A PHASE 1A FIRST-IN-HUMAN CLINICAL TRIAL OF HER-096, A SUBCUTANEOUSLY ADMINISTERED CDNF-DERIVED PEPTIDOMIMETIC

Kira M. Holmström[1], Katarina Jääskeläinen[1], Natalia Kulesskaya[1], Jani Koskinen[1], Päivi Vuorio[1], Antti Vuolanto[1], Marica T. Engström[2], Mika Scheinin[3], Charlotte Videbaek[1], Aleksi Tornio[2,3] & Henri J. Huttunen[1]

[1]Herantis Pharma Plc, Espoo, Finland; [2]Bioanalytical Laboratory, Institute of Biomedicine, University of Turku, Finland; [3]Clinical Research Services Turku – CRST Oy, Finland

SUMMARY

HER-096 is a peptidomimetic compound developed from the active site of human neurotrophic factor CDNF. In preclinical studies, HER-096 has shown brain penetration and protection of nigrostriatal dopamine neurons. In this first-in-human study, we aimed to assess (1) the safety and tolerability of subcutaneously administered HER-096 in healthy volunteers (HV), and (2) its pharmacokinetic properties, including blood-brain barrier penetration in humans.

METHODS

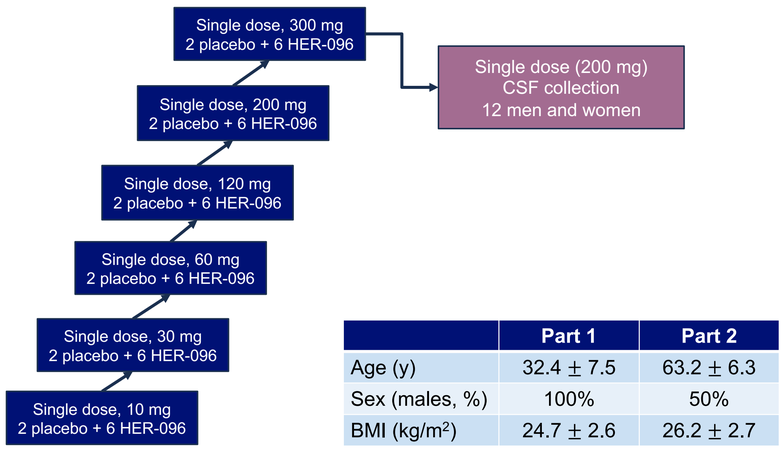
A randomised, double-blind, placebo-controlled, safety, tolerability and pharmacokinetic study of single ascending subcutaneous doses of HER-096 was conducted at a single site in Finland.

Part 1: 48 young (20-45 years) male HV subjects were randomised to receives one subcutaneous (s.c.) dose of HER-096 (10, 30, 60, 120, 200 or 300 mg) or placebo at a 6:2 ratio in six dosing cohorts.

Part 2: 6 older (50-64 years) and 6 elderly (65-75 years) male and female HV subjects were administered a single 200 mg dose of HER-096 (jointly referred to as 'elderly').

The primary endpoint was safety, assessed by incidence, type and severity of treatment-emergent adverse events (TEAE), including injection site-related events, as well as standard clinical and laboratory assessments.

Secondary endpoints were pharmacokinetic properties of HER-096 (up to 24 h) in plasma and urine in the young HVs, and in plasma, urine and cerebrospinal fluid (CSF) in the elderly subjects.



	Part 1	Part 2
Age (y)	32.4 ± 7.5	63.2 ± 6.3
Sex (males, %)	100%	50%
BMI (kg/m^2)	24.7 ± 2.6	26.2 ± 2.7

Figure 1. *Summary of Phase 1a study design and demographic data. BMI = body mass index.*

RESULTS

Plasma Pharmakokinetic Data Showed Expected Absorbtion and Elimination Profile

After a single s.c. administration, the peak plasma concentration was reached at 0.7 – 2.1 hours. In all dose groups in young subjects (Part 1), the plasma level declined similarly with a terminal half-life of 1.8 - 2.2 hours, while in elderly subjects dosed with 200 mg the mean half-life was about 2.5 hours (Table 1). Exposure to HER-096 demonstrated dose-linearity in plasma in young male subjects after single s.c. administration of the compound in the dose range 10-300 mg (Figure 2A). In the elderly cohort (Part 2), the perceived higher plasma C_{max} and exposure (AUC) can largely be explained by adjusting for weight (Figure 2B and C).

	Part 1: Dose escalation cohorts						Part 2: Elderly cohort	
	Male						Male	Female
	10 mg	30 mg	60 mg	120 mg	200 mg	300 mg	200 mg	200 mg
C_{max} (ng/ml)	363	906	2235	3468	5406	9663	5573	7333
T_{max} (h)	2.01	1.34	0.71	1.14	1.06	0.81	0.84	0.91
$T_{1/2}$ (h)	1.78	1.91	1.90	1.91	1.97	2.18	2.66	2.39
AUC_{last} (h*ng/ml)	1655	4302	8453	15446	24530	42510	31354	42202
AUC_{inf} (h*ng/ml)	1687	4231	8462	15464	24552	42584	31455	42279
Lambda Z (1/h)	0.394	0.372	0.367	0.364	0.355	0.334	0.268	0.292

Table 1. *Plasma pharmacokinetic parameters of HER-096 after single s.c. administration in young males and elderly males and females.*

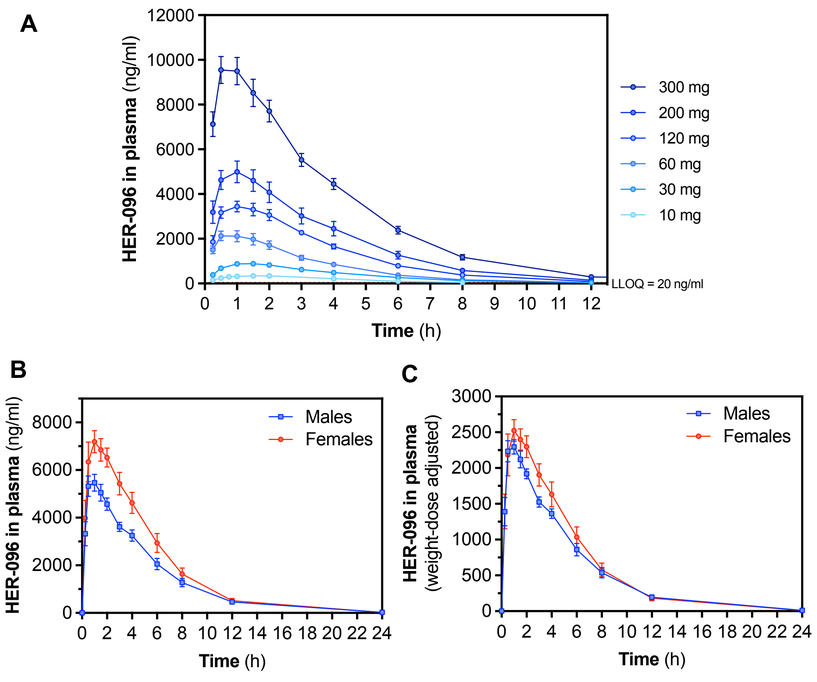


Figure 2. *Plasma concentration of HER-096 after a single s.c. dose administration in young males (**A**) elderly males and females (**B**). Weight-dose adjusted HER-096 in plasma **(C).** Elderly subjects received a single 200 mg dose. n=6 per group except for young 200mg group; n=5.*

Pharmacokinetic Data Demonstrated Efficient Blood-Brain Barrier Penetration in Elderly Subjects

CSF exposure of HER-096 was tested by lumbar puncture in the elderly cohort at a single timepoint per subject (2, 4, 6, 8 or 12 hours) after dosing. The concentration of HER-096 in CSF varied between 15 ng/ml at 2 hours and 96.9 ng/ml at 12 hours (Figure 3), and it was not possible to determine the C_{max} and $AUC_{0\text{-}inf}$ due to the limited number of observations.

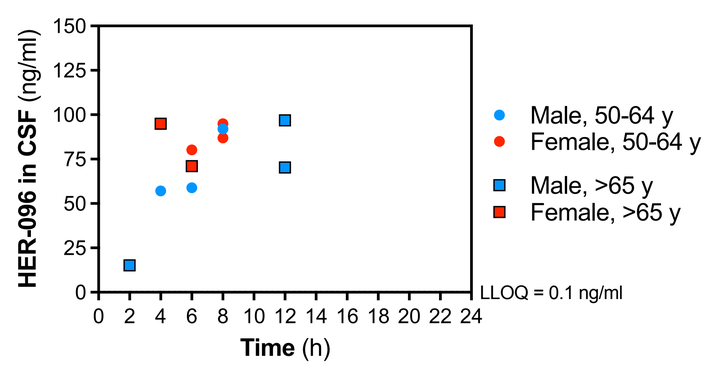


Figure 3. *CSF concentration of HER-096 after a single s.c. dose (200 mg) administered to elderly males and females.*

HER-096 Demonstrated Renal Clearance

Analysis of HER-096 recovery in urine showed that HER-096 was almost completely eliminated unchanged by renal excretion within 24 hours after a single s.c. dose to young males and elderly males and females (drug excreted in urine 84-113%). The renal clearance in males was 6139 – 8079 ml/h independently of the dose level. The renal clearance in elderly females was 4401 ml/h.

HER-096 Demonstrated a Good Safety and Tolerability Profile After Single s.c. Dose Administration

	Part 1: Dose escalation cohort							Part 2: Elderly cohort	
	Male							Male	Female
	10 mg	30 mg	60 mg	120 mg	200 mg	300 mg	Placebo	200 mg	200 mg
AEs	8 / 4	11 / 6	10 / 4	14 / 5	17 / 6	25 / 6	11 / 7	19 / 6	35 / 6
TEAEs	6 / 4	11 / 6	8 / 3	13 / 5	17 / 6	25 / 6	9 / 5	17 / 6	33 / 6
Related TEAEs	6 / 4	11 / 6	5 / 3	9 / 5	14 / 6	21 / 6	7 / 5	16 / 6	30 / 6
Severe TEAEs	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
Serious AEs	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0	0 / 0
Other significant AEs	0 / 0	0 / 0	0 / 0	0 / 0	1 / 1	0 / 0	0 / 0	0 / 0	0 / 0

Table 2. Summary of adverse events (AE). *Data presented as: the number of adverse events / the number of subjects with at least one adverse event. n=6 except for placebo n=12*

No severe treatment emergent adverse events (TEAEs) or serious adverse events (SAE) were recorded during the study. One significant adverse event was recorded where a subject experienced a vasovagal reaction (fainted) during dosing, and dosing was discontinued (Tables 2 and 3).

	Part 1: Dose escalation cohort							Part 2: Elderly cohort	
	Male							Male	Female
	10 mg	30 mg	60 mg	120 mg	200 mg	300 mg	Placebo	200 mg	200 mg
Systemic Adverse Events									
Ear and labyrinth disorders	0	0	0	0	0	0	0	1	0
Gastrointestinal disorders	1	1	0	1	0	1	1	1	3*
Injury and post-procedural complications (post lumbar puncture syndrome)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	0
Nervous system disorders (headache, dizziness, postural syncope)	2	4*	1	1	1**	3	3	1	5*
Skin and subcutaneous tissue disorders other than administration site	0	0	0	0	0	0	0	0	1
Vascular disorders (hot flush)	0	0	0	0	0	0	0	0	1
Local Adverse Events (Injection Site Reactions)									
Injection site AE (pain, tenderness, erythema, swelling, pruritus, discomfort, haematoma or bruising)	3	6	4	7	13	17	3	12	20

Table 3. Frequency and severity of related TEAEs. *TEAEs possibly, probably or definitely related to study treatment were classified as related TEAEs. Data is presented as the number of adverse events. All events were considered mild except for those marked with * = mild-to-moderate, ** = moderate. n=6 except for placebo n=12*

Most adverse event were related to local tolerability at injection site and were associated with higher doses and injection volume. Elderly females had a higher number of haematoma than males at the site of s.c. injection. Mild pain and tenderness at the injection site subsided within 6 hours after administration. Mild erythema was observed for up to 3 days in some subjects (Table 4).

	Part 1: Dose escalation cohort							Part 2: Elderly cohort	
	Male							Male	Female
	10 mg	30 mg	60 mg	120 mg	200 mg	300 mg	Placebo	200 mg	200 mg
Pain or tenderness	1	1	2	4	6	11	1	6	8
Swelling	0	0	0	0	1	0	0	0	0
Erythema	2	3	2	3	4	3	2	5	7
Haematoma	0	0	0	0	2	2	0	1	5
Pruritus	0	0	0	0	0	1	0	0	0
Discomfort	0	2	0	0	0	0	0	0	0

Table 4. Frequency and severity of related TEAEs at injection site. *Data presented as: the number of adverse events. All events were considered mild. n=6 except for placebo n=12*

CONCLUSIONS

The study met the primary endpoint: single subcutaneous doses of HER-096 (from 10 to 300 mg) were found to be safe and well-tolerated in healthy subjects.

Secondary endpoints demonstrated:

- Single ascending doses of HER-096 in healthy subjects showed an expected linear plasma pharmacokinetic profile in both young and elderly healthy subjects
- Blood-brain barrier penetration was assessed in elderly healthy subjects; CSF levels of HER-096 were found to be in a pharmacologically active range (based on preclinical data)

In summary, the safety and pharmacokinetic data support moving forward with development of subcutaneous HER-096.

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