UPPDRAGSANALYS

Improving cash position

Dividend payout extends cash runway

ExpreS²ion Biotechnologies reversed cash burn in Q1 and increased its cash position. By the end of the quarter cash deposits were SEK 60m, SEK 2m above year-end level. More importantly, a dividend payout of SEK 22m in Q2 will further improve the cash runway, taking the company into 2025.

The cash accrual in Q1 was due to a grant payment in one of the ongoing explorative programs, possibly the VICI consortia. Strict cost control and a difficult comparison reduced underlying operational losses to SEK 13m from last year's level at SEK 26m.

Clinical trial application possible in Q3

The struggle to bring its proprietary vaccine candidate, the breast cancer project ES2B-C001, to a clinical phase 1 trial is gaining ground. A clinical trial application (CTA) may be possible already in Q3, a major reward after an extensive period of investments in animal studies and manufacturing processes, which started already in 2020.

Assuming a swift reply from regulatory agencies, possibly the Danish Medicines Agency, the trial should be able to start recruiting breast cancer patients in the first half of 2025. We take a conservative stance with a 75 percent chance for this scenario to materialize.

EUR billion market opportunity

At its investor conference management pinned down a market estimate for the breast cancer vaccine candidate of EUR 2,8bn. The vaccine is designed to treat patients with overexpression of the Human Epidermal Growth Factor 2 (HER2), present in around 25 percent of all breast cancer cases.

The program is based on preclinical data in transgenic mice, while detailed data on the recent toxicology trials in Non-Human Primates have not yet been released.

Fair value after dilution lowered to SEK 2,2

In April ExpreS²ion announced a new share issue which will bring a further cash injection of SEK 60m, assuming full subscription at SEK 1.0 per share. On top of this, two new warrants were issued free of charge, one of which expires in Q4. The proceeds from the new share issues are primarily aimed for the start of the clinical trial with ES2B-C001.

Our updated projection of the diluted number of shares by end of 2025 is increased to 152 mln, up by 85 percent. We lower our fair value to SEK 2,2 (3,0), a 27 percent reduction given the progress in the ES2B-C001 program.

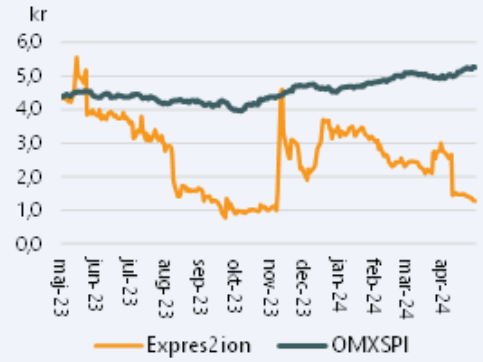
ExpreS²ion Biotech

Date	23 maj 2024
Analyst	Sten Westerberg

Facts

Industry	Vaccine Development
Chairman of the Board	Martin Roland Jensen
CEO	Bent U. Frandsen
Year of Listing	2016
Stock List	First North Growth Market
Ticker	EXPRS2
Share price, SEK	1,3
No. of shares, mln.	53,4
Market cap, SEKm	70
Cash, SEKm	60
Fair value, SEK	**2,2**
Web site	www.expres2ionbio.com

Kursutveckling senaste året



Source: Refinitiv

Forecasts & Key ratios, SEKm

	2023	2024p	2025p	2026p
Revenues, risk-adjust.	9	29	10	58
R&D expenses	-51	-37	-70	-65
Net income	-96	-30	-78	-26
Earnings per share	-1,5 kr	-0,6 kr	-1,5 kr	-0,5 kr
Revenue growth	43%	223%	-66%	478%
Cash	58	122	84	58
New share issue	58	82	40	0

Source: Company, Analysguiden forecasts

Fair value is an idea of what the company should be worth given Analysguiden's main scenario. It does not mean that the share price should reflect this value.

Focus on breast cancer project

Cancer vaccines are increasingly being studied as a possible strategy to prevent and treat cancers. Several preventive vaccines for virus-caused cancers are approved and used worldwide. However, the development of vaccines in breast cancer still has not yielded any approved products. Vaccines are seen a potential therapeutic alternative to monoclonal antibodies against HER2+ breast cancer, which currently dominate treatment of this disease.

The human epidermal growth factor receptor-2 (HER-2) is a surface receptor-like tyrosine kinase which plays a role in many human breast carcinoma and in a few other tumor types, including bladder, colorectal, lung, stomach, and musculoskeletal cancers. In breast cancer, amplification of the HER-2 gene and/or overexpression of its protein product occurs in 20–25% of all cases. This type is associated with a poor survival prognosis.

Animal toxicity trials concluded in April

ExpreS²ion Biotechnologies is developing ES2B-C001, a vaccine candidate for HER2+ breast cancer. During 2023 and the beginning of this year management has conducted toxicology studies in two animal species models, rats and a Non-Human Primate (NHP). NHP is the closest homologue available to the human species.

This broader toxicology program was initiated early last year after feed-back from a scientific advice meeting with the Danish Medicines Agency in February 2022. The studies have been carried out by a contract-research organization and the result in the studies were signed off in April.

Latest update on progression in ES2B-C001 program

Source: ExpreS²ion Q1 investor presentation

In parallel with animal studies, management has invested in an engineering process for Good Manufacturing Practice (GMP) of the drug substance, which it intends to bring to the human trial. GMP

describes the minimum standard that a manufacturer must meet in their production processes, which in general is a more demanding process for biological materials such as vaccines. GMP requires that medicines are of consistent high quality, appropriate for their intended use and meet the requirements of the clinical trial authorization (CTA).

At the Q1 teleconference management declared that manufacturing of the drug substance, i.e. the antigen (the full length of the extracellular domain of the HER2 protein) mounted on a virus like particle (VLP), was completed this month of May. Next step in the process is the production of the final drug product, which also include inactive substances as well as formulation in a vial. The manufacturing of the final drug product has been initiated lately and is expected to be completed this summer.

Application for initiating clinical trial

When a final drug product is established, ExpreS²ion will be able to apply for starting a first-in-human phase 1 trial, a clinical trial application (CTA). Before doing so, we assume that the company will have to assign a CRO, Contract Research Organization, which will oversee practicalities such as recruiting patients and analyzing data as the trial moves along. We interpret management communication so that a CTA to a regulatory agency may be submitted in Q3, possibly to the Danish Medicines Agency, which was approached for scientific advice already in 2022.

A CTA is generally approved by the regulatory agency within a three-month period. Given the tight schedule for the manufacturing of the final drug candidate and the very recently concluded toxicology studies, we prefer a conservative stance on the chances for a positive regulatory action. We rate a 75 percent likelihood of a positive action in Q4 which reflects a minor concern that the medicinal agency will like to see additional data.

Regulatory action possible in Q4

It is our belief that production of vaccine materials involves a more complex process than traditional small-molecules drugs and possibly also than monoclonal antibodies. We also note that the toxicology studies have been conducted with a prototype vaccine which to some extent may differ from the final product.

A CTA also involves a draft of the trial design which also will have to be signed off by the agency. Assuming an approval of the CTA in Q4 this year, we expect a first patient treated with ES2B-C001 in the first half of next year. Given the costly nature of a CRO-managed phase 1 studies, as well as the expensive manufacturing of clinical material, we speculate that phase 1 will not include more than twenty-five patients. This may allow the company to finalize the study in 2027 after having released interim data in 2026.

In Q1 a payment of SEK 3,5m was made to AdaptVac as milestone after achieving a clinical ready GMP vaccine candidate and another payment of SEK 3,5m will be made upon initiation of the phase 1 study.

Basic scenario involves licensing deal in 2026-27

Assuming a positive read-out in 2026-27, we have an aggregated likelihood of 38 percent of a partnering deal with an initial downpayment of EUR 25m. To get to a licensing deal, we have included partial financing from TO 10 and 11, on top of the rights issue in June.

We have raised the likelihood of marketing approval (LOA) after phase 2b and 3 studies to 9 percent from 6 percent, based on the progress in animal studies and manufacturing processes. Our base case is an approval by 2030, which starts to look optimistic.

Estimated sales potential of EUR 2,8bn

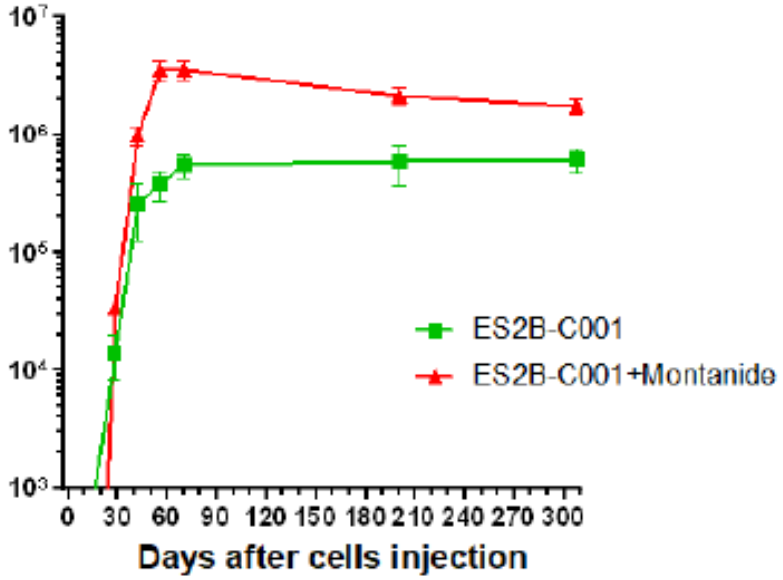
In the recent announcement, management defined the obtainable market opportunity for a HER2+ vaccine as more than EUR 2,8bn. A previous number in the annual report stated a total market opportunity in breast cancer of more than EUR 10bn, which should be seen as broader definition of the market.

Our valuation is based on a peak sales estimate of EUR 2,7bn, close to the obtainable opportunity. We thus conclude that our peak sales estimate is close to the conservative company definition of the obtainable market,. It is also implying that there will be no competing HER2+ vaccines approved, which may prove wrong.

Proof-of-concept in mice model

The preclinical proof-of-concept of the breast-cancer program is based on an academic collaboration with researcher at the Universities of Bologna and Pavia in Italy[1]. ES2B-C001 was tested both prophylactically, in mice which later was injected with human carcinoma cells, and therapeutically in mice with tumor cells already present.

Anti-HER2 antibodies (ng/ml) in active cohorts



[1] Ruzzi et al; Biomedicines 2022, vol 10, 2654

All untreated transgenic mice exposed to HER2+ mammary carcinoma cells developed progressive tumors, whereas mice vaccinated with ES2B-C001 plus an additional adjuvant (Montanite ISA 51) remained tumor-free. Seventy percent of mice vaccinated with ES2B-C001 monotherapy without additional adjuvant remained tumor-free. Treated mice remained tumor-free for more than one year after cell injection, whereas all control mice developed progressive tumor within 1–2 months. Interestingly, ES2B-C001 inhibited lung metastases in mice exposed to the cancer cells. As for the elicitation of anti-HER-2 antibody responses there was a marked improvement in the cohort receiving Montanide adjuvanted ES2B-C001 compared to ES2B-C001 monotherapy (see table above).

In mice already infected with cancer cells ES2B-C001 and the antibody trastuzumab were effective in trastuzumab-responsive tumor cells, while as expected ES2B-C001 alone did show a potent effect in trastuzumab-resistant cells. The article also pointed out the potential of a longer duration of the elicited antibody response compared to the therapeutic antibody trastuzumab. In immunotherapeutic terminology, monoclonal antibodies are classified as passive immunotherapy, whereas vaccines are called active immunotherapy.

Potential mechanistical advantage

A potential advantage of the ES2B-C0001 vaccine candidate is the mechanistic fact that it binds to all four extracellular domains of the HER2 protein, while trastuzumab only binds to one of all four domains. On the other hand, virus-like particles might theoretically interfere negatively with anti-tumor immunity through the induction of anti-VLP antibodies, an effect termed carrier-induced epitopic suppression (CIES)[2]. We note that no such adverse events were reported in the phase 3 program with ABN-CoV2

The ES2B-C001 vaccine candidate administered in the Ruzzi study published in Biomedicines in 2022 was a re-engineered version for human administration with 50 antigens per particle, the maximum number of HER2 antigens which can be mounted on a VLP scaffold. In the first published research on ES2B-C001 in 2018, the scaffold was presented as a carrying 360 HER2 peptides[3]. By that time, no additional adjuvant was added to the mice model. Somewhat contradictory, in the latest poster presented by Ruzzi at last year's AACR meeting, it is referred to a version based on 180 antigens per particle. This may point to the evolving status in the program by that time and we expect the maximum number attached to the scaffold to be limited to 50.

Competing academic research

Due to its proven effectiveness in the metastatic setting, HER2 is becoming a popular target for BC immunotherapy. However, due to

[2] Vaccine, 2010 Jul 26;28(33):5503-1

[3] Palladini et al; ONCOIMMUNOLOGY 2018, VOL. 7, NO. 3,

the loss of HER2- specific immunity, its modest adaptive immune response leads to reduced drug efficacy following disease progression, despite HER2 still being overexpressed (Ritter et al. 2007).[4]

Different vaccine approaches, based on both mRNA and VLP technologies, are currently being pursued in many oncology areas. The most advanced mRNA programs are in late clinical testing. Several anti-HER-2 cancer vaccines based on VLP platforms have shown to be effective in inducing specific antibody responses and having anticancer activity in preclinical trials. Below is a table reprint from a scientific article published last year by the same research group which has been involved in the ES2B-C001 program.

Academic research in VLP based HER2 vaccines

Cell Line	Mouse Model	Tumor Antigen	VLP Platform	Adjuvant or Combination Therapy
MamBo89 (HER2-positive cell line derived from a hHER2 transgenic mouse model)	FVB (FVB/NCrl) F1 HER2/Delta16 (FVB background)	HER2	AP205 phage	None
D16-BO-QD (HER2-positive cell line derived from a hHER2 transgenic mouse model)	FVB Delta16 (FVB background)	HER2	AP205 phage	Montanide ISA 51
DDHER2 (mouse cell line expressing rat HER2)	BALB/c	CH401 (rat HER2-derived epitope)	Physalis mottle virus (PhMV)	CpG (TLR-9 agonist loaded on VLPs)
TuBo (HER2-positive cell line derived from a NeuT transgenic mouse model)	BALB/c	HER2	Recombinant baculovirus (rBV)	Glycosylation patterns AddaVax Poly (I:C)
TuBo	BALB/c	GP2 (HER2/neu derived peptide)	Bacteriophage lambda (λF7)	None
TuBo	BALB/c	E75 (HER2-derived peptide)	λF7	None
D2F2/E2 (mouse cell line transfected with hHER2)	BALB/c	GPI-HER2	rBV	None
TuBo 4T1	BALB/c	xCT	MS2	None
4T1	BALB/c	IL-33	HBcAg	None
4T1	BALB/c	P53 and MUC1	VP2 B19	None
4T1	BALB/c	NeoAG	Qβ	G10 (TLR-9 agonist loaded on VLPs)

Source: Ruzzi et al; Int. J. Mol. Sci. 2023, 24

As far as we can judge, ExpreS²ion has taken the lead in the field of developing a VLP-mounted HER2 vaccine to treat and prevent breast cancer. All the projects listed in the table above are examples of published animal research with breast cancer vaccine candidates based on a VLP platform. The ES2B-C001 program is represented in the two upper quotations, both making use of AP205 phage display.

Like in all cancer research and development, which is funded by both public and industrial means, there is a lot of competition. However, it is our impression that none of the other academic groups have progressed to a clinical stage with an VLP-based candidate in HER2+ breast cancer.

[4] mRNA vaccination in breast cancer; Journal of Cancer Research and Clinical Oncology, Jiang et al; 2023.

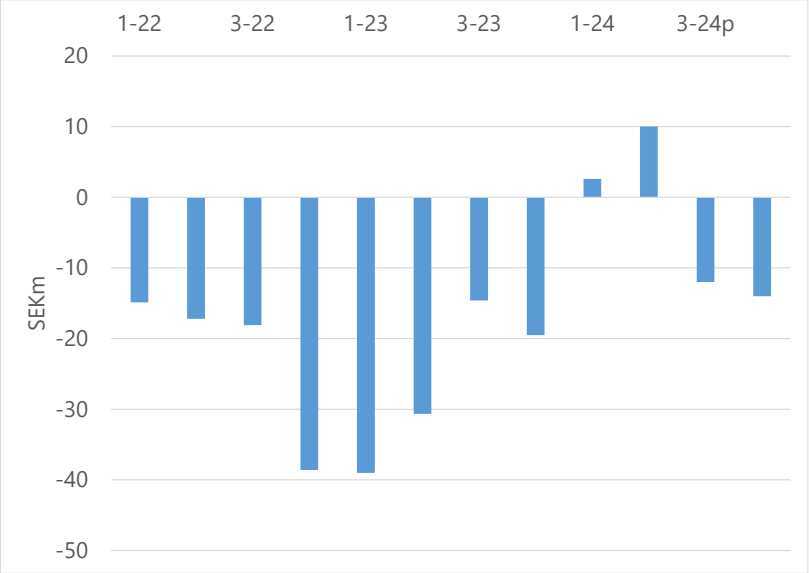
Financial discussion and valuation

We are lowering a fair value of ExpreS²ion Biotechnologies to SEK 2,2, down SEK 0,8 from our previous report. The subscription price in the newly announced share issue at SEK 1.0, as well as possible dilution from TO10 and TO11, leads us to raise the projected number of shares by the end of 2025 to 152 mln, up 85 percent from our latest estimate at 82 mln shares.

The dilution is countered by advances in preclinical toxicology research as well as investments in the manufacturing processes for the breast cancer vaccine. We have increased the likelihood of marketing approval for ES2B-C001 to nine percent from a previous six percent.

This scenario may be turned upside down by a partnership ahead of the initiation of the phase 1 trial. Speaking in favor of such a development is the benefit of teaming up with a partner with previous experience in clinical trials, complementing the development and biological skills of the ExpreS²ion team. However, a deal with a preclinical asset may prove expensive, leaving ExpreS²ion with less upside than if management decides to pursue phase 1 on their own.

Cash burn in SEKm, outcome and forecast



Source: ExpreS²ion Biotechnologies, Analysguiden forecasts

We remain cautious of the scope for a VLP technology platform as long as the mRNA programs have not yet proven to have an inferior immunogenic longevity. The Covid-19 pandemic proved the mRNA companies to have a greater flexibility and speed in addressing new mutations of the virus, a competitive advantage which may also prove relevant for oncology vaccines. Still, we believe that the longevity data being rolled out from ABNCoV2 program, together with robust immune responses, allows for alternatives to the mRNA platform, especially in genetically more stable diseases.

Sum-of-The-Parts valuation of ExpreS²ion Biotech

	Project value (MSEK)	Value / share (SEK)	Peak sales (MEUR)	LOA*	WACC	Share of NPV	Comments
ES2B-C001	123	0,8	2 525	9%	15%	100%	Approaching CTA
Adaptvac holding	92	0,6		100%	12%	34%	Minority holder
Platform	41	0,3	0,6	100%	10%	100%	cash flow based
Malaria project	30	0,2	175	10%		6%	of consortium
Indigo (influenza)	17	0,1	952	3%		6%	of consortium
CMV program	14	0,1	900	3%	20%	100%	CD election 2025
Nipha program	20	0,1	100	3%		53%	of consortium
Administration	-20	-0,1					
Sum	303	2,2					*diluted no. of shares, incl TO 9, 10,11 (mln) 151,6*
**) Likelihood of approval*							*current number of shares, mln 53,4*

Forecasts by Analysguiden

Assumptions of risk adjusted NPV calculation

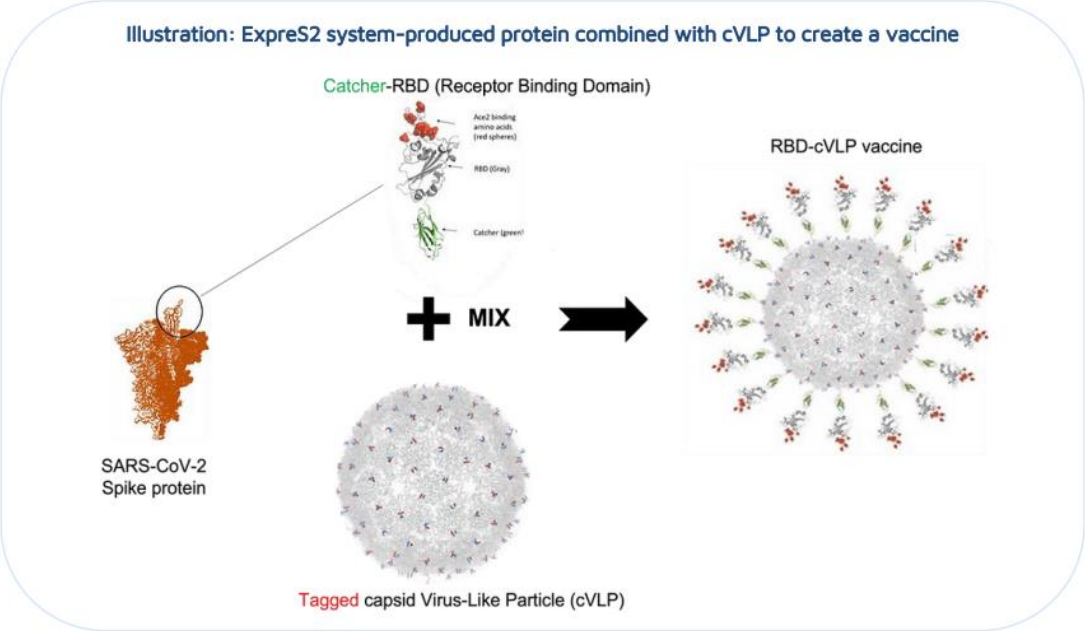
SEKm, ExpreS2ion Bio	2022	2023	2024p	2025p	2026p	2027p	2028p	2029p	2030p
Operating revenue	6	9	29	10	58	8	480	9	754
ABNCoV-2				*0*					
ES2B-C001				*0*	*48*	*0*	*472*	*0*	*745*
platform/services	*6*	*7*	*7*	*6*	*6*	*8*	*8*	*9*	*9*
EBIT	-127	-106	-30	-78	-25	-50	477,4	6,0	
Cash	111	58	122	84					
AdaptVac	2022	2023	2024p	2025p	2026p	2027p	2028p	2029p	2030p
Net income			10	0	5	75	0	0	
Milestones, ERUm			*10*	*0*	*5*	*75*			
Risk adjustment			*1,0*	*1,0*	*1,0*	*1,0*	*1,0*	*1,0*	
Risk-adjusted NPV (SEKm)			64,3	-2,4	19,5	254,3	-1,2	5,0	
WACC	12%								
NPV, AdaptaVac (EURm)	29,1								
Likelihood of approval	100%								
ExpreS2ion share, SEK	0,6								
ES2B-C001 (SEKm)	2022	2023	2024p	2025p	2026p	2027p	2028p	2029p	2030p
Costs, preclinical / clinical	-70	-60	-44	-54	-50	0	0	0	0
milestones to Adaptvac			*-3,5*	*-3,5*	*0*	*-14*	*0*	*0*	*-285*
Sales, EURm								0	473
Total milestones, licensing	450				25	0	75	0	100
Royalty 12%									*57*
Expres2ion revenues, SEKm	-70	-60	-44	-54	275	0	825	0	1724
Risk-adjusted			*0,75*	*0,38*	*0,38*	*0,19*	*0,10*	*0,10*	*0,09*
Risk adjusted revenues, NPV (SEKm)			0	-20	78	0	49	0	65
WACC	15%								
NPV, SEKm	123								
Likelihood of approval	123								
Diluted value/share, SEK	0,8								

Analysguiden forecasts and assumptions

Appendices - Summary of the technology

We classify the joint AdaptVac and ExpreS²ion platforms as a combined protein subunit antigen vaccine platform. Protein expression is provided by ExpreS²ion's EXPRES2 technology, coupled with a capsid Virus Like Particle (cVLP) of the AdaptVac platform. In the case of ABNCoV2, which has completed a phase 3 study, the capsid-like particle is coated with 60-80 particles of the recombinant RBD protein fragment. Researchers showed in a Nature article that RBD proteins glued to the CLP had a 3-4-fold higher immunogenicity compared to soluble RBD proteins injected without being mounted to the capsid-like particle, a strong rationale for the technology behind the ABNCoV2 cVLP vaccine.

Schematic figure of cVLP expression and construct



Source: Company presentation

Vaccine candidate in development

The breast cancer vaccine candidate ES2B-C001 is ExpreS²ion Biotechnologies in-house proprietary program which is progressing toward a clinical trial. It was licensed from AdaptVac based on an option agreement signed in 2020. In May 2022 ExpreS²ion Biotechnologies announced positive preclinical proof-of-concept results for this HER2-breast cancer vaccine candidate from a therapeutic study in HER2-transgenic mice. In the study, all transgenic mice vaccinated with ES2BC001 formulated in an adjuvant were metastasis-free, while all control mice had lung nodules. Furthermore, 73% of mice vaccinated with ES2B-C001 without adjuvant were metastasis-free.

Later ExpreS²ion initiated animal studies on non-human primates which are soon to be completed. This program has been slow in progression and still has some way to go before entering a first in

human clinical trial. In 2020 it was expected that the program would be ready for a CTA, Clinical Trial Application, by the first half of 2022. This CTA has for several reasons been pushed into 2024.

In 2020 the program was developed by AdaptVac and called AV001. In the option deal which ExpreS²ion signed with AdaptVac in February 2020 described AV001, later to be ES2B-C001, as having shown proof-of-concept in animal testing on mice in an article published 2018 by researchers at the University of Bologna. However, this study was based on a non-proprietary tag catcher method and had to be redone with a proprietary tag catcher system developed by AdaptVac.

There are currently other vaccine candidates being developed for HER2 positive breast cancer in clinical trials. The list of preclinical programs is long and include candidates based on mRNA vaccine platforms. What may be the selling point of ES2B-C001 is the claim to both a preventive and therapeutic effect. ES2B-C001 is developed as a therapeutical vaccine for patients with HER2 positive breast cancer, having progressed after initial treatment with the standard anti-HER2 therapy Avastin (trastuzumab).

According to the published prospect, two weeks after the inoculation of tumor cells, the first vaccine administrations were given. ES2B-C001 formulated in an adjuvant was found to totally block tumor development, whereas the control group progressively expanded with lung metastases and subcutaneously growing local tumors. Additionally, ES2B-C001 without adjuvant was found to inhibit, but not prevent, tumor development.

Study Title	Study Phase	Stage of Disease	Study Population	Tumor Type	Study Treatment	NCT Number
A Phase II Study of Concurrent WOKVAC Vaccination with Neoadjuvant Chemotherapy and HER2-Targeted Monoclonal Antibody Therapy	Phase II	I, II, III	Patients with HER2+ breast cancer, regardless of hormone receptor status, who are planning to receive neoadjuvant cytotoxic chemotherapy and HER2-targeted monoclonal antibody therapy prior to planned surgery.	Breast	Vaccine + chemo+HER2-targeted monoclonal antibody	NCT04329065
A Phase II Study to Evaluate the Efficacy and Safety of an Adjuvant Therapeutic Cancer Vaccine (AST-301, pNGVL3-hICD) in Patients with HER2 Low Breast Cancer (Cornerstone-001)	Phase II	I, II, III	Patients with histologically or cytologically confirmed HER2 low expression (1+ or 2+) and hormone receptor-negative (both ER- & PR-) breast cancer who have completed neoadjuvant systemic chemotherapy and have residual disease.	Breast	Vaccine	NCT05163223
A Phase I Dose Escalation Trial of Alpha-tocopheryloxyacetic Acid (α-TEA) in Patients with Treatment Refractory HER2+ Metastatic Breast Cancer	Phase I	IV	Stage IV HER2+ breast cancer who have been treated with definitive therapy and received maintenance HER2-targeted monoclonal antibody therapy; and currently have measurable disease not considered curable by conventional therapies.	Breast	Vitamin E derivative + HER2 targeted monoclonal antibody	NCT04120246
Phase I trial of intravenous administration of TAEK VAC-HerBy vaccine alone and in combination with HER2 antibodies in patients with advanced cancer (Stage 2 only)	Phase I	II, III, IV	Patients with HER2+ breast or gastric/gastroesophageal junction cancer who have locally advanced metastatic tumors	Breast and gastric/gastroesophageal junction	Vaccine + chemo+HER2-targeted monoclonal antibody	NCT04246671

Source: Cancer Vaccine Institute, University of Washington

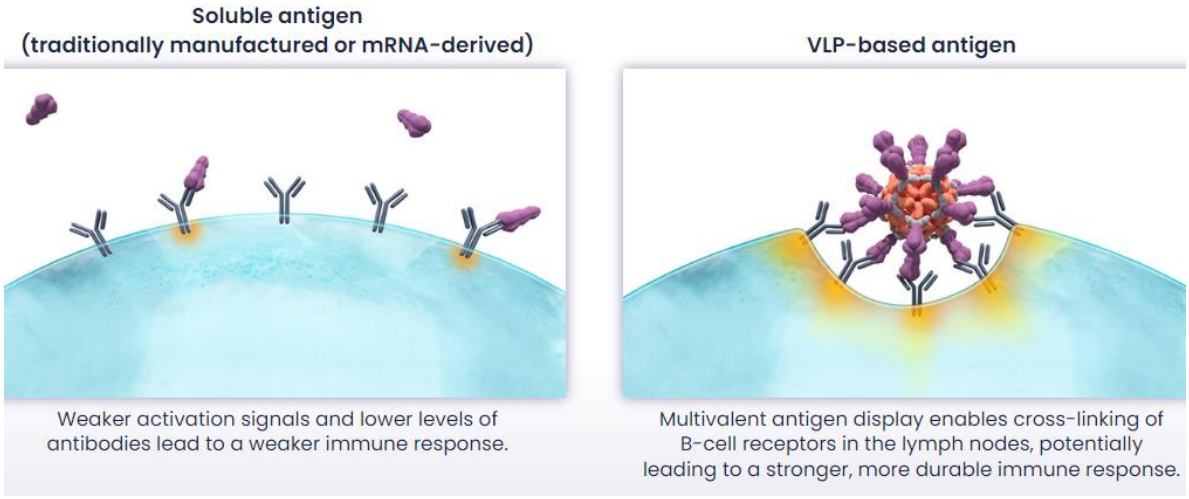
Competitive landscape in HER2+ breast cancer

Several earlier studies are also in different clinical phases with patients suffering from HER2 positive breast cancer. A sample is shown in the table below.

AstraZeneca acquisition of VLP vaccine

In 2023 AstraZeneca announced the acquisition of the US-based vaccine developer Icosavax, which is considered a market leader in the field of virus-like particle mounted vaccine development. Icosavax' most advanced project, IVX-A12, is ready to start phase 3 study in the prevention of infections of the respiratory syncytial virus (RSV) and human metapneumovirus (hMPV). The antigen protein of the vaccine is mounted on a virus-like particle (VLP) scaffold, much like the scaffold of AdaptVac.

Icosavax platform compared to traditional platform



Source: Icosavax home page

AstraZeneca pays upfront USD 838m for Icosavax, of which we estimate that the phase 3 program makes up at least 85 percent. Another approx. USD 300m are contingent on future milestones of the Icosavax pipeline.

We judge the AstraZeneca acquisition primarily as a way of boosting its position in the RSV market, where AstraZeneca has lost substantial market shares to newer products. But the acquisition clearly signals a belief in the VLP technology, which is an important vote of confidence in a vaccine industry otherwise focused on mRNA-based technology.

In a press statement AstraZeneca points out that the VLP technology is a proven technology with multiple products on the market, including vaccines for human papillomavirus and hepatitis B. So far, this technology has been limited to a smaller number of proteins which naturally fold into the VLPs, while the Icosavax protein VLP platform builds this success with the intention to create a more differentiated response.

Icosavax's VLP platform technology is designed to enable multivalent, particle-based display of complex viral antigens, which it believes will

induce durable virus protection. The AstraZeneca acquisition supports the notion that the VLP technology may induce a stronger and more durable immune response versus traditional soluble antigens as well as mRNA-based approaches.

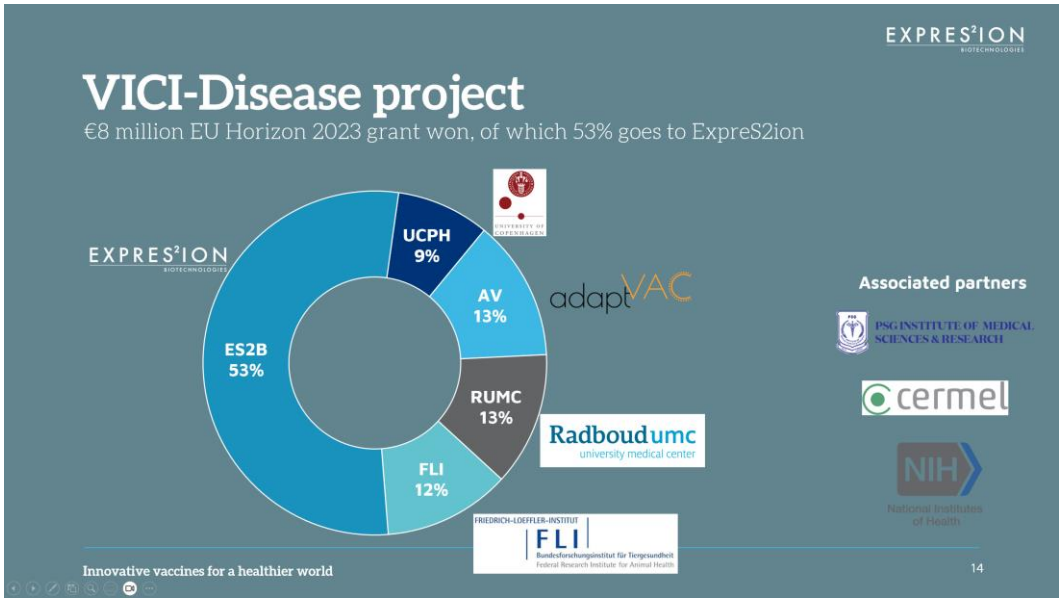
New program adds value to portfolio

In December ExpreS²ion announced that it will be part of a new consortium, the VICI-Disease consortium, with the aim to develop a vaccine against viruses with pandemic or endemic potential, starting with the Nipah virus. This virus causes severe infections such as acute respiratory infection and fatal encephalitis in humans primarily in tropical regions. Mortality rate is estimated at 40% to 75%.

The virus is transmitted to humans from animals (such as bats or pigs), or contaminated foods and can also be transmitted directly from human to human. Fruit bats of the *Pteropodidae* family are the natural host of Nipah virus. There is no treatment or vaccine available for either people or animals.

Horizon Europe is granting 8 million EUR, approximately 90 million SEK, to the consortium, of which 53% is direct contribution for ExpreS²ion' s part of the project costs. The aim is to obtain clinical proof-of-concept of a Nipah virus (NiV) vaccine candidate within four years.

Several vaccine institutions in VICI collaboration



Source: ExpreS²ion Biotechnologies

Cooperation with Oxford University

Malaria is a major public health problem in developing countries. It is a mosquito-borne disease and places a particularly high burden on children in the African Region. There were around 240 million cases of malaria and 627,000 deaths worldwide in 2020, mostly children.

For 20 years the University of Oxford has been carrying out extensive research in this field and has several programs ongoing. In October this year the WHO recommended the R21/Matrix-M vaccine, which has been sponsored by University of Oxford in collaboration with the Serum Institute of India and Novavax. Novavax is the proprietary owner of the Matrix-M adjuvant and will market the vaccine in non-endemic countries. The vaccine is expected to be launched by the Serum Institute and Novavax next year.

This is the second malaria vaccine to be approved and recommended by WHO after RTS,S/AS01 (Mosquirix, GlaxoSmithKline), which was developed in the late 80's and received a WHO recommendation only in 2021. Both vaccines have shown to be safe and effective in preventing malaria in children and, when implemented broadly, are expected to have a high public health impact.

The R21/M vaccine shows a reduction of symptomatic cases of malaria by 75% during the 12 months following a 3-dose series. Mosquirix is believed to be less efficient in the region of 50 percent. In a phase 3 trial, Mosquirix efficacy was 56% in children aged 5–17 months.

Last year UNICEF paid up to USD 170 million to access eighteen million doses of Mosquirix over a three-year period, corresponding to a price per dose of 9,4 USD. We estimate that Mosquirix is selling at around EUR 75m annually. Low unit prices are likely to remain but the launch of the second more efficient vaccine should expand the market. ExpreS²ion refers to a Data Bridge study projecting an EUR 1,8 bn malaria market by 2029, which should assume the entry of more efficient vaccines.

ExpreS²ion vaccine will have to prove higher efficacy

ExpreS²ion is currently involved in four different projects undergoing in total six clinical studies, all sponsored by University of Oxford. All these studies have progressed to a clinical phase or are currently preparing to recruit. A cooperation with the world leader in malaria research and development is an asset for ExpreS²ion. However, to enter this vaccine market, a new vaccine will have to prove higher immunogenicity than the two marketed products.

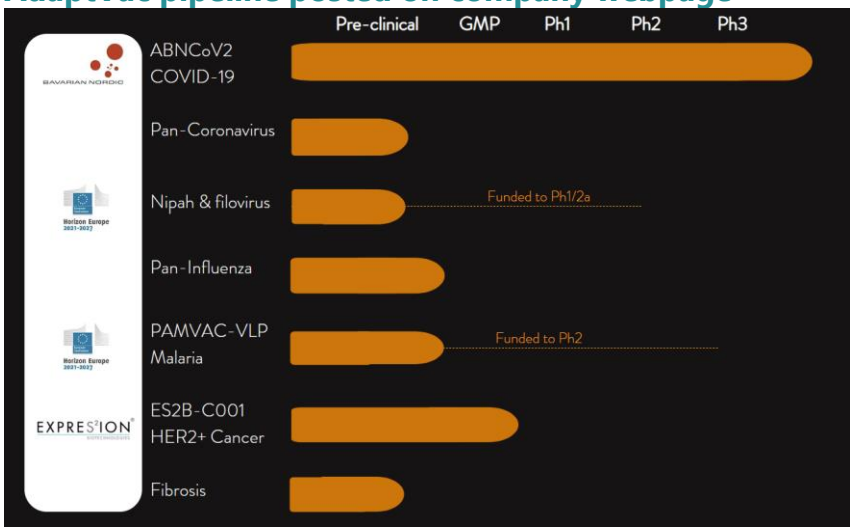
Oxford programs involving ExpreS²ion proteins

Trial abbreviation	Phase	Sites	Vaccines in trial	Trial status	Year started
VAC089	Ia	Oxford, UK	RH5.1 in Matrix-M R78C in Matrix-M	Vaccinations on-going	2023
VAC086	Ib	MRC Unit, The Gambia	RH5.2 VLP in Matrix-M R21 VLP in Matrix-M	Vaccinations on-going	2023
VAC091	IIb	IRSS CRUN, Burkina Faso	RH5.1 in Matrix-M RH5.2-VLP in Matrix-M	Vaccinations on-going	2023
BIO-001	I/IIa	Oxford, UK	RH5.2 VLP in Matrix-M RH5.1 in Matrix-M	Screening & vaccinations on-going	2023
BIO-002	I	Sheffield, UK	RH5.1 in Matrix-M	Vaccinations on-going	2023
BIO-003	I	IHI Bagamoyo, Tanzania	RH5.1 and R78C with Matrix-M	In set-up	N/A

Source: ExpreS²ion Biotechnologies (participation in VAR2CSA and CyRPA discontinued)

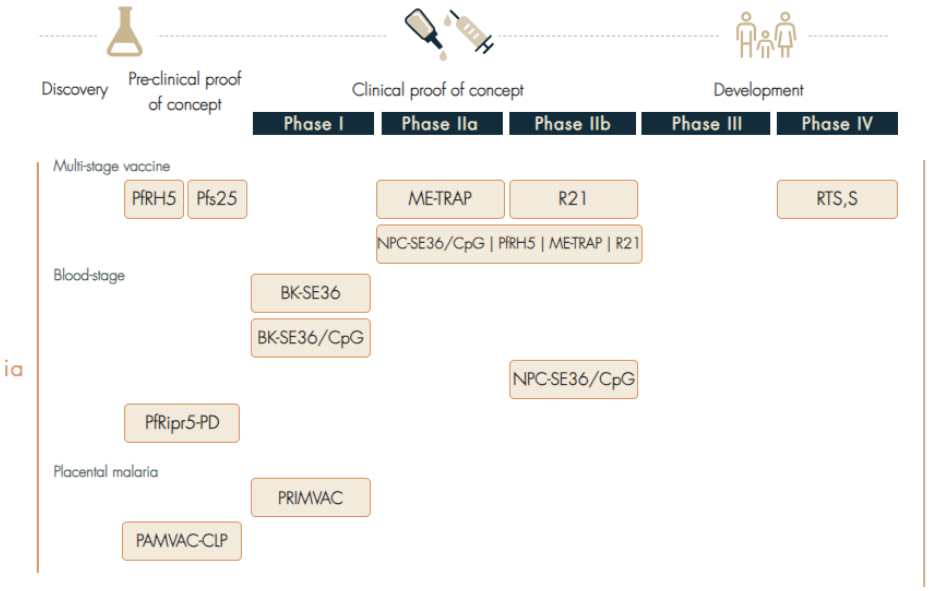
According to clinicaltrials.gov University of Oxford is currently sponsoring thirty-five ongoing trials in malaria vaccination. Four of these trials involve ExpreS²ion as a subcontractor of the RH5 expression protein. The most advanced is VAC091 (NCT05790889) which will involve 360-460 participants in Burkina Faso and report results late in next year. At this point in time, we find it difficult to assess the possibility for this row of programs to reach success, but serving as a subcontractor to University of Oxford is a meriting feature. We view the continuous efforts of University of Oxford in this field as a second or third wave of new Oxford malaria cures.

AdaptVac pipeline posted on company webpage



However, in absence of a commercial agreement between University of Oxford and the involved parties, such as ExpreS²ion Biotechnologies, we remain cautious on the value of these programs.

Malaria portfolio of the European Vaccine Initiative



Source: European Vaccine Initiative

A second factor behind a cautious approach to the value of AdaptVac is the lack of external validations other than from Bavarian Nordic. There are several different virus-like particle (VLP) vaccine platforms, both involving capsids or other scaffolds. The VLP technology was first described in animal models in 2007. Since then, VLPs are considered as promising nanotools for the development of subunit vaccines due to high immunogenicity and safety. The proprietary knowledge of AdaptVac is based on a method of displaying the isopeptide (spike protein) on the surface of the VLP, a method which we believe has distinctive features over similar generic techniques, such as the SpyTag/Catcher system.

The most advance program in AdaptVac after ABNCoV2 is PAMVAC-VLP (also PAMVAC-CLP). This program is a malaria vaccine candidate sponsored and coordinated by the European Vaccine Initiative (EVI) in collaboration with the Oxford University.

The PAMVAC program is still in a phase of preclinical proof-of-concept. The basis of the project was invented by University of Copenhagen and later transferred to AdaptVac. A randomized phase 1 clinical trial was conducted in Germany and Benin in 2015-17. It was published in 2019[5] and the authors concluded that a follow-up trial in in women before first pregnancies in an endemic area was to come next. Since then, the program has not advanced to a new clinical trial.

The parties received financing of EUR 10m by the European Union in 2022 which is expected to last until 2027. The PAMVAC-VLP program is a placenta-borne concept as opposed to the RH.5 blood stage programs of ExpreS²ion. In the ExpreS²ion Q3 report it was announced that the company is discontinuing collaboration in the placenta-borne malaria program after the decision of University of Copenhagen to contract a different manufacturer of the expressed protein.

[5] *Clinical Infectious Diseases*, Volume 69, Issue 9, 1 November 2019, Pages 1509–151

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