hardman&co

Pharmaceuticals & Biotechnology

Source: Eikon Thomson Reuters

Market data	
EPIC/TKR	**AVCT**
Price (p)	35.0
12m High (p)	83.3
12m Low (p)	27.0
Shares (m)	69.0
Mkt Cap (£m)	24.1
EV (£m)	8.3
Free Float*	60%
Market	AIM

**As defined by AIM Rule 26*

Description

Avacta is a pre-clinical stage biotechnology company developing biotherapeutics based on its proprietary Affimer protein technology. It benefits from near-term revenues from research and diagnostic reagents.

Company information	
CEO	Alastair Smith
CFO	Tony Gardiner
Chairman	Eliot Forster
	+44 1904 217 070
	www.avacta.com

Key shareholders	
Directors	6.1%
IP Group	24.8%
Lombard Odier	10.8%
Aviva	9.6%
Ruffer LLP	7.1%
JO Hambro	6.7%

Diary	
Oct-18	Finals
Jan-19	AGM
1H'19	PD-L1/LAG-3 drug candidate selection

Analysts

Martin Hall 020 7194 7632
mh@hardmanandco.com
Dorothea Hill 020 7194 7626
dmh@hardmanandco.com
Grégoire Pavé 020 7194 7628
gp@hardmanandco.com

Avacta

Ground-breaking new drug conjugate platform

Avacta (AVCT) is a pre-clinical biotechnology company and the proprietary owner of Affimer technology. Affimers represent a radical alternative to the established antibody technology, which continues to dominate the drug industry, despite its limitations. The significant technical and commercial benefits of Affimers are being recognised increasingly through corporate and academic interest, on-going evaluations, and deal flow. A co-development partnership has been signed with Bach Biosciences (Tufts) for development of a new type of Affimer-drug conjugate (AfDC), that is already attracting attention from large pharma companies.

- **Strategy**: AVCT is aiming to commercialise its Affimer technology through licensing for research and diagnostics, and by identifying and developing its own proprietary therapeutic pipeline for partnering. AVCT has sufficient cash resources to identify an Affimer lead to be ready for first-in-man trials in 2020.

- **Major co-development partnership:** AVCT and Bach Biosciences (Boston, MA) have agreed a co-development partnership to advance a new class of Affimer-drug conjugate, that combines technologies from both parties. The first example of such therapeutic will combine Affimer PD-L1 blockade and I-DASH inhibitors.

- **New class of therapeutics:** Unlike traditional antibody-drug conjugates (ADCs), the mechanism of this ground-breaking new approach is to be effective at the tumour micro-environment. It has a dual and synergistic effect, with checkpoint blockade and enhancement of the immune response at the tumour site.

- **Risks:** Affimers represent a new disruptive technology and the potential customer base might take time to recognise their advantages. While all new drug development carries a high risk, Avacta has hit a number of important milestones over the last two years which have reduced the risk profile greatly.

- **Investment summary:** AVCT has made considerable progress towards its goal of having its own proprietary Affimer-based drugs and growing a separate profitable reagents business. The company has identified potential therapeutic leads and completed both *in-vitro* and *in-vivo* pharmacokinetic pre-clinical, efficacy tests. The rising number of collaborating deals being signed is a clear sign of the value of the technology the market does not seem to recognise yet.

Financial summary and valuation

Year-end July (£m)	2015	2016	2017	2018E	2019E	2020E
Sales	1.81	2.17	2.74	3.00	3.50	5.40
R&D spend	-0.03	-1.50	-2.60	-3.25	-4.50	-5.50
EBITDA	-2.28	-4.79	-6.66	-7.95	-9.30	-9.20
Underlying EBIT	-2.85	-5.39	-7.60	-9.02	-10.37	-10.27
Reported EBIT	-5.51	-5.66	-7.98	-9.44	-10.84	-10.78
Underlying PBT	-2.83	-5.29	-7.51	-8.98	-10.37	-10.32
Statutory PBT	-5.48	-5.57	-7.89	-9.40	-10.84	-10.84
Underlying EPS (p)	-4.38	-6.46	-8.75	-11.55	-12.92	-12.48
Statutory EPS (p)	-9.72	-6.86	-9.31	-12.17	-13.59	-13.23
Net (debt)/cash	7.33	19.52	13.17	4.50	-5.98	-16.01
Capital increases	0.02	21.05	0.01	0.06	0.00	0.00
EV/sales (x)	19.3	16.2	12.8	11.7	10.0	6.5

Source: Hardman & Co Life Sciences Research

A new class of therapeutic

A co-development partnership has been signed with Boston-based biotech group Bach Biosciences, to develop a new type of therapeutic...

Avacta recently announced a co-development and risk-sharing partnership with Bach Biosciences, a company that commercialises research from the Chemical and Molecular Biology Group at Tufts University School of Medicine, Boston. This partnership will develop a new type of therapeutic Affimer-drug conjugate (AfDC) that combines the selective PD-L1 Affimer checkpoint inhibitor (CPI) discovered by AVCT with an inhibitor of the I-DASH (pan-**d**ipeptidyl peptidase IV **a**ctivity and/or **s**tructural **h**omologs) family of enzymes. What it is new here is not the AfDC molecule itself, but the specific mechanism of action of the combination (see below), representing a new class of therapeutic. This partnership was originated by Avacta's new US Business development office in Boston. The advantages conferred by the Affimer technology platform compared with antibodies were the key attraction for the Tufts laboratory to collaborate with AVCT, together with the potential for a broad patent position. Avacta already has a collaboration with Glythera for the development of conventional drug conjugates using Affimers, which has provided a solid foundation from which to conclude this new co-development partnership.

Novel Affimer drug conjugate

... that combines the Affimer platform with a cytotoxic drug to generate a synergistic effect

In this co-development partnership, each party will bring their proprietary technologies to the collaboration, with the aim of producing new drugs with improved clinical outcomes. The molecule, which could be considered as a targeted pro-drug as it is inactive until it encounters specific enzymes within the tumour environment, consists of three parts:

- **An Affimer inhibitor** that targets immune checkpoint on the tumour cell. This has the dual role of targeting the cytotoxin to the tumour to improve safety, and also inhibiting the immune checkpoint to allow the immune system to attack the tumour more efficiently.
- **A linker selectively cleavable** by an enzyme over-expressed in the tumour microenvironment. The linker has been developed at the Tufts laboratory.
- **A small molecule cytotoxin,** which kills cells in the tumour micro-environment causing an inflammatory response that recruits the immune system to attack the tumour. This attack is enhanced by the fact that the Affimer has a synergistic immune system effect.

The first product to come from the agreement will combine the PD-L1 Affimer with the I-DASH immune system stimulator

The PD-L1/I-DASH AfDC represents the first example of this new class of compound. Inhibiting PD-L1 alone is known to lead to a modest overall response rate in patients. The addition of the cytotoxic I-DASH compound causes a powerful recruitment of the immune system to the tumour that can then work synergistically with the PD-L1 blockade of the Affimer. The I-DASH inhibitor kills macrophages in the tumour causing:

- Potent priming of tumour antigen-specific CD8+ T-cell responses.
- Enhanced trafficking of key effector immunocytes to the tumour.
- Increased levels of dendritic cells, responsible for presenting antigens to the T-cells.
- Activated natural killer (NK) cells, a type of lymphocyte and a component innate immune response that plays an important role in the host-rejection of tumours and viral infected cells.
- Accelerated expansion of tumour-specific T-cells.

As for the traditional type of antibody-drug conjugates (ADCs), the key and crucial point is the nature of the linker. Many ADCs have failed to enter the clinic or failed in the clinic due to the instability of the linker in the body and/or an unreliable drug-to-antibody ratio (DAR).

New mode of action

Unlike traditional ADCs, this new therapeutic does not need to be internalised to exhibit its anti-tumour activity

Unlike the traditional ADCs currently available commercially or in development, which must become internalised within individual tumour cells in order for the cytotoxin to be released and to have an effect. The aim of the new AfDC is not to be internalised but to work at the tumour micro-environment, where the linker is cleaved by specific enzymes overexpressed at the tumour site, thereby releasing the toxic I-DASH warhead. Therefore, the AfDC will have a novel dual and synergistic mode of action in a single molecule.

The synergistic effect aims to enhance the effect of the PD-L1 inhibitor at the tumour micro-environment

Despite having a different mechanism of action compared with ADCs, the new AfDC will have the same effect in reducing systemic exposure to the toxic drug, with the Affimer component directing the combination right where it is needed at the tumour site, to exhibit its cytotoxic effect. That will potentially generate a greater therapeutic window for the I-DASH inhibitor, with fewer side effects and lower systemic toxicity.

Bach's I-DASH inhibitor

Bach Biosciences commercialises the research of William Bachovchin, at the School of Medicine in Boston. The I-DASH small molecule inhibitor is an inducer of the innate immune response. It has extensive clinical data having been into Phase III trials. The inhibitor selectively targets tumour-associated macrophages causing major inflammatory events that stimulate the patient's immune system to specifically recognise and attack the tumour. *In-vivo* studies showed that the I-DASH inhibitor possessed potent anti-tumour activity in colorectal and rhabdomyosarcoma mouse models, which was even greater when combined with a cancer immunotherapy. Clinical trials showed the I-DASH inhibitor to be highly potent with a dose limiting toxicity common to many of these types of cytotoxin. The targeting of the I-DASH inhibitor using PD-L1, and the selective cleavage of the toxin only within the tumour will improve the safety profile of the drug when incorporated into the AfDC.

Patent position

A broad patent encompassing the platform has been filed already...

Broad patent protection has been filed jointly with Tufts to protect the whole concept that, together, could be considered as a platform technology. The patent application covers a broad range of checkpoint receptors that are upregulated in tumours, linkers that are cleaved by a range of enzymes that are also upregulated in the tumour micro-environment and a range of cytotoxins that causes a major inflammatory event stimulating the patient's immune system. This would be a highly valuable patent if granted, covering the broad concept of a dual mode of action, immune active drug conjugate, however it is implemented.

Next steps and conclusion

... and Avacta having the exclusive right to commercialise

Avacta has discussed the concept already with its pharma industry contacts to evaluate the appetite for the new approach and for future licensing. From the clear interest shown in these discussions for this novel drug conjugate platform, AVCT has confidence that a licensing deal can be secured for specific targets at the pre-clinical stage, when it has animal data, which should be in 2019. Avacta has the exclusive rights to commercialise these novel drug conjugates. Together with the PD-L1/LAG-3 bi-specific Affimer project, which Avacta should take into the clinic in 2020, this AfDC programme represents AVCT's second major drug development programme.

Disclaimer

Hardman & Co provides professional independent research services. Whilst every reasonable effort has been made to ensure that the information in the research is correct, this cannot be guaranteed.

The research reflects the objective views of the analysts named on the front page. However, the companies or funds covered in this research may pay us a fee, commission or other remuneration in order for this research to be made available. A full list of companies or funds that have paid us for coverage within the past 12 months can be viewed at http://www.hardmanandco.com/

Hardman & Co has a personal dealing policy which debars staff and consultants from dealing in shares, bonds or other related instruments of companies which pay Hardman for any services, including research. They may be allowed to hold such securities if they were owned prior to joining Hardman or if they were held before the company appointed Hardman. In such cases sales will only be allowed in limited circumstances, generally in the two weeks following publication of figures.

Hardman & Co does not buy or sell shares, either for its own account or for other parties and neither does it undertake investment business. We may provide investment banking services to corporate clients.

Hardman & Co does not make recommendations. Accordingly, we do not publish records of our past recommendations. Where a Fair Value price is given in a research note this is the theoretical result of a study of a range of possible outcomes, and not a forecast of a likely share price. Hardman & Co may publish further notes on these securities/companies but has no scheduled commitment and may cease to follow these securities/companies without notice.

Nothing in this report should be construed as an offer, or the solicitation of an offer, to buy or sell securities by us.

This information is not tailored to your individual situation and the investment(s) covered may not be suitable for you. You should not make any investment decision without consulting a fully qualified financial adviser.

Hardman Research Ltd, trading as Hardman & Co, is an appointed representative of Capital Markets Strategy Ltd and is authorised and regulated by the Financial Conduct Authority (FCA) under registration number 600843. Hardman Research Ltd is registered at Companies House with number 8256259. However, the information in this research report is not FCA regulated because it does not constitute investment advice (as defined in the Financial Services and Markets Act 2000) and is provided for general information only.

Hardman & Co Research Limited (trading as Hardman & Co)
35 New Broad Street
London
EC2M 1NH

+44 (0) 20 7194 7622
Follow us on Twitter @HardmanandCo

(Disclaimer Version 4 – Effective from January 2018)

Status of Hardman & Co's research under MiFID II

Some professional investors, who are subject to the new MiFID II rules from 3rd January, may be unclear about the status of Hardman research and, specifically, whether it can be accepted without a commercial arrangement. Hardman's company research is paid for by the companies about which we write and, as such, falls within the scope of 'minor non-monetary benefits', as defined in the Markets in Financial Instruments Directive II.

In particular, Article 12(3) of the Directive states: 'The following benefits shall qualify as acceptable minor non-monetary benefits only if they are' (b) 'written material from a third party that is commissioned and paid for by an[sic] corporate issuer or potential issuer to promote a new issuance by the company, or where the third party firm is contractually engaged and paid by the issuer to produce such material on an ongoing basis, provided that the relationship is clearly disclosed in the material and that the material is made available at the same time to any investment firms wishing to receive it or to the general public;'

The fact that we are commissioned to write the research is disclosed in the disclaimer, and the research is widely available.

The full detail is on page 26 of the full directive, which can be accessed here: http://ec.europa.eu/finance/docs/level-2-measures/mifid-delegated-regulation-2016-2031.pdf

In addition, it should be noted that MiFID II's main aim is to ensure transparency in the relationship between fund managers and brokers/suppliers, and eliminate what is termed 'inducement', whereby free research is provided to fund managers to encourage them to deal with the broker. Hardman is not inducing the reader of our research to trade through us, since we do not deal in any security.

Hardman & Co

35 New Broad Street
London
EC2M 1NH

Tel: +44(0)20 7194 7622

www.hardmanandco.com