Lipigon

Sector: Biotech

Expert in Blood Lipid Diseases

Redeye initiates coverage of Lipigon, a biotech company developing Lipisense, a new first-in-class ANGPTL-4-targeting candidate, based on modern, state-of-the-art, antisense technology. We believe Lipisense could reduce blood fat in the several million people suffering from SHTG, a condition of extreme triglyceride blood levels that leaves patients at high risk for pancreatitis—implying potential blockbuster status for the candidate.

Lipisense: an ANGPTL4-targeting antisense drug

ANGTPL4 is a protein that reduces the body's uptake of triglycerides. By blocking the production of this protein, Lipisense can potentially increase the clearance of triglycerides, thus reducing triglyceride blood levels in those with abnormal levels. The current treatment regimens of fibrates and omega-3 FAs are less than optimal. Lipisense could be positioned as an alternative for non-responders or those who are intolerant. A phase I trial (n=52) is scheduled to start in Q2, with results in Q4.

Major catalyst in a short time

The CTA was submitted in March. Lipigon might be able to demonstrate triglyceride reduction as early as in this phase I trial—headway that would amount to proof-of-concept, which normally necessitates a phase II trial. This would be a major share catalyst. This could make Lipisense a potential outlicensing candidate by 2023. Very large deals have been made recently with similar candidates.

Valuation and finances

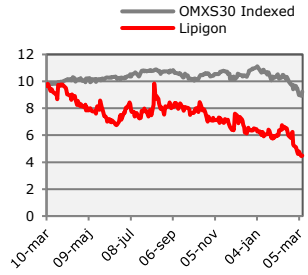
Lipigon needs to address its financial position in the near term to fund the phase I trial. We therefore apply a short term higher WACC of 20 percent, implying a Base Case of SEK 12. We see a major upside to the share price in the short term when this is resolved.

Key Financials (SEK	2019	2020	2021E	2022E	2023E
Revenues	2	4	3	0	0
Revenue growth	NA	146%	-26%	-100%	NA
EBITDA	-5	-8	-41	-42	-23
EBIT	-5	-8	-41	-42	-23
EBIT Margin (%)	-283%	-181%	-1295%	NA	NA
Net Income	-5	-8	-41	-42	-23
EV/Revenue	12,4	2,2	10,9	NA	NA
EV/EBITDA	NA	NA	NA	NA	NA
EV/EBIT	NA	NA	NA	NA	NA

FAIR VALUE RANGE

BEAR	BASE	BULL
3.6	12	31

LPGO.ST VERSUS OMXS30



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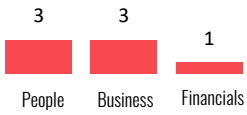

KEY STATS

Ticker	LPGO.ST
Market	First North
Share Price (SEK)	5
Market Cap (SEKm)	50
Net Debt (SEKm)	NA
Free Float (%)	85
Avg. daily volume ('000)	13000

Important information: All information regarding limitation of liability and potential conflicts of interest can be found at the end of the report
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Investment Case

Phase I is a proof-of-concept trial

The reason for investing in Lipigon is their main candidate Lipisense. Lipigon handed in a clinical trial application for the phase I trial with Lipisense in March 2022. It plans to treat the first subject in June. The trial is composed of two parts: a single dose ascending study (SAD) followed by a multiple dose ascending study (MAD). Healthy volunteers will be recruited. A small group of type 2 diabetics will also be recruited to the MAD group. The single-dose (SAD) part should allow a readout as early as Q4 this year, a few months into the trial. Each patient's triglyceride levels will be measured before and after treatment. Substantial reductions in triglyceride levels would be a major catalyst, triggering us to increase our LOA forecast.

The second part, MAD, where patients are given multiple doses, should start in early Q4 2022 and finish in Q2 2023. If Lipisense works as intended, this part should hold even better potential to demonstrate triglyceride clearance. Based on the FDA's and EMA's guidelines for the development of SHTG drugs, this is likely to be the endpoint required for market approval, and so proving triglyceride reduction would amount to a proof-of-concept. As this is a comparatively normal phase I trial, with up to 52 (including 8 diabetes type 2 patients) participants, the data could be of comparatively high quality and more like that from a phase IIa trial. This could allow Lipigon to land a licensing deal at that early stage. Assuming good results and funds or a partner in place, a phase II trial could start in H2 2023.

We believe that a reduction in triglyceride levels of around 25-50 percent is a reasonable benchmark for approval, depending on tolerability. Reductions greater than this have been demonstrated in preclinical experiments. If a reduction of this magnitude can be demonstrated in the phase I trial, the Lipigon share should face considerable revaluation. An optimal safety profile with no to very limed side effects is also essential.

Large deals for new cardiovascular/dyslipidemia therapies

In a benchmark with five deals for similar drugs in similar therapeutic areas, ranging from preclinical to the NDA stage, the median upfront payment was USD 175m, while the median total deal value was USD 825m. If an effect can be proven in phase I, a large licensing deal could be possible already at this point.

Low barrier for approval through biomarker endpoint

Longer term, it should be possible to gain market approval by reaching an endpoint of simply lowering triglycerides in certain hypertriglyceridemia indications without needing to prove a reduction in symptoms due to high blood triglyceride levels, as would be the case in cardiovascular indications. This should allow for lower clinical development costs, a quicker path to the market, and a lowering of overall risk, assuming that a reduction in triglyceride levels can be proven in phase I. A long-term investor might want to hold the shares for longer upon demonstration of proof-of-concept.

Large potential for indication expansions

There is even more potential for Lipisense in the long term. In our valuation, we assume that Lipisense's indication is severe hypertriglyceridemia (TG>500mg/dL), SHTG. There are around five million people in the 7MM suffering from this condition. We assume that Lipisense will mainly be used in the subgroup multifactorial chylomicronemia syndrome (TG>1000mg/dL), representing around 1.3 million people in the 7MM (major markets). With strong clinical results, there is an upside to our assumed market penetration (10%). There is even potential to expand Lipisense's use as a combination with statins to decrease cardiovascular risk in hypertriglyceridemia (TG>150mg/dL), which is a major market of 135 million people in the 7MM. This would require very large clinical trials, however. There are also potential orphan indications where Lipisense could be used, such as familial chylomicronemia syndrome, with some thousands of people in the 7MM.

Weak biotech sentiment and weak financial position

Even if the company has great fundamental potential and is set up for important catalysts, biotech is currently experiencing one of its worst bear markets, and there are no signs of this easing in the near term. We believe that biotech has a great future, and bear markets tend to end at some point, so investors should be attentive to signs of a potential turnaround.

We assume that Lipigon will need to raise at least an additional SEK 35-40m before it can sign a licensing deal. The strike price of the warrants from the IPO that could bring in this amount trade out of the money by a large margin. An equity issue in 2022 is likely, as Lipigon's current cash will not fund the entire phase I including the MAD part (part Ib). The market for issuing equity has reversed and is now more difficult. Any equity issue in this climate would likely bring substantial dilution. This is an obvious risk when investing in the short term.

Trading at dysfunctional valuation

The weak sentiment in biotech combined with the need for financing to complete the phase I trial has led to an extremely weak valuation that in our opinion is disconnected from fundamentals. The market value of Lipigon today is only around SEK 50m, less than the money raised at the IPO a year ago. The fundamental upside potential in a short period of time is at the same time substantial, if an effect in the form of lowering of triglycerides can be demonstrated later this year, which is reflected in our Bull Case of SEK 31 (with a WACC of 20 percent).

Company Description

Lipigon was founded in 2010 and was funded by research grants and the founders themselves until 2016, when external capital started to be invested and a defined business plan was laid out. The company is essentially a spin-off from academia, based on research into lipids at Umeå University over the past 50 years by Thomas and Gunilla Olivecrona, who made important discoveries about the lipoprotein lipase enzyme. Lipigon's CEO, Stefan K. Nilsson, was associated with their research group and wanted to move the research into a commercial drug development setting. Stefan and Gunilla Olivecrona, his supervisor, are the main founders of the company. It is based on the knowledge inherited from the research group.

Lipigon does not have a drug development platform; rather, it engages partners to develop and optimize new substances. The partner obtains a share of future revenues. Although this is a future cost to the company, it also means that the optimal tools can be used. Lipigon can focus on target formulation based on scientific understanding.

In 2016, Lipigon initiated a research collaboration with AstraZeneca on a project in dyslipidemia (P3), and in 2017, it initiated a research collaboration with Secarna to develop Lipisense. This program led to the transfer of the project's IP to Lipigon in 2020. In 2019, the company moved from the university site into its own premises. That same year, the lipodystrophy project (P2) was outlicensed to Combigene. Since 2020, Lipigon has had a research collaboration with China's HitGen to discover molecules that target dyslipidemia targets (P3).

Lipigon has a virtual business structure with eight employees (six FTEs), outsourcing a large part of its non-laboratory services. Its business strategy is to develop a diversified pipeline of lipid drugs. As of now, it has four projects, one of which is outlicensed to Combigene. Its main focus is on the phase-I-ready project 1 (P1), Lipisense, against various hypertriglyceridemia indications—extreme triglyceride blood levels, and potentially also against cardiovascular disease.

In early 2020, Lipigon acquired the rights to the patents in cardiovascular and metabolic indications related to Lipisense from Secarna. Since then, Lipigon has worked on preparing Lipisense for a clinical trial. The establishment of a GMP process through a contract manufacturer and four preclinical safety studies have since been successfully concluded. The project is now ready for a phase I trial. If successful, Lipigon can choose between several dyslipidemia indications for phase II. Two potential indications are severe hypertriglyceridemia (SHTG) and the ultra-rare familial chylomicronemia syndrome.

Orphan indications are a potential strategic focus area for the company, thanks to the shorter development times and reduced costs of these smaller clinical trials. They typically also reduce endpoint requirements for approval. Orphan drugs are typically sold at very high prices. Familial chylomicronemia syndrome is a potential orphan indication for Lipisense with just some thousands of patients in developed markets.

If Lipigon chooses the SHTG for P1, the clinical pathway to the market would still be comparatively short and inexpensive, as the main endpoint for approval would likely be a reduction in blood triglyceride, which is essentially a biomarker. It is a comparatively large indication. We believe that the treated population would consist of the subgroup multifactorial chylomicronemia syndrome (around 1.3m patients on the seven major markets). Lipigon judges that the cost of phase I, II, and III trials would be around SEK 200-300m. A phase III trial would have to include around 500 patients. This is not a large trial in relation to the size of the indication. According to the company prospectus, around SEK 47m of the proceeds from the

IPO and TO1 are earmarked for the phase I trial, including substance production. Although phase I includes healthy volunteers and the main endpoint is safety, the patients' triglyceride levels before and after treatment will be measured, allowing Lipigon to potentially demonstrate proof-of-concept, or effect, at this early stage. Proof-of-concept in humans is generally the point at which transactions are made. Assuming significant results and a good safety profile, Lipigon could be in a position to outlicense Lipisense already after phase I.

Management and Board

Lipigon's two main founders, Stefan K Nilsson (CEO) and Gunilla Olivecrona (director), are major shareholders. The company has good mix of personnel in its management and on its board to handle drug development, clinical trials, business development, financing, and financial statements.

Lipigon: Management

Name	Position	Experience
Stefan K Nilsson	CEO	He is co-founder and has been CEO of the company since 2016. He has a PhD in blood lipids. He owns 619,860 shares.
Michael Owens	CFO	He has held the position of CFO since 2020. He is a former authorized public accountant. He has extensive experience of financial reporting in the healthcare sector. He owns 332,029 shares.
Lars Öhman	CBDO	He has worked as a consultant for Lipigon since 2012. He has more than 35 years of experience in business development in the pharmaceutical industry. He owns 209,120 shares.
Eva Arlander	COO	She is a pharmacist and has a PhD in clinical pharmacology. She has broad experience from various Swedish pharmaceutical companies. She owns 5,325 shares.
Stefan Pierrou	CPM	He has a PhD in molecular biology with 20 years of experience from project management in drug development. Has held several positions at AstraZeneca. He owns 893 shares.

Source: Lipigon

Five people sit on the Board of Directors, bringing experience of academic medical research, drug development, and business development, while the chairman, Urban Paulsson, has a legal background. Mr Paulsson is co-founder of four life science companies: Cinclus Pharma, Cormorant Pharmaceuticals, Gesynta Pharma, and Buzzard Pharmaceuticals. Cormorant was sold to BMS in 2016 for USD 520m, of which USD 100m was an upfront payment.

Lipigon: Board of Directors

Name	Position	Experience
Urban Paulsson	Chair	He was appointed to his present position in 2020. He is a lawyer with experience from the life science sector, including as an investor. He holds 332,019 shares.
Lars Öhman	Director	He has held this position since 2012. He has more than 35 years of experience in business development in the pharmaceutical industry. He holds 203,048 shares.
Gunilla Olivecrona	Director	She has held this position since 2010. She is a professor at Umeå University, where she is a leading expert in the molecular basis of lipids, with more than 45 years' experience and more than 200 publications. She is co-founder of the company and owns 419,628 shares.

Johannes Hulthe	Director	He has been a director since 2020. He is an MD and lecturer in cardiovascular prevention at the University of Gothenburg. He is CEO at Antaros Medical, one of the top 15 owners.
Jessica Martinsson	Director	She has held this position since 2020. She has 25 years' experience from the pharmaceutical industry. She is the co-founder of Sprint Bioscience. She owns 10,000 shares.

Source: Lipigon

The ownership of Lipigon consists mainly of private investors (e.g., Nordnet Pensionsförsäkring), some professional investors, some family offices, and three founders (Stefan K Nilsson, prof. Gunilla Olivecrona and prof. Mikael Elofsson). Fort Knox, Partnerinvest and Antaros made the first external investments in the company (2016) and together own almost 17 percent of the shares. Nylöf is a party related to CFO Michael Owens and included in the tally in the management description above. There are no large institutional investors, which is typical for a company with Lipigon's market capitalization, as such investors tend to require a market cap of at least SEK 500m.

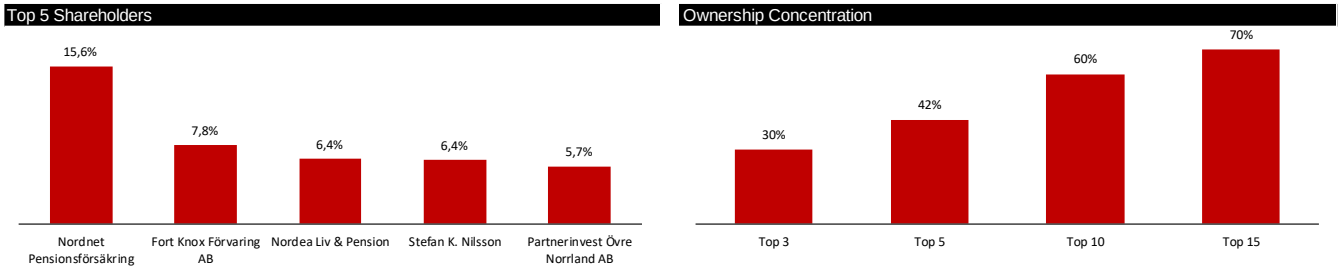
For small early-stage biotech companies, the most important aspect of having a strong ownership basis is the ability it provides to support the company with capital. Lipigon has around 2,000 owners, which is likely enough to support the raising of a further SEK 35-40m. The exception would be the two main founders (together owning less than 11 percent), who are probably unable to defend their respective shares. Ownership in Lipigon is not particularly concentrated.

Shareholders

Shareholder	Total Shares	Share Capital
Nordnet Pensionsförsäkring	1,519,676	15.6%
Fort Knox Förvaring AB	762,374	7.8%
Nordea Liv & Pension	626,840	6.4%
Stefan K. Nilsson	619,861	6.4%
Partnerinvest Övre Norrland AB	558,988	5.7%
John Fällström	437,975	4.5%
Gunilla Olivecrona	419,628	4.3%
Antaros Invest AB	329,925	3.4%
Avanza Pension	300,943	3.1%
Sonja Agneta Nylöf	295,858	3.0%
Günther & Wikberg	227,985	2.3%
Lars Öhman	218,048	2.2%
Swedbank Försäkring	207,804	2.1%
Mikael Elofsson Kemi & Musik AB	165,868	1.7%
Svante Larsson	133,009	1.4%
Total 15 Largest Shareholders	**6824782**	**70%**
Others	*2908116*	*30%*
Total Number of Shares	**9732898**	**100%**

Source: Holdings

Ownership concentration

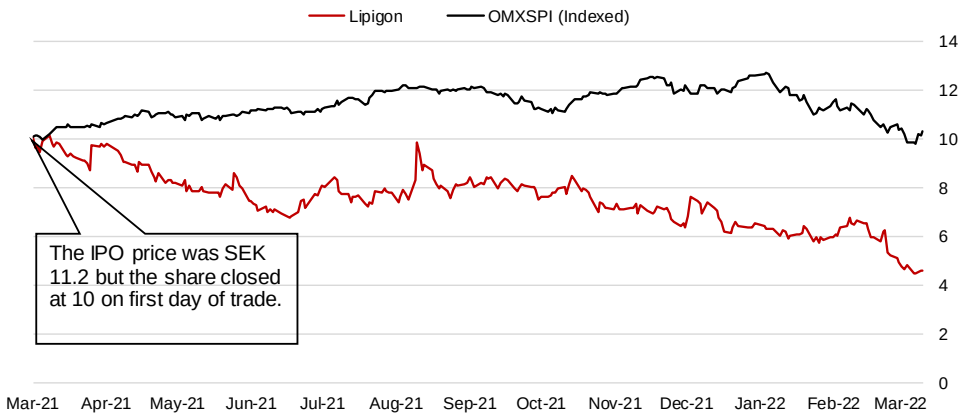


Source: Holdings

Share Price Performance

Lipigon was listed in March 2021 at a subscription price of SEK 11.2 and a post-money valuation of SEK 108m. It was fully subscribed (479 percent of the shares available to the public were subscribed, with 1,950 new shareholders), and the company raised SEK 56m (with listing costs of SEK 5.2m). It traded at around SEK 9-10 for the first month of trading but has since gradually declined to the present level of SEK 5.0-6.0. The share is now valued no higher than the money raised at the IPO. We believe this is largely on account of the weak market for biotech and pre-revenue companies during 2021 and 2022, resulting in a market valuation that makes little sense from a fundamental point of view.

Lipigon's share price performance (in SEK)



Source: Redeye Research

Projects

Lipigon has four active projects:

- Lipisense (P1) in dyslipidemia to reduce excessive blood fats
- P2 in lipodystrophy to correct abnormal fat distribution; outlicensed to Combigene
- P3 in dyslipidemia to reduce excessive blood fats
- P4 in acute respiratory distress syndrome (ARDS)

Almost all the company's focus is on P1 at the moment.

Lipisense (P1)

Lipisense is an ANGPTL4-reducing drug candidate designed to reduce blood triglycerides. It also corrects remnant lipoprotein cholesterol and low HDL cholesterol levels. It has been designed to specifically silence the expression of ANGPTL4 in the liver. It is administered by subcutaneous injection, making administration possible by the patient. Its half-life is long; one injection should last around one month.

Lipisense is protected by a patent application registered in 2019. Lipigon has considered ANGPTL3 as a target as well. However, Lipigon is concentrating on ANGPTL4 as there is competition in the ANGPTL3 space. Furthermore, the advanced ANGPTL3 project vupanorsen (licensed by Pfizer) was recently cancelled after a phase IIb trial due to a reduction in triglycerides and cholesterol that was significant but not large enough. This leaves questions about ANGPTL3 as a target and could lead to a shift in interest towards ANGPTL4 instead.

Antisense RNA technology

Lipigon uses antisense technology from Secarna, with origins in Santaris Pharma (now Roche) technology, to produce Lipisense, an antisense RNA drug consisting of a single-stranded RNA strain that is the mirrored part of the messenger RNA that codes for a protein. After entering the cell, Lipisense binds to its mirrored RNA part, blocking it from translating into a protein. Through this technology, proteins can be silenced, i.e., stop being produced by the cells.

On March 19, 2020, Lipigon signed an agreement with Secarna Pharmaceuticals that provides Lipigon with the complete rights to antisense candidates developed against cardiovascular and metabolic diseases by the parties. This includes present and future patents (including EP 18206083.0, EP 18206087.1, 18206084.8, PCT/EP2019/081169, PCT/EP 2019/081161, and PCT/EP2019/081250). Lipigon now formally owns the patents. Lipigon bears all future development costs, and Secarna has the right to revenue sharing at an undisclosed rate. We expect this to be in the low, or possibly mid-, double-digit range. Any future milestones or royalties will thus have to be shared with Secarna.

Lipoproteins

Along with glucose, triglycerides—which consist of glycerol and three fatty acids—are the principal fuel for many different cells in the body. Fat derived from food is first hydrolysed to free fatty acids in the intestine and then converted into triglycerides in the enterocytes in the intestines. From there, the insoluble triglycerides are packed into a shell of soluble phospholipids and apolipoproteins to make up a fat droplet (lipoprotein) that can be transported in the body. This lipoprotein containing dietary fat is transported through the lymphatic system, eventually entering the bloodstream.

Lipoproteins are spherical packages of triglycerides, cholesterol, and proteins, in particular apolipoproteins. Chylomicrons (ultra-low-density lipoproteins) transport dietary lipids from the

intestines. They are the largest lipoproteins, with the largest proportion of lipids. There are also large lipoproteins derived from the liver – VLDL – which through enzymatic activity by lipases lose their triglyceride rich core, leaving the cholesterol part untouched. VLDL is subsequently converted to the much smaller cholesterol-rich LDL particle, also known as the bad cholesterol. HDL, high density lipoprotein, also carries a high proportion of cholesterol and is known as the good cholesterol, since it can take up triglycerides and act like a vacuum cleaner in the bloodstream.

Triglycerides are mainly cleared from large lipoproteins through the enzyme lipoprotein lipase (LPL). Triglycerides then either provide energy directly to tissues that consume a lot of it, such as heart or muscles, or it can be stored for later use by adipose tissue. The enzyme LPL is highly expressed in adipose tissue, the heart and the muscles. The liver is also important as it processes fat.

ANGPTL3, ANGPTL4, and ANGPTL8

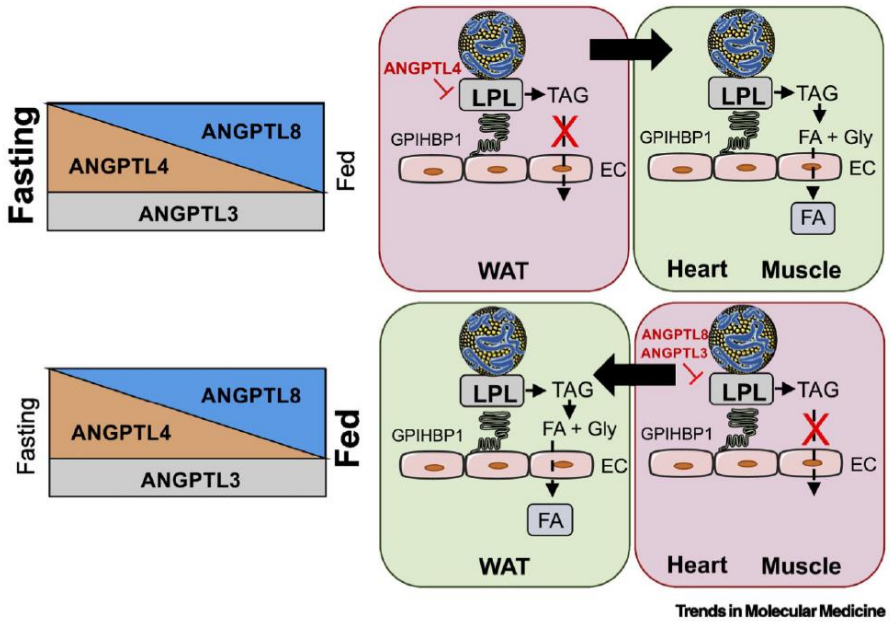
One of the discoverers of ANGTPL4 and its regulation of triglycerides is Prof. Sander Kersten, who is scientific advisor to Lipigon.

Knowledge about the metabolic regulation of fatty acids has increased considerably over the last 20 years. It has been demonstrated that ANGPTLs (angiopoietin-like proteins) regulate triglyceride levels in various tissues. ANGPTL4 is highly expressed in adipose tissues and the liver, while ANGPTL8 activates ANGPTL3 to inhibit LPL (lipoprotein lipase) activity in the heart and muscles in an endocrine manner. ANGPTLs regulate triglyceride levels by inhibiting fat hydrolysing lipases (i.e., they inhibit enzymes that break down fat). High ANGPTL levels thus lead to lower lipase activity and higher triglyceride levels.

During fasting, ANGPTL4 is highly expressed, thereby inhibiting triglyceride absorption in adipose tissue, making it available for the heart and muscles. During fed state, ANGPTL8 is over-expressed, forming an active complex with ANGPTL3, which inhibits LPL activity in the heart and muscles, thereby redirecting excess triglycerides to adipose cells and the liver tissue for storage. ANGPTLs enable the distribution of fatty acids to adipose tissue during feeding, and release it from storage during fasting, making the energy rich fat available for different parts of the body at all times.

ANGPTLs regulate LPL, which is secreted by different cells and transported across endothelial cells (EC) of capillaries where it binds to and is stabilized by GPIHBP1. Once in position, LPL hydrolyzes triglycerides (TAG in the figure below) from triglyceride-rich lipoproteins in the blood to release FA (fatty acids) and glycerol (Gly). Fatty acids are transported back through the endothelial cells to the final destination, either adipose tissue (WAT in the figure below) or the heart and muscles. The inhibitory action of ANGPTL4 during fasting and of ANGPTL8 (which activates ANGPTL3 that is always present) during fed state is shown in the figure below.

Lipid partitioning by angiopoietin-like proteins (ANGPTLs).



Source: Aryal et al. 2019

In liver cells, ANGPTL4 functions as a local inhibitor of hepatic lipase, an enzyme that converts intermediate-density lipoprotein (IDL) to low-density lipoprotein (LDL). Overexpression of ANGPTL4 in mice leads to the silencing of hepatic lipase in the liver and an increase in IDL, which is taken up by the liver and can result in non-alcoholic fatty liver disease. It leads to an imbalance between HDL and LDL, with elevated high-density lipoprotein (HDL) levels and too low levels of LDL.

Lipisense inhibits the formation of ANGPTL4 in the liver. The exact functioning of ANGPTL4 in the liver is not yet understood to the full extent. Lipoprotein lipase (LPL) is actually minimally expressed in the liver. However, ANGPTL4 is secreted by the liver into the blood stream and should thus have an endocrine effect. ANGPTL4 decreases plasma LPL activity and increases circulating triglycerides. It is also possible that ANGPTL4 might regulate the clearance of remnant lipoproteins. In theory, Lipisense should not affect triglyceride clearance in adipose tissue, but it should suppress the secretion of ANGPTL4 into the blood, thus reducing triglyceride blood levels. Lipisense should also activate hepatic lipase, possibly increasing remnant (i.e., lipoprotein rest particles) clearance in the liver.

ANGPTL4 is a protein with several biological functions. Although its overall functioning is fairly well understood, more research is needed to understand it fully (such as where it is located inside cells, how it is released, and how it binds to endothelial cells and LPL). Its main relevant function is as an inhibitor of LPL, although it is involved in other bodily functions, including angiogenesis, wound healing, and extracellular matrix remodelling, and it also plays a role in cancer. On a molecular level, ANGPTL4 disables LPL by splicing the catalytically active LPL dimer into inactive LPL monomers. Furthermore, ANGPTL4 seems to function as a conventional, non-competitive reversible inhibitor that binds to LPL, preventing its functioning.

There is genetic evidence for the biological effects of ANGPTL4 (Aryal et al. 2019). Around 1.3-3 percent of populations of European decent have mutations in the ANGPTL4 gene. This is associated with reduced triglyceride blood levels. Carriers of the E40K mutation have comparatively low triglyceride but high HDL-C (the "good" cholesterol) levels, which gives the carriers of the mutation protection against cardiovascular disease, according to some,

admittedly, preliminary evidence. There is also some evidence that carriers of the mutation have lower fasting glucose levels and a somewhat lower risk of developing type 2 diabetes. This is an area that is still under investigation, however, with no entirely conclusive evidence.

ANGPTL4 has been considered a promising target for the prevention and treatment of cardiovascular disease and type 2 diabetes. However, antibodies against the target have created severe inflammation in preclinical studies in mice and monkeys. Global deficiency in ANGPTL4 primes macrophages to become foamy and more plaque-inducing. ANGPTL4 has an immunoprotective role in these cells, as it inhibits lipid overloading of macrophages, which otherwise leads them to develop into foam cells. When foam cells die, they induce plaque formation in blood vessels (i.e., atherosclerosis). Systemic ANGPTL4 silencing could thus be expected to have some negative side effects. It has taken some time to overcome this issue, and Lipisense is the first new candidate to target ANGPTL4 since these failed antibodies. Lipigon believes that the inflammatory issues will be controlled with Lipisense, as it is a liver-targeted antisense oligonucleotide. In fact, none of the previously seen side effects have been observed in preclinical safety studies with Lipisense.

Hypertriglyceridemia indications

Hypertriglyceridemia is the hyper-abundance of triglycerides in the blood. There are several reasons for increased triglyceride levels—genetic, medical, and lifestyle-related. A normal triglyceride level is <150 mg/dL. An increase above these levels elevates the risk for cardiovascular disease. When the level surpasses 500, which is defined as severe hypertriglyceridemia, there is an increased risk for pancreatitis. When triglycerides exceeded 1,000 mg/dL, a patient will likely experience pancreatitis at some point and medical treatment is necessary. The chylomicronemia syndrome (CS) is a term that is used to describe individuals with either intermittent or persistent fasting chylomicronemia causing severe hypertriglyceridemia.

Lipigon is considering one of two main hypertriglyceridemia indications for further development of Lipisense. The first indication that Lipigon is contemplating is severe hypertriglyceridemia (SHTG). In particular, we believe that the subgroup of patients with multifactorial chylomicronemia syndrome (MFCS), which is similar to FCS (see below), but caused by a mixture of factors (such as predisposition combined with diet, a disease, or a medicine) would be a likely target for Lipisense, even though MFCS is not a medical indication in itself as of today. This group has a higher rate of cardiovascular comorbidities, such as diabetes type 2. MFCS (from any cause) has been estimated to occur in one in every 600 in the population. It is associated with triglyceride levels exceeding 1,000 mg/dL and requires medical treatment. In our Base Case, we assume further development in the SHTG indication with focus a on MFCS. We use chylomicronemia syndrome (CS) prevalence to calculate the market potential for Lipisense. The number of people with this condition in the seven major market (including six western countries and Japan) is around 1.3 million.

Treatment consists of a low-fat diet and weight reduction. Drugs in the form of fibrates and high-dose omega 3 fatty acids are often used simultaneously. Fibrates improve uptake of fat from the blood and decrease low-density lipoprotein levels. The two major fibrate drugs are gemfibrozil and fenofibrate. Fibrates can reduce triglyceride levels by 25-50 percent, but their toxicity profile is not ideal and includes nausea, an unwell stomach, increased liver enzymes, and some other, more severe but rare conditions. Lipisense is likely to be positioned for patients who do not benefit enough from existing therapies, those who are intolerant, or who need to combine their medication with statins (which is a major group).

Familial chylomicronemia syndrome (FCS) is the second potential indication and is, we believe, less prioritized than SHTG. It is an ultra-rare genetic disease affecting around one per one million. Faulty genes cause impaired production or functioning of lipoprotein lipase

enzyme (LPL), which breaks down chylomicrons. The result is extremely high triglyceride levels, leading to several complications, in particular a severely heightened risk of acute pancreatitis, which can be fatal. Cardiovascular disease, obesity, insulin resistance, diabetes, hypertension, and hyperuricemia are other effects.

Chylomicronemia syndrome (CS), both FCS and MFCS, is, in general, associated with several clinical conditions and medications, and causes severe hypertriglyceridemia. In particular, diabetes is associated with 25-76 percent of cases, depending on the study (Goldberg & Chait 2020). Obesity is also a common comorbidity. The frequency of most of these conditions is expected to increase substantially over the coming decade. The same can be said about medications (e.g., most adults in the US take prescription drugs). Increased prevalence of CS is likely to follow in their wake. We calculate a 1.5 percent annual increase in the number of patients in the US and a one percent in the other markets for the MFCS subgroup that we believe is the most likely treatment group for Lipisense.

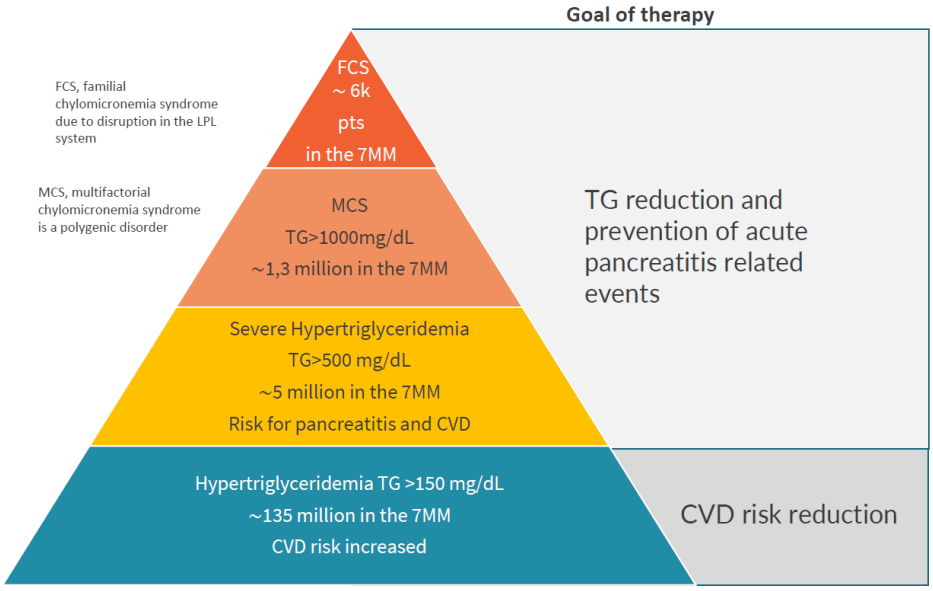
Clinical conditions and medications associated with CS

Factors associated with CS	
Clinical conditions	Diabetes
	Obesity
	Alcohol excess
	Chronic kidney disease
	Nephrotic syndrome
	Pregnancy
	Hypothyroidism
Medications	Diuretics
	Antihypertensives
	Estrogen and estrogen receptor agonists
	Corticosteroids
	Protease inhibitors
	Antipsychotics and antidepressants
	Immunosuppressives
	Retinoids
	Propofol
	L-asparaginase

Source: Goldberg & Chait 2020

If approved in SHTG, Lipisense would, we believe, in the first hand be used in patients with triglycerides exceeding 1000 mg/dL to prevent pancreas complications, a group of around 1.3m people in the 7MM. People with triglyceride levels slightly above 500 mg/dL group is at a lower level of risk for direct complications than CS patients, but treatment to lower triglycerides is still justified for them, so there is potential for growth within the indication, which represents about five million people in the 7MM. It might have further potential in reducing the incidence of cardiovascular diseases in the same population, although this would require further and larger studies. Having high triglyceride levels is comparatively common. In a NHANES cohort of 5,680 adults representative of the US population, the prevalence of moderate to severe hypertriglyceridemia (500-2,000 mg/dL) was 1.7 percent.

Potential medical indications for Lipisense



Source: Lipigon

An even larger group is those with hypertriglyceridemia, or triglyceride levels exceeding 150 mg/dL. There are more than 100 million people with this condition in the seven major markets. Hypertriglyceridemia is a risk factor for cardiovascular disease, as it typically leads to elevated remnant cholesterol levels which causes atherosclerosis. Lipisense could potentially be used to reduce cardiovascular risks in this group. Statins dominate the market and are likely to maintain this position. Fibrates are used in this indication, but they have not demonstrated any benefit in overall survival, and they should, if possible, be avoided in combination with statins. Lipisense could be an interesting add-on to statins instead of fibrates if its safety profile proves favorable in humans. The economic potential in cardiovascular risk reduction would be considerable and greater than in MFCS. Very large trials (n~10,000) would be required to demonstrate any benefit, though. Assuming that Lipisense was approved in SHTG, such trials sponsored by a partner would certainly be conceivable for this large and growing market after a few years of active use in more critical groups.

Competing targets

ApoC-III and ANGPTL3 are two other novel therapeutic targets for treating dyslipidemia and cardiovascular diseases for which drugs have been recently approved. The fourth major dyslipidemia target is LPL (lipoprotein lipase), whose function we have previously described. Lipigon's P3, which is in discovery phase, is targeting LPL. However, there are no approved drugs for it as of today.

ApoC-III is a protein mainly produced in the liver that plays a central role in the regulation of plasma triglycerides. Waylivra (volanesorsen) is approved in the EU for the ultra-rare FCS orphan indication, which is also the second potential indication for Lipisense. Like Lipisense, volanesorsen is an antisense oligonucleotide. It was designed to reduce the production of apolipoprotein C-III (apoC-III). The phase III pivotal trial (double-blinded placebo) involved 66 patients from 12 countries. Patients treated with Waylivra achieved a statistically significant mean reduction in triglycerides of 77 percent from baseline compared with placebo. However, questions have been raised regarding the safety profile owing to a decrease in thrombocytes.

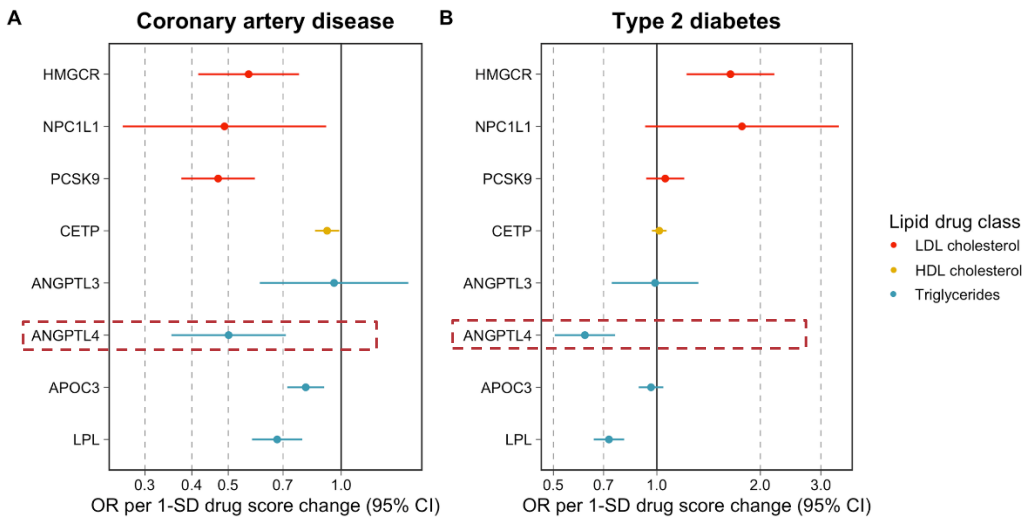
Waylivra was rejected by the FDA in 2018 despite support from an advisory committee but approved by the EMA in 2020. Waylivra is owned by Ionis Pharmaceuticals.

Evkeeza (evinacumab) is an antibody that binds to ANGPTL3. It is approved for the treatment of homozygous familial hypercholesterolemia (HoFH), another ultra-rare indication. Like volanesorsen, it was also approved after a comparatively small phase III trial (65 participants). Patients receiving evinacumab saw a 47 percent decrease in LDL-C compared with an increase of two percent in the control arm. Evinucamab is currently in a phase II trial for a new indication, patients with severe hypertriglyceridemia. It is owned by Regeneron.

As we mentioned earlier, vupanorsen is an antisense ANGPTL3 blocker developed by Ionis and licensed by Pfizer that reported a disappointing phase II outcome in January 2022 in dyslipidaemia patients. This casts some doubt about ANGPTL3 as a target in dyslipidaemia indications, such as severe hypertriglyceridemia.

Drugs targeting all of the above-mentioned targets, ANGPTL3, ANGPTL4, ApoC-III and LPL, have demonstrated significant reductions in triglycerides. However, their clinical effects can vary. Furthermore, their effect on secondary parameters vary widely. In a recent mendelian randomisation study (Richardson et al., 2022) that looked at gene expressions of various lipid modifying targets and their correlations with illnesses and related biomarkers, ANGPTL4 appeared to be the best among eight targets in terms of reducing cardiovascular disease and type 2 diabetes. This implies that Lipisense could have an advantage over the other three triglyceride reducing targets (ANGPTL3, ApoC-III and LPL), as it could potentially reduce cardiovascular disease and type 2 diabetes in addition to preventing conditions resulting from high triglyceride levels such as pancreatitis. LPL also seems to a good target from this perspective.

Plot visualising genetically predicted effect of lipid-modifying targets



Source: Richardson et al., 2022

Pre-clinical evidence

ANGPTL4 has been considered a promising target for some time, but earlier drug development was cancelled due to negative side effects, as systemic administration of antibodies against ANGPTL4 in animals led to lymphatic inflammation. The same effect was seen in mice in which the ANGPTL4 gene had been knocked out. In this case, a high-fat diet led to lymphadenopathy, as macrophages in lymph nodes became pro-inflammatory giant

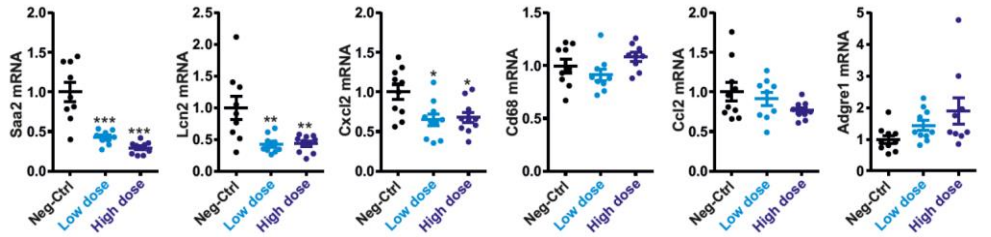
cells because of lipid "overeating". Due to these issues, Lipigon has developed a liver-targeted drug, which seems able to evade these side effects.

Some caution is always mandated when interpreting results from preclinical experiments. E.g. mice and humans have remarkably similar immune systems, but they are clearly not identical.

Safety will be paramount if Lipisense is to be approved beyond orphan indications. Lipigon has performed four preclinical studies as a basis for handing in a new trial application (for phase I), in which Lipisense has been demonstrated to be safe. Studies have been performed in Lipigon's lab and repeated in Prof. Sander Kersten's lab, where the original finding of the side effects were observed. So, it would seem that Lipigon has been successful in addressing the previous safety issues. This is of course no guarantee for tolerability in humans, but it allows the project to progress to a phase I trial.

In one of the studies, a preclinical murine experiment with two doses of Lipisense, 1.25 mg/kg and 0.625 mg/kg, for 20 weeks, no signs of inflammation showed up. Several biomarkers for inflammation showed either decreased or stable levels compared with the negative control group. The only biomarker that showed a slight increase was Adgre 1 mRNA, which is associated with monocyte macrophages. SAA2 mRNA, indicating systemic inflammation, decreased, as did Lcn2 mRNA, which is a sign of neutrophil activity, and Cxcl2 mRNA, which is a macrophage inflammatory protein. Cd68 mRNA, expressed by monocyte macrophages, and Ccl2 mRNA, also expressed by inflammatory monocytes, were stable. These biomarkers would have shown increased inflammation if systemic ANGPTL4 were administered instead.

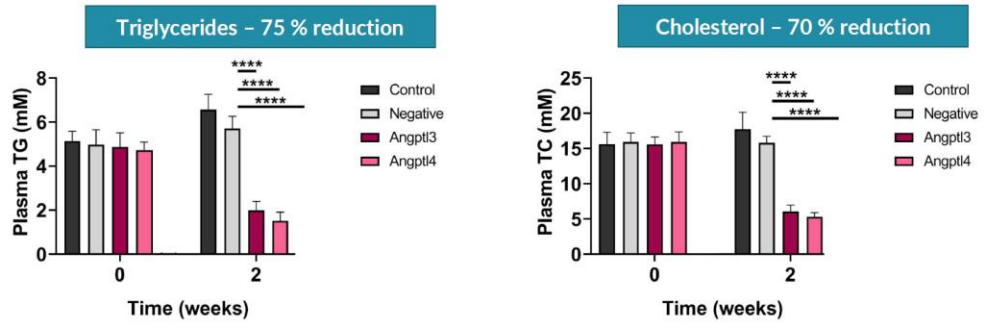
Liver-specific ANGPTL4 mouse antisense oligonucleotide does not induce lymphadenopathy



Source: Lipigon

Several experiments with mice have shown that animals deficient in ANGPTL4 exhibit increased plasma LPL activity, increased triglyceride clearance, and decreased plasma TAG levels. Lipigon has performed several pre-clinical experiments that provide evidence for Lipisense's mode of action. Lipisense improved dyslipidemia significantly in an animal model. Reduction of ANGPTL4 showed similar effects in reducing ANGPTL3, which is a more established target, reducing triglyceride plasma levels by around 75 percent. It also reduced cholesterol levels by around 70 percent.

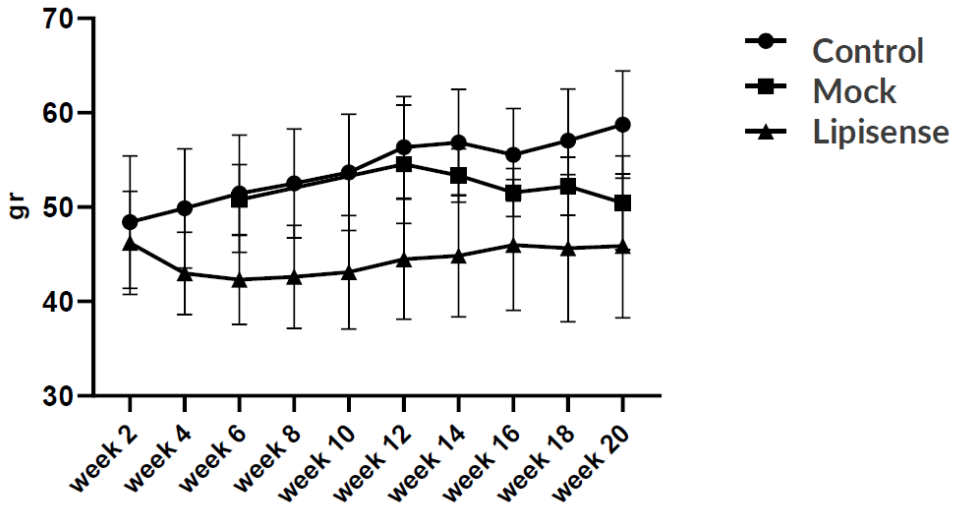
Lipisense corrects dyslipidemia in humanized mice



Source: Lipigon

In another preclinical experiment, Lipisense demonstrated significant protection against diet-induced weight gain. The control group weighed almost 60 grams, while the placebo group weighed around 50 grams and the treatment group 45 grams.

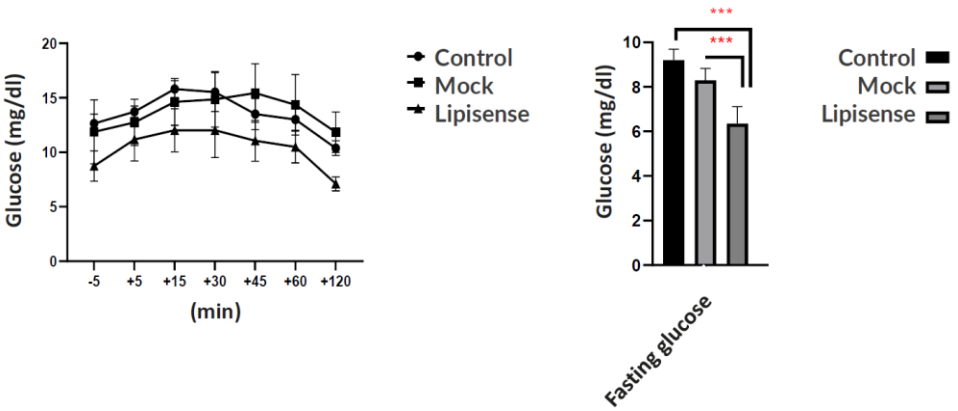
Lipisense protects against diet-induced obesity



Source: Lipigon

Glucose levels clear faster in mice treated with Lipisense. In fasting mice that have not eaten recently, Lipisense also reduced glucose levels from 8-9 mg/dL to 6 mg/dL. Several other studies also suggest that ANGPTL4 depletion in mice improves glucose metabolism in a number of ways. This is an obvious benefit as a large proportion, if not most, people with hypertriglyceridemia also have type 2 diabetes.

Lipisense improves blood glucose handling



Source: Lipigon

Phase I design

Lipigon plans to hand in a clinical trial application for the phase I trial with Lipisense during Q1 2022, with the first subject treated in June. It selected a contract research organization, Clinical Trial Consultants in Uppsala, in 2021. In addition to safety, each patient's triglyceride levels will be measured before and after treatment. Further biomarkers related to blood fats and metabolism will be investigated.

The phase I will be conducted in two parts. The first part is a single-dose ascending study (SAD), while the second part is a multiple-dose ascending study (MAD). In total, 52 subjects will be recruited. Mainly healthy volunteers will be included, but also eight patients with type 2 diabetes in the MAD part. This gives Lipigon the opportunity to investigate how Lipisense affects glucose metabolism and liver lipid levels in a group of major interest. The single-dose (SAD) part should allow a readout as early as this year, a few months into the trial. The second part, MAD, where patients are given multiple doses, should start in early Q4 2022 and should probably be completed in Q2 2023.

Due to the long half-life, the effect of the first part, SAD, could show an effect. If ANGPTL4 expression were to be reduced for a few weeks, it is reasonable to assume that triglyceride levels should also decrease. The quantity obviously remains to be seen. The MAD part should lead to more stable levels of Lipisense during a longer period of time, which might lead to a more pronounced effect that could be even easier to read.

Valuation Assumptions for P1

Price and peak sales

For our Base Case, we assume development of Lipisense in the indication severe hypertriglyceridemia (SHTG), with a focus on the subgroup multifactorial chylomicronemia syndrome (MFCS). There are around 765m inhabitants in the seven major markets (top 4 EU, the UK, Japan, and the US). Using the prevalence figure of one in 600 for MFCS, we calculate an intention-to-treat population of 1.3m patients. Assuming a price of USD 6,000 per year in the US, USD 4,500 in the rest of the world, and a sales penetration of 10 percent, we calculate a sales potential today of around USD 660m and peak sales of USD 825m in 2039. Based on Lipisense's effect on glucose levels in preclinical models, we believe that patients with diabetes as co-morbidity could be the ideal target group, as hypertriglyceridemia patients have diabetes in 25-76 percent of all cases, based on different studies (Goldberg & Chait 2020). We assume a conservative market penetration at this point due to the fact that only preclinical evidence is available. If it could be proven that Lipisense has clear effect in humans, and also controls glucose levels in humans, we would have to assume greater market penetration.

As Lipisense has been developed by Secarna using its technology, and Lipigon has formally licensed the candidate, Lipigon will have to share some of the potential revenues. We assume this amounts to a low-double-digit percentage in revenue sharing. Revenue sharing is different from an absolute royalty rate. Lipigon will have to share all revenue from the project, including upfront and milestones from a licensing deal, at a low-double-digit percentage.

We assume a licensing deal after a phase IIa trial in 2024. We assume a total deal value of USD 825m, an upfront payment of USD 35m, and a royalty rate of 15 percent. We assume a backloaded structure, with USD 665m constituting commercial milestones. We assume market launch in the US in 2028 and in 2029 on the other markets.

If developed in orphan indications, the pricing would be very different. Evinacumab, an antibody against the ANGPTL3 protein, costs up to USD 450,000 per year. It is used against HoFH, for which there are only 1,300 patients in the US. Waylivra is approved in the EU for FCS but was rejected by the FDA. It has a price tag of around USD 300,000 per year. It is approved for familial chylomicronemia syndrome. The prevalence of FCS is usually stated as around one in one million, but recent studies suggest that it is somewhat less rare, perhaps one per hundred thousand. If Lipisense were to be developed in FCS, Lipigon calculates a sales potential of around USD 80m-100m. It could be a quick way to the market after phase I, and once on the market an indication expansion might be possible (together with a price adjustment), but this strategy is not our Base Case scenario at this point.

Probability of success

The probability of success of phase I in dyslipidemia/hypercholesterolemia is 52 percent, adjusting to 30 percent in phase II, 60 percent in phase III, and 90 percent with NDA (Pharmapremia, October 22, 2021). Since Lipigon aims for approval in SHTG or another hypertriglyceridemia indication, applying the simple endpoint of decrease in triglyceride blood levels, the probability of success could be higher than in the overall dyslipidemia market. Antisense However, as we have no clinical data from human subjects yet, we adopt a conservative approach and use the historical dyslipidemia/hypercholesterolemia success rates pending clinical data. This translates into an LoA of 9 percent. If evidence for reduction of triglycerides can be proven in phase I, we would have to increase the probability of success for phase II.

Lipodystrophy (P2)

The P2 project is being developed by Combigene as a gene therapy. Combigene recently out-licensed its main project in epilepsy to Sparks Therapeutics. This means it is likely that its new focus will be the P2 project. Lipodystrophy is a group of genetic disorders that stop the body from building up and maintaining normal adipose tissue. The patient may have abnormal fat distribution, which is called partial lipodystrophy, often with low levels of fat on the limbs.

P2 consists of plasmid genes that are inserted in the liver through a vector, thus restoring the damaged function. It is intended for familial partial lipodystrophy and is designed to reduce the build-up of fat in the liver. Fatty liver disease, which might later require a liver transplant or could shorten the patient's life span if a transplant is not possible, is the main potential complication of lipodystrophy.

Inherited lipodystrophies are extremely rare genetic diseases. Familial partial lipodystrophies (FPLDs) have a prevalence rate of around one per one million. Other inherited lipodystrophies are even rarer. We assume a total patient population of less than 1,000 in the 7MM.

Valuation Assumptions for P2

Price and peak sales

Myalept (metreleptin) is approved and carried a price tag of almost USD 900,000 per year. It is an analogue of leptin and is used for patients with generalized lipodystrophy with deficiency in this hormone. Gene therapy requires only one treatment, or in some cases treatment that lasts at least a decade or two. This means the price of a single treatment has to be economically equivalent to chronic treatment with competitive drugs. A ten-year treatment with metreleptin discounted at 15 percent equates to a present value of around USD 5m. Metreleptin is one of the more expensive drugs on the market and is not necessarily a good benchmark. The price model of gene therapy is still under discussion. It could be a subscription model. We will assume an annual price of USD 0.6m in the US and USD 0.4m in the rest of the world.

We assume revenue sharing between Combigene and Lipigon, with Lipigon obtaining 10 percent of all payments, including royalties. In our model, we assume that Combigene signs a deal after phase I is concluded with a total deal value of USD 360m, of which USD 25m is an upfront payment, and with royalties of 13 percent.

Probability of success

The probability of success for phase I in dyslipidemia/hypercholesterolemia is 52 percent, adjusting to 30 percent for phase II, 60 percent for phase III, and 90 percent at NDA. For rare

diseases, these figures are 76 percent for phase I, 60 percent for phase II, 73 percent for phase III, and 89 percent for NDA.

As Combigene is targeting approval in the orphan disease FPLD, the probability of success is arguably higher than for the overall dyslipidemia market. We use probabilities of 70 percent for phase I, 60 percent for phase II, and 70 percent for phase III. We use success rates of 55 percent for lead candidate optimization and 50 percent for preclinical development, which is lower than our customary 70 and 65 percent, respectively, and is justified by the earlier technological stage of gene therapy compared with traditional drug development. This translates into an LoA of seven percent.

P3 and P4

We do not include P3 or P4 in our valuation at this stage, but as they might be added at a later stage, we provide a brief description of them now.

Project 3, a potential LPL candidate, is in a very early drug development phase. Lipigon has assigned HitGen to discover small molecules against dyslipidemia targets proposed by Lipigon. The companies have a revenue-sharing agreement (similar to that with Secarna). Dyslipidemia means an unhealthy amount of lipids in the blood. P3 is thus similar to P1, but it targets the much larger cardiovascular risk-reduction market (estimated 135 million potential patients). We do not include P3 in our valuation due to its very early stage and limited financing.

Project 4 is a side-track from project 1. Lipigon noticed that ANGPTL4 is up-regulated in ARDS patients, a highly lethal sepsis-like condition of the lungs. It is commonly the terminal state of lung infections, including Covid-19. Lipigon has demonstrated proof-of-principle in vitro with human epithelial cells and in an animal model of lung injury. Lipigon saw the potential for a quick breakthrough during 2021 and had plans to out-license the project. Now, however, with demand for Covid-19 drugs decreasing and substantial competition from other Covid-19 projects, we believe the opportunity in P4 has passed. ARDS is still not unusual in intensive care patients, and as there is no approved specific drug for the condition, there is a high unmet need. However, we believe it will be challenging for Lipigon to find a partner at this early stage, and the company does not have the financing to develop P4 much further.

Cardiovascular Reference Deals

Several of the deals included below concern innovative research platforms. The upfront payments can thus be substantial even though the projects are in the research stage. For this reason, we do not consider the upfront payments in the table entirely relevant for a potential deal between Lipigon and a pharmaceutical company. We instead use a minimum value of USD 35m in our valuation model. However, we believe the milestone payments are representative of a deal. We use the median of USD 825m from the table in our valuation model.

Cardiovascular reference deals

Company	Partner	Project	Phase	Date	Royalty	Upfront	Milestones
Esperion	Daiichi Sankyo	Nexletol/Nexlizet	NDA	Apr-21	5-20	180	1,075
Dicerna	Novo Nordisk	GalXC™ RNAi	Research	Nov-19	5-15	175	733
Akcea	Pfizer	vupanorsen	II	Oct-19	10-15	250	1,300
Akcea	Novartis	APO(a)-LRx/APOCIII-LRx	I/IIa	Jan-17	15-23	75	825
Arrowhead	Amgen	RNAi ARC-LPA	Research	Sep-17	~12	35	617
Average						143	910
Median						175	**825**
Minimum						**35**	617

Source: Redeye Research

Esperion Therapeutics and Daiichi Sankyo, 2019/2021 – NDA

Esperion Therapeutics Inc. licensed to Daiichi Sankyo Europe, its bempedoic acid, Nexletol/Nexlizet, in 2019. It had completed phase III in 2018. Daiichi paid USD 150m in upfront and near-term milestones, 15-25 percent in tiered royalties, and regulatory and sales milestones of up to USD 900m. An expansion to Asia in 2021 led to an upfront payment of USD 30m, USD 175m in additional milestones, and royalties rising from five to 20 percent on net sales.

Dicerna and Novo Nordisk, 2019 – preclinical research

Dicerna Pharmaceuticals agreed to license candidates from its RNAi platform against more than 30 liver cell targets related to cardio-metabolic diseases. It would pay USD 175m upfront, make a USD 50m equity investment, and pay USD 25m annually during each of the first three years of the collaboration, as well as paying up to USD 357.5m per target in milestone payments, plus tiered royalties. We include one program in our table.

Dicerna's deal with Novo Nordisk led to the latter acquiring Dicerna in November 2021 for a total equity value of USD 3.3bn. Novo Nordisk thus gains control of Dicerna's proprietary GalXC™ RNAi platform technology, which targets cardiometabolic diseases.

Akcea (Ionis) and Pfizer, 2019 – phase II

Pfizer paid USD 250m in an upfront payment and potential milestones of up to USD 1.3bn, as well as tiered, double-digit royalties on annual worldwide net sales following marketing approval of candidate vupanorsen. This is an antisense medicine developed to treat cardiovascular and metabolic diseases. It had an ongoing phase II trial at that time in 2019. Pfizer terminated the deal in January 2022. A significant reduction in triglycerides and cholesterol was demonstrated, but the magnitude was not large enough.

Akcea (Ionis) and Novartis, 2017 – phase I/IIa

Akcea licensed options on two drugs that were in phase I/IIa to Novartis in 2017 for a USD 75m upfront option payment and USD 150m in near-term payments, plus a USD 100m equity investment in Ionis, the majority owner of Akcea, and an additional USD 50m after 18 months. Ionis and Akcea are also eligible to receive up to USD 600m and USD 530m in milestone payments for AKCEA-APO(a)-LRx and AKCEA-APOCIII-LRx, respectively.

Afterward, Novartis paid USD 150m in 2019 to license antisense oligonucleotide AKCEA-APO(a)-LRx TQJ230. This inhibits the production of apolipoprotein(a), which reduces Lp(a). The deal includes tiered royalties in the mid-teens to low twenty percent range on net sales of

each drug, plus an outstanding option to license the APOC3 candidate. We only include the first program in our table.

Arrowhead and Amgen, 2016 – preclinical

Arrowhead licensed the RNA interference (RNAi) cardiovascular disease program to Amgen Inc. in 2016. Arrowhead receives USD 35m upfront, an equity investment of USD 21.5m, up to USD 617m in option payments and milestone payments, plus low double-digit sales royalties for the ARC-LPA project and single-digit royalties for an undisclosed program. The RNAi molecules are designed to reduce elevated lipoprotein(a) levels.

Other

Ionis Pharmaceuticals acquired around one-quarter of its daughter company, Akcea, in 2020, corresponding to a market valuation of around USD 2bn, although Akcea also had a large cash position.

Dicerna's deal with Novo Nordisk let to the latter acquiring Dicerna in November 2021 for a total equity value of USD 3.3bn. Novo Nordisk thus gains control of Dicerna's proprietary GalXC™ RNAi platform technology, which targets cardiometabolic diseases.

Gene Therapy Reference Deals

We use the average of the total milestones from the deals listed here when valuing P2. We assume that a licensing deal is made after phase I, with a subsequent higher upfront payment of USD 25m.

Gene therapy reference deals

Company	Partner	Project	Phase	Date	Royalty	Upfront	Milestones
Combigene	Sparks	GC01	Preclinical	Dec-21	~10	8.5	320
Hansa	Sarepta	imflidase	Preclinical	Jul-20	13-16	10	397.5
Average						9	359
Median						9	359

Source: Redeye Research

Combigene and Sparks Therapeutics, 2021 – preclinical

Combigene licensed the gene therapy GC01 against focal epilepsy to Sparks Therapeutics globally in 2021. The project is in a preclinical stage. Combigene received USD 8.5m in an upfront payment with an additional USD 320m in milestones, of which USD 50m are regulatory. Commercial tiered royalties up to low double-digit percentages also apply.

Hansa and Sarepta Therapeutics, 2020

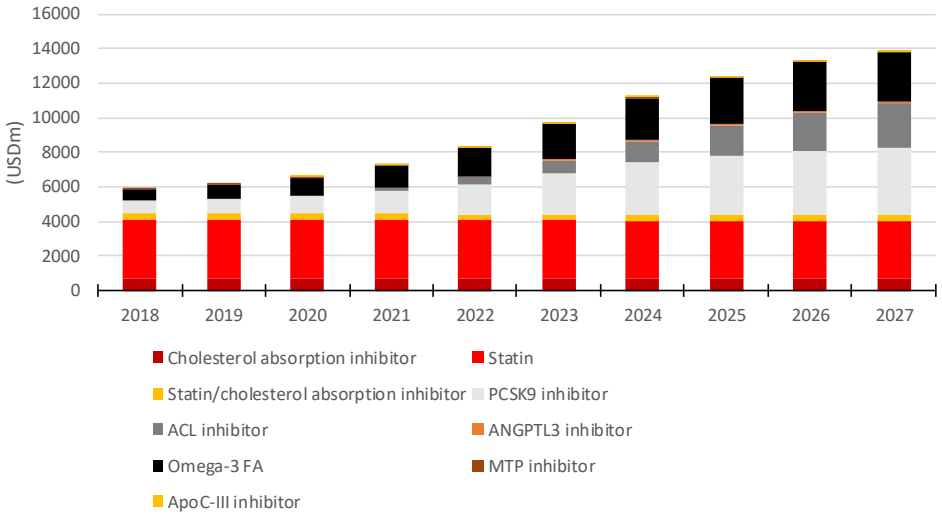
Hansa licensed the enzyme-drug imflidase as a pre-treatment for gene therapy. Hansa will receive up to USD 397.5m in total payments and USD 10m in an upfront payment, as well as royalties on sales in the high single digits to mid-teens.

Market Overview

According to Datamonitor Healthcare, there were approximately 1.5 billion prevalent cases of dyslipidemia in adults aged 20 years and older worldwide as of 2021, and it expects this to increase to 1.7 billion by 2027. The market today is dominated by generic statins, accounting for sales of more than USD 3bn on the seven major markets. PCSK9 inhibitors, omega-3 FA, and ACL inhibitors are seeing sales increase and are expected to reach annual sales of USD 4bn, USD 2.8bn and USD 2.5bn, respectively, by 2027.

PCSK9 inhibitors, which are long-acting injectables, are typically used as an add-on to statins, for high-risk groups or statin-intolerant patients. Omega-3 fatty acids are dietary supplements that have been shown to reduce triglyceride levels. ACL inhibitors reduce LDL cholesterol by inhibiting liver cholesterol synthesis. Fibrates are commonly used to treat very high lipid levels, although they are less commonly used than statins. As they are sold as generics, and in moderate numbers compared to statins, the market value for fibrates is more limited.

Dyslipidemia: Sales (7MM)



Source: Datamonitor Heathcare

Interestingly, Datamonitor forecasts limited sales on drugs targeting ANGPTL3 (evinacumab for homozygous familial hypercholesterolemia) and ApoC-III (volanesorsen for familial chylomicronemia syndrome in the EU): USD 114m for ANGPTL3 and USD 56m for ApoC-33 by 2027. This is because they are approved in ultra-rare orphan indications and are not expected to achieve large market penetration. Datamonitor does not assume that they will be used in other indications at this point in time.

Although the general mass market is comparatively well served, there is a need for well-tolerated drugs that reduce abnormally high lipid levels (TG>500mg/dL), around five million patients in the 7MM), as current drugs are not always effective enough. This is particularly the case for severe multifactorial chylomicronemia syndrome (TG>1000mg/dL). There is potentially also room for new drugs for hypertriglyceridemia (TG >150 mg/dL) that can reduce the risk for cardiovascular diseases, which is a large mass market (~135 million in the 7MM). However, this is more highly contested space and safety will be even more important here. As an illustration, Lipitor (a statin) became the world's best-selling drug, with total sales of USD 125bn between 1996 and 2012. Generic statins should continue to dominate the CVD market for the foreseeable future. Future drugs will likely be add-ons or complements.

Financials

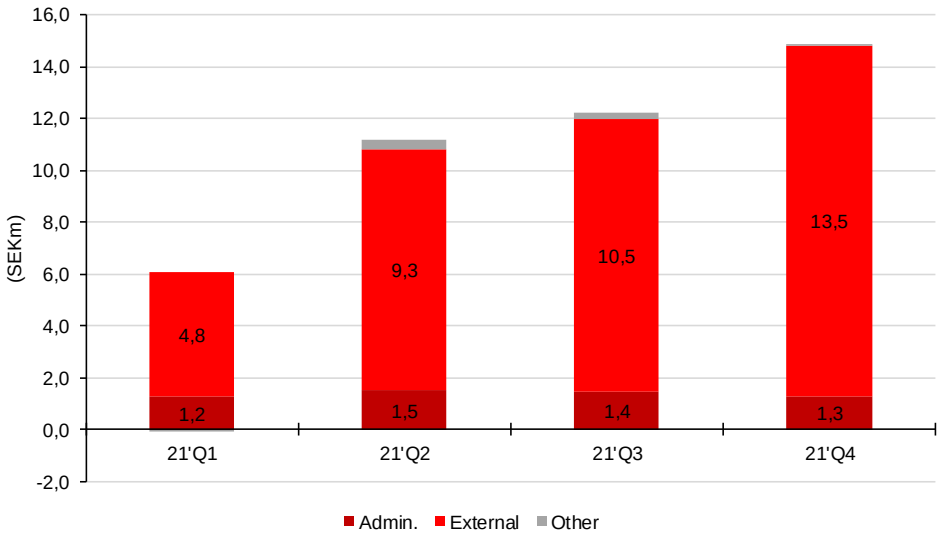
In early 2021, Lipigon raised SEK 51m after transaction costs. Lipigon's cash position was expected to last it roughly through 2022 and the SAD part of the phase I trial. The additional SEK 36m from the warrants TO1 will be required to finance Lipigon until the completion of the entire phase I trial in 2023. The money was intended to fund safety and toxicology for Lipisense (20 percent), substance for the P1 clinical trial (35 percent), the P1 clinical trial (20 percent), and other costs and projects (25 percent). However, TO1 is almost certainly going to expire out of the money as the last subscription date is April 30.

The main expense is for manufacture of material for the clinical trials (i.e., Lipisense), which should cost around SEK 30m, while the clinical trial itself (including both the SAD and MAD parts) was projected to cost SEK 17m.

A phase II trial would require additional financing. If we assume inclusion of 100 patients or slightly more, the cost of phase II would probably be in the range of SEK 50m or slightly more, including the manufacture of the clinical material.

Operating expenses for 2021 totaled SEK 44m. Cash flow during 2021 was SEK 15.6m. Removing the equity issue and related charges, cash flow in 2021 totalled around SEK -35m. Adjusting for working capital, cash flow was SEK 41m in 2021. Total income was SEK 3.2m.

Lipigon: Operating expenses



Source: Redeye Research

The company's cash position at the end of Q4 2021 was SEK 28m (although working capital is negative by almost SEK 6m). If costs remain at the same level as last year, this should last Lipigon into Q3 2022. If the company slows down spending, it could last somewhat longer. The company has low fixed costs, mainly consisting of annual administrative costs which should be around SEK 6m. However, we believe that the company will stick to its original plan and seek financing for the entire phase I trial so that it can start and be completed as scheduled. This could make Lipisense ready for phase II at the end of 2023.

Valuation

We use a sum-of-the-parts model to value Lipigon, including P1 and P2, together with cash and overhead (including future taxes). As the company lacks the funds to finance the phase I trial of Lipisense in a tough market environment, we use a comparatively high WACC of 20 percent. This is the sum of 15 percent based on Redeye's proprietary rating model and a 5 percent short term financial risk premium, which will be revised upon an improvement in financial position.

For our Base Case, we assume a licensing deal for Lipisense after a phase II trial in 2025 worth up to USD 825m, of which USD 35m up front, and a royalty rate of 15 percent; while 12 percent of all revenue has to be shared with Secarna.

Sum-of-the-parts valuation:

Project	Indication	Development stage	Peak sales (USDm)	Potential launch year	Market penetration	LOA	Risk adjusted NPV
Lipisense	SHTG	Phase I ready	820	2028	10%	9%	158
P2	Partial Lipodystrophy	Preclinical	90	2030	25%	7%	5
Subtotal projects							**163**
Overhead organization, incl. taxes							-77
Net cash							28
Total NPV							**115**
No. Shares (mil.)							*9.73*
Per share							**12**

Bear Case: SEK 3.6

We assume that Lipisense clears triglycerides by a significant but not great percentage and that the safety profile is good. This leads to us halving the peak sales estimate as well ass the milestones and upfront.

Base Case: SEK 12

We assume out-licensing of Lipisense after a phase II trial by Lipigon. We assume a likelihood of approval of 9 percent.

Bull Case: SEK 31

We assume that a significant lowering of triglycerides is demonstrated in phase I with an excellent safety profile. This leads to a licensing deal in 2023/24. We raise the likelihood of approval to 14 percent.

Catalysts

Lipisense: Readout of effect data from phase Ia SAD in Q4 2022

Safety data and a potential effect in the form of a reduction in patients' triglyceride levels from the phase Ia will be presented. As Lipisense is an antisense therapy with a half-life of around one month (i.e., it should continue blocking ANGPTL1 for an extended period), just one injection should, in theory, have the possibility to demonstrate a therapeutic effect.

IMPACT				
Downside		**Upside**		**Time Frame**
Significance	Likelihood	Significance	Likelihood	
Major	Possible	Major	Possible	Short

Lipisense: Readout of effect data from phase Ib MAD in H1 2023

We expect the multiple-dose ascending part to report in H1 2023. As multiple doses are used over a longer period, this part could have a better possibility of demonstrating a higher effect. It reflects real-world use of the therapy better than part 1a (SAD).

IMPACT				
Downside		**Upside**		**Time Frame**
Significance	Likelihood	Significance	Likelihood	
Major	Possible	Major	Possible	Mid

Appendix: Bibliography

Aryal et al. 2019	Aryal B, Price NL, Suarez Y, Fernández-Hernando C.; 'ANGPTL4 in Metabolic and Cardiovascular Disease'; *Trends Mol Med. 2019 Aug*; 25(8):723-734.
Goldberg & Chait 2020	Goldberg RB, Chait A.; 'A Comprehensive Update on the Chylomicronemia Syndrome'; *Front. Endocrinol (Lausanne). 2020 Oct 23*; 11:593931.
Richardson et al. 2020	Richardson TG, Leyden GM, Wang Q, Bell JA, Elsworth B, Davey Smith G, Holmes MV.; 'Characterising metabolomic signatures of lipid-modifying therapies through drug target mendelian randomisation'; *PLoS Biol.* 2022, 20(2).

Summary Redeye Rating

The rating consists of three valuation keys, each constituting an overall assessment of several factors that are rated on a scale of 0 to 1 points. The maximum score for a valuation key is 5 points.

Rating changes in the report

People: 3

The company has a small but focused management team, its main expertise being scientific. The board adds other important qualities, such as business development. The chairman has "done it before"; he was the founder of Cormorant Pharmaceuticals, which was sold to BMS in 2016 for USD 520m, of which USD 100m was an upfront payment.

Business: 3

Lipigon develops candidates for conditions with abnormal lipids. This includes large cardiovascular diseases groups and conditions related to unhealthy lifestyles, which is a growing global problem. The company is still at a pre-clinical stage. If it obtains clinical evidence for its products, a higher rating might be justified.

Financials: 1

The company is in an early clinical stage of development and would need additional funds before a potential exit.

	2020	2021E	2022E	2023E
INCOME STATEMENT				
Revenues	4	3	0	0
Cost of Revenues	0	0	0	0
Gross Profit	4	3	0	0
Operating Expenses	12	44	42	23
EBITDA	-8	-41	-42	-23
Depreciation & Amortization	0	0	0	0
EBIT	-8	-41	-42	-23
Net Financial Items	0	0	0	0
EBT	-8	-41	-42	-23
Income Tax Expenses	0	0	0	0
Non-Controlling Interest	0	0	0	0
Net Income	-8	-41	-42	-23
BALANCE SHEET				
Assets				
Current assets				
Cash & Equivalents	13	28	14	0
Inventories	0	0	0	0
Accounts Receivable	1	0	0	0
Other Current Assets	2	0	0	0
Total Current Assets	15	29	14	0
Non-current assets				
Property, Plant & Equipment, Net	0	0	0	0
Goodwill	0	0	0	0
Intangible Assets	0	0	0	0
Right-of-Use Assets	0	0	0	0
Shares in Associates	0	0	0	0
Other Long-Term Assets	0	0	0	0
Total Non-Current Assets	0	0	0	0
Total Assets	15	29	14	0
Liabilities				
Current liabilities				
Short-Term Debt	0	0	0	8
Short-Term Lease Liabilities	0	0	0	0
Accounts Payable	1	5	0	0
Other Current Liabilities	1	1	0	0
Total Current Liabilities	2	6	0	8
Non-current liabilities				
Long-Term Debt	0	0	0	0
Long-Term Lease Liabilities	0	0	0	0
Other Long-Term Liabilities	0	0	0	0
Total Non-current Liabilities	0	0	0	0
Non-Controlling Interest	0	0	0	0
Shareholder's Equity	13	23	15	-8
Total Liabilities & Equity	15	29	15	0
CASH FLOW				
NOPAT	-8	-41	-42	-23
Change in Working Capital	0	6	-6	0
Operating Cash Flow	-9	-35	-48	-23
Capital Expenditures	0	0	0	0
Investment in Intangible Assets	0	0	0	0
Investing Cash Flow	1	0	0	0
Financing Cash Flow	0	51	34	8
Free Cash Flow	-9	-35	-48	-23

	2020	2021E	2022E	2023E
CAPITAL STRUCTURE				
Equity Ratio	0,9	0,8	1,0	NA
Debt to equity	0,0	0,0	0,0	-1,1
Net Debt	-13	-28	-14	8
Capital Employed	13	22	14	-8
Working Capital Turnover	9,9	-0,5	NA	NA
GROWTH				
Revenue Growth	146%	-26%	-100%	NA
Basic EPS Growth	NA	NA	NA	NA
Adjusted Basic EPS Growth	NA	NA	NA	NA
PROFITABILITY				
ROE	-123%	-229%	-223%	-666%
ROCE	-60%	-183%	-293%	270%
ROIC	-3594%	1482%	1411%	NA
EBITDA Margin (%)	-181%	-1295%	NA	NA
EBIT Margin (%)	-181%	-1295%	NA	NA
Net Income Margin (%)	-187%	-1293%	NA	NA
VALUATION				
Basic EPS	NA	NA	NA	NA
Adjusted Basic EPS	NA	NA	NA	NA
P/E	NA	NA	NA	NA
EV/Revenue	2,2	10,9	NA	NA
EV/EBITDA	NA	NA	NA	NA
EV/EBIT	NA	NA	NA	NA
P/B	1,7	2,8	3,0	NA

SHAREHOLDER STRUCTURE	**CAPITAL %**	**VOTES %**
Nordnet Pensionsförsäkring	15,6%	15,6%
Fort Knox Förvaring AB	7,8%	7,8%
Nordea Liv & Pension	6,4%	6,4%
Stefan K. Nilsson	6,4%	6,4%
Partnerinvest Övre Norrland AB	5,7%	5,7%

SHARE INFORMATION	
Reuters code	LPGO
List	First North
Share price	4,6
Total shares, million	9,7329

MANAGEMENT & BOARD	
CEO	Stefan K. Nilsson
CFO	Michael Owens
Chairman	Urban Paulsson

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Redeye Rating and Background Definitions

Company Quality

Company Quality is based on a set of quality checks across three categories; PEOPLE, BUSINESS, FINANCE. These are the building blocks that enable a company to deliver sustained operational outperformance and attractive long-term earnings growth.

Each category is grouped into multiple sub-categories assessed by five checks. These are based on widely accepted and tested investment criteria and used by demonstrably successful investors and investment firms. Each sub-category may also include a complementary check that provides additional information to assist with investment decision-making.

If a check is successful, it is assigned a score of one point; the total successful checks are added to give a score for each sub-category. The overall score for a category is the average of all sub-category scores, based on a scale that ranges from 0 to 5 rounded up to the nearest whole number. The overall score for each category is then used to generate the size of the bar in the Company Quality graphic.

People

At the end of the day, people drive profits. Not numbers. Understanding the motivations of people behind a business is a significant part of understanding the long-term drive of the company. It all comes down to doing business with people you trust, or at least avoiding dealing with people of questionable character.

The People rating is based on quantitative scores in seven categories:

- Passion, Execution, Capital Allocation, Communication, Compensation, Ownership, and Board.

Business

If you don't understand the competitive environment and don't have a clear sense of how the business will engage customers, create value and consistently deliver that value at a profit, you won't succeed as an investor. Knowing the business model inside out will provide you some level of certainty and reduce the risk when you buy a stock.

The Business rating is based on quantitative scores grouped into five sub-categories:

- Business Scalability, Market Structure, Value Proposition, Economic Moat, and Operational Risks.

Financials

Investing is part art, part science. Financial ratios make up most of the science. Ratios are used to evaluate the financial soundness of a business. Also, these ratios are key factors that will impact a company's financial performance and valuation. However, you only need a few to determine whether a company is financially strong or weak.

The Financial rating is based on quantitative scores that are grouped into five separate categories:

- Earnings Power, Profit Margin, Growth Rate, Financial Health, and Earnings Quality.

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Redeye Rating (2022-03-15)

Rating	People	Business	Financials
5	32	15	4
3-4	149	131	46
0-2	5	40	136
total	186	186	186

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Richard Ramanius owns shares in the company : No
Johan Unnerus owns shares in the company : No
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