EDISON

RhoVac

Company outlook

Good execution in challenging times for industry

Pharma & biotech

On the back of a crystal-clear R&D strategy, to conduct a proof-of-concept study and then seek a partnership deal, RhoVac completed a successful fundraise in June 2019 and started enrolling patients in the Phase IIb BRaVac study in November 2019. Due to the COVID-19 pandemic full enrolment is now expected by end-2020 vs the original target of Q320. In our view the delay is modest and easily covered by the existing budget. Clinical trial centres are up and running, including in the US, and treatment results are still expected by the end of 2021. So overall, this shows good execution in what has been a challenging period for the whole industry. Our updated valuation is SEK1.18bn or SEK61.8/share.

Year end	Revenue (SEKm)	PBT* (SEKm)	EPS* (SEK)	DPS (SEK)	P/E (x)	Yield (%)
12/18	0.0	(20.2)	(1.95)	0.0	N/A	N/A
12/19	6.0	(35.9)	(1.55)	0.0	N/A	N/A
12/20e	12.0	(37.4)	(2.19)	0.0	N/A	N/A
12/21e	8.0	(41.6)	(2.61)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles and exceptional items.

Novel concept with no competition in lead indication

RhoVac is developing RV001, a tissue-agnostic cancer immunotherapy specifically designed to prevent or limit metastasis by activating T-cells against cells with metastatic potential. This preventive concept is a very differentiated approach in oncology. RV001 is positioned to target prostate cancer patients with localised disease who have relapsed after a treatment with curative intent (ie radical prostatectomy or radiotherapy). A relapse in these patients is known as biochemical recurrence/biochemical failure and can be defined as a rise in prostate-specific antigen (PSA) ≥0.2ng/ml. Practically the only approach currently used for these patients is watchful waiting. As a result, in this specific patient population RV001 would have no competition. Also, if PoC could be obtained for this patient group, it is highly likely RV001 could also be developed for other stages of prostate and other types of cancer.

Phase IIb BRaVac study up and running; data in Q421

RhoVac's technology involves the use of immunotherapy to activate T-cells against the protein RhoC, for the treatment or prevention of metastasis. The lead product, RV001, contains a 20 amino acid peptide fraction of RhoC protein. Sites in all six European countries and the US are enrolling patients. The primary endpoint is time to PSA progression, defined as the time from randomisation to the doubling of PSA from the baseline value. Key results are expected in Q421, while 12-month follow-up data in patients without further RV001 treatment should be ready in Q422.

Valuation: SEK1.18bn or SEK61.8/share

Our RhoVac valuation is higher at SEK1.18bn or SEK61.8/share due to revised rNPV assumptions, rolling the model forward and a lower cash position (SEK109.7m at end-Q220). As RhoVac is making progress with the Phase IIb trial and more details about RV001's potential are available, our review is primarily focused on the licensing potential, which is presented in the valuation section.

5 October 2020

Price	**SEK18.96**
Market cap	**SEK360m**
Net cash (SEKm) at end-Q220	109.7
Shares in issue	19.0m
Free float	85%
Code	RHOVAC
Primary exchange	Spotlight Stockholm
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	3.2	31.5	17.5
Rel (local)	4.5	29.1	29.8
52-week high/low	SEK20.75	SEK8.75	

Business description

RhoVac is an immunotherapy company listed on the Spotlight stock market in Sweden, with a 100%-owned subsidiary in Denmark. It is developing a peptide-based immunotherapy, RV001, which aims to train the immune system to specifically target cancer cells with metastatic potential. This is a novel approach that could have utility across a range of cancer settings.

Next events

Phase IIb study fully enrolled	End-2020
Interim results from the Phase IIb study	H121
Start of exploratory clinical study in other cancer indications	H220
Updates on partnering process	H220/21

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Edison profile page

Investment summary

Company description: Focused Swedish biotech

RhoVac is an immunotherapy company listed on the Spotlight exchange in Stockholm, Sweden. RhoVac AB is the listed entity, however most company R&D activities are controlled by its wholly owned subsidiary (and only holding) RhoVac ApS based in Hørsholm, Denmark. RhoVac ApS was founded in 2007 around the original technology, and RhoVac AB was created in 2015 in order to access capital from an IPO in Sweden. RhoVac operates as a lean organisation supported by partnerships, with few full-time staff and a low fixed-asset base. The 2019-20 period was transformative for RhoVac in terms of management and access to scientific advice. Anders Månsson joined the company in May 2019 and became the CEO in September 2019. Mr Månsson brought extensive experience from pharmaceutical and biotech companies including licensing, divestment and acquisition of assets. Under the supervision of Mr Månsson, RhoVac has established a scientific advisory board and engaged four new experts, who joined co-founder Professor Per thor Straten. We highlight that one of them, Professor Emeritus Per-Anders Abrahamsson, has acted as secretary general of the European Association of Urology.

Valuation: SEK1.18bn or SEK61.8/share

We include a single asset in a single indication in our valuation, which is RV001 in prostate cancer, specifically in patients with biochemical recurrence following radical prostatectomy or radiotherapy. There is a clear rationale for RV001 to be expanded in other prostate cancer patient populations, both earlier and more advanced. In addition, RV001 is tissue agnostic, so theoretically it could be used in many other cancers that metastasise. With this in mind, we have reviewed the comparable licensing deals we use in our valuation, which is the key change from our last published report. The main criterion for us was the deal terms including the potential for expansion of the drug in multiple indications. Over that last five to six years we have identified the licensing deals listed in the Exhibit 9. We take the median upfront ($121m) and milestone payment ($1.07bn) values, but in our model we risk adjust these by 40% to reflect lack of clinical proof-of-concept at the moment and inherent uncertainty in partnering discussions.

Financials: Financed until Phase IIb BRaVac readout

H120 operating costs were SEK24.8m vs SEK31.3m a year ago. The Phase IIb BRaVac study started recruiting patients in November 2019, so in 2020 and 2021 we expected stable cash burn. RhoVac was awarded an EU Horizon 2020 grant of €2.5m (c SEK27m) to support the ongoing Phase IIb study. To date, the company has received SEK12m of that amount. The reported end-Q220 cash position was SEK109.7m with no interest-bearing debt. RhoVac will also receive the remaining part of the grant of c SEK15m and expects around SEK18m in tax credits during the duration of the BRaVac trial. These expected amounts in addition to prepaid expenses of SEK15m (current asset on the balance sheet) mean that the total expected funding is around SEK158m, which is more than sufficient to complete the ongoing Phase IIb study and other planned activities.

Sensitivities: Single-asset, early-stage biotech

RhoVac is subject to typical biotech company development risks, including the unpredictable outcome of trials, regulatory decisions, success of competitors, financing and commercial risks. Our model assumes that RV001 will be out-licensed; therefore, our valuation is sensitive to potential licensing timing and actual deal terms. The near-term R&D sensitivities are tied to RV001 in prostate cancer, which is the only clinical-stage programme. Any setbacks with this asset will influence RhoVac's share price significantly. In our model, we assume a four-year Phase III trial in prostate cancer. However, there is a risk that the trial could take longer than expected.

RhoVac: Developing immunotherapy for metastasis

RhoVac's technology involves the use of immunotherapy to activate T-cells against the protein RhoC, for the treatment or prevention of metastasis. The lead product, RV001, contains a 20 amino acid peptide fraction of RhoC protein plus the adjuvant Montanide ISA 51. The treatment of metastatic cancer remains a significant unmet need; most patients who reach this advanced stage are terminal, and yet the treatment of metastasis remains challenging. The metastatic cascade is generally believed to be 'undruggable' using traditional small molecule drugs or antibodies.[1] Therefore, the idea of preventing or limiting metastasis through T-cell activation is an attractive one. RhoVac's chosen target RhoC is a promising target since it is overexpressed in cancer cells with metastatic potential compared with healthy cells across multiple cancer types. Currently, RhoVac is focused on one clinical programme, which is in localised prostate cancer, but it intends to explore further indications preclinically.

Management's current strategy is to develop RV001 to proof-of-concept stage before securing a partnership agreement or sale, which could generate returns for shareholders. The ongoing lead study BRaVac is a double-blind, placebo-controlled Phase IIb study (n=180) evaluating RV001 in patients (men) with biochemical recurrence following radical prostatectomy or radiotherapy.

RV001 clinical development in prostate cancer

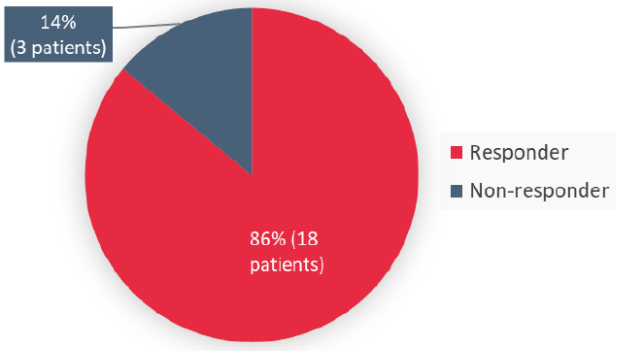
Phase I/II study final results released

RV001 was studied in a Phase I/II study (NCT03199872). In this study, the 22 prostate cancer patients who were enrolled to the trial received 11 subcutaneous injections over 30 weeks. The **primary objective** was to evaluate safety and tolerability, while the **secondary objective** looked at immune response. The patients were monitored for 12 months. Treatment-related reactions and immunological response (measured by IFNγ ELISpot analysis) were assessed at three, six, nine and 12 months. The last and final follow-up update (at 12 months) was released in July 2019. In summary:

- All 22 patients completed the follow-up and no treatment-related adverse reactions were observed. In total 21 patients were evaluable for immune activation.
- In total, 18 out of 21 patients (86%) showed significant treatment-related immunological response after treatment with RV001. This significant response was maintained in the same 18 patients at three-, six- and nine-month follow-ups. At the 12-month point, 17 patients still showed significant immunological response. In the few patients that had measurable PSA in this study, the PSA doubling time was markedly prolonged. This is the key parameter now being tested in a large and placebo-controlled setting in Phase IIb.

[1] Lin Y, Zheng Y. Approaches of targeting Rho GTPases in cancer drug discovery. *Expert Opin Drug Discov*. 2015;10(9):991–1010. doi:10.1517/17460441.2015.1058775

Exhibit 1: Phase I/II follow-up results



Follow up Time Point	% Responding
3 months post-vacc.	86%
6 months post-vacc.	86% (90%)*
9 months post-vacc.	86% (90%)*
12 months post vacc.	81% (86%)*

** One patient developed RV001 specific response 6 months after end of treatment*

Source: RhoVac

We view the Phase I/II results as positive, as RV001 looks to be a very safe treatment and elicits a long-lasting immune response in a large majority of patients. So, RV001 appears to do what it was designed for. The question of whether immune activation will translate into clinical efficacy will be addressed in a controlled trial that is already underway. RhoVac should publish the Phase I/II results in a peer-reviewed article in the near future.

Phase IIb controlled trial in Europe and US; fast-track designation likely

Following the positive Phase I/II study, RhoVac has designed a larger Phase IIb study, BRaVac, to explore efficacy in the same patient group (prostate cancer patients who have experienced biochemical failure after curative intent therapy). The patient recruitment started in November 2019. In total, over 180 prostate cancer patients, who experienced biochemical failure after a curative therapy (surgery or radiation therapy), are being enrolled in five European countries (Sweden, Germany, Denmark, Finland, Belgium) as well as the US. The therapy will be administered as 12 subcutaneous injections, over several months. The **primary endpoint** is time to PSA progression. Patients with biochemical failure will be included in the study who:

- have had biochemical recurrence where their PSA level reaches ≥0.2ng/mL, and
- have PSA doubling time of between three months and 12 months.

During the study, patients' PSA will be measured to calculate the doubling time. RhoVac is aiming to reduce the PSA progression rate by 50% compared with the placebo group, which is an outcome that would be interesting to urologists. The COVID-19 pandemic caused a modest recruitment delay, but other than that the effect was limited. The delay is easily manageable with the existing budget. The study is expected to be fully recruited in Q420, key interim results should be reported in Q421, while follow-up data should be ready in Q422.

PSA progression is a good endpoint for this group of patients (biochemically recurrent prostate cancer following radical therapy) in a Phase II trial, mainly because it allows RhoVac to perform a relatively small and fast study. Feedback from both the EMA and FDA was positive on the endpoints, and other studies in the same group of patients are also using PSA endpoints in Phase II, eg nivolumab (Bristol-Myers Squibb) and olaparib (AstraZeneca). PSA is known to be a reliable measure of disease progression/metastasis in prostate cancer.

Exhibit 2: Planned Phase IIb trial design	
Summary design	A Phase II, double-blind, placebo-controlled study of RV001V in adult males with biochemically relapsed prostate cancer following definitive local therapy (eg prostatectomy, radiotherapy)
Objective	To investigate whether a vaccination regimen with multiple subcutaneous administrations of RV001 0.1mg/mL (RV001V) can reduce prostate-specific antigen (PSA) progression compared to the control group
Number of patients	c 180
Treatment groups	Experimental treatment arm: RV001 (12 subcutaneous vaccinations: priming period of six vaccinations – one every two weeks, then a boosting period of five vaccinations – one vaccination every four weeks, then final vaccination given six months after the 11th vaccination) Control: placebo (same dosing as RV001)
Endpoints	Primary endpoint: time to documented PSA progression or clinical recurrence, death of any cause Secondary endpoints: safety and tolerability, time to subsequent antineoplastic therapy, disease-free survival Exploratory endpoints: relationship between immune-response and anti-tumour efficacy, identification of predictive biomarkers, metastasis-free survival
Key inclusion criteria	Biochemical recurrence after radical prostatectomy (PSA ≥0.2ng/mL, PSA doubling time > three months and <12 months, or definitive radiotherapy (same definitions except PSA >nadir + 2ng/mL)
Key exclusion criteria	No distant metastasis or locoregional recurrence No castration-resistant prostate cancer Not receiving androgen-deprivation therapy PSA>10ng/mL
Clinical trial sites	Denmark, Finland, Germany, Belgium, Sweden, UK and US
Sponsor	RhoVac
Timelines	Study start: Q319 Study duration (approximate): two years (one-year enrolment, one-year follow-up) Expected data readout: Q421

Source: RhoVac

Fast-track designation from the FDA likely

The FDA approved the IND in February 2020 and in September RhoVac applied for a fast-track designation. The requirements for this designation are that the drug is meant to treat an important disease and that the drug addresses an unmet need that the drug in question has a reasonable likelihood of addressing. Prostate cancer is one of the most prevalent malignancies and there is no treatment available for the specific indication that RhoVac is initially targeting, ie prevention of cancer metastases after curative intent therapy of the local tumour. 'Watchful waiting' is common practice in this setting, and since there is a significant risk of recurrence, waiting without knowing what will happen can very negatively affect the mental health of the patients and their families. The FDA has agreed that RhoVac can use placebo in the control arm, which is another sign that the regulator agrees there is no other option than just waiting. Should there be a viable intervention, it would be unethical to use placebo and RhoVac would have been asked to use standard of care treatment as the control instead. Also, the fact that RhoVac has an approved IND and the Phase IIb trial is ongoing in the US means the FDA has already taken a stance before on the likelihood that RV001 can address the unmet medical need. So, all in all, we believe there is a good chance that the application will be approved.

The benefits of fast track designation include more frequent meetings and written correspondence with the FDA, potential for accelerated approval or priority review if additional criteria are met, and rolling review, which means a company can submit completed sections of its new drug application (NDA) for review by the FDA, rather than waiting until every section of the application is completed.

Near-term newsflow

Near-term newsflow includes:

- filing for fast-track designation in **September;**
- completion of patient enrolment **by the end of 2020**; although this is contingent on the basis of the volatile COVID-19 situation;
- initiation of exploratory preclinical studies in other cancers by **end-2020**; and
- the publication of the full article with data from the completed Phase I/II study, likely **in Q320**.

The article publication will be particularly interesting, as this will be a peer-reviewed article, a form of external validation. It should also contain a more detailed background description of the science, as well as some additional data. The full results of the Phase I/II study have already been published via a press release, so we do not expect substantial modifications to our R&D model, but RhoVac mentioned the article will contain indicative PSA data as well as in-depth analysis of RV001's pharmacodynamics.

With regards to background on the target RhoC (and as a reminder), a comprehensive third-party review article on this target was published in July 2019 for the first time to our knowledge (Thomas et al, 'RhoC: a fascinating journey from a cytoskeletal organizer to a Cancer stem cell therapeutic target'. In cancer, RhoC is responsible for enhanced migration, invasion and metastasis. Existing data show that it is essential for cancer metastasis, which is how RhoVac is developing its vaccine (prevention of prostate cancer spreading). We reviewed this article in detail in our January 2020 report.

RhoVac aims to initiate exploratory preclinical studies in other cancers later this year. The company has a clear strategy to complete the ongoing Phase IIb trial and then to out-license the asset. To increase the attractiveness of RV001's data package, however, RhoVac plans to conduct one or more small exploratory preclinical and potentially clinical trials in other cancer indications.

Strategic options for late-stage development

If the Phase IIb study is positive, at least one successful Phase III study will likely be required for regulatory approval. RhoVac's current strategy is to partner following the Phase IIb outcome, but it is open to options including selling the company. Management currently envisages a single Phase III study. In our model we also assume a licensing deal in 2022 following the Phase IIb readout followed by a single Phase III study (full out-licensing, costs to be borne by the partner), which we assume will be a global study including both European and US sites, and will take approximately four years to complete. However, we cannot exclude the possibility an additional Phase II or Phase III study would be required, or that the Phase III study will take longer. That will depend on further regulatory interactions and any potential partnership with pharma companies, which may set their own goals. The key value inflection point, however, is the results of the ongoing Phase IIb study.

Likely endpoint for a Phase III study: Metastasis-free survival

So far, the only endpoints that have been the basis for FDA approval in prostate cancer are overall survival (OS), progression-free survival (PFS) and metastasis-free survival (MFS). Based on discussions with the FDA and EMA, RhoVac expects MFS to be accepted as the primary endpoint. Both the FDA and EMA now accept this endpoint in non-metastatic, castrate-resistant prostate cancer patients at high risk of developing metastases, demonstrated by recent apalutamide and enzalutamide approvals in this patient population using the same endpoint. RhoVac is targeting a slightly earlier patient population, but expects MFS to be acceptable based on discussions with the regulators. Studies with MFS as the primary endpoint can take several years to complete. There is a call for other surrogate endpoints in prostate cancer trials, including PSA endpoints, which could shorten trials.[2,3] Time to biochemical failure has been proposed as a surrogate endpoint, as demonstrated in a Phase III study in localised disease, but no products have been approved on PSA. According to RhoVac, the EMA and FDA are open to discussing the use of such endpoints,

[2] Kyriakopoulos CE, Antonarakis ES. Surrogate end points in early prostate cancer clinical states: ready for implementation? *Ann Transl Med*. 2017;5(24):502. doi:10.21037/atm.2017.10.25

[3] Williams S. Surrogate endpoints in early prostate cancer research. *Transl Androl Urol*. 2018;7(3):472–482. doi:10.21037/tau.2018.05.10

because they recognise the problem of designing trials in this group of patients, where there is a significant unmet need. However, further discussions with the regulators are needed.

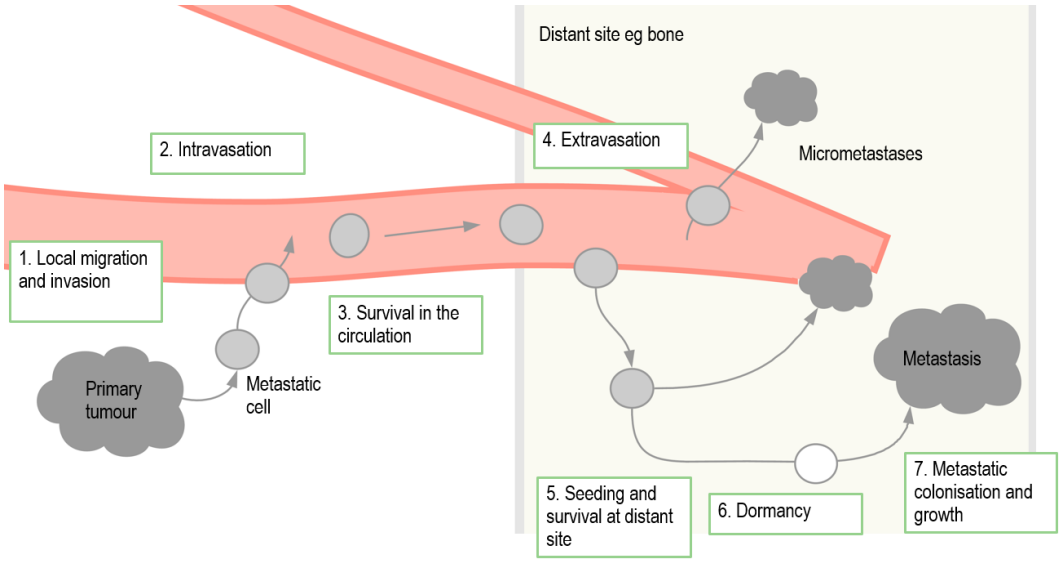
Understanding the process of metastasis

Metastatic cancer is the most advanced stage of cancer and is terminal. Unfortunately, a large proportion of patients who are diagnosed with cancer already have metastases. As a result, advanced cancer is a key focus area for pharmaceutical development. Metastases are difficult to treat because they are heterogeneous and can develop drug resistance. Despite the significance of metastasis, there is much less research in this area compared to the treatment of primary tumours. This could be due to the fact that the mechanisms of metastasis are less known than the mechanisms of primary tumour development. This represents both a challenge and an opportunity for companies developing treatments targeting metastasis.

Cancer metastasis is a complex process and still is not fully understood. However, it is generally accepted that the 'metastatic cascade' includes:

1. **Local migration and invasion** after cancer cells from the primary tumour gain metastatic potential and start to migrate out of the primary tumour and invade local tissues.
2. **Intravasation.** Tumour cells enter the blood or lymph from the local tissues through a process called epithelial mesenchymal transition (EMT), and become circulating tumour cells or 'CTCs'.
3. **Survival in the circulation.** Many CTCs die in circulation, due to the harsh environment including attack by immune cells, and this is why metastasis is a very inefficient process.
4. **Extravasation.** Of the cells that entered the circulation, only a small portion survive and enter distant tissues.
5. **Seeding and survival at a distant site.** Different cancers favour different sites, for example the most common metastatic site in prostate cancer is the bone (84%) (Gandaglia et al 2013).
6. **Dormancy.** Cancer cells that are 'disseminated', ie that have left the primary tumour, can remain dormant. It is thought that these cells could be cancer stem cells.
7. **Metastatic colonisation and growth.** The new metastasis then grows, supported by a changing tumour microenvironment.

Exhibit 3: Metastatic cascade



Source: Edison Investment Research

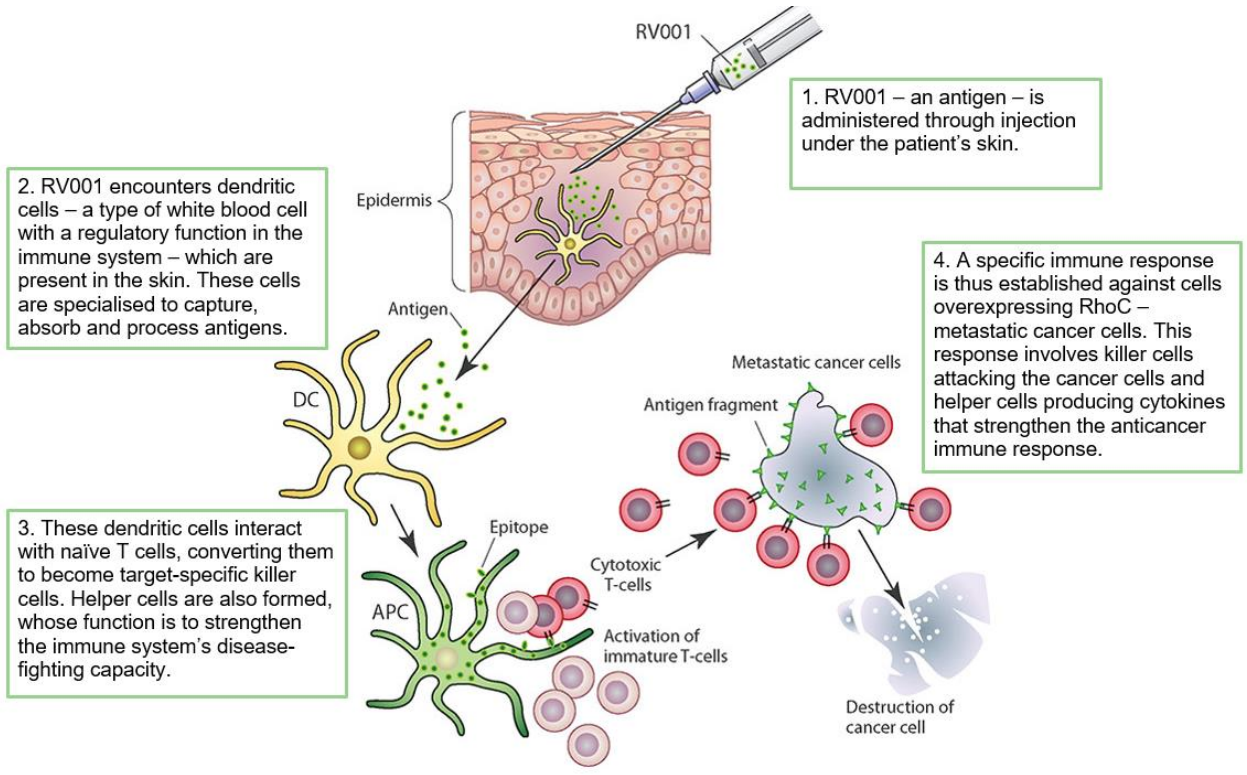
Despite the significance of the metastatic cascade in cancer progression, there has been an apparent lack of interest in this area from the pharmaceutical industry. According to one review article published in *Nature*, 'overt scepticism exists in the pharmaceutical industry and some academic quarters about the concept of drugging metastasis.'[4] Suggested reasons for failure in this field so far include poor understanding of metastatic pathways, trial design and difficulties in diagnosing cancer before it has metastasised.

Denosumab, a RANKL inhibitor, has been the most successful at inhibiting metastasis so far, since it actually helps to delay the time to bone metastasis and bone MFS in solid tumours. This drug, however, is mainly used to treat bone diseases including osteoporosis.

RV001: A peptide-based immunotherapy

RV001 is a peptide-based immunotherapy that contains fragments of a protein called RhoC, which is overexpressed in cells with metastatic potential in a range of cancers (Karlsson et al 2009). It has been found to be essential for metastasis (Hakem et al 2005), and to cause metastasis in animal models (Clark et al 2000). The adjuvant Montanide ISA 51 is used together with the peptides to increase the immune response. The strategy that RhoVac is employing is similar to other peptide immunotherapies in that the aim is to elicit a T-cell response against a particular protein expressed by tumour cells. RhoVac expects RV001 to elicit a T-cell response against RhoC through major histocompatibility (MHC) class I and II (Exhibit 4).

Exhibit 4: RV001 proposed mechanism of action



Source: RhoVac with Edison explanations

RhoC is a Rho GTPase. Rho GTPases have a role in important cellular processes such as migration and cell adhesion. Since metastasis employs these mechanisms, Rho GTPases are also

[4] Steeg PS. Targeting metastasis. *Nature Reviews Cancer* volume 16, pages 201–218 (2016)

associated with metastasis. Rho GTPases and their pathways have already been investigated as targets for cancer treatment, but so far unsuccessfully.

RhoC is on the National Cancer Institute list as a priority cancer antigen. RhoC regulates the cytoskeleton at the point of the cell that is infiltrating the cellular matrix so it is directly associated with invasion. This is not a cancer-specific mechanism as any cell involved in tissue repair or angiogenesis will use the same mechanism. However, this protein is overexpressed in tumour cells, including metastatic lesions. So, RhoC is tissue-agnostic, but specific to cancer metastases. An interesting finding is that RhoC overexpression is maintained as the secondary tumours develop (Liu et al 2007). This observation further supports the rationale to use RV001 for metastases prevention and control or treatment of secondary tumours.

What are peptide-based immunotherapies?

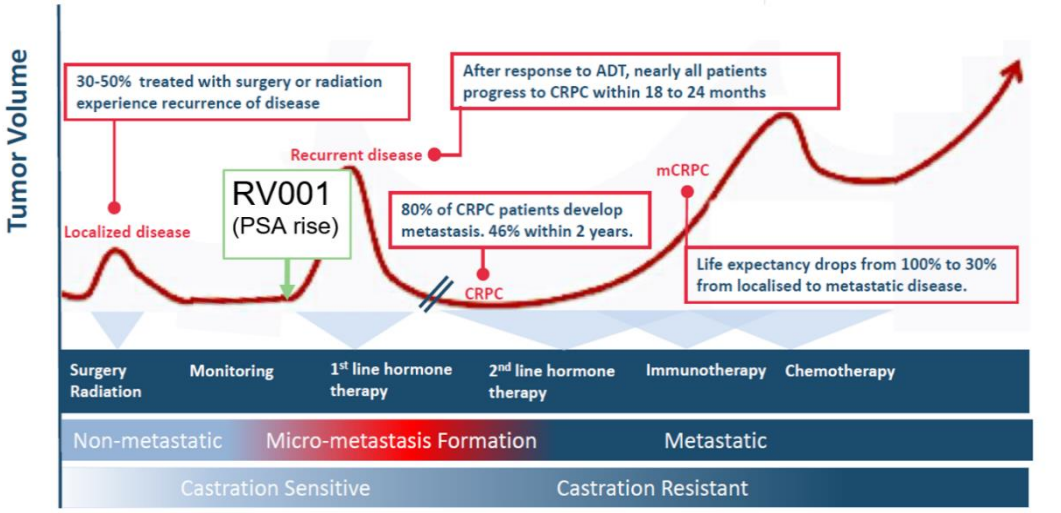
In a malignant process, cancer cells die and proteins/antigens are released. These are then taken up by the patient's own antigen-presenting cells, or dendritic cells (DCs), and in lymph nodes they present these antigens to T-cells. This leads to an activation and production of populations of T-cells, which can now recognise and destroy cancerous cells that display the same antigens as those previously presented. However, this process is not perfect, which is why not every malignant process is stopped. Once a tumour develops, it often also has multiple ways to suppress the immune response and enable the tumour to 'hide' from the immune cells. The goal of cancer immunotherapies is to expose the tumour cells as foreign to the patient's immune system so the tumour is recognised and immunologically attacked.

Targeting an unmet need in prostate cancer

Prostate cancer is a common cancer in men over the age of 50. The National Cancer Institute estimates that 174,650 patients in the US will be diagnosed with prostate cancer in 2019 and there will be an estimated 31,620 deaths from the disease in the US during 2019. Prostate cancer is usually diagnosed by carrying out a mixture of PSA blood test, digital rectal examination and biopsy. PSA is an important tool also to monitor patients for relapse. The stage of prostate cancer at diagnosis is a significant contributor to survival as patients with early local disease have a five-year survival rate of 98%, while patients with advanced metastasis have five-year survival of 28% (Tewari et al 2014). The stage of prostate cancer together with the risk level determines treatment options:

- **Localised prostate cancer with low risk or intermediate risk** is treated with active surveillance or radical therapy (either radical prostatectomy or radiation therapy). Low-risk patients might get watchful waiting with delayed androgen deprivation therapy (or hormone therapy) as an alternative if they are very low risk. Intermediate-risk patients might also receive adjuvant hormone therapy with their radiation therapy. Many patients will relapse after radical therapy, and will move on to hormone therapy or salvage radiotherapy. Most patients live for many years with localised disease, but most will eventually still progress.
- **Patients with high-risk localised or locally advanced prostate cancer** might receive a hormone therapy, radical prostatectomy or radiotherapy, and on relapse additional hormone therapy or radiotherapy. Many patients will progress to metastatic disease, which is most often bone metastases.
- **Metastatic disease can be either hormone-naïve or castrate-resistant**. Hormone-naïve patients can receive androgen deprivation therapy, but castrate-resistant prostate cancer patients have to move on to other options. These include abiraterone and enzalutamide (other hormone drugs), sipuleucel-T (Provenge, dendritic cell vaccine), Radium-223 and docetaxel. Radium-223, denosumab and zoledronate can be used for patients with bone metastases.

Exhibit 5: Prostate cancer progression and RV001 positioning



Source: RhoVac

RhoVac is targeting patients with localised disease who have relapsed after a treatment with curative intent (ie radical prostatectomy or radiotherapy). A relapse in these patients is known as biochemical recurrence/biochemical failure and can be defined as a rise in PSA ≥0.2ng/mL (American Urological Association, European Association of Urology). Currently these patients will move on to hormone therapy or salvage radiotherapy, but RhoVac wants to delay disease progression by extending the effect of the radical therapy. RV001 will be given therefore as an 'adjuvant' treatment to the radical therapy. Discussions with the EMA and FDA highlight that this is an area of unmet medical need.

There is potential for RV001 to expand into other patient populations. RV001 could be used as a non-invasive therapy instead of just watchful waiting in low-risk localised prostate cancer patients, who are not candidates for radical prostatectomy or radiotherapy (earlier stage than that currently targeted). There is also a rationale to use RV001 in later stages, for example in patients with metastasised cancer who are receiving androgen deprivation therapy. Not all cancer cells are sensitive to antiandrogens, which is why the cancer ultimately relapses and becomes castrate-resistance prostate cancer. The addition of RV001 to complement the antiandrogen therapy could either slow down the development of antiandrogen resistant cells or eradicate them.

Competitive landscape

Currently, RV001 is positioned to target patients who had just undergone a radical therapy with curating intent. Virtually the only approach used for these patients is watchful waiting. As a result, in this specific patient population RV001 as a monotherapy would have no competition.

Overall, the best-selling drugs in 2019 have been the branded hormone drugs targeting advanced disease, ie Xtandi (enzalutamide, Astellas) with sales of $3.7bn and Zytiga (abiraterone acetate, Janssen Biotech) with sales of $2.8bn (EvaluatePharma). In 2019, EvaluatePharma estimates the revenues per patient per year in the US from Xtandi to be around $66,000 and Zytiga to be around $85,000.

Clinical studies in biochemical failure

The majority of clinical development is for metastatic castrate-resistant prostate cancer. However, there are a few ongoing studies with immunotherapeutics being conducted in patients with

biochemical recurrence – the same population as RhoVac's planned Phase IIb study (Exhibit 6). To our knowledge, there have not been any Phase III studies carried out in this group of patients. Results from these studies could provide insights for RhoVac, and if any Phase III studies are initiated it will also be helpful for RhoVac when discussing endpoints with the regulators.

Exhibit 6: Drugs in development for biochemical recurrence in localised prostate cancer

Product	Pharmacological class	Company	Phase of development	No. patients	Primary endpoint(s)	Estimated primary completion date
RV001	Peptide-based immunotherapy (RhoC)	RhoVac	Phase IIb-ready	150	Time to documented PSA progression or clinical recurrence, death of any cause	H221
ProscaVax	PSA/IL-2/GM-CSF vaccine	OncBioMune Pharmaceuticals Inc	Phase II [NCT03579654]	120	Prostate cancer progression measured by PSA test, digital rectal examination and prostate biopsy	February 2021 (potentially delayed as not yet recruiting and last update posted in March 2019)
Prostvac	Vector-based vaccine (PSA)	National Cancer Institute	Phase II [NCT02649439]	98	Time to progression	January 2021
Enzalutamide	Anti-androgen	Astellas	Phase II [NCT02203695] (marketed in other prostate cancer populations)	122	Rate of Freedom-from-PSA-progression (FFPP) at 2-years	December 2021
Nivolumab	PD-1 inhibitor	Bristol-Myers Squibb	Phase II [NCT03637543]	34	Disease control (proportion of patients that experiences decline or stabilisation of PSA)	March 2022
Olaparib	PARP inhibitor	AstraZeneca	Phase II [NCT03047135]	50	Response rate (decline in PSA to 50% of baseline level)	March 2021
Rucaparib	PARP inhibitor	Clovis Oncology	Phase II [NCT03533946]	32	50% reduction in PSA levels	July 2023

Source: Evaluate Pharma, Clinicaltrials.gov

Patent protection to 2028/32, plus BLA exclusivity

RhoVac has a single patent family based on the PCT application WO2009076966 and a priority date of December 2008. It has patents in Europe, Australia and Japan (EP2234635B1, AU2008338063B2, JP5813801B2 expected expiry December 2028), and the US (US9163077B2, expected expiry March 2032), and patents pending in Canada. This patent family covers RV001 and any other immunotherapies that RhoVac may develop relating to RhoC. According to our model, if RV001 reaches the market in prostate cancer, this will likely be in 2027 (assuming a four-year Phase III study that includes a longer endpoint such as MFS or PFS). Patent protection could be extended, but we expect that RhoVac or a potential partner would rely on market exclusivity resulting from the Biologic License Application (BLA). Since RV001 is an immunotherapy, we expect it will go down the BLA pathway, which would secure 12 years' exclusivity in the US and at least 10 years in Europe (upon market authorisation). To achieve patent extension in the US, RhoVac would benefit from including clinical trial centres in the US as early as possible, ie in the Phase IIb study.

Sensitivities

RhoVac is subject to typical biotech company development risks, including the unpredictable outcome of trials, regulatory decisions, success of competitors, financing and commercial risks. Currently, RhoVac is a single technology company, which is high risk since if the technology is not successful in treating metastasis the company cannot fall back on any alternatives. Our model assumes that RV001 will be out-licensed; therefore, our valuation is sensitive to potential licensing timing and actual deal terms.

RhoVac is an early-stage drug developer, therefore in the foreseeable future the value creation will depend on successful R&D progress and any potential partnering activities, although typically the

timing of licensing deals is difficult to forecast. The near-term R&D sensitivities are tied to RV001 in prostate cancer, which is the only clinical-stage programme. Any setbacks with this asset will influence RhoVac's share price significantly. As additional indications reach clinical development, this risk will be diversified. The design of the Phase III study in prostate cancer as well as the cost and length of the study are unknown. In our model, we assume a four-year Phase III trial in prostate cancer. However, there is a risk the trial could take longer if a different endpoint is required.

Valuation

Our RhoVac valuation (Exhibit 7) is higher at SEK1.18bn or SEK61.8/share due to rolling the model forward, which offset the lower cash position (SEK109.7m at end-Q220) and revised rNPV assumptions. Exhibit 8 summarises our detailed assumptions for the rNPV valuation. We have made several adjustments in our risk-adjusted net present value (rNPV) model.

For now, we include a single asset in a single indication in our valuation, which is RV001 in prostate cancer, specifically in patients with biochemical recurrence following radical prostatectomy or radiotherapy. There is a clear rationale for RV001 to be expanded in other prostate cancer patient populations, either earlier or more advanced. In addition, RV001 is tissue agnostic, so theoretically it could be used in many other cancers that metastasise. Although all these new avenues will require dedicated clinical trials, in case of an out-licensing, the label and indication expansion would be considered and reflected in the total deal value.

In our initiation report, which was published before the start of the Phase IIb trial, we narrowly focused on RhoVac's core indication and used comparable licensing deals specifically involving prostate cancer indication. Since then, the company has initiated the Phase IIb trial, as expected, and is considering possible ways to demonstrate RV001's potential across various stages of prostate cancer, but more importantly in other cancer types. A positive Phase IIb study would demonstrate the first RV001's clinical proof-of-concept. Because its mechanism of action is tissue agnostic, and not tied specifically to prostate cancer, RV001's potential in other indications could expand drastically after proof-of-concept, and this broader potential would be a key part of any licensing deal.

With this in mind, we have reviewed the comparable licensing deals we use in our valuation. The key criterion for us was the deal terms include the potential for expansion of the drug in multiple indications. Over the past five to six years we have identified the licensing deals listed in the Exhibit 9. **We take the median upfront ($121m) and milestone payment ($1.07bn) values, but in our model we risk adjust these by 40% to reflect lack of clinical proof-of-concept at the moment and inherent uncertainty in partnering discussions.** Because of this substantial expansion potential, the comparable deal terms stipulate impressive upfront and milestone payments, which is not reflected in the current market capitalisation. We believe the repricing could be rapid if clinical proof-of-concept is successfully demonstrated in the ongoing trial. We use tiered 10–13% royalty rates.

We also increased the assumed penetration rate to 40% from 20% in our rNPV model that calculates RV001's potential in the current narrow prostate cancer indication (biochemical recurrence after a curative treatment). As we described above, the company has made progress in this setting, while at the same time no competition has emerged even in the early stages, so a larger market penetration assumption is warranted.

Exhibit 7: Sum-of-the-parts RhoVac valuation

Product	Launch	Peak sales (US$m)	Unrisked NPV (SEKm)	Technology probability (%)	rNPV (SEKm)	rNPV/share (SEK)
RV001 – prostate cancer	2027	1,775	5,338.9	15%	1,068.1	56.1
Net cash, last reported			109.7	100%	109.7	5.8
Valuation			**5,448.6**		**1,177.9**	**61.8**

Source: Edison Investment Research. Note: WACC = 12.5% for product valuations.

Exhibit 8: Assumptions for RV001 valuation

Product/indication	Comments
RV001 – prostate cancer	■ Target population: c 22k prostate cancer patients in the US who have biochemical recurrence annually, and c 41k in EU14. This is reached by taking the incidence of prostate cancer in each region (175k US and 324k in EU14) x proportion that are diagnosed with local disease (approx. 66%) x proportion treated with radical prostatectomy or radiotherapy (approx. 55%) x proportion having biochemical recurrence per year (approx. 35%). 40% peak penetration. ■ Pricing: $50k per patient per year in the US, 30% discount in Europe. Peak sales in five years. ■ R&D cost: SEK122.6m to complete Phase IIb, then out-licensed. ■ IP rights: proprietary technology; patent protection until 2028 (Europe, Australia, Japan) and 2032 (US). Biologicals market exclusivity 12 years in the US and 10 years in Europe.

Source: Edison Investment Research. Note: Target geographies used in the model are the US, and top 14 European countries (EU5 + Netherlands, Belgium, Luxembourg, Denmark, Finland, Norway, Sweden, Austria and Switzerland).

Exhibit 9: Comparable deals for immunotherapy assets in late stage development for prostate cancer

Date	Licensor	Licensee	Product	Pharmacological class / target	Upfront ($m)	Total milestones	R&D milestones	Sales milestones
28/03/2019	AstraZeneca	Daiichi Sankyo	Enhertu	Topoisomerase I inhibitor; HER-2 antibody	1,350	5,550	3,800	1,750
03/11/2014 02/03/2015	Novartis	Arzerra	Genmab	B-lymphocyte antigen CD20 antibody	102	1,600	1,600	
17/08/2018	OncologiE	Lefitolimod	Mologen	Toll-like receptor 9 (TLR9) agonist	27	1,270	1,270	
04/03/2015	Bristol-Myers Squibb	Prostvac	Bavarian Nordic	Prostate-specific membrane antigen (PSMA) regulator	140	835	340	495
24/09/2014	Baxter International	Onivyde	Merrimack	Topoisomerase I inhibitor	100	870	620	250
24/08/2015	Medivation	Talzenna	BioMarin Pharmaceutical	PARP1,2 inhibitor	410	160	160	0
Median					**121**	**1,070**		

Source: Edison Investment Research, EvaluatePharma, company press releases.

Positive Phase IIb study scenarios

To model a **successful Phase IIb outcome**, as an indicative scenario we have set the model to a future date (1 January 2022) and increased the technological success probability to 40% from 15%. Because a successful Phase IIb outcome would also be the first clinical proof of concept, we believe this would increase RV001's potential in other indications. This would allow us to reflect a larger portion of comparable deal economics (which are currently set only at 40%, as explained above). There are no historical comparators as to how much this portion should increase, so we will review the totality of data (RhoVac may also conduct preclinical studies in other indications in parallel to the Phase IIb trial). Exhibit 10 provides a sensitivity analysis.

Exhibit 10: Valuation per share sensitivities in positive Phase IIb study scenarios

Comparable licensing deal value adjustment	60%	80%	100%
Valuation per share	**176**	**211**	**235**

Source: Edison Investment Research

Financials

H120 operating costs were SEK24.8m vs SEK31.3m a year ago. The Phase IIb BRaVac study started recruiting patients in November 2019, so in 2020 and 2021 we expected stable cash burn. Our previous operating cost estimates for 2020 and 2021 were c SEK60m, which we now lower to

SEK50m. RhoVac is considering exploratory preclinical and potentially clinical trials in parallel to BRaVac study, in which case we may adjust our estimates once more.

RhoVac was awarded an EU Horizon 2020 grant of €2.5m (c SEK27m) to support the ongoing Phase IIb study. To date, the company has received SEK12m of that amount, which is already reflected in the balance sheet and P&L. The remaining part of the grant of SEK15m is yet to be received. Tax credits in H120 were SEK4.4m versus SEK5.1m in H119.

The reported end-Q220 cash position was SEK109.7m with no interest-bearing debt. RhoVac will also receive the remaining part of the grant of c SEK15m and expects around SEK18m in tax credits during the duration of the BRaVac trial. In addition to prepaid expenses of SEK15m (current asset on the balance sheet), these expected amounts mean that the total expected funding is around SEK158m, which is more than sufficient to complete the ongoing Phase IIb study.

Exhibit 11: Financial summary

SEK000s	2018	2019	2020e	2021e
Year end 31 December	Local GAAP	Local GAAP	Local GAAP	Local GAAP
PROFIT & LOSS				
Revenue	0	5,979	12,000	8,000
Cost of Sales	0	0	0	0
Gross Profit	0	5,979	12,000	8,000
Research and development	(19,154)	(38,570)	(50,000)	(50,000)
EBITDA	(20,148)	(36,325)	(37,997)	(41,992)
Operating Profit (before amort. and except.)	(12,857)	(20,148)	(20,148)	(36,325)
Intangible Amortisation	0	0	0	0
Exceptionals	0	0	0	0
Other	0	0	0	0
Operating Profit	(20,148)	(36,325)	(38,000)	(42,000)
Net Interest	(64)	382	577	363
Profit Before Tax (norm)	(20,212)	(35,943)	(37,423)	(41,637)
Profit Before Tax (reported)	(20,212)	(35,943)	(37,423)	(41,637)
Tax	2,936	3,837	7,900	0
Profit After Tax (norm)	(17,276)	(32,106)	(29,523)	(41,637)
Profit After Tax (reported)	(17,276)	(32,106)	(29,523)	(41,637)
Average Number of Shares Outstanding (m)	8.9	14.3	19.0	19.0
EPS - normalised (SEK)	(1.95)	(1.55)	(2.19)	(2.61)
EPS - normalised and fully diluted (SEK)	(1.34)	(1.95)	(1.55)	(2.19)
EPS - (reported) (SEK)	(1.95)	(1.55)	(2.19)	(2.61)
Dividend per share (SEK)	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	100.0	100.0	100.0
EBITDA Margin (%)	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A
BALANCE SHEET				
Fixed Assets	2,848	3,021	3,021	3,021
Intangible Assets	2,848	3,021	3,021	3,021
Tangible Assets	0	0	0	0
Investments	0	0	0	0
Current Assets	20,372	149,928	119,431	77,239
Stocks	0	0	0	0
Debtors	240	14,391	14,391	14,391
Cash	16,060	129,543	99,046	56,854
Other	4,071	5,994	5,994	5,994
Current Liabilities	(4,380)	(12,574)	(12,574)	(12,574)
Creditors	(4,380)	(12,574)	(12,574)	(12,574)
Short term borrowings	0	0	0	0
Long Term Liabilities	(596)	(624)	(624)	(624)
Long term borrowings	0	0	0	0
Other long term liabilities	(596)	(624)	(624)	(624)
Net Assets	18,245	139,751	109,254	67,062
CASH FLOW				
Operating Cash Flow	(17,097)	(43,309)	(37,997)	(41,992)
Net Interest	(64)	(1,834)	200	200
Tax	2,229	2,986	7,900	0
Capex	0	0	(600)	(400)
Acquisitions/disposals	0	0	0	0
Financing	21,756	154,715	0	0
Other	(191)	925	0	0
Dividends	0	0	0	0
Net Cash Flow	6,632	113,483	(30,497)	(42,192)
Opening net debt/(cash)	(9,428)	(16,060)	(129,543)	(99,046)
HP finance leases initiated	0	0	0	0
Other	(0)	0	0	0
Closing net debt/(cash)	(16,060)	(129,543)	(99,046)	(56,854)

Source: RhoVac accounts, Edison Investment Research

Contact details	Revenue by geography
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Management team

CEO: Anders Månsson	CFO: Henrik Stage
Anders Månsson has extensive experience from the pharmaceutical world both internationally and locally. He has worked in senior positions in major pharmaceutical companies in Sweden, Denmark, the UK and Switzerland. His focus was on sales and the market, as well as on business development including distribution and licence agreements, divestments and acquisition agreements worth over several billion Swedish kronor. In recent years, he has also held a number of board positions in biotech/life science in southern Sweden.	Henrik Stage has an MSc in finance and more than 25 years' experience in leading biotechnology and finance sectors positions. Mr Stage's background includes several pharmaceutical deals and he was involved in the successful exit of Santaris Pharma, which was sold to Roche for US$450m in 2014. Mr Stage is a part-owner of Ventac Holdings (Cyprus) Ltd., which owns shares in RhoVac.
Chief Development Officer: Steffen Wad Jørgensen	
Steffen Wad Jørgensen has a pharmacy degree, and also a PhD in immunology and clinical chemistry. Wad Jørgensen has extensive experience in formulation development and analysis as well as project coordination of both early and late clinical development projects. During his time at Lundbeck, he held significant positions within the corporate project management and business development activities.	

Principal shareholders	(%)
Rutger Arnhult	20.41
Nordic Cross Asset Management	9.32
RQ Solutions ApS	7.56
Avanza Pension	3.95
Göran Källebo	3.34
Nordnet Pensionsförsäkring	2.49

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