EDISON

Herantis Pharma

Initiation of coverage

Innovation at its core

Pharma & biotech

Herantis Pharma is focused on the development of innovative regenerative medicines targeting unmet needs. Its two lead assets are cerebral dopamine neurotrophic factor (CDNF), a potential disease-modifying treatment for Parkinson's disease (PD), and Lymfactin, the only gene therapy in development for breast cancer-related associated (BCAL) secondary lymphedema. The underlying science for both is novel and positive efficacy/safety data from ongoing proof-of-concept clinical trials expected in 2019–20 would serve as validation of the research efforts and additionally could crystallise value through partnering opportunities for these unique assets. We value Herantis Pharma at €9.3/share.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/16	0.0	(4.4)	(1.1)	0.0	N/A	N/A
12/17	0.0	(0.1)	(0.0)	0.0	N/A	N/A
12/18e	0.0	(3.2)	(0.6)	0.0	N/A	N/A
12/19e	0.0	(3.4)	(0.7)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Neuroprotective CDNF for PD

As the second most common neurodegenerative disease in the world (c 10 million patients) and no treatment options that slow disease progression, PD is a significant problem for healthcare providers. The standard of care typically consists of daily L-DOPA treatment; however, it only improves motor symptoms over a limited time (three to five years). Herantis is developing CDNF, a neurotrophic factor that is believed to promote neurone survival and could potentially have an effect on motor and non-motor symptoms, in addition to potentially slowing down disease progression. It is in a Phase I/II trial and initial data are expected in H219.

Lymfactin gene therapy for lymphedema

Lymphedema can be primary (faulty genes) or secondary to other conditions (eg surgery, trauma or cancer). It is estimated that up to 60% of breast cancer survivors develop quality of life-affecting lymphedema, mainly as result of cancer-related surgery (removal of auxiliary lymph nodes). Herantis is developing Lymfactin, a gene therapy (adenovirus vector that delivers genes for transient VEGF-C expression) to stimulate lymph vessel growth as a therapy for BCAL secondary lymphedema. It is in a Phase II trial with data forecast for end 2020.

Financials: Cash runway to POC

Herantis's gross cash of €4.0m suggests a cash runway into 2019; we forecast additional illustrative financing of €10m in FY19. The majority of funding for Phase I/II CDNF trial is through an EU grant. H118 net loss was €1.8m (H117: €2.1m).

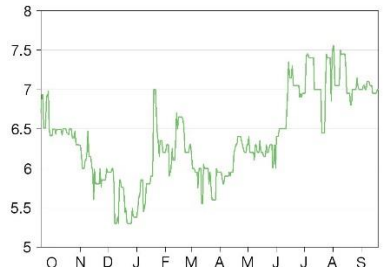
Valuation: rNPV suggests €45.8m or €9.3/share

Our valuation of €45.8m or €9.3/share including net debt of €1.7m is based on a risk-adjusted model for CDNF in PD (€4.0/share) and Lymfactin in BCAL (€5.7/share) with no contribution from CDNF for other neurodegenerative diseases.

20 September 2018

Price	**€7.00**
Market cap	**€34m**
Gross cash (€m) at June 2018	4.0
Shares in issue	4.9m
Free float	68.4%
Code	HRTS
Primary exchange	NASDAQ OMX
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	0.7	(0.7)	4.5
Rel (local)	(1.0)	(1.6)	(1.1)
52-week high/low		€7.6	€5.3

Business description

Herantis Pharma is a Finnish innovative biopharmaceutical company focusing on regenerative medicines for unmet needs. Key assets include CDNF for Parkinson's disease and Lymfactin for breast cancer associated lymphedema.

Next events

CDNF PD Phase I/II data	H219
Lymfactin Phase II data	End 2020

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Herantis Pharma is a research client of Edison Investment Research Limited

Investment summary

Company description: Finnish innovation

Herantis Pharma was created by a merger of two Finnish pharmaceutical companies, Hermo Pharma and Laurantis Pharma. Its research is a result of scientific discoveries made by Professor Mart Saarma (CDNF for neurodegenerative diseases, eg PD) and Professor Kari Alitalo (Lymfactin gene therapy for lymphedema) at the University of Helsinki. Preclinical data on CDNF and Lymfactin are compelling and success in human clinical trials would be ground-breaking in these therapeutic areas of high unmet clinical need. Safety and efficacy data from proof-of-concept trials anticipated during 2019 and 2020 are major inflection points for the company and could crystallise value through partnering opportunities. Herantis listed on NASDAQ OMX Helsinki First North Finland in 2014. The company is based in Helsinki, Finland and employs nine personnel.

Exhibit 1: Herantis R&D pipeline

Product	Indication	Phase	Notes	Plans
CDNF neuroprotective factor (intracranial administration)	Parkinson's disease	Phase I/II (placebo-controlled)	Top-line efficacy read out H219	Initiate Phase II in PD (2020) Assess opportunities in other neurodegenerative diseases
Non-invasive CDNF	Neurodegenerative conditions	Pre-clinical	N/A	Development programme initiated
Lymfactin gene therapy	BCAL	Phase II (placebo-controlled)	Efficacy data H220	Initiate Phase III in BCAL (2021-2023) Assess opportunities in other secondary lymphedemas (2019 onwards)

Source: Edison Investment Research, Herantis presentations

Valuation: €45.8m or €9.3/share

We value Herantis at €45.8m or €9.3/share based on a risk-adjusted NPV analysis, which includes €1.7m net debt at end June 2018 and risk-adjusted contributions for CDNF in PD (€4.0/share) and Lymfactin in BCAL (€5.7/share). As detailed later in the note, we have applied a top-down analysis of the PD and BCAL markets, which form the basis of our sales projections for these clinical-stage assets. We use a 12.5% discount rate for assets in development. We assume both products are out-licensed after proof-of-concept data.

Sensitivities: Novel science, so higher risk

Herantis Pharma is subject to the usual risks associated with drug development including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks and financing risks. Herantis Pharma is an early-stage drug developer; therefore value crystallisation in the future will depend on successful R&D progress and any potential partnering activities. The biggest near-term development sensitivity relates to its key assets CDNF and Lymfactin.

Financials: Funded into proof of concept

In the near term, Herantis will continue to be cash consumptive and operate as a non-revenue-generating biotech. Gross cash as of 30 June 2018 was €4.0 (net debt of €1.7m), which we forecast will be sufficient to fund operations into 2019 and should enable initial readouts from both the CDNF and Lymfactin trials. We note that our net debt includes €5.7m in Business Finland loans. These will not reach maturity until the product either commercially succeeds or has failed; if the product fails, these loans will be written off. We forecast FY18 net loss of €3.2m and FY19 loss of €3.4m and anticipate a raise of €10m in 2019 to fund Herantis past initial data from both its trials.

Neuroprotective factor CDNF in PD

CDNF, a naturally occurring protein in the human body, was discovered at the University of Helsinki, through work by professor Mart Saarma (on the scientific board at Herantis). Herantis is developing its innovative recombinant factor CDNF for the treatment of a range of neurodegenerative conditions. This protein-based therapy is being evaluated for its potential neuroprotective and neuro restorative properties in PD. Herantis believes this is the only scalable, recombinant factor CDNF in development globally. Herantis has patented the global rights to CDNF and the US rights to the closely related protein mesencephalic astrocyte-derived neurotrophic factor (MANF) (US-based Amarantus Biosciences has a MANF treatment in pre-clinical development) for the treatment of neurological conditions including PD, epilepsy and ischaemic brain injury.

CDNF and MANF are a novel family of neurotrophic factors that are located and secreted by the endoplasmic reticulum (ER) (an intracellular organelle that functions as a protein manufacturing and packaging system). CDNF's exact mode of action in PD is still being evaluated as it appears to exert its neuroprotective function through multiple mechanisms of action. In addition to PD, CDNF could have utility in amyotrophic lateral sclerosis and Huntington's disease (both are severe and incurable neurodegenerative disease) as preclinical data support further development in this area. This report, however, focuses on the PD opportunity given its Phase I/II clinical trial status.

In preclinical studies CDNF has protected dopaminergic (DA) neurons, restored function to degraded neurons and thus affected motor and non-motor symptoms of PD in addition to slowing down disease progression. If replicated in human clinical trials these attributes would enable CDNF to be a truly differentiated treatment for PD and could address two major unmet clinical needs in PD patients (treatment of non-motor symptoms and slowdown of disease progression) in addition to efficacious treatment of the well-known motor symptoms (eg tremor, dyskinesia, rigidity, loss of autonomic movement, speech changes).

PD: A common neurodegenerative condition

PD is a common neurological condition affecting 2.25 million people in the US, Japan and the five main EU countries (EU5) in 2012 (source: Globaldata 2015) and further growth will be driven by an increase in the ageing population. Many individuals are misdiagnosed or undiagnosed (PD can have an insidious onset over many years and patients may not consult a physician in the early years), so the actual prevalence is likely to be higher.

PD is characterised by the progressive loss of DA neurons within the basal ganglia in the brain, leading to a decline in dopamine levels. The causes of the reduction in DA neurons in PD are unknown and are an ongoing area of scientific research. Because dopamine plays a critical role in movement and co-ordination, a reduction in its levels leads to the common features of PD: tremors, slowness of movement and rigidity (motor symptoms). Progression of disease is always associated with non-motor symptoms such as sleep disturbance, depression and anxiety. PD is characterised by the selective loss of DA neurons of the substantia nigra pars compacta (SN), which forms part of the basal ganglia in the midbrain. The dopamine neurons in the brain are crucial in the facilitation of movement. As a major dopamine-producing area of the brain, the SN functions are involved in motor control as well as non-motor function and behaviours.

Dopamine replacement is the cornerstone of PD management

There is no cure for PD. The current mainstay of drug treatment is limited to oral therapies such as Levodopa (L-DOPA), dopamine agonists (eg pramipexole, ropinirole, apomorphine) and monoamine oxidase-B inhibitors (eg selegiline, rasagiline, safinamide); drugs that aim to increase or substitute for dopamine. While existing medications do alleviate motor symptoms of PD, they have no impact on non-motor symptoms and are not believed to halt disease progression.

However, we note accurately monitoring the progression of PD is difficult and data so far are conflicting over whether many treatments have a disease-modifying benefit.

The benefits of drug treatment diminish (L-DOPA is a 'precursor' to dopamine and once it is inside the brain it is turned into dopamine; however, it only provides symptomatic relief of around three to five years) as the disease progresses due to a reduction in DA neurons. As the disease progresses, symptoms of advanced PD develop, such as motor and non-motor complications (eg dyskinesia, motor fluctuations, dementia, depression and psychosis), which severely impact quality of life. There is an unmet need for disease-modifying drugs for this progressive disease that slow or alter its advancement.

Nondrug treatment options include deep brain stimulation (DBS) a surgical technique (FDA approved in 1997) reserved for very advanced PD patients who have unstable L-DOPA response. The aim is to stabilise medication fluctuations and effectively control the erratic responses to Levodopa or to control the dyskinesias (involuntary movements) that do not improve with medication adjustments. DBS is not a cure, however, and does not address the progressive nature of PD. There is a significant unmet need for advanced PD patients who are no longer well controlled on L-DOPA.

CDNF multiple mechanism of action in PD

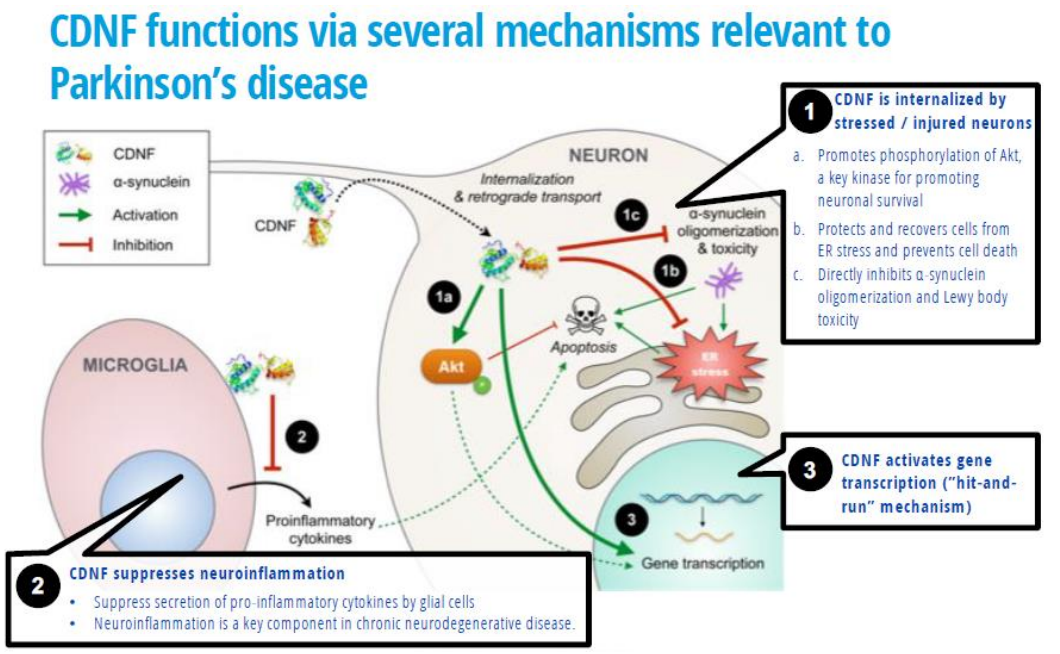
CDNFs potential in PD is based on its multiple mode of action that targets several mechanisms relevant to the underlying pathophysiology in PD. A number of biochemical and molecular mechanisms are involved in pathogenesis of PD including synaptic dysfunction, neurotrophic impairment, energetic deficit triggered by mitochondrial disorder, oxidative stress and neuroinflammation. The science to the mechanism of action for CDNF is still in its nascence but we outline what is presently believed to be its MOA.

A reduction of classical neurofactors (NF) levels (BDNF and GDNF) has been documented in DA areas (SN in the midbrain) in PD. More recently, naturally occurring CDNF and MANF have been discovered to have neurotrophic and neuroprotective properties that in animal models of PD protect and repair DA neurons, regulate ER stress and thus improve motor function.

CDNF functions via several mechanisms of action relevant to PD (Exhibit 2).

- CDNF modulates ER stress. The aetiology of the loss of DA cells in the SN is unclear. Recent scientific research suggests that oxidative stress, ER stress and mitochondrial dysfunction are involved in DA neuronal death. When internalised by stressed or injured neurons, CDNF leads to the regulation of ER stress response and thus protects and recovers DA neurons, preventing neuronal apoptosis. The hypothesis is CDNF leads to the activation of the intracellular signally pathway, PI3K/Akt pathway, which results in phosphorylation of Akt, a key tyrosine kinase enzyme that promotes neuronal survival. This mode of action differentiates CDNF from classical NF agents. Another pathological hallmark in PD is the presence of Lewy bodies (abnormal deposits of a protein called α-synuclein), accumulation of which interferes with the regulation of proteins and induces ER stress. CDNF acts to directly inhibit α-synuclein oligomerisation (formation of protein complexes) and therefore may reduce Lewy body toxicity.
- CDNF modulates neuroinflammation a key component in chronic neurodegenerative disease. Microglia cells are central nervous system immune cells that mediate immune response through production of pro-inflammatory cytokines such as IL-1, Il-6 and TNF-α. Chronic microglial activation is thought to play a part in the development and progression of neurodegenerative disease. CDNF may function as a regulator of neuroinflammation as it suppresses secretion of these pro-inflammatory cytokines.
- CDNF also activates gene transcription, although the mechanism for this is unclear.

Exhibit 2: CDNF multiple mode of action in PD



Source: Herantis presentations

POC top-line safety and efficacy data expected H219

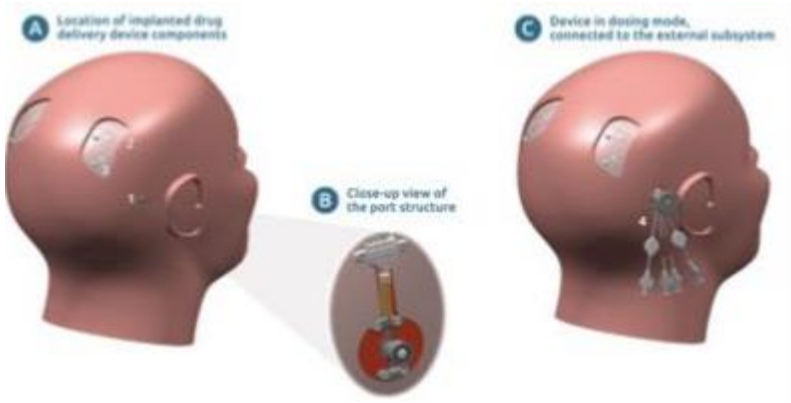
CDNF is being evaluated in a proof-of-concept Phase I/II study (randomised, placebo controlled) in PD across three clinical sites (two in Sweden and one in Finland). The study will enrol 18 patients in total; six on mid-dose active treatment, six on high-dose active treatment, six on placebo (artificial cerebrospinal fluid) for once-a-month treatment over an initial six-month period. At six months placebo patients may be switched to drug treatment in the six-month expansion phase of the study. We note frequency of dosing remains uncertain at this time, once-monthly dosing may not be sufficient. Top-line safety and efficacy data are expected by the end of 2019. Depending on the strength of the Phase I/II data, a Phase II/III confirmatory trial could initiate in 2020 in Europe. We believe US development will lag EU development by one to two years. We believe FDA could require US patients (given the device and intra-cranial method of administration) as part of the filing. Beyond Phase II, a partner will be required for late-stage clinical development and commercialisation for the PD indication.

CDNF is a recombinant factor, large molecule-based treatment that is unable to cross the blood brain barrier in its current formulation; it therefore needs to be administered into the exact region of the brain (the putamen) where it can target its effect. CDNF is dosed intracranially once a month (two- to three-hour infusion in the outpatient setting) using an implanted drug delivery device with portal access located behind the patient's ear. The novel drug delivery system (DDS) being used in the study has been developed by Renishaw, a global metrology company headquartered in the UK. The DDS consists of four catheters that are surgically implanted into the putamen area of the midbrain. The catheters converge in a port that is mounted to the skull behind the ear, and treatment is administered via this port (Exhibit 3).

We note that this DDS system has only been utilised in approximately 40 patients, including in Phase II clinical trials carried out by MedGenesis Therapeutix (clinical trials testing GDNF). The device has been modified from these trials as some patients experienced infections. The ongoing Phase I/II trial will monitor the safety of the device, particularly in relation to infections that may result from the once-monthly administration of CDNF.

Herantis's CDNF Phase I/II clinical study in PD has received funding from Horizon 2020, the EU's research and innovation programme. The TreatER project has two independent goals, proof-of-concept of CDNF protein therapy for disease modification in PD and clinical validation of the DDS.

Exhibit 3: CDNF is dosed via Renishaw's drug delivery device



Source: Herantis presentations

Non-invasive CDNF in drug discovery phase

Herantis has initiated a non-invasive CDNF development programme (announced July 2018) for neurodegenerative disorders including PD. Herantis has licensed the global rights from the University of Helsinki for the therapeutic application of a non-invasive CDNF approach based on a modification of the natural CDNF. While in the early stages of development, this is of importance for the longevity of the franchise and could provide patients with a non-invasive drug treatment option.

PD the commercial opportunity for CDNF

The majority of drugs for PD are available as generics with limited new treatment options, only one drug has been approved in PD in the last decade (Newron's Xadago, approved March 2017). The significant unmet need of patients with PD mean any treatment that has a major impact on the disease could have significant commercial opportunity. The societal costs of PD in the US are high and estimated at $14.4bn, which includes $6.3bn in indirect costs. The National Parkinson's Foundation (NPF) have used predicative economic modelling to estimate that slowing disease progression by 20% would save $60,657 per patient, and stopping disease progression could save $442,429 per patient.

For Herantis, we forecast a partnering deal on CDNF after positive proof-of-concept data are achieved on the modification of disease progression in PD. A partnering deal is necessary to take CDNF through mid- to late-stage clinical trials and for commercialisation. While early in development, we envision commercial manufacturing and scalability would be relatively straightforward for CDNF and could be produced in sufficient quantities through Chinese Hamster Ovary (CHO) protein production (a well-known and commonly utilised commercial production system).

Given the patient population size and the unmet need in PD, we estimate a price per year of $80k for the drug treatment alone. We note that each DBS surgery can cost between $35,000 and $50,000 and upwards of $70,000 to $100,000 for bilateral procedures; these estimates include the cost of the surgery, devices, anaesthesia, hospital fees and physician fees. Because DBS is approved by the FDA for the treatment of PD, Medicare and most private insurance carriers cover most, if not all, of the costs of the operation. We anticipate the same for CDNF, particularly if there is an impact on disease progression in addition to an efficacious impact on motor and non-motor symptoms with no major side effects.

For modelling CDNF we consider the total PD prevalence in the context of the DBS patient population. Special consideration has been given to the intracranial method of administration, as patients will need to be fit and healthy (despite the PD diagnosis) to be eligible for the therapy. We forecast an eligible peak patient population of c 74,000 in the US and c 66,000 in EU5. We forecast peak penetration rates of 30% of this defined population are achievable in 2035 in the EU and 2039 in the US, eight years after launch. We model a slower uptake trajectory than small molecule drugs reflecting the need for patient acceptance of the drug delivery method and requirement for a permanent device to be in place.

We forecast a tiered royalty rate starting from 5% and increasing to 20% on sales above $600m on worldwide sales; however, we do not include any licensing or developmental milestones in our valuation. While data on CDNF will be limited to one year with the Phase I/II trial, Herantis expects patients to be on drug indefinitely. This number will again depend on side effect issues and whether CDNF does impact disease progression.

We forecast peak sales of $2.6bn in the US in 2039 and €1.4bn in Europe in 2035. In Europe we estimate a 30% discount to price versus the US. We forecast that CDNF treatment will compete with DBS for patients. Both our pricing and penetration rates assume that CDNF acts on both motor and non-motor symptoms in addition to a moderate (<20%) change in disease progression. If this was achieved and approved commercially, it would be the only compound to have done so and, as such, we believe the penetration rate and price would be justified. However, we note significant sensitivity remains around pricing and penetration, upcoming clinical data will better define the opportunity.

Competitive space: Gene therapy on the horizon

While limited treatments have been approved for patients over the last couple of decades, changes in the treatment landscape, particularly within the advancement of gene therapies, mean the competitive landscape is changing quickly.

Gene therapies for PD are in investigational stages. We note two gene therapies are in development: Axovant's AXO-Lenti-PD and Voyager Therapeutic's VY-AADC, which both aim to deliver genes that encode for dopamine synthesis enzymes, either to be given alongside L-DOPA in the case of VY-AADC or as a one-off treatment, as in the case of AXO-Lenti-PD. Both look to increase dopamine levels in the brain striatum and improving symptoms. Advantages of gene therapy are the potential benefit on motor symptoms over a number of years following a single administration of gene therapy injected into the brain. However, this may not slow disease progression and, importantly, as the gene editing is permanent, side effects could be challenging. Clinical data to date have been limited, with mixed results from Voyager's VY-AADC the most advanced.

Given the likely high price of potential gene therapies, we believe success will be determined by their impact on disease progression. Furthermore, depending on safety and tolerability profiles we envisage potential for combining treatments such as CDNF with DBS or with gene therapies in the future armament for PD.

Lymfactin: A novel gene therapy for lymphedema

Herantis is developing Phase II asset Lymfactin gene therapy as a potential therapy for BCAL secondary lymphedema administered as a single-dose injection in combination with lymph node transfer surgery. Lymphedema is one of the most dreaded and unfortunate outcomes of breast cancer treatment and is an unavoidable consequence of having surgical treatment

(lumpectomy/mastectomy plus auxiliary lymph node dissection), radiotherapy or chemotherapy that prolongs patients' survival.

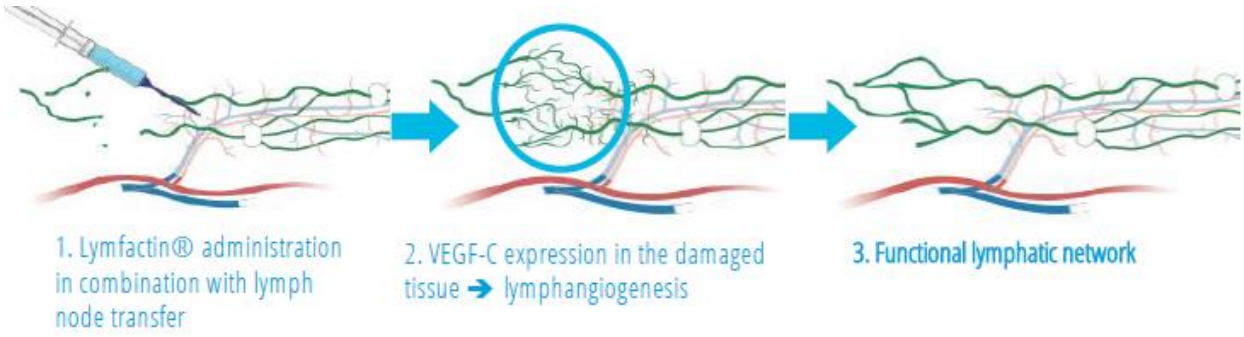
Lymfactin is based on the scientific research of professor Kari Alitalo at the University of Helsinki (who is on the scientific board at Herantis). While BCAL is the primary area under evaluation, Lymfactin could have wider utility in other types of secondary lymphedema and potentially even primary lymphedema. However, the focus for Herantis is to establish Lymfactin proof of concept for BCAL patients prior to addressing other indications and is thus the focus of this report.

Lymphedema (retention of fluid in body tissues, particularly the legs or arms) is a painful and extremely uncomfortable condition that severely impacts sufferers' quality of life. It may be associated with specific causal factors referred to as secondary lymphedema (factors that have caused damage to a previously functioning system) or primary lymphedema, which is caused by mutations in the genes responsible for the development of the lymphatic system. Causes of secondary lymphedema include certain cancers (due to the side effect of radiation and surgery or proliferation of cancer itself blocking drainage), infections and trauma. Lymphedema of any cause is incurable and treatment options are focused on physical management (eg exercise, compression garments and manual lymphatic drainage) with limited success rates. Breast cancer-associated lymphedema results from obstruction or disruption of the lymphatic system associated with cancer treatment (removal of auxiliary lymph nodes and radiotherapy); infections or trauma can also trigger lymphedema.

Lymfactin is a recombinant replication deficient Adenvovirus 5 gene transfer vector that delivers VEGF-C growth factor to stimulate lymphangiogenesis (formation of new lymphatic vessels). Delivery of Lymfactin in combination with surgical lymph node transfer leads to VEGF-C production localised to the targeted area of damage; expression of the gene is limited to a couple of weeks. Adenovirus is the optimal viral vector, given the need for small amounts, relative low cost of production and requirement for the expression to be transient (long-term expression of VEGF-C could be oncogenic). However, we note that treatment with adenovirus will probably be limited to one or two attempts per patient as the immune system will likely build a response to the treatment.

Specifically, Lymfactin is administered by ex vivo perinodal injection into the fat pad of a piece of tissue containing lymph nodes taken from the abdominal wall of the patient. This piece of tissue is then surgically implanted into the axillary region of the affected arm (Exhibit 4). The hypothesis is that the Lymfactin injection promotes lymphatic growth (over a number of months) and connection to the lymph nodes, therefore enabling drainage of interstitial fluid in the affected arm and a reduction of the lymphedema in the affected patient.

Exhibit 4: Lymfactin administration in secondary lymphedema



Source: Herantis

Phase II AdeLE trial read out at the end of 2020

Following encouraging Phase I data that evaluated 15 patients with BCAL, a randomised, placebo-controlled efficacy, safety and tolerability Phase II trial AdeLE (adenoviral gene therapy for the

treatment of LE) initiated in H118 (n=40) and 12-month proof of concept safety and efficacy data are expected by end 2020. The study is taking place across clinical sites in Sweden and Finland. Primary endpoints include volumetric measurements of the arm, quantitative lymphoscintigraphy, and quality-of-life assessment. In the Phase I trial few side effects were seen and a transient elevation in liver enzymes attributable to the adenovirus component was noted. If the Phase II trial completes successfully then a phase III programme in BACL could initiate in 2021 either by Herantis or a potential development and commercialisation partner. While we assume Herantis will partner the asset post the Phase II trial; however, the company could potentially further develop Lymfactin in BCAL for commercialisation itself. However, for other more sizeable opportunities in secondary lymphedema and primary lymphedema we would anticipate development by a future partner given the need for larger clinical trials in these conditions and thus the requirement for much higher associated R&D and regulatory and commercialisation expenses.

BCAL secondary lymphedema

Breast cancer accounts for 23% of all diagnosed cancers in women, with ~1.67m women globally diagnosed in 2012. Advancements in the treatment of breast cancer mean the five-year survival rate for breast cancer is 90% and at present there are 2.9 million breast cancer survivors in the US alone. While chemotherapy, targeted therapies and hormone therapies are critical in the management of breast cancer, surgical removal (lumpectomy, mastectomy) plus/or axillary lymph node removal plus radiotherapy remains cornerstone alongside medical management (depending on the subtype of breast cancer). Removal of the corresponding auxiliary lymph nodes leads to the complication of secondary lymphedema in up to 40% of patients due to damage to the lymphatic vessels and absence of lymph nodes. It is estimated that up to 60% of breast cancer survivors develop symptoms of lymphedema. Herantis estimates that in the US and Europe there are 30,000 diagnosed cases per year. For breast cancer survivors, quality of life remains of utmost importance; development of lymphedema, which is a chronic condition, significantly reduces quality of life and additionally is associated with higher treatment costs. Shih et al estimated the economic burden of breast cancer associated lymphedema in working-age women based in the US (n=1877) for the two years after cancer treatment was initiated; and concluded the BCAL group had significantly higher medical costs ($14,877–23,167) and were twice as likely to suffer complications of lymphangitis and cellulitis, which can be life threatening if they lead to bacteria and sepsis. Boyages et al's study on the financial cost of lymphedema borne by women with breast cancer highlights that patients with BCAL are worse off in terms of out-of-pocket financial costs (relating mainly to costs of compression garments) and this plus other costs associated with lymphedema needs to be better understood and assessed to help shape policy for health insurers and the government. A challenge for Herantis for commercialisation in the BCAL setting therefore could relate to reimbursement across different markets. We believe that if Lymfactin has the desired efficacy of a significant reduction in BCAL, it could become a standard-of-care injection alongside lymph node transfer surgery in high-risk patients. Furthermore, adequate lymphatic growth leading to a functioning lymphatic network in the auxiliary region could result in more lymph node transfers being carried out.

Lymfactin: The opportunity

We forecast peak sales of $1.2bn for Lymfactin in the BCAL setting in the US and €600m in Europe. We model an initial pricing of $50k for a single dose of Lymfactin and take into consideration 40% of breast cancer patients that undergo surgery as the eligible patient pool. We assume 80% receive surgical treatment and removal of their lymph nodes and 95% of patients will survive five years and 40% of these will develop lymphedema. In these patients we assume a peak penetration of 20% for Lymfactin.

We forecast a launch in 2022 in the EU, 2026 in US and for the product to be out-licensed post Phase II data. As an unmet need with limited treatment options, we assume that Lymfactin will receive accelerated approval in the EU based on Phase II data; however, we assume further locally based trials will be required for approval in the US. We do not assume development or commercial milestones but a blended tiered royalty rate that takes into account any potential milestone value. On Phase II data, we forecast a 15% peak royalty rate.

Major swing factors are reimbursement and uptake; if Lymfactin is covered widely by governments or insurance, we believe it could be incorporated into treatment at earlier points of care in high-risk factor BCAL patients.

While gene therapy manufacturing is often inherently costly, adenovirus manufacturing remains comparatively low cost. As one of the first vector systems to be developed, procedures, quality control and scaled manufacturing are well understood. We envision that a contract manufacturing operation would be able to provide sufficient vector at appropriate cost to enable commercial operations.

Sensitivities

Herantis Pharma is subject to the usual risks associated with drug development including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks and financing risks. Herantis Pharma is an early-stage drug developer; therefore value crystallisation in the future will depend on successful R&D progress and any potential partnering activities. The biggest near-term development sensitivity is related to key assets CDNF and Lymfactin. For CDNF, risks related to treatments and medical devices remain; long-term risks of the DDS relate to the potential risk of infections. The science for CDNF's mechanism of action in particular in still in its nascence and will be in part led by Herantis's Phase I/II clinical trial findings as well as ongoing work within academia. Its underlying mechanism of action is not fully understood; efficacy and safety data signals may not be replicated in Phase I/II, which would lead to the discontinuation of the programme. Herantis is funded through to proof-of-concept data based on net cash at 30 June 2018 and current cash burn; however, any increases in clinical trial costs or head count could reduce our forecast cash runway.

Valuation

We value Herantis at €45.8m or €9.3/share based on a risk-adjusted NPV analysis, which includes $1.7m net debt at the end of June 2018 and risk-adjusted contributions for CDNF in PD and Lymfactin in BCAL. The breakdown of our NPV valuation, which uses a 12.5% discount rate, is shown in Exhibit 5. As detailed in the note, we have applied a top-down analysis of the PD and BCAL markets, which form the basis of our sales projections for these clinical-stage assets. We utilise a 12.5% discount rate for assets in development. Partnering deals could provide valuation uplift.

Exhibit 5: Valuation breakdown

Product	Indication	Phase	Probability of success	rNPV (€m)	Per share (€)
CDNF	Parkinson's disease	I/II	5%	19.5	4.0
Lymfactin	BCAL	II	10%	28.0	5.7
Net cash at 30 June 2018				(1.7)	(0.4)
Valuation				45.8	9.3

Source: Edison Investment Research

CDNF

For our valuation of CDNF we assume US prevalence of PD of 0.4%, of which 20% of patients have moderate to severe PD that is no longer symptomatically controlled by L-DOPA. We forecast 35% of these would be eligible for treatment with an experimental therapy. We assume the main limiting factor for utilisation of an experimental therapy is patient mortality, as most PD patients will not be typically considered for treatment until they have been on L-DOPA for five years. We forecast that CDNF treatment will compete with DBS for patients. We forecast a peak penetration of 30% for CDNF with the assumption that it improves motor and non-motor signs and symptoms in most importantly has a moderate (<20%) change in disease progression. If this is achieved and approved commercially, CDNF would be the only compound to do so in PD and as such we believe this high penetration rate would be justified.

However, as no therapy that is able to achieve this in PD has been approved (in terms of disease modification benefit), we ascribe a modest 5% probability of success, which is a lower probability of success than usual for a Phase I asset. We also anticipate that even with a disease-modifying effect, it would be unlikely that it would be utilised in PD patients who have other illnesses (eg cardiovascular) due to the intracranial administration of the drug. However, the development of an oral therapy, even if less efficacious, could address this patient population.

Our model uses an $80,000 price in the US. In Europe we model the same in terms of eligible patient population and penetration rates; however, we apply a 20% discount to the EU price. Pricing is based on assumed cost savings to US and European healthcare systems. Studies have demonstrated a wide spectrum of associated costs for PD, with costs per patient per year varying drastically depending on the rate by which a disease can be slowed or potentially stopped. The direct and indirect costs have been estimated to be around $35,000 per patient; however, other forecasts have demonstrated that a treatment that slows PD progression by 20% could generate c $60,000 in net monetary benefits, while a treatment that stops PD progression could generate c $450,000 in benefit. We assume that for the aforementioned price to be achieved, CDNF will need to be able to impact motor and non-motor symptoms and slow disease progression by at least 20%. We note significant sensitivity remains around this as no PD drug that is able to achieve all three parameters has ever been approved.

We forecast a launch in 2027 in the EU, 2031 in US, and for the product to be out-licensed post Phase II data. We do not assume development or commercial milestones but a blended tiered royalty rate that takes into account any potential milestone value. On Phase II data we forecast a 20% peak royalty rate. We forecast peak sales of $2.6bn in the US in 2039 and €1.4 bn in Europe in 2035.

Lymfactin

For the valuation of Lymfactin in breast cancer associated lymphedema we assume 0.09% incidence rate of breast cancer. We assume 80% receive surgical treatment and removal of their lymph nodes, we forecast 95% of patients will survive five years and 40% of these will develop lymphedema. In these patients we assume a peak penetration of 20% for Lymfactin.

Our model utilises a $50,000 price in the US. In Europe we model the same in terms of eligible patient population and penetration rates; however we apply a 30% discount to the EU price.

We forecast a launch in 2022 in the EU, 2026 in the US, and for the product to be out-licensed post Phase II data. As an unmet need with limited treatment options, we assume that Lymfactin will receive accelerated approval in the EU based on Phase II data; however, we assume further locally based trials will be required for approval in the US. We currently do not assume development or commercial milestones but a blended tiered royalty rate that takes into account any potential milestone value. On Phase II data we forecast a 15% peak royalty rate. We forecast peak sales of

$1.2bn in the US and €600m in Europe. We assume the product is conditionally approved on the back of the Phase II data due to the high unmet need.

While we only value Lymfactin in breast cancer-associated lymphedema, we note opportunities remain in primary lymphedema and other secondary lymphedemas.

Financials

In the near term, Herantis will continue to be cash consumptive and operate as a non-revenue generating biotech. Gross cash as of 30 June 2018 was €4.0m (net debt €1.7m), which we forecast will be sufficient to fund operations into 2019 and should enable initial readouts from both the CDNF and Lymfactin trials. We note that our net debt includes €5.7m in Business Finland loans. These will not reach maturity until the product either commercially succeeds or has failed; if the product fails, these loans will be written off.

R&D costs in H118 were €1.1m and we forecast R&D costs will remain low due to studies being academically run with the majority of costs related to producing drugs. We forecast FY18 R&D costs of €2.1m and FY19 of $2.3m. We forecast that SG&A will remain relatively flat over the coming years and forecast €1.03m in FY18 of and €1.04m in FY19.

We forecast FY18 net loss of €3.2m and FY19 loss of €3.4m and anticipate a raise of €10m in 2019 to fund Herantis past initial data from both its trials. Herantis has previously been granted R&D loans from Business Finland, of which €1.1m remains to be drawn down; in H118 the company drew down €0.3m. Additionally, the European Union was awarded a grant (Horizon 2020) of €6.0m for the project TreatER (Phase I-II study of CDNF in PD).

Exhibit 6: Financial summary

Accounts: IFRS, Year-end: December, €m	2016	2017	2018e	2019e	2020e
INCOME STATEMENT					
Total revenues	25	0	0	0	0
Cost of sales	0	0	0	0	0
Reported gross profit	25	0	0	0	0
SG&A (expenses)	(942)	(1,024)	(1,034)	(1,045)	(1,055)
R&D costs	(27)	0	(2,140)	(2,311)	(2,311)
Other (includes exceptionals)	(2,273)	(1,928)	0	0	0
Adjusted EBIT	(4,420)	(1,915)	(3,174)	(3,356)	(3,366)
Reported EBIT	(4,420)	(1,915)	(3,174)	(3,356)	(3,366)
Finance income/ (expense)	(4)	1,780	0	0	0
Other income (expense) (includes exceptionals)	0	0	0	0	0
Adjusted PBT	(4,425)	(135)	(3,174)	(3,356)	(3,366)
Reported PBT	(4,425)	(135)	(3,174)	(3,356)	(3,366)
Income tax expense	0	0	0	0	0
Adjusted net income	(4,425)	(135)	(3,174)	(3,356)	(3,366)
Reported net income	(4,425)	(135)	(3,174)	(3,356)	(3,366)
Earnings per share					
Basic EPS (€)	(1.1)	(0.0)	(0.6)	(0.7)	(0.7)
Diluted EPS (€)	(1.1)	(0.0)	(0.6)	(0.7)	(0.7)
Adjusted basic EPS (€)	(1.1)	(0.0)	(0.6)	(0.7)	(0.7)
Adjusted diluted EPS (€)	(1.1)	(0.0)	(0.6)	(0.7)	(0.7)
Average number of shares - basic (m)	4.1	4.2	4.9	4.9	0.0
Average number of shares - diluted (m)	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET					
Property, plant and equipment	9	7	7	7	8
Goodwill	0	0	0	0	0
Intangible assets	0	0	0	0	0
Other non-current assets	712	392	392	392	392
Total non-current assets	7,311	6,061	6,061	6,062	6,062
Cash and equivalents	2,047	5,311	2,107	8,751	5,384
Inventories	0	0	0	0	0
Trade and other receivables	65	109	109	109	109
Other current assets	782	91	91	91	91
Assets classified for sale	0	0	0	0	0
Total current assets	2,895	5,511	2,307	8,951	5,584
Non-current loans and borrowings	8,018	6,022	6,022	16,022	16,022
Trade and other payables	0	0	0	0	0
Other non-current liabilities	0	0	0	0	0
Total non-current liabilities	8,018	6,022	6,022	16,022	16,022
Trade and other payables	186	186	186	186	186
Current loans and borrowings	103	547	547	547	547
Other current liabilities	332	883	883	883	883
Liabilities of assets held for sale	0	0	0	0	0
Total current liabilities	613	1,460	1,430	1,430	1,430
Equity attributable to company	1,575	4,090	916	(2,440)	(5,806)
Non-controlling interest	0	0	0	0	0
CASH FLOW STATEMENT					
Profit before tax	(4,425)	(2,165)	(3,174)	(3,356)	(3,366)
Depreciation of tangible assets	1,203	1,218	0	0	0
Amortisation of intangible assets	0	0	0	0	0
Share based payments	(0)	(2,021)	(120)	0	0
Other adjustments	5	240	0	0	0
Movements in working capital	166	372	0	0	0
Net cash from operating activities (pre-tax)	(3,052)	(2,355)	(3,295)	(3,356)	(3,366)
Interest paid / received	16	(244)	0	0	0
Income taxes paid	0	0	0	0	0
Cash from operations (CFO)	(3,036)	(2,599)	(3,295)	(3,356)	(3,366)
Capex (includes acquisitions)	(10)	0	(0)	(0)	(0)
Other investing activities	(61)	(0)	0	0	0
Cash used in investing activities (CFIA)	(71)	(0)	(0)	(0)	(0)
Net proceeds from issue of shares	0	4,680	0	0	0
Movements in debt	0	0	0	10,000	0
Changes in debt	0	0	0	10,000	0
Other financing activities	396	492	0	0	0
Cash from financing activities (CFF)	396	5,172	0	10,000	0
Currency translation differences and other	0	0	0	0	0
Increase/(decrease) in cash and equivalents	(2,711)	2,573	(3,295)	6,644	(3,367)
Cash and equivalents at beginning of period	5,541	2,829	5,402	2,107	8,751
Cash and equivalents at end of period	2,829	5,402	2,107	8,751	5,384
Net (debt) cash	(6,073)	(1,258)	(4,463)	(7,819)	(11,186)
Movement in net (debt) cash over period	N/A	4,815	(3,204)	(3,356)	(3,367)

Source: Company accounts, Edison Investment Research

Contact details	Revenue by geography
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Management team

CEO: Pekka Simula	Chief scientific officer: Henri J Huttunen
Mr Simula joined Herantis Pharma as CEO in November 2013. Previously he was founding CEO of Oncos Therapeutics, successfully building it into a clinical-stage company. Mr Simula has also served as project director for CRF Health, a leading ePRO provider for clinical trials, and as global programme manager at Varian Medical Systems. Mr Simula also served as board member of Oncos Therapeutics from 2009 until the company's merger with Norwegian Targovax in 2015 and is a board member of Finnish Bioindustries since 2016. He holds an MSc in physics.	Dr Huttunen co-founded Herantis Pharma in 2008 and served as the company's founding CEO until February 2010. He has previously held research positions at the University of Helsinki, Orion Pharma, and Massachusetts General Hospital, Harvard Medical School (US). Dr Huttunen has a PhD in biochemistry and more than 15 years of experience in neuroscience research. As an adjunct professor, Dr Huttunen also leads an academic research group focusing in molecular mechanisms of neurodegenerative diseases at the Neuroscience Center, University of Helsinki.

Principal shareholders	(%)
Inveni Life Sciences Fund	13.5
InnovestorKasvurahasto	11.0
HelsinginYliopistonRahastot	10.1
KeskinäinenEläkevakuutusyhtiöIlmarinen	4.8
Sijoitusrahasto Nordea Nordic Small Cap	4.7
OP Suomi Pienyhtiöt	4.6
Pensionsförsäkringsaktiebolaget Veritas	4.1
Saarma Mart	3.2
CastrenEeroHemminki	3.2
RauvalaHeikki	3.2

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