HERANTIS PHARMA

A First-in-Human Clinical Study to Test Safety and Preliminary Efficacy of CDNF in Parkinson's Disease

Henri J. Huttunen, Sigrid Booms, Jani Koskinen, Magnus Sjögren, Mart Saarma, Max Woolley, Barry Murphy, Paul Fielder, Jim Baker, Paul Skinner, Riku Kivisaari, Hjalmar Bjartmarz, Per Almqvist, Filip Scheperjans, Håkan Widner & Per Svenningsson

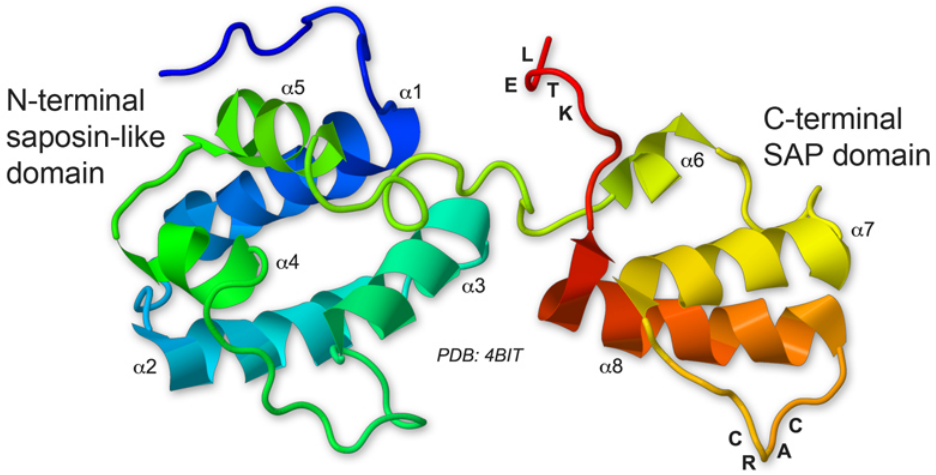
AD/PD Congress 2019
Lisbon, Portugal
28 March 2019

Disclaimer

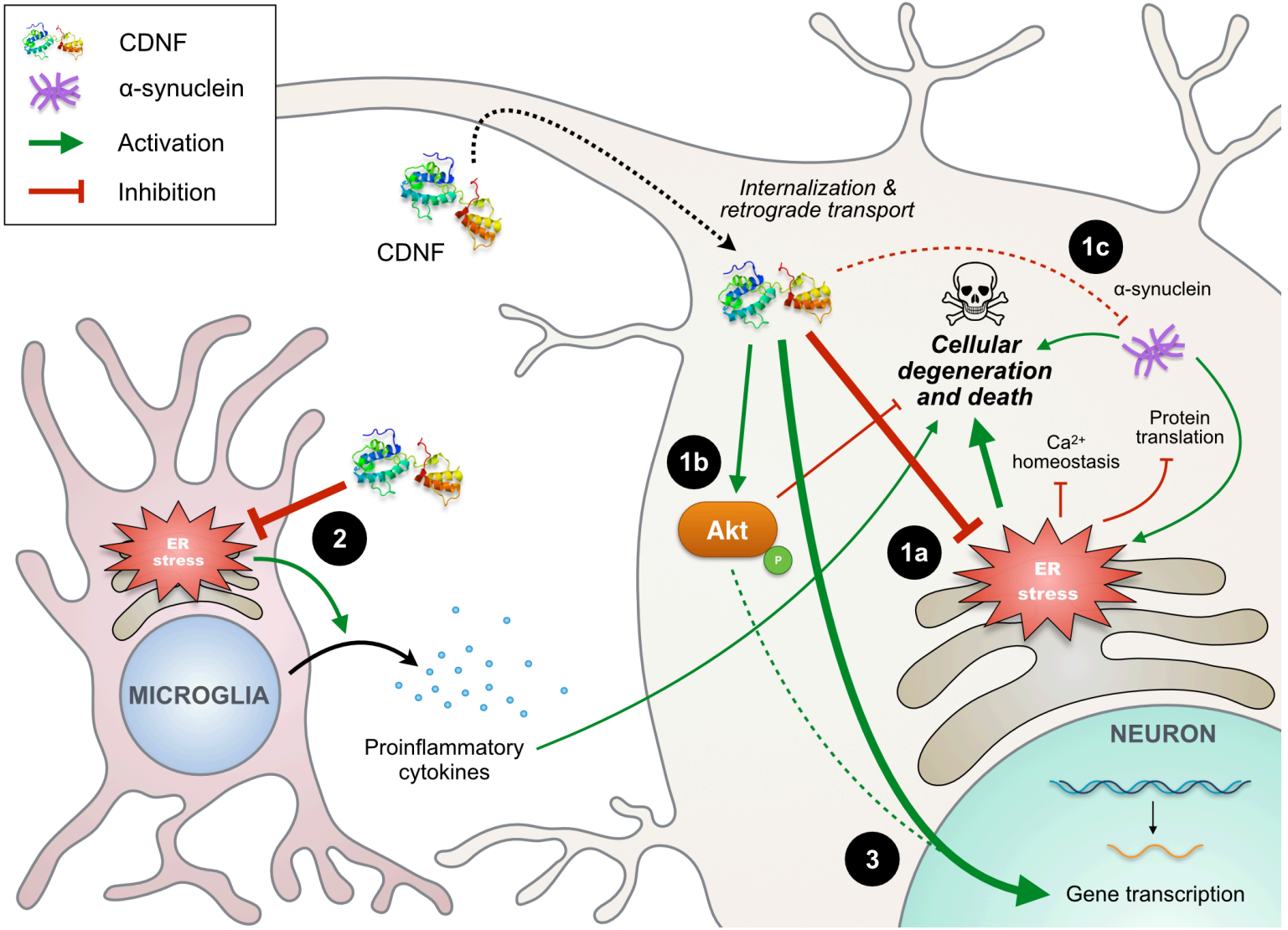
- This presentation does not intend to provide a thorough and detailed view of Herantis Pharma Plc ('Company'). The information provided in this presentation shall not be considered sufficient for making any investment decisions related to the Company. Anyone considering an investment in the Company shall read and consider carefully all information provided in the formal prospectus approved by Finland's Financial Supervisory Authority (Finanssivalvonta).
- This presentation may include forward-looking statements, estimates, and calculations related e.g. to the Company and its markets. Such forward-looking statements, estimates, and calculations are based on expectations and assumptions of the Company, which may be inaccurate or untrue. They also involve known and unknown risks and other factors, which might cause any estimates made by the Company to materially deviate from those actualized, including the operations, financial situation, and achievements of the Company. The Company cannot be held liable for any such deviations or for any actions taken by any party based on this presentation. Known risks related to the future of the Company and its business have been described in the formal prospectus approved by Finland's Financial Supervisory Authority (Finanssivalvonta).

CDNF is an unconventional neurotrophic factor

- Expressed in the brain but also in e.g. skeletal muscle, enteric nervous system etc
- CDNF and MANF are ER-localized proteins with ER-retention signal (KDEL-like)
- They interact with ER proteins such as BiP/GRP78, modulate unfolded protein response (UPR) signaling and protect from ER stress-induced cell death
- They can be secreted and are found in normal human plasma
- Therapeutic effects in multiple preclinical models of neurodegenerative diseases (Parkinson, ALS, stroke etc)



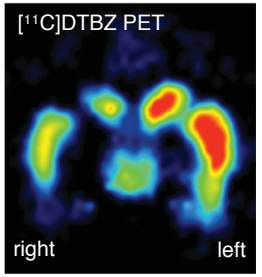
CDNF has a multi-modal mechanism with distinct PD targets

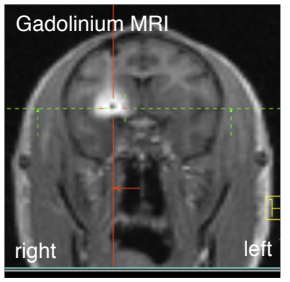


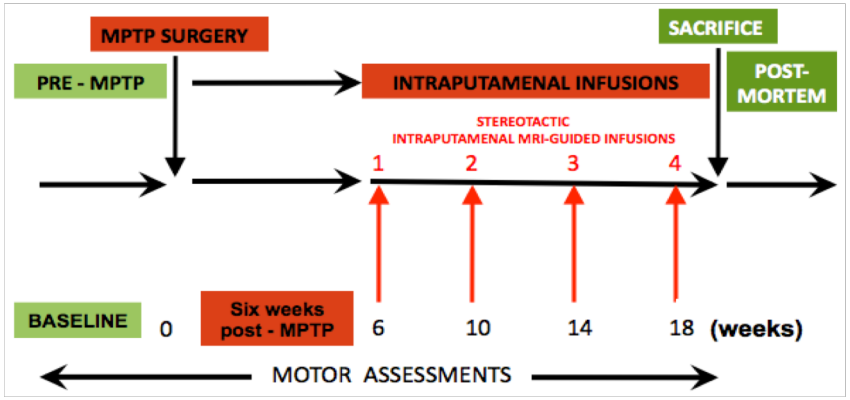
Huttunen & Saarma. Cell Transplant. 2019.

Neurorestoration model of PD in aged Rhesus macaques

- Unilaterally MPTP-lesioned aged (15-22 y) rhesus monkeys
- **Repeated monthly intraputamenal CED infusions of CDNF**; comparison to GDNF and vehicle
- Experimental measures included:
  - Motor function (MPRS, mMAP, actigraphy)
  - Non-motor symptoms: depressive behaviour, motivation and sleep
  - Post-mortem analyses (dopamine neuron counts, CDNF levels and diffusion, dopamine levels etc)
- Collaboration with Dr. Judy L. Cameron, Univ of Pittsburgh and Dr. Zhiming Zhang, Univ of Kentucky (study director: prof. Mart Saarma, Univ of Helsinki)
- Supported from Michael J. Fox Foundation







Group 1: MPTP + Vehicle (n=4)
Group 2: MPTP + GDNF comparator (450 µg)* (n=5)
Group 3: MPTP + CDNF test (450 µg) (n=4)
Group 4: MPTP + CDNF test (150 µg) (n=6)

* Optimal dose for GDNF infusion in Rhesus monkeys based on Gash et al. Nature 380: 252-255, 1996 & Don Gash, personal communication.

CDNF is the first treatment to improve both motor and non-motor symptoms in a rhesus monkey PD model

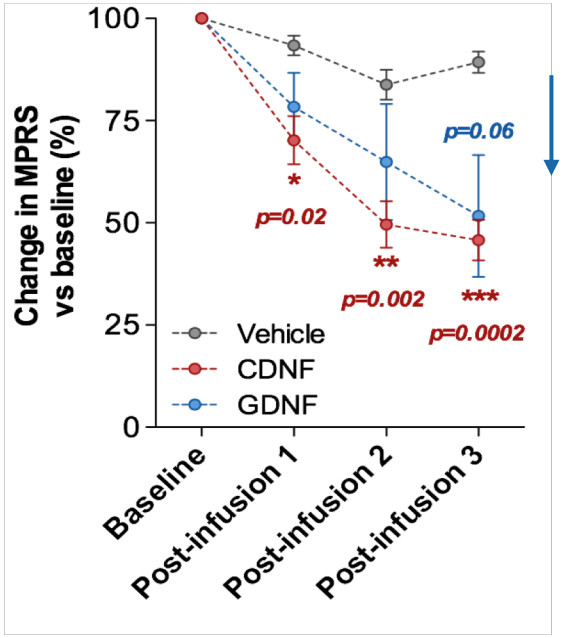
Improvement in Motor Symptoms

- **Gross motor functions** measured with monkey Parkinsonian disability rating scale (MPRS)
- **Fine motor functions** measured with monkey movement analysis panel (mMAP)
  - Improvement shown in recovery of the use of the affected-side hand

Improvement in Non-Motor Symptoms

- **Significantly reduced depressive behavior** measured with Human Intruder Test
  - First treatment to show this response
- **Significantly improved motivation** measured with Wisconsin General Apparatus
  - GDNF group showed no improvement

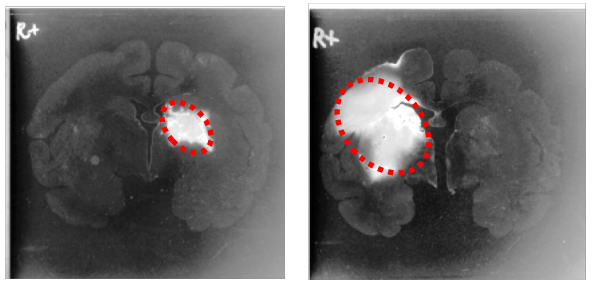
CDNF significantly improved motor symptoms in a MPTP rhesus monkey model of PD



Improved gross motor functions

Gross motor function was improved by **53%** after 3 months of dosing compared to vehicle control

Infused CDNF diffuses more broadly in the monkey brain



HERANTIS PHARMA

CDNF is the first treatment to improve both motor and non-motor symptoms in a rhesus monkey PD model

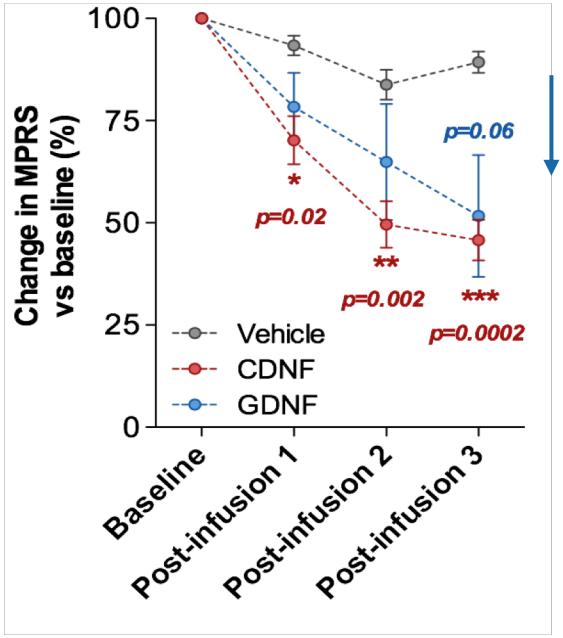
Improvement in Motor Symptoms

- **Gross motor functions** measured with monkey Parkinsonian disability rating scale (MPRS)
- **Fine motor functions** measured with monkey movement analysis panel (mMAP)
  - Improvement shown in recovery of the use of the affected-side hand

Improvement in Non-Motor Symptoms

- **Significantly reduced depressive behavior** measured with Human Intruder Test
  - First treatment to show this response
- **Significantly improved motivation** measured with Wisconsin General Apparatus
  - GDNF group showed no improvement

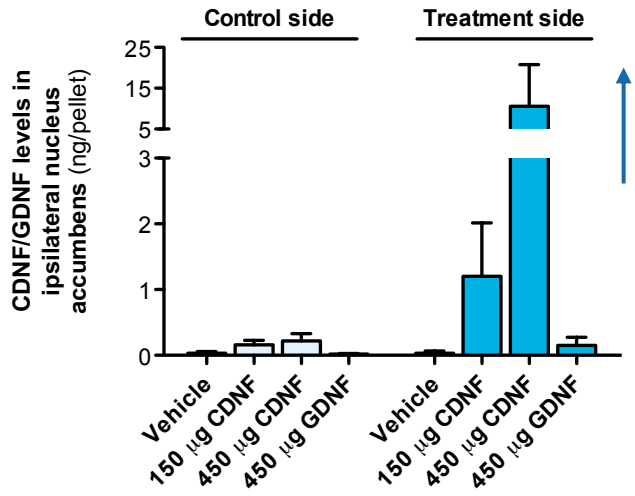
CDNF significantly improved motor symptoms in a MPTP rhesus monkey model of PD



Improved gross motor functions

Gross motor function was improved by **53%** after 3 months of dosing compared to vehicle control

Improvement in non-motor symptoms correlate with elevated CDNF levels in the ipsilateral nucleus accumbens

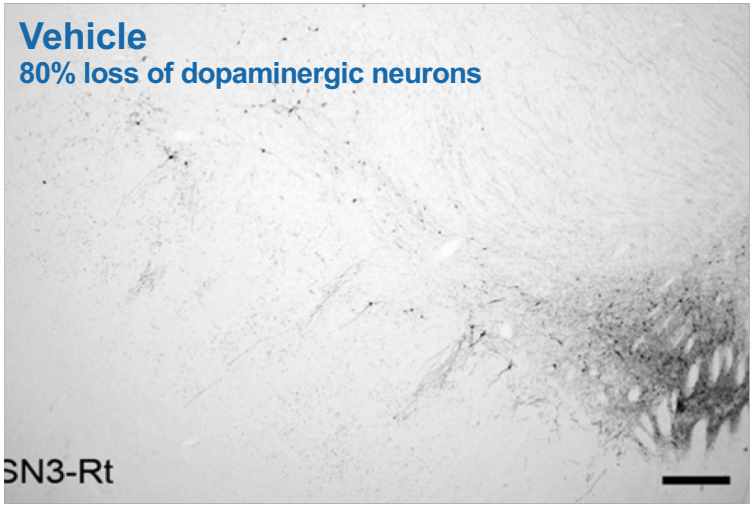


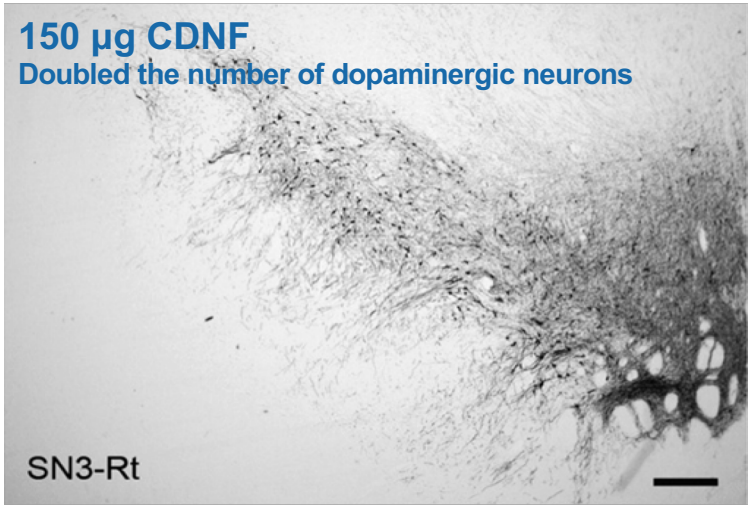
Elevated CDNF in ipsilateral nucleus accumbens

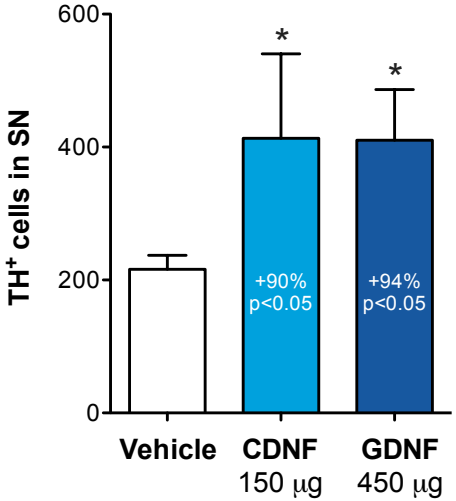
HERANTIS PHARMA

CDNF protects and recovers dopaminergic neurons in a rhesus monkey PD model

Three months of CDNF treatment nearly **doubled the number of dopaminergic neurons** in a true neurorestoration model







KEY: dark staining indicates dopaminergic neurons
MODEL: MPTP neurotoxin-induced lesions in rhesus monkeys
STUDY: First dose of CDNF given 6 weeks after lesioning. Thereafter, 4 monthly doses; animals were sacrificed immediately after the fourth dose. Tyrosine hydroxylase-staining of lesion-side substantia nigra sections from monkeys

HERANTIS PHARMA

CDNF first-in-human study consortium

- The TreatER consortium consists of
  - Herantis Pharma Plc, the sponsor of the clinical study
  - Renishaw Plc, the co-sponsor of the clinical study
  - Three study centers in Sweden and Finland
  - Academic partners in UK and Finland
  - European Parkinsons's Disease Association
  - Two pharma partners (follow-up role)
- TreatER project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 732386
- ClinicalTrials.gov: NCT03295786
- EudraCT: 2015-004175-73
- www.treater.eu

TreatER

Horizon 2020
European Union funding
for Research & Innovation

RENISHAW
apply innovation™

KAROLINSKA UNIVERSITETSSJUKHUSET

REGION SKÅNE

HUS

Karolinska Institutet

UNIVERSITY OF HELSINKI

UNIVERSITY OF OXFORD

EPDA

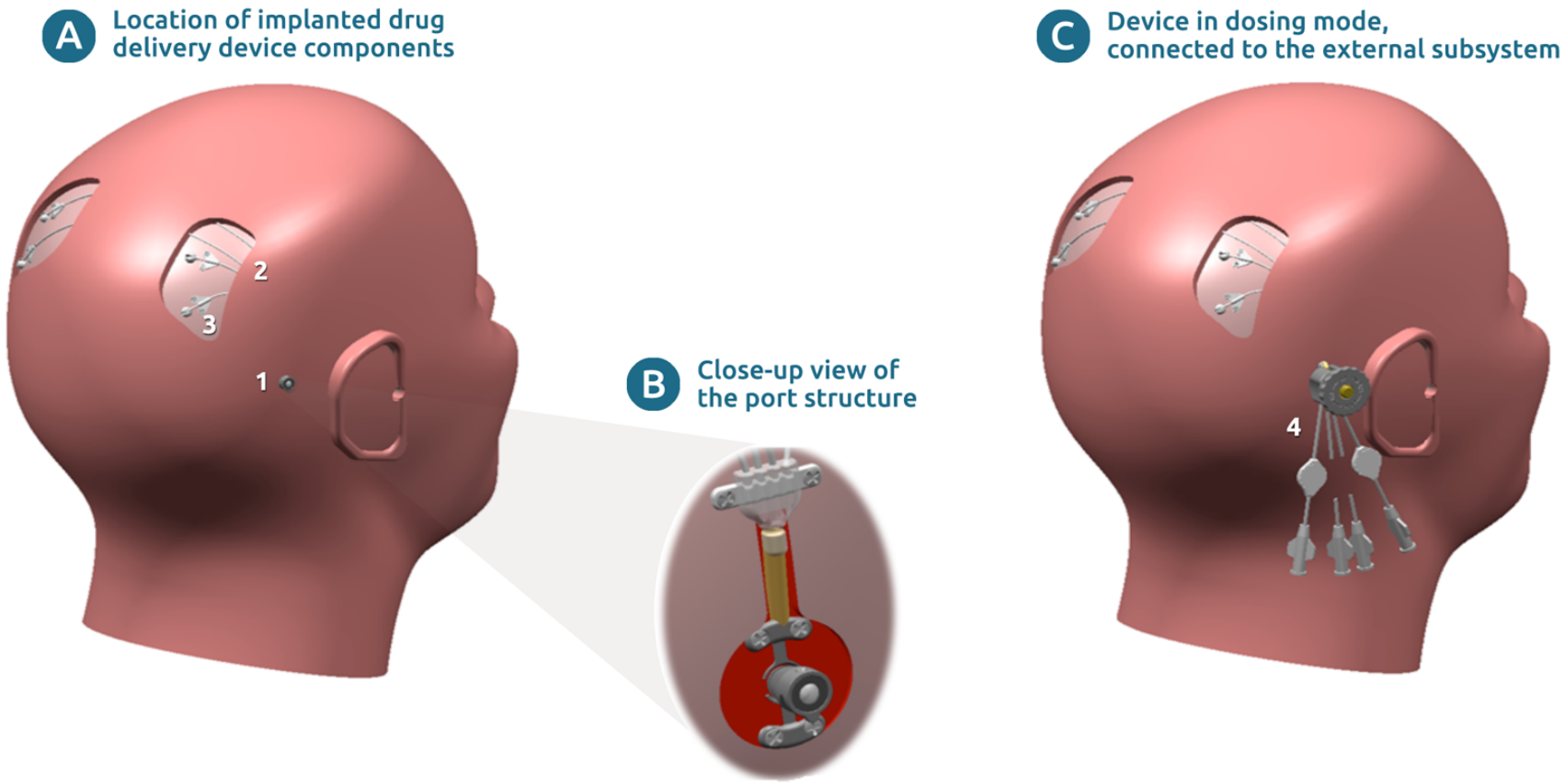
Lundbeck

ORION

Study centers and investigators

Study center	Neurologist	Neurosurgeon	PET imaging
Karolinska University Hospital (Stockholm, Sweden)	**Prof. Per Svenningsson** (principle investigator)	**Dr. Per Almqvist**	**Dr. Andrea Varrone** (Karolinska Institutet)
Skåne University Hospital (Lund, Sweden)	**Prof. Håkan Widner**	**Dr. Hjalmar Bjartmarz**	
Helsinki University Hospital (Helsinki, Finland)	**Dr. Filip Scheperjans**	**Dr. Riku Kivisaari**	**Prof. Juha Rinne** (Turku PET Center)
Turku PET Center (Turku, Finland)			

Device for intermittent intracerebral drug delivery

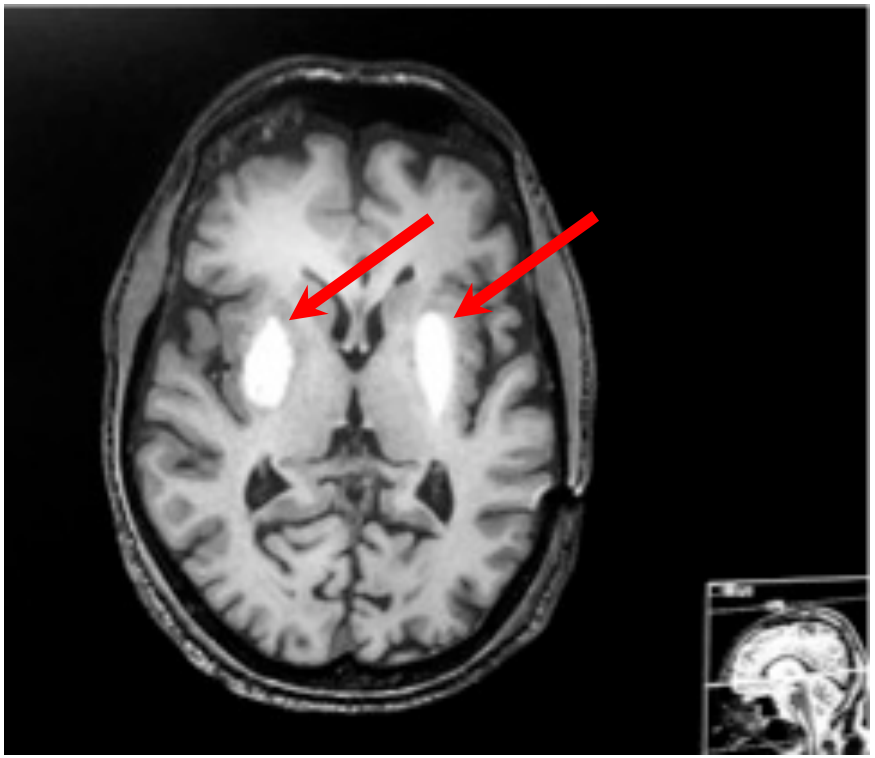


RENISHAW
apply innovation™

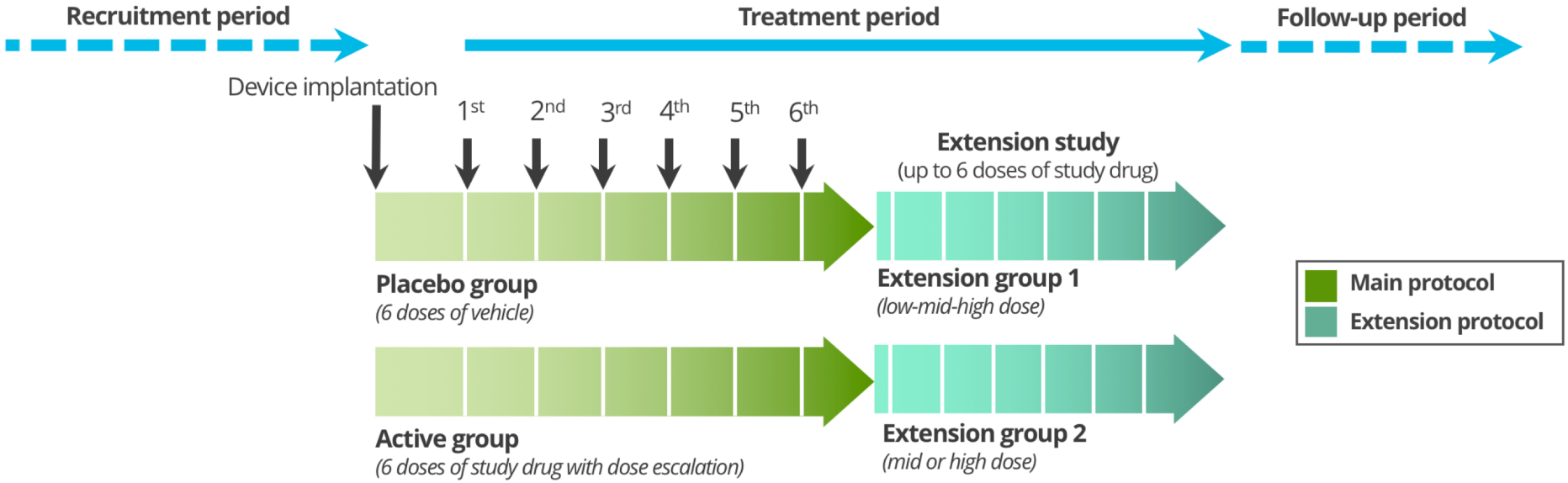
Barua et al. J. Neurosci. Methods 214: 223-232, 2013.

Test infusion shows excellent diffusion in putamen

- Two catheters placed in putamen in both hemispheres (total: 4)
- First test infusions conducted in 2017, 3 weeks after surgical implantation of the drug delivery system
- Test infusion protocol (CED):
- 400 µl of 2 mM Magnevist® infused per catheter over 160 min followed by MRI
- Ramped infusion rate up to 5 µl/min
- Results confirm that:
  - All device components are functional
  - Infusion protocol results in excellent coverage of the entire putamen



Main study design: placebo controlled, within-patient dose escalation; followed by an open-label extension study



Randomisation	1st dose	2nd dose	3rd dose	4th dose	5th dose	6th dose
Vehicle Group, n=6	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle	Vehicle
Mid-dose Group, n=6	Low dose (=120 µg)	Low dose (=120 µg)	Low or Mid-dose	Mid-dose (=400 µg)	Mid-dose (=400 µg)	Mid-dose (=400 µg)
High-dose Group, n=6	Low dose (=120 µg)	Low dose (=120 µg)	Mid-dose (=400 µg)	Mid-dose (=400 µg)	High-dose (=1200 µg)	High-dose (=1200 µg)

The 120 µg dose has a 68-fold safety margin to the NOEAL from NHP toxicology studies.

Patient recruitment criteria and study endpoints

- Key inclusion criteria:
  - Diagnosed with idiopathic PD (UK Brain Bank Criteria), bilateral findings at study entry
  - Age 35-75 years (inclusive), duration of PD motor symptoms 5-15 years (inclusive)
  - Presence of motor fluctuations, at least 5 daily doses of levodopa
  - UPDRS motor score (part III) in a practically defined OFF-state between 25-50 (inclusive)
  - Hoehn and Yahr ≤ stage III in the OFF-state
- Primary endpoints:
  - Drug-related: safety and tolerability of the IMP (change from baseline to 6 months)
  - Device-related: occurrence of adverse device effects (ADE)
- Secondary and exploratory endpoints:
  - UPDRS part III (OFF), UPDRS total (OFF), timed up-and-go test, home diary, PDQ-39, CGI (change from baseline to 6 months)
  - PET imaging using [^{18}F]FE-PE2I, a novel DAT tracer (baseline, 6 and 12 months)
  - Actigraphy with Parkinson's KinetiGraph™
  - CSF levels of total, oligomeric and Ser129-phosphorylated α-synuclein

Current study status

- 17 of 18 patients recruited, 15 implantation surgeries completed
- 11 randomized patients receiving doses
- 2 patients in Extension study
- 2 patients have completed the Main and Extension studies (in Follow-up study)

- Expected schedule:
  - Last patient, last visit (Main study): January 2020
  - Last patient, last visit (Extension study): July 2020

Safety data

- 111 adverse events reported in the Main study and 10 adverse events in the Extension study, most are considered mild or moderate and have recovered
- Skin reactions and swelling around the port after surgery are a common AE
- Two patients have discontinued the study (not considered to be related to CDNF)
- One patient experienced dyskinesias after receiving twelve treatment infusions, which was considered possibly related to CDNF

Summary and conclusions

- CDNF is an unconventional neurotrophic factor with potential to improve both motor and non-motor symptoms of Parkinson's disease
- CDNF alleviates ER stress, modulates aSyn oligomerization and reduces neuroinflammation
- Intermittent monthly intraputamenal CED infusions of CDNF in Phase 1-2 (first-in-human) study
- Same intracranial drug delivery used as in the recent GDNF Phase 2 study (Renishaw)
- Test infusions show excellent distribution in putamen bilaterally
- Recruitment nearly completed, end of main study expected in January 2020

Acknowledgements

- Patients for their courage and enthusiasm
- Our neurology and neurosurgery teams and other excellent study center personnel at Karolinska, Lund and Helsinki
- DSMB members and technical and clinical advisors
- Renishaw Plc and other collaborators and partners
- Our long-term collaborators at the University of Helsinki (prof. Mart Saarma's lab)
- European Union / Horizon 2020 program
- Business Finland
- Our investors