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Avacta

Affimer Drug Conjugates a reality

Avacta is the proprietary owner of Affimer technology for the development of bio-therapeutics, diagnostic tests and research reagents. Affimers represent a radical alternative to established antibody technology which dominates the drug industry. Avacta has made considerable progress towards its strategic goal to be ready to enter first-in-man Affimer trials by the end of 2019. In addition, Avacta is using external collaborations to expand the opportunities for its Affimer technology. A proof-of-concept study combining its Affimer technology with Glythera's Permalink chemistry to generate Affimer Drug Conjugates has concluded successfully.

- **Strategy:** To commercialise its Affimer technology through a combination of bespoke research tools, collaborative deals and by identifying and developing its own proprietary therapeutic Affimer leads. Avacta has sufficient cash resources to identify an Affimer lead to be ready for first-in-man in 2019.

- **Affimer Drug Conjugates (AfDC):** Drug conjugation is an approach to get cytotoxic drugs targeted directly at cancer cells. In July 2016, Avacta tied-up with Glythera to combine the advantages of Affimers with Glythera's chemistry to develop AfDC in an attempt to overcome these problems.

- **Proof-of-concept study:** This study has demonstrated that Avacta's Affimer technology can be combines successfully with Glythera's Permalink chemistry to generate AfDC that not only eliminate the well documented disadvantages of ADC, but also to generate a technically superior drug conjugate platform.

- **Licensing deal:** As a consequence of the study outcome, Avacta and Glythera have signed a licensing deal for the further development of their respective proprietary technologies to generate a clinic-ready AfDC drug. Avacta would receive milestones and royalties on the sales of any regulatory approved drug.

- **Investment summary:** Avacta has made considerable progress towards its goal of having its own proprietary Affimer-based drugs and growing a profitable reagents business. By itself, AVCT has identified potential leads and completed both *in vitro* and *in vivo* pharmacokinetic pre-clinical tests, efficacy and immunogenicity tests. The Glythera collaboration provides another platform on which Avacta could generate long-term returns for shareholders.

Financial summary and valuation

Year end July (£m)	2015	2016	2017	2018E	2019E	2020E
Sales	1.81	2.17	2.74	3.25	3.70	5.60
R&D spend	-0.03	-0.86	-1.95	-3.80	-4.30	-4.50
EBITDA	-2.28	-4.15	-6.01	-7.97	-8.42	-9.40
Underlying EBIT	-2.85	-4.75	-6.94	-8.91	-9.35	-10.33
Reported EBIT	-5.57	-5.66	-7.33	-10.13	-10.77	-11.84
Underlying PBT	-2.83	-4.65	-6.86	-8.86	-9.35	-10.38
Statutory PBT	-5.54	-5.57	-7.24	-10.09	-10.77	-11.89
Underlying EPS (p)	-4.38	-5.51	-7.79	-10.71	-11.09	-12.57
Statutory EPS (p)	-9.84	-6.86	-8.36	-12.50	-13.16	-14.78
Net (debt)/cash	7.33	19.52	13.17	4.05	-5.51	-15.96
Capital increase	0.02	21.05	0.01	0.00	0.00	0.00
EV/sales (x)	36.1	30.3	23.9	20.2	17.7	11.7

Source: Hardman & Co Life Sciences Research

Pharmaceuticals & Biotechnology

Source: Eikon Thomson Reuters

Market data

EPIC/TKR	AVCT
Price (p)	65.5
12m High (p)	98.2
12m Low (p)	60.0
Shares (m)	69.0
Mkt Cap (£m)	45.2
EV (£m)	32.0
Free Float*	59%
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	Trevor Nicholls
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	www.avacta.com

Key shareholders

Directors	4.2%
IP Group	24.8%
Lombard Odier	11.5%
Aviva	9.8%
Baillie Gifford	6.6%
Ruffer LLP	7.1%

Diary

18 Jan	AGM
7 Feb	Capital Markets day
Apr-18	Interims
1H-18	Sloan Kettering feasibility

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Glossary

ADC	Antibody Drug Conjugates
AfDC	Affimer Drug Conjugates
AML	Acute Myeloid Leukemia
COGS	Cost of Goods Sold
DMF	Dimethyformamide
DMSO	Dimethyl sulfoxide
mAb	Monoclonal antibody
NHL	Non-Hodgkin's Lymphoma

Affimer Drug Conjugates

Glythera collaboration

On 14th July 2016, Avacta and Glythera announced a collaborative agreement for the development of a new potential class of bio-therapeutics: Affimer Drug Conjugates (AfDC). Each party was to contribute its proprietary technology – Glythera's PermaLink conjugation chemistry plus Avacta's engineered Affimer protein scaffolds – to the collaboration, with the aim of producing new drugs with improved clinical outcomes.

Under the terms of the agreement, both companies aimed to investigate the rationale, and to undertake proof-of-concept studies, in order to demonstrate the technical and commercial benefits of this combination over traditional antibody drug conjugates (ADCs). Ultimately, the aim was for Avacta and Glythera to provide clients with AfDC development services, know-how and licensing opportunities from this new service platform in return for milestones and long-term royalties from a successful drug commercialisation.

Avacta and Glythera have now announced that the initial proof-of-concept studies have been concluded successfully. Consequently, the two companies have signed a licensing agreement allowing them to develop drug conjugates combining their respective proprietary technologies. This is the first step in paving the way for Avacta and Glythera to gain an entry into the drug conjugates market that is estimated to be worth ca.$15bn in 2030[1].

Feasibility study outcomes

- Affimers can be conjugated successfully to a cytotoxic payload using Glythera's Permalink technology.
- Affimers show good stability in commonly used organic solvents (up to 30% DMSO or DMF) which makes the conjugation process easier – cytotoxins used in ADC are generally very hydrophobic and antibodies are not stable in such high solvent concentrations.
- Affimer conjugates remain functional as demonstrated in immunoassays with the target.

Antibody drug conjugates (ADC)

Chemotherapy is an important component of most cancer treatment regimens and within this broad category, cytotoxic drugs, which kill cells by preventing them from dividing, play a key role. However, by their very nature, they are limited by a narrow therapeutic window before serious toxic effects are seen and by their lack of specificity. Hence the concept of antibody-drug conjugates (ADC) arose, which combines the specific cancer killing ability of cytotoxic drugs with unique targeting capabilities of monoclonal antibodies (mAb) for cancerous cells.

- Increased differentiation between healthy and diseased cells.
- Specific targeting of cancerous cells with cytotoxic drugs.
- Greatly improved therapeutic window – lower starting dose needed to produce therapeutic effect and higher maximum dose tolerated.

[1] Antibody Drug Conjugates Market (4th Edition) 2017-2030 Roots Analysis

- The toxic component of the ADC is effectively hidden while circulating in the blood system.
- Toxic payload is only released after the antibody is bound to the target cancer cells and internalised.

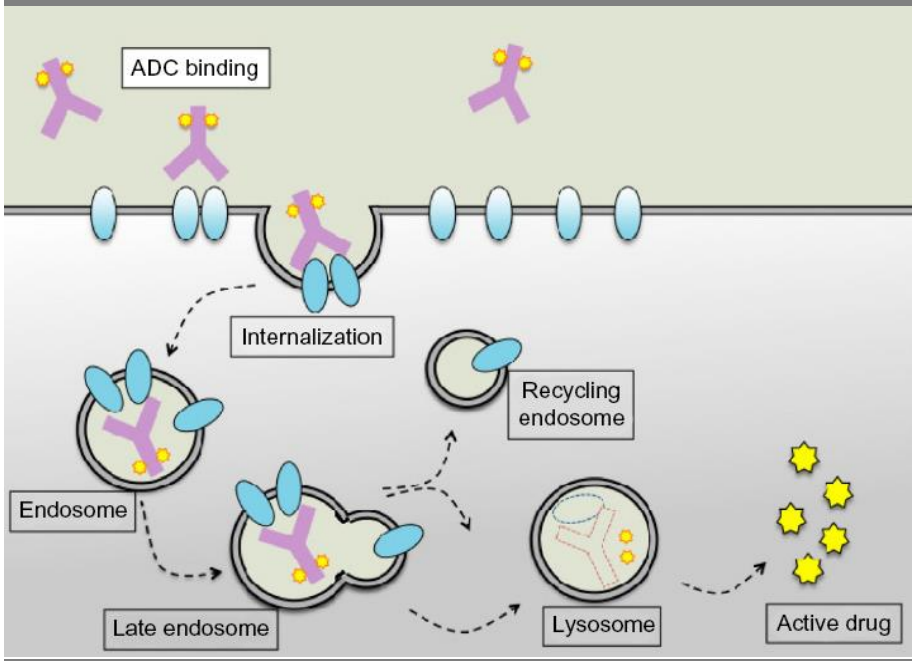
However, while the theoretical application of ADC is sound, the clinical application has been associated with a number of problems. The main issue is the limited stability of ADC where the bond between the antibody and the cytotoxic is severed too soon – e.g. in the bloodstream – causing a systemic dose of toxin which could be fatal. This caused an initial decline in interest in ADC.

To date, only four ADC-based drugs been approved for commercialisation – Mylotarg (Pfizer), Adcentris (Seattle Genetics), Kadcyla (Roche) and Bespona (Pfizer). The recent approval of Bespona (August 2017) and re-approval of Mylotarg (September 2017) has reignited this area of drug development. There are thought to be about 200 putative drugs at different stages of development, of which an ca.75 molecules are in different stages of clinical development with a variety of cytotoxic drugs for multiple indications, including breast cancer, non-Hodgkin's lymphoma (NHL), acute myeloid leukemia (AML) and multiple myeloma.

Affimer Drug Conjugates (AfDC)

Affimers have a number of well-known advantages over antibodies, being relatively small (ca. 10% of an antibody), highly stable engineered proteins with high affinity binding surfaces. During the recombinant engineering development process, these non-antibody scaffold proteins have become stable, non-toxic and biologically neutral. Avacta and Glythera have been working together to determine whether AfDC could not only eliminate the problems seen with commercialised products that were described above, but also to provide some advantages over ADC.

ADC/AfDC – mechanism of action



Source: Scotti et al[2]

[2] Scotti et al, Antibody Technology Journal, 2015:5 1–13

Glythera

Glythera is a biotechnology company based in Newcastle that specialises in the application of its advanced proprietary linker and stable glycan technologies for the development of next generation biotherapeutics. Glythera has developed two proprietary linker platforms – PermaLink® and PermaCarb®– that have the potential to enhance and strengthen pharmaceutical drug candidates. It is Glythera's PermaLink conjugation chemistry that is particularly attractive to Avacta.

PermaLink®

PermaLink chemistry targets the less abundant cysteine residues of a protein and is a controlled, stable conjugation platform composed of a portfolio of linker designs. PermaLink can be employed for the selective and stable functionalisation and conjugation of various payloads to proteins and peptides.

This technology can be used in the development of:

- Antibody or Affimer Drug Conjugates – to improve stability
- Conjugate vaccines – to enhance antigen presentation bringing a longer immune response
- PEGylation – to enhance bioavailability and efficacy of biotherapeutics

Currently, in an ADC, the chemical bond (ligation) between the targeting antibody and the cytotoxic drug is quite labile (prone to change) and therefore, unstable, allowing the toxin to break off the chemical complex before it should. If this happens in the bloodstream, the ADC is converted from a safe drug to something that is potentially toxic. Glythera has demonstrated that PermaLink provides a very strong bond between the targeting protein and the cytotoxic agent. In the AfDC, the benefits of this linker stability are combined with the benefits of Affimers (small size, stability, specificity, controllable serum residence time) to create a potentially best-in-class drug conjugate platform.

Potential advantages

In the proof-of-concept study, Avacta and Glythera believe that the combination of Affimer technology with Permalink conjugation chemistry will provide a technically superior drug conjugate platform with shorter development times, simpler, more consistent production and greater chemical stability. This has the potential to generate a more effective medicine with fewer toxic side effects.

Cytotoxic drugs are usually insoluble in water and have to be dissolved in organic solvents such as dimethyl sulfoxide (DMSO) and dimethylformamide (DMF). However, high concentrations of these commonly used solvents are detrimental to antibodies. Therefore, concentrations of DMSO up 10% only can be used when manufacturing an ADC, which limits the solubility of the cytotoxic drug. In contrast, Affimers are much more stable than antibodies and were shown in this study to tolerate solvent concentrations up to 30% which, in turn, would significantly increase the solubility of the cytotoxic agent.

Another limiting factor seen with ADC technology is the potential for systemic exposure to the cytotoxic drug that increases the possibility of non-targeted toxic effects on healthy cells. With Affimers, the shorter half-life associates with their small size, greatly reduces the systemic exposure. This can be modulated during the structure optimisation programme, thereby modifying the therapeutic window.

Size of antibodies is a limiting factor regarding tissue penetration. By using much smaller Affimer technology, the AfDC is likely to be able to penetrate the tumour far more readily and to a much deeper level.

Potential advantages of AfDC

Advantages	Comment
PermaLink improves stability of the linker	Most ADC utilise maleimide as the linker, reputedly unstable in serum due to de-conjugation of drug from the antibody and its subsequent cross-conjugation to the free-thiol groups of circulating albumin Almost non-labile preventing early release of cytotoxic drug before it reaches the target cancer cells, potentially causing severe toxicities
Size of the Affimer	Small size of the complex allows a better penetration into tissues and the cell/tumour The small size also brings greater stability The small protein means that the half-life of the conjugate is short – no two week systemic exposure as seen with mAb – and can be fine-tuned from an hour to a few days. If the AfDC doesn't hit its target, the therapeutic window can be tailored to limit toxicity
Lower heterogeneity	The small size of the Affimer allows a more controlled Affimer-Drug Ratio – position and number of toxins in the payload
Better solubility	Affimers can tolerate concentrations of DMSO or DMF of up to 30% compared to antibodies which can only withstand up to 10% Higher solubility of toxin improves large-scale manufacturing efficiency, with potential for reduced COGS
Low cost	Cost of production of Affimers is lower compared to antibodies
Shorter development time	About 14 weeks to generate the Affimer lead molecules

Source: Hardman & Co Life Sciences Research

Next steps

The fact that Avacta and Glythera have signed a licensing agreement that will allow them to develop drug conjugates that combine their respective proprietary technologies demonstrates a clear belief that AfDC not only have the potential to eliminate the disadvantages of ADC, but also to provide some added benefits. The next step will be to develop an AfDC with a cytotoxic to a point where it could be taken into the clinic.

Back in April 2017, Avacta undertook independent immunogenicity testing on three Affimer constructs to ascertain if they trigger an unwanted immune response. All of the constructs tested were shown to produce low to no immunogenicity, with results similar to those generated by the marketed antibody drug Avastin. Therefore, the data demonstrated that there were no immunogenicity issues with the Affimer technology platform, providing reassurance on the Affimer platform as a therapeutic tool.

Both sets of data tick an important box with respect to major pharma/biotech looking to licence the Affimer technology platform, and further de-risk Avacta's therapeutic programme.

Forecast summary

No changes to our forecasts. Full financial tables were last published on 16th October 2017 in our report entitled: '*R&D accelerated to advance assets*', and available on our website:

http://www.hardmanandco.com/docs/default-source/company-docs/avacta-documents/16.10.17-r-d-accelerated-to-advance-assets.pdf

Profit & Loss account						
Year end July (£m)	**2015**	**2016**	**2017**	**2018E**	**2019E**	**2020E**
Profit & Loss:						
Sales	1.81	2.17	2.74	3.25	3.70	5.60
COGS	-0.53	-0.90	-0.94	-1.05	-1.15	-1.35
SG&A	-4.11	-5.16	-6.79	-7.31	-7.60	-10.09
R&D	-0.03	-0.86	-1.95	-3.80	-4.30	-4.50
Other income	0.00	0.00	0.00	0.00	0.00	0.00
Underlying EBIT	**-2.85**	**-4.75**	**-6.94**	**-8.91**	**-9.35**	**-10.33**
Share based costs	-0.25	-0.27	-0.39	-0.42	-0.47	-0.51
Statutory EBIT	-5.57	-5.66	-7.33	-10.13	-10.77	-11.84
Net financials	0.03	0.10	0.09	0.04	0.00	-0.05
U/L Pre-tax profit	**-2.83**	**-4.65**	**-6.86**	**-8.86**	**-9.35**	**-10.38**
Tax payable/credit	0.65	0.92	1.53	1.54	1.76	1.76
Underlying net income	-0.12	-0.16	-0.21	-0.15	-0.16	-0.15
Underlying Basic EPS (p)	**-4.38**	**-5.51**	**-7.79**	**-10.71**	**-11.09**	**-12.57**
Statutory Basic EPS (p)	-9.84	-6.86	-8.36	-12.50	-13.16	-14.78
Balance sheet:						
Share capital	5.06	6.92	6.92	6.92	6.92	6.92
Reserves	14.08	28.94	22.97	14.42	5.41	-4.72
Debt	0.00	0.00	0.00	0.00	0.00	0.00
less: Cash	7.33	19.52	13.17	4.05	-5.51	-15.96
Invested capital	**12.67**	**16.68**	**17.06**	**17.63**	**18.17**	**18.49**
Net cash/(debt)	7.33	19.52	13.17	4.05	-5.51	-15.96
Cashflow:						
Underlying EBIT	-2.85	-4.75	-6.94	-8.91	-9.35	-10.33
Change in working capital	-0.17	-0.31	0.04	-0.26	-0.35	-0.62
Tax & interest	0.03	0.67	1.83	1.24	1.53	1.71
Operational cashflow	**-2.52**	**-4.23**	**-4.24**	**-6.96**	**-7.21**	**-8.20**
Capital expenditure	-0.81	-2.86	-0.66	-0.55	-0.65	-0.75
Capitalised R&D	-3.06	-1.76	-1.47	-1.60	-1.70	-1.50
Free cashflow	**-6.38**	**-8.86**	**-6.37**	**-9.12**	**-9.56**	**-10.45**
Capital increases	0.02	21.05	0.01	0.00	0.00	0.00
Change in net debt	**-4.15**	**12.19**	**-6.36**	**-9.12**	**-9.56**	**-10.45**

Source: Hardman & Co Life Sciences Research

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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

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