

**Market data**

EPIC/TKR	AVCT
Price (p)	66.0
12m High (p)	123.0
12m Low (p)	65.0
Shares (m)	68.4
Mkt Cap (£m)	45.2
EV (£m)	29.7
Free Float*	57%
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 which benefits from near-term revenues from research and diagnostic reagents

Company information

CEO	Alastair Smith
CFO	Tony Gardiner
Chairman	Trevor Nicholls
	+44 1904 217 046
	www.avacta.com

Key shareholders

Directors	4.2%
IP Group	24.8%
Henderson	11.8%
Aviva	9.7%
Baillie Gifford	7.2%
Ruffer LLP	7.1%

Next event

3 April	Interims
Oct-17	Finals
Jan-18	AGM

Analysts

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Avacta**Low response would be positive!**

Avacta is the proprietary owner of Affimer technology for the development of biotherapeutics, diagnostic tests and research reagents. Affimers represent a radical alternative to established antibody technology which dominates the drug industry despite its limitations. During 2016, Avacta made considerable progress towards its strategic goal to have a first-in-man Affimer therapeutic by the end of 2019. During coming weeks the company is expected to report on the next step in the pre-clinical development process: whether or not Affimer scaffolds are immunogenic. A positive outcome would be a low immune response rate.

- **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. The company has sufficient cash resource to identify an Affimer lead through to IND submission (end fiscal 2018).
- **Immunogenicity:** This describes the ability of biotherapeutic agents, considered as foreign by the body, to provoke an immune response. While this is desirable with some drugs (e.g. vaccines), in the case of antibodies and Affimers, immunogenicity is an unwanted event that might affect patient safety.
- **What to look for:** Avacta is using the services of a specialist organisation, ImmunXperts, to run a number of Affimer scaffolds through its well-recognised test for immunogenicity acceptable to the drug regulators. The hope is that Avacta's Affimer scaffolds generate only a small response compared to controls.
- **Relevance:** Such is the importance of immunogenicity, the FDA has published industry guidance (August 2014) on the subject. Unwanted immune responses might neutralise the drug effect; or induce serious side effects such as anaphylactic shock. Therefore, early elimination of immunological issues is essential.
- **Investment summary:** Avacta has made considerable progress towards its goal of having its own proprietary Affimer-based drugs. In just 18 months, it has identified potential leads and completed *in vitro* and *in vivo* pharmacokinetic pre-clinical tests. The next step is to prove lack of immunogenicity before selecting its immuno-oncology lead candidate and filing an Investigational New Drug (IND) in 2018, as a prelude to beginning clinical testing in 2019.

Financial summary and valuation

Year end July (£m)	2014	2015	2016	2017E	2018E	2019E
Sales	3.18	1.81	2.17	3.00	3.40	3.80
EBITDA	-1.33	-2.34	-4.59	-6.20	-6.68	-7.26
Underlying EBIT	-1.86	-2.91	-5.39	-7.50	-8.03	-8.66
Reported EBIT	-2.07	-5.57	-5.66	-7.80	-8.36	-9.03
Underlying PBT	-1.83	-2.89	-5.29	-7.43	-7.99	-8.67
Statutory PBT	-2.04	-5.54	-5.57	-7.72	-8.32	-9.04
Underlying EPS (p)	-3.07	-4.50	-6.46	-9.59	-10.24	-11.05
Statutory EPS (p)	-3.57	-9.84	-6.86	-10.03	-10.72	-11.58
Net (debt)/cash	11.48	7.33	19.52	11.58	2.82	-6.61
Capital increases	14.54	0.02	21.05	0.00	0.00	0.00
P/E (x)	-	-	-	-	-	-
EV/sales (x)	-	-	-	-	-	-

Source: Hardman & Co Life Sciences Research

Affimers and immunogenicity

Introduction

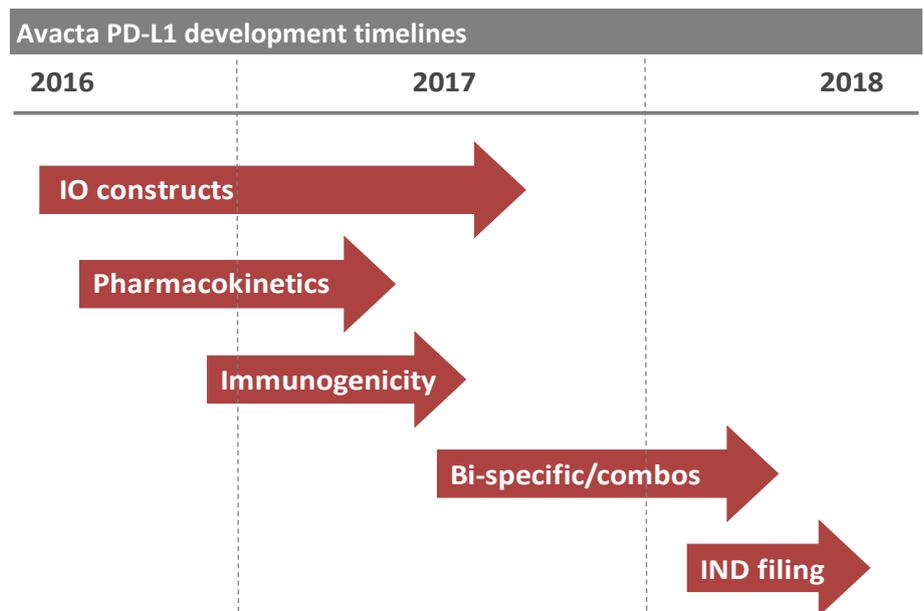
About 18 months ago, Avacta took the decision to embark upon a discovery programme to generate its own therapeutic Affimer leads, with the aim of developing them either by itself or in partnership, dependent on the therapy area, potentially moving much further up the value chain. Although it could foresee numerous opportunities, management decided to focus on areas of unmet medical need, where its Affimer technology has competitive advantages compared to antibodies in terms of formatting for bi-specifics, tissue penetration and speed of development, eg. in oncology. A key strategic objective for the company was to have a therapeutic drug candidate ready for early clinical trials as soon as possible, ideally within three years. Since that decision, enormous progress has been made in a relatively short timeframe in terms of drug development.

Enormous progress in 18 months towards a therapeutic Affimer...

...with goal to reach first-in-man trial by end of 2019

Progress to date

- ▶ Identification of a number of potential Affimer candidate leads that bind with high affinity to the Programmed Death Ligand 1' (PD-L1) checkpoint protein
- ▶ Successful manufacturing of multimeric Affimer constructs with high production yield, suggesting leads can be produced in commercial quantities
- ▶ Successful completion of *in vivo* pre-clinical pharmacokinetic studies showing that Avacta's PD-L1 Affimer inhibitors had good half-life in serum and were well tolerated at clinically relevant doses
- ▶ Early evidence of efficacy in a mouse model which showed that the PD-L1 Affimer lead produces a reduction in tumour growth indicating bioavailability and functionality



IO = immuno-oncology

Source: Adapted from Avacta by Hardman & Co Life Sciences Research

Next key milestone is immunogenicity testing

At the investor presentation given at the time of its AGM (21st January), management indicated that it was expecting to announce a key technical milestone towards the end 1Q 2017, with the publication of results from its pre-clinical immunogenicity assays of PD-L1 Affimer constructs.

Immunogenicity

Importance of immunogenicity testing highlighted by specific FDA guidelines on the subject

Given the large number of biotherapeutics and personalised medicines currently in development, immunogenicity represents an increasing concern for the drug regulators, such as EMA and FDA, that request evaluation of anti-drug antibodies (ADA). Measurement of the immunogenic effect of biotherapeutics is required by the regulatory bodies because these agents run the risk of being recognised as a foreign agent by a host immune system, and may increase the potential and the scale of any adverse event. Even if lack of immunogenicity is not a binding condition for approval, it can be detrimental, slow down the regulatory process and narrow the therapeutic population. In this regard, the FDA has published detailed industry guidance on the subject with a view to speeding up the process of measuring and assessing immunogenicity.

First ever results on whether Affimers cause immunogenicity

Importance to Avacta

It will be the first time that such results have been collected on the Affimer technology. A positive result (low immunogenic response) will bring confidence in the platform and generate increased external interest in the technology. In relation to Avacta’s biotherapeutic products, a positive outcome would add further to the positive characteristics of Affimers compared to antibodies.

Possible advantages of Affimers vs Antibodies		
Characteristic	Comment	Potential effect on immunogenicity*
Size	Affimers are 10 times smaller compare to antibodies	
Source	Affimers used as a therapeutic, derive from human source, the Stefin A protein	
Specificity	Highly and controllable specificity, easy to modulate	
Manufacturing process	Affimers easy to express, leading to higher purity products	

**when compared to an antibody
Source: Hardman & Co Life Sciences Research*

A low response would potentially confer another advantage of Affimers over antibodies

A low immunogenic response would provide further evidence of the superior potential of Affimers as a competitive therapeutic platform. Such data would also confer greater confidence in Avacta’s Affimer leads in the run-up to its first Phase I study, with a PD-L1 Affimer checkpoint inhibitor, targeted for 2019.

Background

Definition

Immunogenicity describes the ability of a biotherapeutic agent to be considered as foreign by the body, provoking an immune response. All protein drugs have the potential to trigger an immune response that could vary in intensity and also be specific for each patient. Some agents, such as vaccines, trigger a desired immunogenic response aimed at protecting the body against certain epitopes.

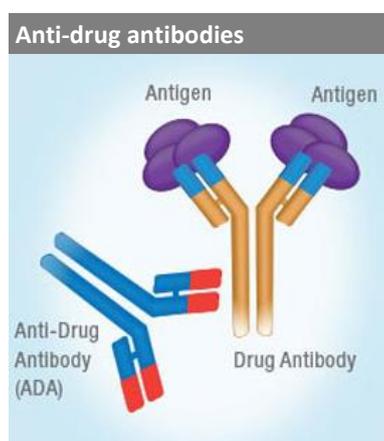
With vaccines, the aim is to elicit a strong response...

...whereas for Affimers the aim is for a low response

In the case of Affimers (and antibodies), a high immunogenicity is an unwanted event, which might affect patient safety, efficacy of the drug and its pharmacokinetics.

Consequences of immunogenicity	
On the drug	On the body
Drug neutralisation – Anti-drug antibody(ADA)	Anaphylactic shock: a serious and rapid allergic reaction
Abnormal biodistribution	Cytokine release syndrome
Enhanced clearance rate	Non-acute immune response
Alteration of the pharmacokinetic properties	Cross reaction with a critical autologous protein

Source: Hardman & Co Life Sciences Research



Source: abgent.com

The generation of ADAs is one of the major factors influencing the efficacy of a biopharmaceutical agent and is a potential outcome for almost all such therapeutics. Indeed, the human body sees the biotherapeutic as foreign and, as a result, it produces antibodies to fight against it. These can form immune complexes with the therapeutic which in turn can drive even more ADA formation.

Factors affecting immunogenicity

The clinical effects of patient immune responses are highly variable, ranging from no effect at all to extremely harmful effects on patient health. Detection and analysis of ADA formation is a helpful tool in understanding potential patient immune responses. Information on immune responses observed during clinical trials, particularly the incidence of ADA induction and the implications of ADA responses for therapeutic protein product safety and efficacy, is crucial for any therapeutic protein product development program. ADA could explain why an agent fails to demonstrate efficacy, or to lose its effectiveness over time despite a good initial response.

Factors influencing immunogenicity		
Biotherapeutic considerations	Comments	Incidence
-Structural and amino-acid sequence	Non-human or low degree of humanisation Humanised sequence	High Low
-Foreign protein	Used for enzyme replacement therapy	High
-Location of therapeutic target		High
-Mode of action	Immunomodulatory treatment, Check point inhibitors Immunosuppressive treatment	High Low
-Chemical modifications	Oxidation, deamination, isomerisation generating a new immunogenic specie	Varies
-Protein degradation	Generating a new immunogenic protein	High
-Aggregation	Protein aggregation augment a protein-specific immune response	High
-Impurity	From manufacturing process	High
-Size	Small proteins should in theory be less immunogenic	Varies
Patient considerations		
-Age	Paediatric vs adult immune system	Varies
-Genetic predisposition	Genetic defect	varies
-Disease status and chronicity	Autoimmune or proinflammatory predisposition	Varies
-Concomitant medications		Varies
-Life threatening disease	Immunogenicity vs. risk depending on alternative therapy available	Low
Treatment considerations		
-Route of administration	Risk highest: Inhalation>Subcutaneous>Intraperitoneal>Intramuscular>Intravenous	Varies
-Dose	Higher doses more likely to increase risk	Varies
-Frequency and duration of administration	Repeat dose and prolonged exposure may either break or lead to tolerance	Varies
-Other therapeutic programmes		Varies

Source: Adapted from Krishna M et al (2016) Immunogenicity to Biotherapeutics – The Role of Anti-drug Immune Complexes. Immunol. 7:21.

**Independence of data guaranteed
by out-sourcing to experts**

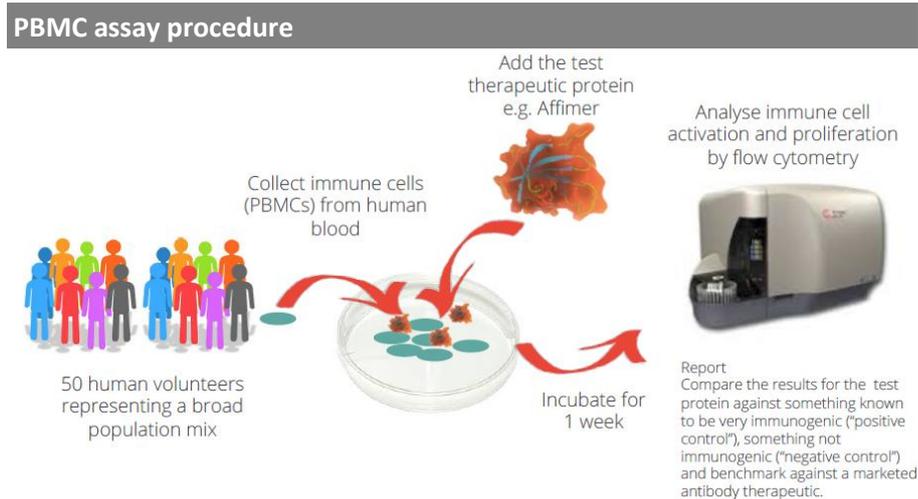
**ImmunXperts has a well
characterised test that uses 50
human donors**

Measurement of immunogenicity

Avacta is employing the service of ImmunXperts, an independent service partner that specialises in immunology assessment projects. Several approaches, such as *in silico* and *in vivo* screening, are used to measure immunogenic responses. The gold standard of immune cell assay used to estimate human immunogenicity is the *in vitro* "T-cell activation/proliferation assay using human peripheral blood mononuclear cells", or PBMC, assay, consisting of lymphocytes, monocytes and macrophages coming from human donors. PBMC are a critical component in the immune system that fight against infection and foreign bodies.

The PBMC test

This well validated test is described in the following graphic and consists of incubating the desired biotherapeutic agent with samples of PBMCs from 50 diverse human donors, meaning that each Affimer construct is tested against all 50 donors, individually, at high concentration. The volunteers are selected on the basis of their Human leukocyte antigen (HLA) type, in order to get a representative sample of the world population.



Source: Avacta

After a week of incubation, activation and proliferation, the immune cells are analysed by flow cytometry and compared to a standard agent, usually a marketed therapeutic with an extensive and well-documented immunogenicity profile.

Testing Affimers

Avacta has submitted a number of Affimer constructs for immunological assessment. A low immunogenicity score across all the Affimers would further validate the technology and provide a boost to future clinical trials. On the other hand, if a higher immunogenicity effect is observed, it would damage the development timelines. However, it would not be totally detrimental because the Affimer constructs can be re-engineered to remove the immunologic-causing element. Ultimately, regulatory bodies require that all biotherapeutics must go through immunogenicity assessment, meaning that each individual lead Affimer that goes into the clinic would have to be tested. Knowing that the core scaffold passes the test is a critical first step.

**Results will be for a number of
Affimer constructs...**

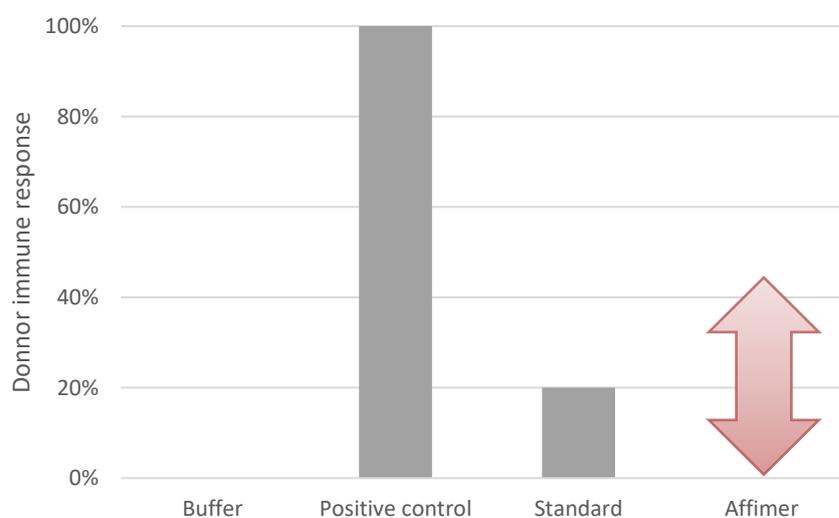
**...potentially providing further
validation of technology...**

**...and required by the regulators
before clinical trials begin**

Each Affimer is tested individually against a donor using the following test design:

- ▶ A negative control, consisting of the buffer that should not induce any immune response
- ▶ A positive control with high immunogenicity profile; in this case, keyhole limpet hemocyanin (KLH) protein
- ▶ Bevacizumab (Avastin, Roche) will be used as the standard. It is a well-documented marketed protein with a known and acceptable immunogenicity profile

PBMC potential result



Source: Hardman & Co Life Sciences Research

Immunogenicity of a biotherapeutic is hard to predict when it is inoculated into humans but this test will provide a first indication. The fact that Affimers are small, specific and coming from a human source could bring confidence in their immunogenic characteristics.

Conclusion

It is important to note that non-clinical immunogenicity data are not predictive, but are useful for risk assessment as to whether there is altered pharmacokinetic, efficacy data and immune-related adverse effects. A positive outcome will provide further evidence of the advantages of Affimer technology as a competitive therapeutic platform, which will be important when Avacta is looking for a development and commercial partner. This data will also boost confidence in Avacta's strategy to have a therapeutic PD-L1 Affimer checkpoint inhibitor entering clinical trials, currently targeted for 2019.

Avacta is hoping that Affimers produce only a small effect...

...that would boost confidence in its therapeutic Affimer strategy

Financial summary

- ▶ Full accounts were last published in our most recent report, 'Great strides towards strategic goals', dated 17th October 2016
- ▶ Interim results for fiscal 2017 are scheduled to be released to the market on Monday 3rd April
- ▶ R&D is rising to reflect all the activities to develop a pipeline of therapeutic Affimers, and to write this investment off through the P&L account in the year in which it is incurred
- ▶ At the end of July 2016, Avacta had net cash of £19.5m. Our forecasts suggest that the company will have net cash of £15.5m at the end of January 2017, reflecting a cash burn on -£4.0m in the first half of fiscal 2017

Summary of financial forecasts						
Year end July (£m)	2014	2015	2016	2017E	2018E	2019E
Profit & Loss:						
Sales	3.18	1.81	2.17	3.00	3.40	3.80
COGS	-1.14	-0.53	-0.90	-1.10	-1.12	-1.18
SG&A	-3.90	-4.17	-5.16	-6.90	-7.30	-7.78
R&D	0.00	-0.03	-1.50	-2.50	-3.00	-1.98
Other income	0.00	0.00	0.00	0.00	0.00	0.00
Underlying EBIT	-1.86	-2.91	-5.39	-7.50	-8.03	-8.66
Share based costs	-0.21	-0.25	-0.27	-0.30	-0.33	-0.36
Statutory EBIT	-2.07	-5.57	-5.66	-7.80	-8.36	-9.03
Net financials	0.02	0.03	0.10	0.08	0.04	-0.01
U/L Pre-tax profit	-1.83	-2.89	-5.29	-7.43	-7.99	-8.67
Tax payable/credit	0.55	0.65	0.92	0.87	0.98	1.10
Underlying net income	-0.27	-0.12	-0.16	-0.11	-0.12	-0.12
Underlying Basic EPS (p)	-3.07	-4.50	-6.46	-9.59	-10.24	-11.05
Statutory Basic EPS (p)	-3.57	-9.84	-6.86	-10.03	-10.72	-11.58
Balance sheet:						
Share capital	5.05	5.06	6.92	6.92	6.92	6.92
Reserves	23.79	14.08	28.94	22.09	14.75	6.81
Debt	0.00	0.00	0.00	0.00	0.00	0.00
less: Cash	11.48	7.33	19.52	11.58	2.82	-6.61
Invested capital	18.18	12.67	16.68	17.76	19.18	20.67
Net cash/(debt)	11.48	7.33	19.52	11.58	2.82	-6.61
Cashflow:						
Trading profit	-1.86	-2.91	-5.39	-7.50	-8.03	-8.66
Working capital	0.05	0.04	-0.33	-0.44	-0.33	-0.29
Tax & interest	0.44	0.03	0.67	1.50	0.91	0.97
Operational cashflow	-0.80	-2.52	-4.18	-5.14	-6.10	-6.58
Capital expenditure	-0.92	-0.81	-2.86	-0.94	-0.76	-0.87
Capitalised R&D	-1.86	-3.06	-1.81	-1.85	-1.90	-1.98
Free cashflow	-3.58	-6.38	-8.86	-7.94	-8.76	-9.43
Capital increases	14.54	0.02	21.05	0.00	0.00	0.00
Change in net debt	10.90	-4.15	12.19	-7.94	-8.76	-9.43

*Snapshot from our spreadsheet – Numbers do not necessarily add up in this abbreviated version
Source: Hardman & Co Life Sciences Research*

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