HERANTIS PHARMA

PIPELINE PROGRAMME: CDNF (CEREBRAL DOPAMINE NEUROTROPHIC FACTOR)

Introduction:

Herantis is a NASDAQ Nordic-listed biotech company, founded and headquartered in Helsinki, Finland. Through strong academic collaborations, we have developed a ground-breaking biological therapy for neurodegenerative diseases such as Parkinson's disease. Though a great deal is known about the cellular processes that contribute to neuro-degeneration, remarkably the standard of care for Parkinson's disease has remained largely unchanged since the 1960's. Herantis is aiming to change that by introducing new therapeutics for the 21st century that are focussed on slowing, stopping or even reversing disease pathology.

The Science:

Herantis is pioneering the use of human Cerebral Dopamine Neurotrophic Factor (CDNF) for the treatment of Parkinson's Disease and other neurodegenerative diseases. CDNF exerts a number of protective and stimulatory effects in the brain through its effects on a cellular mechanism called proteostasis. Proteins are the building blocks of the body, and proteostasis is responsible for the balanced synthesis and packaging (folding) of proteins, as well as for the removal of unwanted proteins. Proteostasis is thus a key cell survival and regeneration mechanism. The key proteostasis organelle in the cell is the endoplasmic reticulum (ER), which is responsible for synthesis and folding of both secretory and plasma membrane bound proteins, and also the labelling of "bad" proteins for degradation by the proteasome. When this process falters, such as in cases of cell stress and aging, proteostasis is disrupted such that proteins become malformed, misfolded and dysfunctional, causing "bad" proteins that accumulate in the cell and leading to cell dysfunction and death. In neurons and glial cells within the brain, chronic ER stress can be highly problematic. Cells experiencing ER stress activate the Unfolded Protein Response (UPR), and continuous activation of UPR leads to neuronal dysfunction and cell death and contributes to neurodegenerative disease such as Parkinson's disease. This is where CDNF comes into the picture; working on the three key mechanisms in the ER to restore proteostasis; synthesis, folding, and degradation. CDNF adjusts the cellular response to support proper protein synthesis, folding and functionality, prevent cell death, and support degradation of "bad" proteins.

The Molecule:

CDNF is an ER-located protein that can also be secreted, is expressed in multiple tissues, and comprises a 187 amino acid sequence with a molecular weight of 18 kDa. The recombinant human protein can be expressed in good yield in CHO cells and *E. coli*. As a trophic factor, CDNF has several putative modes of action that positively impact the health and function of cells under conditions of ER stress, i.e. dopaminergic neurons in PD. CDNF is capable of upregulating numerous proteins in the UPR mechanism, including GRP78, ATF4, ATF6, and XBP1. CDNF promotes cell survival by mitigating pro-apoptotic signalling.

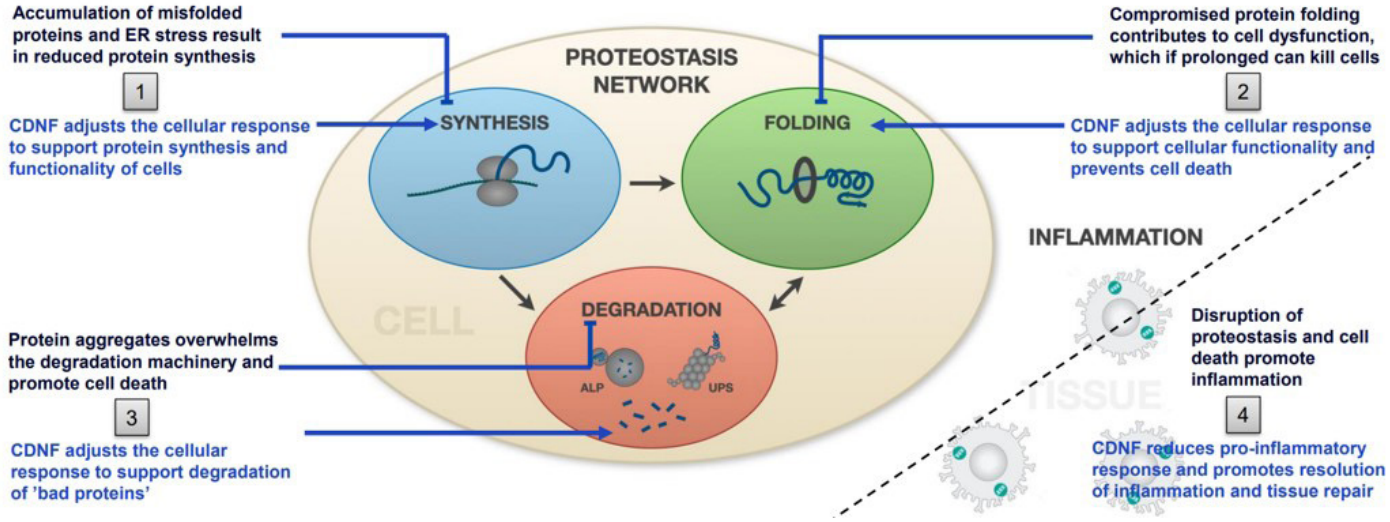

Fig 1: CDNF addresses key mechanisms in proteostasis - protein synthesis, protein folding, protein degradation, and inflammation. i) Synthesis - CDNF acts to restore normal protein synthesis by interacting with PERK, which shifts the UPR signalling from pro-apoptotic to adaptive mode. ii) Folding - CDNF interacts with a number of chaperone proteins and their regulators in the ER lumen, and modulates Unfolded Protein Response UPR signalling, which again promotes adaptive rather than pro-apoptotic response. Effects on calcium and lipid levels also may support the ER protein-folding machinery. iii) Degradation – Reduces "bad" protein accumulation, CDNF adjusts UPR signalling to support autophagy and cell survival. iv) In addition to these mechanisms, CDNF also reduces the extracellular inflammatory response (linked to UPR signalling) thus diminishing broader cellular damage.

The Data:

Herantis recently reported 6 and 12 month readouts from a PhI/II clinical safety study in PD patients (NCT03295786) and subsequent extension study (NCT03775538). As a first-in-human study, the primary endpoints were safety and tolerability. These were successfully met. The study showed excellent tolerability for CDNF, with no dose-limiting toxicities. All treatment emergent adverse events were transient and mild. Importantly, the drug safety profile was similar between the original (0-6 months) and extension studies (6-12 months); and no significant differences were observed between high and low dose groups. These results represent a major milestone for CDNF therapy and Herantis' R&D pipeline.

Herantis has undertaken several studies to explore the therapeutic efficacy of intracranially administered CDNF. In preclinical models of Parkinson's disease, CDNF successfully prevented the loss of dopaminergic neurons after exposure to the neurotoxins 6-OHDA or MPTP.

Moreover, CDNF showed encouraging results in reversing motor and non-motor symptoms in these models.

In a recent primate study, the restorative effects of CDNF on damaged dopaminergic neurons were demonstrated. Specifically, significant improvements were observed in gross motor function, fine motor function, and for the first time improved non-motor functions. The study also measured improvement in gross and fine motor functions, according to the monkey Parkinsonian disability rating scale (MPDRS) and monkey movement analysis panel (mMAP), respectively. As shown in Figure 2, CDNF produced a significant, cumulative improvement in gross motor symptoms of 53%, after 3 months' treatment. Our study also clearly demonstrated that CDNF treatment can improve non-motor PD symptoms. Both anxiety (human intruder test) and motivation (Wisconsin general apparatus) were significantly improved after CDNF treatment. This is the first time a positive effect on a non-motor symptom has been observed with a therapeutic trophic factor.

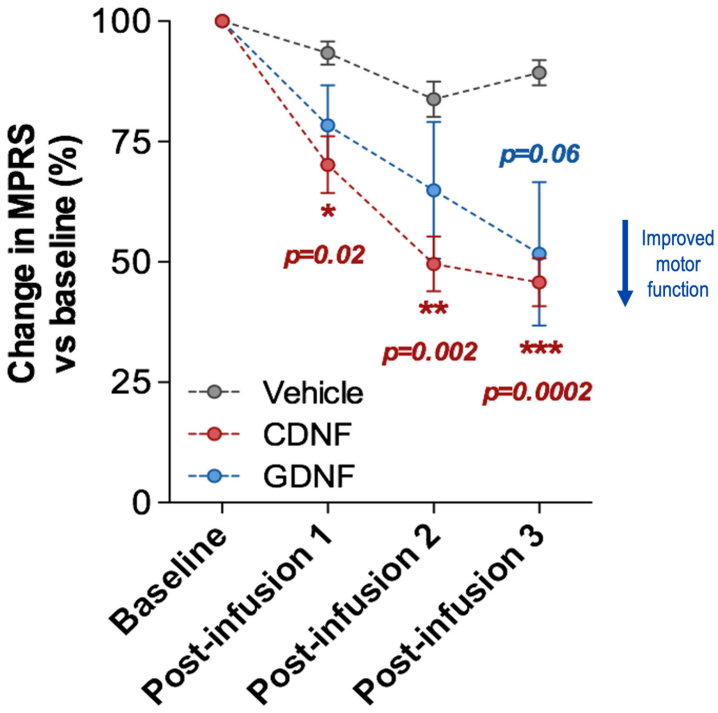

Figure 2: CDNF reduces motor symptoms by 53% in a MPTP rhesus model of PD after 3 monthly infusions, using monkey Parkinson's disability rating scale.

The Administration:

Delivery of CDNF to the mid-brain is influenced by the blood-brain barrier (BBB). CDNF protein does not penetrate the intact BBB, which means intravenous and subcutaneous administration routes are unlikely to be effective in PD and some other neurodegenerative diseases. To circumvent this in our recent clinical study, CDNF was administered directly into the brain via a surgically implanted medical device. Whilst this was a logical approach for a small clinical trial in late-stage patients, this delivery route is highly invasive and could significantly limit the eligible patient population. Herantis aims to treat Parkinson's disease in its early stages, where an appreciable population of dopaminergic neurons still remains and the neuroprotective and regenerative effects of CDNF can be maximised. We have therefore decided to avoid administration routes that necessitate surgery and instead to pursue minimally invasive routes such as intranasal, in order to allow CDNF to be conveniently used as a treatment for all stages of PD.

PD - Intranasal delivery of CDNF

The chronic nature of PD makes ease of administration vitally important for patients' well-being and compliance. Following the recent confirmation of clinical safety for CDNF, Herantis is now moving forward with alternative administration routes that offer minimally invasive delivery. Intranasal delivery of CDNF has previously been shown to be viable, since the vasculature in the upper nasal space is somewhat permeable and allows direct nose-to-brain transfer via the olfactory epithelium. Preliminary data in monkeys and rats using nebulized or liquid formulations are quite promising (Veronesi et al, 2020). Given the significant appeal of this admin-istration route, new nose-to-brain technologies and formulations are rapidly evolving. Herantis has already begun formulation studies to develop an optimised intranasal preparation of CDNF. Thereafter, in vivo studies will confirm whether CDNF can reach the relevant basal ganglia structures in therapeutic concentrations following nasal administration.

In 2014, the Michael J. Fox Foundation for Parkinson's Disease funded research towards an intranasal formulation of GDNF for PD. Although this work showed that GDNF could offer some neuroprotective effects when administered intranasally, the development programme was eventually abandoned. The GDNF protein is heavily positively charged and binds to negatively charged glycosaminoglycans, specifically heparan sulphate. This strong electrostatic binding force has a limiting effect on the diffusion of GDNF. In our own preclinical studies, intracranially infused GDNF remained highly localised at the site of injection and did not diffuse effectively (see Figure 3 below). In contrast, CDNF lacks heparin-binding motifs and is therefore less prone to glycosaminoglycan sequestration. Due to its lower non-specific binding, we expect CDNF will be able to reach the putamen and substantia nigra in higher concentrations than GDNF.

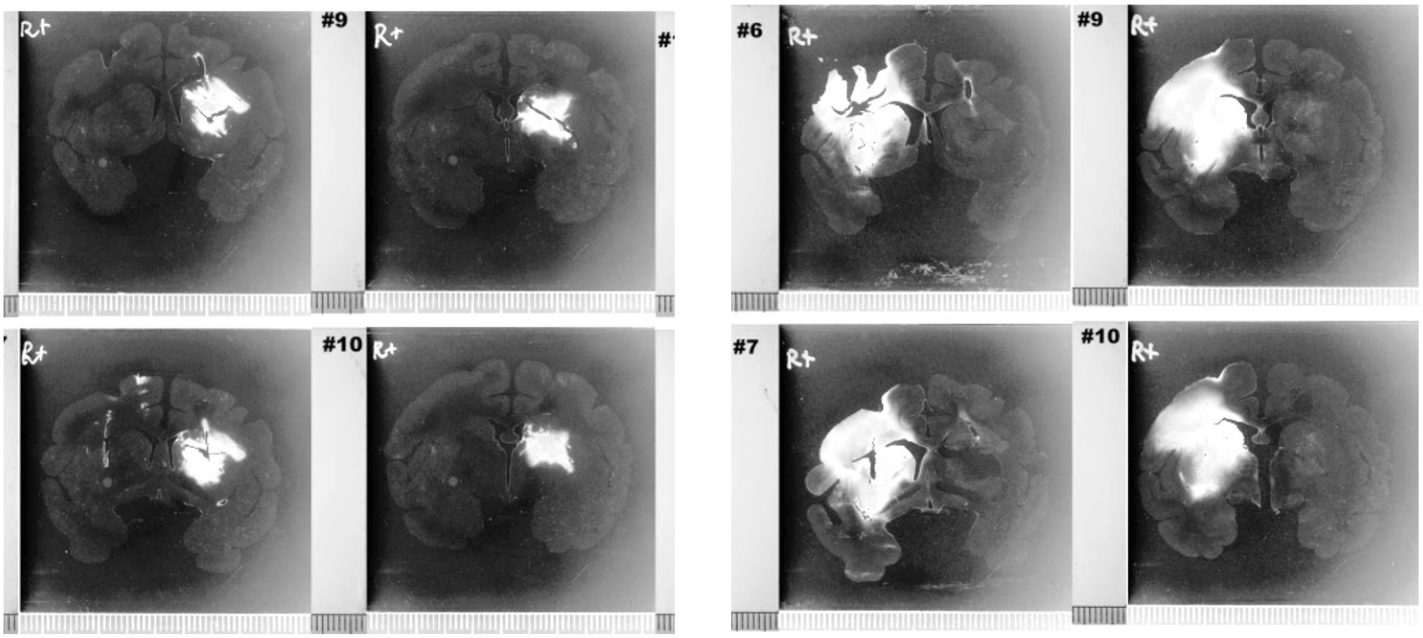

Figure 3: Direct infusion of GDNF and CDNF into the putamen with subsequent immunohistochemical assay. Brain tissue sections were stained with anti-CDNF or anti-GDNF antibodies and imaged. CDNF infusion resulted in significantly greater volume of distribution compared to GDNF.

Subcutaneous delivery of CDNF

In some neurodegenerative conditions, the BBB may be disrupted and consequently become more permeable. It may therefore be possible to administer CDNF via peripheral injection, without intracranial infusion, and still deliver therapeutic concentrations to the disease or injury site in the brain. Herantis is moving forward with preclinical proof of concept studies to establish BBB penetrance and CDNF pharmacokinetic profiles in rodents.

The Diseases

Parkinson's disease is understood to be caused by the deterioration and eventual death of dopamine-producing (dopaminergic) neurons in two principal regions of the mid-brain (the putamen and the substantia nigra). In healthy adults, dopaminergic neurons make up around 3-5% of all neurons in these regions. In Parkinson's patients, this number decreases gradually as the disease progresses over decades. A long-standing, but as yet unrealised therapeutic hypothesis is that by rescuing and restoring the function of these dopaminergic neurons, the progression of PD can be halted, and its symptoms alleviated. While the exact cause of dopaminergic neuron degeneration has not been definitively established, an important hallmark of Parkinson's disease is the formation of aggregated protein structures comprised of insoluble alpha-synuclein and misfolded ubiquitin-tagged proteins. As stated, misfolding and accumulation of "bad" proteins occur when cellular proteostasis is perturbed, and this is a common characteristic in neurodegenerative diseases.

The neuroprotective activity of CDNF and ability to restore proteostatis by reducing ER stress also indicate this therapeutic approach for acute neurodegenerative diseases (such as ischaemic or haemorrhagic stroke). A stroke event is followed by acute, sub-acute and recovery phases. Typical neuroprotective APIs (e.g. citicoline and edaravone) can be of short-term benefit during the acute phase by rescuing cells that are proximal to the ischaemic region (the ischaemic penumbra). However, CDNF can exert beneficial effects in all three phases, offering neuroprotection during the acute phase; immuno-

modulation in the sub-acute phase; and sustained neuronal regeneration in the recovery phase.

An acute ischaemic stroke (AIS) event can disrupt the BBB, increasing its paracellular and transcellular permeability. Furthermore, the use of thrombolytic (clot-busting) drugs (e.g. Alteplase) can also contribute to BBB disruption. This disruption could enable CDNF to cross the BBB into the brain, affording an opportunity to safely administer a potent neuroprotectant via a simple subcutaneous injection. Herantis intends to pursue AIS as a second indication for CDNF therapy, to be used in the acute, sub-acute and recovery phases of stroke. This approach is validated by numerous published examples of the pharmacodynamic effects of CDNF and MANF (another neurotrophic factor with highly similar mode of action) in rodent models of ischaemic stroke. Herantis has also generated preliminary data to support the use of CDNF in haemorrhagic stroke.

The Competition:

Several marketed therapeutics for PD affect only the patient's dopamine deficiency, providing transient motor symptom relief without addressing the underlying disease state. Herantis is seeking to transform Parkinson's disease treatment with the first disease-modifying therapeutic. CDNF therapy addresses a major causal element of neurodegeneration, i.e. the breakdown of proteostasis. By restoring normal production and folding of proteins, CDNF can prevent the deleterious effects of ER stress and chronic UPR activation. Recent immunotherapies may also provide similar neuroprotective effects by binding to and clearing misfolded alpha-synuclein proteins (described below). However, immunotherapies cannot replicate the trophic effects we have observed in CDNF therapy, which can directly promote the regeneration of neurons, and therefore has the potential to stop the progression of Parkinson's disease.

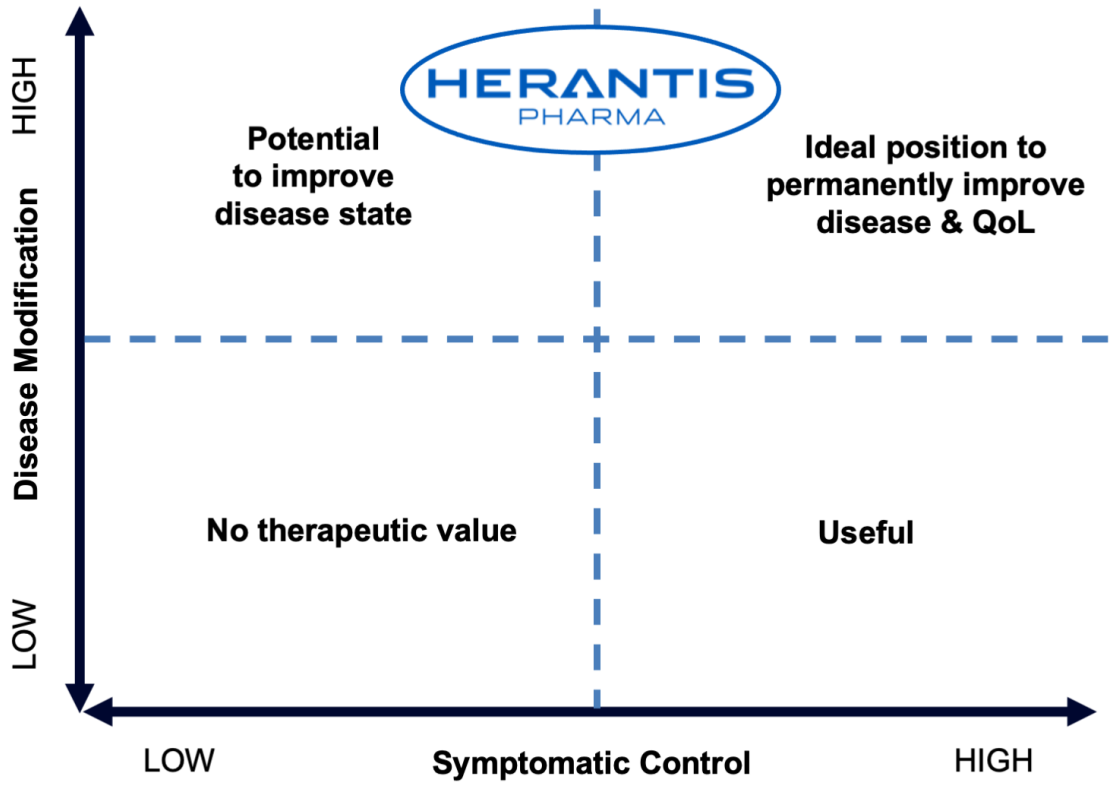

Figure 4: Competitive niche for CDNF therapy

Other Biopharma companies are developing therapeutics for PD that act on the principal "toxic" protein alpha-synuclein, e.g. Prothena/Roche have developed Prasinezumab, a monoclonal antibody targeting alpha-synuclein. This is the most advanced therapy that could have disease-modifying potential for PD, currently in PhII clinical study. Similarly, Yumanity/Merck are testing YTX-7739, a chemical inhibitor of stearoyl-CoA desaturase, which acts to reduce alpha-synuclein toxicity (PhI study). Calico Labs is exploring the role of the integrated stress response in a variety of age-related diseases. This response pathway is activated by various types of cellular stress, including ER stress. Calico develops chemical activators of the signalling protein translation initiation factor 2 (EIF2), which induces the expression of genes that normally combat cellular stress. EIF2 is one of several target proteins for Denali Therapeutics. DNL343 is an early clinical stage candidate that is intended to modulate cellular stress by restoring EIF2B function in amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD) patients.

Despite high expectations of success, the neurotrophic factor GDNF produced underwhelming results in PD patients, with no demonstrable improvement or lessening of PD symptoms after intracranial injection. Although GDNF is also a potent trophic factor, it has a different mode of action to CDNF and does not offer the same breadth of activity. For example, GDNF showed no neuroprotective effects in a rat alpha-synuclein model. Based on scientific literature, CDNF and GDNF differ fundamentally in structure, function and cellular location, and that CDNF should not be classified as a conventional neurotrophic factor. Rather, CDNF is an ER-located protein that exerts several effects that promote proteostasis.

The Market:

Herantis' therapeutic focus is Parkinson's disease and other neurodegenerative diseases. PD is the second most common form of neurodegeneration, affecting 7 to 10 million people worldwide, with over 60,000 new diagnoses in the US each year. Parkinson's is characterised by the progressive deterioration of motor functions, resulting in tremor, muscle stiffness & rigidity, and bradykinesia; and over time the appearance of neuropsychiatric, non-motor symptoms such as Parkinson's dementia, sleep disturbance and depression. In 2010, the annual societal cost of PD in Europe was calculated to be approximately €14 billion. A further study estimated that a disease-modifying therapy capable of stopping PD progression could create a societal cost saving of €400,000 per patient. PD is poorly served, with few durable therapies, none of which are able to stop or slow disease progression. If successful, our CDNF therapy will enable Parkinson's patients to maintain their quality of life, and simultaneously reduce the societal cost of PD markedly. With our global patent portfolio, which affords protection out to 2040, Herantis is well positioned to exploit a significant opportunity to change Parkinson's disease treatment with CDNF, the first clinically proven disease-modifying therapy to address both motor and non-motor symptoms.

Comprehensively, the total available market for neurodegenerative diseases was estimated to be worth €29.2Bn in 2018 and is projected to reach €54Bn by 2026 (CAGR = 7.2%). Parkinson's disease alone represents a serviceable market of €3.8Bn, growing to €5.0Bn by 2024. Based on the market share of incumbent therapeutics for PD (e.g. Levodopa & Deep Brain Stimulation), we project the serviceable obtainable market opportunity for CDNF to be >€2.5Bn.

The next 12 months will be an exciting period of R&D progress for Herantis. Throughout 2021 we will further explore and optimise the intranasal and subcutaneous administration of CDNF, leading to further IND enabling studies and clinical development in 2022.

The IP:

Herantis' assets, including the CDNF programme, are broadly protected by patents, trade-secrets and know-how. Herantis maintains a portfolio of 79 global patents across 11 families, which protect the form and function of our CDNF and xCDNF therapeutics. Our recent filings (2019) ensure continued patent protection until 2040, and several new applications are currently in preparation.

Herantis derives a strong competitive advantage from know-how and trade-secrets relating to the manufacture and control of trophic factors, which we estimate provides at least a five- year head-start over potential competitors. Additionally, upon approval of the first CDNF therapeutic, Herantis expects to be granted 5 and 8 year periods of data-exclusivity for its preclinical and clinical trials in the USA and EU, respectively.

References

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