
RECCURA
THERAPEUTICS
COEGIN
PHARMA
A portfolio company in the
Coegin Pharma Group
AVX001 gel – towards better treatment of patients suffering from
actinic keratosis and basal cell carcinoma

Introduction

Reccura Therapeutics AS is a Norwegian subsidiary company to the Swedish biotechnology company Coegin Pharma AB as part of Coegin Pharma AB's hub & spoke "portfolio" biotech model, with clear benefits to investors. Reccura Therapeutics AS will develop the promising novel and proprietary drug candidate AVX001 further, and will primarily be financed separately from Coegin Pharma AB.

The goal of the hub & spoke business model is to focus on identifying new ground-breaking projects with clear potential for value addition through the following phases: Identification ⇒ Financing ⇒ Value addition ⇒ Exit.

Coegin Pharma AB's hub & spoke model offers lower costs, more flexible financing, increased focus and an effective exit process. The company is driven by a seasoned team with key competencies in dermatology, oncology and inflammation and is governed by a professional board of directors. In the Coegin Pharma AB portfolio of companies exist Avexxin Oncology AS, Follicum AB and Reccura Therapeutics AS.

The skin cancer market

Both actinic keratosis (AK) and basal cell carcinoma (BCC) are very common diseases.

- AK is by far the most prevalent skin cancer condition affecting up 60 million people in the US alone.
- Current drug therapies for AK include topical chemotherapy such as 5-Fluorouracil (5-FU) and the immune modifier imiquimod that are both associated with severe local skin reactions.
- BCC is the most common type of skin cancer. In the US alone there are an estimated 4 million new cases each year. There a limited number of therapies available for BCC and most tumors are removed by surgery that may cause pain and scarring.
- Few drug therapies are available for BCC and may be associated with significant side effects. Hence there is a market opportunity for a safe and efficacious treatment of BCC.
- The global basal cell carcinoma market was estimated to be valued at 6.7 bUSD in 2021, of this approximately 40% is the drug market and hence the value of drugs is estimated at 2.7 bUSD and is forecasted to reach 3 bUSD by 2025.

BCC is the most common type of skin cancer, the global market is valued 6.7 billion USD

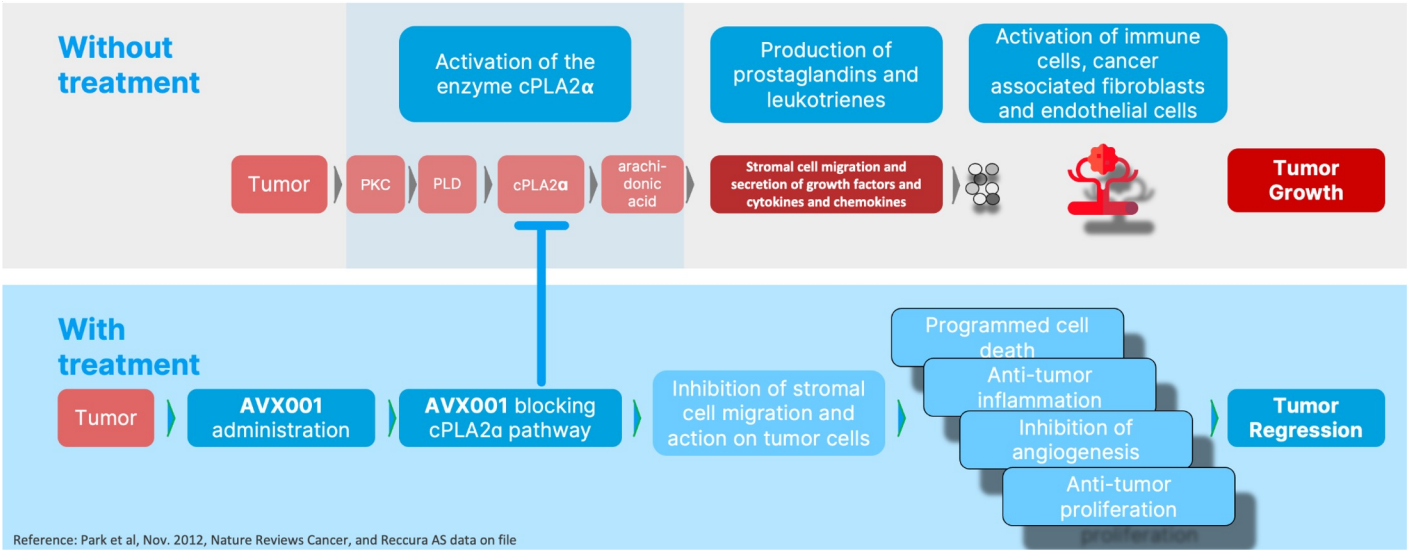
Reccura Therapeutic's drug candidate AVX001

AVX001 is a highly potent and selective small molecule blocking the activity of the key enzyme cPLA2α. The molecule is mimicking the natural substrate of the enzyme and belongs to a chemically class of modified polyunsaturated fatty acids. AVX001 is developed by Professor Berit Johansen at NTNU in Trondheim in close collaboration with Professor Lars Skattebøl at University of Oslo.

A novel and well characterized mode of action targeting the cPLA2α enzyme

Reccura Therapeutic is based on pioneering research on the cPLA2**α** enzyme and represent a potential paradigm shift for the treatment of inflammatory driven cancers.

AVX001 efficiently and selectively blocks the cPLA2**α** enzyme activity leading to significantly reduced levels of arachidonic acid which in turn reduces tumor growth by affecting several key hallmarks of cancer development, including programmed cell death, anti-tumor inflammation, inhibition of angiogenesis, and anti-tumor proliferation.



Reference: Park et al, Nov. 2012, Nature Reviews Cancer, and Reccura AS data on file

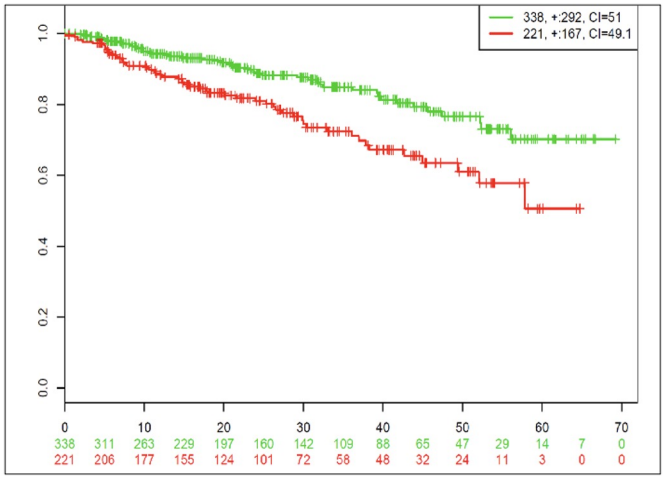
The role of cPLA2α in cancer

There is substantial evidence that cPLA2α plays a key role in the development of cancer and inflammation, two aspects that play a key role in the development of the inflammatory driven diseases AK and BCC. Furthermore, high cPLA2α levels correlate with metastasis and poor prognosis of several cancers. Even poor treatment outcomes of existing treatments have been shown to be correlated with high cPLA2α levels, and inhibiting cPLA2α in combination with existing standard of care treatments, for example radiation, increases the treatment response in preclinical models.

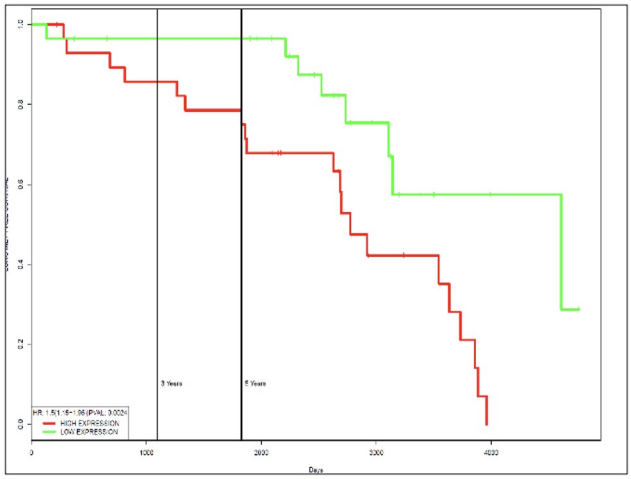
cPLA2**α** as a key biomarker for poor prognosis in cancer

High levels of cPLA2α is associated with poor prognosis for patients

Cytosolic Phospholipase A2 group IVA enzyme (cPLA2**α**) is an emerging and promising new target for treating cancers. The figure below shows that elevated cPLA2α expression is associated with poor prognosis and survival of cancers (red curves), as compared with patients with no or low levels of cPLA2α expression (green curves).



Shaughnessy 2005, myeloma

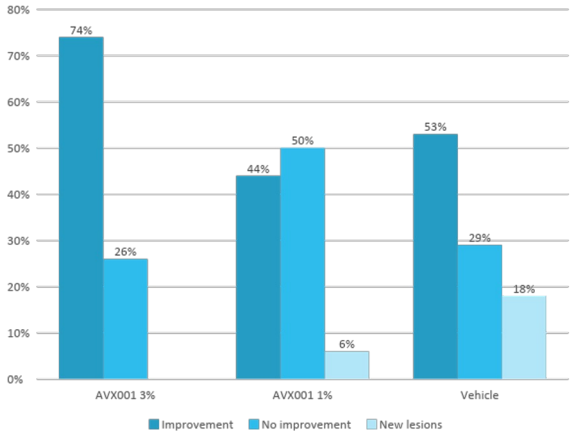


Wang 2007, breast (lung metastasis)

Promising results in completed clinical trials

Previous clinical safety and efficacy experience has been completed and comes from four phase I/IIa clinical studies assessing AVX001. Two studies in a topical ointment formulation for the treatment of mild-to-moderate psoriasis patients, and two in a gel formulation for the treatment of atopic dermatitis and AK. In the latter, we conducted the Copenhagen Actinic Keratosis Study (COAKS), a 12-week single-center, randomized, vehicle-controlled, double-blind, hybrid clinical trial in adults with multiple AK lesions Olsen grade 1 or 2. In this study the AVX001 topical gel-formulation was found to be safe and tolerable, and effectiveness was observed in AK. From the three other studies AVX001 was also found to be safe and effectiveness was shown in treating psoriasis.

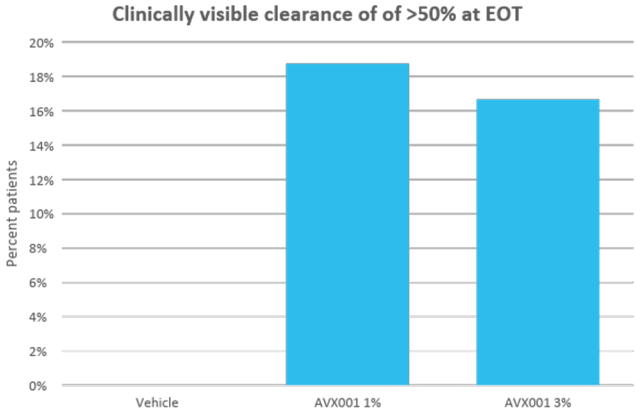
AVX001 3% reduced the number of AK lesions



74% of patients treated with AVX001 3% achieved an improvement in their AK lesions at end of treatment

AVX001 showed overall effectiveness

18% of the AVX001 1% or 3% had a clinically visible clearance of target area of >50%, and no effect was observed in the vehicle arm



AVX001 acts more effectively in more severe AK-grade-2

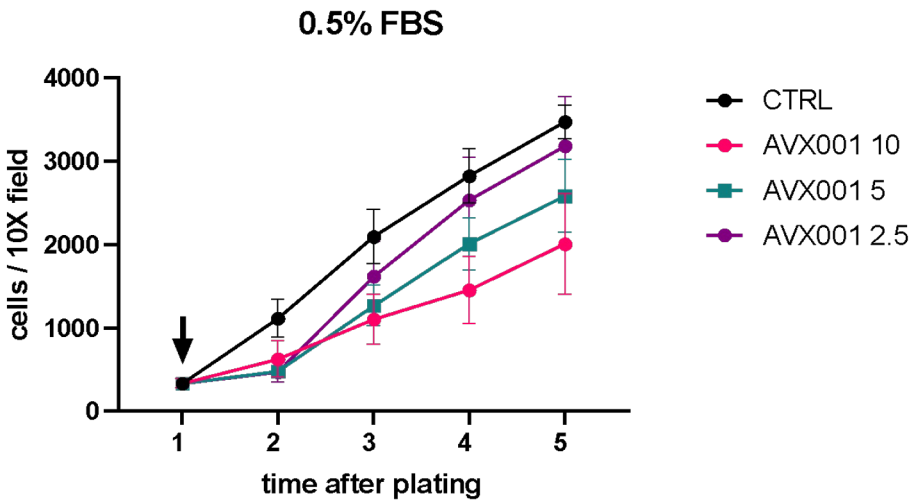
Reduction in Olsen "grade 2" was only evident for the AVX001 1% and 3% groups and increased for the vehicle group at end of treatment (EOT)

Promising data of AVX001 in BCC

BCC cell proliferation is highly dependent on the so-called Hedgehog signaling pathway, and the marketed drug vismodegib has been developed to block this pathway. AVX001 has been investigated in human BCC cell line model. The experiments demonstrated a potent dose dependent effect, being five times as potent as compared to previously published data on vismodegib in the same cell line. These data form a strong rationale for the planned clinical study in superficial basal cell carcinoma.

Dose dependent effect of treating BCC with AVX001

In human Basal Cell Carcinoma cell line (UWBCC1) AVX001 inhibits BCC cell viability (IC50 of 10 µM) dose dependent way.



Compound	IC50
AVX001	2. 8 µM
vismodegib	28 µM

AVX001 is highly potent as compared with vismodegib

In the human Basal Cell Carcinoma cell line (UWBCC1) AVX001 inhibits BCC cell viability (IC50 of 2.8 µM) 10 times more potent than the marketed drug vismodegib (a Hedgehoc inhibitor) (IC50 of 28 µM).

AVX001 inhibits BCC cell viability
5 times more potent than the marketed vismodegib

Reference: Olesen UH, Bojesen S, Gehl J, Haedersdal M. Anticancer drugs and the regulation of Hedgehog genes GLI1 and PTCH1, a comparative study in nonmelanoma skin cancer cell lines. Anticancer Drugs. 2017 Nov;28(10):1106-1117 Reccura Therapeutics data on file. Press release 2023-01-27, Coegin Pharmas portföljbolag Reccura Therapeutics rapporterar nya forskningsresultat inom hudcancer

Strong patent protection

AVX001 has a strong foundation of patents providing solid market protection until 2040. There are three key patents: One patent that protects the use of AVX001 in non-melanoma skin cancers a patent application for actinic keratosis and patent that protects the novel and cosmetically attractive formulation of AVX001. All patents are submitted in major markets including the US, Europe, Canada, Australia, Japan, China and India.

Focus	Molecule	Claims	Number	Earliest Priority Date	Status
Non-melanoma skin cancer	AVX001/002	Use in non-melanoma skin cancer	PCT/EP2015/061534	May 2014	Granted
Formulation	AVX001/002	Formulation of AVX001	PCT/EP2017/073951	Sep 20217	Granted
AK	AVX001/002	Use in actinic keratosis	PCT/EP2021/087848	Dec 2020	Priority application

AVX001 is formulated in a cosmetically attractive gel

Key strengths of the AVX001 gel :

- Clinically validated drug candidate
- Well characterized mode-of-action
- Strong evidence for treating inflammatory driven cancers
- Skin friendly with excellent safety profile and limited skin reactions
- Cosmetically attractive gel formulation with high delivery of the drug candidate into the skin

Next clinical trials designed to demonstrate the full potential of AVX001 in AK and BCC

The planned clinical studies include an AK phase IIb study with a lesion directed therapy treating up to 8 weeks and a phase 2a in basal cell carcinoma (BCC) treating up to 8 weeks under occlusion.

In order to extend the treatment period up to 8 weeks in both AK and BCC, a preclinical extended safety period of tolerability is planned early prior to the next clinical studies. In parallel we will produce the study medicine and prepare the clinical trial applications.

Roadmap towards exit

The plan is to complete the extended safety period and initiate, phase IIb in AK and IIa in BCC. The hub & spoke business model from Coegin Pharma AB will ensure support as a very cost-effective execution model. The goal is an exit at an early stage with a co-development partner being identified. **Total capital demand 2023, 2024, and 2025 (towards phase 2a BCC results) is 50 mSEK.**

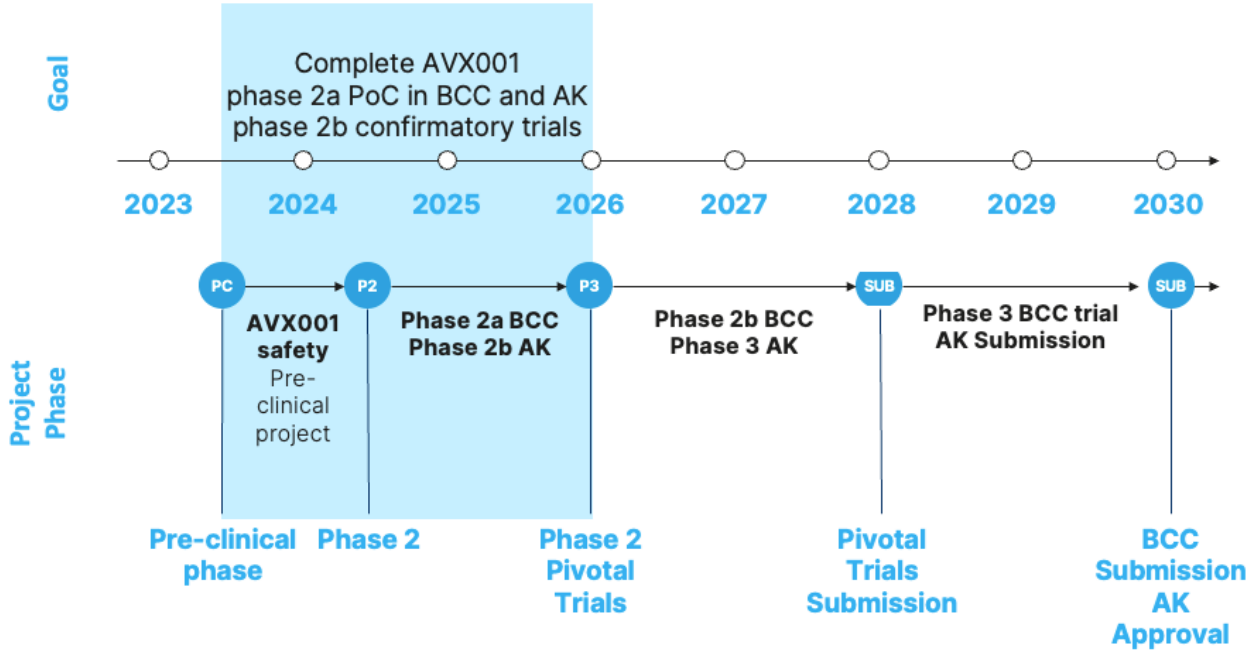
A clear road map is based on co-development and exit:

2023: Partner discussions ongoing aiming at outlicensing and co-development.

2023: Additional skin tolerability studies to extend the treatment period, produce study medicine and prepare the clinical trial applications.

2024: First patient in phase IIb in AK and IIa in BCC clinical trials.

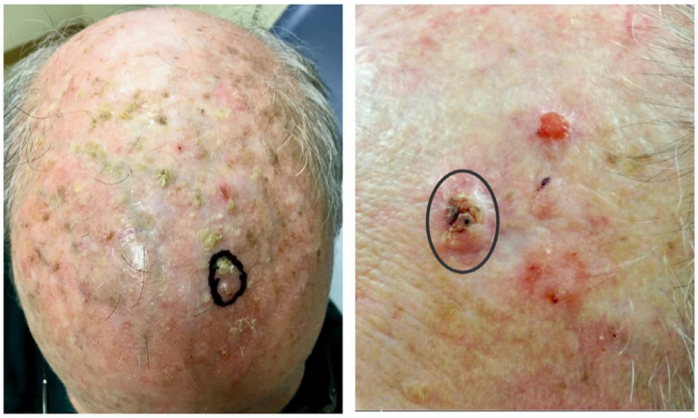
2025: Key results from the clinical trials.



Actinic keratosis is the most common precancerous skin condition

60% of Caucasians older than 60 years has actinic keratosis (AK) ranging from 10% in people aged between 20 and 30 years, whereas it is more than 90% in people over 80 years. There is substantial evidence that AK may develop into squamous cell carcinoma (SCC), a skin cancer, and it may also serve as a marker for higher risk of developing BCC and even malignant melanoma.

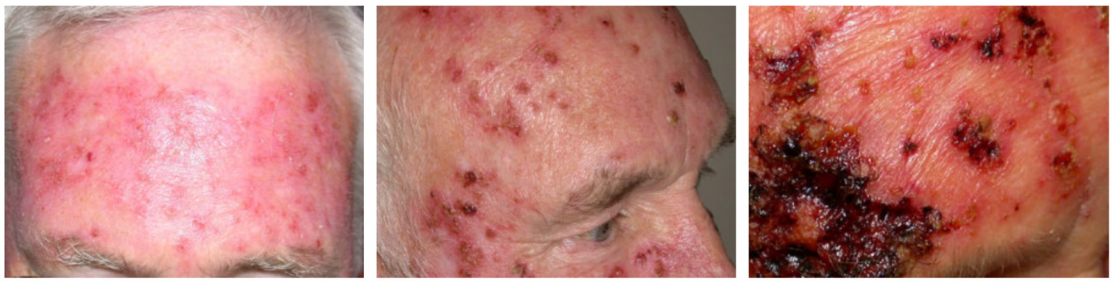
The skin cancer SCC develop from AK.



Scalp and temple with chronic AK field cancerization and innumerable small, gritty actinic keratoses, circled lesions are skin cancer (SCC)

Existing topical treatments

- Diclofenac, is a topical non-steroidal anti-inflammatory agent, applied twice daily for 8-12 weeks, with expected 25-40% clearance after 2 months. The recurrence rates after treatment is stopped is high but local skin reactions are low. Imiquimod, is a topical immune modulating agent applied once daily for 2 weeks, followed by 2 weeks rest and 2 weeks treatment it has an expected 40% complete clearance after 2 months and with moderate recurrence rates. Side effects of the treatment are several and can be of severe character.
- 5-FU, is a topical cytotoxic chemotherapeutic agent applied twice daily for 2-4 weeks, it typically results in an up to 90% clearance rate of lesions but is associated with side effects that may be of severe.
- The side effects of existing treatments are often associated with debilitating severe local skin reactions (LSR). The LSR's are transient and resolve after end of treatment, however they may impact the quality of life and adherence which limits the effect of the treatments.



Mild reaction | Moderate reaction | Severe reaction

Local skin reactions of existing treatments affect patient adherence to therapy and therefore compromise patient satisfaction.

There is an unmet need for safe and effective treatments for AK

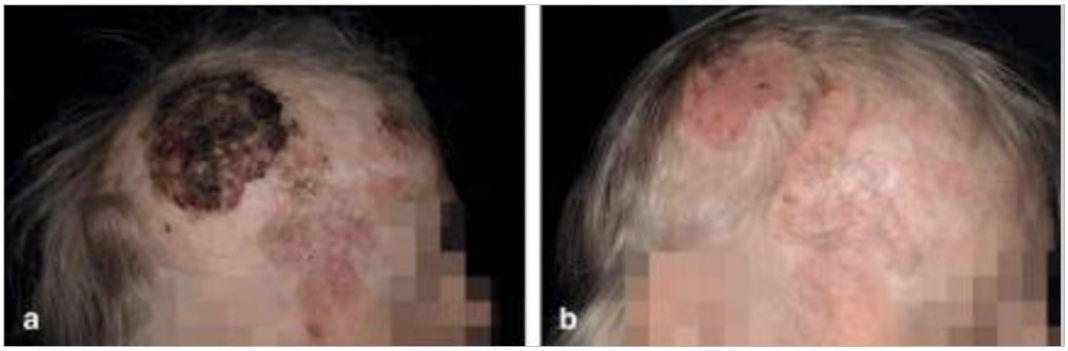
Refrence: https://www.coherentmarketinsights.com/market-insight/actinic-keratosis-market-1006

BCC is a very common disease

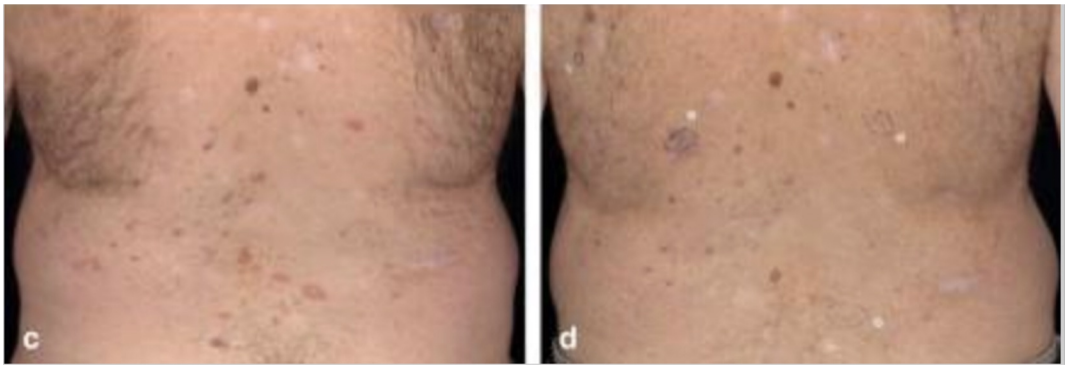
Basal cell carcinoma is the most common non-melanoma skin cancer, accounting for about 80% of all cases of non-melanoma skin cancer. Newly diagnosed cases (incidence) in US alone is 3.6 million patients with BCC each year. The global market is estimated to 6.7 B US$ in 2021, of this more than 50% are from medical procedures, 40% are from medical treatment and 10% with other treatments, hence the value of medical treatment is estimated at around 2.7 B US$ and forecasted to grow to reach 3 B US$ by 2025.

The most common treatment for BCC is surgery. For superficial BCC, approved medications such as immune modulators (imiquimod) and topical chemotherapy (topical 5-fluorouracil) are available, as are medical procedures such as photodynamic therapy, lasers and cryosurgery.

For more serious cases, radiotherapy and the systemic treatment vismodegib with severe side effects is available. Vismodegib is branded under the name Erivedge from Roche, and has a yearly revenue in 2021, around 800 million SEK.



Locally advanced basal cell carcinoma on the scalp of an 89-year-old woman a) before and b) after 10 weeks of therapy with the hedgehog signal pathway inhibitor vismodegib.



Multiple BCC on back of a 62-year-old man with nevoid BCC syndrome c) before and d) after 8 months of therapy with a hedgehog signal pathway inhibitor LDE225. His seborrheic keratoses did not change during therapy.

Vismodegib is branded under the name Erivedge from Roche
Yearly revenue in 2021, around 800 million SEK

Reference: Berking C, Hauschild A, Kölbl O, Mast G, Gutzmer R. Basal cell carcinoma-treatments for the commonest skin cancer. Dtsch Arztebl Int. 2014 May 30;111(22):389-95.

An opportunity for novelty in the dermato-oncology market

The non-melanoma skin cancer market is substantial and dominated by specialty pharma companies with a dedicated focus on skin diseases. The market is generally characterized by older drugs, lack of innovation and a large number of patients with a clear need for better treatment options. Existing drugs are associated with significant drawbacks and there is a large unmet need for new drug-treatments that are both safe and efficacious. Chemotherapies (e.g. 5FU) causes damage of the genes inside the nucleus of cells that are dividing. Other treatments stimulate the immune system to destroy cancer cells (e.g. topial imiquimod). Several medical procedures are common in the treatment of AK (e.g. liquid nitrogen) and BCC (surgery) – these therapies are generally effective but may result in pain and severe scarring which compromise the patients' quality of life. These procedures often have to be repeated several times due to recurrence of the lesions.

AVX001 inhibits cPLA2α, a key enzyme which causes release of arachidonic acid resulting in activation of multiple inflammatory and proliferative processes play a fundamental role in cancer cells and their micro environment, hence acting on several key hallmarks of cancer growth. The cPLA2α inhibitor AVX001 has been shown to exhibit effect in preclinical and clinical studies with a better safety profile over existing treatments and medical procedures.

Exit by outlicensing and partnering deals

We are very familiar with the commercial players in dermatology and we are in active dialogue with potential partners which can either acquire AVX001 or can be a valuable co-development partner sharing the risks of the planned clinical trials. We are seeking global and regional license agreements and we acquire aim to outlicense or partner AVX001 to one or several commercial companies before the next clinical Phase IIb in AK and Phase IIa in sBCC. The two clinical trials are designed to demonstrate the potential of the new treatment in both indications and to significantly increase the commercial value of the asset. This is a well-established commercial strategy for small and agile companies in the pharmaceutical space and will generate income from upfront and milestone payments and from royalties from product sales.

Parties	Asset	Year	Indication	Phase	TDV (MUSD)
Almirall – Athenex	Tirbanibulin	2017	Actinic keratosis	III	275*
LEO - Peplin	Ingenol mebutate	2009	Actinic keratosis	III	287,5
Dermavant - GSK	Tapinarof	2018	Atopic dermatitis/ psoriasis	III	298
Union – LEO	UNI500	2020	Atopic dermatitis/ psoriasis	II	200*
Dermavant - Portola	Cerdulatinib	2016	Atopic dermatitis/ psoriasis	II	145*
Arcutis – JHM	Ivarmacitinib	2018	Atopic dermatitis/ psoriasis	I	223

The table shows relevant dermatology benchmark deals. Naturally, deals for Phase 3 projects represent higher value than deals for Phase I/II projects which is why we continue to invest in AVX001 while actively seeking the right partner(s). The most recent licensing deals with topical assets suggests a potential total deal value of between 200 to 250 million US$ for AVX001.

Benchmark deals, reference: Global Data.

Reccura Therapeutics builds on a strong Norwegian and North American scientific foundation

AXV001 was developed by prof. Berit Johansen at NTNU in Trondheim, Norway and Professor Leif Skattebøl at Univerity of Oslo, Norway. The groundbreaking research of the key enzyme cPLA2**α** and its central role in inflammation and cancer has been performed in close collaboration with prof. Edward Dennis at University of California, San Diego and Professor Joseph Bonventre at Harvard Medical School, Boston. The research of cPLA2**α** and the role of AVX001 in AK and BCC has been investigated by Professor Berit Johansen, NTNU and Professor Merete Hædersdal at the Danish Research Center for Skin Cancer, University of Copenhagen.

Reccura Therapeutic's world Leading Scientific Advisors and Key Collaborators

Professor Berit Johansen – International Expert in cPLA2 Compounds and inventor of the AVX-compounds
Department of Biology, Faculty of Natural Sciences, Norwegian University of Science and Technology (NTNU).
Dr. Johansen is a Professor and Ph.d. in Molecular Genetics. She has a vast experience in molecular biology, inflammation, cancer research and cPLA2. Dr. Johansen did hold distinguished positions at: UCLA, US; University of Uppsala, Sweden; NTH, Department of Technical Biochemistry; at Unigen, University of Trondheim, Norway; Institute of Molecular Genetics, University of Göttingen, Germany; Biogen Research Corporation, Cambridge, MA ; Department of Chemistry and Biochemistry, University of California, San Diego, CA., and Harvard Medical School, Boston, MA, USA.

Professor Edward A. Dennis – International Expert in PLA2
Department of Chemistry Biochemistry, University of California, San Diego, USA
Dr. Dennis is distinguished Professor of Chemistry and Biochemistry and pharmacology, and Chair of the Department of Chemistry and Biochemistry at UCSD. The Dennis group has studied the structure and function of phospholipases for about three decades. He has contributed significantly to the AVX chemistry.

Professor Joseph Bonventre – International Expert in Renal Diseases and PLA2
Brigham and Women's Hospital, Renal Unit, Harvard Medical School, Boston, USA
Dr. Bonventre is Chief of the Renal Unit and Director of the Bioengineering Division at Brigham and Women's Hospital and has had a long-standing interest in various aspects of cellular injury and repair mechanisms in the kidney with a special emphasis on the role of inflammation, biomarkers and stem cells. One of his key focus research areas has and is still PLA2, contributing to the understanding of cPLA2**α** as a target..

Professor, Dr. med., PhD, MD Merete Hædersdal – International Expert in Skin Cancer
Danish Research Center for Skin Cancer, University of Copenhagen, Denmark
Dr. Merete Haedersdal is leading a research team of 10 researchers, focusing on translational medicine in the field of skin cancer and laser dermatology. Merete is chief consultant in dermatology at Bispebjerg Hospital and clinical professor at University of Copenhagen, Denmark. She is Visiting Scientist at Wellman Center for Photomedicine, Massachusetts General Hospital, Harvard Medical School, collaborating with professor R. Rox Anderson and his team to develop better treatments for patients with skin cancer by means of lasers and light-based techniques.She is heading the Danish Research Center for Skin Cancer and the SCIN Clinical Academic Group.

UNIVERSITY OF COPENHAGEN NTNU HARVARD MEDICAL SCHOOL UC San Diego

Management and Board of Directors

- Experienced team with a strong track record, broad Nordic outreach and key competences

Jesper Kihl

Chief Executive Officer and Board Member

- Currently, independent life science consultant and board member Coegin Pharma AB
- Former VP Global Regulatory Affairs, LEO Pharma A/S, and several senior level roles at Novo Nordisk A/S
- Vast experience in dermatology and regulatory affairs and safety

Erlend P. Skagseth

Chairman of the Board

- Currently, Managing Partner, Sarsia Management AS and CEO of Sarsia Seed AS
- Former experience from Christian Mikkelsen Research, Forinnova, and Sarsia Innovation
- Vast experience in turnarounds, licensing and exits.
- Board Member of Coegin Pharma AB

John R. Zibert

Board Member

- Currently Chief Medical Officer at Coegin Pharma AB
- Former founder and CEO at the digital CRO Studies&Me, Chief Medical Officer at LEO Innovation Lab, Head of Medical Affairs EU+ LEO Pharma A/S.
- Ph.D. in immunology, M.Sc. human biology/medicine, with academic focus within Dermatology, Oncology, Cancer Biology and digital health solutions
- Extensive experience in drug discovery and development

Key publications

Ortner, V. K., Johansen, B., Kilov, K., Mondragón, A. C., Duvold, T., Kihl, J.R. Zibert & Haedersdal, M. *The Copenhagen Actinic Keratosis Study (COAKS). A decentralised clinical trial to evaluate tolerability, safety and efficacy of daily field-directed topical treatment with cytosolic phospholipase A2 inhibitor, AVX001, in participants with actinic keratosis: protocol for a randomised controlled phase I/IIa trial.* BMJ open, 12(10), 2022, e061012.

Ashcroft FJ, Mahammad N, Midtun Flatekvål H, Jullumstrø Feuerherm A, Johansen B. *cPLA2α Enzyme Inhibition Attenuates Inflammation and Keratinocyte Proliferation.* Biomolecules. 2020 Oct 2;10(10):1402. LINK

Mahammad N, Ashcroft FJ, Feuerherm AJ, Elsaadi S, Vandsemb EN, Børset M, Johansen B. *Inhibition of Cytosolic Phospholipase A2α Induces Apoptosis in Multiple Myeloma Cells.* Molecules. 2021 Dec 9;26(24):7447. LINK

Feuerherm AJ, Dennis EA, Johansen B. *Cytosolic group IVA phospholipase A2 inhibitors, AVX001 and AVX002, ameliorate collagen-induced arthritis.* Arthritis Res Ther. 2019 Jan 21;21(1):29. LINK

Omland SH, Habicht A, Damsbo P, Wilms J, Johansen B, Gniadecki R. *A randomized, double-blind, placebo-controlled, dose-escalation first-in-man study (phase 0) to assess the safety and efficacy of topical cytosolic phospholipase A2 inhibitor, AVX001, in patients with mild to moderate plaque psoriasis.* J Eur Acad Dermatol Venereol. 2017 Jul;31(7):1161-1167. LINK

Kim E, Kim J, Maelandsmo GM, Johansen B, Moestue SA. *Anti-angiogenic therapy affects the relationship between tumor vascular structure and function: A correlation study between micro-computed tomography angiography and dynamic contrast enhanced MRI.* Magn Reson Med. 2017 Oct;78(4):1513-1522. LINK

Kim E, Tunset HM, Cebulla J, Vettukattil R, Helgesen H, Feuerherm AJ, Engebråten O, Mælandsmo GM, Johansen B, Moestue SA. *Anti-vascular effects of the cytosolic phospholipase A2 inhibitor AVX235 in a patient-derived basal-like breast cancer model.* BMC Cancer. 2016 Mar 7;16:191. LINK

Sommerfelt RM, Feuerherm AJ, Jones K, Johansen B. *Cytosolic phospholipase A2 regulates TNF-induced production of joint destructive effectors in synoviocytes.* PLoS One. 2013 Dec 12;8(12):e83555. LINK

Huwiler A, Feuerherm AJ, Sakem B, Pastukhov O, Filipenko I, Nguyen T, Johansen B. *The ω3-polyunsaturated fatty acid anaolgues AVX001 and AVX002 directly inhibit cytosolic phospholipase A(2) and suppress PGE(2) formation in mesangial cells.* Br J Pharmacol. 2012 Dec;167(8):1691-701. LINK

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