UPPDRAGSANALYS

At the gates of phase 1

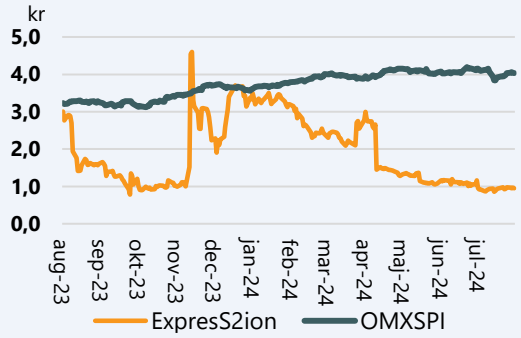
ExpreS2ion Biotech

Date	22 augusti 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	1,0
No. of shares, mln.	85,6
Market cap, SEKm	86
Cash, SEKm	69
Fair value, SEK	**2,4**
Web site	www.expres2ionbio.com

Kursutveckling senaste året



Source: Refinitiv

Phase 1 study planned in Austria

ExpreS2ion Biotech has recently filed for starting a first-in-human study of its breast cancer vaccine candidate ES2B-C001 in women with a HER2 positive breast cancer. The application is a major step forward in its proprietary pipeline and the company expects first patient to start study treatment in Q1 next year.

The Clinical Trial Application was submitted to the Austrian Agency for Health and Food Safety, BASG. Assuming no further questions are raised, we understand the agency has 35 calendar days to review the application. Once cleared by the authority and the ethics committee, the study will be conducted at the Medical University of Vienna.

Study will look for signs of efficacy

The study will include an initial number of 18 breast cancer patients. Participants will be tested for toxicities and safety with escalating doses of ES2B-C001. At the highest tolerated dose, it will be possible to expand the study with another 18 patients. As in all phase 1 studies, safety is the main primary endpoint. The vaccine's immunogenicity and its preliminary anti-tumor activity in HER2-positive breast cancer will be assessed as secondary and exploratory endpoints.

The full study is expected to last for 20 months, which should allow a final result by the end of 2026. In the meantime, we expect preliminary results from different stages to be released regularly.

The promise of a potent vaccine candidate

In the phase 1 trial, ES2B-C001 will be studied as a therapeutical agent, not in the preventive setting generally assigned to vaccines. The vaccine antigen is designed to overcome treatment resistance that limits current treatments, mainly monoclonal antibodies, by producing polyclonal antibodies binding to the entire HER2 protein instead of a single epitope.

In the longer run, the vaccine candidate may also show a longer protection to relapsed disease. If these properties can be proven in a phase 3 study by a future partner, we expect sales of ES2B-C001 to surpass USD 3bn.

Fair value raised to SEK 2,4

In our previous report we had a 75 percent likelihood of ES2B-C001 initiating a clinical phase 1 trial early next year. We are raising this likelihood to 90 percent after the recent CTA submission and the successful preparation of GMP batches.

This positive component is trimmed by our calculation of the future number of shares. After the recent new shares issue, we have raised our projected number of new shares by the end of 2026 to 162 mln (152). This base scenario leaves our fair value at SEK 2.4 (2,2).

Forecasts & Key ratios, SEKm

	2023	2024p	2025p	2026p
Revenues, risk-adjust.	9	7	9	9
R&D expenses	-51	-49	-65	-72
EBIT	-106	-76	-87	-96
Earnings per share	-1,5 kr	-1,4 kr	-1,6 kr	-1,8 kr
Revenue growth	43%	-17%	21%	0%
Cash	58	95	85	16
New share issue	58	56	45	30

Source: Company, Analysguiden forecasts

Breast cancer vaccine approaches clinic

On August 6 ExpreS2ion Biotech submitted a Clinical Trial Application for its vaccine candidate ES2B-C001. The submission was made to the Austrian Agency for Health and Food Safety, BASG.

According to the homepage of BASG, the authority has a 35-calendar day period to respond to the application. This period may also include a decision by the local ethics committee at the Medical University of Vienna, which will be responsible for conducting the trial.

In the meantime, management has assigned a Contract Research Organization, which will be responsible for the practicalities in the study. A finalization of the study protocol, which describes in detail the design of the study, is under discussion with scientific boards at different medical authorities.

Second part will look at clinical response

Management expects to start the study in the first quarter of next year. Study duration is estimated to be 20 months, assuming all 36 patients will be included. The first part of the study will include 18 patients divided into two groups, one with an adjuvanted formulation of ES2B-C001 and another with an unadjuvanted formulation. The last patient in the study is expected to be enrolled 15 months after the first patient.

The adjuvant to ES2B-C001 will be Montanide, a mineral oil, which provokes an early boost of the immune response to the vaccine antigen. The HER2 antigen is displayed on AdaptVac's proprietary capsid Virus-Like Particle (cVLP), which also was tested in the phase 3 trial with the covid 19 vaccine ABNCoV2.

Initially three ascending single doses, yet to be disclosed, will be tested to establish safety, tolerability and the maximum tolerated dose (MTD). As in all phase 1 studies the primary endpoint will be safety. The secondary endpoint is immunogenicity, a measure of the number of antibodies to HER2 proteins generated by the adaptive immune system in response to the antigen of ES2B-C001.

In a second part of the study, expansions of cohorts by another 18 patients are foreseen to gather more safety and immunogenicity data.

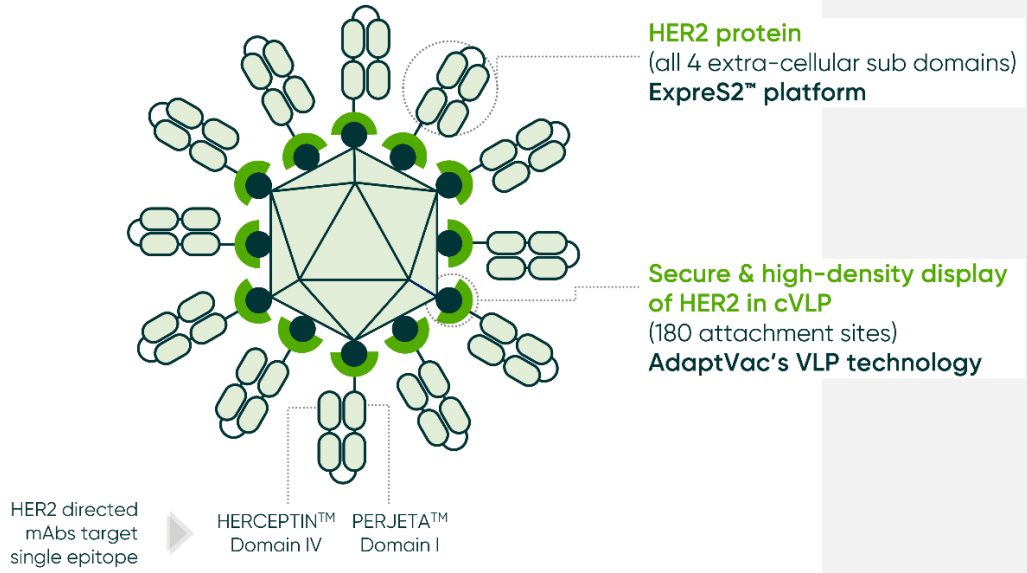
Polyclonal response distinguish ES2B-C001

Current treatments of metastatic HER2-positive breast cancer are dominated by the monoclonal antibodies trastuzumab (Herceptin) and pertuzumab (Perjeta), both produced by Genentech which is part of the Roche Group. The monoclonal property means that the antibody has been expressed by a single B-cell clone, which is considered a safety measure but also narrows its action to one single epitope of the HER2 protein.

A challenge for monoclonal antibodies is the lack of durable therapeutic response and acquired resistance due to mutations in the HER2 receptors. Antibodies also tend to upregulate alternate pathways for tumor growth. In contrast, vaccines can induce polyclonal responses from several different antibodies which may induce a broader immunogenic effect at the target molecule.

The vaccine antigen included in ES2B-C001 thus has the potential to involve a broader B cell response by binding to numerous epitopes of all four domains of the HER2 protein.

Illustration of ES2B-C001 interaction with HER2



Source: ExpreS2ion Biotech

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 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 HER2 gene and/or overexpression of its protein product occurs in 20–25% of all cases. This type is associated with a poor survival prognosis.

Base scenario involves licensing deal in 2027

Assuming a positive read-out late in 2026, we have an aggregated likelihood of 43 percent of a partnering deal in 2027. In our previous report we speculated that this would be possible in late 2026, but this no longer appears to be a main scenario as long as final clinical data from phase 1 is pending. We have included an initial downpayment of EUR 25m in 2027, an optimistic assessment reflecting the innovativeness of the project.

We have assumed that ExpreS2ion will receive a 10 percent royalty on licensee sales and that AdaptVac will receive another 2 percent of sales. AdaptVac also has the right to receive a further SEK 3.5m upon initiation of the phase 1 study in 2025.

To arrive at a licensing deal in 2027, we have included full financing from TO 10 and 11, on top of the latest rights issue in June. An

additional minor bridge financing in late 2026 or early 2027 may be necessary.

We have raised the likelihood of marketing approval (LOA) after partner-initiated phase 2b and 3 studies to 10 percent from 9 percent, based on the CTA and the establishment of manufacturing processes. Our optimistic base case is a marketing approval of ES2B-C001 by 2030.

Estimated sales potential of EUR 3.2bn

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 NPV valuation is based on a peak sales estimate of EUR 3,2bn.

Oxford publishes malaria study

ExpreS2ion Biotech is a prominent supplier of antigens to the clinical efforts by Oxford University in the research after a more potent and convenient malaria vaccine. In June researchers linked to the university published results in the medical review Lancet Infectious Diseases.

The authors conclude that the RH5.1/Matrix-M vaccine candidate shows an acceptable safety and reactogenicity profile in both groups. The vaccine candidate is meant to be a second line of defense in blood-stage malaria infection after vaccination with the current type of products. The antigen which targets the RH5.1 protein is produced by ExpreS2, ExpreS2ion Biotech's proprietary protein expression platform.

Oxford programs involving S2-expressed antigens

Trial abbreviation	Phase	Sites	Vaccines in trial	Trial status	Year started
VAC-085	I	Oxford, UK	Pfs48/45	Vaccinations on-going	2023
VAC-086	Ib	MRC Unit, The Gambia	RH5.2-VLP in Matrix-M R21 in Matrix-M	Vaccinations on-going	2023
VAC-089	Ia	Oxford, UK	RH5.1 in Matrix-M R78C in Matrix-M	Vaccinations on-going	2023
VAC-091	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 in Matrix-M	In set-up	N/A

Source: ExpreS2ion Biotech

The article makes no mentioning of the antigen producer and at the moment there is no commercial agreement entered between ExpreS2ion Biotech and Oxford University. If the product advances

to a phase 3 set-up, ExpreS2ion has the right to negotiate a license agreement. We have so far not made any assumption of the possibility of a commercial scenario materializing in the Oxford collaboration before 2027. ExpreS2ion Biotech is involved as antigen supplier to Oxford University in seven different clinical studies on four different vaccine candidates.

Financial discussion and valuation

ExpreS2ion Biotech enters the third quarter with a solid cash position in the region of SEK 95m, including the SEK 30m gross proceeds from the new share issue in June. In the fourth quarter the subscription period for warrant TO10 expires, involving a total number of 32 million potential new shares. The warrant has a striking price of 70 percent of the volume weighted average price (VWAP) in the period of 1-14 November. We assume that the VWAP in the period will be at least SEK 1,1 in the wake of a positive decision by the Austrian authority.

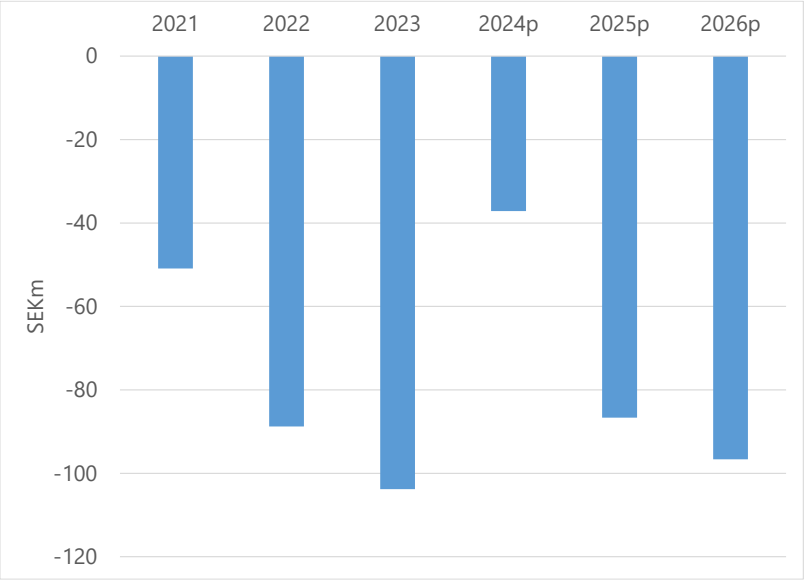
Assuming full subscription of TO10, well above the 50 percent rate in the recent new share issue, we expect this warrant to result in gross proceeds of SEK 26m. By this action, ExpreS2ion Biotech should maintain a cash position of some SEK 95m when entering 2025.

As for the TO11 warrant due in September-October 2025, we have assumed an VWAP of SEK 2.2 on the back of a positive progression in the phase 1 study during the course of 2025.

Assumed cost of phase 1 at SEK 45m

We have assumed a cost of the phase 1 study at some SEK 45m, mainly spread out over 2025 and 2026. In this scenario we see a risk that the cash position will not have a runway into 2027 ant that a minor bridge financing in late 2026 may be necessary to get to a read-out of the study.

Cash burn in SEKm, outcome and forecast



Source: ExpreS2ion Biotechnologies, Analysguiden forecasts

Number of shares further increased

Given the scenario drafted above, including a full subscription we now assume a 64 percent dilution from the TO10 and 11 warrants, resulting in a diluted number of shares of 147 million by the end of 2025. On top of this we are adding 15 million new shares in a minor bridge financing in late 2026. In our previous report we arrived at a total number of shares at 152 million.

Discussion of a LOA at 10 percent

In our base case we assume a VWAP of SEK 1.1 in the TO 10 period and a VWAP of SEK 2,2 in the TO 11 period. Our base scenario is built on a 10 percent likelihood of approval (LOA) for ES2B-C001, which we perceive as slightly above industry average in cancer drug development for a phase 1 project in its early stages.

The industry average of an oncology product at the gate of phase 1 is more in the region of 5-6 percent. In our valuation we have assumed a 10 percent LOA which more correlates to the LOA of a cancer drug development project having complete phase 1. We justify this level by the vaccine approach of ES2B-C001, which may be associated with a lower development risk than a TKI inhibitor or a monoclonal antibody.

The number of shares we have included in our valuation, 161 mln, is the number of shares we expect the company to have when the read-out is completed, which would place the phase 1 program in its final stages.

The current pricing of ExpreS2ion assumes a lower LOA than 10 percent. If there is not a shift in this sentiment, the resulting number of new shares from the warrant programs may be higher and trim our base case scenario by some SEK 0.5.

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	168	1,0	3 248	10%	15%	100%	Submitted CTA
Adaptvac holding	92	0,6		100%	12%	34%	Minority holder
Platform	42	0,3	0,6	100%	10%	100%	cash flow based
Malaria project	40	0,2	175	10%		6%	of consortium
Indigo (influenza)	17	0,1	952	3%		6%	of consortium
CMV program	18	0,1	900	3%	35%	100%	CD election 2025
Nipha program	25	0,2	100	3%		30%	of consortium
Administration	-20	-0,1					
Sum	358	2,4					

Projected no. of shares, end of 2026 (mln) 161,7

current number of shares, mln 53,4

**) Likelihood of approval*

Forecasts by Analysguiden

A more serious event would be a rejection of the ES2B-C001 application by the Austrian authority BASG, which could cause us to substantially lower the value of ES2B-C001, leaving our SOTP at SEK 0,6-1,2, depending on the possible financing of the remaining programs.

Assumptions of risk adjusted NPV calculation

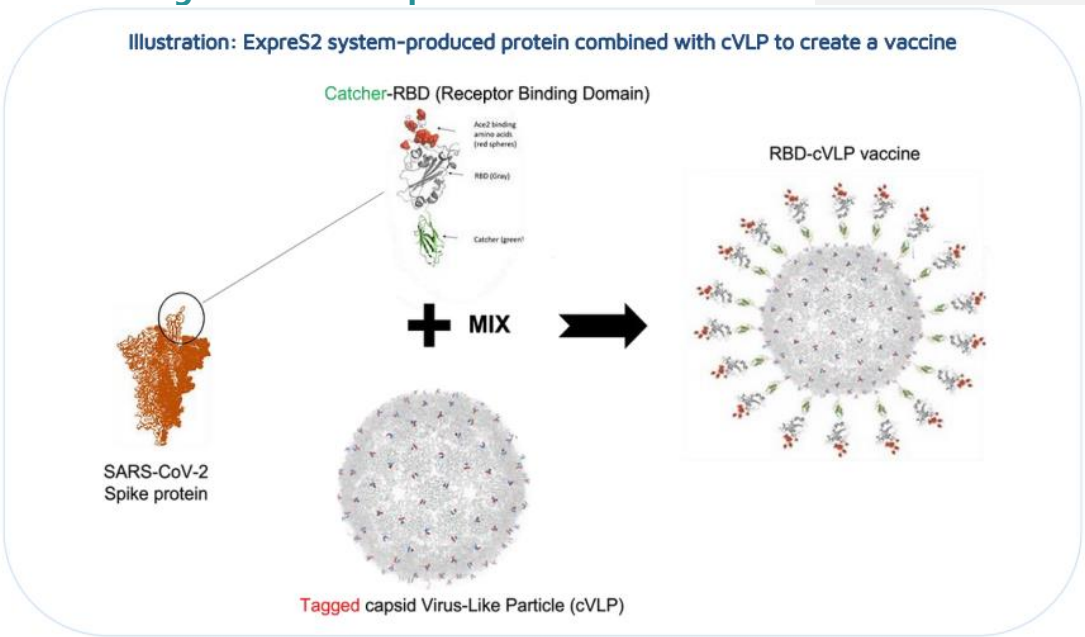
SEKm, ExpreS2ion Bio		2022	2023	2024p	2025p	2026p	2027p	2028p	2029p	2030p
Operating revenue		6	9	7	9	9	197	8	9	745
ABNCoV-2					*0*					
ES2B-C001					*0*	*0*	*190*	*0*	*0*	*736*
platform/services		*6*	*7*	*6*	*6*	*6*	*8*	*8*	*9*	*9*
EBIT		-127	-100	-54	-87	-96	140	5,7	6,0	
Cash		111	58	95	85	16				
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	
Risk-adjusted		*0,00*	*0,00*	*1,00*	*1,00*	*1,00*	*1,00*	0,00	0,00	
WACC	12%									
NPV, SEKm	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	-29	-19	-25	0	0	0	0
milestones to Adaptvac				*-3,5*	*-3,5*	*0*	*0*	*0*	*0*	*0*
Sales, EURm									0	473
Total milestones, licensing	475					0	25	0	50	100
Royalty	*10%*									*47*
Expres2ion revenues, SEKm		-70	-60	-29	-19	0	190	0	575	1694
Risk-adjusted				*0,90*	*0,43*	*0,43*	*0,43*	*0,43*	*0,22*	*0,10*
Risk adjusted revenues, NPV (SEKm)				0	-8	0	82	0	62	73
WACC	15%									
NPV, SEKm	168									
Likelihood of approval	10%									
Diluted value/share, SEK	1,0									

Analysguiden forecasts and assumptions

Appendices - Summary of the technology and programs

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 now have been completed. 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 2023 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.

Vaccine candidates to HER2+ in clinical 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

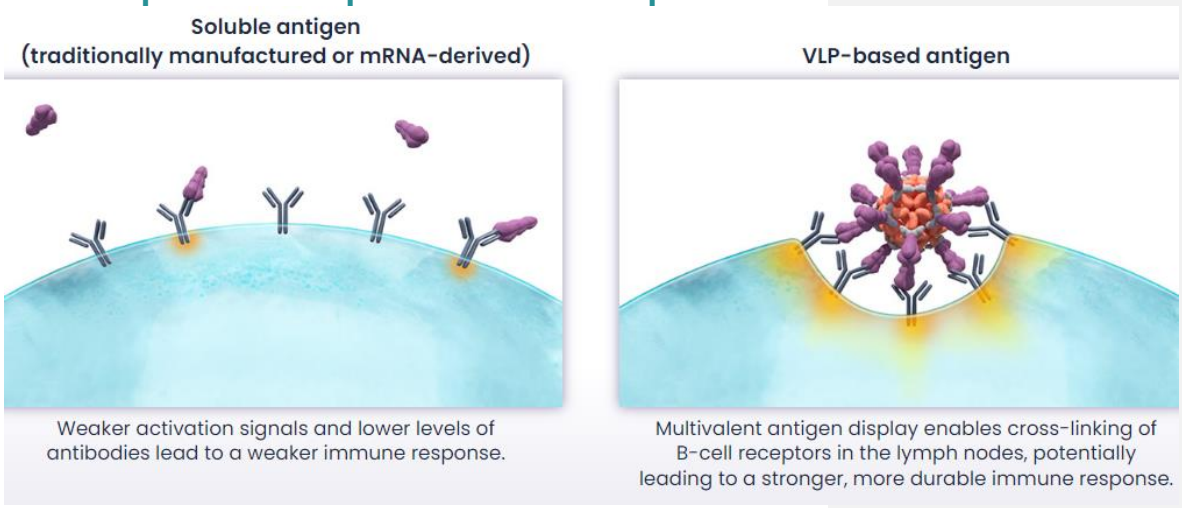
Competitive landscape in HER2+ breast cancer

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

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.

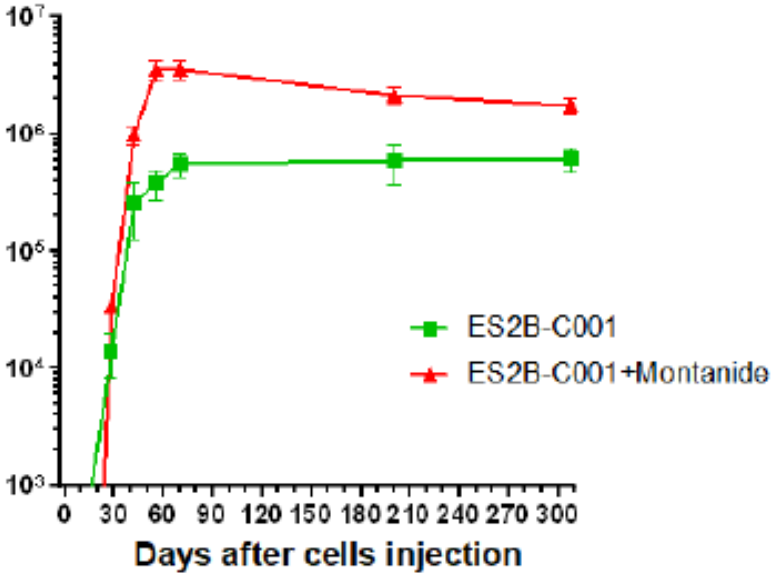
Icosavax's VLP platform technology is designed to enable multivalent, particle-based display of complex viral antigens, which it believes will induce durable virus protection. The AstraZeneca acquisition supports the notion that the VLP technology may induce a stronger

and more durable immune response versus traditional soluble antigens as well as mRNA-based approaches.

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



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

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

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.

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

Competing academic research

Due to its proven effectiveness in the metastatic setting, HER2 is becoming a popular target for BC immunotherapy. However, due to the loss of HER2- specific immunity, its modest adaptive immune

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

formaterade: Engelska (USA)

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

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.

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.

New program adds value to portfolio

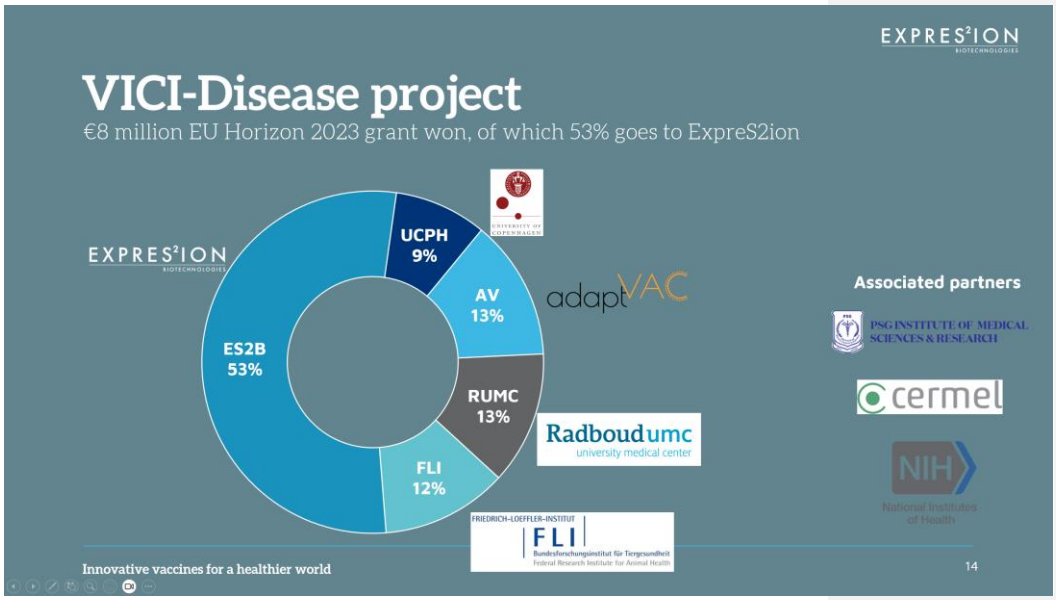
In December ExpreS2ion announced that it will be part of a new consortium, the VICI-Disease consortium, with the aim to develop a vaccine against viruses with pandemic or endemic potential, starting with the Nipah virus. This virus causes severe infections such as acute respiratory infection and fatal 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.

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

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

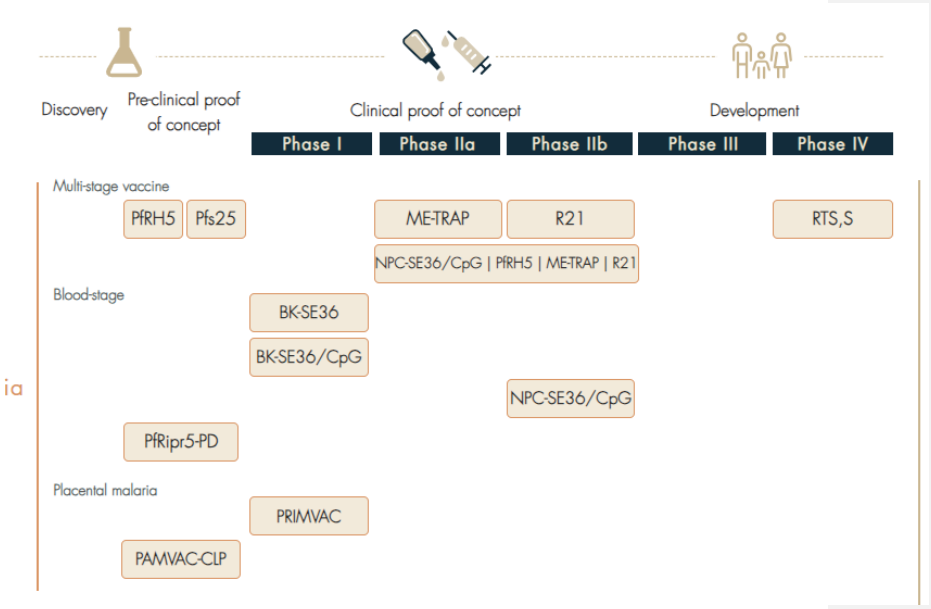
Trial abbreviation	Phase	Sites	Vaccines in trial	Trial status	Year started
VAC-085	I	Oxford, UK	Pfs48/45	Vaccinations on-going	2023
VAC-086	Ib	MRC Unit, The Gambia	RH5.2-VLP in Matrix-M R21 in Matrix-M	Vaccinations on-going	2023
VAC-089	Ia	Oxford, UK	RH5.1 in Matrix-M R78C in Matrix-M	Vaccinations on-going	2023
VAC-091	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 in 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.

However, in absence of a commercial agreement between University of Oxford and the involved parties, such as ExpreS2ion Biotech, 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 advanced 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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