EDISON

RhoVac

Company update

Phase IIb BRaVac study enrolling patients

Pharma & biotech

RhoVac's Phase IIb BRaVac study with RV001 (a cancer immunotherapy targeting RhoC) is up and running with patients being recruited since November 2019. In total, over 175 prostate cancer patients, who experienced biochemical failure after a curative therapy (surgery or radiation therapy), are expected to be enrolled by the end of Q320 in six European countries as well as the US. The primary endpoint is time to PSA doubling or clinical progression and key interim results are expected in H221 (the treatment part of the study), with follow up data due in H222. Besides the BRaVac study progress updates, RhoVac released more supportive immunological data from the completed Phase I/II trial, and, unexpectedly, an unrelated group of researchers published a detailed review of RhoC as a target. Our valuation stays virtually unchanged at SEK888.6m or SEK46.7/share.

Year end	Revenue (SEKm)	PBT* (SEKm)	EPS* (SEK)	DPS (SEK)	P/E (x)	Yield (%)
12/17	0.0	(12.9)	(1.34)	0.0	N/A	N/A
12/18	0.0	(20.2)	(1.95)	0.0	N/A	N/A
12/19e	0.0	(54.6)	(3.27)	0.0	N/A	N/A
12/20e	0.0	(59.4)	(2.71)	0.0	N/A	N/A

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

Additional immunological data from Phase I/II

Final long-term follow up results from the Phase I/II study were announced in July 2019. No major side effects were reported after 12 months of treatment with RV001 and 18 out of 21 (86%) evaluable patients showed an immune response (measured by IFNγ ELIspot analysis). The immune response was still detectable in all 18 patients at three-, six- and nine-month follow ups. At the 12-month follow up, 17 out of 18 patients still showed significant immunological response.

More evidence supporting RV001 immunogenicity

RhoVac is collaborating with the University of Tübingen on the immunological studies and in November 2019 the company further reported that the treatment with RV001 was shown to activate both CD4+ and CD8+ T-cells. CD8+ (cytotoxic) T-cells are traditionally considered to be the main type of lymphocytes that can directly attack the cancer, but sufficient evidence indicates that CD4+ T-cells (helpers) also play a crucial role by supporting long-term tumour specific memory. There is also evidence that CD4+ T-cells themselves can attack the tumour cells directly via T-cell receptor (TCR) and MHC class II interaction, and indirectly via the release of immunomodulatory molecules (Haabeth et al, 2014).

Valuation: SEK888.6m or SEK46.7/share

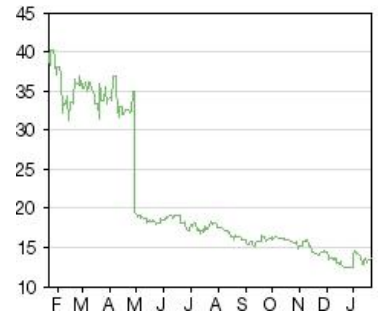
We keep our RhoVac valuation virtually unchanged at SEK888.6m or SEK46.7/share, as rolling the model forward was offset by a lower cash position. We maintain other assumptions in our rNPV model. Near- to mid-term share price drivers are associated with the ongoing Phase IIb BRaVac study. Key interim results are expected in H221, while follow up data should be ready in H222. Other significant R&D events include the start of an exploratory clinical study in other cancer indications (2020), and any potential updates on the partnering process.

21 January 2020

Price	**SEK13.54**
Market cap	**SEK257m**

Net cash (SEKm) at end Q319	129.0
Shares in issue	19.0
Free float	85%
Code	RHOV
Primary exchange	Spotlight Stockholm
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	8.3	(15.3)	(67.9)
Rel (local)	6.7	(18.3)	(69.0)
52-week high/low	SEK40.3		SEK12.5

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

Q419 results	11 February 2020
Interim results from the Phase IIb study	H121
Start of exploratory clinical study in other cancer indication	2020
Updates on partnering process	2020/2021

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Edison profile page

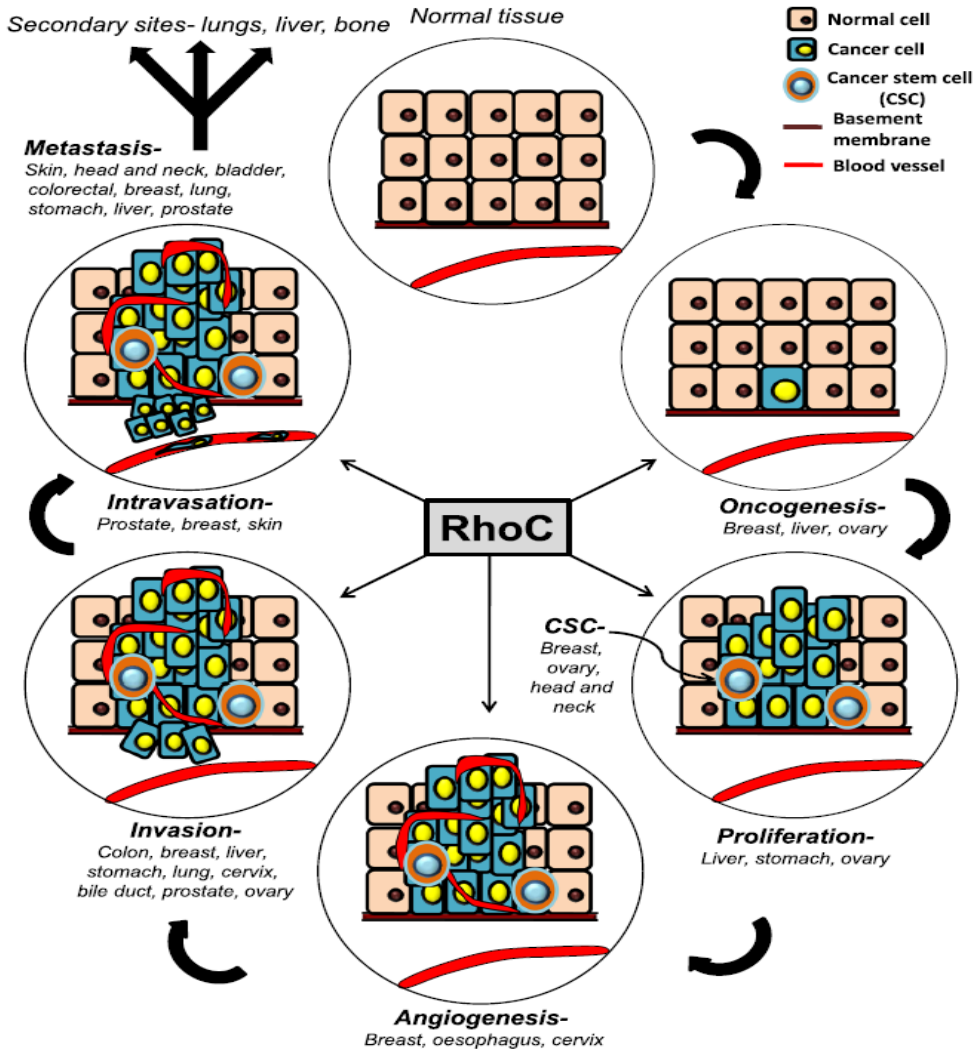
Third-party review of RhoC target

In July 2019, Thomas et al published an article 'RhoC: a fascinating journey from a cytoskeletal organizer to a Cancer stem cell therapeutic target', which to our knowledge is one of the most comprehensive and up to date reviews of RhoC. RhoVac's RV001 is a cancer immunotherapy comprised of a 20 amino acid fraction of the protein RhoC. The expectation is that it will elicit an immune response against RhoC, which is highly expressed in cells with metastatic potential.

RhoC belongs to the Rho family of proteins and is responsible for cytoskeletal organisation and protein structures in the cells that are involved in multiple cellular functions, including motility and division. In cancer, RhoC is responsible for enhanced migration, invasion and metastasis. Existing data show that it is essential for cancer metastasis (Hakem et al, 2005), which is the core rationale in how RhoVac is developing its vaccine (prevention of prostate cancer spreading). Our more detailed review of RhoC as a target is in our initiation report.

An increasing amount of data show that RhoC has a rather diverse role in various aspects of cancer progression (summarised in Exhibit 1). In various models, RhoC significantly contributed to cancer initiation, proliferation, angiogenesis, invasion, intravasation and metastasis (Thomas et al, 2019). We described the metastatic cascade in our initiation report.

Exhibit 1: RhoC has diverse role in cancer progression



Source: Thomas et al, 2019

Two other members of the Rho family are RhoA and RhoB, however, only RhoC is expressed at significantly higher levels in metastatic tumours than in primary tumours (Suwa et al, 1998). RhoVac is focusing on prostate cancer as its primary indication, however, as Thomas et al describe, RhoC's importance in cancer spreading was implicated in many other cancers, including breast, skin, ovarian, liver, head and neck cancers and several others. RhoVac 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, the company plans to conduct one or more small exploratory clinical trials in other cancer indications.

We understand that melanoma could be one of the potential indications for the exploratory trial, although the final decision has not been made. From Thomas et al's review it is clear that melanoma is one of the better investigated cancers with respect to RhoC's involvement in the malignant process. Various authors showed that:

- RhoC is important in the melanoma metastasis process.
- In a mouse model, inhibition of a factor downstream to RhoC led to decreased lung metastases.
- Statins (popular cholesterol lowering drugs) are able to reduce RhoC activation via HMG-CoA inhibition and were shown to be potentially useful as a primary prophylaxis for melanoma to inhibit invasion and metastasis (Collisson et al, 2003).

Our view

Although the final decision has not been made, existing knowledge supports investigating melanoma in the exploratory trial. It is a rather crowded field, but we believe that RhoVac's primary intention is to gather an attractive data package with proof-of-concept of the mechanism of action that can be used in out-licensing discussions. In this regard, it makes sense to make a small investment in the indication where RV001 can be expected to generate the most interesting data.

Potential clinical applications

Thomas et al in their review also present an interesting discussion about potential therapeutic applications of targeting RhoC. Highlights include:

- RhoC has been shown to contribute to therapy resistance in some tumours, therefore, inhibition of it could be part of a combination therapy.
  - Specifically in prostate cancer, RhoC may have a role in the of hormone therapy resistance. Hormone therapy (eg anti-androgens, LH treatment, inhibitors such as Zytiga and Xtandi) is the mainstay treatment for advanced prostate cancer, resistance to which leads to poor outcomes.
- Wenandy et al suggested that 'RhoC may serve as an important and widely applicable target for anti-cancer immunotherapeutic strategies', which is what RhoVac is doing.
- As mentioned, prophylactic treatment of primary melanoma metastasis with statins, which due to downstream effects reduces the activity of RhoC, led to inhibition of invasion and metastasis. This effect was also seen in head and neck cancer.
- Prolonged use of statins was linked to reduction of oesophageal cancer.
- In another study, statins in combination with celecoxib (anti-inflammatory, selective COX-2 inhibitor) induced colorectal cancer cell death in vitro.
- Treatment of breast cancer cell lines in vitro with anti-RhoC siRNA led to decreased invasion, motility and migration.

Our view

While a number of reports from various parties describe RhoC as a potential target, to our knowledge there are no ongoing clinical trials testing therapies that target RhoC. This implies a relatively high RV001 technology risk, although it is true with virtually all pioneering approaches. In terms of indication choice (prostate cancer, melanoma), a large existing body of literature supports RhoVac's current R&D strategy.

Financials and valuation

RhoVac reports no income, while the operating spend was SEK41.9m in 9M19, up from SEK13.1m in 9M18, mainly because of the preparations and initiation of the Phase IIb study. We already expected operating expenditure to increase as the Phase IIb accelerates. We have only slightly increased our operating loss estimate to SEK55m in 2019, but keep our SEK60m estimate in 2020 unchanged. RhoVac received SEK6.7m in tax credits in 9M19. The reported 9M19 cash position was SEK129m in cash and no debt, which should be sufficient to finish the ongoing Phase IIb study.

Our RhoVac valuation is virtually unchanged at SEK888.6m or SEK46.7/share, as rolling the model forward was offset by a lower cash position. We maintain the other assumptions in our risk-adjusted NPV model. Our valuation is based on RV001 in prostate cancer only, specifically in patients with biochemical recurrence following radical prostatectomy or radiotherapy.

According to our model, a successful Phase IIb outcome would result in RhoVac's rNPV increasing to SEK2.05bn or SEK107.1/share (not including the net cash estimate). This would include setting the probability of success at 40% as a Phase III-ready asset and changing the date of the valuation to the start of 2022, but leaving all other inputs unchanged.

Exhibit 2: 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	888	3,451.1	15%	759.5	39.9
Net cash at end-Q319			129.0	100%	129.0	6.8
Valuation			**3,580.1**		**888.6**	**46.7**

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

Exhibit 3: Financial summary

SEK'000s	2017	2018	2019e	2020e
December	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	0	0	0	0
Cost of Sales	0	0	0	0
Gross Profit	0	0	0	0
Research and development	(12,243)	(19,154)	(55,000)	(60,000)
EBITDA	(12,857)	(20,148)	(55,000)	(60,000)
Operating Profit (before amort. and except.)	(12,857)	(20,148)	(55,000)	(60,000)
Intangible Amortisation	0	0	0	0
Exceptionals	0	0	0	0
Other	0	0	0	0
Operating Profit	(12,857)	(20,148)	(55,000)	(60,000)
Net Interest	(5)	(64)	382	577
Profit Before Tax (norm)	(12,861)	(20,212)	(54,618)	(59,423)
Profit Before Tax (reported)	(12,861)	(20,212)	(54,618)	(59,423)
Tax	1,911	2,936	7,900	7,900
Profit After Tax (norm)	(10,950)	(17,276)	(46,718)	(51,523)
Profit After Tax (reported)	(10,950)	(17,276)	(46,718)	(51,523)
Average Number of Shares Outstanding (m)	8.2	8.9	14.3	19.0
EPS - normalised (SEK)	(1.34)	(1.95)	(3.27)	(2.71)
EPS - normalised and fully diluted (SEK)	(1.34)	(1.95)	(3.27)	(2.71)
EPS - (reported) (SEK)	(1.34)	(1.95)	(3.27)	(2.71)
Dividend per share (SEK)	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	N/A	N/A
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	2,342	2,848	2,848	2,848
Intangible Assets	2,342	2,848	2,848	2,848
Tangible Assets	0	0	0	0
Investments	0	0	0	0
Current Assets	13,598	20,372	127,061	75,538
Stocks	0	0	0	0
Debtors	1,141	240	240	240
Cash	9,428	16,060	116,578	65,055
Other	3,029	4,071	10,243	10,243
Current Liabilities	(2,177)	(4,380)	(3,055)	(3,055)
Creditors	(2,177)	(4,380)	(3,055)	(3,055)
Short term borrowings	0	0	0	0
Long Term Liabilities	(505)	(596)	(613)	(613)
Long term borrowings	0	0	0	0
Other long term liabilities	(505)	(596)	(613)	(613)
Net Assets	13,258	18,245	126,241	74,718
CASH FLOW				
Operating Cash Flow	(13,853)	(17,097)	(62,479)	(60,000)
Net Interest	(6)	(64)	382	577
Tax	1,945	2,229	7,900	7,900
Capex	0	0	0	0
Acquisitions/disposals	0	0	0	0
Financing	1,182	21,756	154,714	0
Other	(241)	(191)	0	0
Dividends	0	0	0	0
Net Cash Flow	(10,973)	6,632	100,517	(51,523)
Opening net debt/(cash)	(20,401)	(9,428)	(16,060)	(116,578)
HP finance leases initiated	0	0	0	0
Other	0	(0)	0	0
Closing net debt/(cash)	(9,428)	(16,060)	(116,578)	(65,055)

Source: RhoVac accounts, Edison Investment Research

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