 (-0.05, 0.04) p=0.7832	-0.03 (-0.07, 0.00) p=0.0683
LSEQ: Getting to sleep	0.5617	1.59 (-1.37, 4.55) p=0.2860	-0.74 (-3.31, 1.82) p=0.5645	0.82 (-2.31, 3.96) p=0.6005	1.01 (-1.71, 3.73) p=0.4619	-0.02 (-2.48, 2.43) p=0.9838	-0.79 (-3.71, 2.12) p=0.5818	1.72 (-0.51, 3.95) p=0.1246
LSEQ: Quality of sleep	0.7988	2.42 (-5.47, 10.31) p=0.5408	-1.37 (-8.02, 5.27) p=0.6804	-5.14 (-13.38, 3.10) p=0.2168	-2.18 (-9.34, 4.97) p=0.5430	7.30 (0.79, 13.81) p=0.0293*	-0.26 (-8.18, 7.66) p=0.9473	6.49 (0.57, 12.41) p=0.0328*

		Contrasts						
Parameter	Treatment P-value	15 mg HTL0018318 + donepezil vs Placebo	25 mg HTL0018318 + donepezil vs Placebo	15 mg HTL0018318 alone vs Placebo	25 mg HTL0018318 alone vs Placebo	Placebo alone vs placebo + donepezil	15 mg HTL0018318 alone vs 15 mg HTL0018318 donepezil	25 mg HTL0018318 alone vs 25 mg HTL0018318 donepezil
LSEQ: Awake following sleep	0.3958	3.50 (0.19, 6.81) p=0.0385*	0.52 (-2.39, 3.42) p=0.7232	-1.72 (-5.17, 1.74) p=0.3222	-1.85 (-4.85, 1.15) p=0.2213	3.29 (0.17, 6.41) p=0.0389*	-1.93 (-5.55, 1.70) p=0.2909	0.93 (-1.86, 3.71) p=0.5073
LSEQ: Behaviour after wake	0.8954	1.51 (-3.87, 6.90) p=0.5738	-0.80 (-5.54, 3.95) p=0.7367	-1.00 (-6.57, 4.56) p=0.7185	-0.60 (-5.46, 4.26) p=0.8036	1.66 (-2.12, 5.45) p=0.3755	-0.85 (-5.19, 3.48) p=0.6887	1.86 (-1.50, 5.22) p=0.2670

FEV1 = forced expiratory volume in 1 second; FVC = Forced vital capacity; LSEQ = Leeds Sleep Evaluation Questionnaire; PEF = peak expiratory flow; VAS = visual analogue scale