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Aiming at a breakthrough in Parkinson's: Topline data on first 6 months of Phase 1-2 clinical study with CDNF

Webinar 28 Feb 2020

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Topics of the webinar

- Webinar practicalities
- Introduction to CDNF as a potential Parkinson's therapy
- Phase 1-2 clinical study: design, dose groups, and demographics
- Safety summary
- Exploratory endpoint: DAT PET
- Conclusions and questions by the audience

Webinar practicalities: Estimated duration < 30 mins

- Speakers: Pekka Simula (CEO), Dr. Henri Huttunen (CSO)
- This presentation will be available on Herantis web site
  - → News & Events / Public materials
- Questions have been received beforehand
- Please note that the **clinical study is still ongoing:**
  - → Patient treatments continue
  - → Investigators and patients remain blinded, i.e. do not know who has received placebo
  - → Therefore, **full details cannot be shared yet** in a public presentation

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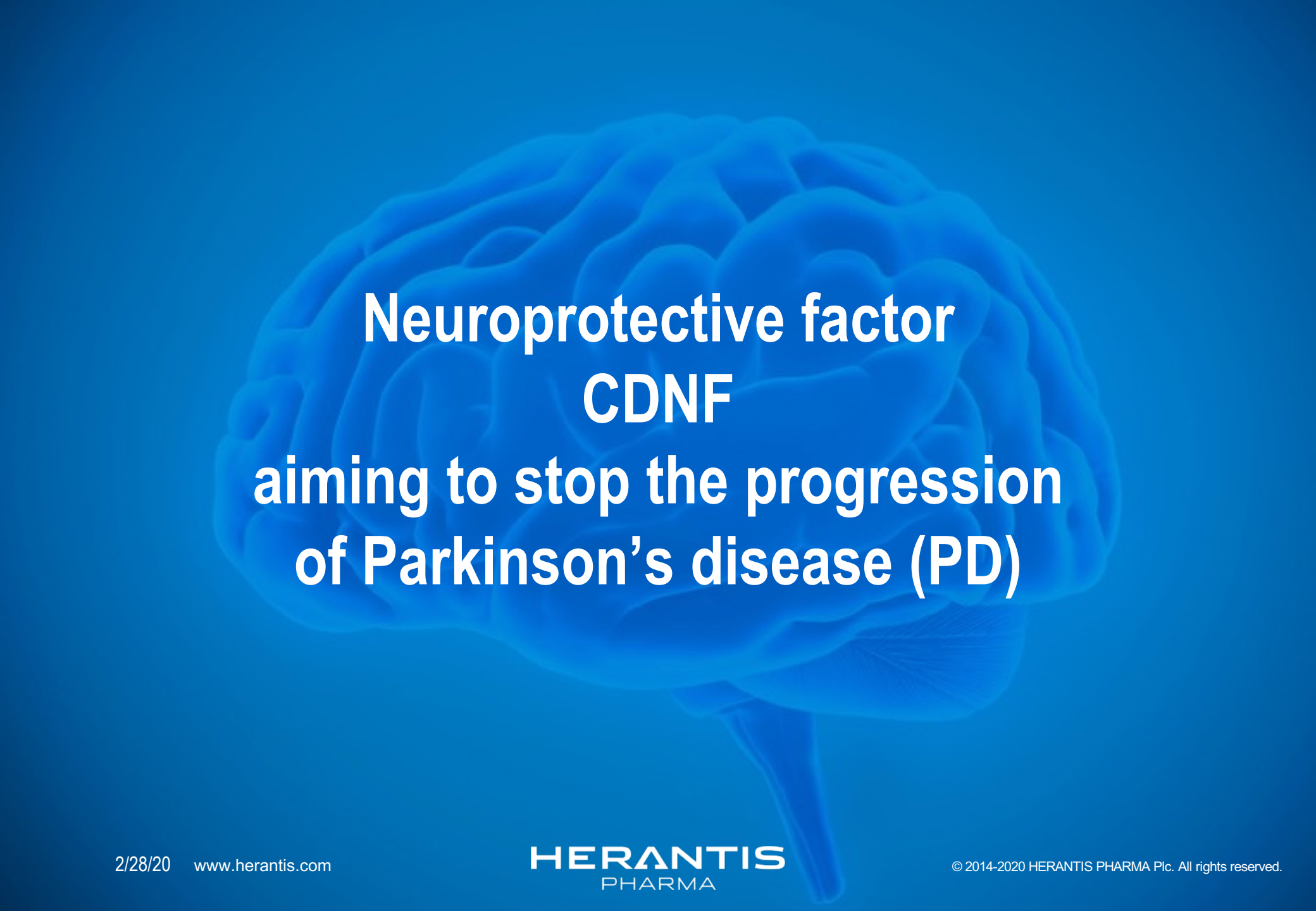

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CDNF aims at true disease modification

- Available PD therapies such as levodopa only alleviate motor symptoms
- There are no disease-modifying treatments
- CDNF targets at a **significant breakthrough in Parkinson's disease** by helping the dopaminergic neurons survive and recover, which could stop disease progression

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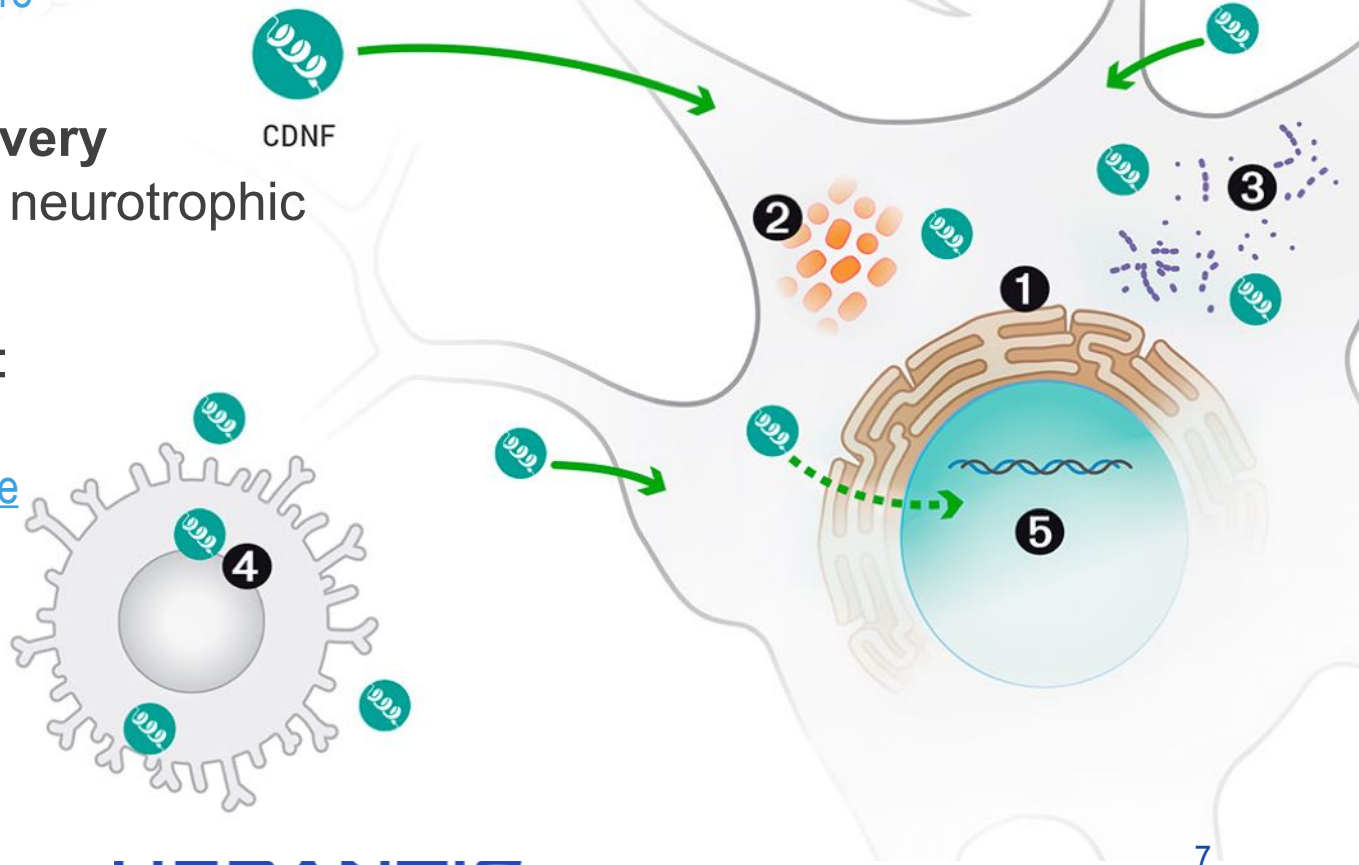
CDNF is a natural protein that helps our neurons survive

- Promising preclinical data in **several neurological diseases**
  - → CDNF functions via several mechanisms relevant to PD and other neuro-degenerative diseases
- Despite its name CDNF is **very distinct** from conventional neurotrophic factors such as GDNF
- For details please see e.g.:
  - → Herantis website: Patients / Parkinson's disease
  - → Scientific publications, e.g. Huttunen HJ & Saarma: *CDNF Protein Therapy in Parkinson's Disease.* (Cell Transplant. 2019)



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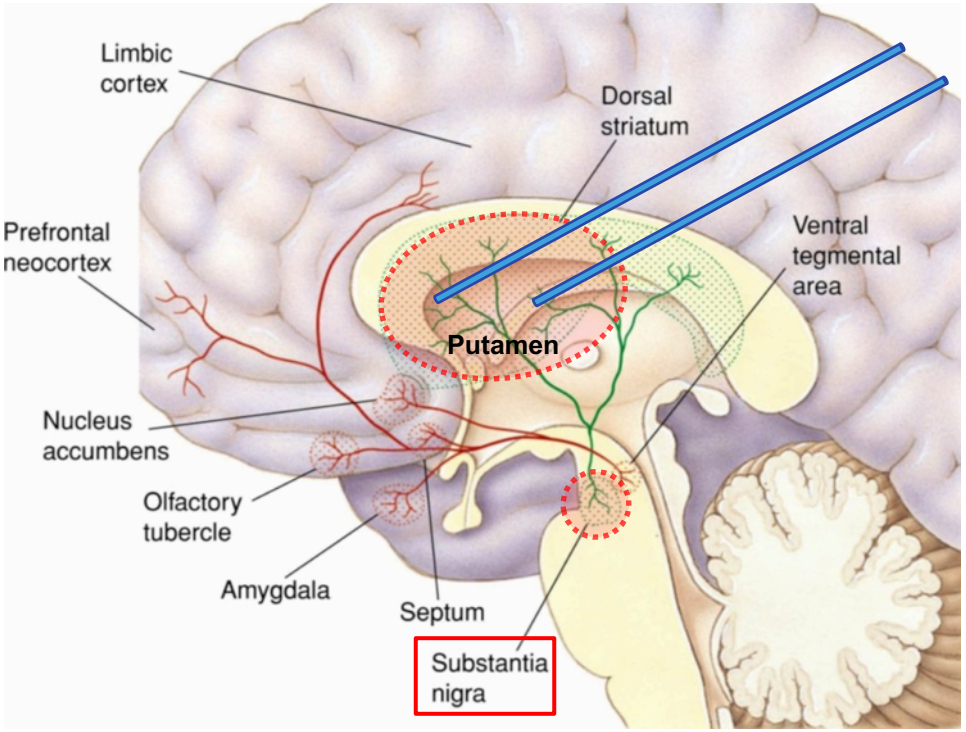
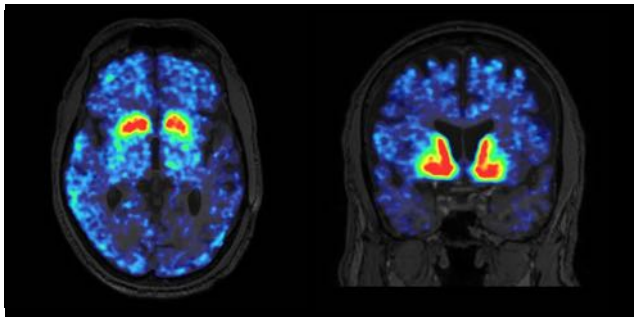
Intraputamenal CDNF infusions in Parkinson's disease

- PD is caused by the **death of dopaminergic neurons** of the nigrostriatal pathway
  - → Reduced striatal dopamine levels
  - → Motor symptoms
- Based on preclinical data:
  - → CDNF promotes functional recovery of dopaminergic terminals in the putamen
  - → CDNF is transported from the putamen to the substantia nigra to protect the cell bodies of dopaminergic neurons
- Blood-brain barrier is a common challenge for drug delivery in brain
  - → CDNF is dosed directly in the brain with a sophisticated medical device
- Changes in the functional state of the nigrostriatal pathway can be seen with PET imaging





PET imaging using a radioligand binding to dopamine transpoter (DAT)

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Phase 1-2 clinical study: design, dose groups, demographics

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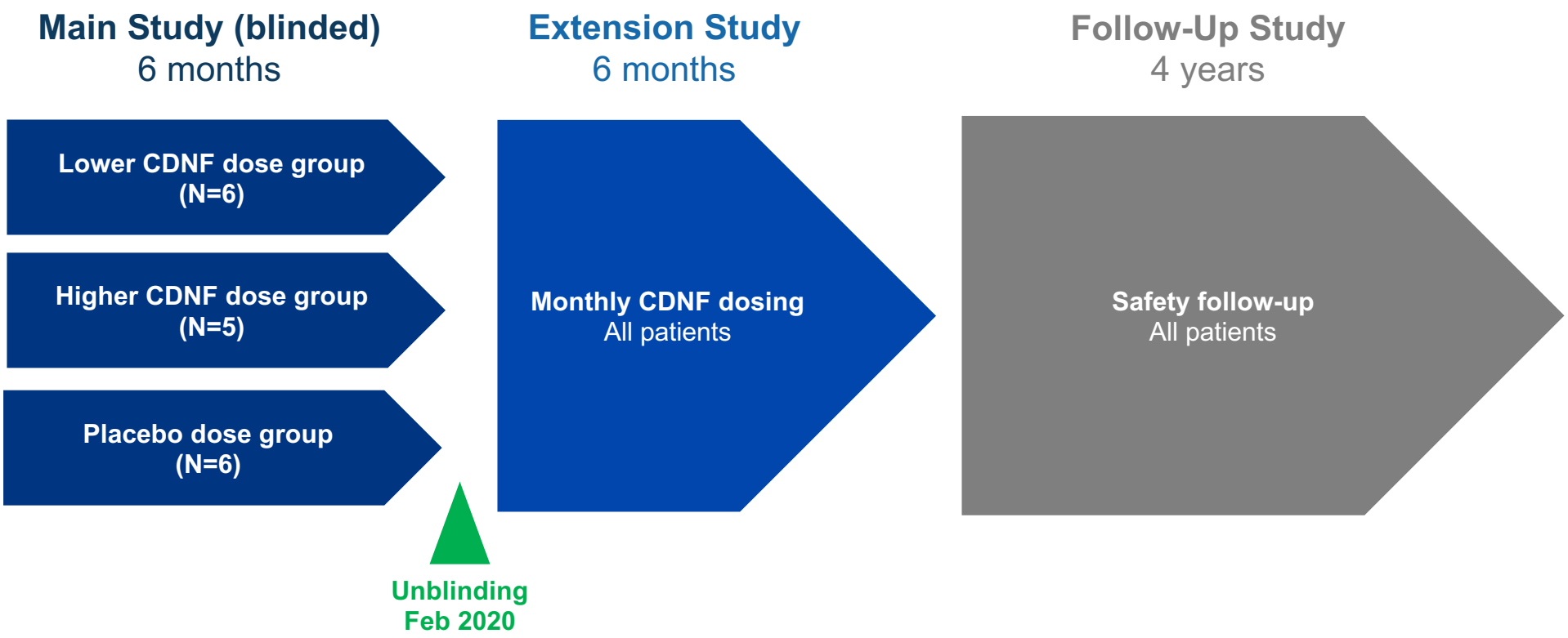
Clinical study design: Three groups, three parts



- This presentation focuses on **Main Study**
- Topline results from Extension Study expected in Q3/2020

EudraCT number: 2015-004175-73
NCT number: 03295786

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Study is conducted at leading Nordic hospitals

Important to keep in mind when assessing the Main Study results:

- First-in-human study with CDNF → **primary endpoint is safety**
- Patients have an advanced PD → **suboptimal patients for neuroprotective CDNF** with significant loss of dopaminergic neurons
- 6 months is a very short follow-up time in a PD study aiming at disease-modification
- Even from the Main Study, not all data are yet available
  → For instance, alpha-synuclein analysis are still ongoing

Demographic and PD characteristic data at screening

Characteristic	Placebo	CDNF (low-mid-mid)	CDNF (low-mid-high)
Age (years)	63.8 ± 6.4	63.2 ± 8.9	57.8 ± 6.7
Male sex, n (%)	5 (83.3%)	3 (50%)	4 (80%)
White race, n (%)	6 (100%)	6 (100%)	5 (100%)
Hoehn & Yahr (OFF), n (%)			
Stage 2	4 (66.7%)	3 (50%)	2 (40%)
Stage 2.5	1 (16.7%)	1 (16.7%)	2 (40%)
Stage 3	1 (16.7%)	2 (33.3%)	1 (20%)
Disease duration since first motor symptoms (years)	**10.5 ± 2.7**	**10.7 ± 3.1**	**10.8 ± 2.3**
UPDRS III, OFF	33.3 ± 7.6	34.7 ± 7.3	31.0 ± 6.8
UPDRS III, ON	14.8 ± 6.9	14.3 ± 4.5	11.8 ± 7.1
Levodopa response, %	60.7 ± 13.9	57.6 ± 11.8	57.0 ± 20.4
OFF-time per day, h	4.7 ± 0.7	6.1 ± 1.5	4.4 ± 1.5

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Safety summary

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Safety: The most common study drug-associated AEs

- 39 adverse events (AE) possibly or probably related to CDNF were recorded in the Main study, experienced by at least two subjects

Study drug-related AEs experienced by at least two patients	**Intensity**	**Outcome**	**TOTAL** (n=17)	
NERVOUS SYSTEM DISORDERS			# patients	# events
Cerebral gas embolism*	Mild-Moderate	Recovered	3 (17.6%)	5
Dyskinesia	Mild-Moderate	Recovered	2 (11.8%)	2
Headache	Mild-Moderate	Recovered	2 (11.8%)	2
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Chills	Mild	Recovered	2 (11.8%)	2
Fatigue	Mild-Moderate	Recovered	2 (11.8%)	2
Fever	Mild-Moderate	Recovered	2 (11.8%)	2
GASTROINTESTINAL DISORDERS				
Nausea	Mild	Recovered	2 (11.8%)	3
PSYCHIATRIC DISORDERS				
Impulse-control disorder	Moderate	Recovered	2 (11.8%)	2

* An imaging finding near the catheter tips, not associated with any clinical symptoms.

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Safety summary after Main Study

- Similar safety profiles in the placebo group and the two CDNF dose groups
  - → Current data suggest CDNF is safe and well tolerated by patients with advanced PD
  - → The main study **met its primary endpoint** on safety and tolerability of CDNF
- Certain Serious Adverse Events (SAE) were considered probably related to device surgery and the drug administration process
  - → Two patients were discontinued from the study due to SAE (infections requiring hospitalization). Both patients have recovered
  - → The surgical and infusion procedures were improved to avoid any such incidents in the future

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Exploratory endpoint: DAT PET

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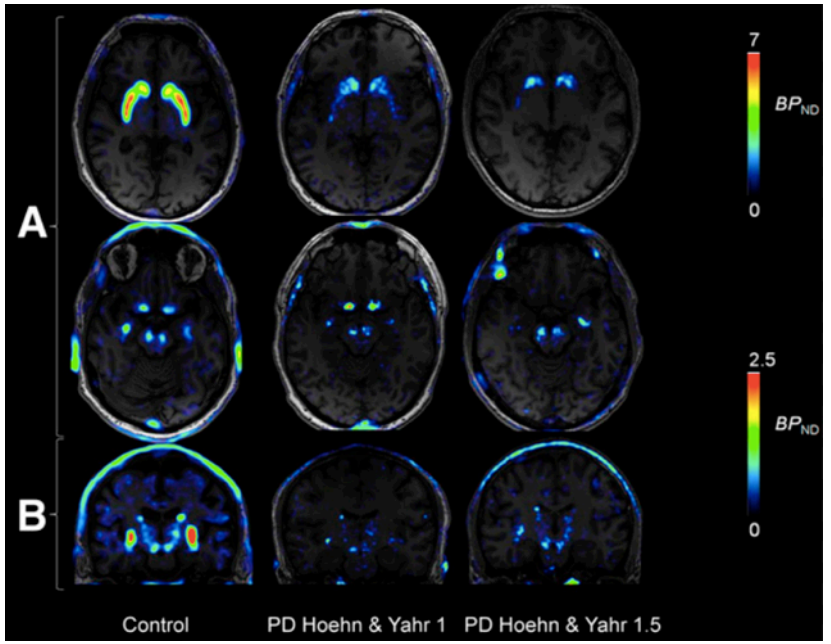
Imaging of dopamine transporter activity in the brain

- Dopamine transporter (DAT) is a presynaptic membrane protein which has a major role in the regulation of extracellular dopamine levels
  - → DAT is enriched in nigrostriatal axons and terminals
- In Parkinson disease, DAT is a useful biomarker for following **dysfunction and restoration of dopaminergic terminals** in nigrostriatal pathway
  - → Annual rate of reduction of striatal DAT uptake in PD patients is **6-13%** compared to 0-2.5% in healthy, age-matched controls
  - → On the average, a visible decline in DAT update is expected already during a 6-month follow-up of PD



Fazio et al. *J. Nucl. Med.* 56: 714-720, 2015

- ^{18}F-FE-PE2I is a novel radioligand, developed by the Karolinska PET Center in Sweden, for quantification and imaging of DAT activity in the brain
  - → For details please see e.g. Fazio et al: *Quantitative analysis of ^{18}F-FE-PE2I binding to the dopamine transporter in Parkinson's disease.* J. Nucl. Med. 2015

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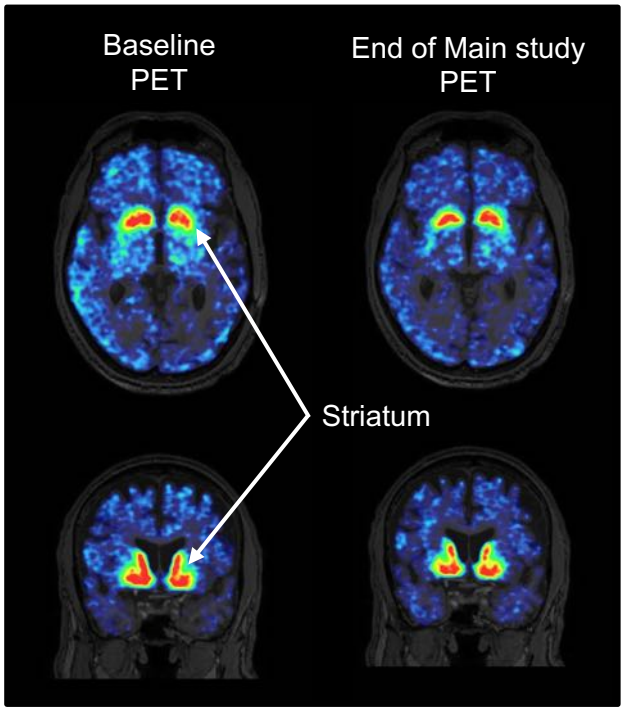
Exploratory outcome measures: DAT PET at 6 months

- DAT PET signal in the putamen between Baseline and End of Main study (6 months):
  - → Decrease in average DAT binding potential in placebo and in one CDNF group (-6-21%)
  - → **Increase in average DAT binding potential in the other CDNF group (+17%)**
- Two patients receiving CDNF treatment **showed 37-51% increase** in DAT binding potential in putamen
- No increase in DAT binding potential in nucleus caudate indicating the **effect is specific for the target/infused area**
  - → Very unlikely to be a 'placebo effect'
- Further PET scans are performed at 12 months and 19 months



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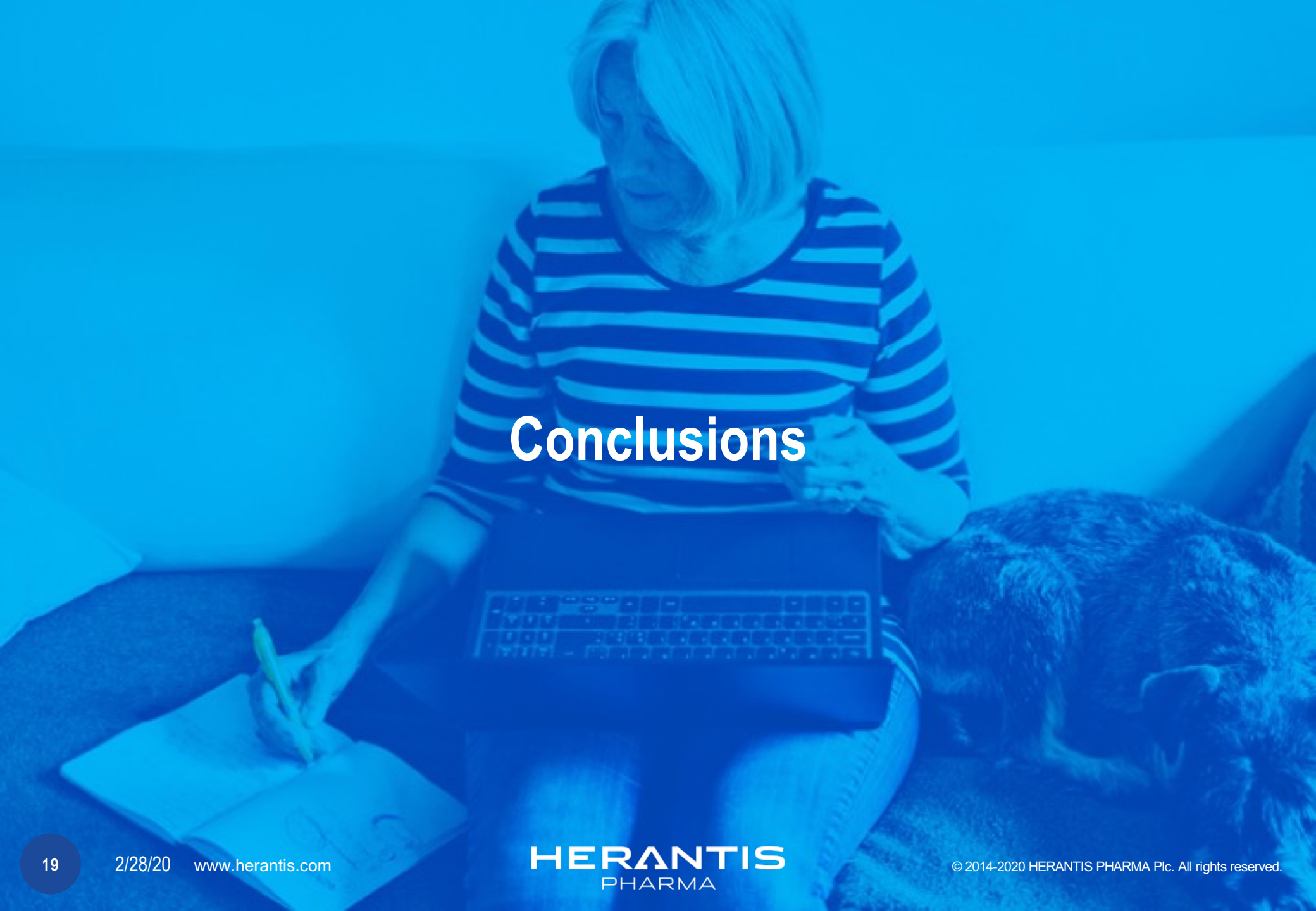

Conclusions

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Conclusions

- **Primary endpoint met**: CDNF is safe and well tolerated in **advanced PD patients**
  - → These are patients who have lost most of their dopaminergic neurons; therefore, not optimal patients for the neuroprotective and neurorestorative CDNF
- In PET imaging after 6 months, two patients show **significant increase** in putamenal DAT binding potential, suggesting biological response to CDNF in the target infusion area
  - → We have seen promising signals in some patients also in other endpoints; this will be investigated further in the Extension study
- Data analysis of the Main study (first 6 months of treatment) continues
- **Next read-out expected in Q3 2020** (Extension study = second 6 months of treatment)
- These initial signals on CDNF are also encouraging for xCDNF, based on the same mechanisms and expected to enable **significantly easier administration**

Questions received from the audience, page 1

- I have Parkinson's disease. Can I volunteer for CDNF therapy?
  - → Clinical development is strictly regulated. That applies to all new therapeutics-in-development, not just CDNF. We will keep our web site updated on future clinical studies. Please be patient!
- When will the next clinical study with CDNF begin and what are its goals, number of patients, and other details?
  - → Please keep in mind that the first clinical study is still ongoing. Our current plan is to launch a Phase 2 study in 2021, in earlier stage PD patients. However, that of course depends on many things; most importantly, more complete results from the ongoing study. The more promising the results are in the first study, the more likely we can plan a larger Phase 2 in earlier-stage, well-characterized patients.
- Do you plan to move forward in future trials with the same drug-device combination or do you plan to investigate other drug delivery approaches?
  - → The current plan is to move forward with the same combination, while we continue developing xCDNF as the next generation 'no-device' compound. However, we also monitor other possibilities; for us it is most important that, if CDNF is safe and efficacious, it could help as many patients as possible, with an as patient-friendly approach as possible.

Questions received from the audience, page 2

- Why were effects of CDNF not seen in every patient?

  → This is a first-in-human study with CDNF. The primary endpoint in first-in-human studies is **always safety;** typically you don't expect any efficacy signals in Phase 1. In this case:

  - PD patients in this study have lost most dopamineric neurons. Based on preclinical data CDNF can **protect and restore the function of neurons**, which would be a significant breakthrough. However, no treatment creates new neurons.
  - In clinical development, the optimal dose is typically defined in Phase 2 dose ranging studies. It is expected that the dose in this Phase 1 study is not optimal.
  - 6 months is a short period; part of the patients have only received placebo.
  - PD is a very heterogeneous disease. No two patients are the same; for instance, the standard-of-care levodopa dosing is customized for each Parkinson's patient.

- Do you have any anecdotal stories from the patients in the study?

  → The clinical investigators remain blinded to the study, i.e. they don't know which patients received placebo for the first 6 months. We are therefore very cautious in commenting on individual patients at this stage, even if otherwise possible while protecting their privacy.

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Thank you

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