EQUITY RESEARCH
Research report prepared by DNB Markets, a division of DNB Bank ASA
Health Care
Initiating coverage
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11 March 2021

ESG insight

ARCTIC BIOSCIENCE

The alpha to omega-3 of psoriasis

Arctic Bioscience is a Norwegian bioscience company developing a herring roe extract-based drug to treat mild to moderate psoriasis. The drug candidate has a unique oral formulation that addresses unmet medical needs; it is in Phase II and two more trials are needed before approval. We initiate coverage with a BUY and NOK60 target price.

Transforming into a pharmaceutical company. Arctic Bioscience has its roots in the manufacturing and marketing of herring roe-based omega-3 supplements, and its Food Supplement operation has partnerships to sell its products in most major markets, including the US and China. However, more interesting to us is its Pharmaceutical operation, which is developing a herring roe oil based drug – HRO350 – to treat mild to moderate psoriasis. The company recently announced positive pilot clinical trial results for HRO, and the results of the open-label extension trial (published in Q1 2021) make this drug candidate even more promising. Arctic Bioscience plans to conduct at least one more trial before considering out-licensing HRO350. We assume commercialisation starts in 2027.

HRO350 uses a by-product from herring fillet production. Immature herring roe is a by-product in the fishing industry, and Arctic Bioscience has developed a way to extract high levels of phospholipid bound omega-3 fatty acids from it. Sourcing and manufacturing is done locally in a facility that is being expanded over the coming years.

Addressing unmet medical needs in mild to moderate psoriasis. There is a growing need for a safe and effective oral treatment for mild and moderate psoriasis. Current treatments are mostly topical (can be greasy and difficult to apply), with an unfavourable long-term safety profile. Few companies seem to be developing oral alternatives, so HRO350 has the potential to carve out a niche and give psoriasis patients a better treatment alternative.

Good efficacy in pilot clinical trial and mild safety profile. Based on the recent pilot clinical trial results and open-label extension study, HRO350 has a good treatment effect (albeit with a slower onset of action than others). Moreover, its side-effect profile is milder than the alternatives and its oral administration is a positive, but we believe simplifying the dosage regimen would improve compliance.

Initiating coverage with a BUY and NOK60 target price. If HRO350 gets approved in late 2026 as we expect, revenues should grow until at least 2036. Our base case for commercialisation involves the company out-licensing the drug and receiving royalties and milestones. We believe the most likely category for significant penetration is moderate psoriasis. The market is large, with c4m–5m patients in the moderate segment of the psoriasis market alone in the US, EU5 and Scandinavia.

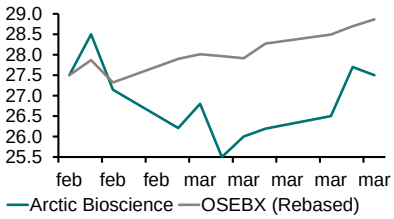
Year-end Dec	2017	2018	2019	2020	2021e	2022e	2023e
Revenue (NOKm)	18	25	30	20	35	45	55
EBITDA adj (NOKm)	-1	-1	-2	-20	-23	-58	-49
EBIT adj (NOKm)	-1	-1	-3	-22	-27	-65	-60
PTP (NOKm)	-2	-2	-4	-23	-28	-66	-61
EPS rep (NOK)	-0.12	-0.12	-0.27	-1.55	-1.08	-2.56	-2.35
DPS (NOK)	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Revenue growth (%)	57.3	35.3	20.9	-31.8	70.8	28.6	22.2
EV/Sales adj (x)					13.56	13.65	10.46
Dividend yield (%)	nm	nm	nm	nm	0.0	0.0	0.0
FCF yield (%)	nm	nm	nm	nm	-12.0	-18.4	-8.6

Source: Company (historical figures), DNB Markets (estimates)

BUY

TP: NOK60.0

ABS versus OSEBX (12m)



Source: Factset

SUMMARY

Recommendation (prev.)	BUY ()
Share price (NOK)	27.5
Target price (previous) (NOK)	60.0 (N/A)
Upside/downside potential (%)	118
Tickers	ABS NO

CAPITAL STRUCTURE

No. of shares (m)	27.0
No. of shares fully dil. (m)	27.0
Market cap. (NOKm)	742
NIBD adj end-2021e (NOKm)	-233
Enterprise value adj (NOKm)	509
Net debt/EBITDA adj (x)	10.27
Free float (%)	100

Source: Company, DNB Markets (estimates)

Note: Unless otherwise stated, the share prices in this note are the last closing price.

NEXT EVENT

H1 report 2021	26/08/2021

DNB Markets acted as Joint Global Co-ordinator in the recent private placement in Arctic Bioscience and subsequent listing on Euronext Growth Oslo

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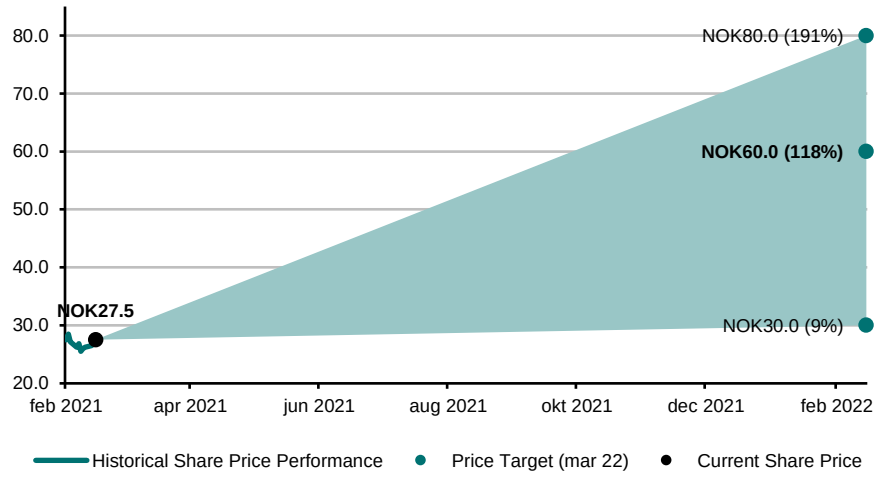
Investment case overview

Share price performance, DNB Markets' target price, bear- and bull-case scenarios



Source: FactSet, DNB Markets

Target price methodology

- We mainly use a DCF model with probability weighted scenario analysis to calculate our target price.
- Our bull-case fair value is based on a higher LOA than in our base case (50%) and a higher realised price for the drug (USD7,500 per patient per year).
- Our bear-case fair value is based on a lower LOA than in our base case (20%) and a lower realised price for the drug (USD3,000 per patient per year).

Source: DNB Markets

Downside risks to our investment case

- If the Phase IIb or Phase III trials fail due to poor efficacy or safety, it could lead to the discontinuation of its only development project.
- Delayed launch of the next clinical trial due to Covid-19 or other factors and slower than expected market penetration.
- Failing to gain and protect as large a market share as we assume.

Source: DNB Markets

DNB Markets investment case and how we differ from consensus

- There is no consensus on Arctic Bioscience yet.

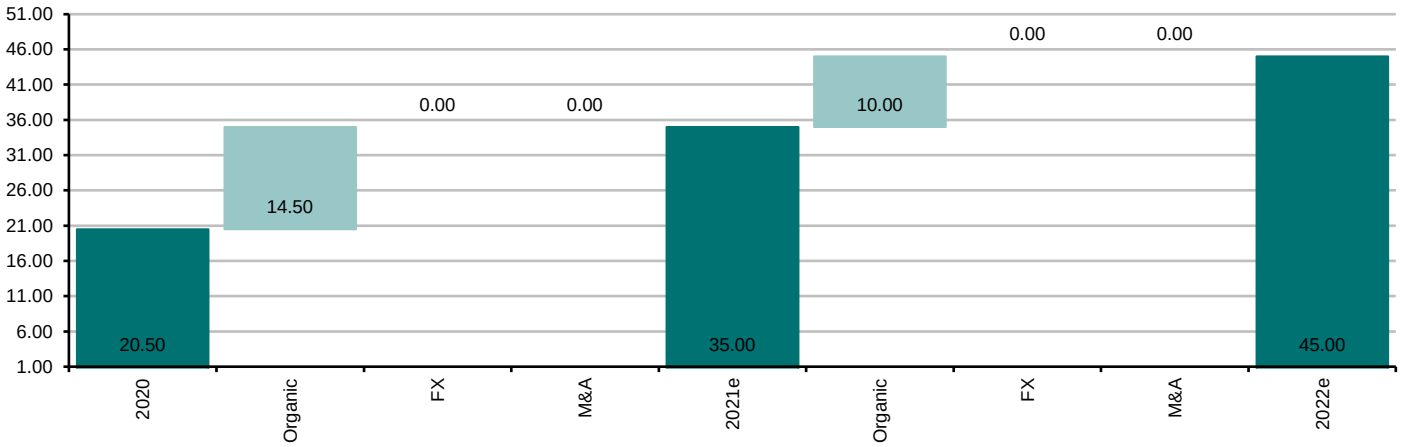
Source: DNB Markets

Upside risks to our investment case

- Better than expected results (mainly on efficacy) in upcoming trials would increase confidence in its drug candidate.
- Entering more markets than we include in our valuation, e.g. China where it already has a partner selling its omega-3 supplements.
- Tapping into the pool of diagnosed but untreated patients, which would likely give a significant revenue boost.

Source: DNB Markets

Sales bridge 2020–2022e (NOKm)



Source: DNB Markets (forecasts), company (historical data)

ESG overview

Sustainability assessment

	Positive	Negative
Conclusions	■ Arctic Bioscience is developing an innovative psoriasis drug to address an unmet medical need. ■ It uses naturally occurring compounds to improve patients' health and contribute to the population's sufficient nutrition. ■ Its raw material, immature herring roe, is a residual product of the fish industry and sourced from sustainable fisheries.	■ The outcome of drug development is highly uncertain, as the drug candidate's attributes along with economic and other considerations can affect development. Thus, some drug candidates never reach the market. ■ Drugs inevitably have side effects that can hurt patients' health and quality of life.
Actions being taken by company	■ The company's operations are in alignment with UN Sustainability Development Goals number 3, 9, 12 and 14. It works towards improved nutrition and health, is engaged in innovation, is committed to responsible consumption and production, and aims to preserve life below water. ■ It is committed to operating sustainably.	■ The company sponsored animal studies and conducts clinical trials in humans. ■ Some components that cannot be recycled during the herring roe extraction go to waste waters and can burden the environment.
Key ESG drivers		
Short-term	■ The pharmaceutical industry has strict regulations to ensure the safety of patients and clinical trial participants. ■ The company is developing an oral psoriasis drug to address an unmet medical need and to improve patients' health and quality of life.	■ A treatment-related adverse event in a clinical trial. ■ Clinical drug development is a time and resource consuming activity with an uncertain outcome. ■ The company's entry to the pharmaceutical market depends on the success of a single drug candidate.
Long-term	■ Arctic Bioscience's raw material is immature herring roe, a highly underutilised source of omega-3 fatty acids available in large quantities. ■ Omega-3 fatty acids have several benefits to human health, yet the majority of the global population consumes less than is recommended.	■ Climate change can increase water temperature and adversely affect herring populations, particularly spawning rates.

Source: DNB Markets

Sustainability assessment

	Risk	Company's risk mitigation
Transition risks		
Policy and legal	■ Drug development and manufacturing is highly regulated; processes and product attributes have to be accurately monitored to comply with laws and regulations.	■ Communication with authorities and other stakeholders to comply with legislation.
Technology	■ Its development/manufacturing processes and product quality must be documented.	■ The company has dedicated personnel for quality assurance and regulatory affairs. Its nutritional supplements have minimal levels of environmental contaminants in compliance with the Global Organization for EPA and DHA Omega-3 (GOED) voluntary monograph.
Market	■ Arctic Bioscience's expansion into the pharmaceutical market depends on the uncertain outcome of its current drug development process.	■ Management has extensive experience in drug development. Furthermore, it has established partnerships to support the development process.
	■ The shipping of products to international markets could have negative environmental effects.	■ Arctic Bioscience has a short supply chain and conducts most of its operations locally to minimise the harmful effects of shipping.
Reputation	■ Scientific evidence about the effects of omega-3 fatty acids is inconclusive in some areas. Negative scientific results and waning public perception of omega-3 health benefits could affect sales.	■ It is actively engaged in R&D to explore the effects of omega-3 fatty acids. More than 2,400 randomised clinical trials have been conducted about the effects of omega-3 fatty acids.
Physical risk		
Acute	■ The R&D of new drugs is inherently risky. Development takes many years and requires substantial financial commitment. Projects can be discontinued at any point if a drug candidate does not have sufficient efficacy, or if it causes adverse effects that outweigh the potential benefits of the therapy.	■ The company collaborates with several partners and stakeholders and actively seeks new connections to support its drug development efforts.
Chronic	■ Psoriasis therapies and omega-3 nutritional supplements are competitive markets with several companies. The emergence of better drugs and nutritional supplements is a constant risk. Future products could be superior in safety, efficacy and dosing among other factors.	■ The company aims to constantly improve and develop to prepare for future challenges. Management is experienced in the pharmaceutical and nutraceutical industries with a good grasp of industry-wide trends.

Source: DNB Markets

Sustainability assessment

	Opportunities	Company's utilisation of opportunity
Resource efficiency	■ Effective utilisation and recycling of materials in its manufacturing and raw materials sourcing.	■ The company's main raw material is herring roe, a residual product of local fisheries. ■ It is recycling a substantial part of the solvent used to extract omega-3 fatty acids from the herring roe.
Products/Services	■ Utilisation of every output of the manufacturing process.	■ Besides the lipid extract, its manufacturing process yields marine protein, which is sold as a separate product.
New markets	■ Apart from the EU and US, Arctic Bioscience could also target emerging markets with its psoriasis drug and its nutritional supplements. ■ Development of omega-3 based drugs for other conditions with a similar pathomechanism to psoriasis.	■ The company has distribution partners in the EU and the US and is also present in China and Malaysia with their nutritional supplements. These connections and knowledge could support the commercialisation of its drug in other markets. ■ Further projects in its pipeline related to autoimmune diseases.
Supply chain resilience	■ Support of sustainable fishing and local resources.	■ Herring roe is harvested by fisheries certified by the Marine Stewardship Council (MSC). Arctic Bioscience has a short supply chain with local manufacturing.

Source: DNB Markets

Contents

Investment case

Looking at the whole Arctic Bioscience picture, we like what we see: an innovative company developing a promising drug asset. The company address a fairly large, growing patient population with large unmet medical needs. It is still a relatively early-stage company but the development path for its lead asset – HRO350 – is straight-forward we believe.

Fairly large and growing market

Addressing a large market in terms of money and patients

Between 100m and 120m people suffer from psoriasis globally – and the figure is rising. The psoriasis market aims to improve the quality of life of patients and is worth cUSD14bn, with an estimated CAGR of 4.7% in the next couple of years – to USD20bn+ by 2030 according to GlobalData. Mild and moderate cases make up the majority of patients and this is the group Arctic Bioscience is targeting, thereby addressing a large market in monetary terms and patient numbers.

Addressing multiple unmet needs

Oral treatment options needed for mild to moderate psoriasis

The treatment landscape for mild and moderate psoriasis patients has been largely unchanged for many years, so patients only have limited treatment options. According to key opinion leaders, there is a need for new treatments. Most options for mild and moderate psoriasis patients are topical. Although they are quite effective, they can be difficult or messy to apply, so adherence is generally low. Based on this, there is a need for safe and effective oral treatments. Additionally, more safe options are needed for pregnant women, as there is only one drug they can take. In our view Arctic Bioscience is well positioned to address these needs.

Carving out a niche among psoriasis drugs

Few oral projects under development for mild/moderate psoriasis

Despite the unmet needs there are surprisingly few projects in the industry's pipeline to address them. The bulk of the development takes place in biologics that address moderate and severe patients. Most of the oral treatments being developed also target moderate and severe patients, while emerging drugs for mild patients are mostly topical. We found only two corporate projects targeting mild to moderate patients with an oral formulation – and both failed their trials.

Mechanism of action with strong scientific rationale

Anti-inflammatory and immune modulation the likely mechanism of action for HRO350

The link between inflammation and omega-3 fatty acids has been described in numerous scientific publications. Metabolites of omega-3 fatty acids can dampen inflammation by changing the ratio of n-6:n-3 metabolites. They are connected to the production of prostaglandins and leukotrienes, which are key mediators of inflammation. Furthermore, the beneficial effects of omega-3 fatty acids have been well documented.

Successful pilot clinical study

Strong data from its pilot clinical trial – will have to be confirmed in Phase IIb and Phase III trials

Arctic Bioscience published positive pilot clinical trial results in May 2020, meeting the primary endpoint in a randomised, double-blind, placebo-controlled study. The difference between herring roe oil (HRO) and placebo was statistically significant (p=0.045). HRO showed adequate efficacy with a mild safety profile. In the open-label extension study, HRO showed good efficacy results with clinically meaningful improvement. Thus, a lot depends on the upcoming Phase IIb and Phase III trials. Strong results would strengthen our confidence in HRO350.

Drug candidate with additional benefits

Additional potential benefits from HRO350 could strengthen its position over time

Oral administration is obviously more convenient than other routes of administration. This increases adherence, which we believe could be substantially higher than with topical treatments. Also, omega-3 fatty acids have potential benefits on psoriasis comorbidities such as cardiovascular disease, which can result in a more holistic therapy. However, we do not believe the company will look at this in the upcoming trials – this will most likely come at a later stage but we see this as longer-term upside potential as patients with psoriasis have an above-average rate of CV morbidities for example.

Experienced management team

Management has relevant experience

Management has decades of diverse experience of pharmaceuticals and nutritional supplements. Many of them have worked together for years, and several held executive positions at key companies of the omega-3 industry that are now Arctic Bioscience's

competitors. Consequently, they know their competition very well. They are aware of the challenges ahead of them and working on ways to address them.

Herring roe is an underutilised by-product of the fish industry

Herring roe a waste product in the fishing industry – can increase the sourcing if needed

Its raw material is herring roe, an underutilised residual product of the fish industry. It is available in big quantities. Arctic Bioscience sources it from local suppliers, giving a short, local value chain. It uses every output of its patented extraction process. The company has access to c50% of all herring roe in Norway (through contracts), but could easily increase the sourcing if needed.

Nutritional supplement business has synergies with drug development

Nutritional operations have some synergies with the drug development operation

The company started as a nutritional supplement business and is still developing this operation. However, we believe that from an investment perspective the development in the Pharmaceutical operation is more interesting long-term. That said, there are some synergies between the two when it comes to development, processing, and manufacturing. Additionally, its Food Supplement operation should give it a growing revenue stream that could – to some extent at least – support the drug development. Most early-stage companies have no revenue and are entirely dependent on external funding. Although this revenue is a fraction of what is needed to take its drug candidate to the market, it is more than many others have.

Fatty profits on the horizon – key assumptions in the valuation

Out-licensing strategy after phase IIb most likely – although we would prefer pragmatism

We believe the most reasonable route to market for Arctic Bioscience is to out-license HRO350 to a global pharmaceutical partner that takes the product to market in return for milestones and royalties on sales. The company has said it plans to out-license HRO350 after phase IIb, and this is our base-case. That said, we would prefer pragmatism about the route to market in terms of considering driving the development even further before out-licensing. This could be a very attractive option given the phase III trial is planned to be smaller than the phase IIb (as it would include only one dose of HRO350 compared to placebo while the phase IIb trial contains two doses of HRO350 versus placebo).

Key assumptions on timelines, pricing and penetration

In our valuation we have assumed the drug candidate produces data in line with what has been seen in the pilot clinical trial and is out-licensed to a partner. In return the company receives up-front payments and milestones totalling cUSD250m and a 20% royalty on end-user sales. We have factored in use only in the moderate psoriasis population in the US, the five largest EU countries, and Scandinavia. We have priced the drug in line with treatment alternatives for mild/moderate psoriasis. Our price assumption per patient per year is cUSD6,500 for the US and cUSD3,400 for Europe. Overall, we assume patients will have average compliance of c75%. With the development plan presented by the company we believe the drug could reach the market in 2027 and hence generate first sales that year. We assume penetration in the moderate patient group of c5% in the US, c7.5% in Europe, and c12% in Scandinavia.

Initiating coverage with a BUY and NOK60 target price

We initiate coverage with a BUY and NOK60 target price

We consider Arctic Bioscience an attractive investment opportunity based on our valuation and the lack of oral treatment alternatives for the mild to moderate patient population. We initiate coverage with a BUY and NOK60 target price.

Company overview

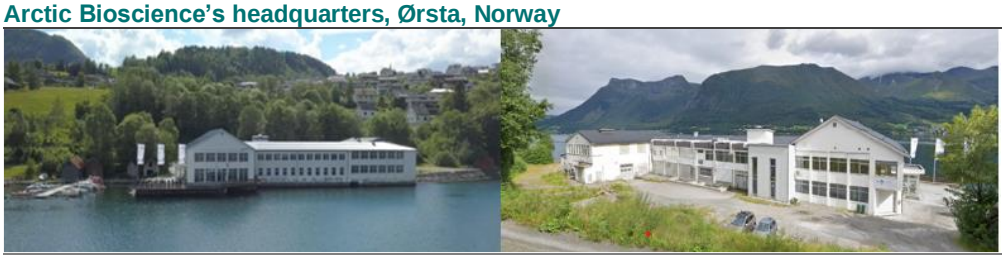
Arctic Bioscience is at the intersection of two themes: psoriasis and omega-3 fatty acids.

Business summary

Arctic Bioscience is a Norwegian biotechnology company focused on herring roe extracts. It is headquartered in Ørsta (west coast of Norway) and has an office in the Aleap incubator (in the Oslo Science Park[1]).

Norwegian biotechnology company focused on herring roe extracts

Arctic Bioscience's headquarters, Ørsta, Norway



Source: Company and Google Maps

Initially, it used roe extracts to produce nutritional supplements, but in recent years it started to develop a herring roe-based drug to treat mild and moderate psoriasis. It met the primary endpoint in its clinical pilot trial that was published in May 2020 and is now preparing a larger Phase IIb trial to establish the final dose used in the treatment and plans to follow-up with a large registration-based Phase III study to establish the safety and efficacy of its drug. Its goal is to get its product approved by 2026–2027. In H1 2020 several new people joined the company, in preparation for future challenges including R&D, regulatory affairs (outsourced to its CRO), and commercialisation.

Developing a herring roe-based drug to treat mild and moderate psoriasis

Besides this, we note the company's favourable ESG profile and synergies between the nutritional and pharmaceutical businesses that strengthen its position. It has numerous channels and partners to sell its nutritional product in the EU and the US. When it comes to its drug candidate, it has stated its plan to use a partnering strategy and out-license the product after phase IIb. Overall, it seems well positioned to face the next high-stake challenge, its Phase IIb clinical trial.

Favourable ESG profile and notable synergies between the two businesses

History

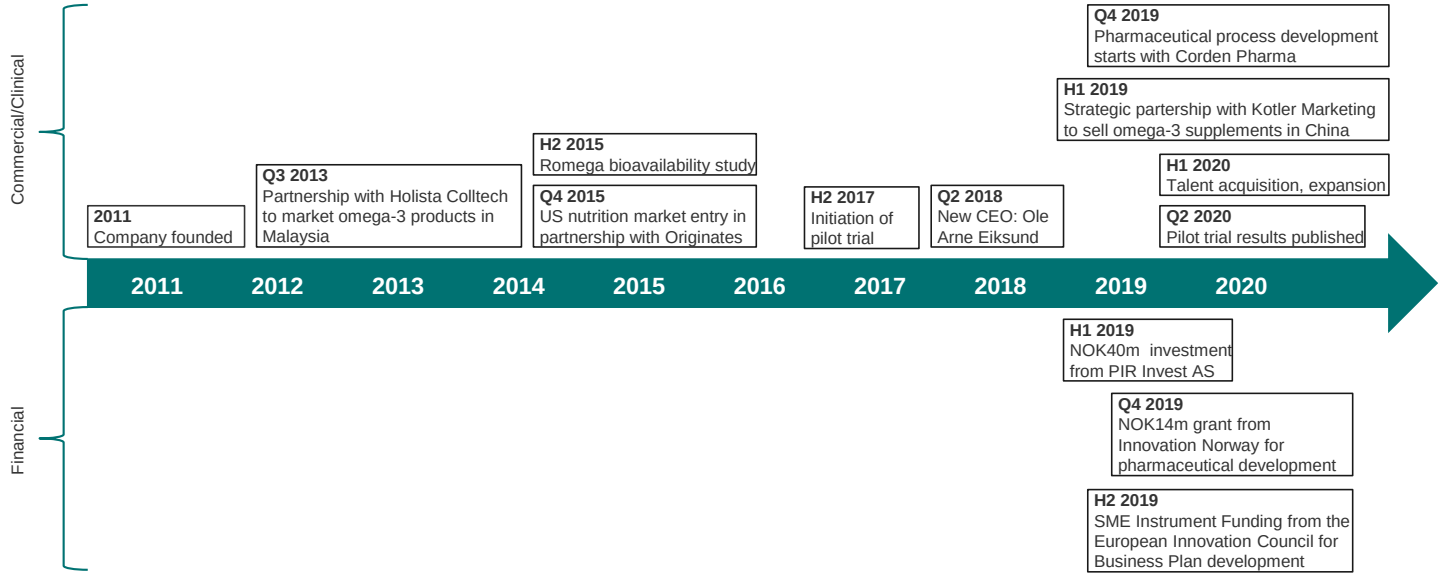
The company was founded in 2011 by Hogne Hallaråker (current CSO) based on his findings on the benefits of herring roe extract on halibut breeding. The company started to produce omega-3 supplements with high phospholipid (PL) content. In late 2013, it partnered with Holista Colltech to market its products in Malaysia. It entered the US dietary supplements market in 2015 by forming a partnership with Originates for US distribution. In 2015–2016 it patented its extraction process and composition of its extracts. Following patients' anecdotes about the therapeutic effects of the supplement, it started to develop a herring roe-based product to treat mild and moderate psoriasis. Arctic Bioscience sponsored several trials to explore its bioavailability and other features. It started a clinical pilot trial in 2017.

In 2018 the company announced its plan to carry out a Phase IIb trial with c400–500 patients. In April 2018, Ole Arne Eiksund became CEO. In 2018, the company joined the Norwegian Association of Pharmaceutical Manufacturers (LMI). 2019 was similarly eventful, with the company receiving a NOK40m investment from PIR Invest AS and a NOK14m grant for pharmaceutical development from Innovation Norway. Also, it formed two new alliances: a strategic partnership with Kotler Marketing to sell omega-3 supplements to pregnant women in China and a partnership with CordenPharma to facilitate pharmaceutical process development. 2020 saw more new hires – in preparation for future challenges – that strengthened the company in R&D, production and marketing. May 2020 saw the results of the clinical trial, laying the foundations for the upcoming Phase IIb trial[2]. It is clear from the

[1] https://www.aleap.no/ourmembers
[2] Company

timeline that things are accelerating for Arctic Bioscience and many more developments are expected to come during the next couple of years.

Arctic Bioscience's history



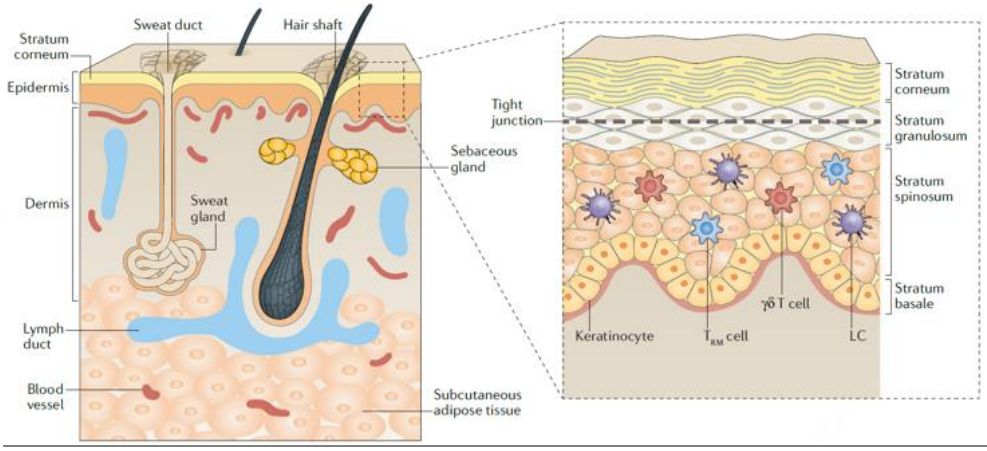
Source: Company

Disease state fundamentals

Anatomy of the skin

The skin is the first line of defence that separates us from the environment and protects us from various physical, chemical and biological damage. It consists of three layers that form a strong physical barrier and hosts a variety of immune cells waiting to combat external threats[3].

Structure of the skin



Source: Kabashima K et al. Nature Reviews Immunology. 2019 Jan;19(1):19–30

The first layer of the skin is the epidermis. The outermost layer of it is called Stratum corneum and consists mainly of corneocytes. They start life as keratinocytes in the basal layer of the epidermis (Stratum basale). This is the bottom layer of the epidermis that proliferates constantly, producing keratinocytes that undergo a differentiation process. Keratinocytes migrate towards the Stratum corneum and can become spinous keratinocytes creating Stratum spinosum or granular keratinocytes forming the Stratum granulosum, where tight junctions between cells provide an effective barrier against outside agents. As these cells mature, proliferation from Stratum basale pushes them towards the surface of the skin, where they eventually lose their nucleus, flatten, and acquire a special cross-linked protein membrane called cornified envelop. At this point keratinocytes become corneocytes, forming the 10–30µm thick Stratum corneum. The intercellular space is filled with lipids creating a hydrophobic barrier[4].

Apart from being a physical barrier, the epidermis also supports the immune system. Keratinocytes are important parts of the innate immune system. They can express various receptors and release antimicrobial peptides such as psoriasin, calregulin and lipocalin 2. They constantly produce CCL27, a chemokine that attracts CCR10+ T cells to the skin for immune surveillance. When triggered by inflammation, they release cytokines like tumour necrosis factor (TNF), IL-33 and other interleukins to activate and recruit further immune cells. Additionally, special antigen-presenting-cells (APC), Langerhans cells (LCs) can be found between keratinocytes. Once activated, they carry antigens to lymph nodes and present them to T cells (mainly Th2 and Th22) to activate them[5]. Apart from LCs, certain types of T cells also reside in the epidermis. The skin also contains cutaneous lymphocyte antigen (CLA)+ T cells, called resident memory T cells (Trm) that mediate protective immune processes [6].

A second layer is the dermis, which is mainly collagenous collective tissue. It is richly interwoven with a network of blood vessels, lymph vessels and neurons. Recruited immune cells exit the blood vessels and migrate through the extracellular matrix to the venue of inflammation. Several types of immune cells can be found here also in steady state including dermal dendritic cells (DCs), mast cells, macrophages, monocytes, neutrophils and T cells.

[3] Kabashima K et al. Nature Reviews Immunology. 2019 Jan;19(1):19–30.
[4] Kabashima K et al. Nature Reviews Immunology. 2019 Jan;19(1):19–30.
[5] Lowes MA et al. Annu Rev Immunol. 2014;32:227–55.
[6] Gebhardt, T. et al. Nat. Immunol 2009. Mar. 22. 10, 524–530.

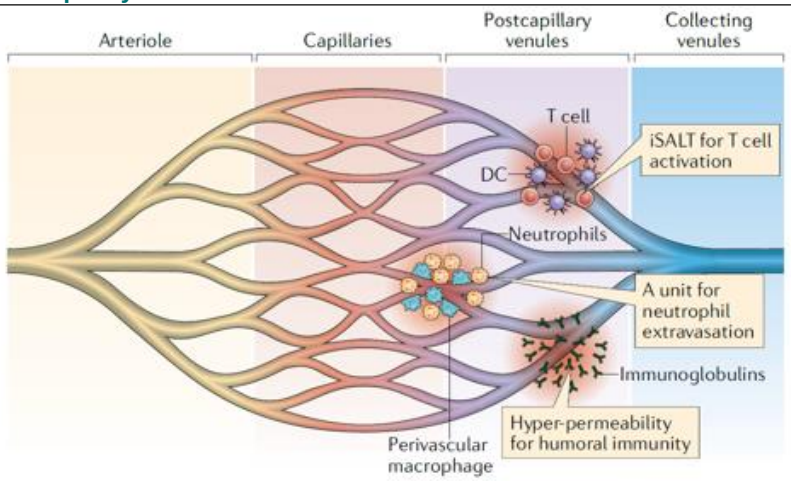
The third layer of the skin is the subcutis, a thick layer of adipose tissue. The lipids that accumulate here serve as an energy reserve and this layer also has a role in thermoregulation, by acting as a barrier for the heat generated by the body and thus helping to maintain the body's core temperature. As in other layers, various immune cells reside in the subcutis as well. Mainly T cells, B cells and macrophages can be found here[7]. Interestingly, in obese people there are four times more macrophages than the normal state. They also have an elevated level of inflammatory mediators called adipokines, for example adiponectin, leptin, IL-6 and TNF. Based on this, obesity can be considered a low-grade inflammation[8].

The cellular immune components form a functional unit in the skin called skin-associated lymphoid tissue (SALT). All the elements related to the immune system in the skin work together as a network to survey antigens in steady state and to execute immune response among other functions[9].

Immune response in the skin

The first physical barriers are the Stratum corneum and the tight junctions in the epidermis. If they are breached due to an injury or infection, antigens are taken up by DCs and LCs, which then present the antigens to T cells and other types of immune cells. APCs also migrate to lymph nodes to present the antigen(s) to further cells. Simultaneously, keratinocytes release a mixture a cytokines and other mediators. The cellular environment created by the cytokines and other signalling molecules attracts further immune cells.

Role of postcapillary venules in cutaneous immune reactions



Source: Kabashima K et al. Nature Reviews Immunology. 2019 Jan;19(1):19–30

Dermal blood vessels also have an essential role in the transportation of immune cells. They have four distinguished parts: arterioles, capillaries, post capillary venules, and collecting venules. Under normal circumstances the endothelial cells are tightly connected preventing any particles larger than 70kDa from exiting the blood vessel. However, in case of inflammation the connection between endothelial cells loosens, but only in postcapillar venules, which leads to increased permeability. This allows key mediators, immunoglobulins to leave the vessel and transfer to the place of inflammation. The extravasation of attracted immune cells such as macrophages and neutrophils also takes place here. Due to changed permeability and concentration gradient, fluid also flows towards the site of inflammation causing the swelling of this area. Increased blood flow causes redness and warmth of this area. T cells, DCs and other immune cells form special clusters called inducible skin-associated lymphoid tissue (iSALT) around the postcapillar venules, which serves as a place of antigen presentation[10]. Beside newly recruited T cells, skin-resident T cells also get activated and they create a self-amplifying loop. Th1 cells produce IFN-gamma, which triggers the production of several chemokines (CXCL9, CXCL10 and CXCL11) that attracts

[7] Lowes MA et al. Annu Rev Immunol. 2014;32:227–55.
[8] Kabashima K et al. Nature Reviews Immunology. 2019 Jan;19(1):19–30
[9] Streilein JW. J Investig Dermatol.1983; 80(Suppl):12s–16s
[10] Kabashima K et al. Nature Reviews Immunology. 2019 Jan;19(1):19–30

more Th1 cells. The same process takes place with Th17 and Th22 cells involving IL-17 and IL-22 and various chemokines. With a regenerative intention IL-22 increases the proliferation rate of keratinocytes causing hyperplasia. As an additional rationale, this process leads to the facilitated loss of keratinocytes on the surface resulting in faster pathogen elimination[11].

In summary, the skin is a complex multifunctional organ that consists of several layers hosting various cells including immune cells. During inflammation or immune response, cells work together as a functional unit to eliminate antigens and repair the damage. This requires a complicated network of signalling molecules to co-ordinate the response. Blood vessels also play a key role in transporting cells and other materials to the place of the immune response.

Disease etiology

After laying the anatomical and immunological foundations, we move on to explore the origins of psoriasis and describe the factors that determine and trigger its onset. Psoriasis is a complex multifactorial disease where genetic susceptibility and environmental triggers together lead to the manifestation of the disease.

Genetics

The likelihood of developing psoriasis is largely determined by genetics. More than 70 loci, spots on chromosomes, have been identified as potential susceptibility regions. Among these, the PSORS1 region is the best known, containing 11 genes including human leukocyte antigens (HLAs). In this region the presence of the HLA-Cw6 allele was found to be associated with greatly increased susceptibility to psoriasis. This allele is expressed in c90% of early-onset psoriasis and c50% of the late-onset cases, compared to c7% in the healthy population. On the level of genes, more than 1,300 are expressed differently in patients with psoriasis. Unsurprisingly, many of the genes associated with the disease are involved in inflammatory processes. This includes genes of various cytokines and mediators such as TNF and IL-23. As for hereditability, if both parents suffer from the disease, there is a c41% chance their child will develop psoriasis. Moreover, c35–90% of patients have positive family history. The findings clearly show that genetic factors play a substantial role in psoriasis[12].

Environmental triggers

Environmental factors can also trigger onset of the disease.

Trauma

It was Heinrich Koebner who recognised patients could develop psoriatic lesions after a trauma. This is now known as the Koebner phenomenon. Injuries and disruptions of the skin are likely to occur in certain areas such as elbows, knees and other extensor surfaces. The patient's body reacts with an inflammatory response, leading to a psoriatic lesion in these areas[13].

Infection

Just like physical traumas, infections also trigger an immune response, which in genetically susceptible people can lead to the manifestation or exacerbation of symptoms. Streptococcal infections, along with Staphylococcus aureus, Candida, Malassezia and human papillomavirus infections can be associated with these changes[14].

Sunlight

Although UV light is used as a treatment for many patients, light – in some cases – can also trigger psoriatic symptoms[15].

Medication

Certain drugs can also trigger the symptoms. Patients and physicians must be aware of them to avoid their harmful effects. The most important ones are beta-blockers, lithium, certain anti-malaria treatments and certain antibiotics[16]. Interestingly, non-steroidal anti-inflammatory drugs (NSAIDs) can also play a role in disease induction and symptom flare-ups. NSAIDs

[11] Lowes MA et al. Annu Rev Immunol. 2014;32:227–55
[12] Bolognia JL et al. Dermatology . 3rd ed. Philadelphia: Elsevier; 2012
[13] Tagami H. Clin Dermatol . 1997;15(5):677–685
[14] Fry L et al. Clin Dermatol . 2007;25(6):606–615
[15] Ros AM et al. Photodermatol . 1986;3(6):317–326 . 17. Verhoeven
[16] Schadler ED et al. Dis Mon. 2019 Mar;65(3):51–90

inhibit the cyclooxygenase (COX) enzymes, and therefore change the metabolism of arachidonic acid (AA) leading to the accumulation of leukotrienes, which can lead to more enhanced symptoms[17].

Stress

It has been shown that elevated stress levels and worrying can result in more severe symptoms and based on patient observation stress also plays a role in the initial manifestation of the disease. The cognitive changes associated with stress influence certain hormone levels that can lead to the worsening of psoriatic symptoms[18].

Obesity

As described earlier, obesity can be interpreted as a low-grade inflammation thus it shares certain pathways and mediators with psoriasis. The connection is supported by the observation that psoriatic patients are more likely to be obese than healthy people. The pooled odds ratio (OR) for the association between the conditions is 1.66 (95% CI=1.46-1.89)[19]. However, it is still not clear whether obesity increases the risk of psoriasis, or psoriasis leads to obesity. The truth is probably somewhere between these two points of view.

Alcohol and smoking

Both of these activities are associated with increased risk of developing psoriasis and having more severe symptoms[20].

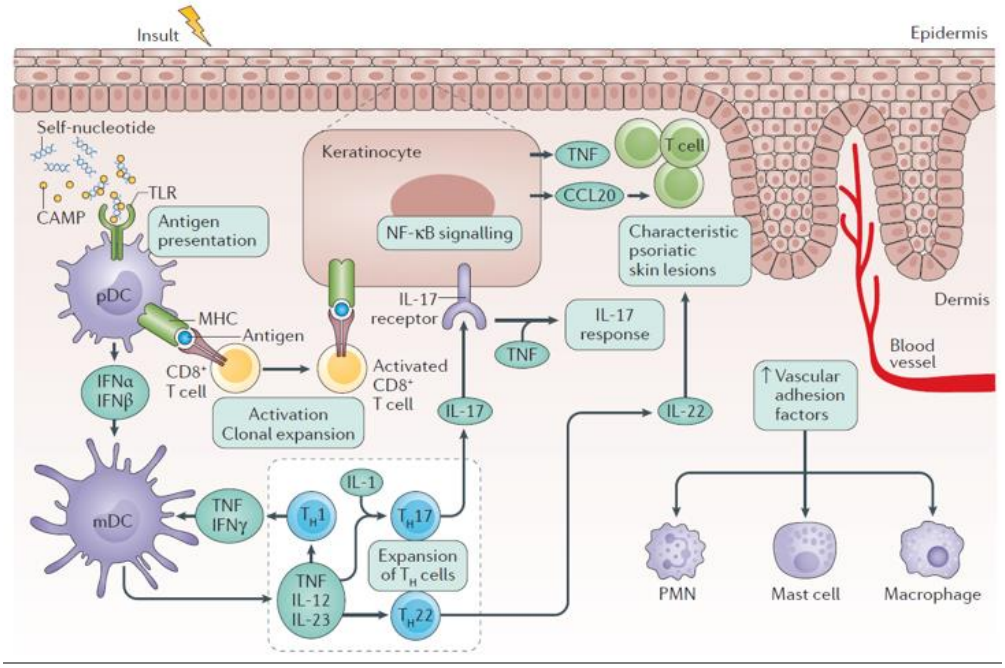
In summary, psoriasis has a strong genetic component, which together with certain environmental triggers can lead to the manifestation of the disease.

Pathophysiology

Now let us explore how the aforementioned trigger factors can lead to the clinical manifestation of the disease. Following a trigger such as a skin injury, self-nucleotides are released from skin cells and keratinocytes start to produce an antimicrobial peptide called LL37 that can form a complex with the released fragments of self-DNA and RNA. Normally, these DNA fragments are not recognised by APCs as they are quickly degraded by nucleases. However, when they are in complex with LL37 they can connect to the DCs Toll-like receptor (TLR) 9 and 7. As a result DCs get activated and start to present this newly encountered self-antigen (LL37-DNA/RNA complexes) to other immune cells (mainly T cells) residing in the skin. Apart from this, they migrate to the lymph nodes to attract and activate more T cells. DCs release a mixture a cytokines including IL-12 and IL-23 and TNF. IL-12 induces Th1 cells while IL-23 activates Th17 cells and Th22 cells are also activated. As more and more T cells arrive to the skin, they recognise the self-antigen presented by DCs and keratinocytes. T cells release further cytokines, chemokines and mediators that lead to local inflammation and the recruitment of additional immune cells. Additionally, Th17 cells release IL-17 that stimulates keratinocyte proliferation and increases the production of chemokines and defensins to attract further immune cells. IL-22 also acts on the epidermis cells and accelerates cell division[21]. As a result, proliferation of basal cells happens in every two days instead of the normal 2–4 weeks. Consequently, the migration of keratinocytes to the Stratum corneum takes only four days and cells do not have time to mature and differentiate. The Stratum corneum becomes 4–6 times thicker than normal[22].

[17] Kim GK et al. J Clin Aesthet Dermatol. 2010 Jan;3(1):32-8
[18] Verhoeven EWM et al. Br J Dermatol . 2009;161(2):295–299
[19] GlobalData
[20] Naldi L et al. Arch Dermatol . 1999;135(12):1479–1484
[21] Greb JE et al. Nature Reviews Disease Primers. 2016 Nov 24;2(1):1–17
[22] Peters BP et al. Am J Health Syst Pharm. 2000 Apr 1;57(7):645-59; quiz 660-1

Pathomechanism of psoriasis



Source: Greb JE et al. Nature Reviews Disease Primers. 2016 Nov 24;2(1):1–17

This process leads to the clinical manifestation of psoriatic lesions. Interleukins also activate transcription factors including cyclic AMP, Janus kinase (JAK) and nuclear factor-κB (NF-κB). They further enhance the production of TNF and various interleukins and lay the foundations of longer-term changes. Changes also occur in vascularisation around the psoriatic lesion thanks to the expression of vascular endothelial growth factor with their receptors, vascular proliferation takes place and blood vessels dilate around the psoriatic lesion contributing to the clinical picture of the disease[23]. In a nutshell, the trigger induces an (auto)immune response, which turns into a self-amplifying loop leading to chronic inflammation, keratinocyte hyperplasia and vascular changes. These factors together form the clinical manifestation of psoriasis.

Clinical presentation

In this section we dive into the clinical aspects of psoriasis. We introduce the main types of psoriasis with their respective symptoms as well as the most common comorbidities. Based on this, we describe the diagnostic process and systems used to measure disease severity.

Types and symptoms

Psoriasis has five distinguished types:

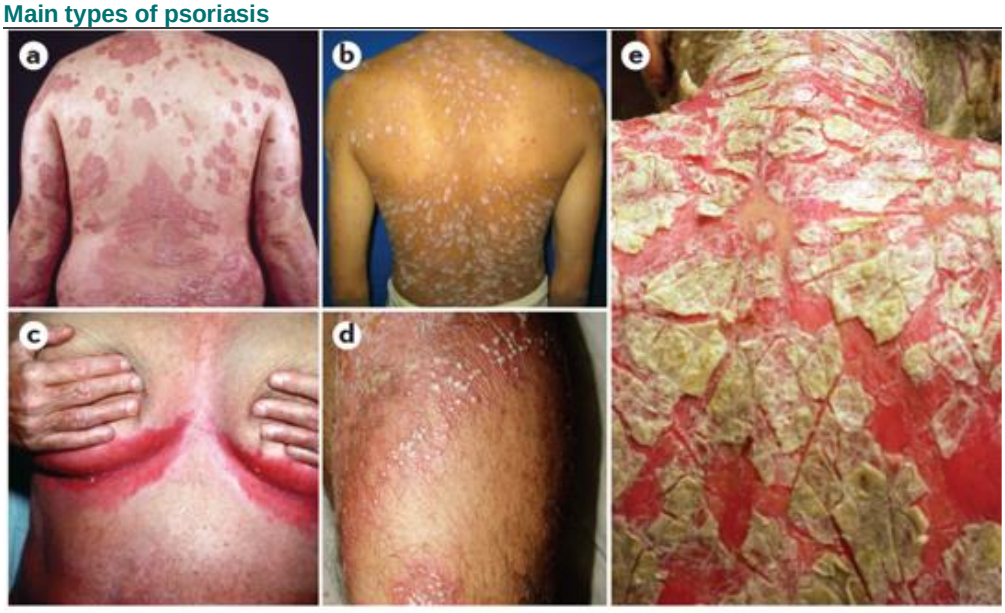
- **Psoriasis vulgaris** or plaque psoriasis is the most common, affecting c80–90% of patients. It is characterised by well-circumscribed red or pink, erythematous, hardened plaques or lesions with a silvery white scale on their surface. Removal of this scale can lead to bleeding due to the enhanced vascularisation of the plaques. This is known as the Auspitz sign. Plaques usually develop on the extensor surface of the knees and elbows, but the scalp and trunk are also commonly affected. Lesions tend to occur in a symmetric orientation.
- **Guttate psoriasis** is the second most common type. Here a lot of small, drop-shaped (gutta means drop in Latin) papules can be observed mostly on the trunk or extremities. This type is thought to be triggered by streptococcal infection, which mainly occurs in children and adolescents making guttate psoriasis particularly prevalent in this group.
- **Inverse psoriasis.** Here, erythematous plaques develop in the body folds and due to more moisture in these places scale occurs less frequently.
- **Pustular psoriasis** can be characterised by numerous point-like painful pustules on an erythematous base, mostly on the extremities, particularly the hands and feet. The

[23] Greb JE et al. Nature Reviews Disease Primers. 2016 Nov 24;2(1):1–17.

pustules are sterile, meaning they are not a result of an infection. This type is extremely difficult to treat and since pustules occur on highly visible places, they can have a huge impact on patients' quality of life.

- **Erythrodermic psoriasis** is the most severe type of psoriasis. Here, the erythematous region covers at least 90% of the body, leading to a severe, potentially life-threatening state. It presents with intense itching, pain and desquamation, meaning the skin can be peeled off in layers. It is quite rare, affecting only c3% of all psoriasis patients[24].

Main types of psoriasis



Source: Greb JE et al. Nature Reviews Disease Primers. 2016 Nov 24;2(1):1–17
Note: a. Psoriasis vulgaris, b. Guttate psoriasis, c. Inverse psoriasis, d. pustular psoriasis, e. Erythrodermic psoriasis

Apart from the visual presentation of the plaques, patients can experience itching to varying extents. The involvement of nails can also be a telling sign of psoriasis. Nail pitting is quite common among patients, and occurs because of the involvement of nail plates and matrix. Enthesitis (inflammation where tendons insert into the bones sometimes causing erosion of the bone) can also be a marker of psoriasis. This can be observed on X-ray images[25].

Comorbidities

Psoriatic arthritis (PsA)

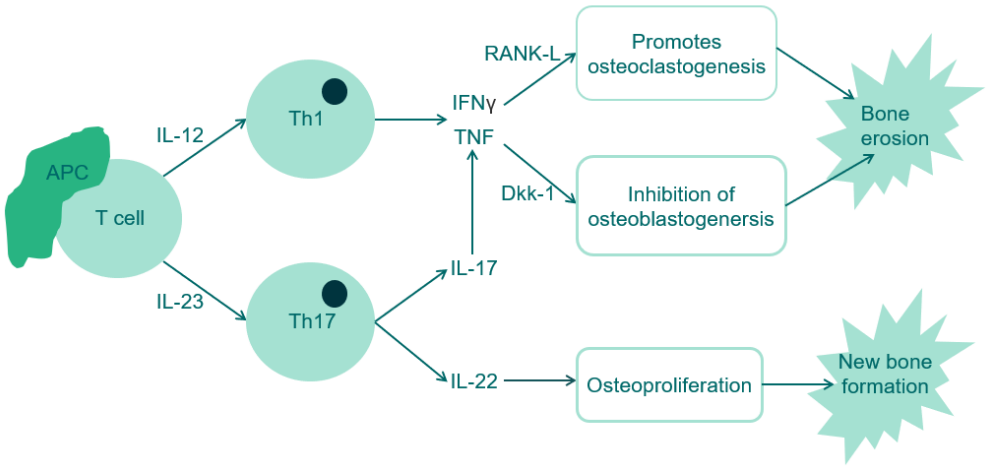
PsA is a condition affecting the joints and it concerns 2.04–26% of psoriasis patients[26] while it has prevalence of only 0.1–0.24% in the general population[27]. Its presence is independent of age, but it has a peak onset at 40–50 years. Approximately 70% of PsA patients show the typical psoriatic skin lesions while signs of PsA usually appear years later than the skin symptoms of psoriasis[28]. As for the clinical presentation of PsA, symptoms usually start with the asymmetric involvement of a few joints. Patients experience inflammatory joint pain and erythema around the affected joint along with prolonged morning stiffness. The stiffness improves when patients are active and worsens when the rest. Other symptoms include enthesitis and dactyilitis, the inflammation of a digit, also called 'sausage digit'[29]. Unsurprisingly, PsA has a great impact on patients' quality of life.

The pathomechanism has several common elements with psoriasis, explaining their frequent occurrence together. PsA shares susceptibility genes with psoriasis. For example, HLA-Cw6 plays a role in the development of both conditions. T cells and TNF along with several interleukins are at the centre of the pathomechanism. TNF is released by T cells and together

[24] Greb JE et al. Nature Reviews Disease Primers. 2016 Nov 24;2(1):1–17
[25] Greb JE et al. Nature Reviews Disease Primers. 2016 Nov 24;2(1):1–17
[26] GlobalData
[27] Gelfand JM, et al. J Am Acad Dermatol . 2005;53(4):573
[28] Liu J-T et al. World J Orthop . 2014;5(4):537–543
[29] Ritchlin,CT. et al. Ann. Rheum. Dis.2009. 68, 1387–1394

with other mediators they lead to a chronic inflammation[30]. Besides, TNF is able to influence bone formation in two ways: 1) via the RANK-L it promotes the production of osteoclasts, cells that dissolve the bone; and 2) via Dkk-1 it stops the generation of osteoblasts, cells forming new bone tissue. These processes lead to the erosion of bones and joints[31].

TNF is involved in pathomechanism of psoriatic arthritis



Source: Adapted from Mantravadi S et al. Expert Rev Clin Pharmacol. 2017 Aug;10(8):899–910.

The diagnosis is supported by the Classification Criteria for Psoriatic Arthritis (CASPAR), a very useful tool to diagnose PSA patients[32]. However, patients should be diagnosed as early as possible since even a delay of six months can lead to severe symptoms and deterioration of quality of life.

Metabolic syndrome

Metabolic syndrome is a constellation of conditions. Therefore, the diagnosis depends on fulfilling a set of criteria determined by the National Cholesterol Education Program Adult Treatment Panel III. The criteria include increased waist circumference, elevated triglyceride levels, and reduced HDL-C along with increased blood pressure and fasting glucose. A large study showed that psoriasis patients are more than twice as likely to fulfil the diagnosis of metabolic syndrome than the rest of the population.

As with PsA, TNF and interleukins are involved in the development of metabolic syndrome. TNF can influence insulin signalling and decrease adiponectin production, which is associated with the regulation of glucose and fatty acid levels. Additionally, IL-6 – an active interleukin in psoriasis – is also related to insulin resistance. Also, metabolic syndrome and psoriasis share some susceptibility regions that increase the risk of developing both conditions[33].

Cardiovascular disease (CVD)

Chronic inflammation induced by the same agents is a shared point in the pathomechanism of psoriasis and CVD. In both conditions Th1 and Th17 cells have an important role. TNF secreted by Th1 cells can induce endothelial dysfunction while IL-17 affects vascular smooth muscles and the endothelium of blood vessels. These agents, together with various mediators, create a self-amplifying feedback loop that can lead to the instability of atherosclerotic plaques[34]. A recent study found that c45% of plaque psoriasis patients had hypertension and almost c49% of them had hyperlipidaemia[35].

Obesity

As indicated earlier, cytokines and several other agents involved in inflammation are associated with obesity and the control of blood sugar levels. Knowing this, it should not

[30] FitzGerald O et al. Arthritis Res Ther . 2009;11(1):214
[31] Mantravadi S et al. Expert Rev Clin Pharmacol. 2017 Aug;10(8):899–910
[32] Taylor W et al. Arthritis Rheum. 2006 Aug;54(8):2665-73
[33] Grundy SM et al. Circulation . 2005;112(17):2735–2752
[34] Armstrong AW et al. Exp Dermatol . 2011;20(7):544–549
[35] Shah K et al. J Am Acad Dermatol. 2017 Aug;77(2):287-292.e4

surprise us that obesity and type 2 diabetes are twice as common among psoriasis patients than the rest of the population[36].

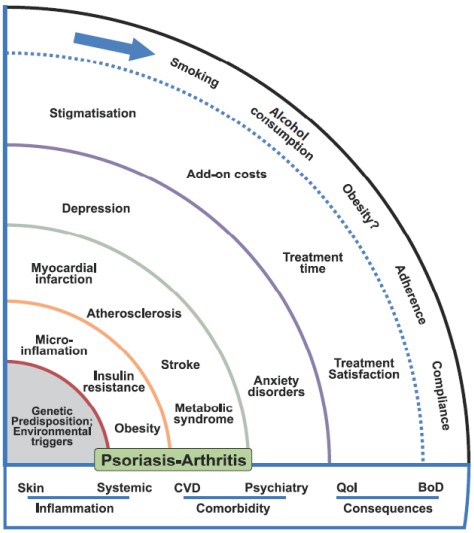
Psychiatric problems

The development of physical symptoms – red, scaling plaques covering highly visible parts of the body – very often lead to severe psychological problems and thereby add an extra layer of challenge and complexity to the management of this disease. Living with psoriatic plaques can alter the way patients' see themselves and can lower self-esteem. The symptoms can lead to social and professional stigmatisation resulting in frustration, anxiety and even depression and suicidal thoughts. These findings are supported by a study involving almost 5,000 patients with dermatological problems[37]. Among psoriasis patients, depression was present in 13.8% (4.3% in the control group), clinical anxiety 22.7% (11.1%), and suicidal thoughts 17.3% (8.3%). If we take a closer look at depression, it shows a close connection with patients' subjective opinion about their disease severity and their negative attitude towards their body.

Addictive behaviour

Stemming mainly from the aforementioned psychological factors, substance abuse is more common among patients with psoriasis. They have higher rates of alcohol consumption and smoking, which increases the risk of further complications even more[38].

Total burden caused by psoriasis



Source: https://www.who.int/publications-detail-redirect/global-report-on-psoriasis

In summary, psoriasis is a very complex disease that shares genetic and immunological features with several other conditions. In most cases the involvement of T-cells and certain cytokines is the common element that plays a role in psoriasis, joint inflammation and adverse metabolic and cardiovascular changes. Psychological problems and substance abuse emerging owing to the highly visible nature of symptoms makes this condition even more complex. These comorbidities cannot be ignored during the management of psoriasis; all of them should be addressed to make the biggest possible improvement on patients' lives.

Diagnosis

The most common way of diagnosing is the physical examination of the lesions. General practitioners look for well-demarcated, red plaques with silvery scale on the top. Patients usually complain about itching, which is present in c65% of cases and irritation (c60%)[39]. They might experience sensitivity, a burning sensation, or even pain or bleeding. Nails and joints could also be examined for telling signs and possible symptoms of PsA. Common plaque psoriasis is usually easy to diagnose, although the differential diagnoses include atopic dermatitis, contact dermatitis and tinea corporis among others. The proper diagnosis of

[36] Sterry W et al. Br. J. Dermatol . 2007;157(4):649–655
[37] Dalgard FJ et al. J Invest Dermatol . 2015;135(4):984–991
[38] Higgins E. Clin Exp Dermatol. 2000 Mar;25(2):107-10
[39] Sampogna F et al. Br J Dermatol . 2004;151(3):594–599

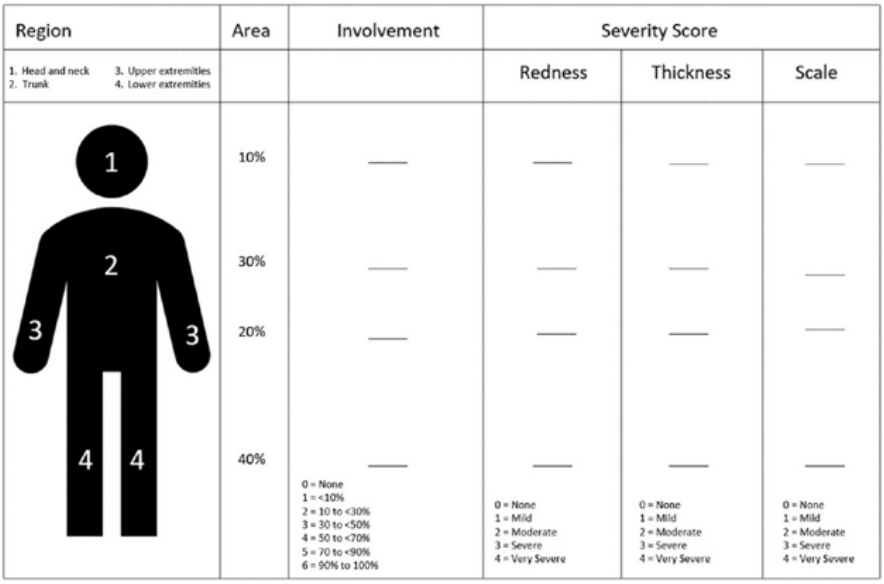
less common types and manifestations of psoriasis usually needs a dermatologist. In some atypical cases, a skin biopsy can be taken to support the diagnostic process[40].

Measurement systems

Psoriasis Area Severity Index (PASI)

There are many tools to assess and quantify the symptoms of psoriasis. The most widely used is the Psoriasis Area Severity Index. Here, physicians grade redness (erythema), scale (desquamation), and thickness (induration) on a 0–4 scale for four body parts: head, upper extremities, trunk and lower extremities. Totalling these scores gives a severity score for each body part. This severity score is then multiplied by an involvement score (0–6) for each body part to account for the extent of involvement. Then these scores are weighted based on the area represented by each body part, so the head score is multiplied by 0.1 (since it represents c10% of the body surface), upper extremities score by 0.2, trunk by 0.3, and lower extremities by 0.4. Totalling these weighted scores gives a final PASI score on a 0 to72 scale, with zero indicating a healthy patient and 72 is the most severe psoriasis[41].

Component of PASI score



Source: Schadler ED et al. Dis Mon. 2019 Mar;65(3):51–90

One advantage of the PASI score is that its widely used, makes examinations and clinical results comparable, and is accepted by authorities as a valid clinical endpoint, since it gives a good general picture of the patient's state and accounts for every area. It correlates with patients' quality of life, albeit not that strongly.

On the other hand, the PASI score is not used by clinicians in everyday practice. It inevitably contains subjective elements, so the final score depends on the clinician's judgment, which makes the results less comparable if assessed by different physicians. Additionally, it is quite complicated to calculate the final score, not to mention that it has poor sensitivity to small improvements at the lower end of the scale (in mild cases), while the upper end of the scale is rarely used in practice[42].

Based on the changes of the PASI score, various clinical endpoints can be constructed. For severe patients a 75% reduction in the PASI score is usually seen as clinically meaningful, therefore the proportion of patients achieving a 75% reduction is frequently used and called PASI75. However, a 50% improvement can also be clinically meaningful, so PASI50 can also be measured. Depending on severity and overall status of the individual's, an even lower

[40] Kim WB et al. Can Fam Physician. 2017 Apr;63(4):278–85
[41] Feldman S et al. Ann Rheum Dis. 2005 Mar;64(Suppl 2):ii65–8
[42] Feldman S et al. Ann Rheum Dis. 2005 Mar;64(Suppl 2):ii65–8

improvement could also be clinically meaningful, but PASI75 and PASI50 are the most widely used measures to assess clinically meaningful responses[43].

Body Surface Area (BSA)

BSA shows what percentage of the body surface is affected by psoriasis. In practice, the area of the palm represents 1% of the body. This measure is mainly used for classification. BSA could be more easily and probably more objectively determined than PASI scores, but it does not account for severity or any other symptom than the area involved.

Classification based on BSA[44]

- Mild disease: BSA <3%, the disease has a minimal effect on quality of life; it can in most cases be effectively controlled with skin care products and topical treatments.
- Moderate disease: BSA 3–10%, more substantial effect on quality of life, the symptoms cannot in most cases be effectively contained with only skin care products.
- Severe disease: BSA >10%, severe effect on patients' quality of life, the condition cannot be controlled with topical treatment. These cases usually require systemic treatments.

Physicians (Static) Global Assessment (PGA or PSGA)

This is another popular score and depends entirely on the clinician's judgment. Physicians simply assess the severity of the disease on a 0–6 scale (0=clear, 1–6 increasing severity). PGA is easy to use and understand. It can, however, be quite subjective so the meaning of each score has to be clearly defined.

There are several others, including the National Psoriasis Foundation Psoriasis Score (NPF-PS), Overall Lesion Assessment (OLA) or the Lattice System Global Psoriasis Score (LS-GPS). In principle, they are very similar to the ones described above but used less frequently used in clinical trials.

Quality of life

Beside the physical symptoms another important are is patients' quality of life. For a general assessment, the Medical Outcome Survey Short Form 36 (SF-36) or the Euro QoL questionnaires can be used. More specific instruments such as the Dermatology Life Quality Index (DLQI) or Skindex are also at the investigators' disposal[45]. The use of DLQI is very popular in clinical trials since it can assess skin disease related quality of life. The questionnaire includes 10 questions in six areas: symptoms and feelings, daily activities, leisure, work and school, personal relationships, and bother with psoriasis treatment. Each question is answered on a 0–3 scale, where zero means not affected at all and three means very much affected. Consequently, a lower score on the 0–30 final scale means better quality of life[46]. Additionally, individual features such as pain or itching can be assessed with a Visual Analogue Scale (VAS) where patients can rate the particular features on a scale[47].

Biomarkers

There are no good biomarkers for psoriasis, but some are used to measure inflammation in clinical trials. In the case of Arctic Bioscience, it used C-reactive protein (CRP) as an endpoint in its pilot clinical trial. Based on scientific literature, the use of CRP seems to be justified with a couple of limitations. CRP is one of the most sensitive markers of inflammation and due to its short half-life (6–8 hours) it can be used to monitor the disease state in a timely manner[48]. It is also a risk factor in CVD, which gives its monitoring extra relevance. In a recent article 28 studies were reviewed[49]. They investigated the difference between the CRP levels of healthy people and psoriasis patients with different severity. According to their results, higher CRP levels can only be observed in moderate and severe forms of the disease. Only two studies out of 28 could observe increased CRP levels even in mild patients, so there is no evidence patients with mild psoriasis have elevated CRP levels. This makes the use of CRP as an endpoint in mild cases questionable. However, the majority of the studies on the topic found a

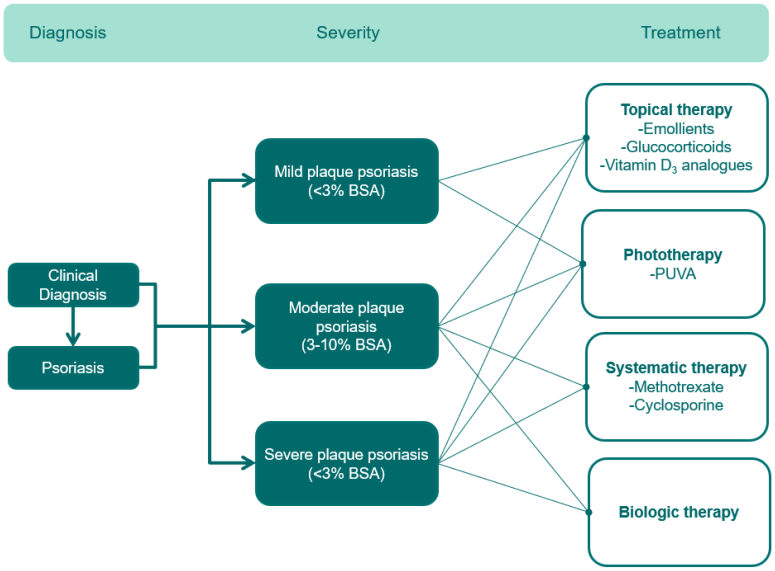
[43] Feldman S et al. Ann Rheum Dis. 2005 Mar;64(Suppl 2):ii65–8
[44] GlobalData
[45] Feldman S et al. Ann Rheum Dis. 2005 Mar;64(Suppl 2):ii65–8
[46] Finlay AY et al. Clin Exp Dermatol. 1994 May;19(3):210-6
[47] Tveit KS et al. Acta Derm Venereol. 2020 May 28;100(10):adv00154
[48] Kanelleas A et al. Clin Exp Dermatol 2011; 36: 845–850
[49] Beygi S et al. J Eur Acad Dermatol Venereol. 2014 Jun;28(6):700–11

significant relationship between CRP levels and disease severity. The use of systemic therapies and the presence of PsA (as a source of extra inflammation) can skew the results and ruin the relationship. Therefore, CRP can only be used reliably in case of untreated patients without PsA. The relationship between treatments and CRP levels was also examined. CRP levels decreased dramatically in every study regardless of the type of the treatment and one study indicated that greater declines in CRP levels can be associated with better clinical response to a treatment. Hence, CRP can be indicative in clinical trials but might only be completely reliable in untreated patients without PsA.

Disease management

After diagnosis, patients are classified based on disease severity and start treatment accordingly. The involvement of a dermatologist in diagnosis and disease management is very common. In fact, it is necessary in more severe cases. If the patient has signs of PsA, a rheumatologist is also involved. Other comorbidities are also diagnosed and treated by specialists. Triggering factors such as smoking, stress, infections, or obesity should also be assessed and handled during the process[50].

Disease management and treatment options for psoriasis



Source: GlobalData

Topical treatments

Topical treatments are applied as monotherapy in mild and even in some moderate cases, but they can also be used in combination with other options. Historically, the first treatments were coal tar and dithranol, also known as anthralin, but they are not used anymore. Coal tar reduced the production of IL-15 and decreased the activity of NO synthase[51]. It was reasonably effective[52], but due to its black colour it stained clothes and was difficult to apply.

Nowadays, the first-line topical treatment is corticosteroids. These are highly efficient anti-inflammatory agents with well-known safety profile. Corticosteroids vary in strength, and are available in various formulations (cream, ointment, foam, gel, shampoo, suspension)[53]. These factors make it easy to treat different sites of the body and adjust the therapy to individual cases. On the other hand, being a topical therapy has its drawbacks[54]. Creams and ointments along with some other formulations are time consuming to apply. Some formulations are also greasy, which many patients dislike. This can be particularly problematic around hairlines, for example in the case of scalp psoriasis. People who are alone cannot reach certain body areas, making the administration of corticosteroids impossible in some cases. Penetration of

[50] https://www.who.int/publications-detail-redirect/global-report-on-psoriasis
[51] Arbiser JL et al. J Invest Dermatol. 2006 Jun;126(6):1396-402
[52] Thawornchaisit P et al. J Med Assoc Thai. 2007 Oct;90(10):1997-2002
[53] Greb JE et al. Nature Reviews Disease Primers. 2016 Nov 24;2(1):1–17
[54] Hoffman MB et al. Expert Opin Drug Deliv. 2016 Oct;13(10):1461–73

the active compound through the skin can also be insufficient. However, the biggest shortcoming of this group is the safety profile[55]. Short-term side effects can be itching, burning sensation and irritation, while long-term adverse effects include skin atrophy, pigment alterations, and acne[56]. Due to these factors, compliance with topical corticosteroid therapy is relatively low and use is only recommended up to four weeks. Patients should usually wait one month after one therapy before they start the next one.

The next widely used therapy is vitamin D analogues including calcitriol, calcipotiene and tacalcitol. They are used as monotherapy and in combination. These molecules normalise the differentiation and proliferation of keratinocytes and have an immune modulatory effect[57]. Their efficacy is comparable to most corticosteroids, but they offer a better safety profile. Their side effects are usually mild, the most frequent is skin irritation. Their main disadvantage is the inconvenience of topical administration.

Vitamin D analogues and corticosteroids can also be used in combination. The most popular one is betamethasone with calcipotriol. As for efficacy, this combination is synergistic as it is more effective than its components alone[58]. According to the systematic review of several clinical trials involving more than 6,000 patients, the combination reduced PASI by 74% in four weeks, while PASI reduction was 59% and 63% for calcipotriol and betamethasone alone, respectively. The safety profile is also more favourable, vitamin D analogues seem to be able to reduce the side effects of corticosteroids[59]. The combination is available in various formulations, making it easier to apply in different therapeutic situations.

Topical retinoids can also be used to ease the symptoms of psoriasis. They act as immune suppressants but also by normalising the maturation of keratinocytes. They can cause strong irritation in many cases; hence they are usually used in combination[60].

Another topical option is calcineurin inhibitors like tacrolimus and pimecrolimus. They can treat the symptoms effectively by suppressing the immune response. They also have a good systemic safety profile due to low rate of accumulation in the adipose tissue. They mainly have local side effects, for example skin burning and itching. However, they are not approved for the treatment of psoriasis, only for atopic dermatitis, thus they are used off-label[61].

Phototherapy

Phototherapy is used in moderate and severe cases, with an overall good efficacy and safety profile. During phototherapy UVB light is used. Broadband UVB was found to increase the likelihood of skin cancer, so today narrowband UVB is the standard therapy since it is not associated with such an adverse effect. UV light induces apoptosis in inflammatory cells and has an immune modulatory effect. The main flaw of this method is its availability. Patients must go to treatment centres 2–3 times a week for several months to receive UVB therapy. This is very time consuming and can put compliance with the therapy in jeopardy. Home therapy units are also available, but they are quite expensive even with insurance coverage or co-payment[62].

Systemic treatments

These agents are only used in moderate and severe cases. Three molecules are worth mentioning here: methotrexate, cyclosporine and acitretin.

- **Methotrexate** is the oldest systemic treatment for psoriasis, and also the cheapest. It is a folate synthesis inhibitor. It has a well-known efficacy and safety profile. In the case of efficacy this is good, as methotrexate is highly effective. On the other hand, it has a very unfavourable safety profile. The main concern relates to hepatotoxicity. Side effects include

[55] Kim WB et al. Can Fam Physician. 2017 Apr;63(4):278–85
[56] Coondoo A et al. Indian Dermatol Online J. 2014 Oct;5(4):416-25
[57] Trémezaygues L et al. Dermatoendocrinol. 2011;3(3):180–6
[58] https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD005028.pub3/full
[59] Kragballe K et al. J Eur Acad Dermatol Venereol. 2006 Jan;20(1):39–44
[60] Lebwohl MG et al. J Am Acad Dermatol. 1998 Oct;39(4 Pt 1):590-6
[61] Freeman AK et al. J Am Acad Dermatol. 2003 Apr;48(4):564-8. doi: 10.1067/mjd.2003.169
[62] Rajpara AN et al. Dermatol Online J. 2010 Dec 15;16(12):2

nausea, vomiting, fatigue, and diarrhoea, not to mention teratogenicity. Due to this, continuous monitoring of blood count, liver and renal function is required during therapy[63].

- **Cyclosporine** is a calcineurin inhibitor and works by inhibiting T-cells. It is one of the most effective therapies with a particularly rapid onset of action. However, just like methotrexate, it has adverse effects. Due to nephrotoxicity, its use is limited to 1–2 years in guidelines. Other side effects include hypertension and adverse changes in blood potassium and magnesium levels (hyperkalaemia, hypomagnesaemia) therefore the therapy requires frequent monitoring, which can be inconvenient for patients[64].
- **Acitretin** belongs to retinoids. If used alone, it has only modest efficacy and an adverse safety profile. Acitretin is a potent teratogen, so women should not get pregnant for three years after finishing therapy, since acitretin accumulates in the adipose tissue and remains in the body for a long period. Besides, it can cause mucocutaneous dryness, inflamed lips (cheilitis), gastrointestinal discomfort, photosensitivity, and joint pain (arthralgia)[65].

Biologics

They are the newest therapeutic group for psoriasis used as first-line treatments or when other systemic treatments fail. They have showed remarkable efficacy in several trials. Several biologic treatments are on the market and several more are under development. These antibodies inhibit various parts of the immune system including TNF, IL-12, IL-23 and IL-17 to ease the symptoms. The first-line treatments among biologics are anti-TNF antibodies such as Humira®, Enbrel® and Remicade® along with anti-IL-23 antibody Stelara®. Anti-IL-17 antibodies (Taltz®, Siliq® and Cosentyx®) are used as second-line treatment. Their main disadvantage is their price, which is much higher than for other therapies[66]. Biologics can cost USD30k–60k per year or more[67]. Additionally, they are all subcutaneous injections, making them more inconvenient than other therapies. However, less frequent administration might compensate patients for the pain of getting injections.

To summarise, mild cases are usually treated with emollients and topical agents including mainly corticosteroids and vitamin D analogues. In moderate cases phototherapy is available, but has certain limitations. UV light can be used together with some topical treatments. If patients do not improve, they can get cyclosporine or methotrexate. As a last step, if patients do not respond to systemic treatment, biologics can be prescribed.

[63] Greb JE et al. Nature Reviews Disease Primers. 2016 Nov 24;2(1):1–17
[64] Amor KT et al. J Am Acad Dermatol. 2010 Dec;63(6):925-46; quiz 947-8
[65] Katz HI et al. J Am Acad Dermatol. 1999 Sep;41(3 Pt 2):S7-S12
[66] Kim WB et al. Can Fam Physician. 2017 Apr;63(4):278–85
[67] GlobalData

Epidemiology

In this section we introduce the epidemiological aspects of psoriasis. We start with data and trends about the global population before we narrow down our analysis to the seven major market (7MM): the US, the UK, France, Germany, Italy, Spain and Japan where we have segmented information based on geography, sex, age, and disease severity. Forecasts to 2027 are also discussed. Then we focus on the Nordics, since this region is the home market for Arctic Bioscience.

Global characteristics

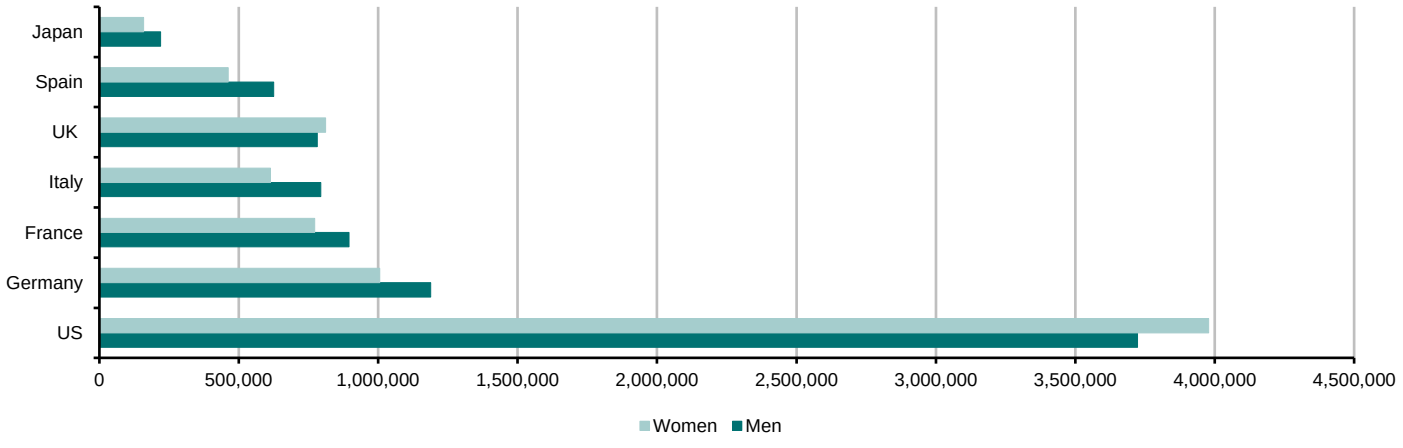
Psoriasis affects c100m–120m people globally[68]. Plague psoriasis alone account for c80–90% of all cases[69]. Prevalence reported by individual countries ranges from 0.09% to 11.43%, with a global average of c2–3%. In the adult US population, average incidence of 78.9 cases per 100,000 person-years was reported. The study looked at 1970–2000, when incidence increased from 50.8 (1970–1974) to 100.5 (1995–1999). Another study, in Italy, reported a 321 per 100,000 person-years incidence in 2001, falling to 230 in 2005. A study in the UK found an incidence of 140 per 100,000 person-years in 1997[70].

On a global scale, psoriasis affects both sexes equally, there is no significant difference between prevalence in men and women. From a geographical perspective, a weak positive correlation was found between higher latitude and prevalence. It is possible that the explanation lies in the higher level of UV light exposure in these regions[71]. Additionally, psoriasis seems more prevalent in countries further from the equator than in warmer areas. The disease also shows higher prevalence in the Caucasian population (mainly Europe, North America and Australia), while psoriasis is apparently less prevalent in Asians and Africans[72].

7MM

In this analysis an artificial measure, age-adjusted one-year diagnosed prevalence was used, which is the weighted average of prevalence measured in various age groups. Different countries have different age distributions, making general prevalence estimates less comparable. Age-adjusted one-year prevalence shows the prevalence as if countries had the same population structure with regards to age[73].

One-year diagnosed prevalent cases of plaque psoriasis, 7MM, men and women, Ages ≥18, 2017



Source: GlobalData

The diagnosed prevalent population in the 7MM was estimated to be 14.9m, of which c10.4m patients were treated. In 2017, 48% of these cases (c7.7m patients) came from the US. This population is expected to have a 2.47% annual growth rate (AGR) until 2027. This is the highest growth rate among the 7MM. In Europe, Germany was the biggest contributor with

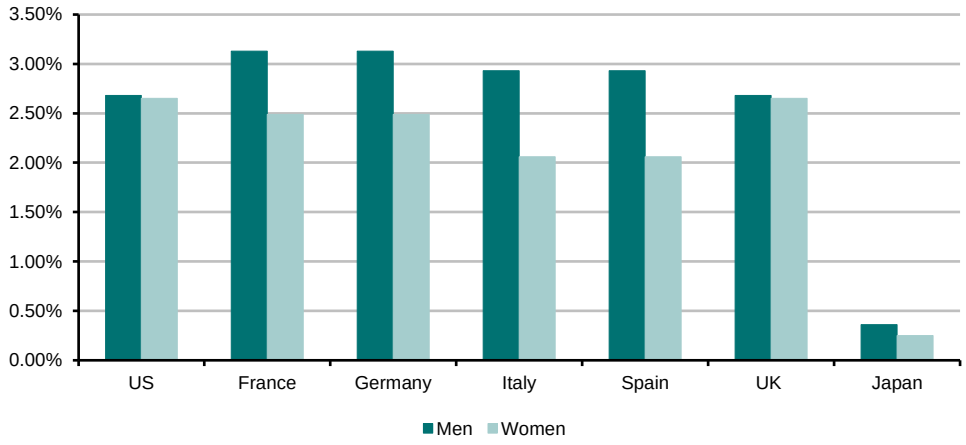
[68] https://www.who.int/publications-detail-redirect/global-report-on-psoriasis
[69] GlobalData
[70] Parisi R et al. J Invest Dermatol. 2013 Feb;133(2):377–85
[71] Jacobson CC et al. J Am Acad Dermatol. 2011 Oct;65(4):870-873
[72] Parisi R et al. J Invest Dermatol. 2013 Feb;133(2):377–85
[73] GlobalData

c2.2m cases, or 13.7% of total cases. However, the German patient population is forecast to shrink by the end of the forecasting period, as it has an AGR of -0.11%. On average, the number of one-year diagnosed prevalent cases is expected to have an AGR of 1.49% across the 7MM. By 2027, the diagnosed population is forecast to increase to c16.9m, with a treated population of c12m.

Segmentation by sex

There were no major differences between the prevalence in men and women but the disease seemed more prevalent in men in several countries. In accordance with the global statistics, the prevalence range was c2–3%, with Japan showing a considerably lower rate of c0.3%.

Age-adjusted one-year diagnosed prevalence of plaque psoriasis (%) men and women, aged ≥18 years, 2017



Source: GlobalData

Segmentation by age[74]

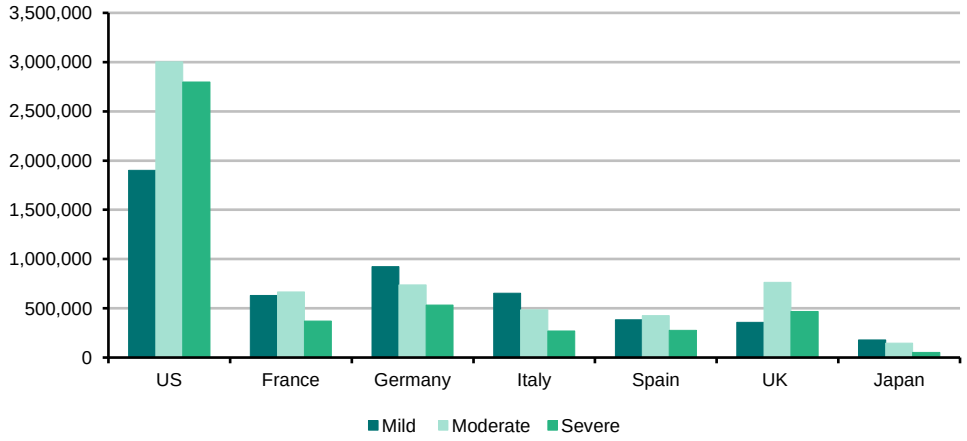
In 2017, patients aged 50–59 years represented the highest proportion of the population (23%). In the US, 25% of all patients belonged to this group, almost c2m people. In the five largest European countries (EU5) c1.8m patients were in this group. Patients aged 60–69 years were the second-largest group across the 7MM accounting for 19% of the total one-year diagnosed prevalent population. The number of such patients in the EU5 was more than c1.4m. The third-largest age group affected was 40–49 years.

Segmentation by disease severity[75]

Looking at disease severity is essential to get a clear picture of Arctic Bioscience's potential patient population as it targets mild and moderate cases. On average c36% of all cases were mild in the 7MM while mild and moderate cases together accounted for more than 75%. In 2017, this gives us c5m mild and c6.2m moderate cases, while c4.8m cases were severe. Japan and the UK were the two extremes when it comes to mild psoriasis. The UK had the lowest rate of mild cases (c22%) and Japan the highest (c47%).

[74] GlobalData
[75] GlobalData

One-year diagnosed prevalent cases of plaque psoriasis by severity, 7MM, men and women, aged ≥18 years, 2017

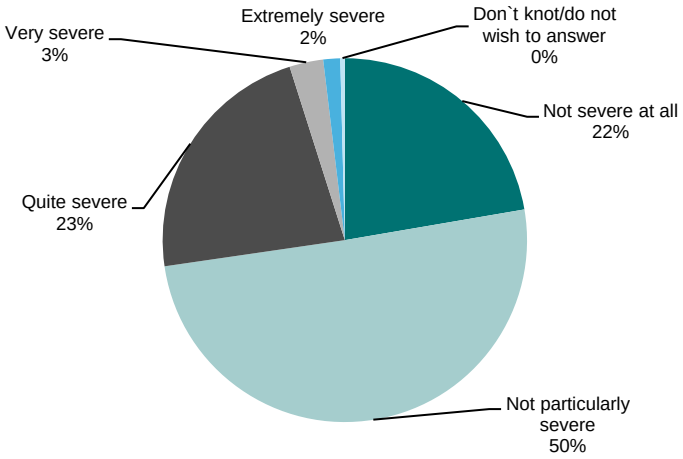


Source: GlobalData

Scandinavia

A comprehensive study was published in 2019 after surveying 22,025 people in Sweden, Norway and Denmark[76]. The results are very revealing about the epidemiology of psoriasis in Scandinavia. Based on pooled data, the average prevalence of physician-diagnosed psoriasis was 5.1% in these countries. Norway had the highest prevalence (both self and physician diagnosed) (11.9%) while the prevalence was similar in Sweden and Denmark, 9.2% and 9.4%, respectively. All these rates are well above the global average of c2-3% indicating the particular importance of psoriasis in this region.

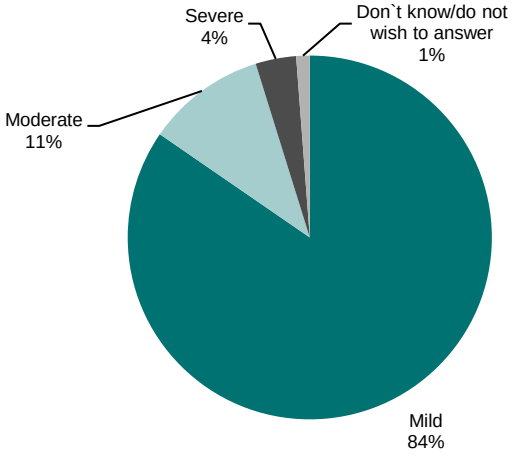
Scandinavian patient segmentation based on self-assessment



Source: Danielsen K et al. Acta Derm Venereol. 2019 01;99(1):18–25

[76] Danielsen K et al. Acta Derm Venereol. 2019 01;99(1):18–25

Scandinavian patient segmentation based on self-reported BSA



Source: Danielsen K et al. Acta Derm Venereol. 2019 01;99(1):18–25

As for severity, c73% of psoriasis patients rated their condition as “not severe at all” or “not particularly severe”. This ratio was lower (c55%) in patients having both psoriasis and PsA. Patients were also classified based on self-reported BSA. Apparently, the vast majority of patients in both groups qualified as mild or moderate. Among patient who only had psoriasis, the proportion of mild or moderate was c95%. In the group with both psoriasis and PsA the ratio was c85%. These proportions are higher than that calculated for the 7MM but could be explained by the higher overall prevalence in the Nordics. However, the segmentation in Scandinavia is based on patient-reported BSA, hence it should be interpreted with caution.

Disease model for mild and moderate psoriasis

At this point we have a lot of information about the population with psoriasis. In this section, we use it to estimate and forecast the number of mild and moderate cases. The exact number of people having psoriasis is of course unknown and constantly changing. Only a proportion of them have access to healthcare and clinicians to get diagnosed. These are the cases we can possibly get information about. Plaque psoriasis patients represent c80–90% of the whole patient population[77]. We have prevalence and incidence rates for psoriasis that together with overall population growth rates can be used to calculate and forecast the number of diagnosed plaques psoriasis patients. From a commercial perspective we are primarily interested in the EU5 and US markets along with Scandinavia. Healthcare information is generally well documented in these countries, so we can have a clear picture about the structure of the patient population. Once diagnosed, patients can be segmented by disease severity, where we are only interested in mild and moderate patients. However, not all diagnosed patients receive treatment. The proportion of the treated patients depends mainly on severity and varies between countries. Based on this, we calculated the number of diagnosed and treated mild and moderate patients across all the markets mentioned above and we made forecasts until 2036.

We assumed the population growth rates and age structure of the populations does not change during our forecast period. We also assumed that the proportion of mild, moderate and severe cases is the same in all Scandinavian countries. Additionally, without sufficient information, treatment rates from the UK were applied to the Scandinavian countries based on geographical proximity and the similarity of their tax-based healthcare systems.

[77] GlobalData

Disease model for HRO350

USA	2021e	2022e	2023e	2024e	2025e	2026e	2027e	2028e	2029e	2030e	2031e	2032e	2033e	2034e	2035e	2036e	2037e
Diagnosed moderate patients, (≥18 Years) (m)	3.053	3.119	3.184	3.249	3.323	3.401	3.483	3.557	3.633	3.710	3.789	3.870	3.952	4.036	4.121	4.209	4.293
Treated moderate patients, (≥18 Years) (m)	2.565	2.620	2.675	2.729	2.792	2.857	2.926	2.988	3.052	3.117	3.183	3.251	3.320	3.390	3.462	3.536	3.606
Penetration of HRO350 (%)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.1%	0.8%	1.5%	2.2%	2.9%	3.6%	4.3%	5.0%	5.0%	5.0%	5.0%
EU5																	
Diagnosed moderate patients, (≥18 Years) (m)	2.897	2.912	2.926	2.939	2.955	2.974	2.992	3.008	3.025	3.041	3.058	3.074	3.091	3.108	3.125	3.143	3.174
Treated moderate patients, (≥18 Years) (m)	1.788	1.799	1.810	1.820	1.831	1.845	1.859	1.871	1.883	1.895	1.907	1.920	1.933	1.945	1.958	1.971	1.991
Penetration of HRO350 (%)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	1.4%	2.3%	3.1%	4.0%	4.9%	5.8%	6.6%	7.5%	7.5%	7.5%
Scandinavia																	
Diagnosed moderate cases, (≥18 Years) (m)	0.129	0.130	0.131	0.132	0.133	0.134	0.135	0.137	0.138	0.139	0.140	0.141	0.142	0.143	0.145	0.146	0.147
Total treated moderate cases, (≥18 Years) (m)	0.094	0.094	0.095	0.096	0.097	0.097	0.098	0.099	0.100	0.101	0.101	0.102	0.103	0.104	0.105	0.106	0.107
Penetration of HRO350 (%)	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.5%	1.8%	3.1%	4.3%	5.6%	6.9%	8.2%	9.4%	10.7%	12.0%	12.0%

Source: DNB Markets

Economic burden

Exploring the economic burden of this disease is inevitable if we want to get a layered, holistic picture about psoriasis. Although economic evaluations have been made in many countries, we focus primarily on Europe and the US.

In Sweden, an annual total cost of EUR11,928 was calculated based on data collected from 164 patients. The total monthly cost of a patient was EUR994, comprising EUR776 direct costs and EUR218 indirect costs[78]. In Germany, the per patient per year (PPPY) cost for moderate-severe cases was cEUR3,000–7,000[79] and in Italy EUR8,372[80]. In the Netherlands two kinds of PPY were calculated, with and without biologic treatment. Without biologics PPY was EUR10,146 and for patients treated with biologics it was EUR17,712[81]. According to this[82], the major direct costs were medication costs, visiting physicians, and hospitalisation. Productivity loss was found to be the biggest element of indirect costs.

An even more comprehensive analysis was done in the US to assess every cost that could be connected to the disease[83]. Instead of insurer expenses or out of the pocket costs, they calculated incremental medical costs, i.e. the additional medical costs that occurred compared to an average person who does not have psoriasis. Productivity loss was also broken down into three categories: presenteeism measures the cost of decreased productivity at work due to the disease, absenteeism accounts for the costs stemming from patients being absent from work, and unemployment measures the cost (or loss) due to disease-related loss of work.

Moreover, psoriasis patients have a lower quality of life, and this analysis accounts for this factor as well and converts it to costs. After the analysis, incremental annual medical cost per patient turned out to be USD2,284. Patients with a mild disease had substantially lower costs (USD1,745) than moderate to severe cases (USD9,041). As for productivity loss, presenteeism accounted for USD4.4bn in total. Absenteeism contributes with USD2.9bn to the total cost. Psoriasis patients spend c1.3% more time away from work due to their disease, this translates into absenteeism costs. As for unemployment, c17% of psoriasis patients were unemployed for reasons attributable to their disease that led to USD4bn unemployment cost. Additionally, reduced quality of life could be translated into USD2,203 per patient per year. Totalling all these components gives a total annual per patient cost of psoriasis of USD6,579. After projecting this to the whole psoriasis population of the US, the total cost was USD35.3bn in 2013.

In summary, psoriasis affects many people globally, causing a substantial economic burden. The majority of the cases are mild or moderate and the number of patients is expected to grow in the next couple years across the major markets.

[78] Ghatnekar O et al. Eur J Dermatol 2012; 22(2):238-45
[79] Feldman SR et al. Expert Rev Pharmacoecon Outcomes Res. 2014 Oct;14(5):685–705
[80] Colombo G et al. Ther Clin Risk Manag 2008;4(2):559
[81] Driessen R et al. Br J Dermatol 2010;162(6):1324-9
[82] Feldman SR et al. Expert Rev Pharmacoecon Outcomes Res. 2014 Oct;14(5):685–705
[83] Vanderpuye-Orgle et al. J Am Acad Dermatol. 2015 Jun;72(6):961-967.e5

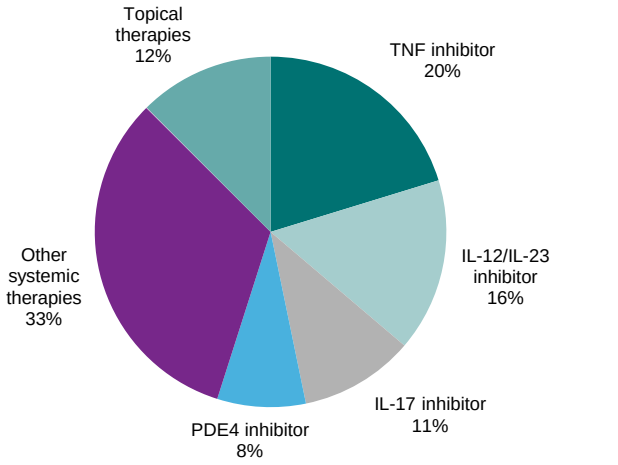
Psoriasis market

Here we look at the state of the global psoriasis market and see how it is expected to change in the next few years. Then we examine the biggest markets (the US, 5EU) and explore the most significant unmet needs, growth drivers and barriers. Finally, we cover emerging treatments that are relevant to understand Arctic Bioscience's competitive position.

Based on the pathomechanism of the disease, the psoriasis market can be considered a specific intersect of the immunosuppressants and dermatological markets. Both look set to be among the highest growing areas until 2024. EvaluatePharma® expects immunosuppressants and dermatological drugs to have a CAGR of 16.9% and 12.6% until 2024, respectively. At the same time, the majority of the therapeutic areas are only forecast to have a c1–4% CAGR. At the same time, anti-rheumatics, a bigger market than the previous two is expected to shrink by 1%. This could also be of interest, since there are several drugs used in both psoriasis and rheumatoid arthritis[84].

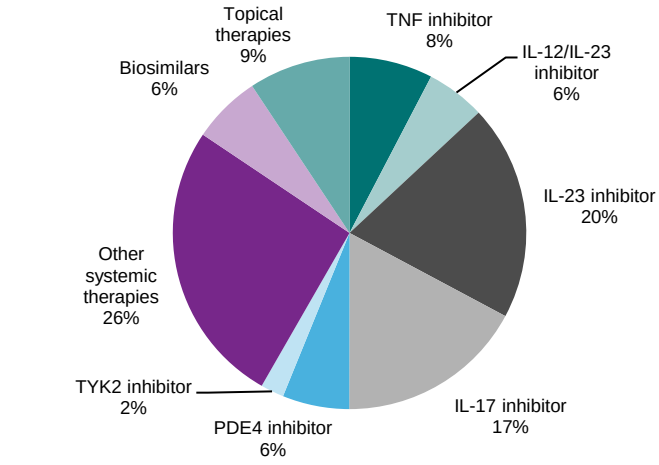
According to estimates from GlobalData, the global psoriasis market was worth USD12.2bn in 2017 and it is expected to have a CAGR of 4.7% to reach the value of USD19.2bn by 2027. The US is the biggest contributor to these values. It accounted for c78% of the global psoriasis market, which indicates a market value of USD9.5bn. The US market is expected to reach the value of USD15.8bn by 2027 and account for c82% of the global market by then.

US plaque psoriasis market in 2017



Source: GlobalData

US plaque psoriasis market in 2027e



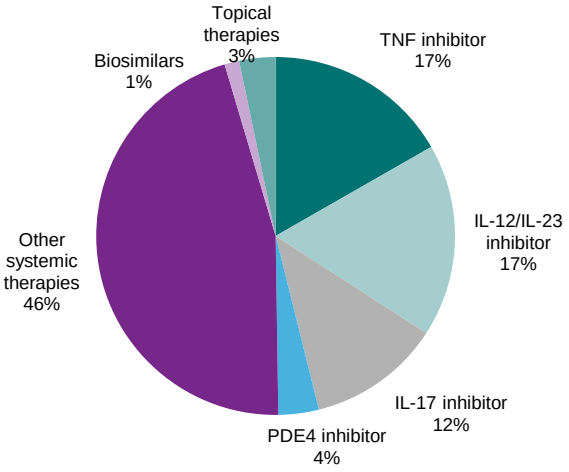
Source: GlobalData

In the US the treatment recommendations concerning psoriasis are detailed in the "Guidelines of care for the management of psoriasis and psoriatic arthritis" from the American Academy of Dermatology. Physicians usually rely on these guidelines together with their own knowledge and experience when they diagnose and treat patients. When it comes to diagnosis, c25% of diagnosed patients have mild, c40% moderate and c36% severe psoriasis. Approximately c69% of mild cases get treated, and the treatment rate rises as the disease gets more severe. The treatment rates are c84% and c91% for moderate and severe cases, respectively.

The market value of the E5U was cUSD2.1bn in 2017, which means a 17.3% market share. In the EU, Germany is the biggest and fastest-growing market with total sales of cUSD654m as of 2017. This market is expected to reach total sales of cUSD800m by 2027. The UK is the second-biggest market (USD503.7m) and it is forecast to remain in this position with a cUSD787m market size in 2027. Then we have France with cUSD410m of sales in 2017 and an estimated cUSD495m by 2027. Spain (cUSD277m in 2017) is also expected to grow during our forecast period to cUSD406m. Italy is the smallest of the EU5 with total sales of cUSD268m, that is estimated to reach cUSD343m by 2027[85].

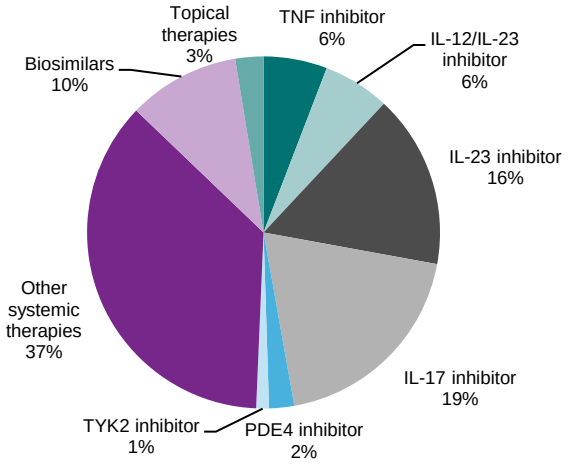
[84] https://info.evaluate.com/rs/607-YGS-364/images/EvaluatePharma_World_Preview_2019.pdf
[85] GlobalData

EU5 plaque psoriasis market in 2017



Source: GlobalData

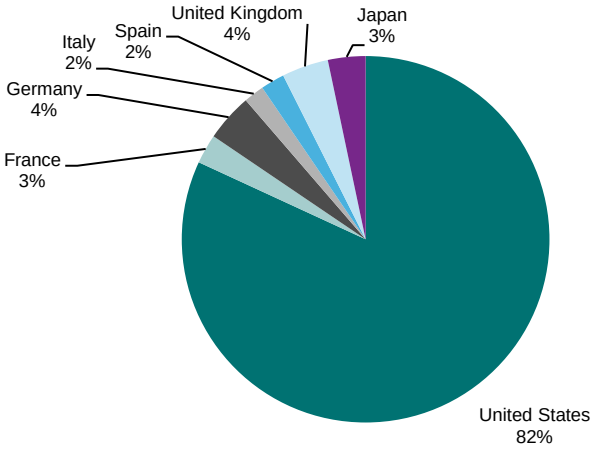
EU5 plaque psoriasis market in 2027e



Source: GlobalData

The European treatment recommendations are detailed in the "European S3-Guidelines on the systemic treatment of psoriasis vulgaris", and physicians tend to follow this combined with their own judgment and knowledge. Understandably, diagnosis and treatment rates vary between countries, so it is more informative to give ranges for each parameter. Based on diagnoses rates, mild cases account for c22–46% of all cases, moderate c34–48% and severe c19–30%. Although rates value greatly, it is clear that mild and moderate cases constitute the majority of psoriasis patients. Similar to the US, treatment rates increase as the disease gets more severe. Approximately 25–56% of mild cases are treated. But as we go to moderate and severe cases the figures rise to 44–72.5% and 63–-95% respectively.

Plaque psoriasis sales forecast by country, 2027e (total sales USD19.2bn)



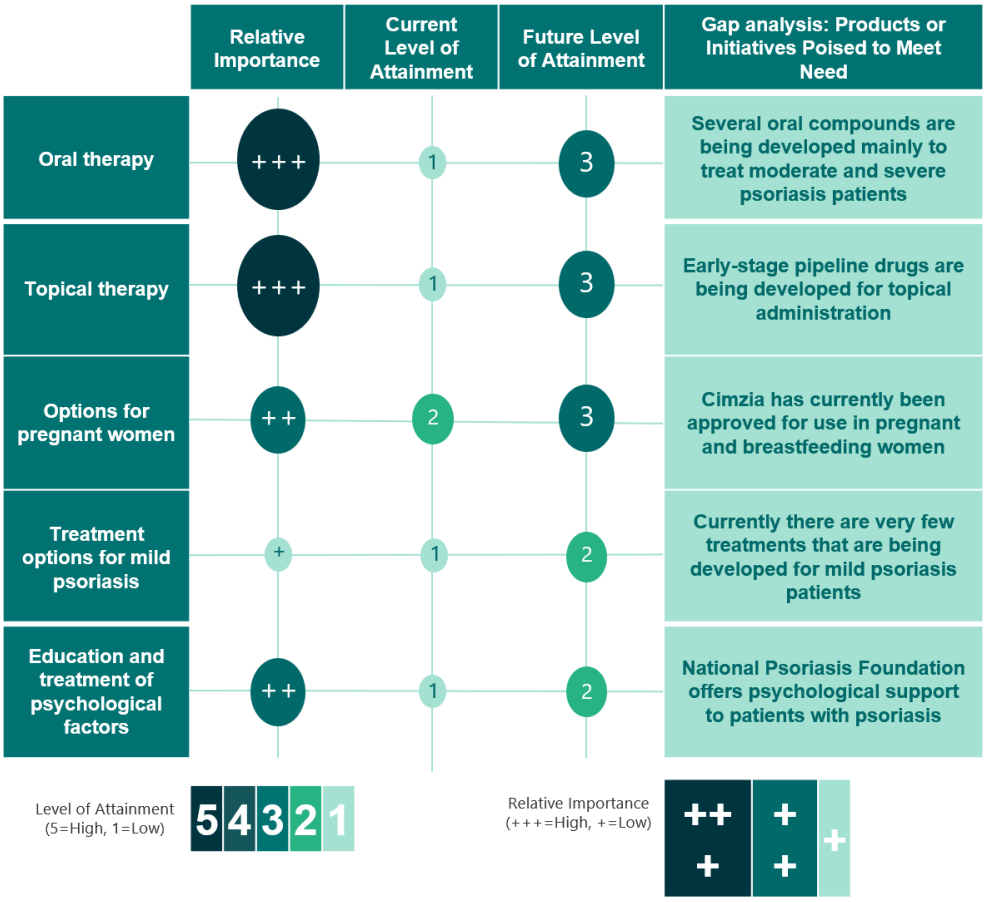
Source: GlobalData

When we examine where product sales will come from in the EU5 and the US, we can see that in the US a fairly big proportion (c20%) comes from topical treatments that are the main competitors of Arctic Bioscience. This percentage is expected to shrink due to new systemic therapies and the growth in sales of new biologics and other systemic therapies. In the EU5 'other systemic therapies' are – and should remain – the biggest product segment, while topical treatment accounts for only 3% of total sales. Arctic Bioscience is expected to compete with topical treatments and systemic therapies used in mild and moderate cases.

Unmet needs, growth drivers and barriers

Now with a clear overview of the market, let us delve into the factors that could well shape the psoriasis market in the next decade and how Arctic Bioscience fits in.

Unmet medical needs concerning psoriasis



Source: GlobalData

The analysis of GlobalData identified five major unmet needs on the psoriasis market and Arctic Bioscience has the potential to address at least three of them:

First, there is a need for oral therapies. Psoriasis is a chronic disease; thus, patients rely on a treatment for a long period. This makes the route of administration a central question that can greatly affect adherence to the treatment. Topical options have some shortcomings as we discovered. Light therapy also has its limits and subcutaneous injections are also not ideal. Both light therapy and biologics require the presence of a healthcare professional, which ties up resources and increases the cost of the treatment. The most convenient way of administration is the oral route, and this is expected to increase adherence. Moreover, oral treatments can unburden the healthcare system by reducing the number of required visits to the dermatologist or general practitioner. Only one oral drug is on the market, Otezla®, which targets patients with moderate and severe psoriasis. There are other oral drug candidates in the pipeline; they will be analysed in detail in the next section.

Second, there is a need for new mild psoriasis treatments. Patients with mild psoriasis have limited options; choices are mainly restricted to topical therapies and light therapy. Additionally, there have been few developments in the treatment of mild psoriasis during recent years as most of the development takes place among biologics targeting moderate and severe cases. Available therapies that address mild psoriasis have been on the market for decades. This need becomes even more justified as we have seen that a substantial part (if not the majority) of patients have mild psoriasis, so there is a huge patient population to address. Additionally, if we had an effective drug to treat mild cases, fewer patients would become moderate and severe, that would decrease the need for expensive biologics and thus reduce healthcare costs. Arctic Bioscience targets mild and moderate patients, so based on this need their product could address a significant gap on the market.

The third need is a safe an effective treatment for pregnant women. Approximately 20–40% of pregnant women suffering from psoriasis experience an increase of symptoms during pregnancy. This makes this need even stronger. Only one drug called, Cimzia®, can be given to pregnant and breastfeeding women as it demonstrated a favourable safety and efficacy profile in a Phase II/III study[86]. In trials assessing the effect of omega-3 fatty acids there was not much information about the involvement of pregnant women and in some trials they were excluded. However, omega-3 fatty acids are natural compounds and women consume them with food during pregnancy. In addition, pregnant women in the US have lower levels of omega-3 fatty acid than is ideal and the supplementation with omega-3 fatty acids is associated with several improved health outcome[87][88]. Moreover, Arctic Bioscience already has an omega-3 supplement for pregnant women in China. The product is marketed in collaboration with Kotler Marketing. Based on these factors, HRO350 could be a safe option for pregnant and breastfeeding women[89].

There are three other global growth drivers that will influence market dynamics in the following years. As seen earlier, a large proportion of the expected market growth will come from biologics. New drugs will enter this segment and together with upcoming biosimilars will put pressure on current biotherapeutics. New therapies mainly target IL-23 and IL-17 with high efficacy. Novel drugs are also expected to have a less frequent administration regimen, which would make them more convenient for patients. Another driver is the rise of new oral formulations. This driver is very relevant for Arctic Bioscience, so we will examine upcoming oral therapies in a later section. Increase in the prevalence and treatment rate of psoriasis will also support the growth of this area[90].

The main barriers are pricing issues of new drugs in the US and the EU. Drug prices are historically lower in the EU and this will limit sales of new drugs in this market. Additionally, the entrance of biosimilars will stimulate competition and put further pressure on prices all over the world. While most of the growth drivers (new oral drugs, prevalence, treatment rates) have a beneficial effect on Arctic Bioscience's business, they are only weakly affected by barriers, because the company does not compete with biologics and the price of its product will be substantially lower than biologics.

To sum up, psoriasis has a large global market with good growth prospects. Geographically, the US is the largest market and it is expected to remain so. There is certainly a need for safe and effective oral treatments and many mild patients also await a better option to ease their symptoms. We believe Arctic Bioscience's HRO350 could well fill these gaps.

Competitive landscape

As detailed earlier, much of the development is taking place in the biologics field, but since they are mainly applied in the most severe cases or if other treatments failed, they do not compete directly with Arctic Bioscience, so we do not cover the competitive landscape of biologics here. Instead, we apply a set of simple criteria to identify relevant emerging therapies. Arctic Bioscience's product is an oral drug, aimed to treat mild to moderate psoriasis. Consequently, we will explore oral drugs and therapies to treat mild and moderate psoriasis and finally, we look for products that are at the intersection of these two criteria.

Marketed products

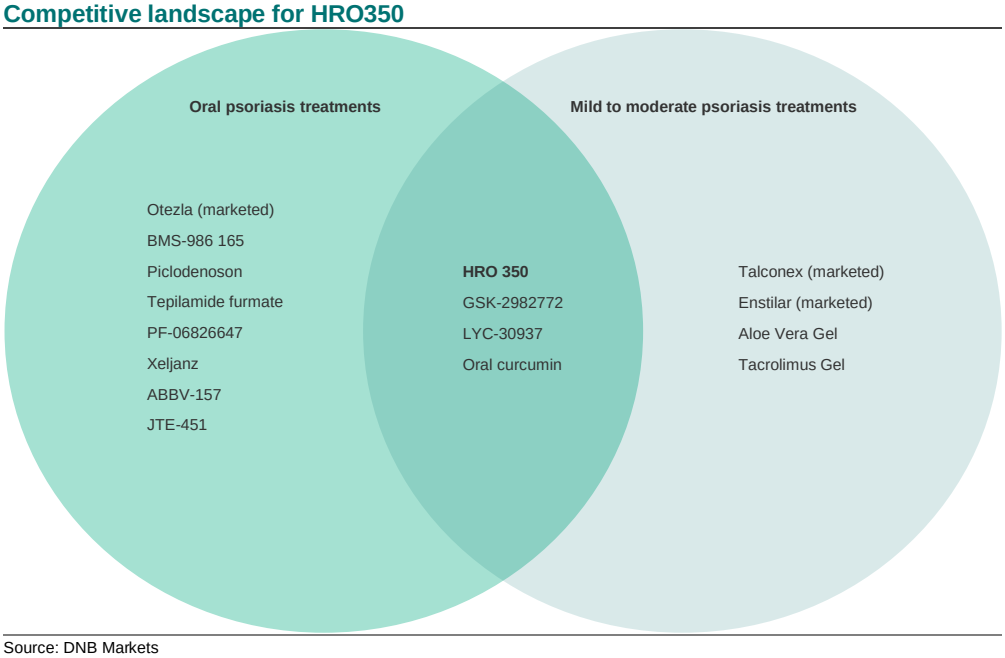
Otezla® (apremilast) is the only oral drug approved to treat psoriasis. It inhibits phosphodiesterase-4 (PDE-4) and reduces cAMP breakdown. This results in the reduction of pro-inflammatory cytokines and in the improvement of psoriasis symptoms. It has been used in numerous indications where this pathway is involved. It was originally developed by Celgene, but when the company was to be acquired by Bristol Myers Squibb Otezla® was sold to Amgen in 2019 to comply with antitrust laws[91]. Otezla® is approved in the US (September 2014) and the EU (January 2015) to treat moderate and severe psoriasis

[86] GlobalData
[87] https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD003402.pub3/full
[88] Zhang Z et al. Nutrients. 2018 28;10(4)
[89] https://arcticnutrition.no/2019/06/27/arctic-nutrition-as-has-signed-a-strategic-partnership-agreement-with-kotler-a-leading-marketing-company-in-china/
[90] GlobalData
[91] https://wwwext.amgen.com/media/news-releases/2019/08/amgen-to-acquire-otezla-for-134-billion-in-cash-or-approximately-112-billion-net-of-anticipated-future-cash-tax-benefits/

patients[92]. Otezla®'s efficacy was proven in two randomised, double-blind, placebo-controlled trials, ESTEEM-1 and ESTEEM-2, involving 844 and 413 patients, respectively[93]. During the trials Otezla® was taken two times a day. On average, c30% of patients achieved PASI75 after 16 weeks. This qualifies as modest efficacy, a bit higher than methotrexate but still below the level of most biologics. As for safety, adverse events (AEs) were mild or moderate; the most common side effects were diarrhoea, nausea, upper respiratory tract infection and nasopharyngitis. Its main benefit, beside the oral administration, is that it does not require laboratory monitoring. According to clinicians, the drug's relatively low efficacy does not justify its relatively high price even if we consider the safety profile and the oral administration. The annual wholesale cost of an Otezla® therapy is cUSD24,000 in the US and cUSD17,000 in Germany. The primary patent on Otezla® expires in 2024 in the US and in 2028 in the EU. Otezla® is forecast to have a CAGR of 37.4% taking US sales to USD927.5m by 2024[94].

There are several options to treat mild and moderate psoriasis. The molecules used in topical formulations are quite old and most of them are no longer patent protected. This is why there are numerous companies manufacturing them. An ointment containing the combination of calcipotriene and betamethasone diproprionate was approved by the FDA under the name **Taclonex®** in 2006. In the EU it is sold under the brand names Dovobet® and Diavobet®. Leo Pharma held patents for Taclonex® that expired in 2015 and has another patent to protect the formulation that expired in 2020. Perrigo and Tolmar Inc. together with Sandoz got an Abbreviated New Drug Approval (ANDA) for a generic product for when Leo Pharma's patent will expire. Leo Pharma also sells this combination formulated as an aerosol foam under the brand name **Enstilar®**. The efficacy of this combination has been established in three trials both involving more than a thousand patients. Two focused on scalp psoriasis and the third evaluated efficacy in body psoriasis. In every trial, the combination showed significantly better results than the two active ingredients alone. Taclonex® was well tolerated during the trials; the most common AEs included itching, redness and irritation. Taclonex® is applied only once a day, which substantially increases the adherence to the therapy. The monthly cost of Taclonex® is cUSD1,600 in the US and a much lower USD250–350 in the EU depending on the country[95]. In summary, Taclonex®/Enstilar® is a safe and effective combination available in various formulations with favourable dosing for a low price. However, it does not have market exclusivity and can be messy to apply for some patients.

Competitive landscape for HRO350



Source: DNB Markets

[92] Drugs@FDA
[93] Rich P et al. J Am Acad Dermatol. 2016 Jan;74(1):134–42
[94] GlobalData
[95] GlobalData

Oral psoriasis drugs in pipeline

To address the unmet need of oral therapies, several companies are developing such formulations. Bristol Myers Squibb's BMS-986165 could be significant contender in the future. It is a Tyk2 inhibitor in Phase III to treat moderate and severe psoriasis[96]. There are numerous Phase III trials under way. Bristol Myers Squibb is recruiting patients for a long-term study that is expected to be completed in 2024[97]. It is also conducting Phase III trials in Japan, China and South Korea[9899]. Favourable Phase II results were published in 2018[100]. At the end of the 12 weeks, PASI75 was achieved by 39–75% of patients in a dose-dependent manner. In the group receiving the highest dose, 89% achieved PASI50 and 25% reached total remission (PASI100). The improvement was significantly bigger than in the placebo group. The product has an average safety profile, 55–80% of patients experienced AEs that included nasopharyngitis, headache, diarrhoea and nausea.

Piclodenoson (also known as CF101) is being developed by Can-Fite BioPharm Ltd. It acts as an A3 adenosine receptor (A3AR) agonist and aims to treat moderate and severe cases. This is an oral pill taken twice a day. The Comfort™ Phase III trial was designed to prove piclodenoson's superiority to placebo and non-inferiority to Otezla®. In the interim analysis conducted by the IDMC, it recommended that the trial continue in its original size and drop one of the piclodenoson dose groups (in the Comfort™ trial 2mg piclodenoson and 3mg are compared to Otezla and placebo). This suggests the drug is on its way to achieving its primary endpoints. However, no details on efficacy and safety were presented.

Tepilamide fumarate (also known as PPC-06, formerly XP23829) was originally developed by Xenoport and was bought by Dr. Reddy`s Laboratories[101]. A Phase II trial in 2015 examined three dosage regimens (400mg once daily, 800mg once daily, 400mg twice daily) compared to placebo. PASI change from baseline was significantly different from placebo, -49.2% and -50.7% for the 800mg and 400mg twice daily groups. Diarrhoea occurred in 22–40% in the treatment groups and 15% in the placebo group. Apart from that, nausea, abdominal pain and vomiting concerned more than 10% of the treatment group respectively[102]. In the next Phase IIb trial in 2019 PASI75 was achieved in c40–45% of patients in a dose dependent manner at the end of the 24-week trial. This was significantly better than the placebo group[103]. To sum up, PPC-06 is a fairly safe drug that can provide patient with clinically meaningful improvement, but it has a quite unfavourable safety profile.

Pfizer has several projects concerning psoriasis. PF-06826647 is a Tyk2 inhibitor aimed at treating moderate and severe psoriasis. It is in Phase II, which is expected to report data in early 2021. Its peak sales estimate is USD230m[104]. Pfizer's other product is Xeljanz® (Tofacinitib), a selective JAK1 and JAK3 inhibitor. It is approved to treat PsA and rheumatoid arthritis. Its efficacy has been proven in several trials but the application was rejected because of safety problems[105]. After the rejection, a Phase III study was conducted to provide more data about the safety profile but the result was similar to the previous trials. The main safety issues included serious infections, increased rate of malignancies and major cardiovascular problems[106]. These results are not likely to support the approval of Xeljanz®, so it is not likely that Xeljanz® will get to the market. Based on this data PF-06826647's future looks brighter in this therapeutic area.

AbbVie also develops an oral treatment together with Inventiva under the name ABBV-157[107]. This molecule is a RORy T inhibitor that reduces the production of IL-17 and IL-23. The development is in Phase I, and the results are expected to be released in 2021[108].

[96] https://www.evaluate.com/vantage/articles/events/company-events/bristol-hopes-tyk-psoriasis-box
[97] https://clinicaltrials.gov/ct2/show/NCT04036435?term=NCT04036435&draw=2&rank=1
[98] https://clinicaltrials.gov/ct2/show/NCT03924427?term=NCT03924427&draw=2&rank=1
[99] https://clinicaltrials.gov/ct2/show/NCT04167462?term=NCT04167462&draw=2&rank=1
[100] Papp K et al. N Engl J Med. 2018 04;379(14):1313–21.
[101] https://www.fiercebiotech.com/r-d/under-pressure-xenoport-sells-u-s-rights-of-failed-psoriasis-pill-to-dr-reddy-s
[102] Gottlieb AB et al. J of Skin. 2017 Oct 27;1:s33–s33.
[103] https://futuremedicineindia.com/ppc-06-shows-promising-results-against-psoriasis-dr-reddys/
[104] https://www.evaluate.com/vantage/articles/news/trial-results/pfizer-bulls-go-search-hidden-gems
[105] https://www.pfizer.com/news/press-release/press-release-detail/pfizer_receives_complete_response_letter_from_fda_for_oral_xeljanz_tofacitinib_citrate_supplemental_new_drug_application_for_moderate_to_severe_chronic_plaque_psoriasis
[106] Valenzuela F et al. Br J Dermatol. 2018 Oct;179(4):853-862
[107] http://www.globenewswire.com/news-release/2019/12/03/1955752/0/en/Inventiva-receives-a-3-5-m-milestone-payment-from-AbbVie.html
[108] https://clinicaltrials.gov/ct2/show/NCT03922607?term=NCT03922607&draw=1&rank=1

Akros Pharma's candidate JTE-451 has the same mechanism of action as AbbVie's molecule, it is also a RORy T inhibitor. The company completed a Phase II study in February 2020 to assess compound efficacy in moderate and severe psoriasis patients[109].

Mild to moderate psoriasis therapies in pipeline

There are a couple of studies about topical options that are outside the realm of corticosteroids or vitamin D analogues. Although not approved, tacrolimus can be used for the treatment of mild and moderate cases in several formulations. In a randomised open-label observer blinded trial, tacrolimus was administered twice a day as a gel, cream, or ointment. The trial involved 124 patients. Tacrolimus showed slightly lower efficacy than the 0.005% calcipotriol ointment that was used as comparator measured by local psoriasis severity index (LPSI), a similar measure to PASI. Tacrolimus treatments reduced LPSI by c50–55% as opposed to the change in the calcipotriol group c59%. Tacrolimus could also reduce BSA by c40%. The proportion of patients who experienced adverse events was comparable across the groups, c62–67%; skin burning was the most common side effect[110].

Aloe vera extract has also been tested in mild and moderate cases and showed positive results. In a double-blind, placebo-controlled trial, involving 60 patients, 0.5% aloe vera extract reduced PASI by 77.3% during four weeks, while in the placebo group the reduction was only 7.9%[111]. In another randomised double-blind trial 0.1% aloe vera was compared to triamcinolone in 80 patients. The effects were similar: aloe vera reduced PASI by c66% and DLQI by c71%.[112]However, another study found aloe vera no different from placebo[113]. It is hard to believe that – according to the first two studies – aloe vera is comparable to or better than standard of care. If it was true, aloe vera would probably be more widely used as a psoriasis treatment. Aloe vera might be able to improve symptoms, but especially in the light of the last study positive results should be taken with a grain of salt.

Oral drug candidates to treat mild and moderate psoriasis

So far, the options were either oral treatments that targeted moderate to severe patients or topical formulations to treat mild and moderate cases. Now we describe the options that fulfil both criteria and aim to treat mild to moderate patients with an oral therapy.

GSK is developing such a drug, a Receptor-Interacting Protein Kinase 1 (RIPK1) inhibitor called GSK-2982772. It was tested in a randomised, placebo-controlled Phase IIa study involving 65 patients. The drug was taken twice a day. The placebo response was unusually high, therefore there was no clear difference between the treatment and placebo groups and the drug failed to meet the primary endpoint. The safety profile was similar to other candidates with the most frequent adverse effects being nasopharyngitis, headache and arthralgia[114]. GSK-2982772 is now being evaluated in a Phase I trial in moderate to severe patients. The study is estimated to be completed in Q3 2021[115].

Another oral formulation is being developed by Lycera Corporation under the codename LYC-30937. The drug has been tested on 33 patients in a Phase II trial, where the primary endpoint was missed. The reduction in PASI caused by the drug candidate (-25.8%) was not significantly different (p=0.2205) from placebo (-12.63%) after 12 weeks. 50% of patients experienced adverse event, mainly diarrhoea, infections and headache[116].

Oral curcumin (Meriva) was also tested in a phase III randomised, double-blind, placebo-controlled trial. In total, 63 patients took part in the 16-week long trial. Both groups received local corticosteroid therapy and the intervention group also received oral curcumin in the form of two 500mg tablets taken twice a day. The intervention group showed significantly bigger reduction in PASI (74.5%) than the control group (48%). Adverse effects in the treatment group included diarrhoea, fever and gastroenteritis, although it is not clear if all of them were study related effects. The authors concluded that oral curcumin could be a good adjuvant

[109] https://clinicaltrials.gov/ct2/show/NCT03832738
[110] Ortonne J-P et al. Acta Derm Venereol. 2006;86(1):29–33
[111] Syed TA et al. Trop Med Int Health. 1996 Aug;1(4):505–9
[112] Choonhakarn C et al. J Eur Acad Dermatol Venereol. 2010 Feb;24(2):168-72
[113] Paulsen E et al. J Eur Acad Dermatol Venereol. 2005 May;19(3):326–31
[114] Weisel K et al. Clinical Pharmacology & Therapeutics. 2020;108(4):808–16
[115] https://clinicaltrials.gov/ct2/show/NCT04316585
[116] https://clinicaltrials.gov/ct2/show/NCT02872285

treatment[117]. Another study found that curcumin nanoparticles were effective as adjuvant treatment in moderate and severe cases[118].

In summary, based on these clinical trials we see a gap in the market for an effective oral therapy to treat mild and moderate psoriasis. Oral therapies are mainly developed to treat moderate to severe patients, thus they do not compete directly with Arctic Bioscience, while mild to moderate treatments are mostly topical. On top of that, two of the three oral treatments we found for mild and moderate cases failed their respective trials. Consequently, there is space for a new oral formulation for mild and moderate patients.

[117] Antiga E et al. Biomed Res Int. 2015;2015:283634
[118] Bilia AR et al. J Pharm Pharmacol. 2018 Jul;70(7):919-928

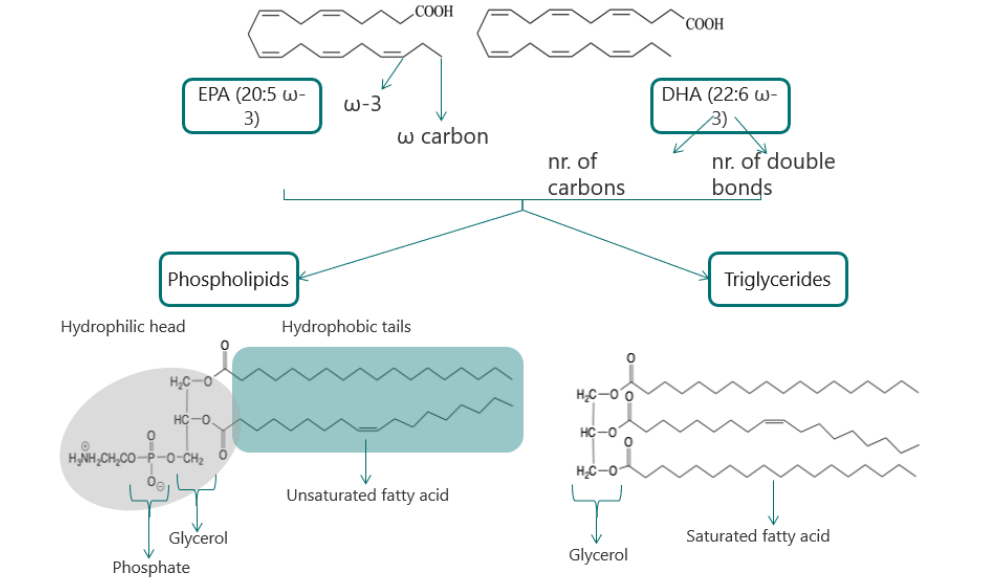
Phospholipid bound omega-3 fatty acids

Arctic Bioscience's product consists of a combination of phospholipid bound omega-3 fatty acids. In this section we examine omega-3 fatty acids to better understand the product and clinical results.

Chemical features

From a chemical point of view, fatty acids are carboxylic acids with a long, straight chain of carbon atoms. They always contain an even number of carbon acids. Omega-3 fatty acids belong to the group of polyunsaturated fatty acids (PUFA), meaning there are double bonds between certain carbons in the chain. The systematic numbering of carbon atoms starts at the carboxylic acid group. The next carbon atoms (number 2 and 3) are commonly referred to as alpha and beta carbons. Consequently, the last carbon at the end of the chain is the omega carbon atom. The position of double bonds is described by their place relative to the omega carbon. For example, the position of a double bond between the third and fourth carbon counting from the omega carbon is called omega-3, so fatty acids that have a double bond at the omega-3 position are referred to as omega-3 fatty acids. Omega-3 fatty acids are also called n-3 fatty acids in some articles. In Arctic Bioscience's drug candidate, there is a specific mix of phospholipid esters of two main omega-3 fatty acids: eicosapentaenic acid (EPA) and docosahexaenic acid (DHA). EPA consists of 20 carbon atoms and has five double bonds, while DHA has contain 22 carbon atoms with six double bonds[119].

Chemical structure of EPA and DHA and possible forms of omega-3 fatty acids in the body



Source: DNB Markets

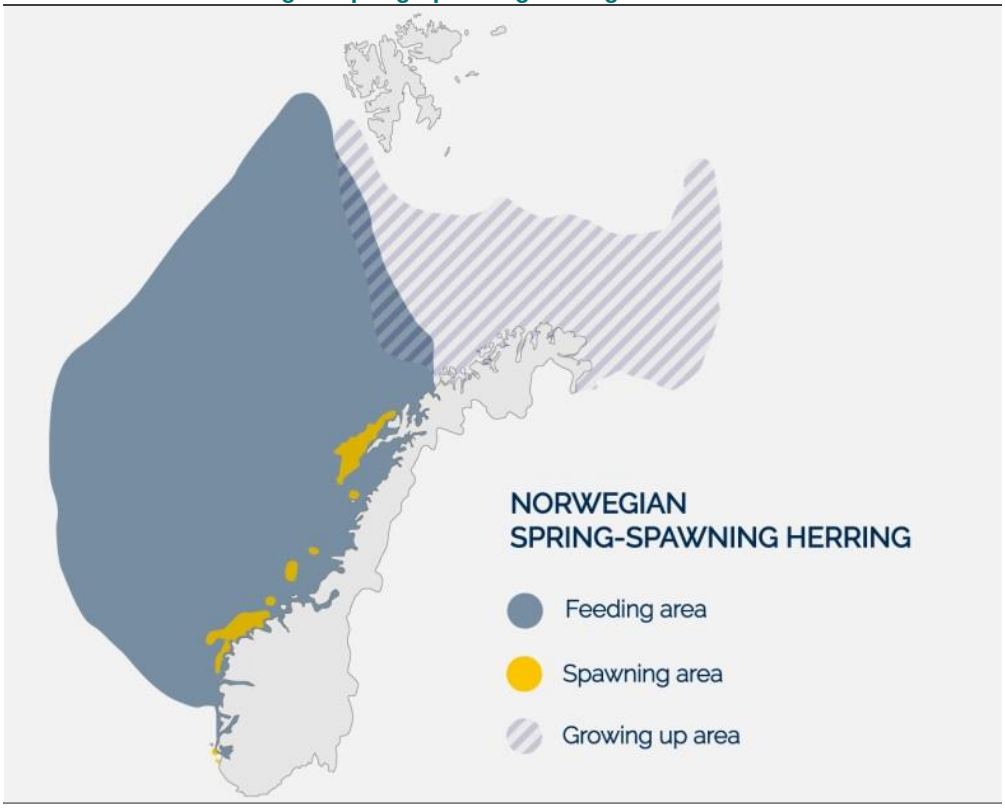
Fatty acids are present in various forms in nature. The chemical structure of the individual fatty acid and the form in which it is present affects their bioactivity and therapeutic effect. They can be present as free fatty acids or esters. Esters are basically a combination of a fatty acid with an alcohol (an organic compound with a hydroxyl group). In nature, the alcohol that most commonly forms esters with fatty acids is glycerol that has three hydroxyl groups on three carbons. If all three hydroxyl groups form an ester with a fatty acid, we talk about triglycerides (TG). These hydrophobic molecules have a very substantial role in the body's lipid homeostasis. Another form is phospholipids (PL), when one of the hydroxyl groups forms a bond with a hydrophilic group that contains a phosphate group. Due to this, PLs are amphiphile compounds. They form the cell membranes but also take part in signalling pathways among others[120].

[119] Drevon CA. Nutr Rev. 1992 Apr;50(4 (Pt 2)):38–45
[120] Burri L et al. Int J Mol Sci. 2012 Nov 21;13(11):15401–19

Sources of Arctic Bioscience's raw material

The essential fatty acids for humans are alpha-linolenic acid (ALA) an n-3 PUFA and linoleic acid (LA) an n-6 PUFA. These compounds can be transformed to other n-3 and n-6 fatty acids by certain enzymes, but the process works slowly so it is better to consume other important fatty acids with food[121]. The original and primary producers of omega-3 fatty acids are plants, including algae in the sea. The main sources of ALA are linseed, canola and soybean[122]. Plants produce omega-3 fatty acids in their chloroplasts[123]. Species that are evolutionary more developed (including humans) cannot introduce a double bond in the n-3 position, so they have to take up these compounds with food. Algae in the sea are among the biggest producers of omega-3 fatty acids. They are consumed by various species and this is how omega-3 fatty acids move upwards in the food chain.

Natural habitat of Norwegian spring-spawning herring



Source: Company

Many species are rich in omega-3 fatty acids including fish, krill, shrimps and seals. Cold water fish are one of the main sources of human omega-3 consumption[124]. The most common species include salmon, sardines, mackerel and herring. They have a TG content of 10–15% and they also contain 1–1.5% PLs. Up to c30% of EPA and DHA in these species is in a form of PLs[125]. The omega-3 fatty acid content of fish can be subject to geographical and seasonal variation[126]. Additionally, there tends to be a difference in the n-3/n-6 fatty acid ratio between farmed fish and wild fish. This ratio is c14.5 in wild fish, while farmed fish have a decreased ratio of c1.5. The reason for this is that farmed fish are fed vegetable oils and seeds rich in n-6 fatty acids. Another valuable source of n-3 fatty acids is krill oil, which is extracted from Antarctic crustacea, a zooplankton species. The PL content of krill oil is usually c40% and it mainly contains EPA and DHA[127]. The source used by Arctic Bioscience is herring roe and it is particularly rich in n-3 PUFAs. Roe means the eggs of the fish. It is a quite underutilised by-

[121] Deckelbaum RJ et al. J Nutr. 2012 Mar;142(3):587S-591S
[122] Drevon CA. Nutr Rev. 1992 Apr;50(4 (Pt 2)):38–45
[123] Adarme-Vega TC et al. Microbial Cell Factories. 2012 Jul 25;11(1):96
[124] Drevon CA. Nutr Rev. 1992 Apr;50(4 (Pt 2)):38–45
[125] Burri L et al. Int J Mol Sci. 2012 Nov 21;13(11):15401–19
[126] Deckelbaum RJ et al. J Nutr. 2012 Mar;142(3):587S-591S
[127] Burri L et al. Int J Mol Sci. 2012 Nov 21;13(11):15401–19

product of herring fisheries[128]. Roe has 38–75% of its omega-3 content in a PL form, most commonly as phosphatidyl choline (PC). EPA and DHA are the predominant fatty acids of fish roe[129].

Role in the body

The role of omega-3 fatty acids is at least threefold. As PLs, they can influence certain features of cell membranes and cellular processes connected to the membrane. They also play a role in metabolism and lipid homeostasis. Additionally, they take part in signalling pathways and in important physiological processes like inflammation. If we consume food that contains omega-3 fatty acids, lingual and gastric lipases in the stomach start to digest TGs, while the hydrolysis of PLs usually starts in the small intestines by various lipases including pancreatic lipase and phospholipase A2. After absorption PLs end up on the surface of chylomicrons while TGs are inside. As the chylomicron circulates with the bloodstream lipoprotein lipases (LPL) bound to the endothelium liberate free fatty acids that can be taken up by the tissues. The rest of the chylomicron circulates and transforms into various lipoproteins that help to maintain blood lipid and cholesterol levels. Fatty acids can be taken up by adipose tissue and turned into TGs again to store energy. Alternatively, PLs can be incorporated in the cell membrane where the proportion of different PLs can affect the fluidity, viscosity and permeability of the membrane. This also has an effect on the membrane proteins and indirectly on signalling pathways. N-3 PUFAs can also be metabolised and modified. They become molecules that regulate various processes including inflammation[130].

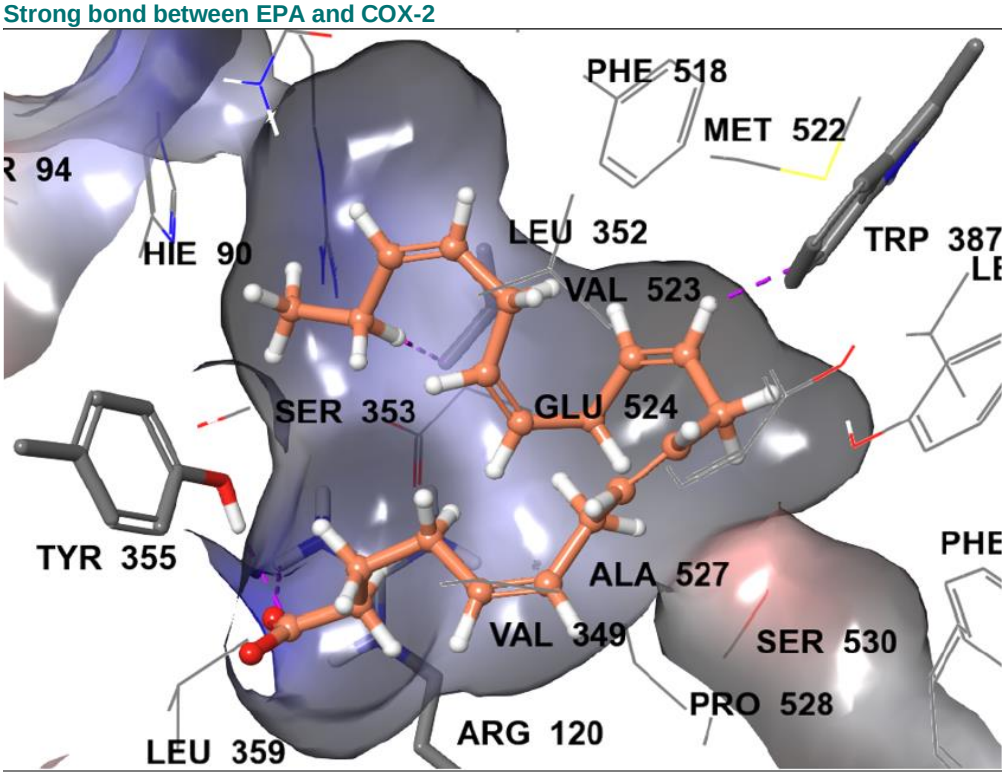
Role in inflammation and psoriasis

The process of inflammation is incredibly complex, and the role of omega-3 fatty acids is only one part. However, they play an important part since their metabolites are significant regulators of inflammation. The way fatty acid metabolites regulate inflammation is connected to the balance of n-3 and n-6 fatty acid metabolites. First, a set of elongase and desaturase enzymes transform ALA (n-3) and LA (n-6) into other fatty acids. LA turns into AA or docosapentanoic acid (DPA), both are n-6 fatty acids. ALA gets transformed into EPA and DHA. Along the whole metabolic process n-3 and n-6 fatty acids compete for the same enzymes. Hence the end result depends on the n-3/n-6 ratio. AA can be a substrate of COX that turn it into cyclic endoperoxides, then after other transformational steps different series 2 prostaglandins (PG) can be produced: PGE2, PGI2 and TXA2 among others.

In a computational chemistry project, conducted at the University of Budapest by one of DNB Markets' interns in the healthcare team, Mr Mark Fabian, docked EPA into the binding pocket of the COX-2 enzyme. After he prepared the protein structure and validated the model, Mr Fabian docked 74 compounds from the DrugBank, and EPA came out as one of the most promising compounds. Docking is a simulation where the computer finds the most ideal 3D orientation for binding between the ligand (EPA) and the enzyme (COX-2). The program (Schrödinger – Maestro) maps the possible interactions between the ligand and the binding site and assigns a docking score to every molecule, which indicates the strength of the bond, the lower the better. This method can be used to screen compounds and those with the lowest score have the potential to be viable COX-2 ligands or inhibitors. In his experiment EPA achieved one of the best docking scores, indicating a strong bond with the COX-2 enzyme. It folds into the binding pocket very nicely despite having a different structure than most of the ligands/inhibitors he examined. This finding reinforced our views on EPA's role in inflammation.

[128] Cook CM et al. Prostaglandins Leukot Essent Fatty Acids. 2016;111:17–24
[129] Burri L et al. Int J Mol Sci. 2012 Nov 21;13(11):15401–19
[130] Burri L et al. Int J Mol Sci. 2012 Nov 21;13(11):15401–19

Strong bond between EPA and COX-2

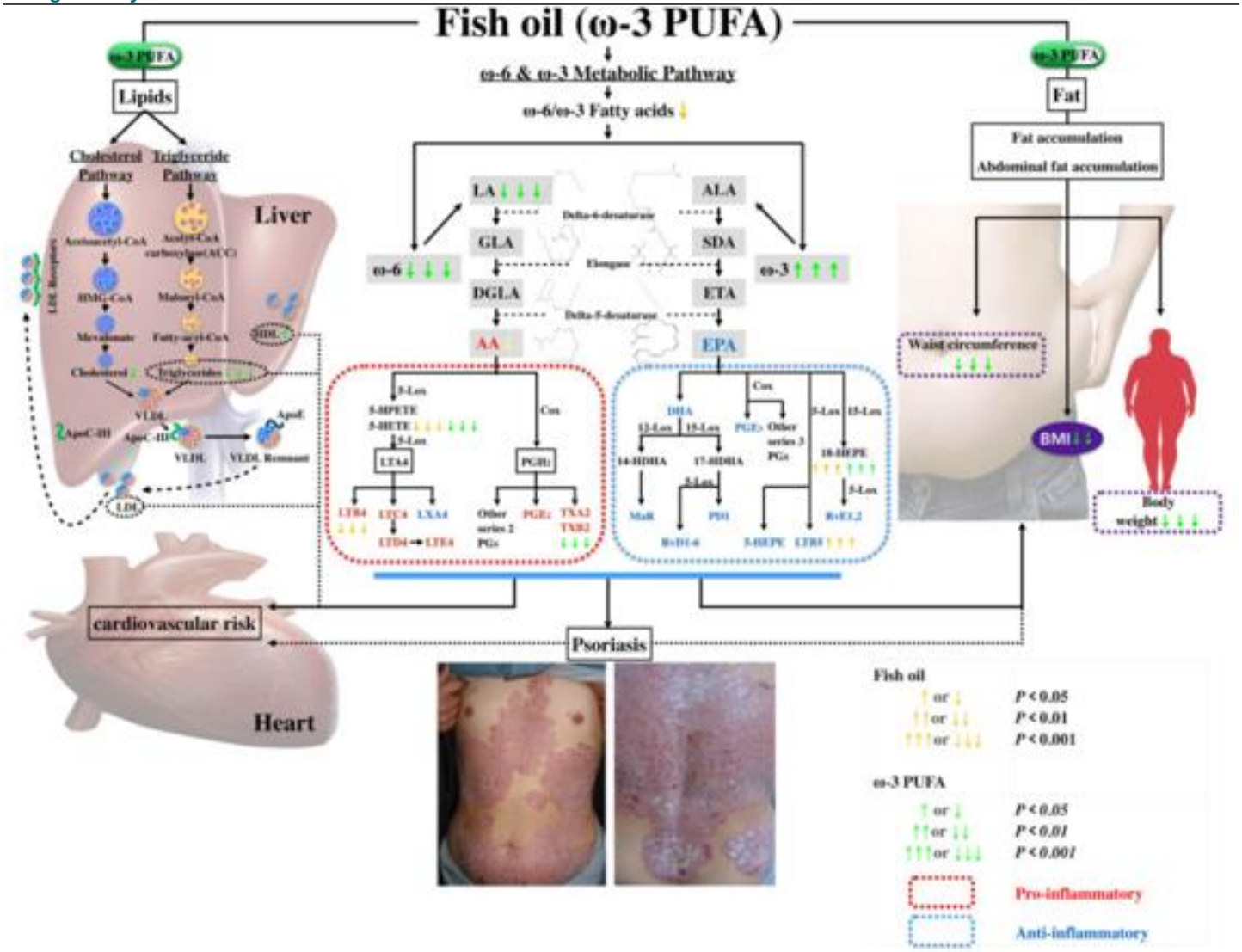


Source: DNB Markets

Instead of COX, AA can bind to the 5-lipooxygenase (5-LOX) to become leukotriene A4. The process can lead to the production of leukotriene B4, C4, D4 and E4. As for the n-3 part, EPA can bind to the same enzymes, but a process leads to different, series 3 PGs, and series 5 leukotrienes and other mediator molecules. In general, the products coming from n-6 fatty acids are pro-inflammatory, while n-3 products are less active and help to dampen the inflammatory response. Apart from this, DHA also has anti-inflammatory features and both DHA and EPA in PLs can be transformed into resolvins and protectins by phospholipases. These docosanoids have strong anti-inflammatory and antiapoptotic features[131].

[131] Deckelbaum RJ et al. J Nutr. 2012 Mar;142(3):587S-591S

Omega-3 fatty acids have an extensive role in metabolism



Source: Chen X et al. Nutr Rev. 2020 Oct 1;78(10):827-840

Apart from the molecular changes, n-3 PUFAs can also affect the immune system. In mice, n-3 PUFAs were able to reduce the activation of CD4+ T cells and suppress their differentiation to Th1 and Th17 cells[132]. These cells play a main role in psoriasis, so this result strengthens the therapeutic rationale of omega-3 fatty acids. In another study, mice fed with DHA enriched fish oil exhibited enhanced B cell activation. B cells release antibodies to combat infections, so their increased activation could lead to a more intense resolution phase of inflammation, which can dampen or possibly shorten the overall immune response[133]. Since psoriasis is characterised by a persistent, chronic state of inflammation, this process might affect the course of the disease in a favourable manner. These molecular and cell level findings can explain the anti-inflammatory properties shown by EPA and DHA in inflamed mouse ears. DHA had a clear effect, after 24 hours it significantly decreased the size of edema, reduced myeloperoxidase activity but also PGE2 and LTB4 levels. The group fed with EPA only showed slight changes, indicating DHA might be a more useful agent in inflammation than EPA[134].

Additional benefits

Besides their role in inflammation, omega-3 fatty acids have some beneficial effects concerning the cardiovascular system, cognition and certain psychiatric conditions among others.

[132] Allen MJ et al. J Nutr. 2014 Aug;144(8):1306-13
[133] Gurzell EA et al. J Leukoc Biol. 2013 Apr;93(4):463–70
[134] Raederstorff D et al. Biochimica et Biophysica Acta (BBA) - Lipids and Lipid Metabolism. 1992 Dec 2;1165(2):194–200

The effect of omega-3 fatty acids on the cardiovascular system is complex. Omega-3 fatty acids are reported to improve lipid profile by increasing high density lipoprotein (HDL) levels and reducing TG levels[135]. Several drugs (Vascepa®, Omacor®, Omtyg®, Lovaza®) have been approved in hypertriglyceridemia containing EPA and DHA[136]. These compounds also have anti-hypertensive and anti-arrhythmic effects. Anti-inflammatory properties and supportive effect on the endothelium also contribute to the beneficial changes. These factors can be preventive in atherosclerosis and certain thrombotic complications[137]. Based on this, omega-3 fatty acid consumption can reduce the risk of coronary heart disease mortality and adverse cardiac events[138]. There is also limited evidence with a high degree of uncertainty that omega-3 intake can have some protective effect against stroke[139]. Because of these effects, n-3 PUFAs could also benefit metabolic syndrome[140]. Some studies attribute a supportive effect of omega-3 fatty acids in cognition and dementia, but there is insufficient evidence for these effects in the whole population with dementia[141], but there seemed to be changes in patients with very mild Alzheimer`s disease[142]. Some products – including Arctic Bioscience's MOPL30 – contain a substantial amount of phosphatidylcholine and can increase plasma choline levels[143]. Since choline is a precursor of acetylcholine, an important neurotransmitter, this change could be beneficial to enhance cognition[144]. Besides, an animal study found the consumption of herring roe was associated with improved learning capacity[145]. As for psychiatric disorders, a systematic review concludes that n-3 PUFAs can offer some benefits to patients diagnosed with depression, but there is no evidence of such effect in healthy people with depressed mood[146]. A small study involving 33 depressed patients found that a low proportion of DHA in the total plasma PUFA pool along with high n-6/n-3 ratio were associated with a higher risk of suicide, which supports the importance of sufficient omega-3 fatty acid consumption and strengthens its relevance for people with depression[147]. As it was described, omega-3 fatty acids have a broad and diverse effect on the body. There is some evidence they can be supportive in many areas that overlap with the comorbidities of psoriasis. They have a particularly pronounced effect on the lipid profile. Their beneficial effect on comorbidities would position n-3 PUFAs as a truly holistic psoriasis treatment. However, popular culture probably attributes a bigger effect to these compounds than has been shown in clinical trials.

In summary, omega-3 fatty acids are essential nutrients that take part in many biochemical processes including inflammation. Their adequate level is associated with health benefits, for example the improvement of triglyceride levels.

Nutraceutical omega-3 market

The global omega-3 market is worth cUSD2.5bn–4bn[148][149] as of 2020 and expected to have a CAGR of 7.7–13.1% until 2025[150]. The main trends that support this growth are increased demand for functional food, rising awareness of nutrition-related health issues, and increasing importance of disease prevention by applying lifestyle medicine. Additionally, there is scientific rationale for the growth of this industry, namely that people consume less omega-3 than ideal[151]. The recommended amount would be 250mg–2g/day of total EPA+DHA[152].

[135] Bjørndal B et al. Lipids Health Dis. 2014 May 17;13:82
[136] Drugs@FDA
[137] Drevon CA. Nutr Rev. 1992 Apr;50(4 (Pt 2)):38–45
[138] Abdelhamid AS et al. Cochrane Database Syst Rev. 2018 Jul 18;7(7):CD012345
[139] Alvarez Campano CG et al. Cochrane Database Syst Rev. 2019 Jun 26;6(6):CD012815
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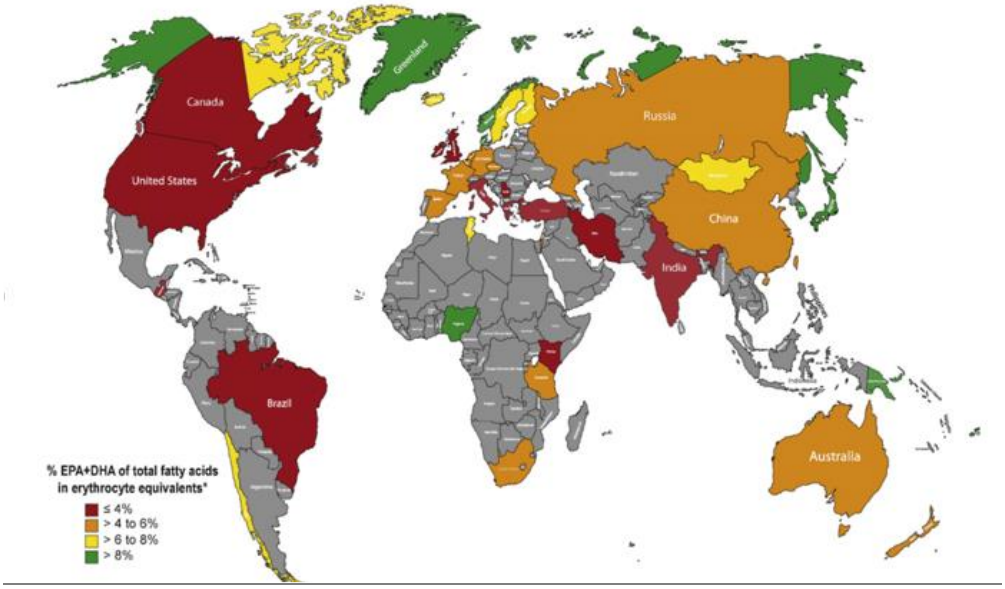
[143] Bjørndal B et al. Lipids Health Dis. 2014 May 17;13:82
[144] Burri L et al. Int J Mol Sci. 2012 Nov 21;13(11):15401–19
[145] Shirai N et al. J Nutr Sci Vitaminol (Tokyo). 2006 Dec;52(6):451-6
[146] Appleton KM et al. Cochrane Database Syst Rev. 2015 Nov 5;2015(11):CD004692
[147] Sublette ME et al. Am J Psychiatry. 2006 Jun;163(6):1100–2
[148] https://www.grandviewresearch.com/industry-analysis/omega-3-market
[149] https://www.globenewswire.com/news-release/2020/01/03/1965968/0/en/Global-Omega-3-Market-by-Type-Application-Source-and-Region-Forecast-to-2025.html
[150] https://www.globenewswire.com/news-release/2020/01/03/1965968/0/en/Global-Omega-3-Market-by-Type-Application-Source-and-Region-Forecast-to-2025.html
[151] Papanikolaou Y et al. Nutr J. 2014 Apr 2;13:31
[152] https://www.who.int/nutrition/topics/FFA_interim_recommendations/en/

Global EPA and DHA consumption are lower than recommended



Source: Stark KD et al. Prog Lipid Res. 2016;63:132–52

North America is expected to remain the biggest market, and together with China it accounts for c70% of the global market[153], while Europe accounts for approximately a quarter. The European market looks set to stay on a growing trajectory together with the emerging Asian market. According to a recent market research report, marine products and the DHA segment will be among the fastest-growing areas in the next couple of years[154]. We believe the future dynamics of the omega-3 market create a promising environment for Arctic Bioscience to grow.

Key companies in the omega-3 market

There are a lot of companies developing, manufacturing and selling omega-3 products. We list the major ones below.

Key companies in the omega-3 market

Norway	Global
Epax	BASF (GER)
Aker Biomarine	KD Pharma (GER)
GC Rieber	DSM (NED)
Pharma Marine	Cargill (US)
Orkla Health	Croda International (UK)

Source: companies webpages

- **Epax** is a fully owned subsidiary of Pelagia AS, a Norwegian fishery company. It is focused on marine extracts, particularly omega-3 concentrations. Its manufacturing facility is Good Manufacturing Practice (cGMP) certified and has been inspected by the FDA and the Norwegian Medicines Agency. These certificates enable it to manufacture APIs. It has numerous concentrates containing various, even customisable amounts of EPA and DHA. It has sponsored more than 100 clinical trials to evaluate its products in several conditions[155]. Psoriasis is not among them. It recently invested USD35m to upgrade its facilities and increase manufacturing output by 50%[156].
- **Aker BioMarine** is a leading supplier of krill and krill oil products. It is a fully integrated company owning krill harvesting vessels, manufacturing facilities, established sales, marketing and R&D units but also a distribution network[157]. It sells krill oil encapsulated in soft- and hard-gel capsules under the SUPERBAKrill™ brand name[158].

[153] Company
[154] https://www.marketsandmarkets.com/ResearchInsight/omega-3-omega-market.asp
[155] www.epax.com
[156] https://www.nutraingredients-usa.com/Article/2019/10/04/Epax-omega-3-plans-include-32m-facility-upgrade#
[157] https://www.akerbiomarine.com/
[158] https://www.superbakrill.com/

- **GC Rieber** has an Oils division that extracts omega-3. Its fish oil is produced mainly from by-products of the fishing industry. Its omega-3 brand is Vivomega™ and is available in three compositions. The fish oil comes mainly from sardines, anchovies and mackerel caught off Peru, Chile and Morocco. Omega-3 fatty acids are mainly in TG form[159]. It is collaborating with Haukeland University Hospital on the effects of omega-3 fatty acids in rheumatoid arthritis in a clinical trial[160].
- **BASF** is a German chemical company that developed Omacor® and Lovaza®, the first two omega-3 products approved and recognised as drugs. It is a pioneer in the pharmaceutical uses of omega-3 fatty acids[161]. It has extensive capacities in manufacturing and R&D including an expert team in Norway focused on omega-3 fatty acid related development[162]
- **KD Pharma** is a German pharmaceutical company focused on omega-3 fatty acids. It mainly offers contract development and manufacturing services. It manufactures Omacor®, Lovaza® and Epanova® among others. It has its own pipeline, with one candidate in Phase III (familial adenomatous polyposis) and another project targeting ulcerative colitis[163].
- **Croda International** is a UK-based omega-3 API and dietary supplement manufacturer. Its facilities are inspected by the FDA, approved by the UK Medicines and Healthcare Regulatory Authority and compliant with the requirements of GMP. Its APIs can be found on the market under the OmeRx™ brand name[164].

[159] https://vivomega.com/
[160] https://www.gcrieber-oils.com/news/gc-rieber-oils-collaboration-with-haukeland-university-hospital-on-omega-3-clinical-study/
[161] https://www.basf.com/global/en/products/segments/nutrition_and_care/nutrition_and_health/omega-3.html
[162] https://www.basf.com/global/en/products/segments/nutrition_and_care/nutrition_and_health/omega-3.html
[163] https://www.kdpharmagroup.com/
[164] https://www.croda.com/en-gb/products-and-markets/dietary-supplements

Clinical results

To put Arctic Bioscience's clinical trials in context, we have reviewed previous studies about omega-3 fatty acids in psoriasis. We then go on to analyse the results produced by Arctic Bioscience and relate them to other studies. And finally we compare Arctic Bioscience's product with other psoriasis treatments, with regards to efficacy, safety and compliance.

It has been suggested that the PL form is a better way to deliver n-3 PUFAs than TGs[165]. Arctic Bioscience funded a randomised, single-blind crossover study in 2016 to evaluate the bioavailability of Romega®, its omega-3 nutritional supplement compared to fish oil. Numerous blood samples were collected during the first 12 hours after a single administration and after two weeks of daily supplementation. The EPA, DHA and EPA+DHA levels were higher in the Romega® group during the first 12 hours, but there was no difference in total plasma PL. The maximum concentration of PC EPA+DHA was also higher in the Romega® group. After two weeks there was no difference between the groups in total fasting PL. The study concluded that herring roe had good bioavailability as a source of omega-3 fatty acids[166].

The clinical evidence on the efficacy of omega-3 fatty acids in psoriasis is at least inconclusive. While we aimed to find every relevant trial, we wanted to identify the studies most comparable to the one conducted by Arctic Bioscience. We found six relevant systemic reviews and meta-analyses. Naturally, the studies they review overlap greatly, yet they come to different conclusions. Millsop et al.[167] found moderate evidence for efficacy after reviewing 15 trials, from which 12 yielded a positive result. Not all of them were randomised controlled trials (RCT) and in some of the positive studies omega-3 was administered intravenously. Gamret et al.[168] on the other hand, did not recommend the use of fish oils based on the examination of 10 RCTs where all patients took fish oil orally. Seven out of ten trials did not show any benefit of omea-3 supplementation. Clark et al.[169] also supported the use of fish oil/omega-3 after reviewing 10 studies. However, Yang et al.[170] and Upala et al.[171] did not find any evidence for benefit after evaluating 13 RCTs and 12 studies respectively. On top of this, Chen et al.[172] looked at 18 RCTs and concluded that fish oil and its components might have a beneficial effect only in combination with other treatments. From these reviews we picked the trials most relevant to Arctic Bioscience. We selected 14 trials where participants were diagnosed with psoriasis (preferably mild to moderate) and received omega-3 fatty acids orally. The studies had to include a comparison group (placebo or another treatment). They also had to measure endpoint(s) that overlap with Arctic Bioscience's endpoints. Of these trials five yielded a positive result and met the determined endpoint(s), while eight did not show any significant difference from the control group. One trial[173] had mixed results concluding that fish oil was useful only as an adjunct therapy. It is worth noting that in every positive study omega-3 fatty acids were given in combination with another therapy, although in one case it was only topical paraffin[174]. Consequently, in most of the positive trials, omega-3 was referred to as an adjuvant therapy not as a monotherapy. One of the positive trials[175] plainly said "In our experience, fish oil, even at high doses, is not a practical monotherapy for psoriasis" (Gupta AK et al. p805). One of the biggest negative trials also mentions that regardless of the negative results fish oil might enhance the effect of other psoriasis therapies[176]. As for safety, fish oil and omega-3 fatty acids were generally well tolerated, the most common adverse effects were fishy taste, gastrointestinal discomfort, nausea and diarrhoea. In summary, the clinical evidence is controversial, but since there are several positive studies, we believe Arctic Bioscience's product could have a place on the market, but depending on the outcome from future trials, HRO350 might possibly be used as an adjunct therapy rather than a monotherapy.

[165] Burri L et al. Int J Mol Sci. 2012 Nov 21;13(11):15401–19
[166] Cook CM et al. Prostaglandins Leukot Essent Fatty Acids. 2016;111:17–24
[167] Millsop JW et al. J Am Acad Dermatol. 2014 Sep;71(3):561–9
[168] Gamret AC et al. JAMA Dermatol. 2018 01;154(11):1330–7
[169] Clark CCT et al. Clin Rheumatol. 2019 Apr;38(4):977–88
[170] Yang S-J et al. BMC Complement Altern Med Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6896351/
[171] Upala S et al. International Journal of Rheumatic Diseases. 2017;20(4):442–50
[172] Chen X,et al. Nutr Rev. 2020 Oct 1;78(10):827-840
[173] Bittiner SB et al. Lancet. 1988 Feb 20;1(8582):378–80
[174] Aldil M et al. Dermatol. Rev. 2017, 104:314-323
[175] Gupta AK et al. British Journal of Dermatology. 1989;120(6):801–7
[176] Søyland E et al. N Engl J Med. 1993 Jun 24;328(25):1812–6

Arctic Bioscience's pilot clinical trial

Arctic Bioscience reported its product had met the primary endpoint in its pilot clinical trial that evaluated its herring roe oil (HRO) capsule. The study[177] was published in May 2020, and was a randomised, placebo-controlled, double-blind study involving 64 patients to compare HRO with placebo (coconut oil). All patients had mild to moderate psoriasis and the study lasted for 26 weeks. One HRO capsule contained 292mg n-3 PUFA, where approximately 35% of DHA and EPA was bound to phospholipids, including phosphatidylcholine. Patients received five capsules twice a day, which means c642 mg EPA and c1.927 g DHA per day. The measured parameters included PASI, DLQI. BSA, PSGA, CRP and VAS (itching) scores. A set of relevant cytokines were also measured.

The trial achieved its primary endpoint, but the difference is PASI reduction between the groups was barely significant (p=0.045). There was no significant difference in any other parameters including PASI50, not even in cytokine levels, which seems to contradict the scientific rationale described earlier. A post-hoc analysis identified significant difference in PASI change compared to placebo in patients with PASI>5.5. They are the moderate patients, and a bigger effect could be observed among them. There was a 38% decrease of mean PASI in the treatment group, while in the placebo group only a 7% decrease could be seen. This might indicate the treatment is more effective in moderate cases. As far as safety is concerned, three patients withdrew from the study in the treatment group (one because of gastritis) while in the placebo group everyone completed the study. The rate of patients who experienced at least one AE was quite high in both groups, 94% in the treatment group, 88% in the placebo group. The rate of gastrointestinal problems was also higher in the treatment group (47%) than placebo (34%). The most common AEs were nausea (16%), diarrhoea (14%) and upper abdominal pain (13%). Interestingly, the rate of muscoskeletal and connective tissue events was higher in the placebo group (41% versus 16%).

Pilot clinical trial results of HRO at week 26

	Herring roe				Placebo				Herring roe oil versus placebo		
	n	mean	SD	95% CI	n	mean	SD	95% CI	Estimate	p-value	95% CI
DLQI											
week 0	32	8.7	6	6.6, 11.0	32	8.6	5.2	6.7, 11.0			
week 26	32	6.8	5.2	5.0, 8.7	32	7.6	6	5.5, 9.8			
change		-1.9	6	-4.1, 0.3		-1	4.2	-2.5, 0.6	-0.9	0.47	-3.2, 1.5
change %		-21.84%				-11.63%					
PASI											
week 0	32	6.1	1.9	5.4, 6.8	32	6	1.7	5.4, 6.6			
week 26	32	4.4	2.4	3.5, 5.2	32	5.4	2.7	4.5, 6.4			
change		-1.8	2.6	-2.7, -0.8		-0.6	1.8	-1.3, 0.06	-1.1	0.045	-2.2, -0.03
% change		-29.51%				-11.11%					
BSA											
week 0	32	7.3	4.6	5.6, 9.0	32	5.9	3.1	4.8, 7.0			
week 26	32	5.8	4.4	4.2, 7.4	32	5.6	4.2	4.1, 7.2			
change		-1.6	4.5	-3.2, 0.09		-0.3	3.3	-1.5, 0.89	-0.5	0.57	-2.2, 1.2
change %		-20.55%				-5.08%					
PSGA											
week 0	32	2.2	0.5	2, 2.4	32	2.1	0.3	2.0, 2.2			
week 26	32	2.1	0.7	1.8, 2.3	32	2.1	0.7	1.8, 2.3			
change		-0.2	0.7	-0.4, 0.1		0	0.7	-0.3, 0.2		0.7	
change %		-4.55%				0					
CRP											
week 0	29	6.1	13.1		32	2.5	2.3				
week 26	29	2.8	2.9		32	2.4	1.9				
change		-3.3	12.4			-0.1	1.9		-0.03	0.69	-0.19, 0.12

Source: Tveit KS et al. Acta Derm Venereol. 28 May 2020;100(10)

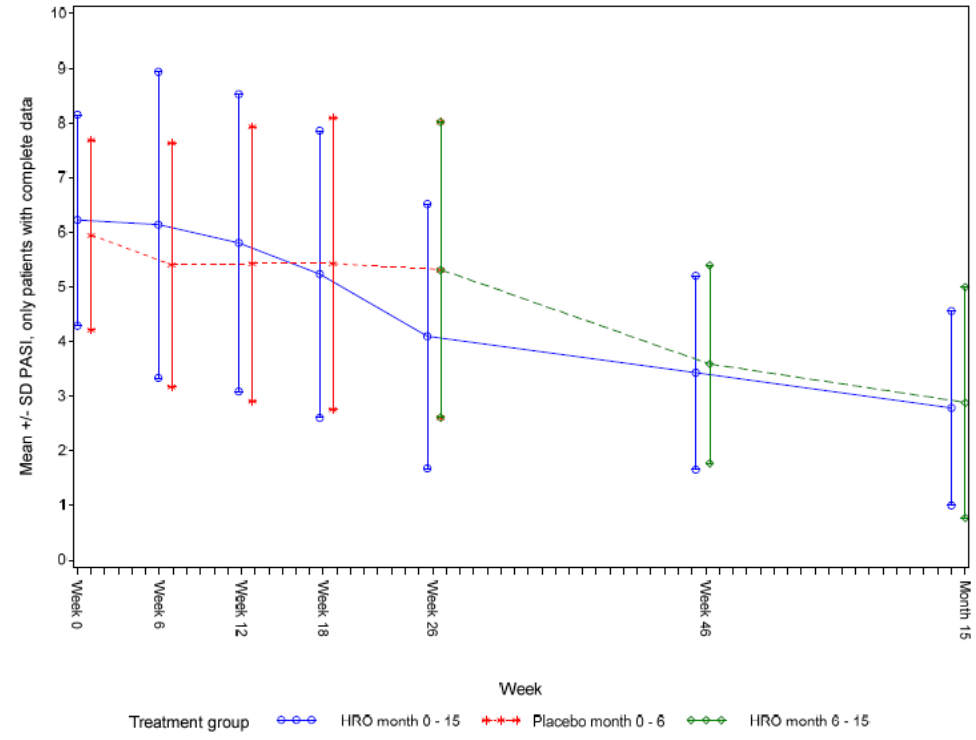
The dose of omega-3 fatty acids in this trial was comparable to the other trials, although the proportion of DHA was higher here than in most of the previous trials. Based on preclinical

[177] Tveit KS et al. Acta Derm Venereol. 2020 May 28;100(10):adv00154

results[178] the increased proportion of DHA is justified and has a potential to achieve higher efficacy. The dosing, trial size and length were also comparable to other trials.

The company continued the trial as an open-label extension study. It switched the placebo group to active treatment, so every patient received HRO capsules until week 60, when the trial was concluded. The results were more revealing than the first half of the trial. The improvement continued in the original treatment group, the placebo group started to improve as they started to receive active treatment, and both groups ended up at a mean PASI of c3.9 at week 60. 67% of patients had more than a 50% reduction in PASI and 40% achieved a clear or almost clear state (PGA 0–1). The moderate subgroup (PASI>5.5) showed a 55% decrease in PASI by week 65[179]. It seems to take longer to achieve a clinically meaningful effect with this medication, but the overall results are promising and the drug seems to have comparable efficacy to other, well-established treatments.

Mean PASI changes during open label extension study (week 26–65)



Source: Tveit et al. International Journal of Clinical and Experimental Medical Sciences 2021; 7(1):13-20.

If we look at the efficacy, Arctic Bioscience's trial was better than most of the previous trials, since it met the primary endpoint at week 26. The PASI change compared to baseline was -29.51% (-11.11% in the placebo group). There were three positive trials where this reduction could be calculated, trials conducted by Aldil[180], Balbas[181] and Guida[182]. In these trials the PASI reductions were 47%, 71% and 66%, respectively. However, in each of these trials fish oil was used in combination with other treatments. In scientific literature a minimum of 50% reduction of PASI qualifies as clinically meaningful[183]. According to this criterion, the improvement showed by the patients treated with Arctic Bioscience HRO capsule is clinically meaningful, but only after 65 weeks. However, PASI is less sensitive to small changes especially at the lower end of the scale, and the scoring process itself also includes subjective elements. These factors can explain the weaker effect among mild patients than the moderate group.

The safety profile matched with the historical data, besides Arctic Bioscience's HRO capsule not having a fishy taste, which is an advantage (but not unique). Older trials did not describe

[178] Raederstorff D et al. Biochimica et Biophysica Acta (BBA) - Lipids and Lipid Metabolism. 1992 Dec 2;1165(2):194–200
[179] Tveit KS et al. Long term efficacy and safety of Herring Roe Oil in the treatment of Psoriasis, a 39-week open-label extension study
[180] Aldil M et al. Dermatol. Rev. 2017, 104:314-323
[181] Balbás GM et al. Clin Cosmet Investig Dermatol. 2011 Jun 20;4:73–7
[182] Guida B et al. Clin Nutr. 2014 Jun;33(3):399–405
[183] Feldman S et al. Ann Rheum Dis. 2005 Mar;64(Suppl 2):ii65–8

safety issues in such detail as this trial, but even if we take this into account the rate of AEs is surprisingly high not only in the treatment group but also in the placebo group. However, there are other omega-3 products on the market, and they are generally well tolerated.

In summary, it met its primary endpoint by showing efficacy at week 26. However, the treatment resulted in a clinically meaningful improvement at week 65 paired with a good safety profile. Moderate patients seemed to benefit more from the treatment than mild cases. Apparently, it just takes longer for the full effect to develop than expected. Other treatments can improve symptoms in less time, but HRO can also cause a comparably big improvement, with an arguably milder safety profile. However, more convincing clinical results are required to say anything definitive about this product and to find out if it should be positioned as a monotherapy or an adjunct therapy.

Comparison with other treatments

In this section we examine how Arctic Bioscience's HRO capsule performs compared to other treatments. This will help us to see its place on the market more clearly.

Efficacy

The HRO capsules have comparable efficacy to competitor treatments if we look at the effects after 65 weeks of treatment. However, short-term efficacy (week 26) seems to be somewhat lower than most competitors. We found 10 competitors that used overlapping endpoints with Arctic Bioscience. As we could see, endpoint measures vary between trials, but by looking at reviews and multiple sources gives a good overview of competitors' general efficacy. LYC-30937[184] and one dosage group of GSK2982772[185] reported lower efficacy in terms of PASI reduction, c25% both. A higher dose in the GSK2982772 trial achieved a 41% mean PASI reduction[186]. It is important to note though that the trials for GSK2982772 and LYC-30937 differed from Arctic Bioscience's pilot clinical trial, as the GSK2982772 and LYC-30937 trials included more severe patients. As we have mentioned before, the more severe the disease, the easier it will be to discern differences in PASI. Note that both of these trials failed to meet their respective endpoints. Otezla® reported c51% mean PASI reduction accompanied by a 48% BSA reduction[187]. This BSA change is more than twice than that observed with Arctic Bioscience HRO capsules (20.5%) at week 26. Tepilamide fumarate had a similar efficacy as Otezla®, a c49% PASI reduction[188]. A 0.3% Tacrolimus gel caused a BSA reduction of 40%[189]. Based on numerous sources, Vitamin D analogues can achieve a c60% PASI reduction[190], and corticosteroids 50–65%[191]. These treatments are also able to increase patients' quality of life as they decreased DLQI by c55–65%[192]. This is like the DLQI reduction caused by Arctic Bioscience's capsule at week 65. According to an extensive review[193], the combination of corticosteroids and vitamin D analogues could achieve an outstanding PASI reduction of 74%. Topical steroids combined with oral curcumin also showed remarkable efficacy, 74.5% reduction of mean PASI[194]. Aloe vera extract also showed high efficacy, with a PASI reduction of 66%[195].

[184] https://clinicaltrials.gov/ct2/show/NCT02872285
[185] Weisel K et al. Clinical Pharmacology & Therapeutics. 2020;108(4):808–16i
[186] Weisel K et al. Clinical Pharmacology & Therapeutics. 2020;108(4):808–16
[187] Rich P et al. J Am Acad Dermatol. 2016 Jan;74(1):134–42
[188] Balogh EA et al. Expert Opin Emerg Drugs. 2020;25(2):89–100
[189] Ortonne J-P et al. Acta Derm Venereol. 2006;86(1):29–33
[190] Ortonne J-P et al. J Eur Acad Dermatol Venereol. 2014 Sep;28(9):1226–34
[191] Kragballe K et al. J Eur Acad Dermatol Venereol. 2006 Jan;20(1):39–44
[192] Ortonne J-P et al. J Eur Acad Dermatol Venereol. 2014 Sep;28(9):1226–34
[193] Kragballe K et al. J Eur Acad Dermatol Venereol. 2006 Jan;20(1):39–44
[194] Antiga E et al. Biomed Res Int. 2015;2015:283634
[195] Choonhakarn C et al. J Eur Acad Dermatol Venereol. 2010 Feb;24(2):168-72

Comparison of HRO's efficacy to competitors'

	HRO	LYC-30937	GSK-2982772	Oral curcumin + steroid	Otezla	Tepilamide fumarate	Tacrolimus gel	Cortico-steroid	Vitamin D analogues	Cortico-steroid + vitamin D analogues	Aloe vera
PASI change	-29.5%	n.a.	-41.0%	-74.6%	-50.8%	-50.7%	n.a.	-50-65%	-59.0%	-74.0%	-77.3%
DLQI change	-21.8%	-25.1%	n.a.	n.a.	n.a.	n.a.	n.a.	-56-68%	n.a.	-65.9%	-70.9%
PSGA change	-4.6%	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	-52-79%	n.a.	-58.0%	n.a.
BSA change	-20.6%	-12.7%	n.a.	n.a.	-48.4%	n.a.	-40.00%	n.a.	-21.1%	n.a.	n.a.

Source: Numerous clinical trials and studies

HRO has positive effects on patients and that was seemingly enough to meet the primary endpoint during the pilot clinical trial. Based on the results of the open-label extension study, it takes longer for the HRO capsules to show a similar effect as other treatments. Based on this data, HRO350's strongest point might not be short-term efficacy, its advantage to competitors probably lies elsewhere: for example, in the route of administration or its effect on psoriasis' comorbidities. On the other hand, if patients are well informed that it will most likely take some time before the effect sets in it should not be a huge issue given the indications of relatively benign side-effect profile for HRO350.

Safety

In terms of safety, HRO capsules have a similar, although slightly more favourable profile than competitors. In the case of Arctic Bioscience's pilot clinical trial, the rate of overall AEs was high in both the treatment (94%) and the placebo group (88%), but the overall side effects were mild. In the case of Otezla®, 1.84% of patients experienced a serious adverse event (SAE) during the 16 weeks of the placebo-controlled phase of the ESTEEM-2 trial, while there were no SAEs with the HRO capsules. However, the rate of non-severe AEs was half as much in the ESTEEM-2 trials (c47% versus 94%) and the side effects were similar, including diarrhoea, nausea and vomiting[196]. LYC-30937 did not cause any SAEs and 50% of patients experienced at least one AE. The side effects varied but included headache, cough, nasopharyngitis and itching[197]. The case of GSK2982772 is somewhat comparable to the HRO capsules; 67–91% of patients experienced any event depending on the dose. Headache and nausea were among the most common drug-related AEs[198]. Curcumin caused similar gastrointestinal AEs as HRO capsules[199]. In a study involving topical tacrolimus on average 65% of patients experienced AEs, with skin burning being the most frequent (31%)[200]. The safety profile of HRO capsules especially in the long run seems to be more favourable than corticosteroids and calcineurin inhibitors as it does not cause any skin related complications, like irritation, itching, burning or skin atrophy. HRO capsules do not seem to have a better safety profile than Vitamin D analogues though. One factor to note about the adverse effects mentioned above is that the Arctic Bioscience trial measured AEs over 26 weeks and, as this is a clearly longer follow-up than the trials mentioned above (12–16 weeks), the data is not fully comparable. As all AEs are reported in a clinical trial, the longer the trial the more common it will be for a patient to experience an AE, even if the AE is not directly associated with the treatment. Hence a longer trial will in most cases report a higher percentage of patients with an AE. In summary, HRO capsules appears to have a similar safety profile to other oral treatments. They mainly cause gastrointestinal side effects, while AEs caused by topical treatments are mostly focused on the skin. HRO capsules might have better long-term tolerability, particularly compared to tacrolimus and corticosteroids. In addition, the pilot clinical trial was in the initial phase slightly longer (26 weeks) than several of the other trials mentioned above and the OLE was for 65 weeks. When looking at AEs over such a long trial we are not surprised that for example events like nausea and diarrhoea affect patients as even healthy patients without treatment might experience an odd case of nausea and diarrhoea during a year.

[196] Rich P et al. J Am Acad Dermatol. 2016 Jan;74(1):134–42.
[197] https://clinicaltrials.gov/ct2/show/NCT02872285
[198] Weisel K et al. Clinical Pharmacology & Therapeutics. 2020;108(4):808–16.
[199] Antiga E et al. Biomed Res Int. 2015;2015:283634
[200] Ortonne J-P et al. Acta Derm Venereol. 2006;86(1):29–33.

Adherence and patient preferences

According to a study involving PsA patients, the most important factors that patients look at when choosing a therapy are route of administration, dosage regimen, efficacy and cost[201]. In this section we look at route of administration and dosage regimen to see how they affect adherence. After assessing these factors, we believe Arctic Bioscience might have an edge when it comes to adherence. According to key opinion leaders and patients, an oral formulation would be more welcome than topical formulations, because it is more convenient than topical steroids[202]. Additionally, the application of topical formulations is time consuming and can be messy. On top of that, there are body areas that patients cannot even reach themselves. Oral therapy is obviously less painful than intravenous and subcutaneous injections, although HRO capsules do not compete directly with biologics as they target different patient groups. Administration of injections also requires assistance from healthcare professionals, while oral treatments can be taken at home, alone.

Dosage regimen is a less clear-cut case. A fairly big amount of HRO is needed to achieve a therapeutic effect. In Arctic Bioscience's trial the daily intake of phospholipid esters and omega-3 comprising 642mg EPA and 1.927g DHA was achieved by taking two times five capsules[203]. The number of capsules taken was similar or even more in comparable trials. The company's plan for the dosage regimen is to test two doses of 3g and 6g taken once or two times three capsules daily, which is better but should still be reduced if possible to achieve maximum adherence. Other oral treatments are also administered once or twice daily, but patients do not have to take many capsules to achieve the recommended dose. Topical treatments should also be applied once or twice daily. The absolute winners in this category would be certain biologics that are only injected once monthly. If we take everything into account, HRO capsules have a favourable dosage regimen, but it might be problematic for some patients to take c6 capsules per day. If the company can tackle this challenge it would be an important step towards increasing adherence.

If we combine these two factors, adherence to HRO capsules should be higher than to topical therapies and comparable to other oral treatments. The adherence to twice daily oral administration is c75% according to our estimates, while the adherence to topical therapies is much lower, less than 50%[204]. A study examining the omega-3 supplementation of pregnant women reported c64% and 68% average adherence for EPA and DHA therapies, respectively[205]. According to another study adherence was 78% among patients with malnutrition on oral nutritional supplements[206]. In a bioavailability study sponsored by Arctic Bioscience, adherence to the Romega® was c77% based on the difference between intended-to-treat and per-protocol populations[207]. There was also an extensive review that incorporated numerous other studies showing c75–80% adherence to twice daily oral administration[208]. Additionally, both the symptoms and their improvement are visible in case of psoriasis and this can give extra motivation to patients to adhere to therapy. Based on the results the overall adherence with twice daily administration is estimated to be 75%.

Additionally, the drug is from a natural source, and patients and physicians in dermatology tend to prefer these products according to a key opinion leader[209]. HRO is also without immunosuppressive effect, which is particularly useful in the Covid-19 pandemic[210].

HRO`s long-term efficacy is on a par with competitors' efficacy and it can offer complementary benefits such as the convenient route of administration leading to higher adherence or its beneficial effects on comorbidities. Mild and moderate psoriasis patients have had the same limited treatment options for years, which further strengthens HRO's claim. Still, a lot depends on the outcome of the upcoming Phase IIb and Phase III trials.

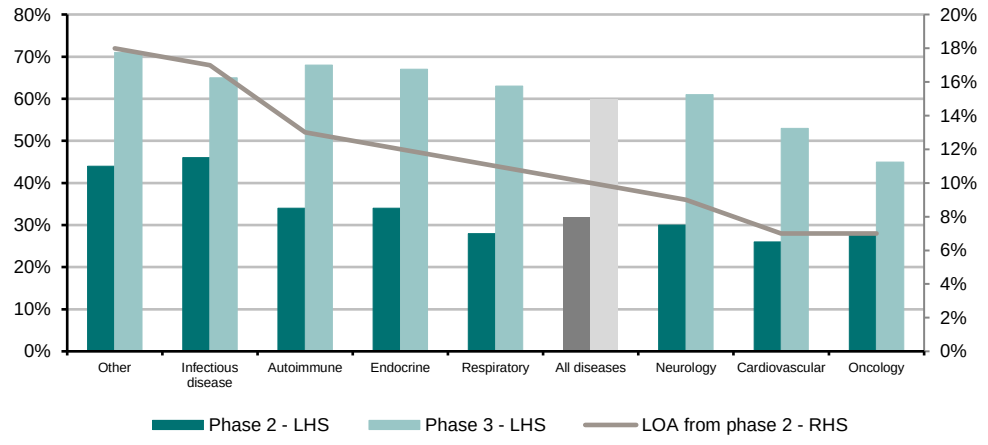
[201] Xu Y et al. Am Health Drug Benefits. 2018 Nov;11(8):408–17.
[202] GlobalData
[203] Tveit KS et al. Acta Derm Venereol. 2020 May 28;100(10)
[204] Alinia H et al.. Br J Dermatol. 2017 Mar;176(3):759–64
[205] Mozurkewich EL et al. Am J Obstet Gynecol. 2013 Apr;208(4):313.e1-9
[206] Hubbard GP et al. Clin Nutr. 2012 Jun;31(3):293–312
[207] Cook CM et al. Prostaglandins Leukot Essent Fatty Acids. 2016;111:17–24
[208] Coleman CI et al. J Manag Care Pharm. 2012 Sep;18(7):527–39
[209] Company
[210] Company

Probability of success

An early-stage biotechnology company's most valuable (and sometimes only) asset is their drug candidate. Therefore, to value a company it is crucial to value its pharmaceutical assets. However, because of the development process, drug assets are subject to the risk of failure during the development. To account for this in our model we must calculate the probability that the drug gets approved. Several studies have been done to estimate these probabilities and success rates. Hay et al.[211] published a very extensive study in Nature Biotechnology in 2014. They examined clinical trials from 2003 to 2013. Their investigation included c4,500 drugs, more than 7,300 development paths, 835 companies and c5,800 phase transitions. They established two important definitions. Probability of success (POS) is the probability that the drug successfully completes a certain phase and moves on to the next phase. Likelihood of approval (LOA) gives the likelihood that a drug reaches the market from a particular phase. For example, a LOA in phase 2 means the probability that the drug candidate completes both Phase 2 and 3, get approved and reaches the market. As drug candidates progress to more advanced phases, their LOA keeps increasing. In a study of similar magnitude Wong et al.[212] looked at almost 15 years of clinical data (2000–2015). More than 21,000 compounds were included in their analysis and more than 400,000 entries of clinical data were evaluated. Thanks to the large data sets, both authors were able to segment their results and determine success rates for several categories and therapeutic areas.

Psoriasis is a chronic inflammatory disease, where the immune system plays a substantial role in the induction of inflammations and contributes to the manifestation of psoriatic lesions on the skin. The closest categories to psoriasis would be autoimmune diseases, dermatological diseases and inflammatory diseases. Hay separates autoimmune diseases and includes dermatology in the "Other" category. Psoriasis is the primary (lead) indication of HRO350 and since Hay has separate success rates for lead indications, this will also be taken into account.

Phase 2 and Phase 3 success rates across therapeutic areas



Source: Hay M et al. Nature Biotechnology. 2014 Jan;32(1):40–51

Autoimmune diseases have a POS of 34% for Phase 2 and 68% for Phase 3 with an overall LOA of 13%. These numbers are slightly higher than the average, indicating the approval of a drug targeting autoimmune diseases is more likely than the approval of an 'average' drug. According to the study, the approval in the drug's lead indication is also more likely than in further indications.

[211] Hay M et al. Nature Biotechnology. 2014 Jan;32(1):40–51.
[212] Wong CH et al. Biostatistics. 2019 Apr 1;20(2):273–86.

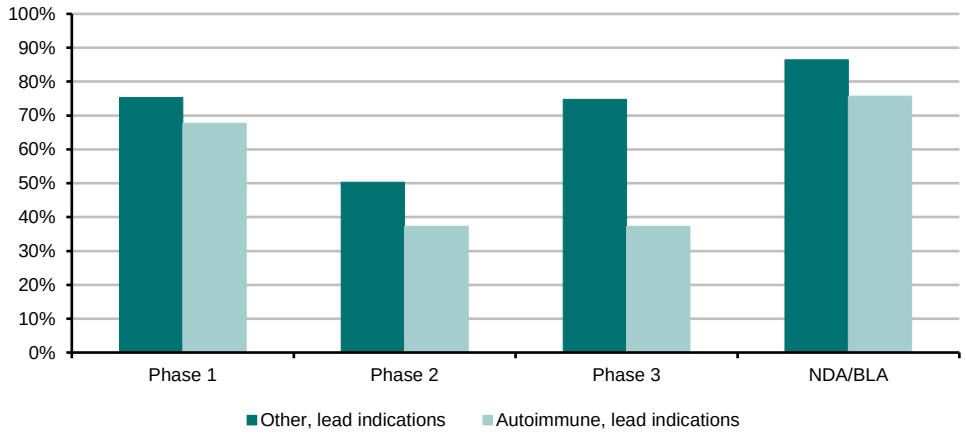
Relevant POS and LOA values

	Phase 1 to Phase 2		Phase 2 to Phase 3		Phase 3 to NDA/BLA		NDA/BLA to approval	
	POS	LOA	POS	LOA	POS	LOA	POS	LOA
All indications	64.50%	10.40%	32.40%	16.20%	60.10%	50.00%	83.20%	83.20%
Lead indications	66.50%	15.30%	39.50%	23.10%	67.60%	58.40%	86.40%	86.40%
Other (lead)	75.30%	24.50%	50.30%	32.50%	74.80%	64.60%	86.40%	86.40%
Autoimmune (lead)	67.70%	15.40%	37.30%	22.80%	80.80%	61.10%	75.70%	75.70%

Source: Hay M et al. Nature Biotechnology. 2014 Jan;32(1):40–51

In the 'Other' category POS and LOA values are substantially higher than the average, but this category is made up of different fields and dermatology is only one of them. Therefore, these promising success rates need to be viewed with caution. If we look at success rates of drugs, where autoimmune disease was the lead indication, they are closer to the average but still above it. The bottleneck is Phase 2 with the POS of 37.3%. After this, the success rates of Phase 3 and the New Drug Application (NDA) are higher, 80.8% and 75.7% respectively.

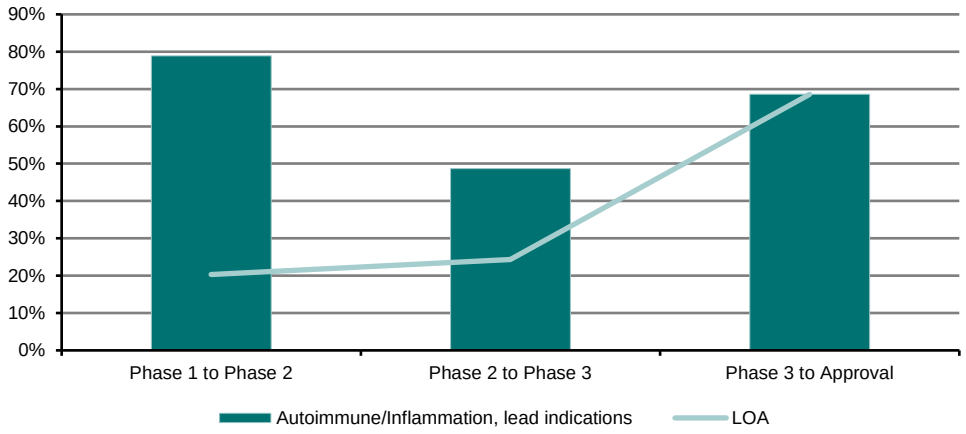
POS by phase for autoimmune and other diseases as lead indications



Source: Hay M et al. Nature Biotechnology. 2014 Jan;32(1):40–51

Wong et al. reported higher success rates on a general level and had a bigger sample than the Hay study. Additionally, the difference in success rates between all indications and lead indications is also present in this study, similarly to Hay. In the Wong study we can find a category that takes both autoimmune and inflammatory diseases into account and they look at drug where this is the lead indication, which is ideal for our psoriasis drug, since this condition has both and autoimmune and an inflammatory element.

POS and LOA of autoimmune/inflammation drugs

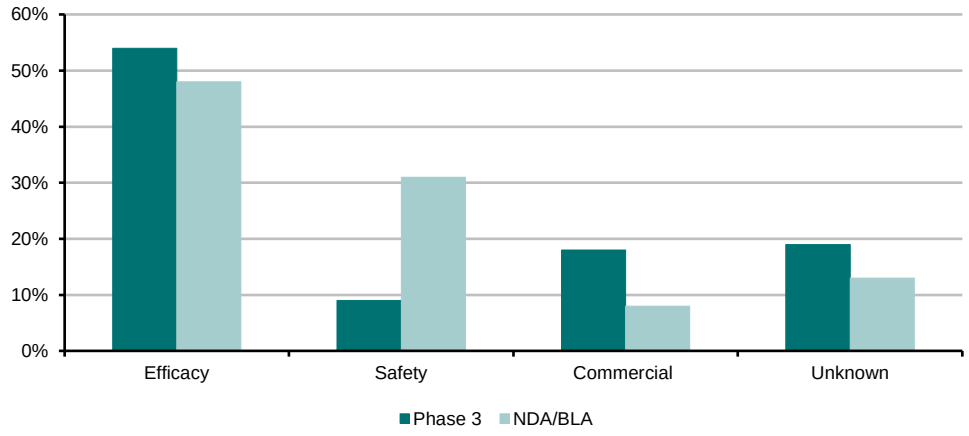


Source: Wong CH et al. Biostatistics. 2019 Apr 1;20(2):273–86

To find a balance between different categories, in the model we use lead indication success rates and take the average of the 'Other' and 'Autoimmune' categories from Hay and the 'Autoimmune/Inflammation' category from Wong. That the pilot clinical trial did show statistical significance in a relatively large patient sample also increases the LOA we believe. The company plans to carry out a larger phase IIb trial with two doses of HRO350 and a long follow-up. Given the compound is in Phase II but has already completed one long-term follow-up trial, the safety profile looks reasonably benign to us. Our weighted overall LOA at this point is c35%, which we believe is reasonable.

Drug development is an inherently risky endeavour. A considerable proportion of candidates do not reach the market for various reasons. Hay et al. examined the reasons of failure and lack of efficacy turned out to be the most frequent one. An unfavourable safety profile can also be a reason a molecule might not get approved and the development can also be discontinued for economic reasons.

Reason of failure during drug development



Source: Hay M et al. Nature Biotechnology. 2014 Jan;32(1):40–51

Operations

Short value chain with a local supply of fish roe from nearby fisheries

Arctic Bioscience has a short value chain with a local supply of fish roe from nearby fisheries. Herrings are caught in February, off the west coast of Norway, during spawning season. The herring meat is processed and the roe is a by-product of herring filleting. The roe is frozen in 20kg blocks and several hundred tons are stored every year[213].

Herring roe, Arctic Bioscience's raw material

Source: Company

The roe is refined, and omega-3 fatty acids are extracted at Arctic Bioscience's facility at Ørsta. The extraction process yields the roe extract rich in phospholipid esters of EPA and DHA but also defatted marine protein that is sold as a separate product. The extract is transported to Frederikstad for encapsulation and packaging. Then products are shipped to – and sold in – many markets including the US and the EU. Besides sales, marketing and e-commerce capacities the company has R&D operations, quality assurance and regulatory affairs (outsourced to its CRO), to navigate drug development and comply with quality and other requirements[214].

[213] Company
[214] Arctic Bioscience

Products

The company has two kinds of dietary supplements on the market under the brand names Romega® and MOPL. It sells roe oil capsules with high EPA and DHA content and also marine protein capsules.

The Romega® herring caviar oil contains various omega-3 fatty acids, mainly DHA and EPA in a 3:1 ratio. A significant part of the fatty acids is in PL form, which has several benefits. The roe oil is rich in choline and has a high absorption rate partly due to the amphiphilic properties of PLs. Romega® is also tested for environmental contaminants to comply with the requirements of Global Organization for EPA and DHA omega-3 (GOED) Voluntary Monograph[215]. The herring oil capsules have no fishy aftertaste, making them more appealing than traditional fish oils.

Romega®, Arctic Bioscience's flagship dietary supplement

Source: Company

Romega® is comparable to competitors in some respects, but also has a few unique features.

Romega's main features

	Content per gram
EPA	100mg
DHA	320mg
Total omega-3	470mg
Omega-3 PLs	340mg
Vitamin D	1µg
Choline	42mg

Source: Company data

There are supplements with higher overall omega-3, EPA or DHA content, but most of them contain the fatty acids in TG from while Romega® has a high PL content. The high DHA:EPA ratio and choline content can also differentiate Romega® from competitors. If we look at competitors, the next challenge for Arctic Bioscience is to increase the omega-3 content of capsules. This concentration is particularly important for the pharmaceutical development.

Romega compared to its competitors

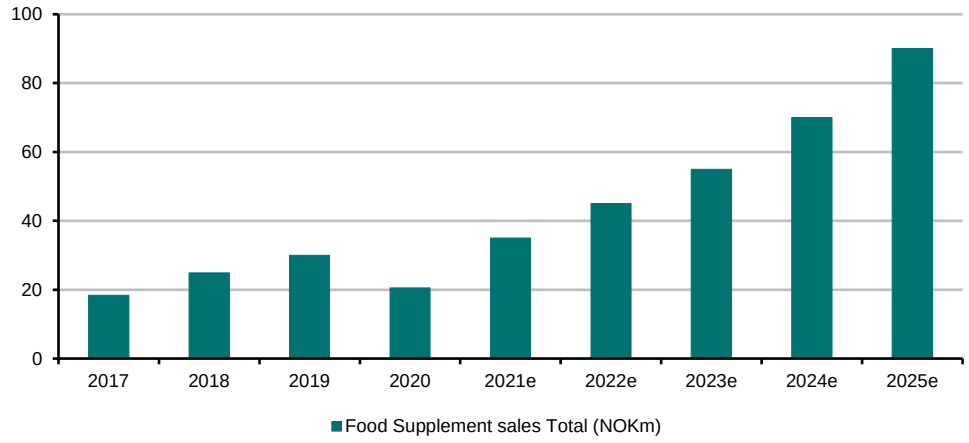
Product	Romega	EPAX 2050 TGN	SUPERBAKrill	Vivomega Platinum	Ultimate Omega
Company	Romega	Epax	Aker BioMarine	GC Rieber	Nordic Naturals
EPA (mg/g)	100	205	140	450	325
DHA (mg/g)	320	500	65	350	225
Total omega-3 (mg/g)	470	700	240	850	640
Phospholipid (mg/g)	340	Max. 70	430	N/A	N/A
Choline (mg/g)	42	N/A	50	N/A	N/A

Source: Products websites

[215] GOED Monograph. [Internet]. [cited 2020 Nov 19]. Available from:. https://goedomega3.com/goed-monograph

Romega® is sold directly to customers as a finished, branded product in Norway. The company expects to see substantial growth in this product segment due to increasing e-commerce sales in Norway.

Total sales in Food Supplement operations



Source: Company (historical figures) and DNB Markets (estimates).

Romega® caviar oil is also sold in a bulk form as capsules or oil. In this B2B segment China is a significant component and Chinese B2B sales are expected to drive the growth of this segment in the next couple of years. The herring protein is another product of the extraction process. It contains 90% pure protein with a full range of amino acids. It also contains a substantial amount of nucleotides and also Vitamin B_{12} and minerals. This product accounts for a small part of total nutraceutical sales, but protein sales are also expected to grow until 2025.

Arctic Bioscience's Arctic caviar protein

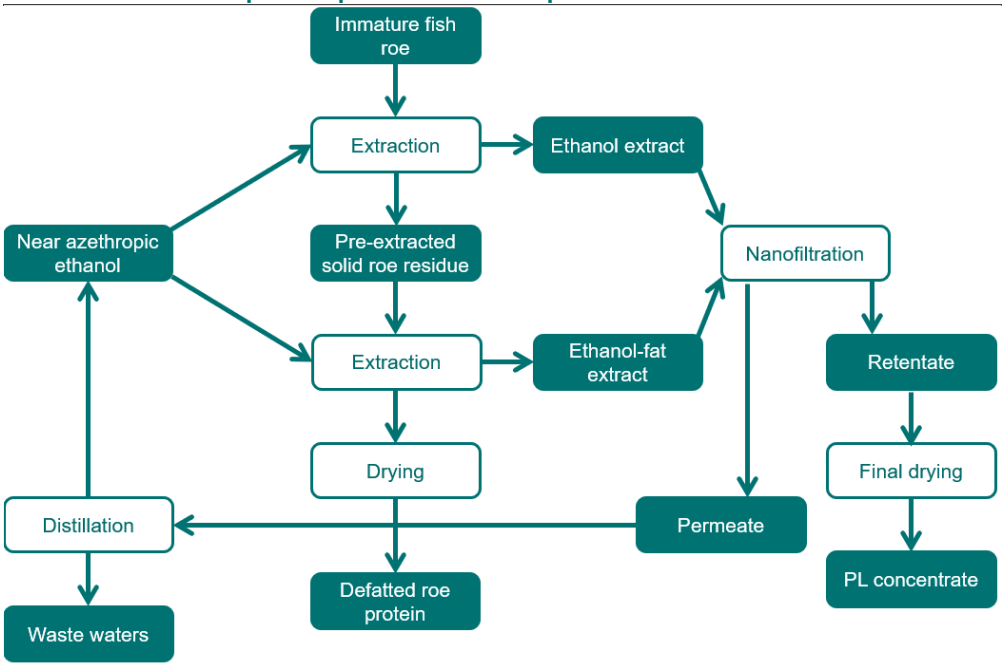
Source: Company

Intellectual property rights

We found two patents in the Espacenet database that contain Arctic Nutrition AS (the previous name for Arctic Bioscience) as applicant.

One of them[216] protects the method for extracting phospholipids and proteins from the fish roe. Basically, the omega-3 fatty acids are extracted twice from the fish roe by a polar solvent such as ethanol. The extracts are filtered and dried to get the PL concentrate. A part of the original extract yields the marine protein, while a big proportion of the solvent is recycled. The inventors are Daniele Mancinelli chief technology officer (CTO) and Per Christian Sæbø chief operating officer (COO) at Arctic Bioscience. The patent's international filing date was 21 March 2016, therefore the invention in protected for the next 20 years until 2036.

Arctic Bioscience's lipid and protein extraction process



Source: Mancinelli D, Saebo PC. Methods for Obtaining Phospholipids and Compositions Thereof. HK1250153A1, 2018.

The second patent[217] that is directly related to Arctic Bioscience describes lipid compositions that contain a substantial amount of DHA. The patent also touches upon the extraction process and defines Marine Omega-3 PhosphoLipid (MOPL) as a mixture of solid omega-3 PLs and carrier oil. The main part of the patent describes features of lipid compositions and their possible uses. The first claim describes the method of psoriasis treatment with these lipid compositions and the remaining claims are built on this. Among the inventors we can find Hogne Hallaråker Chief Scientific Officer (CSO) and founder of Arctic Bioscience. The patent was filed on 3 October 2016, so the invention is protected from this date on for 20 years.

These two patents protect the extraction process, the composition and the treatment method. These components are the core of the business, and are sufficiently secured in our view.

Another set of patents is associated with company employees. Hogne Hallaråker, Per Christian Sæbø, and Daniele Mancinelli appear as inventors in several patents, all of them related to lipids, or omega-3 fatty acids. Aker BioMarine and Natural ASA are the most frequent applicants in these patents.

[216] Mancinelli D, Saebo PC. Methods for Obtaining Phospholipids and Compositions Thereof. HK1250153A1, 2018
[217] Berger A, Hallaraker H, Remmereit J. Lipid compositions with high DHA content. US10076530B2, 2018

Future plans

The next big event for the company is to conduct a Phase IIb and a Phase III trial with c400–500 patients to prove the drug candidate's safety and efficacy. The results of the open-label extension study were promising, but they should be replicated in a bigger patient sample to reinforce the drug's safety and efficacy profile. If the company reports convincing results (the same efficacy and maintained side-effect profile in a larger multi-centre trial), it would be a major step towards commercialisation. The Phase IIb dose-response study is scheduled to be initiated in Q1 2022e. It is expected to last for 60 weeks and involve c519 patients, to test two doses of HRO350. Once the Phase IIb trial is complete in Q1 2024e, a Phase III study should start in the next quarter with c400 patients. According to the company, the Phase III results will be announced during 2026.

Next big event: Phase IIb and Phase III trials with c400–500 patients to prove the drug's safety and efficacy

Clinical development plan

	Pilot clinical trial	Phase IIb dose response	Phase III
Patients (mild/moderate)	64	519	400
Duration	**26 weeks** 15 months open label extension	**60 weeks** Primary endpoint at 26 weeks c130 centres, 7 countries	**72 weeks** Primary endpoint at 26 weeks
Study design	**32 patients** 6g HRO **32 patients** placebo	**173 patients** 3g HRO350 **173 patients** 6g HRO350 **173 patients** placebo	**267 patients** HRO350 **133 patients** placebo
Milestones	Publication of study (May 2020) EMA Scientific Advice (Q4 2020)	Phase IIb initiation (Q1 2022e) Phase IIb results (Q2 2023e – primary endpoint)	Phase III initiation (Q2 2024e) Phase III results (Q2 2026e)

Source: Company data

The company estimates the cost of the phase IIb trial (and other activities related to the drug development programme such as toxicology and CMC (chemistry, manufacturing and controls) activities) to be cNOK210m. The Phase III trial should be slightly less expensive given the need for only two groups of patients and fewer trial centres (on our estimates).

We consider the overall clinical trials costs justified. We examined the size of past Phase III studies (63) of psoriasis treatment and found the average size was 552 patients[218]. Additionally, we found a recent publication that examined clinical trial costs. According to this article, the average cost per patient in a Phase III dermatology study was cNOK200,160[219]. If we multiply it by c520 patients (the size of Phase IIb study) we get cNOK112m. In addition to this CMC is a necessary and, in many cases, more expensive activity than expected. Adding the large number of clinical sites in the trial (c130) resulting in a high infrastructure cost of the trial we believe that a cost of cNOK200m is reasonable. Our take on the large number of clinical trial centres is that the company wants to include not only large dermatology clinics but also a fair number of GPs and these sites might not recruit more than one or two patients per site but still add value as many patients with mild to moderate psoriasis are cared for by GPs.

The company has other development projects in the pipeline targeting autoimmune diseases. If it succeeds with the approval and commercialisation of HRO350, it would have a couple of strategic options. It could expand towards dermatologicals and focus on atopic dermatitis and eczema. It could also opt for autoimmune diseases and inflammation and investigate possibilities in rheumatoid arthritis or maybe ulcerative colitis. The future of its nutraceutical division is also an important question. We note Arctic Bioscience has two fully owned

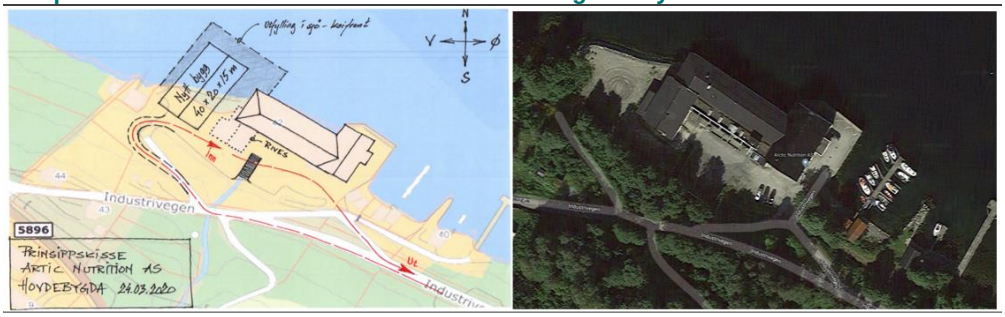
[218] DNB Markets
[219] Moore TJ et al. BMJ Open. 2020 Jun 11;10(6):e038863

subsidiaries – Romega AS and Arctic Biopharma AS – so the pharmaceutical and nutraceutical operations are already separated to some extent.

Planning to build a new manufacturing facility – mostly paid for with grants and bank loans

To prepare for increased demand, the company plans to build a new manufacturing facility next to its headquarters to prepare for increased future demand for nutritional supplements and pharmaceuticals. The plan of the new building was released in early 2020. The company plans to use c15% of the capital raised in the IPO on production and process technology. Most of the capital needed for the expansion of the manufacturing facility has been secured by grants from Innovasjon Norge and loans from a local bank. In total we estimate the company will invest cNOK180m in the manufacturing and process technology, of which c80% has been secured.

The plan of Arctic Bioscience's new manufacturing facility



Source: Company, Google Maps

Busy years ahead

It is clear it has busy years ahead, but we believe that things are going in the right direction. The company is working on clinical development and extending its manufacturing capacity to prepare for commercialisation.

Market model and forecasts

HRO350 is being developed to treat mild and moderate cases of psoriasis. The company has already published its pilot clinical trial results, so the next challenge is the Phase IIb and Phase III trials. So far, the drug seems more effective in moderate cases. The final label and indication depend on the outcome of the upcoming trials, but the drug will target either mild and moderate patients or only moderate. In our market model we forecast the number of diagnosed and treated mild and moderate psoriasis patients in markets that are the most relevant for Arctic Bioscience. The company can either commercialise it alone by building in-house sales, marketing and distribution capacities or can out-license the compound (at least in some markets). In the latter case, it would receive only royalties, but costs would also be lower. This gives us four scenarios to examine.

Possible marketing scenarios

	In-house commercialisation	Out-licensing
Moderate patients	Scenario 1	Scenario 2
Mild and moderate patients	Scenario 3	Scenario 4

Source: DNB Markets

Out-licensing HRO350 to a large pharma company is its main strategy

According to the company, out-licensing the drug to a large pharmaceutical company is its main strategy, and it plans to do this after the completion of the phase IIb trial. We estimate at least a 90% probability of it out-licensing the drug, and just 10% for going it alone. The question is rather more about timing we believe. The company has said it plans to proceed with a licensing deal after phase IIb, but we hope it would be pragmatic and make the decision based on actual phase IIb trial data and – if the data is very convincing – consider taking the drug into phase III on its own. Here, targeting only moderate patients would be the more likely parameter. Based on this, we have assigned probabilities to each scenario.

Probabilities of possible scenarios

	In-house commercialisation	Out-licensing
Moderate patients	7.50%	60.00%
Mild to moderate patients	2.50%	30.00%

Source: DNB Markets

We see a c90% likelihood of out-licensing, giving in-house commercialisation a 10% probability. Targeting only moderate patients seems more likely based on the clinical data so far (it is also a more conservative assumption). Of course, these things are not black and white, so the company might out-license the compound only in some markets.

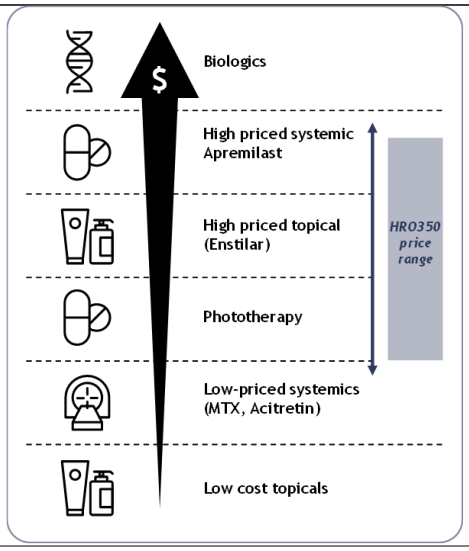
We expect approval in early 2027 and commercialisation from 2027

If successful, we believe the drug will be approved in early 2027 and commercialisation will start in 2027. In our view, the market penetration and market share for HRO350 will vary between markets (EU5, the US, Scandinavia).

Likely pricing between biological and systemic drugs

On pricing we believe the company (most likely a partner) will price HRO350 in line with what Key Opinion Leaders see as reasonable benchmarks for the drug. As shown below, the pricing of HRO350 is likely to be below where biological drugs are priced but above low-price systemic drugs. With this in mind we believe the price for HRO350 per patient per year will be cUSD6,500 in the US and cUSD3,400 in Europe.

Potential price range for HRO350



Source: Company data

The US (the largest psoriasis market) is largely dominated by corticosteroids and Vitamin D analogues, hence we assume slower uptake and a smaller market share. At the same time, we forecast the highest price in the US but still comparable to other treatment options there. We believe the price of HRO350 will be higher than topical treatments, but well below Otezla®'s price in every market. We have adjusted our sales estimates for the drug's LOA and expected adherence. Throughout the model we assume an average NOK/USD of 9.

We assume the same price across the EU5 and Scandinavia (Norway, Sweden, Denmark), which is considerably lower than the US price but still comparable to the price of other options in the EU. The EU market is more balanced with many companies; hence we believe it is easier to gain market share here, and we also expect faster uptake. Furthermore, Arctic Bioscience has an established network and experience in Scandinavia, so we assume it will be able to gain a higher market share there than elsewhere in Europe.

We assume a 20% royalty rate when applicable and that the company will not out-license commercialisation in Scandinavia. Also, we assume it will receive upfront payments and development as well as sales- related milestones of cUSD250m over time. We believe the deal will be back-end loaded, i.e. most of the USD250m in milestones will be related to sales milestones. We assume the company out-licenses the drug after the Phase IIb trial although we cannot rule out a later transaction if the data from the trial is very convincing.

In the table below, we show our base-case for the company (out-licensing the drug after phase IIb, and a focus on commercialisation for moderate psoriasis patients).

Market model Arctic Bioscience HRO350 – US and EU5

	2021e	2022e	2023e	2024e	2025e	2026e	2027e	2028e	2029e	2030e	2031e	2032e	2033e	2034e	2035e	2036e
US																
Diagnosed moderate patients, (≥18 years) (m)	3.053	3.119	3.184	3.249	3.323	3.401	3.483	3.557	3.633	3.710	3.789	3.870	3.952	4.036	4.121	4.209
Treated moderate patients, (≥18 years) (m)	2.565	2.620	2.675	2.729	2.792	2.857	2.926	2.988	3.052	3.117	3.183	3.251	3.320	3.390	3.462	3.536
Penetration of HRO350 (%)	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.10%	0.80%	1.50%	2.20%	2.90%	3.60%	4.30%	5.00%	5.00%	5.00%
Patient treated (N)	0	0	0	0	0	0	2,926	23,907	45,781	68,573	92,314	117,032	142,757	169,518	173,113	176,781
Price/patient (USD)	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500	6,500
Revenue (USDm)	0	0	0	0	0	0	19	155	298	446	600	761	928	1,102	1,125	1,149
Revenues (NOKm)	0	0	0	0	0	0	171	1,399	2,678	4,012	5,400	6,846	8,351	9,917	10,127	10,342
LOA (%)	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%
LOA-adjusted revenue (USDm)	0	0	0	0	0	0	7	54	104	156	210	266	325	386	394	402
LOA-adjusted revenue (NOKm)	0	0	0	0	0	0	60	490	937	1,404	1,890	2,396	2,923	3,471	3,544	3,620
Adherence	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%
Adherence and LOA-adjusted revenue (USDm)	0	0	0	0	0	0	5	41	78	117	158	200	244	289	295	302
Adherence and LOA-adjusted revenue (NOKm)	0	0	0	0	0	0	45	367	703	1,053	1,418	1,797	2,192	2,603	2,658	2,715
Growth YOY								717%	91%	50%	35%	27%	22%	19%	2%	2%
EU5																
Diagnosed moderate patients, (≥18 years) (m)	2.897	2.912	2.926	2.939	2.955	2.974	2.992	3.008	3.025	3.041	3.058	3.074	3.091	3.108	3.125	3.143
Treated moderate patients, (≥18 years) (m)	1.788	1.799	1.810	1.820	1.831	1.845	1.859	1.871	1.883	1.895	1.907	1.920	1.933	1.945	1.958	1.971
Penetration of HRO350 (%)	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.50%	1.38%	2.25%	3.13%	4.00%	4.88%	5.75%	6.63%	7.50%	7.50%
Patient treated (N)	0	0	0	0	0	0	9,293	25,721	42,362	59,220	76,297	93,597	111,122	128,877	146,863	147,837
Price/patient (USD)	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400
Revenue (USDm)	0	0	0	0	0	0	32	87	144	201	259	318	378	438	499	503
Revenues (NOKm)	0	0	0	0	0	0	284	787	1,296	1,812	2,334	2,864	3,400	3,943	4,493	4,523
LOA (%)	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%
LOA-adjusted revenue (USDm)	0	0	0	0	0	0	11	31	50	70	91	111	132	153	175	176
LOA-adjusted revenue (NOKm)	0	0	0	0	0	0	100	275	454	634	817	1,002	1,190	1,380	1,573	1,583
Adherence	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%
Adherence and LOA adjusted revenue (USDm)	0	0	0	0	0	0	8	23	38	53	68	84	99	115	131	132
Adherence and LOA adjusted revenue (NOKm)	0	0	0	0	0	0	75	207	340	476	613	752	892	1,035	1,180	1,187
Growth YOY								177%	65%	40%	29%	23%	19%	16%	14%	1%

Source: DNB Markets

Market model HRO350 – Scandinavia and total

	2021e	2022e	2023e	2024e	2025e	2026e	2027e	2028e	2029e	2030e	2031e	2032e	2033e	2034e	2035e	2036e
Scandinavia																
Diagnosed moderate patients, (≥18 years) (N)	0.129	0.130	0.131	0.132	0.133	0.134	0.135	0.137	0.138	0.139	0.140	0.141	0.142	0.143	0.145	0.146
Treated moderate patients, (≥18 years) (N)	0.094	0.094	0.095	0.096	0.097	0.097	0.098	0.099	0.100	0.101	0.101	0.102	0.103	0.104	0.105	0.106
Penetration of HRO350 (%)	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.5%	1.8%	3.1%	4.3%	5.6%	6.9%	8.2%	9.4%	10.7%	12.0%
Patient treated (N)	0	0	0	0	0	0	491	1,760	3,049	4,360	5,692	7,045	8,420	9,817	11,236	12,678
Price/patient (USD)	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400	3,400
Revenue (USDm)	0	0	0	0	0	0	2	6	10	15	19	24	29	33	38	43
Revenues (NOKm)	0	0	0	0	0	0	15	54	93	133	174	216	258	300	344	388
LOA (%)	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%	35%
LOA-adjusted revenue (USDm)	0	0	0	0	0	0	1	2	4	5	7	8	10	12	13	15
LOA-adjusted revenue (NOKm)	0	0	0	0	0	0	5	19	33	47	61	75	90	105	120	136
Adherence	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%	75%
Adherence and LOA-adjusted revenue (USDm)	0	0	0	0	0	0	0	2	3	4	5	6	8	9	10	11
Adherence and LOA-adjusted revenue (NOKm)	0	0	0	0	0	0	4	14	24	35	46	57	68	79	90	102
Growth YOY								258%	73%	43%	31%	24%	20%	17%	14%	13%
Overall																
Revenues from nutritional supplements (NOKm)	35	45	55	70	90	105	120	130	140	150	168	176	185	194	204	214
Growth YoY of nutritional supplements (%)	71%	29%	22%	27%	29%	17%	14%	8%	8%	7%	5%	5%	5%	5%	4%	3%
Total LOA and adherence-adjusted sales revenue HRO350 (NOKm)	0	0	0	0	0	0	30	131	236	344	456	571	690	812	864	880
Milestones HRO350 (USDm)	0	0	0	25	0	50	0	50	50	50	25	0	0	0	0	0
LOA-adjusted milestones HRO350 (NOKm)	0	0	0	79	0	158	0	158	158	158	79	0	0	0	0	0
Total adjusted revenue (NOKm)	35	45	55	149	90	263	150	419	534	652	703	748	875	1,007	1,068	1,094
Growth YOY	71%	29%	22%	170%	-39%	192%	-43%	180%	27%	22%	8%	6%	17%	15%	6%	2%

Source: DNB Markets

Valuation

Initiating coverage with a BUY and NOK60 target price

We use a DCF model focused on 'scenario 2' (out-licensing HRO350 and focusing on moderate psoriasis). Our revenue forecasts thus form the basis of our valuation. We have assumed that as the company out-licenses the product after phase IIb, it will not have to pay for its continuing development (as a partner would take that responsibility as well as the registration and sales and marketing expenses for the drug). Instead, Arctic Bioscience would receive milestone payments and royalties based on end-user sales. Based on this, we have created four DCF models, using a WACC of 10% and assuming the company is fully equity financed in the upcoming years. This DCF forms the basis of our target price of NOK60.

The revenue stream – and thus the whole model – depends on the success of Arctic Bioscience's drug candidate HRO350. If the trials are successful and the drug gets approved, we expect commercialisation to start in 2027. Until then the revenue stream would mainly consist of revenues from the Food Supplement operation, for which we forecast solid growth as the distribution relationship struck with partners takes effect.

Our DCF model yields a value of cNOK60 per share and the below we show the variability when changing some of the input variables. In the first table we change US and EU prices (in USD per patient per year) and LOA (in percentage). In the second table we show the sensitivity on LOA and WACC, and in the third table the sensitivity on drug price and penetration.

DCF sensitivity US/EU price (USD per patient per year) and LOA, (NOK per share)

		LOA				
EU price	US price	25%	30%	35%	40%	45%
2,877	5,500	43	49	56	62	69
3,138	6,000	44	51	58	65	71
3,400	6,500	45	53	60	67	74
3,661	7,000	47	54	62	69	76
3,923	7,500	48	56	64	71	79

Source: DNB Markets

DCF sensitivity – LOA and WACC, (NOK per share)

		WACC				
		9.0%	9.5%	10.0%	10.5%	11.0%
LOA	25%	50	48	45	43	41
	30%	58	55	53	50	47
	35%	66	63	60	57	54
	40%	74	70	67	63	60
	45%	82	78	74	70	67

Source: DNB Markets

DCF sensitivity – prices in the US and EU and peak penetration, (NOK per share)

		EU uptake:	4.5%	6.0%	7.5%	9.0%	10.5%
EU price	US price	US uptake:	3.0%	4.0%	5.0%	6.0%	7.0%
2,877	5,500		41	49	56	63	70
3,138	6,000		43	50	58	65	73
3,400	6,500		44	52	60	68	75
3,661	7,000		45	53	62	70	78
3,923	7,500		46	55	64	72	81

Source: DNB Markets

Our target price of NOK60 suggests significant upside potential from the current share price, and we therefore initiate coverage with a BUY recommendation.

DCF model scenario 2 (out-license and focus on moderate psoriasis patients) - NOKm

	2021e	2022e	2023e	2024e	2025e	2026e	2027e	2028e	2029e	2030e	2031e	2032e	2033e	2034e	2035e	2036e
Sales	**35**	**45**	**55**	**149**	**90**	**263**	**150**	**419**	**534**	**652**	**703**	**748**	**875**	**1,007**	**1,069**	**1,094**
Total costs	58	103	105	150	97	128	90	139	160	181	157	163	179	195	200	200
EBITDA	**-23**	**-58**	**-49**	**-1**	**-6**	**135**	**60**	**280**	**374**	**471**	**545**	**585**	**696**	**812**	**869**	**894**
Depreciation and amortisation	-4	-7	-10	-10	-10	-10	-10	-10	-10	-10	-10	-10	-10	-10	-10	-10
EBIT	-27	-65	-60	-11	-17	124	50	270	364	461	535	575	686	802	858	884
Net financial items	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1	-1
Result before taxes	-28	-66	-61	-12	-18	124	49	269	363	460	534	574	685	801	857	883
Taxes	0	0	0	0	0	0	-11	-59	-80	-101	-118	-126	-151	-176	-189	-194
Capex	-89	-89	-10	-10	-10	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5	-5
Increase/decrease in NWC	-4	0	0	27	-29	21	-22	16	10	10	4	4	11	11	5	2
Free cash flow	**-108**	**-147**	**-60**	**-38**	**13**	**108**	**66**	**200**	**279**	**355**	**418**	**450**	**530**	**620**	**670**	**693**
Present value of free cash flow	**-99**	**-123**	**-46**	**-27**	**8**	**62**	**34**	**95**	**120**	**139**	**149**	**146**	**156**	**166**	**163**	**153**

Source: DNB Markets

Risks

We see the following risks that every investor should consider before making an investment.

- **Development risk.** Drug development is a risky endeavour and, even after a successful Phase II trial, a drug might not meet its primary endpoint in Phase III. There is a chance a drug will fail because it lacks efficacy or because safety concerns emerge. There is no guarantee severe side effects will not appear in a trial. Thus, development is risky for the company and for the patients involved in the trial. As the company – and indirectly its investors – needs to commit a lot of money and time into the development without knowing until the end whether or not the trials succeed only magnifies this risk. During development, every day matters and some factors can slow down a trial, e.g. slower than expected patient recruitment.
- **Regulatory risk.** Even if a drug succeeds in Phase III, approval is not guaranteed and there is always a chance one or more regulatory authorities will reject the application. There is at least a 15% risk a development project will fail during the approval process. Besides, legislation is different in the EU and the US and if the company wants to be present in both, it will have to comply with both sets of regulations. Consequently, the differences and changes in legislation can also be a risk.
- **Marketing and market access risk.** Once the drug is approved it must reach and convince stakeholders including physicians, patients and healthcare payers. It is possible that Arctic Bioscience (or its marketing partner) will fail to build a big enough sales force and establish a network with key opinion leaders, putting the drug's success in jeopardy. Additionally, the effectiveness of the drug might be different in real life than in a clinical trial setting and patients might not experience a clinically meaningful improvement, which would probably lower their willingness to commit to the drug. To be reimbursed, the drug will have to go through a health economic assessment where its cost effectiveness is examined. If the drug is not cost-effective enough, it might not be able to establish appealing pricing, which would probably weaken its financial attractiveness.
- **Competitive risk.** The pharmaceutical industry is competitive, with an inherent risk of new – and possibly better – treatments entering the market. Should Arctic Bioscience's drug be a success, generics would probably follow as soon as possible (but not near-term owing to the time development takes) to put pressure on its market share and profitability. Also, new companies might enter the market with more resources, becoming tough competitors.
- **Patient preference risk.** Dosing and adherence can be a drug's biggest merit, but also risks. If patients do not find the dosing schedule compelling enough, their adherence might not be as high as expected. Moreover, some patients might be reluctant to stick to the dosing schedule, particularly old patients with possible swallowing difficulties.
- **Differentiation risk.** The company could have problems with differentiation. Many companies manufacture omega-3 nutritional supplements from marine sources particularly in the Nordics. Even if they are not approved pharmaceuticals, there is nothing to stop patients opting for these possibly cheaper alternatives even if they do not have certified quality, safety and efficacy. Patients are not always aware of the differences between pharmaceuticals and dietary supplements. These supplements might take patients and hence market share from Arctic Bioscience and they are direct competitors of Romega®.
- **Financial risk.** Arctic Bioscience is not profitable yet, so is likely to need external funding for the rest of the development. If it completes the development and out-licenses the product it will need a bigger organisation and potentially even larger manufacturing operations than it is planning. To finance this before it has reached break-even, it will most likely have to raise external capital to support its goals despite some income from the sales of nutritional supplements. These financial uncertainties make the company riskier.
- **Intellectual property risk.** It has patents to defend its extraction process and product composition, but patents can be challenged. Other parties could claim Arctic Bioscience

infringed their patent or vice versa. If a conflict cannot be settled with an agreement, the situation could escalate and lead to long and expensive lawsuits. This risk applies to every company that holds patents.

- **Key personnel risk.** Arctic Bioscience is a small company, so some key personnel could be essential. While some employee turnover is to be expected, sudden or unexpected departures of key people could cause significant difficulties. If employees holding patents or important management positions were to leave, it could be particularly painful.

Appendices

Management and board

Management

- **Ole Arne Eiksund – CEO.** Mr Eiksund has 25+ years' experience from the pharmaceutical industry, including as commercial director at GlaxoSmithKline (GSK). He was previously EVP Rimfrost AS, VP global sales Hofseth BioCare AS and area manager at GE Healthcare.
- **Hogne Hallaråker – CSO/founder.** Mr Hallaråker founded Arctic Bioscience and developed its business concept. He has 15+ years' experience in the nutraceutical and biomarine industries. Former positions include VP of R&D at Aker BioMarine, product director at Natural ASA and CEO of Natural Nutrition Development AS. He also has academic experience as Assistant Professor of Natural Sciences at Volda University College. He holds an MSc in Marine Biology and Aquaculture from University of Bergen.
- **Per Christian Sæbø – COO.** Mr Sæbø has 20+ years' experience from manufacturing management and process development. Before joining Arctic Bioscience in 2012 he was a director of technology and site manager at Epax and director of technology at Natural Nutrition Development AS. He also held positions at Aker BioMarine and was director of lipid development at Natural ASA. He holds an MSc in Chemistry from NTNU.
- **Danielle Glenn – CFO.** Ms Glenn has 20+ years' international management experience. She began her career as a sales analyst and trader at Goldman Sachs, then was a portfolio manager at Caxton. She was CEO and CIO at Bywater Capital and more recently was CEO, CSO and CFO at Sensee, Sonitor and Rosalyn AI. She graduated magna cum laude from Harvard University.
- **Daniele Mancinelli – CTO.** Mr Mancinelli specialises in the R&D of omega-3 fatty acids and is experienced in concept architecture, testing and up-scaling. He was previously research manager at Epax, Natural Nutrition Development AS and Aker BioMarine. He holds an MSc in Chemistry and Pharmaceutical Technologies.
- **Runhild Gammelsæter – global medical director.** Dr Gammelsæter is highly experienced in the pharmaceutical industry, including R&D-based entrepreneurship, patenting and managing research units. She was the founder and president of biotech firm Regenics AS and held various leadership roles at GSK, AbbVie, and Abbot.
- **Dr. Yuming Feng – EVP global business development.** Dr Feng has 20+ years' global experience in the food & nutraceutical industry. Previously, he was Sr. Scientist & Procurement Manager at Campbell's, EVP at Zoneco and CEO at Holley International. He also holds a Ph.D. in Food Science from the University of Massachusetts Amherst.
- **Åge Nærdal – EVP pharmaceutical development.** Mr Nærdal has 35+ years' experience in the pharmaceutical industry and has been an industry leader for 20+ years. He held various management positions at GSK, including GM of GSK Norway for 13 years. He has been a board member of Norwegian Association of Pharmaceutical Manufacturers for 10+ years.
- **Rick Pope – SVP B2B Nutraceuticals.** Mr Pope has 30+ years' international experience in sales and marketing in the pharmaceutical and nutritional industries. He was previously director at DSM Nutritional Products and VP of Global Strategic Accounts at Ocean Nutrition Canada.
- **Lauren Jensen – SVP sales and marketing.** Ms Jensen has 15+ years' global marketing, branding, and communications experience. She is also experienced in digital marketing and global marketing strategy development and execution. Previously, she was director of sales and marketing at IC Scandinavia, and digital marketing manager at VitaeLab AS. She was also a PR & marketing consultant at Advania AS and brand manager at MAC Cosmetics. She holds an MBA from Nord University and a BBA from Arizona State University.
- **Gwendolyn Kent – international sales director.** Ms Kent has 20+ years' experience with global sales of patented ingredients. She is highly knowledgeable in developing and

marketing nutraceuticals with clinical documentation. She has experience in MLM, as a practitioner, and in mass-market positioning. Her achievements include taking the top three dietary supplements in the US from patent inception to mass distribution.

Board of directors

- **Harald Nordal – chairman of the board.** Mr Nordal is CEO and chairman of the board at Hyperthermics AS. He is also a board member at Regenics AS, chairman of the board at Intuitive Biosciences, and CEO of Life Capitol AS. He was previously assistant director at Innovation Norway and project manager at Statoil. He holds an MSc in Civil Engineering from NTNU and an MBA from SKEMA Business School.
- **Asbjørn Solevågseide.** Mr Solevågseide is an investor at Ajea Invest AS; he was previously CEO of Optimar AS for 30+ years.
- **Frede Klinkby Uldbæk.** Mr Uldbæk is CEO at several companies including Vikingo AS, a consultancy company, Sydvestor AS and Centraleiendommen AS. He is chairman at Sydvestor Amber AS, Vikingo AS, Finanseiendommen AS and Centraleiendommen AS.
- **Jan Brevig Remmereit.** Mr Remmereit is CEO and chairman of Lifescience AS and Greystone Holding AS. He is on the board of Hyperthermics AS, Sciadonic AS and Viiral AS.
- **Jan Endre Vartdal.** Mr Vartdal is CEO and chairman of the board at Poly Har AS. He is also CEO of Neset Nord AS, Plast-Transport AS, Vartdal Plastindustri AS and Nordic Isoelementer AS. He holds several board positions including at Brødrene Vartdal AS.
- **Jostein Christian Dalland.** Mr Dalland held executive management roles in several companies. He is CEO of SpinChip Diagnostics AS, and was previously EVP at Storebrand, CEO at Inven2, EVP of marketing and sales at Aker BioMarine, and CEO of Natural ASA (which later became Aker BioMarine). He was also chairman of the board at Refleks AS for eight years, and marketing manager at Orkla Foods.
- **Per Magne Eggesbø.** Mr Eggesbø has 20+ years' experience as CEO of Eros AS and is CEO of Ramoen AS and Eggesbø Eiendom AS. He has numerous board positions and holds a Bachelor of Business Administration Degree from BI Norwegian Business School.
- **Reidar Bjerkestrand.** Mr Bjerkestrand sits on the board of numerous companies including Kristiansund Røntgen Holding AS, Kontali Analyse AS, Maritime Partner AS, Møre Maritime AS and Maritech Systems AS. He is also CEO of Bølgen Invest AS. Previously, he was an advisor at ProCorp and Pareto Securities and chief analyst at Norse Securities. He holds an MBA from Norwegian School of Management.

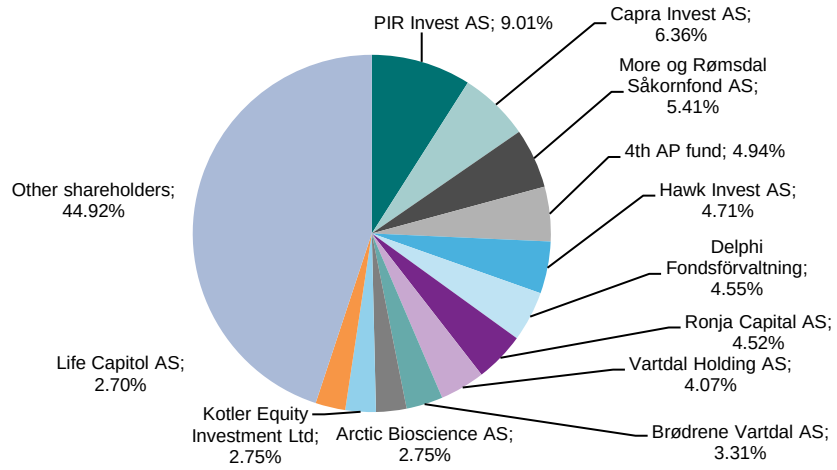
Ownership

The biggest shareholders of Arctic Bioscience are Norwegian investment funds.

- PIR Invest AS is a venture capital firm in Ålesund. According to Arctic Bioscience, it is a group of founders with global scaling experience.
- Capra Invest AS is involved in real estate letting. It is associated with Harald Nordal, the chairman of Arctic Bioscience's board. It also has small stakes in numerous companies including Hyperthermics Holding AS, Regenerics AS and Life Capitol AS.
- More og Rømsdal Såkornfond AS is an investment fund focused on seed investments. It also has an investment in Maritime Partner AS.
- Life Capitol AS is also connected to Harald Nordal (he is CEO). Life Capitol's main owner is Jan Brevig Remmereit through Greyston Holding AS. It also has a 33.7% stake in Regenics AS, a company focused on salmon roe and wound care products, founded by Runhild Gammelsæter.

Besides the biggest shareholders, Ole Arne Eiksund (0.39%) and Per Christian Sæbø (0.143%) are among the direct owners, while Åge Nærdal (0.492%) and Daniele Mancinelli (0.354%) are among the indirect owners of the company.

Owners of Arctic Bioscience – 2021-03-08



Source: Holdings.se

Annual P&L

(NOKm)	2015	2016	2017	2018	2019	2020	2021e	2022e	2023e
Revenues	**8**	**12**	**18**	**25**	**30**	**20**	**35**	**45**	**55**
Cost of sales	-7	-5	-12	-16	-20	-21	-21	-25	-28
Gross profit	**1**	**7**	**6**	**9**	**10**	**-1**	**14**	**20**	**28**
Operating expenses	-8	-4	-7	-10	-12	-20	-37	-78	-77
EBITDA	**-6**	**3**	**-1**	**-1**	**-2**	**-20**	**-23**	**-58**	**-49**
Depreciation	0	-1	-1	-1	-1	-1	-4	-7	-10
EBITA	**-7**	**2**	**-1**	**-1**	**-3**	**-22**	**-27**	**-65**	**-60**
EBIT	**-7**	**2**	**-1**	**-1**	**-3**	**-22**	**-27**	**-65**	**-60**
Net interest	0	-1	0	-1	0	0	0	0	0
Other financial items	0	0	0	0	0	0	0	0	0
Net financial items	0	-1	0	-1	-1	-1	-1	-1	-1
PBT	**-7**	**1**	**-2**	**-2**	**-4**	**-23**	**-28**	**-66**	**-61**
Taxes	0	0	0	0	0	0	0	0	0
Effective tax rate (%)	0	0	0	0	0	0	0	0	0
Net profit	**-7**	**1**	**-2**	**-2**	**-4**	**-23**	**-28**	**-66**	**-61**
Adjustments to net profit	0	0	0	0	0	0	0	0	0
Net profit adj	-7	1	-2	-2	-4	-23	-28	-66	-61
Dividend paid	0	0	0	0	0	0	0	0	0
Avg. number of shares	16	16	16	16	16	16	27	27	27
Per share data (NOK)									
EPS	-0.47	0.10	-0.12	-0.12	-0.27	-1.55	-1.08	-2.56	-2.35
DPS ordinary	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
DPS extraordinary	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
DPS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Growth and margins (%)									
Revenue growth	nm	47.0	57.3	35.3	20.9	-31.8	70.8	28.6	22.2
EPS adj growth	nm	nm	nm	nm	nm	nm	nm	nm	nm
Gross margin	13.8	55.4	32.1	35.7	34.1	nm	40.0	45.0	50.0
EBITDA margin	nm	22.1	nm	nm	nm	nm	nm	nm	nm
EBITDA adj margin	nm	22.1	nm	nm	nm	nm	nm	nm	nm
Depreciation/revenues	-6.0	-5.5	-3.2	-2.1	-3.6	-5.8	-12.0	-16.0	-18.5
EBIT margin	nm	16.6	nm	nm	nm	nm	nm	nm	nm
EBIT adj margin	-88.5	15.9	-7.4	-5.0	-10.6	-106.2	-77.0	-144.4	-108.6
PBT margin	nm	12.0	nm	nm	nm	nm	nm	nm	nm
Net profit margin	nm	nm	nm	nm	nm	nm	nm	nm	nm

Source: Company (historical figures), DNB Markets (estimates)

Adjustments to annual P&L

(NOKm)	2015	2016	2017	2018	2019	2020	2021e	2022e	2023e
EBITDA	**-6**	**3**	**-1**	**-1**	**-2**	**-20**	**-23**	**-58**	**-49**
Gains and losses	0	0	0	0	0	0	0	0	0
EBITDA adj	-6	3	-1	-1	-2	-20	-23	-58	-49
EBITA	**-7**	**2**	**-1**	**-1**	**-3**	**-22**	**-27**	**-65**	**-60**
Gains and losses	0	0	0	0	0	0	0	0	0
EBITA adj	-7	2	-1	-1	-3	-22	-27	-65	-60
EBIT	**-7**	**2**	**-1**	**-1**	**-3**	**-22**	**-27**	**-65**	**-60**
Gains and losses	0	0	0	0	0	0	0	0	0
EBIT adj	-7	2	-1	-1	-3	-22	-27	-65	-60
Net profit	**-7**	**1**	**-2**	**-2**	**-4**	**-23**	**-28**	**-66**	**-61**
Gains and losses	0	0	0	0	0	0	0	0	0
Net profit adj	-7	1	-2	-2	-4	-23	-28	-66	-61
Per share data (NOK)									
EPS	-0.47	0.10	-0.12	-0.12	-0.27	-1.55	-1.08	-2.56	-2.35

Source: Company (historical figures), DNB Markets (estimates)

Cash flow

(NOKm)	2015	2016	2017	2018	2019	2020	2021e	2022e	2023e
Net profit	-7	1	-2	-2	-4	-23	-28	-66	-61
Other non-cash adjustments	0	0	0	0	0	0	0	0	0
Change in net working capital	5	-2	-1	-3	-11	1	4	0	0
Cash flow from operations (CFO)	**1**	**-5**	**-2**	**-5**	**-14**	**-20**	**4**	**-41**	**-51**
Capital expenditure	0	0	0	0	0	-10	-89	-89	-10
Acquisitions/Investments	-2	-1	-1	-4	-7	-9	-2	-2	-2
Divestments	0	0	0	0	0	0	0	0	0
Cash flow from investing (CFI)	**-2**	**-1**	**-1**	**-4**	**-7**	**-19**	**-91**	**-91**	**-12**
Free cash flow (FCF)	**-1**	**-7**	**-3**	**-9**	**-21**	**-39**	**-87**	**-132**	**-63**
Net change in debt	0	-1	0	-1	-1	-3	59	57	5
Dividends paid	0	0	0	0	0	0	0	0	0
Other	1	0	0	-1	-1	11	-5	-8	2
Cash flow from financing (CFF)	**8**	**2**	**7**	**3**	**44**	**27**	**379**	**49**	**107**
Total cash flow (CFO+CFI+CFF)	**7**	**-5**	**4**	**-5**	**23**	**-11**	**293**	**-83**	**45**
FCFF calculation									
Free cash flow	-1	-7	-3	-9	-21	-39	-87	-132	-63
Less: net interest	0	1	0	1	0	0	0	0	0
Less: acquisitions	2	1	1	4	7	9	2	2	2
Less: divestments	0	0	0	0	0	0	0	0	0
Growth (%)									
CFO	nm	-947.4	60.6	-116.3	-204.5	-45.9	122.2	-1022.8	-23.8
CFI	nm	19.9	26.9	-323.6	-67.6	-162.8	-389.6	0.0	86.8
FCF	nm	-517.5	53.7	-183.4	-138.3	-85.7	-124.3	-52.4	52.5
CFF	nm	-75.7	265.0	-51.7	1189.0	-38.1	1294.4	-87.0	117.6
FCFF	nm	nm	nm	nm	nm	nm	nm	nm	nm

Source: Company (historical figures), DNB Markets (estimates)

Balance sheet

(NOKm)	2015	2016	2017	2018	2019	2020	2021e	2022e	2023e
Assets	**37**	**31**	**34**	**45**	**82**	**93**	**466**	**476**	**521**
Inventories	13	9	8	16	17	26	18	18	19
Trade receivables	1	2	2	6	12	11	11	11	11
Other receivables	1	1	1	1	1	3	0	1	1
Cash and cash equivalents	7	2	6	1	24	13	305	223	267
Current assets	**21**	**14**	**17**	**24**	**54**	**53**	**334**	**253**	**298**
Property, plant and equipment	4	3	3	3	3	6	96	185	183
Other intangible assets	12	13	14	18	25	34	36	38	40
Non-current assets	**15**	**16**	**17**	**21**	**28**	**41**	**132**	**224**	**223**
Total assets	**37**	**31**	**34**	**45**	**82**	**93**	**466**	**476**	**521**
Equity and liabilities	**37**	**31**	**34**	**45**	**82**	**93**	**466**	**476**	**521**
Total equity to the parent	14	13	19	22	64	64	385	337	377
Total equity	**14**	**13**	**19**	**22**	**64**	**64**	**385**	**337**	**377**
Trade payables	1	2	2	6	6	10	6	7	8
Other payables and accruals	1	1	1	1	1	2	2	2	2
Short-term debt	6	5	4	5	4	9	5	5	6
Total current liabilities	**8**	**8**	**6**	**11**	**11**	**21**	**13**	**14**	**15**
Long-term debt	14	10	9	12	7	8	67	124	129
Total non-current liabilities	**14**	**10**	**9**	**12**	**7**	**8**	**67**	**124**	**129**
Total liabilities	**22**	**18**	**15**	**24**	**19**	**29**	**81**	**139**	**145**
Total equity and liabilities	**37**	**31**	**34**	**45**	**82**	**93**	**466**	**476**	**521**
Key metrics									
Net interest bearing debt	14	13	7	16	-13	5	-233	-93	-132

Source: Company (historical figures), DNB Markets (estimates)

Valuation ratios

(NOKm)	2015	2016	2017	2018	2019	2020	2021e	2022e	2023e
Enterprise value									
Share price (NOK)							27.50	27.50	27.50
Number of shares (m)	14.62	14.62	14.62	14.62	14.62	14.62	25.72	25.72	25.72
Market capitalisation							707	707	707
Net interest bearing debt	14	13	7	16	-13	5	-233	-93	-132
Adjustments to NIBD	0	0	0	0	0	0	0	0	0
Net interest bearing debt adj	14	13	7	16	-13	5	-233	-93	-132
EV							475	614	575
EV adj							475	614	575
Valuation									
EPS	-0.47	0.10	-0.12	-0.12	-0.27	-1.55	-1.08	-2.56	-2.35
DPS ordinary	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
DPS extraordinary	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
DPS	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P/E							-25.5	-10.8	-11.7
Average ROE		10.4%	-11.0%	-8.4%	-9.4%	-35.3%	-12.4%	-18.2%	-17.0%
Dividend yield							0.0%	0.0%	0.0%
EV/SALES							13.56	13.65	10.46
EV/SALES adj							13.56	13.65	10.46
EV/EBITDA							-21.0	-10.6	-11.6
EV/EBITDA adj							-21.0	-10.6	-11.6
EV/EBIT							-17.7	-9.5	-9.6
EV/EBIT adj							-17.6	-9.5	-9.6
EV/NOPLAT							-17.7	-9.5	-9.6
EV/OpFCF (taxed)							-4.3	-4.2	-9.7

Source: Company (historical figures), DNB Markets (estimates)

Key accounting ratios

	2015	2016	2017	2018	2019	2020	2021e	2022e	2023e
Profitability (%)									
ROA		4.2	-5.3	-4.3	-6.3	-25.7	-9.9	-14.0	-12.1
Return on invested capital (%)									
Net PPE/revenues	46.3	29.0	17.1	12.9	10.5	31.0	273.9	411.9	332.5
Working capital/revenues	169.7	84.7	49.9	69.9	78.8	146.8	63.4	50.2	42.1
Cash flow ratios (%)									
FCF/revenues	-13.6	-57.0	-16.8	-35.1	-69.2	-188.3	-247.3	-293.1	-113.9
FCF yield (%)	nm	nm	nm	nm	nm	nm	-12.0	-18.4	-8.6
CFO/revenues	7.9	-45.3	-11.3	-18.1	-45.7	-97.6	12.7	-90.9	-92.1
CFO/market capitalisation							0.6	-5.8	-7.2
CFO/capex						-200.1	5.0	-46.0	-506.3
CFO/current liabilities	7.8	-69.9	-33.4	-39.3	-120.2	-96.2	33.4	-286.1	-335.4
Cash conversion ratio	15.6	-475.8	178.1	510.1	517.5	170.8	311.9	200.5	103.4
Capex/revenues	0.0	0.0	0.0	0.0	0.0	48.8	254.3	197.8	18.2
Capex/depreciation	0.0	0.0	0.0	0.0	0.0	838.9	2123.1	1237.5	98.1
OpFCF margin	-81.3	22.1	-3.7	-2.5	-6.7	-148.7	-319.0	-326.0	-108.1
Total payout ratio	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Leverage and solvency (x)									
Interest cover	nm	3.75	-3.10	-2.19	-6.12	-42.46	-52.59	nm	nm
EBIT/interest payable	nm	3.71	nm	nm	nm	nm	nm	nm	nm
EBITA adj/interest payable	nm	3.55	nm	nm	nm	nm	nm	nm	nm
Cash coverage	307.76	5.16	-1.81	-1.22	-4.47	-41.63	-46.03	-117.26	-100.49
Net debt/EBITDA	-2.17	4.97	-10.20	-25.38	6.42	-0.24	10.27	1.61	2.68
Total debt/total capital (BV)	0.57	0.49	0.38	0.37	0.13	0.19	0.16	0.27	0.26
LTD / (LTD + equity (MV))							0.09	0.15	0.15
Cash conversion cycle									
Inventory turnover days	711.7	635.5	241.0	364.4	322.2	448.6	305.0	266.0	255.9
Receivables turnover days	53.2	99.8	52.5	107.2	154.1	245.5	114.4	95.6	77.1
Credit period	55.0	166.5	49.9	133.9	119.3	169.7	109.8	106.4	102.4
Cash conversion cycle	709.9	568.9	243.5	337.7	357.0	524.3	309.6	255.2	230.6

Source: Company (historical figures), DNB Markets (estimates)

Important Information

Company: Arctic Bioscience
Coverage by Analyst: Patrik Ling
Date: 11-3-2021

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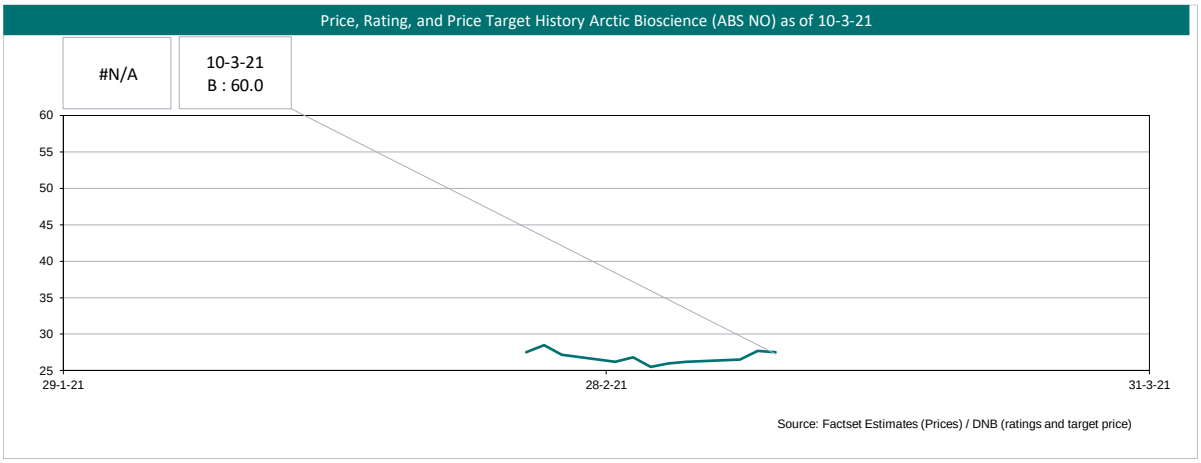

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Alberta: Blake, Cassels & Graydon LLP, 855 - 2nd Street S.W., Suite 3500, Bankers Hall East Tower, Calgary, AB T2P 4J8. British Columbia: Blakes Vancouver Services Inc., 595 Burrard Street, P.O. Box 49314, Suite 2600, Three Bentall Centre, Vancouver, BC V7X 1L3. Manitoba: MLT Aikins, 30th Floor, Commodity Exchange Tower, 360 Main Street, Winnipeg, MB R3C 4G1. New Brunswick: Stewart McKelvey, Suite 1000, Brunswick House, 44 Chipman Hill, PO Box 7289, Station A, Saint John, NB E2L 2A9. Newfoundland and Labrador: Stewart McKelvey, Suite 1100, Cabot Place, 100 New Gower Street, P.O. Box 5038, St. John's, NL A1C 5V3. Nova Scotia: Stewart McKelvey, Purdy's Wharf Tower One, 1959 Upper Water Street, Suite 900, P.O. Box 997, Halifax, NS B3J 2X2. Northwest Territories: Field LLP, 601, 4920 52nd Street, Yellowknife, NT X1A 3T1. Nunavut: Field LLP, P.O. Box 1734, House 2436, Iqaluit, NU X0A 0H0. Ontario: Blakes Extra-Provincial Services Inc., Suite 4000, 199 Bay Street, Toronto, ON M5L 1A9. Prince Edward Island: Stewart McKelvey, 65 Grafton Street, Charlottetown, PE C1A 1K8. Québec: Services Blakes Québec Inc., 1 Place Ville Marie, Suite 3000, Montréal, QC H3B 4N8. Saskatchewan: MLT Aikins, 1500 Hill Centre I, 1874 Scarth Street, Regina, SK S4P 4E9. Yukon: Macdonald & Company, Suite 200, Financial Plaza, 204 Lambert Street, Whitehorse, YK Y1A 3T2.

In Brazil

The analyst or any close associates do not hold nor do they have any direct/indirect involvement in the acquisition, sale, or intermediation of the securities discussed herein. Any financial interests, not disclosed above, that the analyst or any close associates holds in the issuer discussed in the report is limited to investment funds that do not mainly invest in the issuer or industry discussed in the report and the management of which these persons cannot influence.