# Herantis Pharma

**Reason: Initiating coverage**

**Company sponsored research**

**Not rated**

## Novel treatments for Parkinson's and BCAL

- Novel drugs to tackle diseases with high unmet needs
- A new approach to treat Parkinson's disease
- rNPV valuation suggests a range of SEK 39-139

### Herantis Pharma – unique approaches to severe diseases

Herantis Pharma is developing disease-modifying treatments for Parkinson's Disease (PD) and Breast Cancer-Associated Lymphedema (BCAL). In PD, the company is infusing a novel protein that has the potential to restore the deficient function of dopaminergic neurons in PD. In BCAL, which is a disease affecting women undergoing surgery or radiation due to breast cancer, Herantis has developed a novel gene therapy approach – with potential in a broader secondary lymphedema setting. It is estimated that up to 40% of women treated for breast cancer will develop BCAL, which causes debilitating swelling in their arms.

### Could this approach revolutionise the treatment of PD?

The holy grail of PD is to develop a disease-modifying treatment that could reverse this debilitating disease that affects approximately 6 million people globally. We are encouraged by Herantis Pharma's novel approach to use a neuroprotective protein to restore the function of the dopaminergic neurons that are lost in the disease. In this initiation report we explain the pathophysiology of PD, survey the current therapeutic landscape, and outline similar previous efforts to restore dopaminergic neurons.

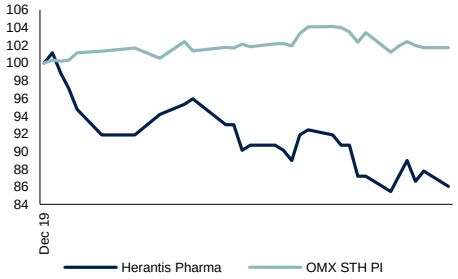
### Valuation range of SEK 39-139 per share

Our valuation range is based on a scenario analysis, which yields different risk-adjusted DCF values. The three different scenarios results in a value range of SEK 39-139 (EUR 3.7-13.0) per share. Our risk-adjustment factors are 8.4% for CDNF and 14.2% for Lymfactin to reflect estimate likelihood of approval from today's clinical stage. In our view, the main long-term opportunity for Herantis lies in the potential to generate a disease modifying benefit to patients with PD, which is the second most common neurodegenerative disease after Alzheimer's.

**Lead analyst:** Viktor Sundberg
Rickard Anderkrans

| | |
|---|---|
| **Share price (SEK)** | 03/02/2020 74.0 |
| Pharmaceuticals, Biotechnology & Life Sciences, Sw | |
| HRNTS.ST/HRNTS SS | |
| MCap (SEKm) | 494 |
| MCap (EURm) | 46.3 |
| Net debt (EURm) | 0 |
| No. of shares (m) | 6.7 |
| *Free float (%)* | *54.7* |
| Av. daily volume (k) | 0.6 |
| Next event | Q4 report: 27 Feb |

Performance




| | 1m | 3m | 12m |
|---|---|---|---|
| *Absolute (%)* | *-12.0* | *na* | *na* |
| *OMX STH PI (%)* | *-0.6* | *6.1* | *21.3* |

*Source: FactSet*

| *EURm* | 2017 | 2018 | 2019e | 2020e | 2021e |
|---|---|---|---|---|---|
| Sales | 0 | 0 | 0 | 0 | 36 |
| EBITDA | -3 | -4 | -5 | -6 | 30 |
| *EBITDA margin (%)* | *-1,211.3* | *-1,594.1* | *-2,155.6* | *nm* | *83.4* |
| EBIT adj | -4 | -5 | -6 | -6 | 29 |
| *EBIT adj margin (%)* | *-1,752.2* | *-2,116.7* | *-2,655.2* | *nm* | *81.7* |
| Pretax profit | -2 | -4 | -7 | -6 | 29 |
| EPS rep | -0.50 | -0.85 | -1.13 | -0.95 | 4.21 |
| EPS adj | -0.50 | -0.85 | -1.13 | -0.95 | 4.21 |
| *Sales growth (%)* | *789.1* | *2.2* | *-2.2* | *-100.0* | *na* |
| *EPS growth (%)* | *53.1* | *-69.7* | *-32.9* | *15.7* | *542.7* |

*Source: ABG Sundal Collier, Company data*

| | 2019e | 2020e | 2021e |
|---|---|---|---|
| P/E (x) | -6.1 | -7.3 | 1.6 |
| P/E adj (x) | -6.1 | -7.3 | 1.6 |
| P/BVPS (x) | 13.92 | -13.82 | 1.69 |
| EV/EBITDA (x) | -9.5 | -9.3 | 0.8 |
| EV/EBIT adj (x) | -7.7 | -8.2 | 0.8 |
| EV/sales (x) | 205.74 | n | 0.63 |
| *ROE adj (%)* | *-404.9* | *######* | *234.6* |
| *Dividend yield (%)* | *0* | *0* | *0* |
| *FCF yield (%)* | *-13.5* | *-11.1* | *68.1* |
| *Lease adj. FCF yld (%)* | *-13.5* | *-11.1* | *68.1* |
| Net IB debt/EBITDA | -0.0 | -0.9 | -0.8 |
| *Lease adj. ND/EBITDA* | -0.0 | -0.9 | -0.8 |

## Opportunities

We believe that Herantis offers an attractive opportunity to address diseases with a large unmet medical need and to compete on the market for neurodegenerative diseases and secondary lymphedema. Additionally, the company's technology could serve as a platform going into several diseases with similar pathologies. If strong clinical data is generated the company could find itself in an attractive position as an acquisition.

## Risks

The key risks for Herantis are related to clinical and development risks of its candidates in terms of failed or delayed studies. Liquidity and financing risks are also important to consider, as Herantis is currently a development-stage company with negative cash flow. The competitive landscape could also be significantly different at the time when Herantis' drug candidates could be approved.

## Company description

Herantis Pharma is a publicly listed (Finland, HRTIS and Sweden, HRNTS) drug development company aiming to revolutionize the treatment of diseases with unmet clinical needs. Based on leading academic research published in high-impact journals including Nature and Science, two ongoing clinical development programs explore the potential of its novel drug candidates in Parkinson's disease and secondary lymphedema. Both Parkinson's disease and lymphedema remain conditions in which current treatments only address symptoms and therefore do not enable long-term improvement for patients.

## Contents

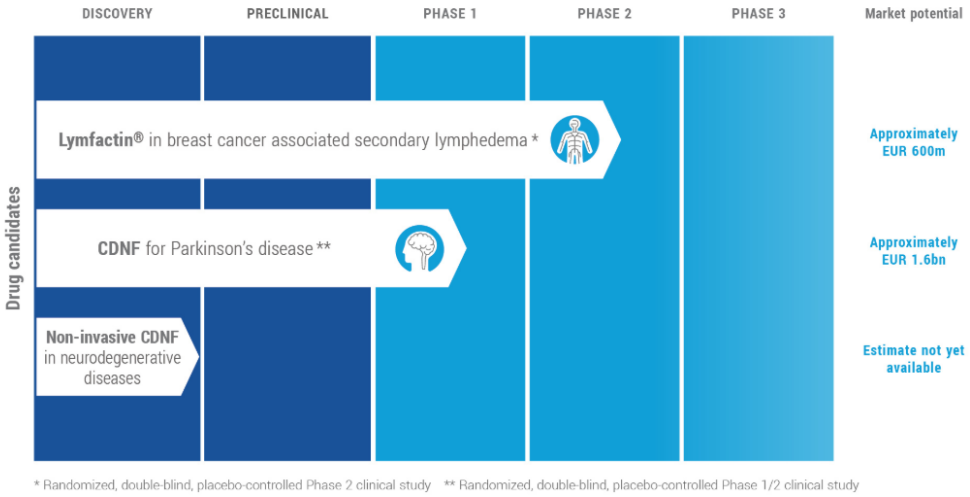
# Summary

***Herantis Pharma is a publicly-listed drug development company aiming to revolutionise the treatment of diseases with unmet clinical needs. Based on leading academic research published in high-impact journals including Nature and Science, the two ongoing clinical development programmes explore the potential of its novel drug candidates in Parkinson's disease and secondary lymphedema.***

## Herantis Pharma

Herantis Pharma ("HRTIS"/"HRNTS") is an innovative drug development company which is pushing the boundaries of standard therapeutic approaches. The company's lead drug candidates, CDNF and Lymfactin, aim to revolutionise the treatment of Parkinson's disease and other neurodegenerative diseases, and secondary lymphedema. Herantis' strategy aims to develop promising drug candidates through early clinical studies and subsequently sign collaboration agreements with large pharmaceutical companies to ensure strong resources for late stage development and commercialisation. We assume out-licensing after successful phase 2 studies proving the efficacy of the treatments, leading to milestone payments and royalty income. Herantis is dual listed on Nasdaq First North Growth Market Finland ("HRTIS") and Nasdaq First North Growth Market Sweden ("HRNTS").

### Pipeline overview




*Source: ABG Sundal Collier, company data*

## Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, affecting more than 6 million patients worldwide. In PD the current gold standard is to treat patients with levodopa (a precursor of dopamine) or other symptomatic treatments. Current treatments cause undesirable side-effects, and a large unmet need remains for treatments that offer disease modification (stops or slows the disease progression). Herantis Pharma is developing a new drug based on the discovery of a novel neuroprotective protein (CDNF) that in pre-clinical studies has shown disease modifying properties in PD. The disease modifying promise of CDNF puts Herantis at the forefront of new emerging therapeutic strategies to tackle PD, and the company is currently testing CDNF in a phase 1-2 clinical trial to evaluate safety and early signs of efficacy.

## Breast Cancer-Associated Lymphedema (BCAL)

Herantis is also developing the Phase 2 asset Lymfactin gene therapy as a potential therapy for breast cancer-associated lymphedema (BCAL), administered as a single-dose injection in combination with lymph node transplantation surgery. Lymphedema refers to the swelling of limbs and is most commonly caused by the removal of or damage to lymph nodes as a part of cancer treatment. Currently, there is no cure or disease-modifying therapies for this chronic condition, indicating a significant unmet medical need given its negative impact on quality of life. Secondary lymphedema (such as BCAL) affects ~1.4 in every 1,000 individuals in the general population, translating to ~450K patients in the US and EU5 respectively. Breast cancer incidence is ~250K in US and EU5; ~20% of those diagnosed patients will undergo a mastectomy (surgery to remove all breast tissue from a breast) and ~30% of patients that undergo mastectomy will present with BCAL. This implies that ~29K patients in the US and EU5 are diagnosed with BCAL each year. The ongoing Phase 2 trial is expected to read-out in the first quarter of '21e, comparing Lymfactin and lymph node transplantation surgery with placebo and surgery.

## Valuation

For our fair value estimation of Herantis, we outline three different scenarios yielding a risk-adjusted NPV fair value range of SEK 39–139 (EUR 3.7–13.0) per share using a WACC of 13%. Scenario 1 (SEK 39/EUR 3.7 per share) assumes that CDNF fails to prove clinical utility, leaving Lymfactin as the sole asset. Scenario 2 (SEK 94/EUR 8.8 per share) maintains the forecasts and assumptions outlined in the 'forecasts and estimates'-section. Scenario 3 (SEK 139/EUR 13.0 per share) assumes stronger-than-expected disease-modifying efficacy, leading to increased peak penetration (+5%) and higher pricing (+20-25%) from Scenario 2. Given its early development stage, we exclude the non-invasive xCDNF compounds from our valuation.

**Herantis share price vs. Scenario 1-3**


*Source: ABG Sundal Collier, InFront*

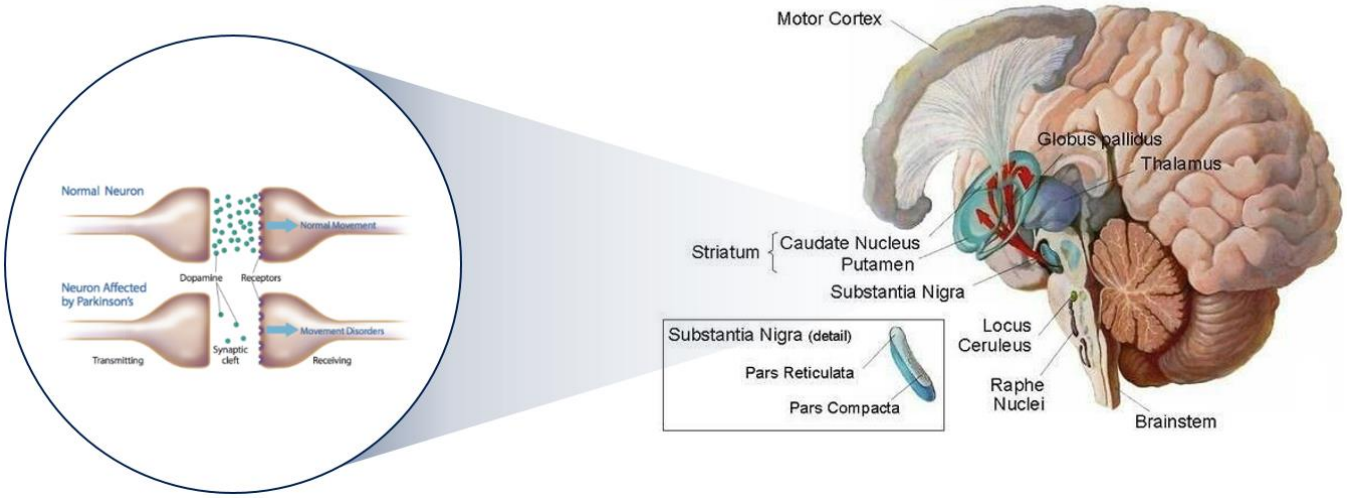
# Parkinson's disease

***Parkinson's disease is the second most common neurodegenerative disease, affecting approximately 6 million people worldwide. The disease causes the dopamine-producing neurons to die in a specific part of the brain, which controls the body's balance and movement. The current gold standard is to treat the disease with a drug called Levodopa, which is converted to dopamine in the brain and was developed over 60 years ago. Herantis Pharma hopes to revolutionise Parkinson's treatment with a specific neuroprotective protein that could re-generate dopamine producing brain cells among its other functions.***

**A brief overview of Parkinson's disease**

It has now gone 203 years since James Parkinson released his paper "An essay on the shaking palsy" which detailed the clinical features of the disease that bears his name. Today, Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, affecting approximately 1 million individuals in the US alone. PD is a disease affecting the dopamine-producing neurons in the substantia nigra pars compacta region that leads to the cardinal symptoms of the disease. These are bradykinesia (slow movement), tremors, rigidity and postural instability (impaired balance and falls). It is estimated that as much as 50-80% of the dopaminergic neurons are already lost when the first symptoms of the disease occur.[1] Apart from the cardinal symptoms, several other non-motor symptoms such as sleep disorders, depression and cognitive changes are also hallmarks of PD. These non-motor symptoms support the hypothesis that other non-dopaminergic neurons are also affected in the disease.

**A brief overview of the pathophysiology of Parkinson's disease**




*Source: ABG Sundal Collier, company data*

[1] DeMaagd et al 2015 "Parkinson's disease and Its Management"

### Why do dopamine and non-dopamine producing neurons die?

There are two forms of PD; familial (genetically inherited) and sporadic (developed from gene-environment interactions that are not fully understood). Familiar PD constitutes 10-15% of all cases. 85-90% are sporadic PD without any known cause.[2] The greatest risk factor for sporadic PD is age, with most cases being presented at 60-65 years. Even though sporadic PD has an unknown etiology several hypothesis that are not mutually exclusive have been investigated, which we describe briefly in this section.

- **The α-synuclein hypothesis**
  In 1997, Polymeropoulos et al. reported case studies of Italian and Greek families that had a rare mutation in genes that produced a protein called α-synuclein and subsequently developed PD.[3] This led to the hypothesis that sporadic PD (without any known inherited genetic cause) was also caused by abnormally functioning α-synuclein proteins. Looking at patients with Parkinson's, α-synuclein aggregates to form insoluble particles called Lewy bodies (aggregated protein clumps). The leading hypothesis is that these clumps of α-synuclein proteins or that the α-synuclein proteins themselves that have the characteristics of clumping could be toxic for neuronal cells. These toxic α-synuclein protein oligomers and fibrils then slowly spread through the brain in a prion[4] like fashion. In addition, the build-up of these toxic proteins is also thought to be mediated by abnormalities in the autophagy/lysosome and the ubiquitin–proteasome system (UPS), which are the two major intracellular degradation mechanisms of dysfunctional components.[5]

- **The neuro-inflammation hypothesis**
  Studies in several animal models of PD have shown that neuro-inflammation also plays an important role in disease progression. Two specific brain cells called microglia and astrocytes are central in the role of neuro-inflammation.

    - **Microglia**
      Microglia (which are macrophage like cells that uphold the immune defence in the brain) comprise about 5-10% of all brain cells and have shown to be pro-inflammatory in disease models of PD, while being more anti-inflammatory in healthy controls. Misfolded proteins such as α-synuclein aggregations also trigger the pro-inflammatory phenotype of microglia.

    - **Astrocytes**
      Astrocytes are the most common brain cells, outnumbering neurons by five times. They provide energy to neurons and maintain brain homeostasis. These cells also react to pro-inflammatory cytokines such as IL-1 β and TNF-α and have shown to undergo astrogliosis (abnormal increase in the number of astrocytes) in PD. These cells also release cytokines and chemokines that promote a pro-inflammatory environment contributing to the pathophysiology of PD.

[2] Ball et al 2019 "Parkinson's disease and the environment."
[3] Polymeropoulos et al 1997 "Mutation in the alpha-synuclein gene identified in families with Parkinson's disease."
[4] Prions are infectious proteins responsible for diseases such as Creutz Feldt Jakobs disease and Scrapie in animals.
[5] Klein et al 2018 "Is Parkinson's disease a lysosomal disorder?"

It is believed that the uncontrolled neuro-inflammation caused by the synergistic activation of microglia and astroyctes lead to the death of dopaminergic and non-dopaminaergic neurons causing PD. However, whether neuro-inflammation is the cause or consequence of dopaminergic neuron degeneration remains debatable among scientists.

## Other hypotheses about why dopaminergic neurons die

- **Mitochondrial hypothesis**
  Many genes connected with familial PD have been shown to affect components of the mitochondrial system (the energy-producing organelles) and therefore contributing to neuronal death. This hypothesis was also strengthened by several case studies from young drug addicts taking a drug named MPTP that caused irreversible Parkinsonism (Parkinson symptoms). The drug MPTP affects the mitochondria in the brain, which was hypothesised to also cause sporadic PD.

- **Gut hypothesis**
  Several findings have supported the view that PD disease could be a consequence of a dysfunctional gastrointestinal system. A study that analysed 1.7 million people, tracked for 52 years, found that people who had their appendix removed had a 19.3% lower chance of developing PD. Researchers have also found the toxic forms of α-synuclein in the appendix of healthy volunteers implicating that the disease might start in somewhere else than in the CNS and then spread to the substantia nigra. In addition, Patients who develop PD often report that they had gastrointestinal problems earlier in life.[6]

## How do we treat Parkinson's disease?

In the following section we go through the current treatment options for PD. Although a number of treatment options exists we want to emphasize that today's standard of care for PD only treats the motor symptoms (symptoms related to movements of the body) of the disease and do not treat the underlying cause of the disease. In addition, no treatment today can alleviate the non-motor symptoms such as the sleep disturbance, depression, anxiety, hallucinations and other cognitive symptoms of PD.

**Levodopa – the gold standard for Parkinson's disease**

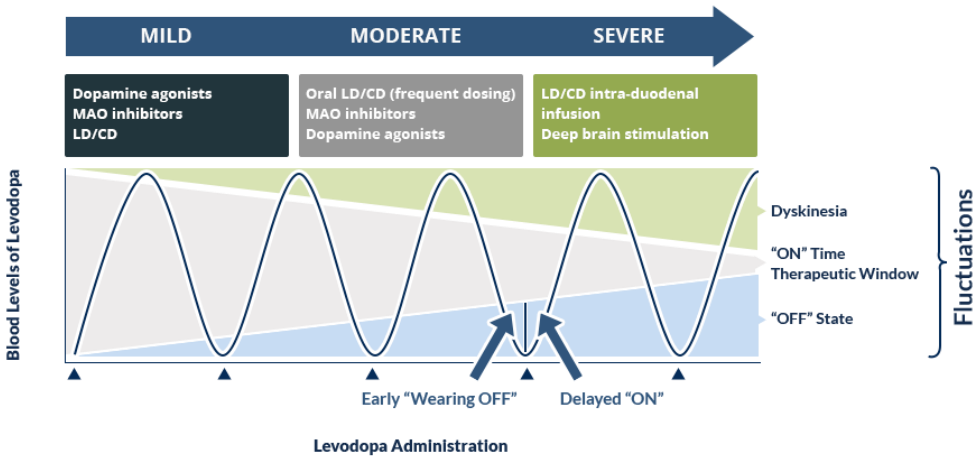
The Swedish Nobel Laureate Arvid Carlsson's discovery at the end of the 1950s that dopamine was an essential neurotransmitter for controlling movement in animals led to the development of the drug levodopa. Levodopa is a precursor to dopamine, which unlike dopamine can cross the blood brain barrier (BBB) and is converted to dopamine by an enzyme called DOPA decarboxylase (DDC). However, DDC is also present outside of the CNS and to avoid conversion to dopamine peripherally, levodopa is given with a decarboxylase inhibitor to inhibit peripheral conversion and allow as much levodopa as possible to pass the BBB. Most patients respond well to levodopa; however, in 40%–50% of patients, motor fluctuations and dyskinesias will develop in five years of chronic levodopa treatment (and in 70%–80%, after 10 years of treatment).[7] These so-called dyskinesias (involuntary muscle movements) and "OFF" episodes (episodes when levodopa is

[6] Houser et al 2017 "The gut-brain axis: is intestinal inflammation a silent driver of Parkinson's disease pathogenesis?"
[7] Rizek et al 2016 "An update on the diagnosis and treatment of Parkinson disease"

no longer working and tremors, rigidity and slow movement re-appear) is the largest unmet medical need in levodopa/carbidopa treated patients, and gets worse as the disease progresses.

In addition, oral levodopa has a poor absorption profile since levodopa is an amino acid that competes with other amino acids from food and carbidopa when taken up by amino acid receptors in the gastrointestinal tract. Therefore, only 30% of the drug enters into the blood stream and only around 5-10% cross the BBB.[8] In addition to the poor absorption, levodopa has a short half-life of 0.75-1.5h which means that patients must take several tablets per day causing fluctuations in dopamine levels and worsening of dyskinesia and "off" episodes.

### Levodopa motor complications explained




*Source: ABG Sundal Collier, Neuroderm corporate presentation*

## Other medications for Parkinson's disease

Since levodopa could cause severe motor symptoms as the disease progresses, some patients opt for other treatments in the early stages of PD. One such treatment is to take dopamine agonists that mimic the function of endogenous dopamine. However, they are not as effective as levodopa and could still cause motor symptoms and increase side effects such as hallucinations and sleepiness.

Another alternative treatment to levodopa is to take monoamine oxidase-B (MAO-B) inhibitors, which will lengthen the time that dopamine is active in the brain by inhibiting dopamine re-uptake by the synapses. Many patients take these drugs to delay the initiation on levodopa treatment in fear of the motor complications that are associated with levodopa. However, MAO-B inhibitors are not as effective as levodopa.

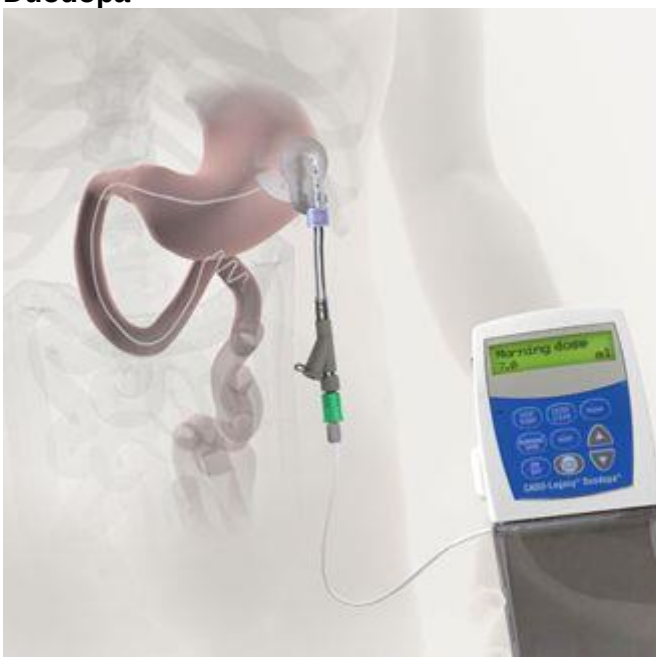
## Severe Parkinson's – limited treatment options

### Duodopa

When the disease cannot be controlled adequately with oral levodopa, patients have the option to install a medical device (Duodopa, Abbvie) that can pump in levodopa/carbidopa directly into the duodenum (first section of the small intestine) where the drug is taken up by the body. This enables levodopa to bypass the impact of intra-subject variability in gastric absorption and the short half-life of the drug. However, even if Duodopa improves the motor symptoms many patients get device-related complications such as abdominal pain, nausea, vomiting, infection and inflammation, tube dislocations, pump malfunction and tube occlusion.[9]

[8] Waller et al 2018 " Extrapyramidal movement disorders and spasticity"
[9] Ciurleo et al 2018 "Assessment of Duodopa effects on quality of life of patients with advanced Parkinson's disease and their caregivers."

**Duodopa**

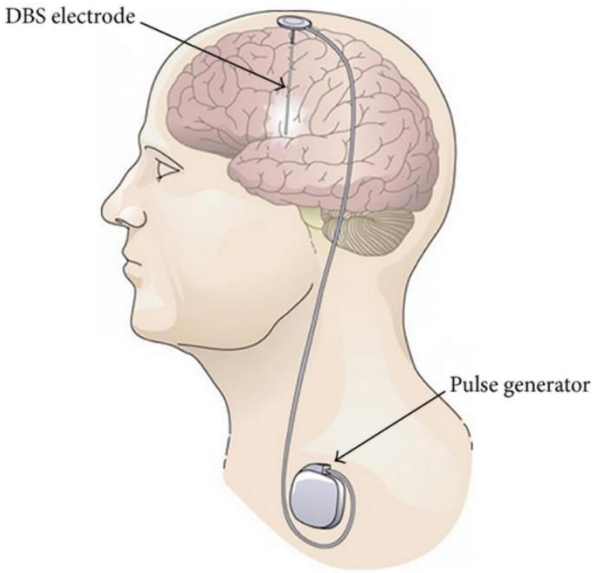


*Source: ABG Sundal Collier, Stawek et al 2010*

**Deep Brain Stimulation (DBS)**

Another treatment option is deep brain stimulation (DBS), which involves implanting programmable multi-contact electrodes deep within the brain at specific sites. It has shown remarkable efficacy in late stage Parkinson's, with surprisingly few serious side effects given the invasive nature of the implantation of the device. The consensus for many years has been that DBS is a treatment for advanced disease given that it requires invasive surgical intervention. However, studies in early stage PD such as EARLYSTIM have shown evidence that DBS can induce significant clinical benefits for early stage PD patients.[10] We view this as a promising trend for Herantis Pharma since it gives support that treatment involving surgical interventions can be moved to earlier stages of PD.

**Illustration of Deep brain stimulation (DBS)**




*Source: ABG Sundal Collier, phys.org*

[10] Lozano et al 2019 "Deep brain stimulation: current challenges and future directions."

**Concluding remarks about the current treatment landscape**

Even though several treatment options exist, PD remains an incurable neurological disease that can only be somewhat managed by non-disease modifying treatments. The current gold standard is levodopa treatment and DBS, but the shortcomings are significant, with diminishing effectiveness over time and medication-related complications such as dyskinesia and OFF symptoms. Moreover, none of the current treatments address the non-motor symptoms, which leaves a significant clinical unmet medical need for new treatments that can target the underlying cause of PD.

## Selection of currently marketed drugs in Parkinson's disease

| | | | | Phase | | | | |
|---|---|---|---|---|---|---|---|---|
| **Sponsor** | **MoA** | **Drug class** | **Therapeutic** | **Preclinical** | **Phase I** | **Phase 2** | **Phase 3** | **Marketed** |
| **MARKETED DRUGS** | | | | | | | | |
| Merck | Levodopa/Carbidopa | small molecule | Sinemet CR (controlled release) | | | | | ● |
| Schwarz Pharma | Levodopa/Carbidopa | small molecule | Parcopa | | | | | ● |
| Impax Pharma | Levodopa/Carbidopa | small molecule | Rytary ER (extended release) | | | | | ● |
| AbbVie | Levodopa/Carbidopa | Device | Duopa | | | | | ● |
| Novartis | COMT inhibitor, inhibi | small molecule | Comtan (entacapone) | | | | | ● |
| Bausch Health | COMT inhibitor, inhibi | small molecule | Tasmar (tolcapone) | | | | | ● |
| Novartis | DOPA decarboxylase | small molecule | Stalevo | | | | | ● |
| Boehringer Ingelheim | Dopamine agonist | small molecule | Mirapex (pramipexole) | | | | | ● |
| GlaxoSmithKline | Dopamine agonist | small molecule | Requip (ropinirole) | | | | | ● |
| US world meds | Dopamine agonist | small molecule | Apomorphine injection (pen) | | | | | ● |
| UCB | Dopamine agonist | small molecule | Rotigotine (transdermal patch) | | | | | ● |
| Mylan | MAO-B | small molecule | Selegline | | | | | ● |
| Valeant | MAO-B | small molecule | Selegiline (desintegrating tablet) | | | | | ● |
| Teva | MAO-B | small molecule | Rasagiline | | | | | ● |
| Zambon | MAO-B | small molecule | Safinamide | | | | | ● |
| Novartis | NMDA+others | small molecule | Amantadine | | | | | ● |
| Adamas | NMDA+others | small molecule | Amantadine (extended release) | | | | | ● |
| Kyowa Kirin | Adenosine 2A | small molecule | Istradefylline | | | | | ● |
| Intas | Anticholinergic | small molecule | Trihexyphenidyl | | | | | ● |
| Bayshore | Anticholinergic | small molecule | Benztropine | | | | | ● |
| Acadia Pharmaceuticals | 5-HT (2A) | small molecule | Pimvanserin | | | | | ● |
| Acorda Therapeutics | Levodopa | small molecule | Inbrija (inhaled L-dopa) | | | | | ● |

*Source: ABG Sundal Collier, company data*

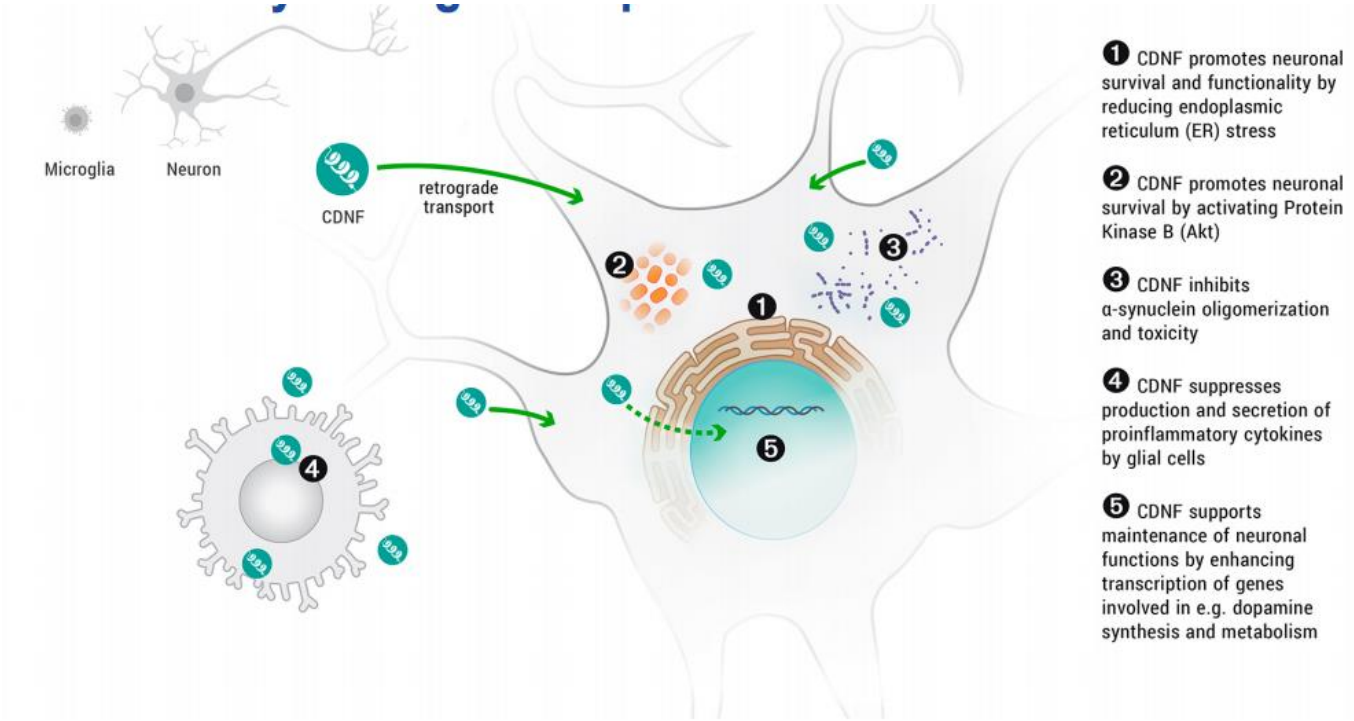
# Herantis Pharma's solution

***Herantis Pharma is investigating CDNF, which is a neuro-restoring and protective protein that has the potential to be a novel disease-modifying treatment for PD. CDNF can protect neurons from degeneration and restore the function of already degenerating neurons. This suggests that CDNF has the potential to stop or slow the progression of Parkinson's disease, which would make a significant therapeutic impact on the lives of patients living with PD. CDNF's multi-modal mechanism of action also implies a platform potential for possibly treating other neurodegenerative diseases such as ALS, Alzheimer and Huntington disease.***

**Cerebral dopamine neurotrophic factor (CDNF)**

CDNF is a protein naturally present in humans. It was discovered by Professor Mart Saarma's group at the University of Helsinki and published in the high-impact science journal Nature in 2007.[11] Initially, CDNF was described as a neurotrophic growth factor (NTF) but subsequent analysis has revealed that CDNF is a distinct protein, functionally and structurally different than NTFs. We view this as an important point since NTFs were investigated at the beginning of the 1990s for PD, with mostly disappointing outcomes (please see appendix B). The mechanism of CDNF action is multi-modal (see illustration below) and CDNF diffuses more broadly in brain tissue compared to NTFs, by inhibiting microglia secretion of pro-inflammatory cytokines, and better targets the injured cells.

**CDNF Mechanism of Action**

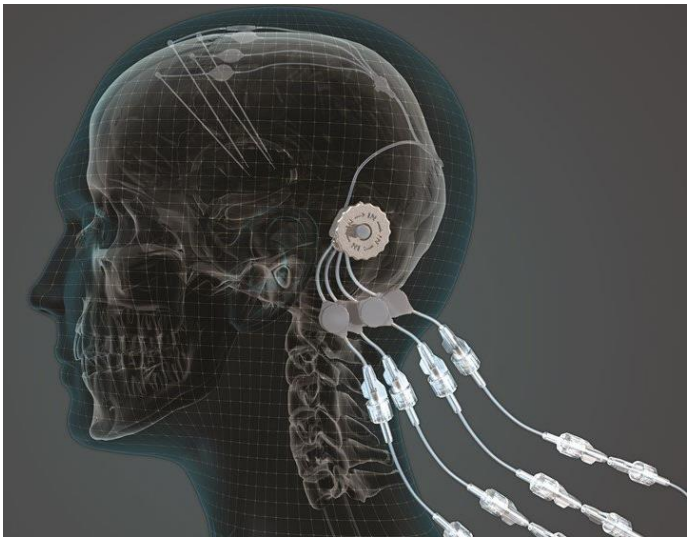



*Source: Herantis Pharma Corporate Presentation*

[11] Lindholm et al. Nature. 2007 Jul 5;448(7149):73-7.

In addition, Herantis Pharma is using a novel intracranial drug delivery system developed by Renishaw Plc, which overcomes the main issues that previous drug delivery systems encountered, including not distributing NTFs properly to the diseased brain areas.

### Renishaw transcutaneous bone-anchored port system



*Source: ABG Sundal Collier, Renishaw Plc.*

Pre-clinical studies on the effects of CDNF have shown promising results in several animal models for PD. In both 6-OHDA and MPTP rodent models of PD, a CDNF injection improved motor functions, protection and regeneration of dopaminergic neurons. In higher order species such as non-human primates with induced PD, CDNF therapy restored substantia nigra dopamine neuron integrity.[12] More importantly, significant improvement was reported in gross motor function, fine motor function and for the first time in the world, non-motor symptoms.[13]In addition, CDNF has been shown to be safe and well-tolerated in toxicology studies in non-human primates.

**Clinical trial ongoing**

Because of the encouraging pre-clinical data, Herantis Pharma initiated its first clinical study in Q1 2018 (NCT03295786). The trial was a randomised, placebo-controlled, interventional, multi-centre, phase I-II study on 17 patients with moderately advanced PD. (≥5 years from diagnosis H&Y[14] ≤3).

Like most proteins, CDNF does not penetrate the blood-brain barrier. For CDNF to function efficaciously and protect the target neurons in Parkinson's disease, it needs to reach the brain. Systemic administration, such as oral or intravenous dosing of CDNF, would not be expected to result in sufficient brain tissue exposure. CDNF is therefore administered intra-cerebrally i.e. directly into the brain. Infusions of CDNF or placebo will be given monthly at three ascending dose levels via a transcutaneous bone-anchored port (Renishaw Drug Delivery System) for six months followed by a six-month extension study where all patients will be given CDNF therapy.

The primary endpoint will be safety and tolerability with secondary endpoints being efficacy with UPDRS (part III), timed up and go, UPDRS (part I-IV), patient home

[12] Huttunen et al 2019 “CDNF Protein Therapy in Parkinson’s disease”
[13] Research collaboration with University of Pittsburgh funded by Michael J. Fox Foundation
[14] Hoehn and Yahr scale of PD symptoms

diary, PDQ–39 Quality-of-Life questionnaire and Clinical Global Scale (CGI), among other measurements. Imaging will also be used to evaluate the effect on the dopamine uptake and the integrity of the nigrostriatal system. The study will also measure levels of different types of α-synuclein in cerebral spinal fluid and plasma. Herantis has not disclosed any plans on the next steps after the first clinical study. The feasibility of the current route of administration for CDNF, i.e. the use of the drug delivery device requiring a surgical procedure and related adverse events, will also need to be evaluated carefully before deciding on the possible next steps in the clinical development of CDNF. The first read-out of the trial is expected in Q1 2020. However, clinical data will continue to accumulate thereafter, as the last CDNF dosing in the extension study is expected in approximately June 2020.

In the first interim readout from the phase 1 study expected in Q1 2020 we are mainly expecting a safety data read-out from events both related to the Renishaw system and CDNF as a drug. We believe that efficacy endpoints will be hard to interpret at this stage. Regarding UPDRS scores, the sample size will probably not produce any statistically significant readings and confounding factors such as co-administration of levodopa might worsen motor symptoms. Worsening of dyskinesia could also indicate that CDNF has restored some of the dopaminergic function in neurons, leading to an oversupply of dopamine from levodopa treatment, but in terms of UPDRS scores it would be negative.

We are more excited about the PET-imaging of the dopamine active transporter protein (DAT), which is a marker for dopaminergic neuron dysfunction. Severe depletion of DAT has been observed in PD patients. Herantis will use a PET imaging protocol developed at Karolinska university hospital that will use a novel tracer [$^{18}$F]FE-PE2I that has shown high contrast of DAT in PET imaging which should correlate to neuro-restorative effects at the cellular level.

In conclusion, we view the initial phase 1-2 study as primarily a safety study with any efficacy signals after just six months being a potential positive for the company.

## Potentially confounding factors in the clinical trial

**Strong placebo effects**

Placebo effects in medicine affect endogenous dopamine release and uptake as it is a key neurotransmitter in the reward system. Studies have documented this effect and that it has lasted for up to six months from initiation of the first dose.[15] In a study of the oral medication pergolide, the placebo group experienced 23% improvements in clinical symptoms of PD. A meta-review of PD and the placebo effect showed that 12 of 36 studies reported a placebo effect of 9-59% improvement in motor symptoms of PD.

However, the study receiving the most attention regarding placebo effects in PD was Goetz et al 2008[16] where they defined a placebo-response as a ≥50% or better improvement in the UPDRS score. They looked across 11 studies and found a placebo response in 16% (134/858) of patients (≥50% improvement in UPDRS) but even more strikingly in surgical interventions they noticed a placebo-response according to their definition in 42% of the patients (15/36 patients). The strong responses in surgical interventions were also evident in the gene therapy trial with CERE-120 where any separation from the placebo group was not evident until 6-9

[15] Goetz el al 2002 “Objective changes in motor function during placebo treatment in PD”
[16] Goetz et al 2008 “Placebo Response in Parkinson’s disease: Comparisons Among 11 Trials Covering Medical and Surgical Interventions”

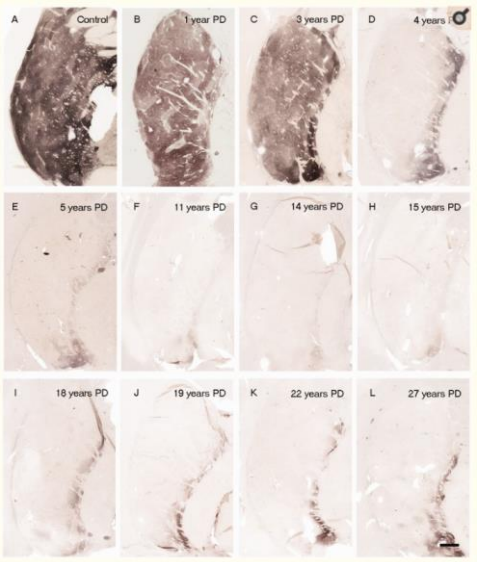
months into the study.[17] In another study, the placebo response in a surgical intervention (sham surgery group) lasted for as long as 18 months.[18]

Since Herantis Pharma's clinical study is a surgical intervention, we have to be careful to draw conclusions from the trial results until we have seen longer-term data, especially if the study duration is less than six months.

**The loss of dopamine producing neurons in PD**

Another thing to keep in mind is that by the time of diagnosis it has been estimated that 50-80% of dopamine producing neurons have lost their ability to produce dopamine. That begs the question as to whether a neuroprotective protein can restore dopamine neuronal loss in late stage patients if there are too few neurons left to restore. A study in 2013 by Dr. Jeffrey Kordower showed that, for his sample of patients, almost all dopamine producing neurons in the dorsal putamen had lost their phenotype >4 years after diagnosis of PD.

**Tyrosine hydroxylase-staining in putamen sections**




*Source: ABG Sundal Collier, Kordower et al 2013*

## Next-generation CDNF therapy (xCDNF)

The reason why CDNF needs to be administered intra-cranially is because CDNF is too large to pass the blood brain barrier (BBB). The intact BBB prevents uptake for most pharmaceuticals apart from lipophilic drugs with a weight of <400 Da, thus preventing most large molecule drugs such as proteins from diffusing across the BBB.[19] However, in many diseases affecting the CNS, the BBB could be compromised passing over some larger molecules such as antibodies.

Due to the limitations of CDNF crossing the BBB, Herantis has developed a family of next-generation molecules, xCDNF, which could provide a non-invasive therapy for PD. xCDNF compounds are peptides (a short chain of amino acids linked together, smaller than a protein) that have retained the protective properties of the full CDNF protein, but could pass the BBB. This discovery could lead to a significant expansion of the number of patients that could be treated with CDNF therapy, as well as further broadening the platform for CDNF to other neurodegenerative diseases. Management has told us that xCDNF is in the lead-optimisation stage at

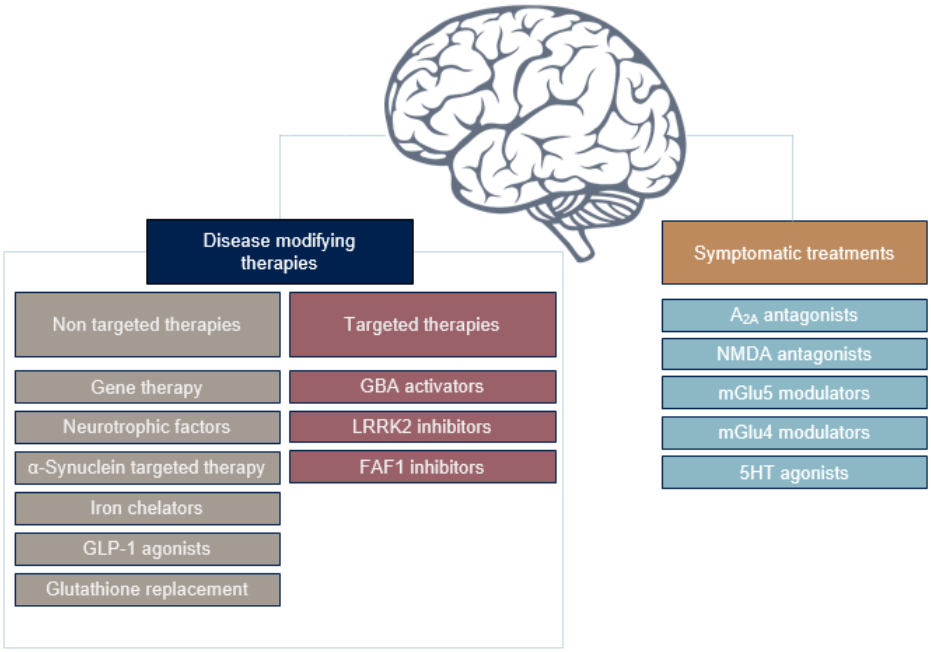
[17] Huttunen et al 2019 "
[18] Fahn et al 2001 "Transplantation of Embryonic Dopamine Neurons for Severe Parkinson's disease"
[19] Pardrige et al 2012 "Drug transport across the blood–brain barrier"

the moment but we view the continued development of this molecule as de-risked if the current intracranial delivery of CDNF will read-out with positive data on safety and efficacy going forward. A peptide based therapy also opens up the opportunity for a subcutaneous administration (injection below the skin, similar to a diabetes drug), which could provide a convenience advantage to intravenously administered drugs.

## Emerging treatments for Parkinson's

New treatments in the pipeline for PD can be divided in disease modifying treatments (treating the underlying disease) and symptomatic treatments (only treating symptoms of the disease). Although the current pipeline looks crowded at first glance, we argue that many programmes have very early or ambiguous clinical data. In addition, the targeted therapies only target <10% of the population. However, the treatment modality that we view as the main competitor to Herantis is the α-synuclein therapies, which we view as a promising clinical programme but even if those therapies would make it to market before Herantis, there is a big enough market for many different treatment modalities in PD.

### An overview of the pipeline in Parkinson's disease




*Source: ABG Sundal Collier, Charvin et al 2018*

### Disease modifying treatments

- **Gene therapy**
  Two approaches with gene therapy are currently under investigation. The first approach is to make more brain cells with the ability to express an enzyme called Aromatic L-amino acid decarboxylase (AADC). This enzyme is responsible for the conversion of L-dopa to dopamine and its expression diminishes as PD progresses leading to motor complications such as "OFF" symptoms. With gene therapy, the idea is to express more AADC and therefore limit the dose of L-dopa by making more L-dopa convert to dopamine. Voyager therapeutics are currently running a phase 2 study in 42 participants with an expected study completion in December 2020 that explores gene therapy with AADC. Although the company claims that its therapy is disease modifying, we argue that it is a symptomatic treatment since it will only enhance the effect of levodopa treatment.

The second approach is to make more brain cells produce dopamine and replace the dying dopamine producing neurons in the substantia nigra. Axovant Sciences is currently testing its gene therapy on 30 patients to evaluate safety and tolerability. The first interim results were presented at the beginning of 2020, with signs of efficacy in UPDRS "OFF" scores.

- **Neurotrophic factors**
  MedGenesis is testing local delivery of Glial Cell-Line Derived Neurotrophic Factor (GDNF) by intracranial infusions as a way to treat PD. A phase 2 study of 41 subjects showed no significant difference in UPDRS part III. However, Serial $^{18}$F-DOPA PET imaging revealed a significant increase in radioligand uptake in the GDNF group compared to the placebo-group. These encouraging results have led the company to prepare for a phase 3 study in PD.[20]

- **α-synuclein therapy**
  Toxic aggregation of α-synuclein is one of the hallmarks of PD. Three approaches to interfere with α-synuclein toxicity have been proposed. 1) Blocking α-synuclein with immunotherapy 2) Inhibit α-synuclein aggregation 3) Increasing the clearance of α-synuclein.

  The most popular approach has been to develop antibodies targeting α-synuclein and Roche is currently testing its antibody prasinezumab in a phase 2 study versus placebo, which is a 52-week study of 316 patients that is expected to read out in early 2020. BioGen is testing BIIB054, which is also an α-synuclein antibody that is in a phase 2 study with 311 patients and is expected to read out in May 2020. AbbVie is also testing ABBV-0805 (in-licensed from BioArctic) and is currently in phase 1 clinical trials.

  Vaccines are also developed by targeting short mimicking peptides of α-synuclein as well as siRNA (technology to silence genes and prevent expression of proteins). Other approaches in early stages are small molecules to increase autophagy (clearance of proteins) and modulators of chaperones (protein stabilization molecules).

- **Iron chelators**
  Iron overload in the substantia nigra pars compacta is a well-known clinical feature of PD but researchers do not understand why iron accumulates in the brain. However, an iron chelator, defiraprone, showed promise in a double blind, placebo-controlled study of 40 patients. It is now being tested on 338 patients with PD, as part of a phase 2 study.

- **GLP-1 agonists**
  Evidence has long suggested a link between diabetes type 2 (DT2) and GLP-1 agonist (Glucagon-like peptide 1) used for diabetes and weight loss and pilot studies in PD has shown initial promise. But these studies have been single centre studies and with a small number of patients (n≤ 62) so these agents will have to be tested in larger randomized and placebo-controlled settings to show if it can have an impact on PD.

[20] Whone et al 2019 "Randomized trial of intermittent intraputamenal glial cell line-derived neurotrophic factor in Parkinson's disease"

**Targeted therapies**

- **LRRK2 inhibitors**
  Mutations in the gene leucine-rich repeat kinase 2 (LRRK2) are the cause of approximately 2% of patients with PD.[21] Several inhibitors have been developed to inhibit the effects of this mutated kinase. Denali Therapeutics is currently the leader in the pipeline and is conducting phase 1-2 studies with its compound DNL151.

- **GBA activators**
  Gauchers disease was one of the first to be treated by a company developing an orphan drug model with high pricing directed to few patients. Research that is more recent has suggested that the same mutation causing Gaucher disease is also present in about 7-10% of patients with PD, making it the most common genetic cause of PD.[22] Missing the enzyme glucocerebrosidase inhibits the lysosomal activity and causes protein aggregation within the neurons, eventually causing neuronal death. Chaperones that could stabilize the mutated enzyme are currently being investigated in clinical trials.

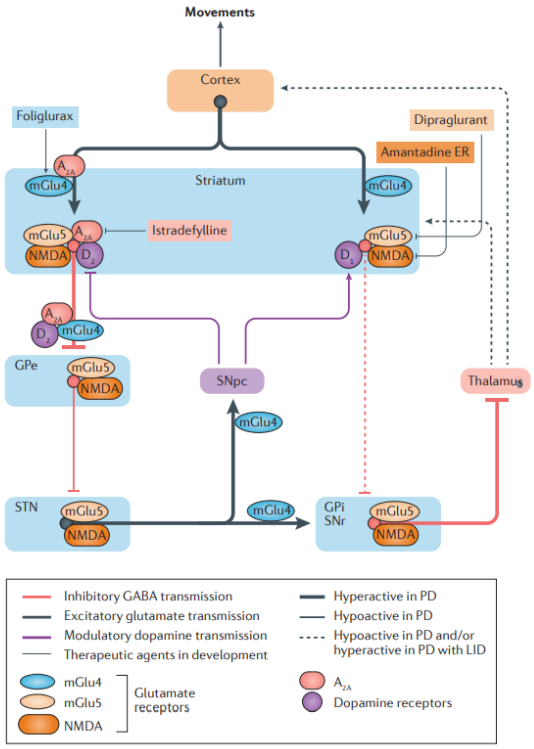
- **FAF-1 inhibitors**
  The parkin gene (PARK2) has been implied as a predictor of early onset PD. The discovery that parkin is an inhibitor of FAF-1 has led to the development of a FAF-1 inhibitor, currently in phase 1 clinical trials in Korea (KM-819), that has shown increased dopamine activity in a MPTP rodent model of PD.

## Symptomatic treatments

Since Herantis Pharma is not developing a drug for symptomatic treatments in PD, we will not go into details of the current pipeline for symptomatic treatments. However, symptomatic treatments can be described briefly as treatments controlling the motor symptoms of PD such as the dyskinesia and “OFF” episodes. Even if you do not target the root cause of the disease, controlling motor symptoms could improve the quality of life and sustain levodopa treatments for a longer period. Many of these agents are non-dopaminergic and target serotonin receptors, adenosine receptors and the glutamatergic system to name a few.

[21] Parkinson’s Foundation Facts about common genetic mutations
[22] O’Regan et al 2017 ” Glucocerebrosidase mutations in parkinson disease”

**Overview of different mechanisms of actions to target symptoms in Parkinson's disease**




*Source: ABG Sundal Collier, Charvin et al 2018*

**NeuroDerm trying to offer a better option than AbbVie's Duodopa**

NeuroDerm was an Israeli company that was acquired by Mitsubishi Tanabe for USD 1.1 billion in 2017. The company has developed a liquid formulation of carbidopa and levodopa that can be administered subcutaneously to patients with PD, bypassing the gastrointestinal tract altogether. This allows for a pump device that is much smaller and could be carried around the belt like a diabetes type I device and limits many of the complications with Duodopa.

The clinical results have been impressive so far with results from their phase 2 trial showing a reduction in OFF time by 51% (5.5 down to 2.2h/day). Even more impressive was the fact that 42% of patients experience zero "OFF" time, which is superior to oral levodopa and duodopa treatment. After the acquisition of Mitsubishi Tanabe we have not seen any further updates from the clinical programme.

## Currently marketed drugs and pipeline of Parkinson's disease

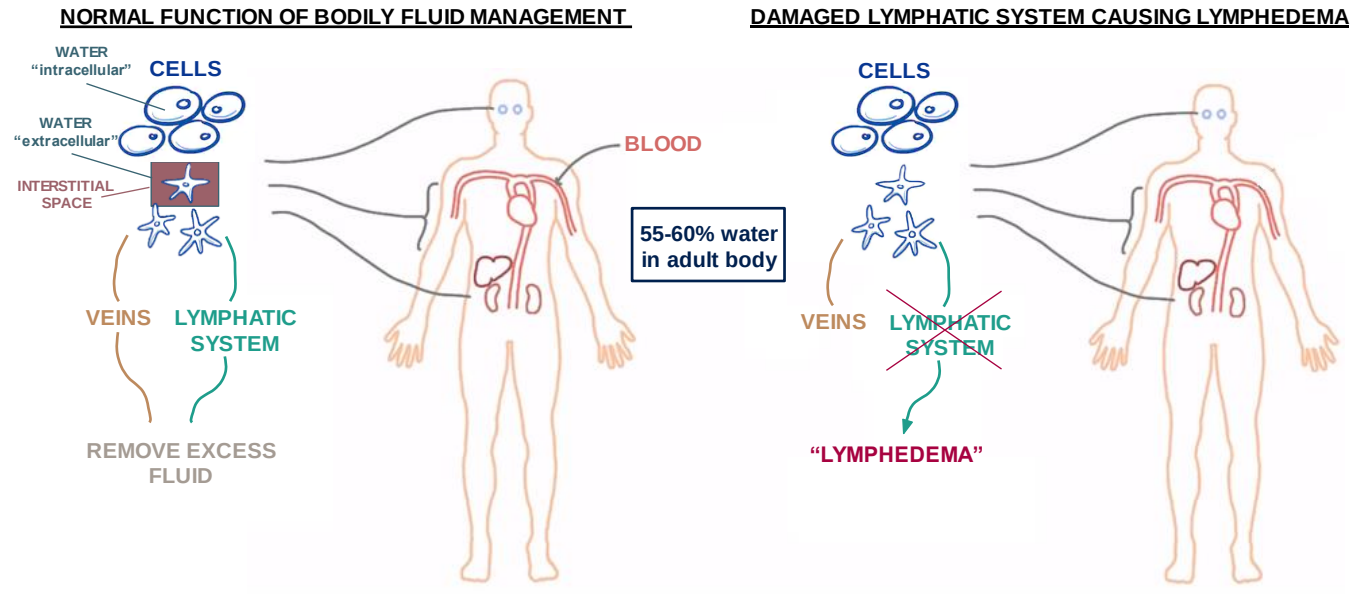
| Sponsor | MoA | Drug class | Therapeutic | Phase: Preclinical | Phase I | Phase 2 | Phase 3 | Marketed |
|---|---|---|---|---|---|---|---|---|
| **MARKETED DRUGS** | | | | | | | | |
| Merck | Levodopa/Carbidopa | small molecule | Sinemet CR (controlled release) | | | | | ● |
| Schwarz Pharma | Levodopa/Carbidopa | small molecule | Parcopa | | | | | ● |
| Impax Pharma | Levodopa/Carbidopa | small molecule | Rytary ER (extended release) | | | | | ● |
| AbbVie | Levodopa/Carbidopa | Device | Duopa | | | | | ● |
| Novartis | COMT inhibitor, inhibi | small molecule | Comtan (entacapone) | | | | | ● |
| Bausch Health | COMT inhibitor, inhibi | small molecule | Tasmar (tolcapone) | | | | | ● |
| Novartis | DOPA decarboxylase | small molecule | Stalevo | | | | | ● |
| Boehringer Ingelheim | Dopamine agonist | small molecule | Mirapex (pramipexole) | | | | | ● |
| GlaxoSmithKline | Dopamine agonist | small molecule | Requip (ropinirole) | | | | | ● |
| US world meds | Dopamine agonist | small molecule | Apomorphine injection (pen) | | | | | ● |
| UCB | Dopamine agonist | small molecule | Rotigotine (transdermal patch) | | | | | ● |
| Mylan | MAO-B | small molecule | Selegline | | | | | ● |
| Valeant | MAO-B | small molecule | Selegiline (desintegrating tablet) | | | | | ● |
| Teva | MAO-B | small molecule | Rasagiline | | | | | ● |
| Zambon | MAO-B | small molecule | Safinamide | | | | | ● |
| Novartis | NMDA+others | small molecule | Amantadine | | | | | ● |
| Adamas | NMDA+others | small molecule | Amantadine (extended release) | | | | | ● |
| Kyowa Kirin | Adenosine 2A | small molecule | Istradefylline | | | | | ● |
| Intas | Anticholinergic | small molecule | Trihexyphenidyl | | | | | ● |
| Bayshore | Anticholinergic | small molecule | Benztropine | | | | | ● |
| Acadia Pharmaceuticals | 5-HT (2A) | small molecule | Pimvanserin | | | | | ● |
| Acorda Therapeutics | Levodopa | small molecule | Inbrija (inhaled L-dopa) | | | | | ● |
| **PIPELINE** | | | | | | | | |
| **Disease modifying treatments** | | | | | | | | |
| Mitsubishi Tanabe Pharma | Levodopa/Carbidopa | small molecule | ND0612 (device) | | | | ● | |
| Amneal | Levodopa/Carbidopa | small molecule | IPX203 (extended release) | | | | ● | |
| MedGenesis | GDNF | peptide | GDNF infusion | | | | ● | |
| Axovant Sciences | AADC/TH/CH1 | gene therapy | Lentiviral (AADC, TH, CH1) | | | ● | | |
| Prothena/Roche | alpha-synuclein | antibody | Prasinezumab | | | ● | | |
| Biogen | alpha-synuclein | antibody | BIIB054 | | | ● | | |
| Affiris | alpha-synuclein | vaccine | PD01 | | | ● | | |
| Prevail therapeutics | GBA | gene therapy | PR-001 | | | ● | | |
| Sanofi Genzyme | GBA (GL-1 inhibitor) | small molecule | SAR402671 | | | ● | | |
| Cure Parkinson/Novo | GLP-1 agonist | peptide | Liraglutide | | | ● | | |
| ApoPharma | Iron chelator | small molecule | Deferiprone | | | ● | | |
| AstraZeneca/Takeda | alpha-synuclein | antibody | MEDI-1341 | | ● | | | |
| Lundbeck | alpha-synuclein | antibody | Lu-AF82422 | | ● | | | |
| AbbVie | alpha-synuclein | antibody | ABBV-0805 | | ● | | | |
| Yumanity | alpha-synuclein | small molecule | YTX-7739 | | ● | | | |
| Neuropore/UCB | alpha-synuclein | small molecule | UCB0599 | | ● | | | |
| Alterity Therapeutics | alpha-synuclein | small molecule | PBT434 | | ● | | | |
| United Neuroscience | alpha-synuclein | vaccine | UB-312 | | ● | | | |
| Lysosomal therapeutics | GBA | small molecule | LTI-291 | | ● | | | |
| NINDS | GLP-1 agonist | peptide | Exenatide | | ● | | | |
| Biogen | LRRK2 | antisense | BIIB-094 | | ● | | | |
| Denali Therapeutics | LRRK2 | small molecule | DNL151 | | ● | | | |
| Denali Therapeutics | LRRK2 | small molecule | DNL201 | | ● | | | |
| Kainos Medicine | FAF1 inhibitor | small molecule | KM-819 | | ● | | | |
| **Symptomatic treatments** | | | | | | | | |
| Voyager Therapeutics | AADC | gene therapy | AAV2–hAADC | | | | ● | |
| Addex Therapeutics | mGlu5 NAM | small molecule | Dipraglurant (immediate release) | | | | ● | |
| Lundbeck (Prexton) | mGlu4 PAM | small molecule | Foliglurax | | | ● | | |
| Rush University/VU Univeristy | Acetylcholine | small molecule | Varenicline | | | ● | | |
| Amarantus Bioscience | 5-HT (1A/1B) | small molecule | Eltoprazine | | | ● | | |
| Acorda Therapeutics | 5-HT (6/2A) | small molecule | SYN120 | | | ● | | |

*Source: ABG Sundal Collier, company data*

# Breast cancer-associated lymphedema

**It all begins with bodily water management**

You may have heard that your body constitutes of ~60% water, but have you ever wondered where that water is? You may think the water is in your blood since blood is liquid, contained inside your arteries and veins. However, blood only contains a small fraction of the water in your body. Many of the structures in your body, your internal organs, your skin, your eyes etc. are made up of cells. Most of the water in your body is either inside those cells or around them. The water in your body is found in two main locations, in your cells (two-thirds) and outside your cells (one-third). The body of a 70-kg man, for example, contains about 42L of water − 28L intracellular and 14L extracellular, of which: 3L is blood plasma; 1L is the transcellular fluid (cerebrospinal fluid, ocular, pleural, peritoneal and synovial fluids); 10L is the interstitial fluid (including lymph) − a watery fluid surrounding the cells.[23]




*Source: ABG Sundal Collier, Tactile Medical*

**The lymphatic system and lymphedema**

Lymph is the fluid circulating in the lymphatic system, and edema refers to fluid build-up in the body's tissues. The body does a good job of keeping the amount of fluid inside the cells at a constant level, but the amount of fluid around your cells can change. Your veins and your lymphatic system work in concert to remove excess fluid from the tissues if it builds up. But if there is impairment to either of these systems, fluids can build up in this interstitial (extracellular) space. In particular, if you have an impairment of your lymphatic system the excessive fluid that builds up leads to chronic swelling known as lymphedema.

To understand how and why this build-up happens we need to talk about your circulatory system; your arteries, veins and lymphatics. When your heart beats, it contracts, and that creates a high pressure in the arteries, which are the vessels that carry oxygen rich blood throughout the body. Since your arteries are made of cells, the high pressure can actually press the smaller components of your blood, like fluid, out of the spaces between the cells. If this were the whole story we would have a

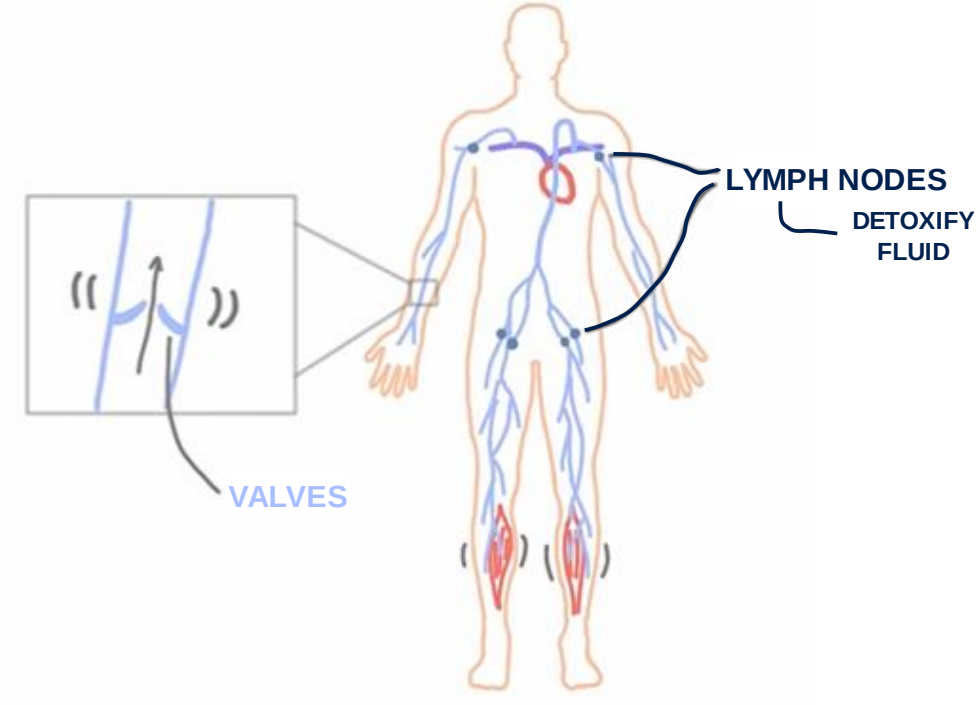
[23]Wang et al. (1996). Am J Clin Nut 69: 833-841; Mitchell et al. The Journal of Biological Chemistry, 1945: 625-637

problem, because fluid would leak out of your arteries and it would accumulate, and too much accumulation leads to what we call “edema” or “swelling”.

To prevent this fluid build-up from happening, the body has developed a transport system called the lymphatic system to help maintain fluid balance. This lymphatic system consists of lymph capillaries, which are located just below your skin. These lymph capillaries are almost everywhere in your body and pick up the extra fluid. The capillaries join together into larger lymphatic vessels and those vessels merge into even bigger ones until ultimately they return the lymphatic fluid to the circulatory system in the large veins near to your heart. Along the way back to the circulatory system, the fluid passes through lymph nodes that detoxify these fluids, which helps the body to eliminate toxins, bacteria and pathogens that might be contained in the fluid, which accumulates in the tissues. How does this lymphatic system work? What helps the lymphatic system propel fluid through the entire body just like our circulatory system does with our arteries and veins?

To answer to this question is important to understand, as the lymphatic system works with pressure as well, but it is a much lower pressure compared to what is generated by our heart. Throughout the day, your muscles contract by the daily activities you perform, creating pressure in the spaces that contain the fluid. The pressure from the muscle contractions facilitate movement into the lymph capillaries, which collect fluid as well as larger proteins and toxins. Fluid is collected in the capillaries and then propelled in one direction through lymph vessels (which have one-way valves) due to your own body movement and the small contractions that occur in and around the lymph transport vessels.

**The lymphatic system runs through the whole body**




*Source: ABG Sundal Collier, Tactile Medical*

**Causes of lymphedema**

As we mentioned earlier, you develop lymphedema when you have a poorly functioning or damaged lymphatic system, and fluids and toxins build up in your system. Primary lymphedema is rare, affecting 1 in 100,000 individuals[24] and is currently not being pursued by Herantis. Primary lymphedema may be caused by defects of the lymphatic system at birth (congenital) and can be passed from parent to child (hereditary). Although primary lymphedema has largely been attributed to genetic causes, lymphedema is also classified as primary when no known cause can be identified.[25] Other primary lymphedema diagnoses include:

Lymphatic damage can also be caused by cancer or cancer treatment, like radiation of chemotherapy, accidents or surgery – this is called secondary lymphedema. Secondary lymphedema is the most common cause of the disease and affects approximately 1 in 1,000 Americans. These factors can disrupt or result in scarring or removal of the lymph nodes. Another important cause of lymphedema is chronic venous insufficiency (CVI). CVI occurs if the veins are obstructed or impaired and not able to carry enough blood and fluid back to the heart.

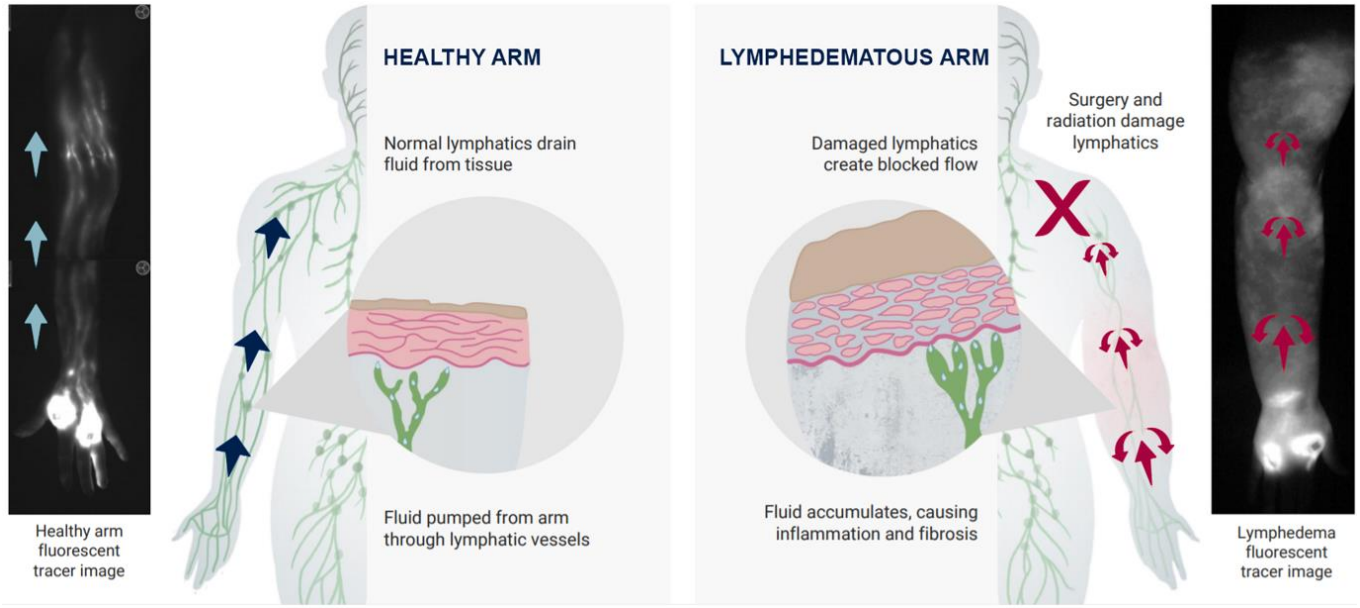
Herantis are primarily pursuing the treatment of breast cancer associated secondary lymphedema (BCAL) in patients who undergo lymph node transplantation surgery. Surgical treatment of breast cancer often includes the removal of axillary lymph nodes to block the spreading of the cancer. Unfortunately, this also damages normal lymphatic drainage. This may cause lymphedema, resulting in the swelling of one arm.

A meta-analysis estimated the overall incidence of chronic arm edema after breast cancer was found to be 21.4%, indicating that BCAL is a widespread problem affecting 1 in every 5 patients following breast cancer treatment[26]. Due to the lack of universal diagnostic criteria for BCAL, the reported incidence varies from less than 5% to more than 50%[27,28,29]. Another recent study showed that the incidence of lymphedema following breast cancer treatment increased over time. The cumulative incidence of lymphedema observed was 13.5% at two years of follow-up, 30.2% at five years and 41.1% at 10 years[30]. Another study evaluating patients operated for primary breast cancer (mastectomy) over the period ’84-’09 found Lymphedema in 27% of patients. Mild, moderate, and severe lymphedema rates were 37%, 29%, and 34%, respectively.[31]

Based on published cancer incident data we estimate that about 30,000 breast cancer associated secondary lymphedema cases are diagnosed annually in the US and Europe. Looking at the US alone, it is estimated that there are roughly 500,000 individuals living with BCAL today.[32] Secondary lymphedema is also associated with other cancers including melanoma, gynaecologic cancers, and genitourinary cancers resulting in an estimated 150,000 secondary lymphedema cases in the USA and Europe. In the USA, it has been estimated that the treatment of breast cancer associated secondary lymphedema costs over USD 10,000 a year per patient.

[24] Sleigh and Manna (2019) Lymphedema. StatPearls.
[25] National Organization for Rare Disorders, 2020
[26] DiSipio et al. 2013, Lancet
[27] Ibid.
[28] Tsai et al. 2009, Ann Surg Oncol
[29] Shah and Vicini, 2011, Int J Radiat Oncol Biol Phys
[30] Pereira et al. 2017, The Breast
[31] Ugur et al. 2013, Lymphat Res Biol.
[32] Garza et al., 2017

**Injury to the lymphatics blocks fluid flow and creates inflammation and fibrosis**

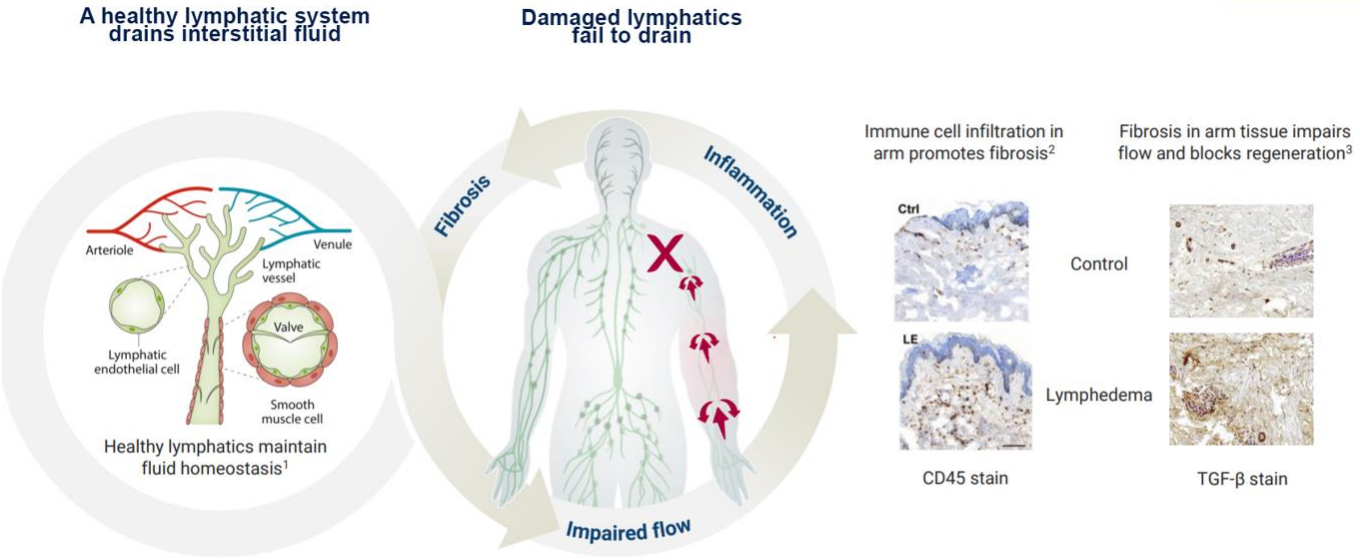



*Source: ABG Sundal Collier, Patient images: Kataru et al., 2019, Translational Res., PureTech*

The build-up of fluid, or lymphedema, can lead to serious health problems. Because the fluid contains proteins it can become a breeding ground for bacteria when it is sitting stagnant in the tissues of the body. When this happens, skin infections known as cellulitis are more likely to occur. The presence of the fluids can also cause the skin to harden and thicken, a condition known as skin fibrosis.

According to the World Health Organization, lymphedema affects over 250 million people worldwide. Despite this, research evaluating the lymphatic system and the effectiveness of treatment has been scarce. The unfortunate result is that far too many patients are left undiagnosed and untreated and therefore suffer unnecessary pain and suffering. Lymphedema is a non-curable condition today and if not effectively managed gets progressively worse by time. Treating it effectively to prevent further swelling and skin damage as early as possible is important. Understanding how your lymphatic system works and what you can do to help stimulate it and manage your condition is a great first step towards a healthier life.

**Lymphedema: A feedback loop between inflammation and fibrosis**

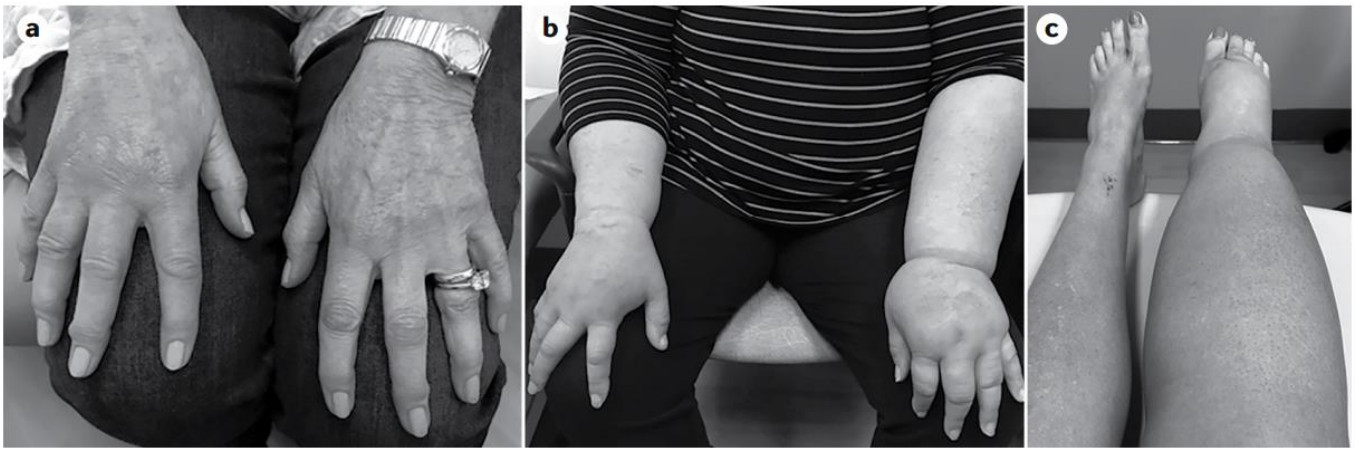



*Source: ABG Sundal Collier, 1. Rockson et al., 2019, Nat Rev Dis Primer, 2. Gousopolos et al., 2016, JCI Insight – CD-45 stain 3. Avraham et al., 2010, AM J Pathology, PureTech*

**Clinical stages of lymphedema**

The International Society of Lymphology has described the distinct stages of the disease that represent the progression of lymphedema. According to this classification, latent or preclinical disease is classified as stage 0, with some damage to lymphatics but no visible edema yet. In stage 1, there is visible swelling of the affected body part and pitting edema may be present (that is, edema in which applying pressure to the skin results in an indentation that may persist after pressure is removed); this edema subsides with elevation of the limb (see image a). In stage 2 (see image b), edema no longer improves with elevation, and the pitting quality may no longer be present as fibrosis emerges. Stage 3 (see image c) is irreversible and usually the limb(s) are very large. The tissue is hard (fibrotic) and unresponsive to touch.

**Clinical stages of lymphedema**




**Note**: a) Early manifestations (International Society of Lymphology (ISL) stage 1) of breast cancer-related lymphedema. Note the subtle loss of surface definition in the affected right hand. b) ISL stage 2 breast cancer-related lymphedema of the left arm. c) ISL stage 3 lymphedema in the right leg of a young woman following treatment for cancer of the cervix.
*Source: Rockson et al. 2019, Nature*

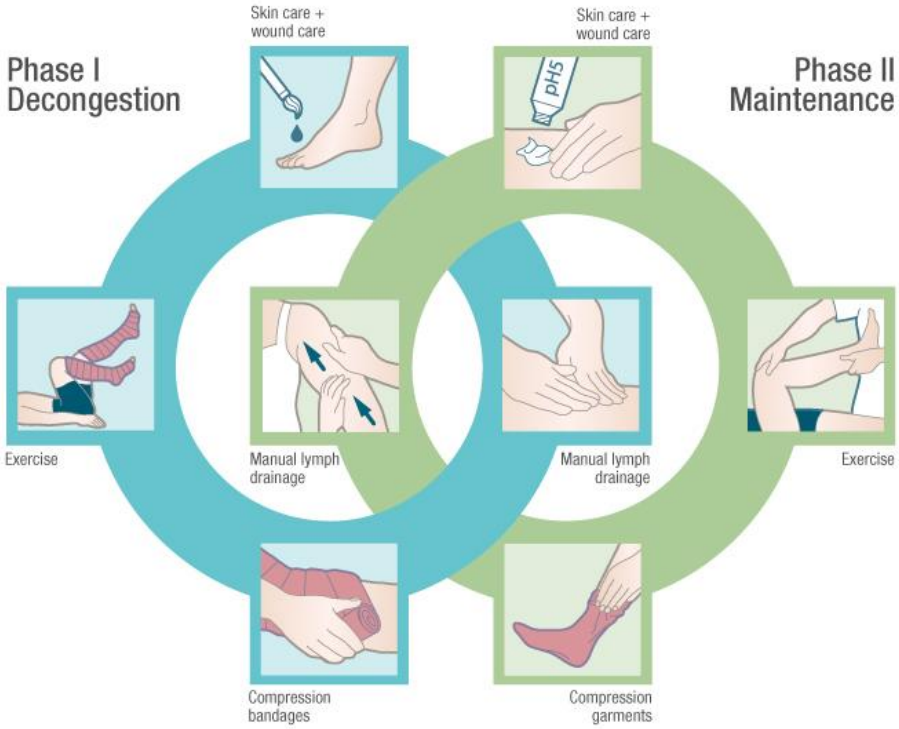
**Treatment alternatives**

Unfortunately, there is no absolute cure for lymphedema today and there are no market approved drugs. Even if there are some treatments that alleviate symptoms, there is a clear unmet medical need in the current treatment landscape. Two main modalities include non-surgical and surgical options (table on page 27). The mainstays of non-surgical LE treatment modalities are complete decongestive therapy (CDT), compression therapy, advanced pneumatic compression pumps and exercise. These treatments are effective mainly in early-stage LE. There is a global trend for surgical intervention and surgical techniques including physiological and reductive methods.[33]

Complete Decongestive Therapy (CDT), illustrated below, is considered the gold-standard treatment method in the management of LE and includes two phases: decongestion (phase 1) and maintenance (phase 2). Although it is safe and generally improves quality of life, it is expensive, time-consuming and needs certified therapists. In addition, patient compliance to long-term CDT is challenging and is not to be viewed as a conservative, non-disease modifying treatment modality.

[33] Kayiran et al. 2017, Turk. J. Surg.

**Complete Decongestive Therapy (CDT)**




*Source: LymphCare*

But there are other measures such as the application of pneumatic compression devices, which can be used to increase the pressure of the lymph capillaries, making it easier for fluid to be transported by veins and lymph vessels. In instances where the damaged lymphatic system leaves some lymphatic vessels intact, pneumatic compression devices such as the Flexitouch system (Tactile Medical), can be used to stimulate the activity of those remaining lymphatic vessels. The Flexitouch system is the only pneumatic compression device clinically proven to stimulate the lymphatic system. Instead of trying to squeeze the limb like a tube of toothpaste, Flexitouch uses dynamic pressure to encourage fluid to move into and through the remaining healthy lymphatic vessels. The Flexitouch system has been clinically proven to reduce fibrosis (the hardening or thickening of the skin) and reducing painful cellulitis skin infections, by as much as 79%.[34]

In the past decade, surgeons at hospitals, such as MD Anderson Cancer Center, have shown that lymphovenous bypass and vascularized lymph node transfer are effective surgical treatments for lymphedema. Lymphovenous bypass surgery, in which the obstructed lymphatic vessels are “connected” to small adjacent veins, often provides an immediate benefit by improving lymphatic drainage, however, effectiveness tends to decrease around 12 months after surgery. In contrast, vascularized lymph node transfer— in which lymph nodes are harvested from an unaffected donor site with their supporting artery and vein and transferred to the recipient site of an affected area—can provide permanent new lymphatic drainage. However, these new lymphatic channels do not begin functioning until 6–9 months after surgery. By combining these surgeries, better outcomes have been achieved.[35]

[34] Blumberg et al. 2015, Annals of Vascular Surgery; Muluk et al. 2013, European J. of Vascular and Endovascular Surgery; Fife et al. 2012, Supportive Care in Cancer
[35] Nguyen et al., 2015, Ann. Surg. Oncol.; OncoLog, April 2017, Volume 62, Issue 4

**Treatment options in lymphedema**

| Non-surgical treatments | Surgical treatments |
|---|---|
| Complete decongestive therapy | Reductive techniques |
| Manual lymph drainage | Direct excision |
| Compression therapy | Liposuction |
| Exercise | Physiological techniques |
| Skin care | Lymphatico-lymphatic by-pass |
| Compression garments | Lymphatico-venous by-pass |
| Advanced pneumatic compression therapy | Lymph node transfer |
| Laser therapy | |

*Source: ABG Sundal Collier, Kayiran et al. 2017*

**Advanced pneumatic compression therapy**


*Source: Tactile Medical*

## Lymfactin aims to become the first drug for treating breast cancer-associated secondary lymphedema

Herantis is presently developing a gene therapy called Lymfactin for the treatment of breast cancer=associated secondary lymphedema (BCAL) in patients who undergo lymph node transplantation surgery. Lymfactin is based on the naturally occurring growth factor VEGF-C (Vascular endothelial growth factor C). As is typical with gene therapy, the VEGF-C gene is delivered to the patient by using an adenovirus. The adenovirus transfers the VEGF-C gene to the human cells in the treatment area and subsequently the human cells produce VEGF-C transiently for 2-3 weeks. Hence, the treatment is a combination therapy aiming to improve the outcome of lymph node transplantation surgeries by repairing the damaged lymphatics, ultimately providing disease-modifying benefits for BCAL patients.

The fundamental rationale for the treatment builds on the reasoning that one would need to grow new lymphatic vessels to cure lymphedema. Preclinical studies have shown that damaged lymphatic vascular networks can be reconstructed and removed or damaged lymph nodes replaced using growth factor therapy in combination with lymph node transfer.[36] Researchers has examined various naturally occurring vascular endothelial growth factors such as VEGF-C, VEGF-D, VEGF-C156S, and VEGF-A. In Appendix A, we present a comprehensive review of the published preclinical literature on targeted therapies associated with lymphedema surgery. The advantage of this rationale, compared with lymph node transfer alone, is the increased incorporation efficiency of the transplanted nodes with the existing lymphatic network. These functional lymph nodes promote a barrier in the immune system against different pathogens (anything that can produce disease) and a barrier against the spreading of cancer cells. Hence, this kind of treatment is believed to combine the essential benefits of the combination therapy compared with that of the growth factor therapy alone.

The image below illustrates Lymfactin's mode of action;

1. Tissue containing healthy lymph nodes are harvested from the BCAL patient's own abdominal wall or groin area.

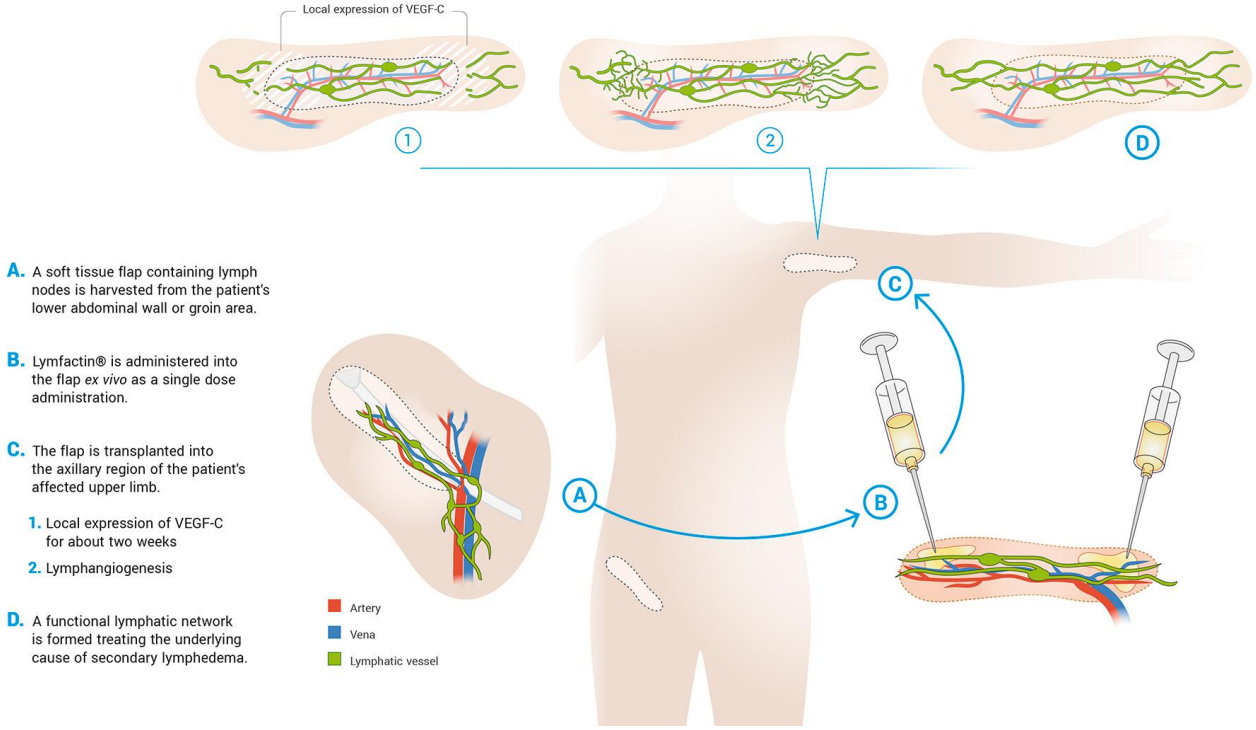
2. A single dose of Lymfactin is injected into the harvested tissue ex-vivo (outside of the body).

[36] Honkonen et al. 2013, Ann. Surg.; Tammela et al. 2007, Nat. Med.; Lahteenvuo et al. 2011, Circulation; Tervala et al. 2015, Journal of Surgical Research

3. The tissue is then transplanted into the axillary region of the arm affected by lymphedema (around the armpit). Lymfactin provides a local expression of the growth factor VEGF-C for 2-3 weeks, aiming to stimulate Lymphangiogenesis (the growth of lymphatic vessels).

4. Over time, a functional lymphatic network is formed, treating the underlying cause of secondary lymphedema (a damaged lymphatic system).

## Lymfactin mode of action

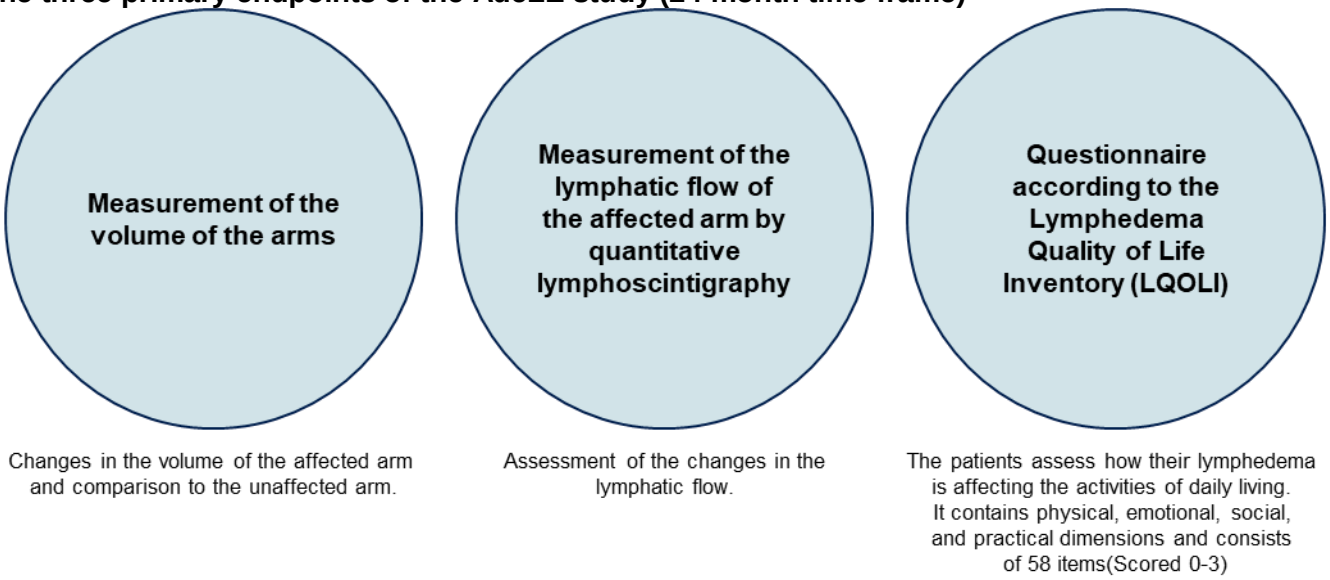



*VEGF-C = Vascular endothelial growth factor C ; Lymphangiogenesis = The growth of lymphatic vessels*
*Source: Herantis*

**Ongoing Phase 2 clinical study now fully recruited (n=39)**
The ongoing Phase 2 clinical study AdeLE (Adenoviral gene therapy for the treatment of LymphEdema) is a multi-center, randomized, double-blind, placebo-controlled study in patients with secondary lymphedema associated with the treatment of breast cancer and is currently in the follow-up stage. A total of 39 patients has been recruited, where the last patient in was announced on 16 December 2019. The study will assess the efficacy, safety, and tolerability of Lymfactin in patients undergoing lymph node transfer surgery. Half of the patients will receive one dose of Lymfactin and half will receive a placebo. All patients will undergo lymph node transplantation surgery, which can be of benefit for the patients regardless of being in the Lymfactin group or placebo group. Herantis expects to unblind the study and announce its top-line results in Q1'21.

The AdeLE study intends to assess the safety and efficacy of Lymfactin in the treatment of breast cancer associated lymphedema when combined with a conventional lymph node transplantation surgery. The impact of the treatment on the lymphedema, quality of life of the patient, and possible adverse reactions, are monitored in the study. In addition, the clinical study will investigate the distribution of the drug substance in the body and compare different methods of assessing the symptoms of lymphedema.

**The three primary endpoints of the AdeLE study (24 month time frame)**




*Source: ABG Sundal Collier, company data*

**Encouraging Phase 1 data with a solid safety profile**

The combination of Lymfactin and lymph node transplantation surgery has been assessed previously in 15 patients in a Phase 1 clinical study in Finland (NCT02994771). Based on the results Lymfactin is safe and well tolerated. At the 12-month follow-up review in April 2019, the study's data monitoring committee (DMC) concluded that the treatment continues to be safe and well-tolerated in all patients with no severe adverse events or dose limiting toxicities observed.

**Lymph transplantation data and risks to consider when evaluating Lymfactin**

As an emerging field, there is still a relative paucity of consistent outcome data following lymphatic microsurgery from which to draw definitive conclusions. Data correlating improved patient outcomes as related to surgical outcomes have been published, but a long-term follow-up (i.e. greater than five years) has yet to be provided in large prospective studies.

Though rare, vascular compromise may cause the tissue to lose its viability. Another risk is fluid collection at the surgical sites. Donor site-associated lymphedema has been reported after lymph node transplantation, but it's also quite rare. To further reduce the risk, some hospitals use a technique called reverse lymphatic mapping using a combination of vital and fluorescent dyes to identify the lymph nodes that are primarily responsible for drainage of the donor extremity. This allows surgeons to harvest lymph nodes for transfer that does not contribute to these important drainage pathways.

Patel et al. (2015) showed improvements of 24.4% in patients with upper-limb lymphedema (n=10). In the follow-up study, the average long-term follow-up was 27 months. The average circumference reduction of the affected extremity was 40.5%. Gratzon et al. (2017) studied the outcomes of lymph node transplants in treated breast cancer patients (n=50). Preliminary results showed a decrease in arm volumes by 35% at 1 month, 52% at 3 months, 42% at 6 months, 65% at 9 months, and 59% at 12 months. Below we show a summary of the outcomes and complications from the clinical series using vascularized lymph node transfer with the axilla as recipient site. With such limited data, it is currently difficult to draw conclusions regarding the expected improvement in the placebo arm, which increases the uncertainty of the trial outcome.

**Outcome data for lymph node transfers is variable and scarce**

| Authors | No. of Flaps | Recipient site | Reduction rate (%) | Donor site complications | Recipient site complications | Follow-up (months, range) |
|---|---|---|---|---|---|---|
| Becker et al (2006) | 24 | Axilla, elbow | n.a. | Lymphorrhea (8) | None | 99.6 |
| Saaristo et al (2012) | 10 | Axilla | 32.2 ± 30.9 | Seroma (n = 1) | Delayed wound healing (2) | 6 |
| Vignes et al (2013) | 34 flaps in 26 pts | Axilla (n = 14) Groin (n = 12) | n.a. | Iatrogenic Lymphedema (n = 6) Lymphocele (n = 3) Donor site pain (n = 3) | None | 40 (14-72) |
| Dancey et al (2013) | 18 | Axilla | n.a. | Seroma (n = 2) | Fat necrosis (n = 1) | 14 (4-22) |
| Granzow et al (2014) | 8 | Axilla | 88.9% | None | Delayed healing (n = 1) | 12 |
| Nguyen et al (2015) | 29 | Axilla | 10% | Delayed wound healing (n = 1) Abdominal hernia (n = 1) Venous thrombosis (n = 1) | Delayed healing (n = 1) | 11 |
| Barreiro et al (2014) | 7 | Axilla and Shoulder (n = 6) Dorsum Foot (n = 1) | n.a. | Prolonged edema (n = 1), Dehiscence (n = 1) | Prolonged flap edema (n = 1) | n.a. |

**Note:** Reduction rate refers to the overall reduction in swelling of the affected limb
*Source: ABG Sundal Collier*

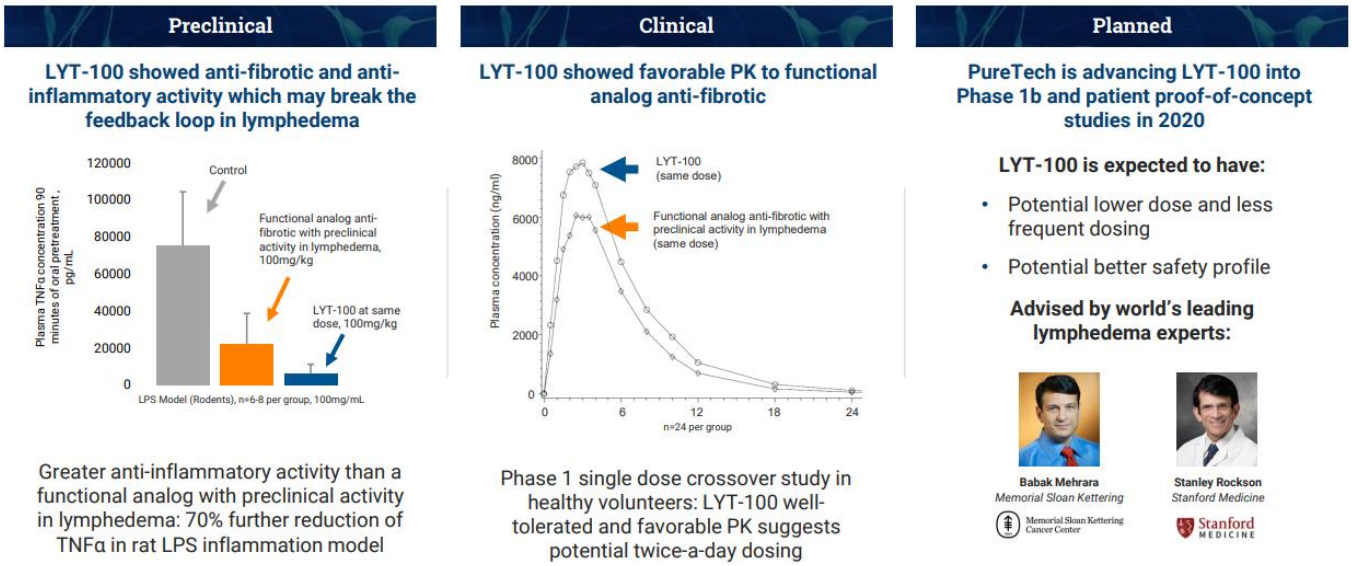
Furthermore, since there are currently no approved therapies for lymphedema, it is yet uncertain whether the FDA/EMA will accept the primary endpoints for the AdeLE study. However, given the considerable unmet medical need for BCAL patients, the regulatory entities are likely to be more lenient in the review and decision process.

An article in Science Magazine by Mitch Leslie (2018), briefly mentions the risks with the development of Lymfactin. The author implies that potential uptake of Lymfactin might be limited *"Although this transfer alone can combat lymphedema, it's unsuitable for many patients and others don't want to risk surgery."* A lymph transfer is an invasive procedure that is likely to add some limitations to the total addressable market. As previously mentioned, it is also a relatively novel therapy, which implies that the success of Lymfactin will correlate with the adaptation of lymph node transfer as a therapy for LE.

## Competing pipeline

We have only been able to identify one competing compound in the pipeline targeting lymphatic flow disorders. US biotech company PureTech is developing its small-molecule product candidate LYT-100 for the treatment of lymphedema, other disorders of impaired lymphatic flow and conditions involving inflammation and fibrosis. Preclinical data showed that LYT-100 induced anti-fibrotic and anti-inflammatory activity, which PureTech believes may break the feedback loop in lymphedema.

**LYT-100 has been studied in a single dose crossover study in healthy volunteers**




*Source: PureTech*

LYT-100 was studied in a single dose crossover Phase 1 clinical trial of 24 healthy volunteers to assess safety and PK. LYT-100 is a deuterated (extended half-life) form of pirfenidone, an approved anti-inflammatory and anti-fibrotic drug. The results demonstrate that LYT-100 displays improved pharmacokinetics (PK) relative to pirfenidone and suggest the possibility of twice-daily dosing of LYT-100 in patients with lymphedema. In addition, LYT-100 was well-tolerated and there were no serious adverse events observed in the Phase 1 clinical trial of healthy volunteers. PureTech intends to commence a multiple dose Phase 1 clinical trial followed by a proof-of-concept (POC) study in lymphedema patients for LYT-100 in 2020, with potential readout for the multiple dose Phase 1 clinical trial in 2020 and POC study in 2021.

Although there is certainly a place for improved anti-fibrotic and anti-inflammatory compounds such as LYT-100 in the lymphedema setting, we are not convinced regarding the potentially disease modifying benefits. The treatment is certainly less invasive and complex (oral administration), but the early data is hardly enough to prove a restoration of damaged lymphatics. As such, we do not view LYT-100 as a direct competitor to Lymfactin as of today.

**The leukemia treatment Ubenimex (bestatin) tried and failed…**

US-based company Eiger Pharmaceuticals conducted a Phase 2 study called ULTRA (NCT02700529), targeting lower leg secondary lymphedema. In October 2018, it announced that it did not achieve its endpoints and that the company would not be pursuing additional clinical trials for this indication. The ULTRA trial was designed to evaluate the possibility that the drug known as Ubenimex (also called "bestatin") could be useful for reducing the symptoms of secondary leg lymphedema. Specifically, they were looking at changes in skin thickness and

excess fluid volume in 46 lymphedema patients treated with either 150mg of ubenimex three times a day for 24 weeks, or placebo pills.

Ubenimex is a safe drug that has been approved and used in Japan as a chemotherapy adjuvant for over 35 years and early mouse studies for lymphedema were certainly promising. Researchers at Stanford found that the build-up of lymph fluid is actually an inflammatory response within the tissue of the skin, not merely a “plumbing” problem within the lymphatic system, as previously thought. Working in the lab, scientists discovered that a naturally occurring inflammatory substance known as leukotriene B4, or LTB4, is elevated in both animal models of lymphedema and in humans with the disease and that at elevated levels it causes tissue inflammation and impaired lymphatic function. Further preclinical research in mice showed that by using ubenimex to target LTB4, scientists were able to induce lymphatic repair and reversal of the disease processes.

However, when digging deeper into the clinical research, it became apparent that Ubenimex (bestatin) may help new lymphatic injuries heal, but only if natural healing is biologically possible and only if it is given at the right time and right dose. Hence, the trial design was flawed and the actual potential efficacious target population slim. We view this oral compound as different to Lymfactin and do not view the trial outcome as a relevant comparator for Herantis.

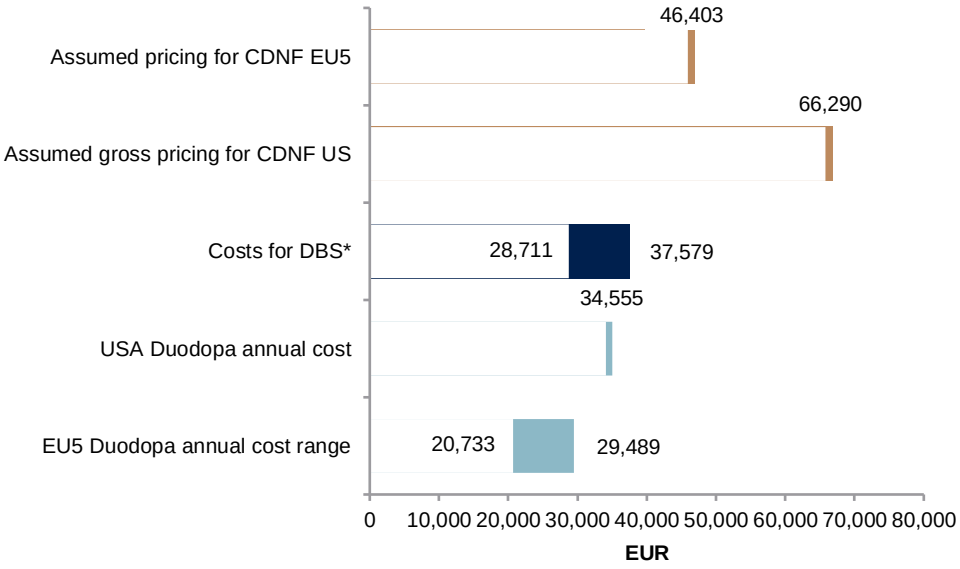
# Uncharted pricing territory

Estimating the pricing of CDNF and Lymfactin is a challenging task. There are currently no comparable products on the market and the currently marketed treatment regimens are not disease-modifying. If CDNF and Lymfactin manage to show clinically significant disease-modifying benefits for these indications with a significant unmet medical need, it would warrant a clear price premium. However, we must also consider the surgery costs associated with the therapies.

**Costs for Duodopa and deep brain simulation (DBS) guides our CDNF pricing**
Duodopa (a gel composed of carbidopa/levodopa), which is a life-changing therapy for patients with severe PD, is significantly more expensive than all other PD medications. As Duodopa is administered via a pump into the intestine, the medication requires surgery. The annual cost of Duodopa in the US is EUR 35k and ranges from EUR 21-30k in EU5, compared to alternatives such as Apokyn/Azilect/Xadago/Stalevo ranging between EUR 1.2-8.4k in the US and EUR 1-11.6k in EU5.[37] However, as CDNF requires surgery (similar to DBS), costs for the surgery have to be considered for CDNF (but not for xCDNF). As illustrated below, total six months post-operation costs for DBS are EUR 29-38k[38]. For the US we assume a gross pricing of 2x the DBS cost mid-point of EUR 33.1k, implying EUR 66.3k per year. We also assume an 18% average annual gross-to-net discount, in line with other CNS drugs for neurodegenerative disorders, implying a net annual US price of EUR 54.4k for CDNF. For EU5 we assume a 30% discount, yielding a net price of EUR 46.4k.

Our pricing estimates assume that CDNF acts on both motor and non-motor symptoms in addition to a moderate (<20%) change in disease progression, noting that stronger clinical outcomes are likely to improve pricing power. We view our current estimates as conservative in light of the societal costs of PD. The National Parkinson's Foundation (NPF) estimates that slowing disease progression by 20% would save USD 61k per patient, and stopping disease progression could save USD 442k per patient. Since DBS is FDA approved for the treatment of PD and covered by Medicare and most insurers, we do not see any reimbursement issues for CDNF.

**For CDNF we assume gross US pricing of EUR 66k and EU5 EUR 46k**




*Source: ABG Sundal Collier, GlobalData Pharma Point, Valldeoriola 2011; * 6 months post-op. costs*

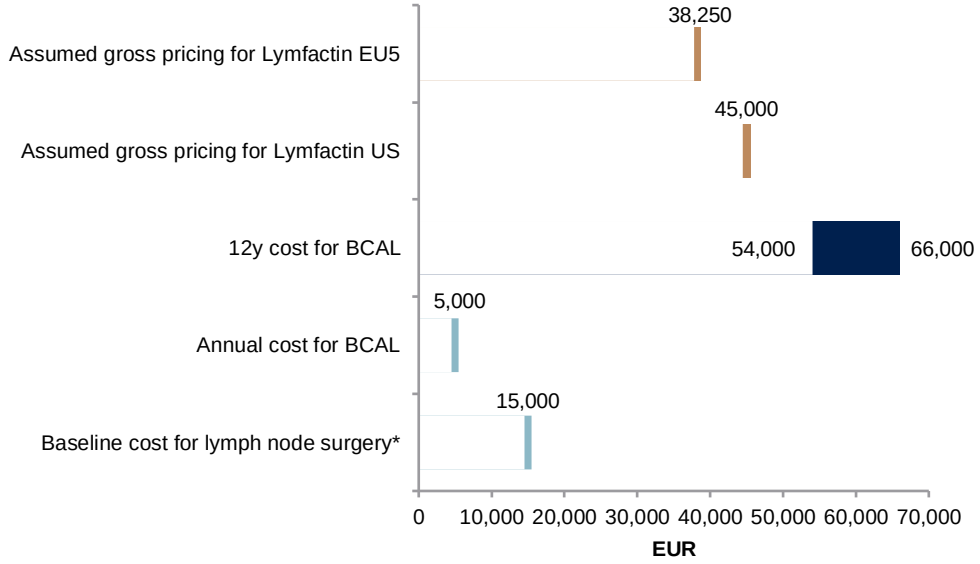
[37] GlobalData Pharma Point: PD - Global Drug Forecast and Market Analysis to '22 (06-2015)
[38] Valldeoriola, 2011. Cost and Efficacy of Therapies for Advanced Parkinson's disease

**For Lymfactin we look at the cost-benefit analysis**

As previously mentioned, BCAL is a chronic condition that currently has no cure. Even more distressing is that women who are treated for breast cancer are facing a lifetime risk of developing lymphedema. Lymphedema causes daily stress and negative impact on breast cancer survivors' quality of life. There is also a significant economic burden that accompanies the management of patients with breast cancer-related lymphedema. Management of moderate BCAL can cost upwards of USD 5,000 annually[39] (see previous section covering treatment alternatives such as CDT); management is lifelong and chronic and increases as the disease progresses. In the US, the median age of diagnosis for breast cancer is 62 years[40]. The long-term follow-up on life expectancy after the curative-intent treatment of breast cancer, indicates that overall survival is "approaching" the overall survival of the general population[41].

If we conservatively assume a 12-year average survival rate for BCAL patients, a curative treatment would imply lifetime cost savings upwards of USD 60,000. Since Lymfactin is combined with the relatively novel treatment method of lymph node transfers, we have to factor in the cost for the surgical procedure, which as of today lacks reliable cost data. Assuming that Lymfactin will prove to be a disease-modifying treatment with an average surgical cost of USD 15,000, we assume a gross pricing of EUR 45,000 in the US. A 15% gross-to-net discount implies a net price of EUR 38,250 in the US. For EU5 we assume a 30% discount to the US, implying a pricing estimate of EUR 31,500. Insurance coverage is still uncertain as of today, but given the clear unmet medical need within BCAL, we believe reimbursement will be resolved. For example, a presentation from the division of plastic surgery at Penn Medicine reviewing lymph node transfers mentions initial success of this procedure at the hospital.[42]

**For Lymfactin we assume gross US pricing of EUR 45k and EU5 EUR 38k**




*Source: ABG Sundal Collier, *simplistic flat-rate assumption given that lymph node surgery is a novel therapy*

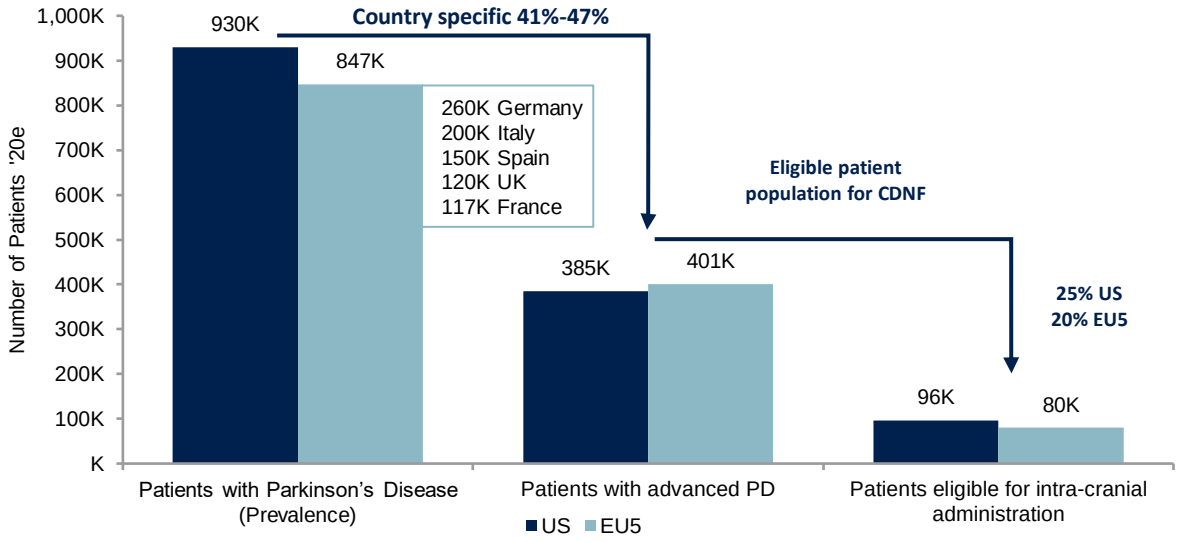
[39] Boyages et al. SprinPlus 5:657. 2016.
[40] SEER Cancer Statistics Review
[41] Arrington et al. 2014 Am Surg. 2014 Jun;80(6):604-9.
[42] Kanchwala, Penn Medicine

# Epidemiology and patients eligible for treatment

**We limit the PD opportunity to 20-25% of advanced patients – for now…**
We let the US and EU5 represent the target markets in our valuation of Herantis. The Parkinson's Foundation Prevalence Project estimates that 930,000 people in the United States will be living with PD by the year 2020. This number is predicted to rise to 1.2 million by 2030, a CAGR of 2.6% with ~60,000 new cases being diagnosed each year. According to the European brain council, 1.2 million people in Europe have Parkinson's, of which 847,000 belong to the EU5, here we assume a CAGR of 2%. Many individuals are misdiagnosed or undiagnosed (PD can take years to develop and patients may not be diagnosed early on), so the actual prevalence is likely higher.

Given the invasive intra-cranial administration of CDNF, we assume that only patients with advanced PD will be eligible for the drug. Patients with early PD could also be eligible for xCDNF, however, this is not included in this report as it currently is a preclinical project. GlobalData estimates that there are some country-specific variations in the prevalence of advanced PD with ~41% of all patients in the US and ~47% in EU5 by 2030. This yields an eligible market of ~385,000 advanced PD patients in the US and ~401,000 in EU5 in '20e. Intra-cranial drug delivery systems are not widely available and the risks and potential adverse effects lead to further patient population limitations in our view. Patients must be healthy enough to go through invasive surgery, accept the risks associated with a novel therapy and have reasonable access to hospitals providing the services needed for the therapy. Although acceptance and physician adoption is likely to develop in the future, especially in the case of established disease-modifying benefits, we conservatively assume that 20% of advanced PD patients in the EU5 and 25% in the US are eligible for the treatment (the US market is assumed to be more prone to accept novel therapies). This yields a final eligible patient population for CDNF of ~96,000 in the US and ~80,000 in EU5.

**Estimated Parkinson's disease (PD) prevalence (diagnosed) and CDNF eligibility**

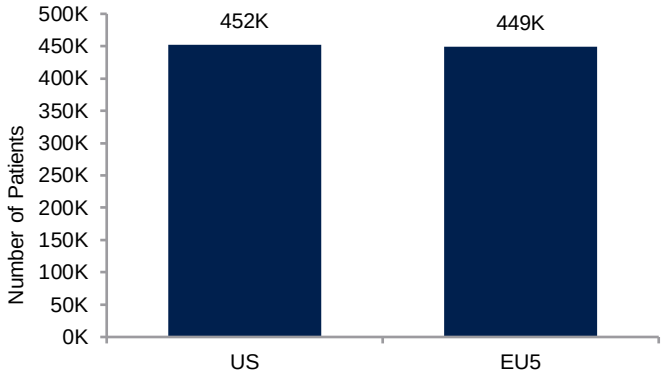



*Source: ABG Sundal Collier, GlobalData Pharma Point: Parkinson's disease – Global Drug Forecast and Market Analysis to 2022*

**~20% of breast cancer patients undergo mastectomy; ~30% probability of developing BCAL**

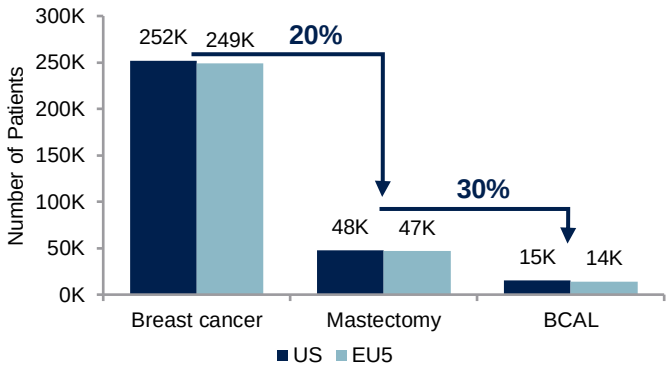
Secondary lymphedema affects ~1.4 in every 1,000 individuals in the general population, translating to ~450K patients in US and EU5. Actual prevalence of BCAL is underestimated, considering that the disease may be subclinical, mild or latent patients may not seek treatment and diagnosis is not highly specific and well defined. Breast cancer incidence is ~250K in US and EU5, based on NIH and WHO data from 2016 and 2012; ~20% of those diagnosed patients will undergo a mastectomy (surgery to remove all breast tissue from a breast) and ~30% of patients that undergo mastectomy will develop BCAL. This implies that ~29,000 patients in the US and EU5 are diagnosed with BCAL each year.

**Estimated secondary lymphedema prevalence (diagnosed and undiagnosed)**




*Source: ABG Sundal Collier, UpToDate*

**Estimated incidence of breast cancer, mastectomy and BCAL**




*Source: ABG Sundal Collier, NIH 2016, WHO 2012*

# Forecasts and estimates

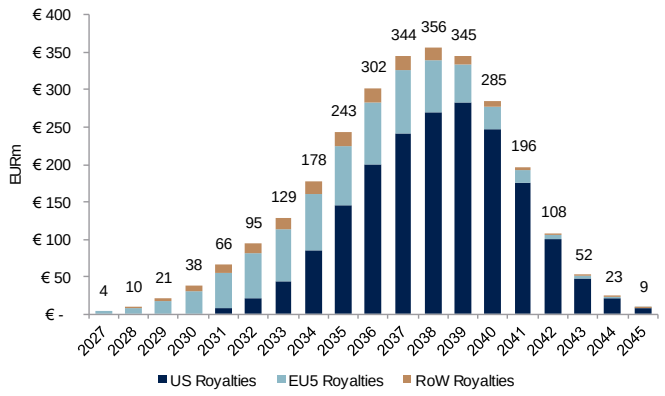
## CDNF revenue modelling; risk-adj. peak sales of EUR 170m by '39e

For CDNF, we forecast approval and a subsequent product launch in '27e in the EU5 and '31e in the US as the FDA is likely to require additional safety and efficacy studies on US PD patients. As a part of Herantis' licensing strategy, we assume CDNF to be out-licensed after successful proof-of-concept data is achieved for disease-modifying benefits. We believe that the resources of a large pharmaceutical player would be required to take CDNF from mid-stage clinical trials to commercialisation. We base our risk-adjustment factor of 8.4% on the historical likelihood of approval for neurology assets from Phase 1 to approval[43].

We forecast a gradual uptake of CDNF for patients with advanced PD eligible for intra-cranial administration of roughly 100K patients per market (eligible patient population discussed under the "Epidemiology and patients eligible for treatment" section). One major point of sensitivity for CDNF's potential market share is its efficacy; we currently and conservatively assume 17% peak market share in the US and 12% in EU5 with a nine-year product life cycle (peak years: '37e in EU5 and '39e in the US). We note that CDNF's product cycle could be drastically shortened in the event of a successful launch of the non-invasive xCDNF, which likely would replace all sales of CDNF. With an annual net price of EUR 54.3K in the US and EUR 46.4K in EU5, we forecast peak sales of EUR 1.6bn (EUR 137m risk-adj.) in the US and EUR 400m (EUR 52m risk-adj.) in EU5. For the rest of the world (RoW) we assume 20% of EU5 sales, reaching a peak of EUR 120m (EUR 10m risk-adj.).

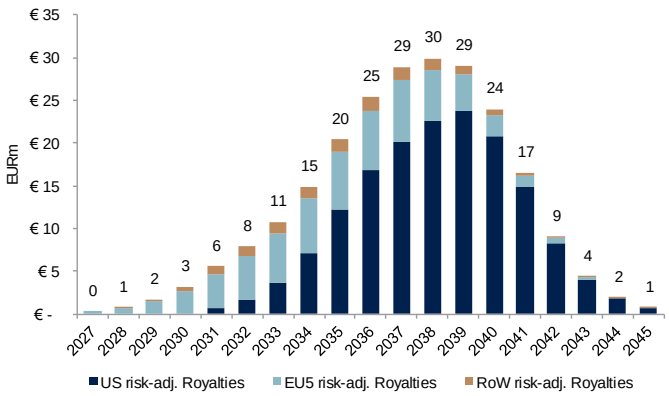
We assume a tiered royalty structure of 12% to 18% on net sales ranging from EUR 100m to EUR 850m for the US and EU5 with a flat royalty of 15% on RoW sales. This yields peak royalties of EUR 283m (EUR 24m risk-adj.) in the US, EUR 85m (EUR 7m risk-adj.) in EU5 and EUR 19m (EUR 2m risk-adj.) in RoW. We forecast an upfront milestone of EUR 72m (EUR 36m with 50% risk-adj.) at the start of a pivotal trial in '25e. We also forecast milestone payments contingent upon approval of EUR 100m (EUR 8m risk-adj.) for approval in the EU '27e and EUR 150m (EUR 13m risk-adj.) for approval in the US '31e. We assume that the partner is fully responsible for developing and commercialising CDNF and all costs associated therewith.

**CDNF royalties '27e-'45e**




*Source: ABG Sundal Collier*

**CDNF risk-adj. royalties (8.4%) '27e-'45e**




*Source: ABG Sundal Collier*

[43] BIO, Biomedtracker, Amplion 2016

## Summary of US and EU5 revenue and royalty model CDNF '20e-'45e

| Parkinson's disease market model (EURm) | Assumptions | 2031e | 2032e | 2033e | 2034e | 2035e | 2036e | 2037e | 2038e | 2039e | 2040e |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **US Market** | | | | | | | | | | | |
| **PD patients (k)** | 930 | 1,233 | 1,265 | 1,298 | 1,332 | 1,366 | 1,402 | 1,438 | 1,476 | 1,514 | 1,553 |
| Growth | 2.6% | | | | | | | | | | |
| **Advanced PD pats. (k)** | 41% | 510 | 523 | 537 | 551 | 565 | 580 | 595 | 611 | 627 | 643 |
| **Early PD pats. (k)** | 59% | 722 | 741 | 760 | 780 | 800 | 821 | 843 | 865 | 887 | 910 |
| **Patients eligible for intra-cranial admin. (k)** | 25% | 127 | 130 | 134 | 137 | 141 | 145 | 148 | 152 | 156 | 160 |
| **Advanced PD patients on CDNF (k)** | **Peak:** | 1.4 | 3.0 | 6.1 | 10.8 | 16.0 | 20.3 | 23.2 | 25.0 | 25.6 | 22.4 |
| CDNF market share | 17% | 1.1% | 2.3% | 4.5% | 7.8% | 11.3% | 14.0% | 15.6% | 16.4% | 17.0% | 13.9% |
| **Annual cost of CDNF (k)** | € 66.3 | € 66.3 | € 67.6 | € 68.9 | € 70.3 | € 71.7 | € 73.2 | € 74.7 | € 76.1 | € 77.6 | € 79.2 |
| Price increase | | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% |
| Gross-to-net adjustment | 18% | 18% | 18% | 18% | 18% | 18% | 18% | 18% | 18% | 18% | 18% |
| **CDNF sales (EURm)** | | **€ 74** | **€ 167** | **€ 345** | **€ 623** | **€ 943** | **€ 1,220** | **€ 1,420** | **€ 1,561** | **€ 1,633** | **€ 1,453** |
| **CDNF risk-adj. sales (EURm)** | **Risk-adj. 8.4%** | **€ 6** | **€ 14** | **€ 29** | **€ 52** | **€ 79** | **€ 102** | **€ 119** | **€ 131** | **€ 137** | **€ 122** |
| **Royalty rate** | | **12.0%** | **12.2%** | **12.5%** | **13.7%** | **15.4%** | **16.5%** | **17.0%** | **17.2%** | **17.4%** | **17.0%** |
| **Royalties, US (EURm)** | | **€ 9** | **€ 20** | **€ 43** | **€ 85** | **€ 145** | **€ 201** | **€ 241** | **€ 269** | **€ 283** | **€ 247** |
| **Risk-adj. royalties, US (EURm)** | | **€ 1** | **€ 2** | **€ 4** | **€ 7** | **€ 12** | **€ 17** | **€ 20** | **€ 23** | **€ 24** | **€ 21** |

| EU5 Market | Assumptions | 2027e | 2028e | 2029e | 2030e | 2031e | 2032e | 2033e | 2034e | 2035e | 2036e |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patients with Parkinson's disease (k)** | 847 | 972 | 992 | 1,012 | 1,032 | 1,053 | 1,074 | 1,095 | 1,117 | 1,139 | 1,162 |
| Growth | 2.0% | | | | | | | | | | |
| **Patients with advanced PD (k)** | 47% | 460 | 470 | 479 | 489 | 498 | 508 | 519 | 529 | 540 | 550 |
| **Patients with early PD (k)** | 53% | 512 | 522 | 532 | 543 | 554 | 565 | 576 | 588 | 599 | 611 |
| **Patients eligible for intra-cranial admin. (k)** | 20% | 92 | 94 | 95 | 97 | 99 | 101 | 103 | 105 | 108, | 110 |
| **Advanced PD patients on CDNF (k)** | **Peak:** | 0.7 | 1.5 | 3.1 | 5.4 | 7.9 | 10.0 | 11.4 | 12.2 | 12.7 | 13.1 |
| CDNF market share | 12.0% | 0.8% | 1.6% | 3.2% | 5.5% | 8.0% | 9.9% | 11.0% | 11.5% | 11.8% | 12.0% |
| **Annual cost of CDNF (30% discount to US) (k)** | € 46.4 | €46.4 | € 46.4 | € 46.4 | € 46.4 | € 46.4 | € 46.4 | € 46.4 | € 46.4 | € 46.4 | € 46.4 |
| **CDNF sales (EURm)** | | **€ 32** | **€ 71** | **€ 143** | **€ 251** | **€ 370** | **€ 467** | **€ 530** | **€ 567** | **€ 592** | **€ 609** |
| **CDNF risk-adj. sales (EURm)** | **Risk-adj. 8.4%** | **€ 3** | **€ 6** | **€ 12** | **€ 21** | **€ 31** | **€ 39** | **€ 44** | **€ 48** | **€ 50** | **€ 51** |
| **Royalty rate** | | **12.0%** | **12.0%** | **12.1%** | **12.3%** | **12.5%** | **12.9%** | **13.2%** | **13.3%** | **13.5%** | **13.6%** |
| **Royalties, EU5 (EURm)** | | **€ 4** | **€ 8** | **€ 17** | **€ 31** | **€ 46** | **€ 60** | **€ 70** | **€ 76** | **€ 80** | **€ 83** |
| **Risk-adj. royalties, EU5 (EURm)** | | **€ 0** | **€ 1** | **€ 1** | **€ 3** | **€ 4** | **€ 5** | **€ 6** | **€ 6** | **€ 7** | **€ 7** |

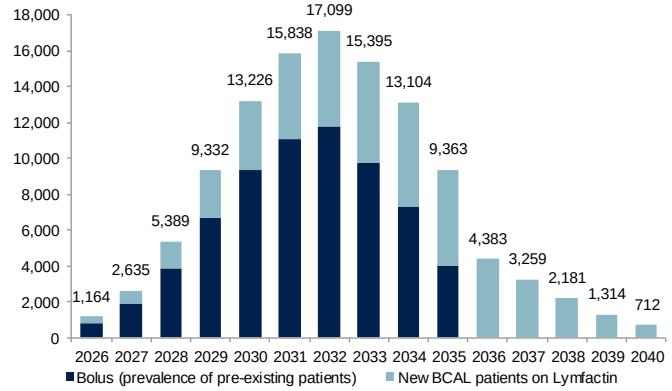
*Source: ABG Sundal Collier*

## Lymfactin revenue modelling; risk-adj. peak sales of EUR 130m by '30e

For Lymfactin, we forecast approval and a subsequent product launch in '23e in the EU5 (after receiving accelerated assessment by the EMA[44]), and '26e in the US as the FDA is likely to require additional safety and efficacy studies on US BCAL patients. As a part of Herantis' licensing strategy, we assume Lymfactin to be out-licensed after successful Phase 2 data is achieved showing disease-modifying benefits. We believe that the resources of a large pharmaceutical player would be required to take Lymfactin from mid-stage clinical trials to commercialisation. We base our risk-adjustment factor of 14.2% on the historical likelihood of approval for neurology assets from Phase 2 to approval[45].

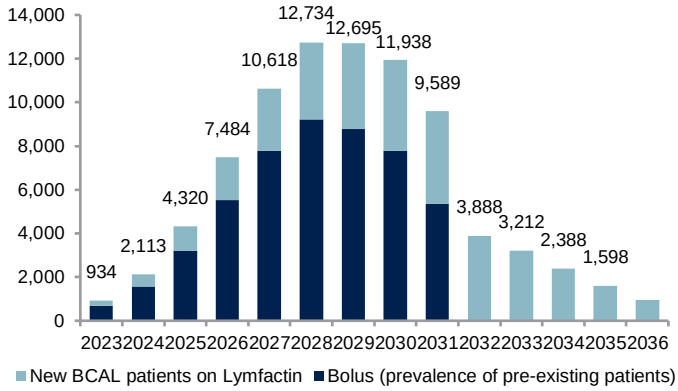
Since lymph node transplantation is a relatively novel therapy, we believe the uptake for Lymfactin will be gradual in the initial years following launch as physicians adopt the novel treatment regimen (eligible patient population discussed under the "Epidemiology and patients eligible for treatment" section). Since Lymfactin is a single-dose gene therapy, we divide the patient population into two categories: (1) a "bolus" of pre-existing BCAL patients (~900K in the US and EU5) eligible for the treatment that is penetrated over ~10 years and (2) the annual incidence of patients developing BCAL (~30K patients in the US and EU5). A major point of sensitivity for Lymfactin's potential market share will be its disease-modifying efficacy. As of now, we assume a 30% peak market share in the US and 25% in EU5 for newly diagnosed patients, with a nine year product life cycle (peak years: '30e in EU5 and '34e in the US). We assume lower penetration in the "bolus" as these patients are less likely to be healthy enough for invasive surgery (median age of breast cancer diagnosis is ~62 years).

**Estimated Lymfactin patients, US ('26e-'40e)**




*Source: ABG Sundal Collier*

**Estimated Lymfactin patients, EU5 ('23e-'40e)**




*Source: ABG Sundal Collier*

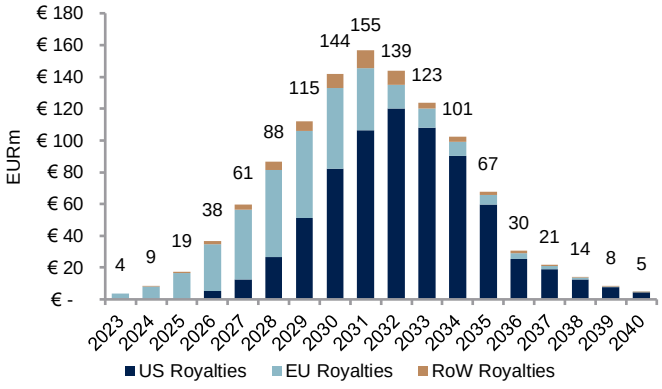
With an annual net price of EUR 38.2K in the US and EUR 31.5K in EU5, we forecast peak sales of EUR 740m (EUR 105m risk-adj.) in the US and EUR 401m (EUR 57m risk-adj.) in EU5. For the rest of the world (RoW), we assume 20% of EU5 sales, reaching a peak of EUR 75m (EUR 11m risk-adj.).

[44] Accelerated assessment reduces the timeframe for the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) to review a marketing-authorisation application (150 days of evaluation vs. 210 days). Applications may be eligible for accelerated assessment if the CHMP decides the product is of major interest for public health and therapeutic innovation.

[45] BIO, Biomedtracker, Amplion 2016

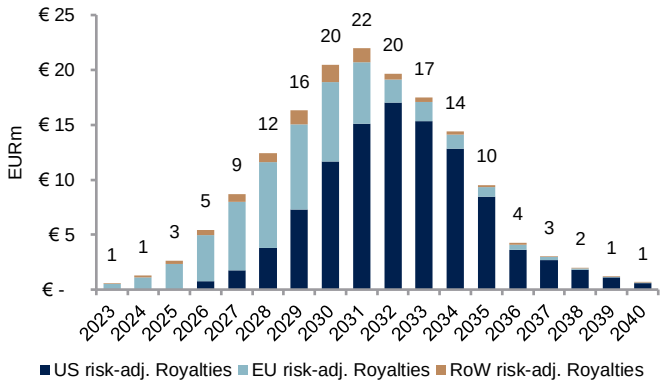
We assume a tiered royalty structure of 12% to 18% on net sales ranging from EUR 100m to EUR 50m for the US and EU5 with a flat royalty of 15% on RoW sales. This yields peak royalties of EUR 120m (EUR 17m risk-adj.) in the US, EUR 55m (EUR 8m risk-adj.) in EU5 and EUR 11m (EUR 2m risk-adj.) in RoW. We forecast an upfront milestone of EUR 72m (EUR 36m with 50% risk-adj.) before the start of a pivotal trial in '21e. We also forecast milestone payments contingent upon approval of EUR 100m (EUR 14m risk-adj.) for approval in the EU late '22e and EUR 150m (EUR 21m risk-adj.) for approval in the US '26e. We assume that the partner is fully responsible for developing and commercialising Lymfactin and all costs associated therewith.

**Lymfactin royalties '23e-'40e**




*Source: ABG Sundal Collier*

**Lymfactin risk-adj. royalties (14.2%) '23e-'40e**




*Source: ABG Sundal Collier*

**Selection of license deals in Parkinson's disease**

| Licensor | Licensee | Date | Drug | MoA | Upfront (mn) | Pot. milestones (mn) | Transaction value (mn) |
|---|---|---|---|---|---|---|---|
| AbbVie | Voyager Therapeutics | 22-Feb-19 | Not specified | Gene therapy | $65 | $245 | $310 |
| AbbVie | BioArctic | 14-Dec-18 | BAN0805 | Anti-synuclein antibody | $50 | $705 | $755 |
| Lundbeck | Prexton | 16-Mar-18 | Foliglurax | mGluR4 compound | €100 | €805 | €905 |
| Takeda | AstraZeneca | 29-Aug-17 | MEDI1341 | Anti-synuclein antibody | - | - | $400 |
| Axovant | Oxford BioMedica | 06-Jun-17 | OXB-102, | Gene therapy | $30 | $812.5 | $842.5 |
| Biogen | BMS | 13-Apr-17 | BMS-986168 | Anti-tau antibody | $300 | $410 | $710 |
| Neurocrine | Bial | 10-Feb-17 | Ongentys | COMT inhibitor | $30 | $115 | $145 |
| Roche | Prothena | 11-Dec-13 | PRX002 | Anti-synuclein antibody | - | - | $600 |

*Source: ABG Sundal Collier*

**Historical transactions guide our upfront milestone estimate**


*Source: ABG Sundal Collier, Bloomberg [Not specific to Parkinson's disease deals]*

## Summary of US and EU5 revenue and royalty model Lymfactin '20e-'45e

| BCAL market model (EURm) | Assumptions | 2026e | 2027e | 2028e | 2029e | 2030e | 2031e | 2032e | 2033e | 2034e | 2035e | 2036e |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **US Market** | | | | | | | | | | | | |
| **Patients with breast cancer (k)** | 252 | 284 | 289 | 295 | 301 | 307 | 313 | 320 | 326 | 333 | 339 | 346 |
| Growth | 2.0% | | | | | | | | | | | |
| **Patients undergoing mastectomy (k)** | 19% | 54 | 55 | 56 | 57 | 58 | 59 | 60 | 62 | 63 | 64 | 65 |
| **Patients developing BCAL (annual incidence) (k)** | 31% | 16 | 17 | 17 | 17 | 18 | 18 | 19 | 19 | 19 | 20 | 20 |
| **New BCAL patients on Lymfactin (k)** | **Peak:** | 0.3 | 0.7 | 1.5 | 2.7 | 3.9 | 4.8 | 5.3 | 5.7 | 5.8 | 5.3 | 4.4 |
| Lymfactin market share | 30% | 1.9% | 4.2% | 8.6% | 14.9% | 21.3% | 25.7% | 28.1% | 29.2% | 30.0% | 26.3% | 21.3% |
| **"Bolus" (prevalence of pre-existing patients) (k)** | 452 | 0.8 | 1.9 | 3.9 | 6.6 | 9.3 | 11.1 | 11.8 | 9.7 | 7.3 | 4.1 | |
| *Implied penetration of "bolus"* | 14.7% | 0.2% | 0.4% | 0.9% | 1.5% | 2.1% | 2.4% | 2.6% | 2.2% | 1.6% | 0.9% | |
| **BCAL patients on Lymfactin (Bolus + New Patient Penetration) (k)** | | **1.2** | **2.6** | **5.4** | **9.3** | **13.2** | **15.8** | **17.1** | **15.4** | **13.1** | **9.4** | **4.4** |
| **Cost of Lymfactin dose (k)** | € 45 | € 45 | € 45.9 | € 46.8 | € 47.7 | € 48.7 | €49.6 | € 50.6 | € 51.7 | € 52.7 | € 53.7 | € 54.8 |
| Price increase | | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% | 2.0% |
| Gross-to-net adjustment | 15% | 15% | 15% | 15% | 15% | 15% | 15% | 15% | 15% | 15% | 15% | 15% |
| **Lymfactin sales (EURm)** | | **€ 45** | **€ 103** | **€ 214** | **€ 379** | **€ 548** | **€ 669** | **€ 737** | **€ 676** | **€ 587** | **€ 428** | **€ 204** |
| **Lymfactin risk-adj. sales (EURm)** | | **€ 6** | **€ 15** | **€ 30** | **€ 54** | **€ 78** | **€ 95** | **€ 105** | **€ 96** | **€ 83** | **€ 61** | **€ 29** |
| **Royalty rate** | | **12.0%** | **12.0%** | **12.4%** | **13.4%** | **14.8%** | **15.8%** | **16.2%** | **15.8%** | **15.2%** | **13.8%** | **12.4%** |
| **Royalties, US (EURm)** | | **€ 5** | **€ 12** | **€ 27** | **€ 51** | **€ 82** | **€ 107** | **€ 120** | **€ 108** | **€ 90** | **€ 60** | **€ 25** |
| **Risk-adj. royalties, US (EURm)** | | **€ 1** | **€ 2** | **€ 4** | **€ 7** | **€ 12** | **€ 15** | **€ 17** | **€ 15** | **€ 13** | **€ 8** | **€ 4** |

*Source: ABG Sundal Collier*

| EU5 Market | Assumptions | 2022e | 2023e | 2024e | 2025e | 2026e | 2027e | 2028e | 2029e | 2030e | 2032e | 2033e |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Patients with breast cancer (k)** | 249 | 259 | 264 | 269 | 274 | 280 | 286 | 291 | 297 | 303 | 309 | 315 |
| Growth | 2.0% | | | | | | | | | | | |
| **Patients undergoing mastectomy (k)** | 19% | 49 | 50 | 51 | 52 | 53 | 54 | 55 | 56 | 57 | 58 | 60 |
| **Patients developing BCAL (k)** | 30% | 14.5 | 14.8 | 15.1 | 15.5 | 15.8 | 16.1 | 16.4 | 16.7 | 17.1 | 17.4 | 17.8 |
| **New BCAL patients on Lymfactin (k)** | **Peak:** | 0.2 | 0.5 | 1.1 | 1.9 | 2.8 | 3.4 | 3.8 | 4.1 | 4.2 | 3.8 | 3.1 |
| Lymfactin market share | 25.0% | 1.6% | 3.5% | 7.2% | 12.4% | 17.7% | 21.4% | 23.4% | 24.3% | 25.0% | 21.9% | 17.7% |
| **Bolus (prevalence of pre-existing patients) (k)** | 449 | 0.7 | 1.6 | 3.2 | 5.5 | 7.7 | 9.2 | 9.9 | 8.8 | 7.4 | 4.3 | |
| *Implied penetration of "bolus"* | 13.0% | 0.2% | 0.4% | 0.7% | 1.2% | 1.7% | 2.1% | 2.2% | 2.0% | 1.6% | 1.0% | |
| **BCAL patients on Lymfactin (Bolus + New Patient Penetration) (k)** | | **0.9** | **2.1** | **4.3** | **7.4** | **10.5** | **12.6** | **13.6** | **12.9** | **11.5** | **8.1** | **3.1** |
| **Annual cost of Lymfactin (30% discount to US) (k)** | € 31.5 | € 31.5 | € 31.5 | € 31.5 | € 31.5 | € 31.5 | € 31.5 | € 31.5 | € 31.5 | € 31.5 | € 31.5 | € 31.5 |
| **Lymfactin sales (EURm)** | | **€ 29** | **€ 66** | **€ 135** | **€ 235** | **€ 333** | **€ 399** | **€ 431** | **€ 406** | **€ 364** | **€ 257** | **€ 99** |
| **Lymfactin risk-adj. sales (EURm)** | | **€ 4** | **€ 9** | **€ 19** | **€ 33** | **€ 47** | **€ 57** | **€ 61** | **€ 58** | **€ 52** | **€ 36** | **€ 14** |
| **Royalty rate** | | **12.0%** | **12.0%** | **12.1%** | **12.5%** | **13.1%** | **13.7%** | **13.9%** | **13.7%** | **13.4%** | **12.6%** | **12.0%** |
| **Royalties, EU5 (EURm)** | | **€ 4** | **€ 8** | **€ 16** | **€ 29** | **€ 44** | **€ 55** | **€ 60** | **€ 56** | **€ 49** | **€ 32** | **€ 12** |
| **Risk-adj. royalties, EU5 (EURm)** | | **€ 0** | **€ 1** | **€ 2** | **€ 4** | **€ 6** | **€ 8** | **€ 9** | **€ 8** | **€ 7** | **€ 5** | **€ 2** |

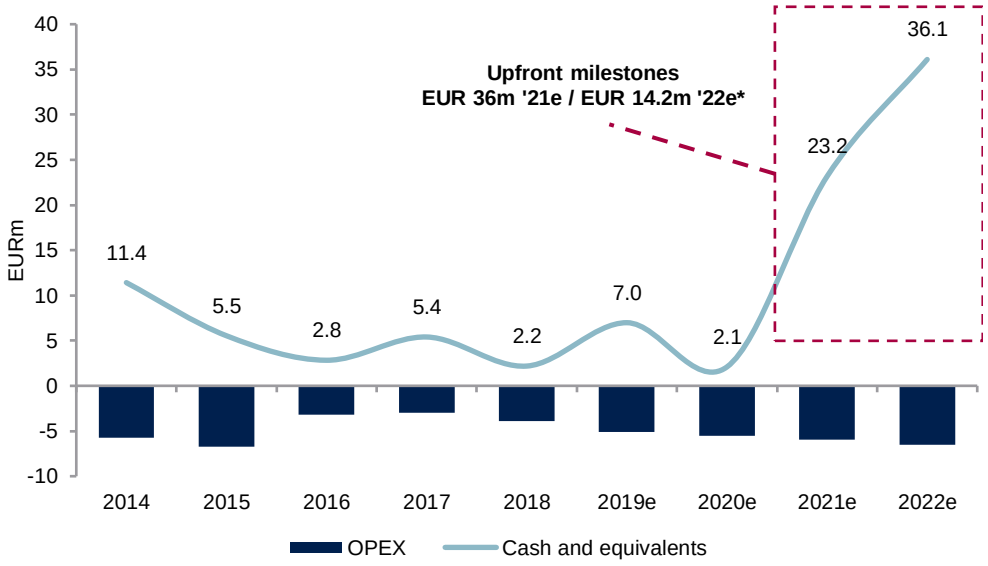
*Source: ABG Sundal Collier*

## Financials

As a pre-revenue research stage company, Herantis will continue to be cash flow negative in the near term. In the latest H1'19 report, Herantis reported a cash position of EUR 4.5m and operating cash flow of EUR -2.7m. A share issue of EUR 5.8m was completed during H1'19, bringing Swedbank Robur Medica in as the largest shareholder. In November 2019, Herantis completed a heavily oversubscribed directed share issue of approximately EUR 4m (~9.25% of shares). For FY'19e, we estimate a cash position of EUR 7m (net cash of EUR 0.5m) with operating cash flow of EUR -5.4m. For our net debt calculation, we conservatively include EUR 6.5m of Business Finland R&D loans. If the project fails or its results cannot be commercially exploited, the loan may be partially converted into a grant[46]. We estimate that the current cash position should fund operations through '20e and that a potential upfront milestone of EUR 72m (risk-adj. EUR 36m) in '21e could mitigate additional capital raises. However, with an estimated cash position reaching EUR 2.1m by the end of '20e and uncertain timing of a potential milestone, we cannot rule out further external financing needs.

We note that Herantis has managed to maintain solid cost control with academically run studies, with R&D expenses coming in at EUR 1.4m in H1'19 (vs. EUR 1.1m H1'18). We model a gradual ramp-up in opex as most of it relates to drug production costs. A significant sensitivity to our opex and cash-burn assumption relates to potential milestones and to what degree a partner would cover costs relating to clinical trials.

**Opex and cash overview**




**EUR 72m upfront for Lymfactin for start of pivotal study (EUR 36m with 50% risk-adj); EUR 100m milestone for approval in Europe (EUR 14.2m with 14.2% risk-adj.)*
*Source: ABG Sundal Collier*

[46] https://www.businessfinland.fi/en/for-finnish-customers/services/funding/research-and-development/research-development-and-piloting/

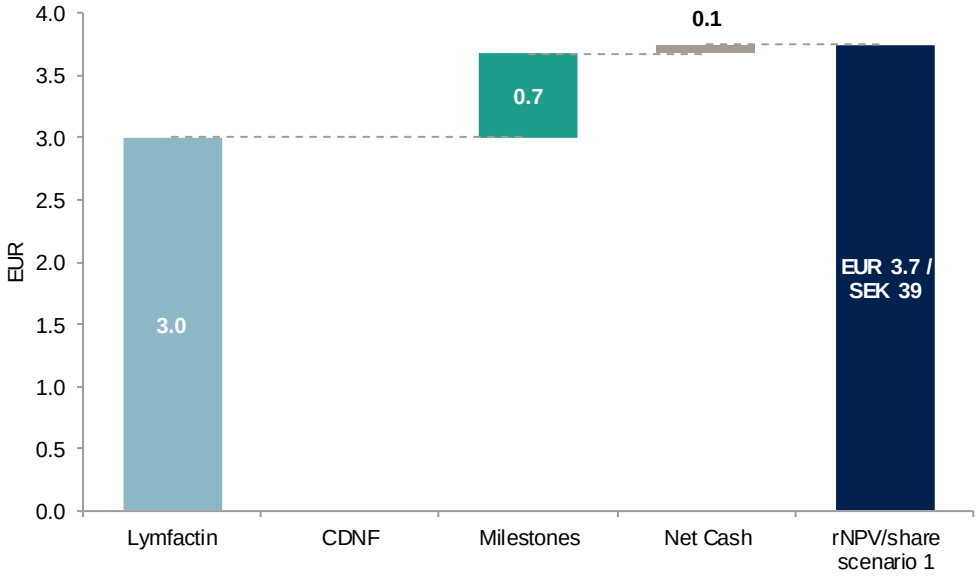
# Valuation

***For our fair value estimation of Herantis, we outline three different scenarios yielding a risk-adjusted NPV fair value range of SEK 39-139 (EUR 3.7-13.0) per share using a WACC of 13%. Scenario 1 (SEK 39/EUR 3.7 per share) assumes that CDNF fails to prove clinical utility, leaving Lymfactin as the sole asset. Scenario 2 (SEK 94/EUR 8.8 per share) maintains the forecasts and assumptions outlined in the 'forecasts and estimates' section. Scenario 3 (SEK 139/EUR 13.0 per share) assumes stronger-than-expected disease-modifying efficacy, leading to increased peak penetration (+5%) and higher pricing (+20-25%) from Scenario 2. Given its early development stage, we exclude the non-invasive xCDNF compounds from our valuation..***

**Key assumptions for Scenario 1:**

- CDNF fails to show clinical utility in its ongoing Phase 1-2 study, thus being abandoned by Herantis, yielding no future royalty income or milestones for the asset.
- Lymfactin assumptions unchanged from 'forecasts and estimates' section with a 14.2% risk-adjustment factor; total milestones of EUR 322m (EUR 72m risk-adj.); peak royalties of EUR 155m (risk-adj. EUR 22m) by '31e.
- Larger amount of "unallocated costs" assigned to the asset yields a lower rNPV per share for Lymfactin.

**Scenario 1 rNPV overview – CDNF fails to show clinical utility**

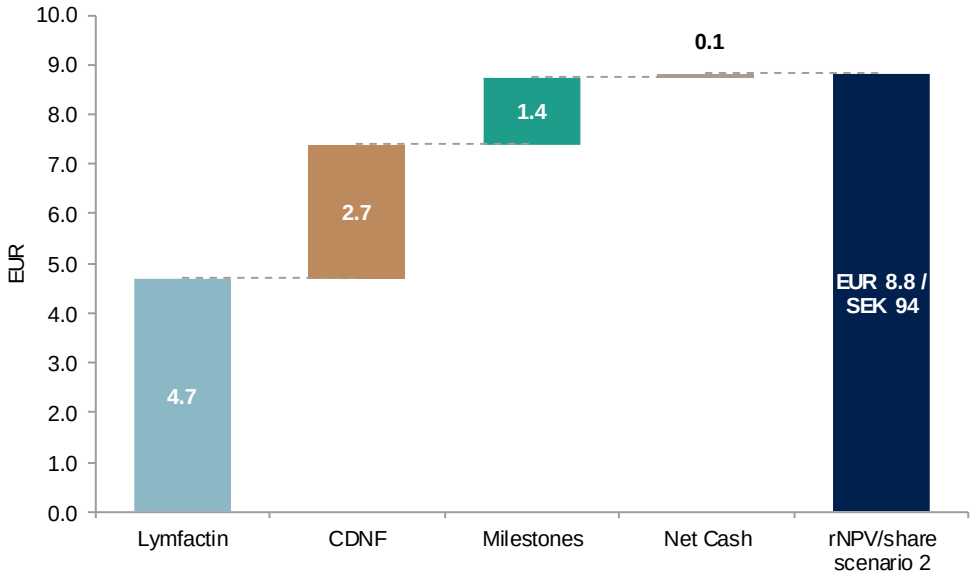



*Source: ABG Sundal Collier*

**Key assumptions for Scenario 2:**

- CDNF shows moderate disease-modifying benefit on motor and non-motor symptoms (<20%). We utilize the assumptions presented in the 'forecasts and estimates'-section; 8.4% risk-adjustment factor; total milestones of EUR 322m (EUR 57m risk-adj.); peak royalties of EUR 356m (EUR 30m risk-adj.) by '38e
- Lymfactin assumptions unchanged from 'forecasts and estimates' section with a 14.2% risk-adjustment factor; total milestones of EUR 322m (EUR 72m risk-adj.); peak royalties of EUR 155m (risk-adj. EUR 22m) by '31e.

**Scenario 2 rNPV overview – CDNF and Lymfactin shows disease-modifying benefits**

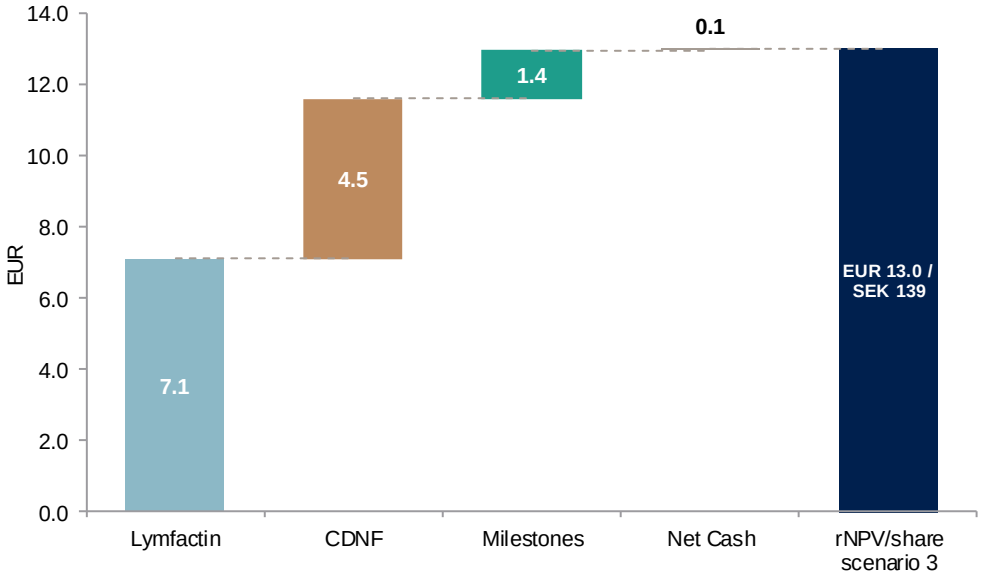



*Source: ABG Sundal Collier*

**Key assumptions for Scenario 3:**

- CDNF shows significant disease-modifying benefit on motor and non-motor symptoms (>20%), which improves the peak penetration of CDNF by 5% and annual pricing of 25% vs. Scenario 2. We assume a risk-adjustment factor of 8.4%; total milestones of EUR 322m (EUR 57m risk-adj.); peak royalties of EUR 681m (EUR 58m risk-adj.) by '38e.
- Lymfactin shows significant disease modifying benefits, improving peak penetration by 5% and pricing by 20% vs. Scenario 2. We assume a 14.2% risk-adjustment factor; total milestones of EUR 322m (EUR 72m risk-adj.); peak royalties of EUR 248m (risk-adj. EUR 35m) by '31e.

**Scenario 3 rNPV overview – CDNF and Lymfactin proves significant disease-modifying benefits and commercial success**




*Source: ABG Sundal Collier, company data*

**Herantis share price vs. Scenario 1-3**


*Source: ABG Sundal Collier, InFront*

# Scenario analysis - details

## Scenario 1

**CDNF** **Lymfactin**

**Key model assumptions - Scenario 1**

*CDNF fails to prove clinical benefit*

**US**

| | |
|---|---|
| CDNF peak year | - |
| Lymfactin peak year | 2034 |
| Peak penetration CDNF | 0.0% |
| Peak penetration Lymfactin | 30.0% |
| CDNF year on the market | - |
| CDNF annual gross cost/pt. (EUR) | - |
| CDNF Annual net cost/pt (EUR) | - |
| Lymfactin year on the market | 2022 |
| Lymfactin gross cost/pt. (EUR) | 45,000 |
| Lymfactin net cost/pt (EUR) | 38,250 |
| CDNF Peak sales, US (EURm) | - |
| CDNF Peak royalties, US (EURm) | - |
| CDNF Risk-adj. Factor (%) | - |
| CDNF Risk-adj. Peak sales (EURm) | - |
| CDNF Risk-adj. Peak Royalties (EURm) | - |
| CDNF peak patients treated (#) | - |
| Lymfactin Peak sales, US (EURm) | 737 |
| Lymfactin Peak royalties, US (EURm) | 120 |
| Lymfactin Risk-adj. Factor (%) | 14.2% |
| Lymfactin Risk-adj. Peak sales (EURm) | 105 |
| Lymfactin Risk-adj. Peak royalties (EURm) | 17 |
| Lymfactin peak patients treated (#) | 17,099 |

**EU5**

| | |
|---|---|
| CDNF peak year | - |
| Lymfactin peak year | 2030 |
| Peak penetration CDNF | 0.0% |
| Peak penetration Lymfactin | 25.00% |
| CDNF year on the market | - |
| CDNF Annual net cost/pt (EUR) | - |
| Lymfactin year on the market | 2022 |
| Lymfactin net cost/pt (EUR) (30% disc. vs U | 31,500 |
| CDNF Peak sales, US (EURm) | - |
| CDNF Peak royalties, US (EURm) | - |
| CDNF Risk-adj. Factor (%) | - |
| CDNF Risk-adj. Peak sales (EURm) | - |
| CDNF Risk-adj. Peak Royalties (EURm) | - |
| CDNF peak patients treated (#) | - |
| Lymfactin Peak sales, US (EURm) | 401 |
| Lymfactin Peak royalties, US (EURm) | 55 |
| Lymfactin Risk-adj. Factor (%) | 14.2% |
| Lymfactin Risk-adj. Peak sales (EURm) | 57 |
| Lymfactin Risk-adj. Peak royalties (EURm) | 8 |
| Lymfactin peak patients treated (#) | 12,734 |

**RoW**

| | |
|---|---|
| CDNF peak year | - |
| Lymfactin peak year | 2030 |
| Peak % of European sales CDNF | - |
| Peak % of European sales Lymfactin | 20.0% |
| CDNF year on the market | - |
| Lymfactin year on the market | 2023 |
| CDNF Peak sales, US (EURm) | - |
| CDNF Peak royalties, US (EURm) | - |
| CDNF Risk-adj. Factor (%) | - |
| CDNF Risk-adj. Peak sales (EURm) | - |
| CDNF Risk-adj. Peak Royalties (EURm) | - |
| Lymfactin Peak sales, US (EURm) | 75 |
| Lymfactin Peak royalties, US (EURm) | 11 |
| Lymfactin Risk-adj. Factor (%) | 14.2% |
| Lymfactin Risk-adj. Peak sales (EURm) | 11 |
| Lymfactin Risk-adj. Peak royalties (EURm) | 2 |

**General**

| | |
|---|---|
| Inflation p.a. | 2.0% |
| Population growth | 2.0% |
| Perpetual growth | 3.0% |
| WACC | 13.0% |

*Source: ABG Sundal Collier*

## Scenario 2

**Key model assumptions - Scenario 2**

*Forecasts and estimates'-scenario*

**US**

| | |
|---|---|
| CDNF peak year | 2039 |
| Lymfactin peak year | 2034 |
| Peak penetration CDNF | 17.0% |
| Peak penetration Lymfactin | 30.0% |
| CDNF year on the market | 2031 |
| CDNF annual gross cost/pt. (EUR) | 66,290 |
| CDNF Annual net cost/pt (EUR) | 54,358 |
| Lymfactin year on the market | 2026 |
| Lymfactin gross cost/pt. (EUR) | 45,000 |
| Lymfactin net cost/pt (EUR) | 38,250 |
| CDNF Peak sales, US (EURm) | 1,633 |
| CDNF Peak royalties, US (EURm) | 283 |
| CDNF Risk-adj. Factor (%) | 8.4% |
| CDNF Risk-adj. Peak sales (EURm) | 137 |
| CDNF Risk-adj. Peak Royalties (EURm) | 24 |
| CDNF peak patients treated (#) | 25,646 |
| Lymfactin Peak sales, US (EURm) | 737 |
| Lymfactin Peak royalties, US (EURm) | 120 |
| Lymfactin Risk-adj. Factor (%) | 14.2% |
| Lymfactin Risk-adj. Peak sales (EURm) | 105 |
| Lymfactin Risk-adj. Peak royalties (EURm) | 17 |
| Lymfactin peak patients treated (#) | 17,099 |

**EU5**

| | |
|---|---|
| CDNF peak year | 2037 |
| Lymfactin peak year | 2030 |
| Peak penetration CDNF | 12.0% |
| Peak penetration Lymfactin | 25.0% |
| CDNF year on the market | 2027 |
| CDNF Annual net cost/pt (EUR) | 46,403 |
| Lymfactin year on the market | 2022 |
| Lymfactin net cost/pt (EUR) | 31,500 |
| CDNF Peak sales, EU5 (EURm) | 621 |
| CDNF Peak royalties, EU5 (EURm) | 85 |
| CDNF Risk-adj. Factor (%) | 8.4% |
| CDNF Risk-adj. Peak sales (EURm) | 52 |
| CDNF Risk-adj. Peak Royalties (EURm) | 7 |
| CDNF peak patients treated (#) | 13,388 |
| Lymfactin Peak sales, US (EURm) | 401 |
| Lymfactin Peak royalties, US (EURm) | 55 |
| Lymfactin Risk-adj. Factor (%) | 14.2% |
| Lymfactin Risk-adj. Peak sales (EURm) | 57 |
| Lymfactin Risk-adj. Peak royalties (EURm) | 8 |
| Lymfactin peak patients treated (#) | 12,734 |

**RoW**

| | |
|---|---|
| CDNF peak year | 2037 |
| Lymfactin peak year | 2030 |
| Peak % of European sales CDNF | 20.0% |
| Peak % of European sales Lymfactin | 20.0% |
| CDNF year on the market | 2028 |
| Lymfactin year on the market | 2023 |
| CDNF Peak sales, US (EURm) | 124 |
| CDNF Peak royalties, US (EURm) | 19 |
| CDNF Risk-adj. Factor (%) | 8.4% |
| CDNF Risk-adj. Peak sales (EURm) | 10 |
| CDNF Risk-adj. Peak Royalties (EURm) | 2 |
| Lymfactin Peak sales, RoW (EURm) | 75 |
| Lymfactin Peak royalties, RoW (EURm) | 11 |
| Lymfactin Risk-adj. Factor (%) | 14.2% |
| Lymfactin Risk-adj. Peak sales (EURm) | 11 |
| Lymfactin Risk-adj. Peak royalties (EURm) | 2 |

**General**

| | |
|---|---|
| Inflation p.a. | 2.0% |
| Population growth | 2.0% |
| Perpetual growth | 3.0% |
| WACC | 13.0% |

*Source: ABG Sundal Collier*

## Scenario 3

**Key model assumptions - Scenario 3**

*Significant success - Strong clinical data for both CDNF and Lymfactin boosts pricing and uptake*

| US | | vs. Scenario 2 |
|---|---|---|
| CDNF peak year | 2039 | |
| Lymfactin peak year | 2034 | |
| Peak penetration CDNF | 22.00% | +5% |
| Peak penetration Lymfactin | 35.00% | +5% |
| CDNF year on the market | 2031 | |
| CDNF annual gross cost/pt. (EUR) | 82,863 | +25% |
| CDNF Annual net cost/pt (EUR) | 67,947 | +25% |
| Lymfactin year on the market | 2,026 | |
| Lymfactin gross cost/pt. (EUR) | 54,000 | +20% |
| Lymfactin net cost/pt (EUR) | 45,900 | +20% |
| CDNF Peak sales, US (EURm) | 2,642 | |
| CDNF Peak royalties, US (EURm) | 485 | |
| CDNF Risk-adj. Factor (%) | 8.4% | |
| CDNF Risk-adj. Peak sales (EURm) | 222 | |
| CDNF Risk-adj. Peak Royalties (EURm) | 41 | |
| CDNF peak patients treated (#) | 33,189 | |
| Lymfactin Peak sales, US (EURm) | 1,022 | |
| Lymfactin Peak royalties, US (EURm) | 177 | |
| Lymfactin Risk-adj. Factor (%) | 14.2% | |
| Lymfactin Risk-adj. Peak sales (EURm) | 145 | |
| Lymfactin Risk-adj. Peak royalties (EURm) | 25 | |
| Lymfactin peak patients treated (#) | 19,771 | |

| EU5 | | vs. Scenario 2 |
|---|---|---|
| CDNF peak year | 2037 | |
| Lymfactin peak year | 2030 | |
| Peak penetration CDNF | 17.00% | +5% |
| Peak penetration Lymfactin | 30.00% | +5% |
| CDNF year on the market | 2027 | |
| CDNF Annual net cost/pt (EUR) | 58,004 | +25% |
| Lymfactin year on the market | 2,022 | |
| Lymfactin net cost/pt (EUR) | 37,800 | +20% |
| CDNF Peak sales, US (EURm) | 1,100 | |
| CDNF Peak royalties, US (EURm) | 177 | |
| CDNF Risk-adj. Factor (%) | 8.4% | |
| CDNF Risk-adj. Peak sales (EURm) | 92 | |
| CDNF Risk-adj. Peak Royalties (EURm) | 15 | |
| CDNF peak patients treated (#) | 18,967 | |
| Lymfactin Peak sales, US (EURm) | 401 | |
| Lymfactin Peak royalties, US (EURm) | 55 | |
| Lymfactin Risk-adj. Factor (%) | 14.2% | |
| Lymfactin Risk-adj. Peak sales (EURm) | 57 | |
| Lymfactin Risk-adj. Peak royalties (EURm) | 8 | |
| Lymfactin peak patients treated (#) | 12,734 | |

| RoW | |
|---|---|
| CDNF peak year | 2037 |
| Lymfactin peak year | 2030 |
| Peak % of European sales CDNF | 20.0% |
| Peak % of European sales Lymfactin | 20.0% |
| CDNF year on the market | 2028 |
| Lymfactin year on the market | 2023 |
| CDNF Peak sales, US (EURm) | 220 |
| CDNF Peak royalties, US (EURm) | 33 |
| CDNF Risk-adj. Factor (%) | 8.4% |
| CDNF Risk-adj. Peak sales (EURm) | 18 |
| CDNF Risk-adj. Peak Royalties (EURm) | 3 |
| Lymfactin Peak sales, US (EURm) | 103 |
| Lymfactin Peak royalties, US (EURm) | 15 |
| Lymfactin Risk-adj. Factor (%) | 14.2% |
| Lymfactin Risk-adj. Peak sales (EURm) | 15 |
| Lymfactin Risk-adj. Peak royalties (EURm) | 2 |

**General**

| | |
|---|---|
| Inflation p.a. | 2.0% |
| Population growth | 2.0% |
| Perpetual growth | 3.0% |
| WACC | 13.0% |

*Source: ABG Sundal Collier*

## Peer overview

We do not utilize peer valuation for our analysis of Herantis, but note that it seems attractively valued compared to other listed CNS focused peers.

### Valuation overview vs. key CNS peers

| EURm | Market cap | Net cash | Technology value (EV) | Compounds in clinical development | Lead compound |
|---|---|---|---|---|---|
| **Nordic peers** | | | | | |
| IRLAB Therapeutics | 115 | 13 | 101 | 2 | Phase 2 |
| BioArctic | 723 | 107 | 616 | 5 | Phase 3 |
| Saniona | 78 | 5 | 73 | 4 | Phase 2 |
| *Average* | *305* | *42* | *264* | | |
| *Median* | *115* | *13* | *101* | | |
| **International peers** | | | | | |
| Addex Therapeutics | 65 | 34 | 31 | 2 | Phase 2 |
| Denali Therapeutics | 2,172 | 373 | 1,800 | 5 | Phase 1b |
| Axovant Gene Therapies | 79 | 22 | 57 | 3 | Phase 2 |
| Voyager Therapeutics | 369 | 250 | 119 | 1 | Phase 2 |
| Wave Lifesciences | 220 | 161 | 59 | 2 | Phase 1b/2a |
| Acorda Therapeutics | 88 | -143 | 231 | 4 | Phase 2 |
| *Average* | *499* | *116* | *383* | | |
| *Median* | *586* | *133* | *453* | | |
| **Herantis** | **50** | **0.5** | **50** | **2** | **Phase 1** |

*Source: ABG Sundal Collier, FactSet*

## Herantis competitive positioning to key peers

| Company | Herantis | | MedGenesis | Calico |
|---|---|---|---|---|
| **Name of compound** | CDNF | xCDNF | GDNF | ISRIB |
| **Development phase** | Clinical Phase 1-2 | Lead Selection | Clinical Phase 2 | Preclinical |
| **Mechanism of action** | Multi-modal: Reduction of ER stress, alpha-synuclein oligomerization and toxicity, and neuroinflammation | | Promotes neuronal survival via activation of GFRα/Ret signaling | Activates eIF2B to reduce integrated stress response |
| **Type** | Protein | Peptide | Protein | Small molecule |
| **Route of administration** | Intracerebral | TBD; subcutaneous *in vivo* proof-of-concept | Intracerebral | Intravenous |

*Source: ABG Sundal Collier, company data*

# Risks

**Development risks**
Drug development is a long-term undertaking that requires significant resources; only a few of thousands of screened molecules eventually become approved drugs. It progresses in stages that include the selection and optimization of a new drug candidate (molecule), the development of its manufacturing process, production, preclinical studies, several phases of clinical studies, and eventually, commercialization. A typical development programme may take 10-15 years. Drug development is always associated with significant risks. The programme can fail at any stage. Only a fraction of all drug candidates reaches clinical studies. Drug candidates, such as CDNF and Lymfactin, which aim at significant breakthroughs in the treatment of a disease, are often based on cutting-edge science. Novel therapies tend to increase risks and are associated with greater uncertainties in the development process.

**Commercial risks**
Herantis intends to sign collaboration agreements with large pharmaceutical companies after successful early proof-of concept clinical studies. The shape and form of potential licensing agreements (milestones, royalties etc.) could imply significant positive or negative impact on our estimates and forecasts. Herantis could also fail to establish partnerships for its current pipeline projects. Should CDNF and/or Lymfactin pass through clinical trials and enter a commercial stage via partnerships, its commercial success would still be subject to many sensitivities. Commercial factors such as pricing and market penetration will depend on clinical efficacy, physician and patient acceptance of invasive administration procedures (intracerebral administration for CDNF and lymph node transplant for Lymfactin), reimbursement from insurance companies etc.

**Intellectual property estate**
The company's competitive position and future revenues rely in part on its ability to protect its intellectual property and know-how. Once these protections expire, there is significant risk that generic products will out-compete the company's products.

**Liquidity risk**
Costly investments are crucial to the continued development of the company's products. Herantis currently relies on external financing to fund ongoing operations.

**Competition**
Other companies have products targeting the same diseases as Herantis products, and others may develop products targeting the same diseases. Failure to convince the market that its products are the better alternative may lead sales to fall short of our estimates. Although Herantis develops novel therapies, the company operates in a competitive industry, which may affect future sales.

# Appendix A

## Targeted Therapies in Surgical Treatment of Lymphedema: A Systematic Review

| Author | Year | Country | Type of study | Model | Technique | Mechanism | Agent | Delivery | Findings | Conclusion |
|---|---|---|---|---|---|---|---|---|---|---|
| Tervala et al. | 2015 | Finland | Experimental | Rat | VLNT | Growth factor | VEGF-C, VEGF-D, VEGF-C156S, VEGF-A | Local Adenoviral vectors | Lymphangiogenesis (VEGF-C and VEGF-D); Improved lymphatic function (VEGF-C); Better lymph node survival compared to control and VEGF-A (VEGF-C, VEGF-D, VEGF-C156S). VEGF-C provided greatest therapeutic results compared to other VEGFs | VEGF-C is the preferred growth factor therapy of lymphedema |
| Hayashida et al. | 2017 | Japan | Experimental | Rat | VLNT | Autologous tissue | Adipose-Derived Stem Cells | Local injection | Mice that received combined treatment (VNLT + Adipose-derived stem cell) had better percentage of improvement and percentage deterioration, increased lymphatic vessels with LYVE-1 immunoreactivity. | Combine VNLT and adipose-derived stem cell may be a effective treatment for secondary lymphedema |
| Lahteenvuo et al. | 2011 | Finland | Experimental | Pig | VLNT | Growth factor | VEGF-C, VEGF-D | Local Adenoviral vectors | Post-operative lymphatic drainage was superior in VEGF-C and VEGF-D treated pigs. VEGF-C and VEGF-D induced growth of functional lymphatic vasculature. Pigs that received VEGF-C had better preservation of the transferred lymph node structure. | VLNT associated with gene therapy can repair lymphatic circulation in large animals, which supports basis for future clinical trials. Brief VEGF-C gene expression through adenovirus can promote formation of stable collecting lymphatic vessels |
| Sommer et al. | 2011 | Germany | Experimental | Rat | VLNT | Growth factor | VEGF-C | Local injection 3 times after transplantation | Histological pattern of regenerated lymph nodes: 74% VEGF-C group (14/19) vs. 59% control group (13/22); Connection of VNLT with superficial lymphatic vessels of the leg: 36% VEGF-C group (5/14) vs. 15% control group (2/13) | Injection of VEGF-C in the VLNT area promotes improved outcomes on lymphatic reconnection and histological regeneration |
| Tammela et al. | 2007 | Finland | Experimental | Rat | VLNT | Growth factor | VEGF-C, VEGF-D | Local Adenoviral vectors | Both VEGF-C and VEGF-D induced robust growth of the lymphatic capillaries. Incorporation to pre-existing lymphatic network: 82% in VEGF-C-treated mice (9/11) vs. 22% of control group (2/9). Injection of human lung carcinoma cells subcutaneously demonstrated that these cells were trapped in 80% of VEGF-C-treated lymph nodes (8/10) vs. 17% of control group (1/6) | VLNT associated with growth factor therapy had improved outcomes and functional immunological barrier against tumor metastases |
| Schindewolffs et al. | 2014 | Germany | Experimental | Rat | Avascular Autologous Lymph Node Fragments | Growth factor | VEGF-C | Local injections | There was a correlation between high doses of VEGF-C and lymphatic regeneration. Application in early postoperative and at the medial thigh seems to promote better results, although not statistically significant | Lymph node fragments transplant associated with VEGF-C might be useful in treatment of secondary lymphedema |
| Honkonen et al. | 2013 | Finland | Experimental | Pig | VLNT | Growth factor | VEGF-C | Local Adenoviral vectors (intranodally vs. perinodally) | Compared to control (saline), both intranodally and perinodally injection induced lymphangiogenesis and helped to preserve transplanted lymph node structure. Intranodal injection had as adverse effect the accumulation of Macrophages inside the node | Perinodal delivery of adenoviral VEGF-C is the better route of delivery for future clinical studies |
| Joseph et al. | 2014 | USA | Experimental | Rat | Avascular Autologous Lymph Node Transplant | Sterile inflammation | Immune adjuvant | Local injection | Compared to control (no-sterile-inflammation) or sterile-inflammation before lymph node transplant groups, the group of sterile inflammation delivered after transplantation had a >2-fold increase in lymphatic function, a increased lymphangiogenesis, and a more functional lymphatics. | Sterile inflammation after lymph node transplantation promotes preservation of lymph node structure. |
| Visuri et al. | 2015 | Finland | Experimental | Pig | VLNT | Growth factor | VEGF-C, VEGF-C156S | Local Adenoviral vectors | Both VEGF-C and VEGF-C156S induced lymphangiogenesis. However, lymphangiogenesis and lymph node preservation was superior with VEGF-C. Enlargement of blood vessels with VEGF-C was not correlated to increased wound exudate through vascular permeability. | VEGF-C is the preferred growth factor therapy of lymphedema |
| Hadamitzky et al. | 2008 | Germany | Experimental | Rat | Avascular Lymph nodes transplant | Autologous tissue | PRP | Local Injection | Strongly contrasted small secondary follicles in the Para cortical region of the transplanted lymph nodes (sign of proliferative reaction) were seen after delivery of PRP, compared to the control group. | PRP could improve regeneration of new lymphatic vessels in transplanted lymph nodes. |

*Source: ABG Sundal Collier, Forte 2019*

# Appendix B

## Neurotrophic factors – a history of learnings from previous clinical trials

Although neurotrophic factors (NTF) are clearly distinct from Herantis Pharma's CDNF therapy, we still think it is important to describe the clinical trial history of NTF, which has led to learnings on how to conduct better studies in new similar treatments, especially when it comes to intracranial drug delivery in PD.

Three different neurotrophic factors have previously been investigated in clinical trials: glial cell derived neurotrophic factor (GDNF), neurturin (NRTN) and platelet derived growth factor (PDGF-BB).

**Previous clinical trials with neurotrophic factors**
Neurotrophic factors have been investigated for PD since the early '90s when a company called Synergen isolated a brain protein made by glial cells. Since the protein was secreted by glial cells, it received the name "glial-cell-derived neurotrophic factor" (GDNF).

Initial pre-clinical GDNF studies showed robust improvements in 6-OHDA- (a neurotoxin that destroys nigrostratial dopaminergic neurons) and MPTP-based animal models and the treatment was moved to clinical trials in the late '90s. Open label studies showed improvements in UPDRS total scores, but later placebo-controlled trials showed no statistically significant differences between the placebo-group and the GDNF-group. More concerning was the development of neutralising antibodies to the recombinant GDNF and cell loss in the cerebellum in a monkey study; the latter eventually caused Amgen (the sponsor of the trial) to shut down the program. However, several case reports of the patients involved in the trial showed sustained clinical improvements over several years.

CERE-120 was a gene therapy programme based on injecting the NRTN gene via an adeno-associated virus serotype 2 (AAV2). It was believed that continuous expression of NRTN in the putamen would provide a lifetime of NRTN support to dopamine-producing neurons. However, in a phase 2 study with a sham surgery control, looking at UPDRS scores compared to sham surgery at 12 months showed the therapy did not provide a benefit. A post-hoc analysis of a subset of patients that had a longer, blinded follow-up period did show a significant benefit in favour of CERE-120, and patients who were diagnosed ≤ 5 years before treatment also showed significant improvement. This should be reasonable since up to 80% of dopamine-producing neurons could be gone at the time of diagnosis of PD.

PDGF-BB was tested in a phase I-II placebo-controlled study with no statistically significant change from placebo. However, other parameters showed a favourable profile for PDGF-BB but the sponsor of the programme decided to discontinue future trials.

## Previous clinical trials with neurotrophic factors

| Growth factor | Delivery | Dosing | Phase | Patients | Stage | Key findings | Reference |
|---|---|---|---|---|---|---|---|
| GDNF | Lateral ventricle | rhGDNF, monthly for 8 months | I-II, placebo controlled | 50 | H&Y 3-4 (off) | No improvement in UPDRS (off) as drug did not reach the target, various AEs (sensory symptoms, weight loss etc.). | Nutt et al |
| | Putamen | rhGDNF, continuous infusion | I, open-label | 5 | Advanced (>6 years from diagnosis) | Safe and well-tolerated. Improvement in motor symptoms (UPDRS, off), [$^{18}$F]dopa uptake increased near the catheter tip (PET). | Gill et al |
| | Putamen (unilateral) | rhGDNF, continuous infusion | I, open-label | 10 | H&Y 3-4 (off) | Improvement in motor symptoms (UPDRS, off), effects maintained 9 months after end-of-treatment. | Slevin et al |
| | Putamen | rhGDNF, continuous infusion | II, placebo controlled | 34 | Advanced (>5 years from diagnosis) | No improvement in UPDRS (off), some increase in [18F]dopa uptake (PET), development of anti-drug antibodies. | Lan et al |
| | Putamen | rhGDNF, CED bolus for 9+9 months* | II, placebo controlled | 41 | H&Y ≤3 (off; >5 years from diagnosis) | No improvement in UPDRS (off), significant increase in [18F]dopa uptake (PET). | Whone, Luz et al |
| | Putamen | AAV2-GDNF | I, open-label | 25 | H&Y 3-4 (off; >5 years from diagnosis | Study on-going. No results available yet. | |
| Neurturin | Putamen | AAV2-NRTN | I, open-label | 12 | H&Y 3-4 (off; >6 years from diagnosis | Safe and well-tolerated. Improvement in motor symptoms (UPDRS, off), no change in [18F]dopa uptake (PET). | Marks et al |
| | Putamen | AAV2-NRTN | II, sham surgery controlled | 58 | Advanced(>5 years from diagnosis | AAV2-NRTN was not superior over sham surgery (UPDRS at 12 months). | Marks et al |
| | Putamen + SN | AAV2-NRTN | I, open-label | 6 | H&Y 2-3 (off; >4 years from diagnosis) | Safe and well tolerated | Bartacus et al |
| PDGF-BB | Lateral ventricle | rhPDGF-BB, continuous infusion | I–II, placebo controlled | 12 | H&Y 2.5-3 (off; >5 years from diagnosis) | Well-tolerated. No change in clinical rating scales. [11C]PE2I DAT binding increased in right putamen (PET). | Paul et al |
| CDNF | Putamen | rhCDNF, CED bolus for 6+6 months* | I–II, placebo controlled | 18 | H&Y 2.5-3 (off; >5 years from diagnosis) | Study on-going. Topline results expected in early 2020. | Herantis Pharma |

*Source: ABG Sundal Collier, Huttunen et al 2019*

# Appendix C - Management

## Experienced management team

**Pekka Simula, M.Sc.**
CEO

**With the company since 2013**

Born: 1974 ; Nationality: Finnish

**Previous experience:** Founding CEO of Oncos Therapeutics, subsequently merged with Targovax in 2015. Previous Project Director for CRF Health and as Global Program Manager ar Varian Medical Systems

**Other current assignments:**

**Education:** *M.Sc.* in Physics from Helsinki University of Technology

**No. shares:** 52,056 directly and through a controlled corporation (0.78%), 16,136 options

**Antti Vuolanto, Ph.D.**
COO

**With the company since 2018**

Born 1975 ; Nationality: Finnish

**Previous experience:** Experience in biological drug development, gene therapy and in-vitro diagnostics. Previously he has served as COO at Valo Therapeutics, EVP at Targovax, and COO and co-founder at Oncos Therapeutics.

**Other current assignments:**

**Education:** *Ph.D.* in Science and Technology at Aalto University, Finland in bioprocess engineering

**No. shares:** 1,100 directly owned (<0.01%), 20,000 options

**Henri Huttunen, Ph.D.**
CSO and co-founder

**With the company since 2008**

Born 1972; Nationality: Finnish

**Previous experience:** Founded Herantis in 2008 (CEO until 2010), previously held research positions at the University of Helsinki, Orion Pharma, Massachusetts General Hospital and Harvard Medical School.

**Other current assignments:** Leading an academic research group at the Neuroscience Center, University of Helsinki

**Education:** *Ph.D.* in Biochemistry from the University of Helsinki (>20 years of experience in neuroscience research)

**No. shares:** 74,050 directly owned (1.11%), 74,050 options

**Sigrid Booms, Licentiate**
Director of Clinical Development

**With the company since 2010**

Born 1969; Nationality: Dutch

**Previous experience:** Almost 20 years of experience in global development of pharmaceuticals, with previous positions in regulatory affairs at Orion Pharma and at a global clinical CRO as Director, Regulatory Affairs.

**Other current assignments:**

**Education:** Licentiate in Pharmacy from the University of Utrecht in the Netherlands

**No. shares:** 2,400 directly owned (<0.01%), 16,018 options

**Jutta Poutanen, M.Sc.**
CPO

**With the company since 2014**

Born 1963; Nationality: Finnish

**Previous experience:** Served as Chief Pharmaceutical Officer at Laurantis Pharma and subsequently Herantis Pharma since Aug. 2010. Prior to the merger that formed Laurantis she was Development Manager of BioCis Pharma since 2008.

**Other current assignments:**

**Education:** *M.Sc.* In Pharmacy from University of Helsinki

**No. shares:** 0 directly owned (0%), 14,000 options

*Source: ABG Sundal Collier, Herantis Pharma*

# Appendix D – Shareholders

### 20 largest shareholders (as of 2019-12-31)

| # | Shareholders | Shares | % | EURm |
|---|---|---|---|---|
| 1 | Swedbank Robur Fonder | 661,000 | 9.9% | 4.5 |
| 2 | Inveni Capital | 646,864 | 9.7% | 4.4 |
| 3 | University of Helsinki Func | 497,438 | 7.4% | 3.4 |
| 4 | Innovestor Kasvurahasto | 428,500 | 6.4% | 2.9 |
| 5 | OP Fonder | 278,121 | 4.2% | 1.9 |
| 6 | Veritas Pension Insurance | 269,246 | 4.0% | 1.8 |
| 7 | Nordea Fonder | 236,990 | 3.5% | 1.6 |
| 8 | Ilmarinen Mutual Pension Ir | 237,700 | 3.6% | 1.6 |
| 9 | Mart Saarma | 159,000 | 2.4% | 1.1 |
| 10 | Eero Hemminki Castren | 155,000 | 2.3% | 1.1 |
| 11 | Heikki Rauvala | 155,000 | 2.3% | 1.1 |
| 12 | Argonius Oy | 145,000 | 2.2% | 1.0 |
| 13 | Säästöpankki Fonder | 130,000 | 1.9% | 0.9 |
| 14 | Kyösti Kakkonen | 97,000 | 1.5% | 0.7 |
| 15 | Markku Kaloniemi | 93,512 | 1.4% | 0.6 |
| 16 | Gerako Oy | 87,280 | 1.3% | 0.6 |
| 17 | Henri Huttunen | 74,050 | 1.1% | 0.5 |
| 18 | Nordnet Pensionsförsäkrir | 71,840 | 1.1% | 0.5 |
| 19 | Pekka Simula | 52,056 | 0.8% | 0.4 |
| 20 | Veikko Juhani Lesonen | 48,077 | 0.7% | 0.3 |

*Source: ABG Sundal Collier, Holdings*

### Overview of insider ownership (as of 2019-12-31)

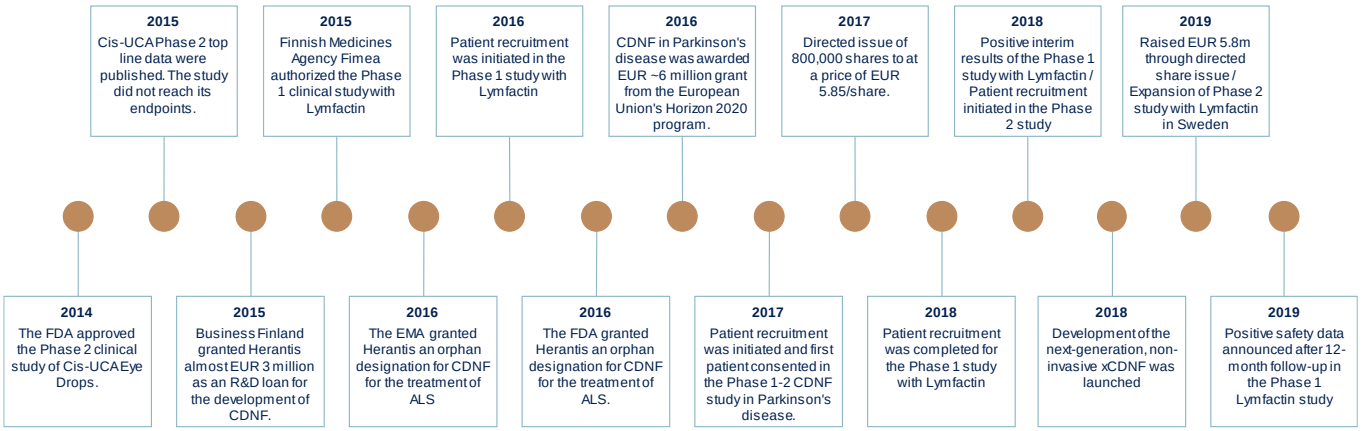
| Age | YOB | Board | Since | Position | Experience (See Appendix C for more details) | Shares | % | EURm |
|---|---|---|---|---|---|---|---|---|
| 61 | 1959 | Pekka Mattila | 2013 | Chairman | Current CEO of Desentum, founder of Finnzymes | 24,350 | 0.4% | 0.2 |
| 60 | 1960 | Timo Veromaa | 2012 | Board Member | Former executive chairman of Domainex | 8,900 | 0.1% | 0.1 |
| 60 | 1960 | Frans Wuite | 2014 | Board Member | CEO of Acesion Pharma | 6,280 | 0.1% | 0.0 |
| 58 | 1962 | James Phillips | 2014 | Board Member | CEO of Imevax | 5,706 | 0.1% | 0.0 |
| 62 | 1958 | Ingrid Atteryd Heiman | 2019 | Board Member | Board positions in several life science companies/organizations | - | 0% | 0 |
| 49 | 1971 | Aki Prihti | 2014 | Board Member | Co-founder of life sciences venture fund "Inveni capital" | - | 0.0% | 0.0 |

| Age | YOB | Management | Since | Position | Experience | Shares | % | EURm |
|---|---|---|---|---|---|---|---|---|
| 48 | 1972 | Henri Huttunen | 2008 | CSO | Founder of Herantis, >20y of research | 74,050 | 1.1% | 0.5 |
| 46 | 1974 | Pekka Simula | 2013 | CEO | Founding CEO of Oncos | 52,056 | 0.8% | 0.4 |
| 51 | 1969 | Sigrid Booms | 2011 | DCD | >20y development of pharma | 2,400 | 0.0% | 0.0 |
| 45 | 1975 | Antti Vuolanto | 2018 | COO | Prev. COO Valo Therapeutics | 1,100 | 0.0% | 0.0 |

*Source: ABG Sundal Collier, Holdings*

# Appendix E – Historical milestones

## Key historical milestones since the company's IPO in 2014




*Source: ABG Sundal Collier, Herantis Pharma*

| Income Statement (EURm) | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019e | 2020e | 2021e |
|---|---|---|---|---|---|---|---|---|---|---|
| Sales | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 36 |
| COGS | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gross profit | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 36 |
| Other operating items | 0 | 0 | -6 | -7 | -3 | -3 | -4 | -5 | -6 | -6 |
| **EBITDA** | **0** | **0** | **-6** | **-7** | **-3** | **-3** | **-4** | **-5** | **-6** | **30** |
| Depreciation and amortisation | 0 | 0 | -2 | -9 | -1 | -1 | -1 | -1 | -1 | -1 |
| Of which leasing depreciation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **EBITA** | **0** | **0** | **-8** | **-16** | **-4** | **-4** | **-5** | **-6** | **-6** | **29** |
| EO items | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Impairment and PPA amortisation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **EBIT** | **0** | **0** | **-8** | **-16** | **-4** | **-4** | **-5** | **-6** | **-6** | **29** |
| Net financial items | 0 | 0 | -1 | 0 | -0 | 2 | 1 | -1 | -0 | -0 |
| **Pretax profit** | **0** | **0** | **-8** | **-16** | **-4** | **-2** | **-4** | **-7** | **-6** | **29** |
| Tax | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | -1 |
| **Net profit** | **0** | **0** | **-8** | **-16** | **-4** | **-2** | **-4** | **-7** | **-6** | **28** |
| Minority interest | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Net profit discontinued | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Net profit to shareholders** | **0** | **0** | **-8** | **-16** | **-4** | **-2** | **-4** | **-7** | **-6** | **28** |
| EPS | 0 | 0 | -3.21 | -3.94 | -1.07 | -0.50 | -0.85 | -1.13 | -0.95 | 4.21 |
| *EPS Adj* | *0* | *0* | *-3.21* | *-3.94* | *-1.07* | *-0.50* | *-0.85* | *-1.13* | *-0.95* | *4.21* |
| Total extraordinary items after tax | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Leasing payments | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Tax rate (%)* | *ns* | *ns* | *0* | *0* | *0* | *0* | *0* | *0* | *0* | *4.0* |
| *Gross margin (%)* | *nm* | *nm* | *nm* | | *100.0* | *100.0* | *100.0* | *100.0* | *nm* | *100.0* |
| *EBITDA margin (%)* | *nm* | *nm* | *nm* | | *-12,598.9* | *-1,211.3* | *-1,594.1* | *-2,155.6* | *nm* | *83.4* |
| *EBITA margin (%)* | *nm* | *nm* | *nm* | | *-17,349.6* | *-1,752.2* | *-2,116.7* | *-2,655.2* | *nm* | *81.7* |
| *EBIT margin (%)* | *nm* | *nm* | *nm* | | *-17,349.6* | *-1,752.2* | *-2,116.7* | *-2,655.2* | *nm* | *81.7* |
| *Pretax margin (%)* | *nm* | *nm* | *nm* | ########## | *-17,366.7* | *-961.4* | *-1,816.5* | *-2,910.3* | *nm* | *81.4* |
| *Net margin (%)* | *nm* | *nm* | *nm* | ######## | *-17,366.7* | *-961.4* | *-1,816.5* | *-2,910.3* | *nm* | *78.2* |
| **Growth rates Y/Y** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019e** | **2020e** | **2021e** |
| *Sales growth (%)* | *na* | *na* | *na* | *na* | *1,195.2* | *789.1* | *2.2* | *-2.2* | *-100.0* | *na* |
| *EBITDA growth (%)* | *na* | *na* | *high* | *-16.8* | *52.7* | *14.5* | *-34.5* | *-32.3* | *-13.5* | *645.2* |
| *EBIT growth (%)* | *na* | *na* | *high* | *-111.1* | *72.8* | *10.2* | *-23.5* | *-22.7* | *-4.6* | *570.7* |
| *Net profit growth (%)* | *na* | *na* | *high* | *-92.1* | *72.6* | *50.8* | *-93.1* | *-56.7* | *2.9* | *542.7* |
| *EPS growth (%)* | *na* | *na* | *high* | *-22.8* | *72.9* | *53.1* | *-69.7* | *-32.9* | *15.7* | *542.7* |
| **Profitability** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019e** | **2020e** | **2021e** |
| *ROE (%)* | *nm* | *nm* | *-77.0* | *-115.9* | *-116.1* | *-76.4* | *-208.9* | *-404.9* | *51,230.4* | *234.6* |
| *ROE Adj (%)* | *nm* | *nm* | *-77.0* | *-115.9* | *-116.1* | *-76.4* | *-208.9* | *-404.9* | *51,230.4* | *234.6* |
| *ROCE (%)* | *nm* | *nm* | *-52.6* | *-76.1* | *-37.0* | *-18.3* | *-48.2* | *-71.4* | *-89.4* | *154.8* |
| *ROCE Adj(%)* | *nm* | *nm* | *-52.6* | *-76.1* | *-37.0* | *-18.3* | *-48.2* | *-71.4* | *-89.4* | *154.8* |
| *ROIC (%)* | *na* | *na* | *-91.0* | *-129.3* | *-58.8* | *-65.6* | *-104.0* | *-160.2* | *-248.6* | *1,043.2* |
| *ROIC Adj (%)* | *na* | *na* | *-91.0* | *-129.3* | *-58.8* | *-65.6* | *-104.0* | *-160.2* | *-248.6* | *1,043.2* |
| **Adj earnings numbers** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019e** | **2020e** | **2021e** |
| EBITDA Adj | 0 | 0 | -6 | -7 | -3 | -3 | -4 | -5 | -6 | 30 |
| *EBITDA Adj margin (%)* | *nm* | *nm* | *nm* | ..... | *-12,598.9* | *-1,211.3* | *-1,594.1* | *-2,155.6* | *nm* | *83.4* |
| EBITDA lease Adj | 0 | 0 | -6 | -7 | -3 | -3 | -4 | -5 | -6 | 30 |
| *EBITDA lease Adj margin (%)* | *nm* | *nm* | *nm* | | *-12,598.9* | *-1,211.3* | *-1,594.1* | *-2,155.6* | *nm* | *83.4* |
| EBITA Adj | 0 | 0 | -8 | -16 | -4 | -4 | -5 | -6 | -6 | 29 |
| *EBITA Adj margin (%)* | *nm* | *nm* | *nm* | | *-17,349.6* | *-1,752.2* | *-2,116.7* | *-2,655.2* | *nm* | *81.7* |
| EBIT Adj | 0 | 0 | -8 | -16 | -4 | -4 | -5 | -6 | -6 | 29 |
| *EBIT Adj margin (%)* | *nm* | *nm* | *nm* | ..... | *-17,349.6* | *-1,752.2* | *-2,116.7* | *-2,655.2* | *nm* | *81.7* |
| Pretax profit Adj | 0 | 0 | -8 | -16 | -4 | -2 | -4 | -7 | -6 | 29 |
| Net profit Adj | 0 | 0 | -8 | -16 | -4 | -2 | -4 | -7 | -6 | 28 |
| Net profit to shareholders Adj | 0 | 0 | -8 | -16 | -4 | -2 | -4 | -7 | -6 | 28 |
| Net Adj margin (%) | nm | nm | nm | | -17,366.7 | -961.4 | -1,816.5 | -2,910.3 | nm | 78.2 |

*Source: ABG Sundal Collier, Company data*

| Cash Flow Statement (EURm) | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019e | 2020e | 2021e |
|---|---|---|---|---|---|---|---|---|---|---|
| EBITDA | 0 | 0 | -6 | -7 | -3 | -3 | -4 | -5 | -6 | 30 |
| Net financial items | 0 | 0 | -1 | 0 | -0 | 2 | 1 | -1 | -0 | -0 |
| Paid tax | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | -1 |
| Non-cash items | 0 | 0 | 1 | 0 | 0 | -2 | 0 | 0 | 0 | 0 |
| Cash flow before change in WC | 0 | 0 | -5 | -7 | -3 | -3 | -3 | -5 | -6 | 29 |
| Change in WC | 0 | 0 | 1 | -1 | 0 | 0 | -0 | -0 | 1 | -0 |
| **Operating cash flow** | **0** | **0** | **-4** | **-7** | **-3** | **-3** | **-4** | **-5** | **-5** | **32** |
| CAPEX tangible fixed assets | 0 | 0 | 0 | 0 | -0 | 0 | 0 | 0 | 0 | 0 |
| CAPEX intangible fixed assets | 0 | 0 | -0 | -0 | -0 | 0 | 0 | 0 | 0 | 0 |
| Acquisitions and disposals | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Free cash flow** | **0** | **0** | **-4** | **-7** | **-3** | **-3** | **-4** | **-5** | **-5** | **32** |
| Dividend paid | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Share issues and buybacks | 0 | 0 | 15 | 0 | 0 | 5 | 0 | 10 | 0 | 0 |
| Lease liability amortisation | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other non cash items | 0 | 0 | -6 | 0 | -0 | 2 | 1 | -0 | 0 | -3 |
| **Decrease in net IB debt** | **0** | **0** | **5** | **-7** | **-3** | **4** | **-3** | **4** | **-5** | **29** |

| Balance Sheet (EURm) | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019e | 2020e | 2021e |
|---|---|---|---|---|---|---|---|---|---|---|
| Goodwill | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other intangible assets | 0 | 0 | 18 | 8 | 7 | 6 | 5 | 4 | 3 | 2 |
| Tangible fixed assets | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Right-of-use asset | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total other fixed assets | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| Fixed assets | 0 | 0 | 18 | 8 | 7 | 6 | 5 | 4 | 3 | 5 |
| Inventories | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Receivables | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 |
| Other current assets | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3 |
| Cash and liquid assets | 0 | 0 | 11 | 6 | 3 | 5 | 2 | 7 | 2 | 31 |
| **Total assets** | **0** | **0** | **29** | **14** | **10** | **12** | **7** | **11** | **5** | **40** |
| Shareholders equity | 0 | 0 | 22 | 6 | 2 | 4 | -0 | 3 | -3 | 27 |
| Minority | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Total equity** | **0** | **0** | **22** | **6** | **2** | **4** | **-0** | **3** | **-3** | **27** |
| Long-term debt | 0 | 0 | 6 | 8 | 8 | 6 | 6 | 7 | 7 | 7 |
| Pension debt | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Convertible debt | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Leasing liability | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total other long-term liabilities | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Short-term debt | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| Accounts payable | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 5 |
| Other current liabilities | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 |
| **Total liabilities and equity** | **0** | **0** | **29** | **14** | **10** | **12** | **7** | **11** | **5** | **40** |
| Net IB debt | 0 | 0 | -5 | 2 | 5 | 1 | 4 | 0 | 5 | -24 |
| Net IB debt excl. pension debt | 0 | 0 | -5 | 2 | 5 | 1 | 4 | 0 | 5 | -24 |
| Net IB debt excl. leasing | 0 | 0 | -5 | 2 | 5 | 1 | 4 | 0 | 5 | -24 |
| Capital invested | 0 | 0 | 17 | 8 | 7 | 5 | 4 | 3 | 2 | 4 |
| Working capital | 0 | 0 | -1 | -0 | -0 | -1 | -1 | -1 | -1 | -1 |

| EV breakdown | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019e | 2020e | 2021e |
|---|---|---|---|---|---|---|---|---|---|---|
| Market cap. diluted (m) | na | na | na | na | na | na | na | 46 | 46 | 46 |
| Net IB debt Adj | 0 | 0 | -5 | 2 | 5 | 1 | 4 | 0 | 5 | -24 |
| Market value of minority | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Reversal of shares and participations | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Reversal of conv. debt assumed equity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **EV** | **na** | **na** | **na** | **na** | **na** | **na** | **na** | **46** | **51** | **23** |

| Capital efficiency | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019e | 2020e | 2021e |
|---|---|---|---|---|---|---|---|---|---|---|
| *Total assets turnover (%)* | *nm* | *nm* | *0* | *0.0* | *0.2* | *2.1* | *2.5* | *2.5* | *0* | *159.1* |
| *Working capital/sales (%)* | *nm* | *nm* | *nm* | *-33,071.9* | *-1,391.0* | *-277.2* | *-336.7* | *-326.5* | *nm* | *-3.5* |

| Financial risk and debt service | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019e | 2020e | 2021e |
|---|---|---|---|---|---|---|---|---|---|---|
| *Net debt/equity* | *nm* | *nm* | *-0.23* | *0.36* | *3.30* | *0.29* | *-47.04* | *0.01* | *-1.50* | *-0.86* |
| *Net debt/market cap* | *na* | *na* | *na* | *na* | *na* | *na* | *na* | *0.00* | *0.11* | *-0.51* |
| *Equity ratio (%)* | *nm* | *nm* | *73.6* | *42.6* | *15.6* | *35.3* | *-1.2* | *29.7* | *-67.1* | *67.9* |
| *Net IB debt adj./equity* | *nm* | *nm* | *-0.23* | *0.36* | *3.30* | *0.29* | *-47.04* | *0.01* | *-1.50* | *-0.86* |
| *Current ratio* | *nm* | *nm* | *7.79* | *9.77* | *4.72* | *3.78* | *1.69* | *5.24* | *1.08* | *5.51* |
| *EBITDA/net interest* | *na* | *na* | *-8.25* | *-61.97* | *-736.76* | *-1.53* | *-5.31* | *-8.45* | *-52.18* | *284.48* |
| *Net IB debt/EBITDA* | *nm* | *nm* | *0.85* | *-0.32* | *-1.63* | *-0.43* | *-1.15* | *-0.00* | *-0.91* | *-0.79* |
| *Net IB debt/EBITDA lease Adj* | *nm* | *nm* | *0.85* | *-0.32* | *-1.63* | *-0.43* | *-1.15* | *-0.00* | *-0.91* | *-0.79* |
| *Interest cover* | *nm* | *nm* | *-8.02* | *-189.61* | *-52.28* | *-6.00* | *-45.17* | *-9.71* | *-59.24* | *278.83* |

*Source: ABG Sundal Collier, Company data*

| Valuation and Ratios (EURm) | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019e | 2020e | 2021e |
|---|---|---|---|---|---|---|---|---|---|---|
| Shares outstanding adj. | 0 | 0 | 4 | 4 | 4 | 5 | 5 | 7 | 7 | 7 |
| Fully diluted shares Adj | 0 | 0 | 4 | 4 | 4 | 5 | 5 | 7 | 7 | 7 |
| EPS | 0 | 0 | -3.21 | -3.94 | -1.07 | -0.50 | -0.85 | -1.13 | -0.95 | 4.21 |
| Dividend per share Adj | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| EPS Adj | 0 | 0 | -3.21 | -3.94 | -1.07 | -0.50 | -0.85 | -1.13 | -0.95 | 4.21 |
| BVPS | 0 | 0 | 5.35 | 1.47 | 0.38 | 0.83 | -0.02 | 0.50 | -0.50 | 4.09 |
| BVPS Adj | 0 | 0 | 0.95 | -0.60 | -1.37 | -0.40 | -1.00 | -0.11 | -0.95 | 3.74 |
| Net IB debt / share | na | na | -1.2 | 0.5 | 1.3 | 0.2 | 0.9 | 0.0 | 0.8 | -3.5 |
| Share price | na | na | na | na | na | na | na | 6.93 | 6.93 | 6.93 |
| Market cap. (m) | na | na | na | na | na | na | na | 46 | 46 | 46 |
| **Valuation** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019e** | **2020e** | **2021e** |
| P/E | na | na | na | na | na | na | na | -6.1 | -7.3 | 1.6 |
| EV/sales | na | na | na | na | na | na | na | 205.74 | nm | 0.63 |
| EV/EBITDA | na | na | na | na | na | na | na | -9.5 | -9.3 | 0.8 |
| EV/EBITA | na | na | na | na | na | na | na | -7.7 | -8.2 | 0.8 |
| EV/EBIT | na | na | na | na | na | na | na | -7.7 | -8.2 | 0.8 |
| *Dividend yield (%)* | *na* | *na* | *na* | *na* | *na* | *na* | *na* | *0* | *0* | *0* |
| *FCF yield (%)* | *na* | *na* | *na* | *na* | *na* | *na* | *na* | *-13.5* | *-11.1* | *68.1* |
| *Lease adj. FCF yield (%)* | *na* | *na* | *na* | *na* | *na* | *na* | *na* | *-13.5* | *-11.1* | *68.1* |
| P/BVPS | na | na | na | na | na | na | na | 13.92 | -13.82 | 1.69 |
| P/BVPS Adj | na | na | na | na | na | na | na | -62.27 | -7.31 | 1.85 |
| P/E Adj | na | na | na | na | na | na | na | -6.1 | -7.3 | 1.6 |
| EV/EBITDA Adj | na | na | na | na | na | na | na | -9.5 | -9.3 | 0.8 |
| EV/EBITA Adj | na | na | na | na | na | na | na | -7.7 | -8.2 | 0.8 |
| EV/EBIT Adj | na | na | na | na | na | na | na | -7.7 | -8.2 | 0.8 |
| EV/cap. employed | na | na | na | na | na | na | na | 4.5 | 14.0 | 0.7 |
| **Investment ratios** | **2012** | **2013** | **2014** | **2015** | **2016** | **2017** | **2018** | **2019e** | **2020e** | **2021e** |
| Capex/sales | nm | nm | nm | 314.7 | 281.7 | 0 | -3.1 | 0 | nm | 0 |
| Capex/depreciation | nm | nm | 0.1 | 0.1 | 5.9 | 0 | -0.6 | 0 | 0 | 0 |
| Capex tangibles/tangible fixed assets | nm | nm | 0 | 0 | 118.6 | 0 | 0 | 0 | 0 | 0 |
| Capex intangibles/definite intangibles | nm | nm | 0.0 | 0.1 | 0.8 | 0 | -0.1 | 0 | 0 | 0 |
| Depreciation on intangibles/definite inta | nm | nm | 10.6 | 111.6 | 16.7 | 20.1 | 24.8 | 27.6 | 25.0 | 25.0 |
| Depreciation on tangibles/tangibles | nm | nm | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

*Source: ABG Sundal Collier, Company data*

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