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 CDN 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
Neuroprotective factor CDNF aiming to stop the progression of Parkinson’s disease (PD)
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
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)
Intraputaminal 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

[Image of brain with PET imaging]
Phase 1-2 clinical study: design, dose groups, demographics
Clinical study design: Three groups, three parts

Main Study (blinded) 6 months
- Lower CDNF dose group (N=6)
- Higher CDNF dose group (N=5)
- Placebo dose group (N=6)

Extension Study 6 months
- Monthly CDNF dosing All patients

Follow-Up Study 4 years
- Safety follow-up All patients

Unblinding Feb 2020

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

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

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

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

* An imaging finding near the catheter tips, not associated with any clinical symptoms.
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
Exploratory endpoint: DAT PET
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

- $^{18}$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
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
Conclusions
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 putaminal 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 dopaminergic 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.
Thank you

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