AVACTA GROUP LTD

THE INVESTMENT THESIS

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Ticker:	**AVCT.L**
Price (p):	**22.75**
Shares in issue (m):	**176.0**
Market cap. (£m):	**40.0**

Introduction

Avacta Group ('Avacta') is a biotechnology company listed on the London Stock Exchange's growth market, AIM. At the core of its business is a proprietary technology, the Affimer® platform. Affimers are derived from small human proteins and possess a number of excellent drug-like qualities. The Affimer platform is a therapeutic platform: it has the capacity to create a wide variety of drugs – some of which are entirely novel –that are based on Affimers, as opposed to the market standard, *antibodies*. Whilst Affimers could be used in a broad range of therapeutic modalities, Avacta is for now using the platform technology to focus its efforts on novel therapeutics in the area of *immuno-oncology* (or 'IO'), which is the use of *immunotherapy* in combatting cancer.

As we examine in detail in this note, Affimers possess a number of key advantages over antibodies. Given that antibodies currently dominate drugs markets worth over $125bn – and forecast to exceed $200bn by 2023 – there is evidently a colossal commercial opportunity for Avacta, if the Company can successfully prove the efficacy and safety profile of Affimer-based therapies in first-time-in-human trials (likely to be H1 2021).

Avacta has also exclusively licensed a second platform technology, named pre|CISION™, from leading US research institution, Tufts University School of Medicine. At the heart of the pre|CISION platform is a novel linker technology that can be used in drug conjugates or in chemotherapy pro-drugs. In short, the drug containing the linker technology will only be activated in the tumour itself; this compares to standard-of-care chemotherapies that are equally active in both tumours and healthy tissue. The implications of this are staggering: the notoriously dire side effects associated with chemotherapy treatment could be largely eradicated via relatively straightforward reformulations of generic chemotherapy drugs. Avacta will be carrying out a Phase I human trial for its first reformulated chemotherapy, pro-doxorubicin, this year.

After Phase I human trials for both the first Affimer-based therapy and the first reformulated chemotherapy have been successfully completed, Avacta will be in a position to advance a novel class of immuno-oncology drug conjugates that utilise both technology platforms, i.e. immunotherapies coupled with targeted chemotherapies. This platform is referred to as TMAC ('tumour microenvironment activated drug conjugates'). Avacta has already generated highly encouraging data in pre-clinical animal studies for its first TMAC molecule.

In addition to developing a proprietary pipeline of Affimer-based immunotherapies and immuno-chemo-conjugates in-house, Avacta is using its Affimer platform to enter into drug collaborations with third parties in the pharmaceutical space. In the past 16 months alone, the Company has entered various forms of commercial partnerships with four separate major pharma entities. Whilst each of these partnerships varies in regard to how the Affimer technology is being utilised in the drug class that the partnership is developing, the collaborations have a number of similar characteristics. For example, all four partnerships are *fully funded* by the partner in question – that is to say, all of Avacta's R&D costs incurred in each project are covered by that project partner. The partnerships are also potentially extremely lucrative for Avacta over an extended time period: we believe that two of the four collaborations alone (namely with LG Chem and with ADC Therapeutics) could be worth almost $500m to Avacta over the coming 5-10 years, through various milestone payments. On top of that, Avacta would receive royalties on sales of any products that were successfully commercialised by the collaborations.

The Company also has a second business unit, the *Diagnostics* division. This division offers Affimer reagents (tools used in chemical testing) to the pharma industry in a wide variety of diagnostic and research applications. Over the past 2-3 years, Diagnostics has been involved in paid-for technology evaluations and custom Affimer services projects with a multitude of potential customers. The strategy is to convert these evaluations into (very high margin) licensing agreements that would deliver long-term royalties to Avacta. 18 months ago, management realised that the average timeframe for a potential customer to carry out a thorough evaluation of the desired Affimer reagent was much longer than initially anticipated (in reality around 2 years). As such, in order to accelerate growth, the division is currently completing the development of several proprietary Affimer diagnostic assays that would be ready-made for customers to license and develop into products.

At its current share price of 22.75p, Avacta has a market capitalisation of £40.0m. It has net cash of circa £8m, which is sufficient to fund operations through to end 2020. We believe that Avacta is chronically undervalued at the current price and offers substantial upside to investors in the near-term. However, the purpose of this note is to examine the *long-term* investment thesis. We feel that it is entirely plausible that Avacta could, in as little as 3 years' time, command a market capitalisation of over £1bn – and crucially for the investment case, with very limited, or indeed quite possibly *no*, dilution to the existing equity base along the way.

In the following pages we set out our rationale for why we believe that this seemingly pie in the sky target valuation is potentially achievable.

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Company Snapshot and Affimer Technology

Company snapshot

Avacta listed on AIM in 2006 via a reverse takeover of an existing business. At this point in time, Avacta was a biophysics company focussed on developing proprietary technologies for the detection and identification of biological and chemical hazards. The Company targeted customers in homeland security and defence. In January 2012, Avacta completed the acquisition of Aptuscan Ltd, a spin-out company from Leeds University that owned the Affimer technology, for £1.5m. Since then, one legacy business division was sold in 2015, and the other – Avacta Animal Health ('AHH') – is still operating. AHH is generating ~£1.5m in revenue per annum and running at a loss of ~£0.5m pa. The division is non-core, and not relevant to our investment thesis. We believe that it will be closed down or disposed of in the relatively near-term, so that management can focus exclusively on its Therapeutics and Diagnostics divisions.

The Company has approximately 80 employees and operates in two locations in the UK: the Therapeutics division is based in Cambridge, and the Diagnostics division in Wetherby.

Affimer technology

At the heart of the investment thesis lies the Company's patented Affimer technology. Affimers are based on the naturally occurring human protein, stefin A: they constitute a 'protein scaffold' and are an alternative to antibodies (known as an 'antibody memetic'). In the same way as an antibody, an Affimer molecule is capable of binding to and capturing a target molecule (such as a peptide or another protein). Affimers have a number of technical advantages over antibodies that make them a first-in-class therapeutic protein platform:

- Affimers are approximately 90% smaller than antibodies. This provides several performance advantages, such as allowing for better tissue penetration and increased packing density on surfaces.

- Affimers are approximately 90% cheaper to produce than antibodies. Antibodies are often generated by immunising an animal and purifying the antibodies from the animal's blood. This process can take many months. In contrast, Affimers are generated via a standard in-vitro process which does not use animals, but E. coli – consequently the process takes only a matter of weeks.

- In addition to a lower cost, the method of manufacturing guarantees a consistent and high-quality supply, which is not always the case with antibody production.

- As Affimers are 'fully-human' proteins – as opposed to antibodies which are often generated from animals – this ensures a low immunogenicity risk (i.e. they are more likely to have a good safety profile in humans).

- The loop structure of an Affimer creates an antigen binding surface: this ensures flexible formatting, which in short makes Affimers easier to modify and develop than many antibodies.

Avacta has a strong patent protection programme that not only safeguards the background platform IP, but also ensures that any individual Affimer loop sequence that the Company generates can be uniquely patented. Accordingly, Avacta has freedom to operate in developing alternative, Affimer-based therapies wherever there is already existing antibody-based IP. In essence, it has an almost *limitless market to target*.

That does not mean to say that the Company intends to challenge antibody-based therapeutics across the entire spectrum. Rather, management is focussing on areas where the current (antibody-based) standard-of-care can be radically improved. Avacta has chosen immunotherapy, and specifically immuno-oncology, as its first target market.

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Diagnostics Division

Building a very high margin royalty-based business

After acquiring the Affimer technology in 2012, Avacta originally set about building a business that focussed on using Affimers as affinity reagents for Life Sciences R&D and as protein microarrays for drug and biomarker discovery and diagnostics. The rationale for going down this route – as opposed to developing a therapeutics division instead or in tandem – was that a diagnostics and reagents-focussed business would offer lower risk (owing to lower regulatory hurdles) and much faster revenue growth.

The *Diagnostics* division, as this operation is now known after the launch of the Company's second division, *Therapeutics*, is focussing on applications and markets in which Affimer reagents are strongly differentiated from antibodies – namely diagnostics, bio-assays and affinity separations. Through evaluations with numerous customers to date, the division has proved that in many cases Affimer-based reagents possess superior qualities to antibody-based ones.

The Diagnostics division has refined its business strategy over the past five years and is now focussing on three types of work stream:

1) Paid-for evaluations of Affimer technology by a third party. The aim of these is for the evaluations to be converted into long-term, royalty bearing licensing deals for Affimer molecules incorporated into third party products (that are primarily focussed on the diagnostics sector);

2) Customised services to generate Affimer molecules that will be used in-house by a third party to support their own R&D workstreams (a typical service might generate circa £40k in revenue for Avacta);

3) Development of an in-house pipeline of Affimer diagnostic assays for licensing.

In October 2018, Avacta announced its first conversion of a successful evaluation into a royalty bearing licensing agreement. The agreement is with private US company, New England Biolabs, Inc. ('NEB'), the global leader in the discovery and production of enzymes for molecular biology applications. NEB has developed a product that incorporates Affimer technology for use in both life science research and diagnostics assays. Although terms of the agreement have not been disclosed, Avacta will receive a royalty on product sales. We believe that the deal will generate annual revenue for Avacta in the region of £200k to £400k, with potential further upside as the product becomes more established in its market.

As at October 2019, the Diagnostics division had seven ongoing Affimer evaluations with major partners – four of them being in the top ten global diagnostics companies. The Company believes that these evaluations could be converted into similar licensing deals as the one with NEB.

The third prong to the division's strategy – the development of in-house assays – was devised in H2 2018, as a result of the conversion process of evaluations to licensing deals (see 1) above) taking significantly longer than originally anticipated (the evaluation with NEB for example lasted for over two years before a licensing agreement was signed). Avacta is close to completing the development of its first two proprietary Affimer-based diagnostic assays. These "off-the-shelf" assays will be ready-made for immediately licensing out to customers, which the customers themselves will then be able to develop into products. The strategy should enable a much faster route to commercial license deals, as potential partners would not be required to commission Avacta to carry out the evaluation process for the desired assay first.

In the 12 months to end July 2019, the Diagnostics division generated £1.2m in sales – an increase of 130% YoY. Whilst the starting base was modest, the growth demonstrates that the division's efforts over the past several years are beginning to pay off. We believe that the three-pronged strategy being implemented could result in similar levels of revenue growth in the coming years. We estimate that a licensing deal such as the one with NEB might generate annual revenues (via royalties) for Avacta of anywhere between £0.2m and £1m (we believe that the NEB agreement will be towards the lower end of that range). Given the number of evaluations ongoing, it is simple to perceive how Diagnostics' revenues could be scaled up rapidly.

Royalty revenue is of course both recurring and extremely high margin. The Company has not yet provided a breakdown of individual cost bases for its divisions, and so it is difficult to estimate at what level of revenue the Diagnostics division will move into profitability. However, what we can say is that – especially with the off-the-shelf products coming into play – the division's overheads should be relatively fixed. Consequently, as more licensing deals are secured, the operating margin will continue to trend upwards.

Comparable company analysis

A useful comparator listed in the UK is Bioventix Plc. Bioventix manufactures and supplies high affinity sheep monoclonal antibodies for use in diagnostic applications such as clinical blood testing. In short, it does exactly what Avacta's Diagnostics division does, but with antibodies. In FY 2010, Bioventix generated revenues of £1.58m, and PBT of £0.68m. Its gross margin was 87.5%, and PBT margin, 43.3%. Following nine years of steady growth, by FY 2019 revenue had increased to £9.3m, and PBT to £7.0m. The gross margin was 90.6%, and the PBT margin, 75.0%.

The business model enables Bioventix to maintain an impressive dividend pay-out ratio (64% in FY 2019, not including a special dividend). The UK investment community evidently holds the business in extremely high regard: the shares trade on a trailing price-sales ratio ('PSR') of 20.6x, and a trailing price-earnings ratio ('PER') of 30.6x. Bioventix's current market capitalisation is £192m.

These are the sort of sales figures, margins and valuation that Avacta's Diagnostics division should be aiming to achieve over the next five years. One could even argue that, owing to the proprietary IP inherent in the Affimer technology, and the advantages it possesses over antibody-based reagents, the Diagnostics might be able to achieve a greater top line growth rate than Bioventix has over the past nine years.

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Therapeutics Division: Overview

Why the move into Therapeutics?

In May 2015, the Company announced that it had entered into a collaboration, licensing and option agreement with Moderna Therapeutics, Inc. The agreement provided Moderna with exclusive access to Affimers against certain targets, and the option to enter into exclusive license agreements with Avacta for selected therapeutic Affimer candidates for clinical development. Moderna made an upfront payment of $0.5m and would be obliged to pay up to "several tens of millions of dollars" in various milestone payments for each Affimer candidate that it licensed. [We discuss the agreement in greater detail on pp.16-17.]

Our understanding is that Moderna approached Avacta about the possibility of using the Affimer technology in its various messenger RNA ('mRNA') workstreams. Moderna is the world leader in drug discovery and drug development based on mRNA. The company creates synthetic mRNA that can be injected into patients to help them create their own therapies. Moderna has raised circa $3bn in equity financing since its inception only a decade ago, including $604m upon its NASDAQ IPO at the end of 2018, and a further $500m last month. Its current market capitalisation is $9.6bn.

Having drawn the attention of such a major player as Moderna, Avacta's management was suitably convinced of the potential to expand its own operations into the therapeutics space. In the CEO's own words:

"*The collaboration with Moderna is an important validation of the Affimer technology, highlighting the potential for Affimers to become a real alternative to antibodies. I have no doubt that this early adoption of Affimers in the therapeutic field will act as a catalyst for others and it represents a step change in the valuation of the Affimer technology.*"

Whilst there is much greater development risk associated with therapeutics (in comparison to diagnostics), as well as much longer lead times to commercialisation, the rewards to be had can potentially be much greater. As such, the Company raised £22.0m in July 2015 to predominantly fund the establishment and fast-track of a second business division, Therapeutics.

A three-pronged strategy

Using its Affimer technology platform, the Therapeutics division was initially solely focussed on the area of immunotherapy. However, in 2018 the Company secured an exclusive license for a targeted chemotherapy technology – the pre|CISION platform – from Tufts University School of Medicine. Consequently, the activities of the division have broadened considerably over the past 18 months: it is now developing two technology platforms in tandem – one, immunotherapy-based, and the other chemotherapy-based. It is also developing a hybrid platform – "TMAC" – that incorporates the technologies of both Affimer® and pre|CISION to develop powerful drug conjugates.

The division's development strategy is based around delivering three core objectives:

1) Build a pipeline of commercially valuable therapeutic drugs in-house, using the three platform technologies.

2) Progress the first developed drug from each of the three platforms into clinic, to prove efficacy, safety and tolerability in man. A first Phase I human trial for a pre|CISION developed drug will be occurring this year. Subject to funding (and the result of this year's Phase I trial), human trials for the Affimer platform and the TMAC platform will likely occur in 2021 and 2022, respectively.

3) Securing licensing agreements with third parties. Avacta's three platform technologies are broadly applicable: the usage of collaborations with other pharma players enhances data generation for the platforms, and ultimately commercialisation opportunities for each of them, across a wide range of therapeutic modalities.

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Therapeutics Division: 1) Affimer® Platform

Focussing on immuno-oncology

Whilst Affimers could be used in a broad range of therapeutic modalities, Avacta's Therapeutics division is for now using the platform technology to focus its efforts on novel therapeutics in the area of *immuno-oncology* (or 'IO'), which is the use of *immunotherapy* in combatting cancer. The two key reasons for this initial area of focus are that:

i) Affimers possess characteristics that provide technical advantages over the prevailing platform technology in the space, antibodies (see bullet points on p.3).

ii) There is colossal commercial interest in IO assets across the globe.

The human immune system and the basics of immunotherapy

To function properly, an immune system must detect a wide variety of agents, known as pathogens, from viruses to parasitic worms to cancer / tumour cells, and distinguish them from the organism's own healthy tissue. Specifically with regard to cancer cells, 'T-cells' (a type of white blood cell in the immune system of humans) detect cancer cells by various receptors that both have on their cell surfaces. However, many types of cancer cells have evolved to block their own give-away signals by instead presenting seemingly healthy receptors to T-cells: in layman's terms, cancer cells can pretend that they are actually healthy cells, and thus avoid attack from the T-cells of the immune system.

IO therapies work in two core ways. Firstly, they *block* the 'fake' healthy signals presented by a cancer cell, thus allowing the patient's own immune system to recognize that the cell is indeed unhealthy, and to consequently attack and destroy it (this is known as an *antagonist* immunotherapy). Secondly, they stimulate immune system cells (such as T-cells) to maintain their attack on cancer cells (this is referred to as an *agonist* immunotherapy).

IO has become a field of intense focus in recent times for numerous reasons. A major one is that IO treatments usually have fewer, and much less severe, side effects than other cancer treatment types such as chemotherapy and radiation therapy. The first IO treatment – a monoclonal antibody named Rituximab – was granted marketing approval by the US Food and Drug Administration ('FDA') in 1997. Since then, a further ~75 IO therapies have been granted approval by the FDA.

Despite the vast potential of IO therapies – and indeed their many successes to date – in the treatment of cancer, it is well documented that 'monotherapies' (i.e. therapies that target only one type of receptor on the cancer cell) developed thus far only work for approximately 20% of patients. This is largely as a result of variation amongst different types of tumour, in how the immune system's T-cells have already penetrated the tumour (known as *immune infiltration*).

For circa 30% of tumours, the immune system is already present in the tumour mass – even if not active. An IO therapy is therefore able to catalyse the immune system into action. Such tumours are known as 'hot' tumours. In the other ~70% of tumours, there is no immune infiltration. No T-cells are present within the tumour. These are referred to as 'cold' tumours.

In order to overcome this low success rate of the first generation of IO therapies, biotech and pharmaceutical companies are now focussing on developing a range of alternative treatments to IO monotherapies. These include:

- ***Multi-specific therapies***. This type of treatment involves using two or more immunotherapies, either in a single molecule or in combination, to enhance the potency of the treatment by targeting multiple types of receptors on the cancer cells.

- ***Combination therapies***. This involves one or more immunotherapies being used in conjunction with (but separately administered to) another form of therapy such as chemotherapy.

- ***Drug conjugates***. This is the process of combining one or more immunotherapy with another therapy – such as chemotherapy – in the *same* drug molecule.

Below, we examine Avacta's immunotherapies under development, which include both monotherapies and multi-specific therapies. We examine Avacta's immunotherapies as part of its drug conjugates programme in detail on pp.11-14.

Affimer platform: lead monotherapy programme – AVA004

The Company's lead monotherapy, an Affimer molecule named AVA004, is an inhibitor of the well-known immune checkpoint, PD-L1. The molecule was selected because of its excellent in-vitro and in-vivo pharmacological properties. This Affimer has been shown to have equivalent tumour growth inhibition to three approved monoclonal antibody inhibitors of PD-L1 (namely Tecentriq, Imfinzi and Bavencio) in several animal efficacy models.

With its partner, leading cell line development company Selexis SA, Avacta is in the process of preparing AVA004 for clinical manufacturing. The Company's stated goal is to file an Investigational New Drug ('IND') application in the US and a Clinical Trial Authorization ('CTA') in the EU by the end of 2020. This will ensure that a Phase I human trial can take place early in 2021. The study will explore both intra-venous and sub-cutaneous routes of administration to provide proof-of-concept with primary endpoints of safety, tolerability and appropriate pharmacokinetics/pharmacodynamics, and with a secondary efficacy endpoint. The study will include 20-30 patients in at least two sites in North America and Europe. Top-line data from the study should be available by mid-2021.

We estimate that it will cost Avacta as much as £10m to see the programme through from now until completion of Phase I (~£5m for good manufacturing process ('GMP') and other study preparations, and a further ~£5m for the execution of Phase I itself).

Affimer platform: second monotherapy programme – AVA017

AVA017 is a similar monotherapy to AVA004. It is an inhibitor of another immune checkpoint receptor, named LAG-3. These receptors are not located on the tumour cell, like PD-L1, but on the T-cells. In short, LAG-3 plays an important role in modulating T cell expansion and function. The *blockade* of LAG-3 can thus *augment* T-cell functionality. In layman's terms, the blockade of LAG-3 with a monotherapy prevents exhaustion of T-cells, enabling them to sustain their attacks on cancer cells.

Unlike PD-L1, no monotherapy inhibitor of LAG-3 has yet been granted marketing approval by the FDA in the US or the European Medicines Agency ('EMA') in the EU. However, numerous monoclonal antibodies are currently being progressed through clinical trials, with promising data generated thus far.

In pre-clinical work, Avacta has generated positive data showing that AVA017 inhibits the LAG-3 immune checkpoint. But as we explain below, we think it highly unlikely that the Company will progress AVA017 into clinic as a standalone monotherapy.

Phase I human trials for AVA004 – the rationale and implications

Avacta has selected AVA004 as its first Affimer molecule to bring to clinic not because of its potential commercial value, but rather to demonstrate safety and tolerability of the Affimer platform as a whole. There are already numerous – and very successful – PD-L1 inhibitors in the marketplace. One could argue that AVA004 might be able to wrestle a significant slice of market share from these already established products: it has demonstrated comparable efficacy in animal studies, and crucially would be easier, faster and ultimately much cheaper to produce.

However, as Avacta is a small company with limited cash resources at present, management has – quite rightly, in our view – decided to focus on developing much higher value therapies using its Affimer platform. Simply put, PD-L1 and the various monotherapies that target it are well understood in the industry. The Company has

generated excellent results for AVA004 thus far in in-vitro and in-vivo studies. Management believes that of all its Affimer-based immunotherapies under development, it poses the least risk of failure in Phase I human trials.

If the AVA004 Phase I trial next year is successful, it will effectively derisk the entire Affimer platform technology. Subsequently, the Company itself will be able to progress with the in-house development of a whole range of novel, much higher value therapies that incorporate the Affimer technology. It will also facilitate the securing of more (and higher value) licensing deals with biotech and pharma majors.

Moreover, a successful Phase I trial for AVA004 will provide Avacta with a proprietary PD-L1 inhibitor that will be a central component to those novel, high value therapies. As we explain below, the multi-specifics and the drug conjugates that the Company is developing include PD-L1 (and/or other) checkpoint inhibitors.

It is unlikely that the Company will progress AVA004 beyond Phase I trials – at least as a standalone monotherapy. It is also improbable that AVA017 will be progressed into Phase I trials at all. As previously mentioned, the real value upside for Avacta does not lie in developing monotherapies (a market now saturated by proficient antibody-based therapies such as Merck's *Keytruda*, Bristol Myers Squib's *Opdivo,* Roche's *Tecentriq*, AstraZeneca's *Imfinzi* and Pfizer and Merck's *Bavencio*), but rather in its novel therapies – multi-specifics and drug conjugates.

Using the Affimer platform to develop multi-specific therapies

Even for patients with hot tumours, monotherapy is not always effective (as explained on p.7, ~20% of patients respond to immunotherapy, although ~30% have hot tumours). It is easy to appreciate that by targeting *multiple* receptors on cancer cells and/or T-cells – by encompassing *multiple* immunotherapies into one treatment plan (either separately administered or as a single drug molecule) – it is more likely that a greater percentage of patients with hot tumours will respond positively to treatment.

This is a novel approach that companies are now taking, with a number of bispecific (i.e. 'two-in-one') immunotherapies under development. To our knowledge, the most advanced is a bispecific *antibody*-based molecule named FS118, developed by F-star Biotechnology Ltd. FS118 has been in a Phase I human trial for the past two years and is due to complete the trial imminently. Animal studies for FS118 have already demonstrated its superiority over existing monotherapies (i.e. inhibitors of PD-L1 alone) in the marketplace.

Avacta's Affimer technology is ideal for developing this novel class of drug. As referenced on p.3, the Affimer protein scaffold enables flexible formatting: Affimers can be easily linked together into 'multimers' – aggregates of multiple molecules bonded together – much more easily than can antibodies.

Moreover, such Affimer molecules are far cheaper to manufacture than the equivalent antibody molecules. Given that the average monoclonal antibody-based monotherapy (such as a PD-L1 inhibitor) already costs on average ~$150k per annum for the patient, the cost of a *bispecific* antibody-based therapy will likely render it prohibitive to most patients.

Owing to the rapid manufacturing process, which is 2-4x as fast as that of antibodies (2-3 months, instead of 6-12 months) – and to not requiring the use of animals in the process – Avacta believes that the cost of developing Affimer-based multimers will be as much as 90% cheaper than of developing antibody-based ones. This provides the Company with a major competitive advantage in this novel therapeutic space.

Affimer platform: lead multi-specific therapy – AVA021

The first multi-specific therapy that the Company is developing is a bispecific Affimer molecule, named AVA021. It combines its two most advanced monotherapies, AVA004 and AVA017, into a single molecule. This is the same combination of checkpoint inhibitors as F-star's antibody-based bispecific, FS118 – namely, the inhibitors of PD-L1 and LAG-3.

Initial in-vitro work on AVA021 has been promising, with the binding of the Affimers to the immune checkpoints working as well as it does in monotherapies. Management is also encouraged by the pre-clinical

animal studies carried out by F-star, which demonstrated that their bispecific produced superior results to the two checkpoint inhibitors being administered in combination but as separate monoclonal antibodies.

We believe that management will seek to bring AVA021 into Phase I human trials in 2022, provided that the Phase I trial for AVA004, the PD-L1 inhibitor, is successful next year.

The rationale for developing AVA021 – and other similar multi-specific therapies in the future – is that it will provide the Company with a clinically differentiated pipeline of therapies that will be able to address the lack of a durable response to immune checkpoint monotherapies for most patients.

Comparable company analysis

In June 2017, F-star announced that it had formed a new strategic collaboration with multinational pharma, Merck & Co., to develop and commercialise five of F-star's bispecific antibodies. In return for Merck being granted exclusive development and commercial rights over the therapies (which included the lead programme, FS118), F-star was to receive up to €115m over the first two years of the collaboration, in upfront, R&D funding and milestone payments.

Moreover, Merck was granted the option to acquire the bispecific programmes for a further circa €900m, taking the total deal value to over €1bn.

The collaboration was amended in May 2019 – it appears that Merck passed on its option over FS118 which has reverted to F-star's full control, but did exercise its option for one discovery stage programme and retained the right to option a second discovery programme.

Even so, the value of the original deal is useful in providing a rough guideline to the potential value of AVA021 to Avacta, even before it reaches the clinic (i.e. enters Phase I human trials).

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Despite the obvious promise of bispecific immunotherapies, the fact is that they would still only have an effect on 'hot' tumours – which account for only ~30% of tumours. Patient response might increase from an average of ~20% today (the current success rate of monotherapies) to closer to that 30% mark, but still a full ~70% of cancer patients would not benefit from immunotherapy treatment.

Avacta believes that it has devised an entirely novel class of drug that could enable <u>all</u> patients to benefit from immunotherapy. This new drug platform, named TMAC, utilises Avacta's proprietary Affimer technology and the pre\|CISION technology that it has licensed from Tufts.

In the next two sections, we will first examine the pre\|CISION platform as a standalone asset. We will then revert to the TMAC platform and explain how it has the ability to turn 'cold' tumours into 'hot' tumours – thus enabling those ~70% of patients who currently do not respond to immunotherapy, to now benefit from it.

Therapeutics Division: 2) pre|CISION™ Platform

Avacta enters into a collaboration with Tufts

In July 2018, the Therapeutics division announced that it had entered into a collaboration with leading US research institution, Tufts University School of Medicine. The collaboration is centred upon a ground-breaking co-invention – a platform to develop a new class of drug conjugate – that utilises the technologies of both parties.

The commercial terms of the collaboration have not been publicly disclosed. However, we believe that it is based on a royalty agreement on any sales of commercialised products that have originated from the collaboration. For the sake of our basic financial modelling, we assume a flat 20% of all gross sales will be due to Tufts.

Affimer-drug conjugates: the mechanics

The 'TMAC platform', as it has been named – derived from 'tumour microenvironment activated drug conjugates' – incorporates Avacta's Affimer® technology and Tufts' pre|CISION™ technology. It is able to generate 'Affimer-drug conjugates' ('AfDC'), which are intended as first-in-class treatments for cancer patients. In essence, AfDCs utilise immunotherapy and chemotherapy in a single treatment.

An AfDC combines an Affimer with a cytotoxic drug (i.e. a chemotherapy) – in a single drug molecule (or 'conjugate'). The chemical 'linker' that attaches them together has a special ability: it renders the powerful cytotoxin *inert* until it reaches the tumour cell. Once in the tumour mass, the cytotoxin becomes active and attacks the tumour.

There are three key components to the AfDC. It is important to understand each of these components and how they work together, in order to appreciate the potential clinical value of this novel drug class to cancer patients, and its potential commercial value to Avacta.

1) **The Affimer**

   The Affimer component of the AfDC provides the attributes of an immunotherapy (such as the PD-L1 inhibitor, AVA004). Firstly, its tumour-targeting capabilities come into play: it takes the AfDC directly to the tumour mass. Once the tumour becomes inflamed as a result of the cytotoxin getting to work (see below), the Affimer then acts as an immunotherapy in assisting the patient's immune system to combat the tumour, either by preventing evasion by the tumour cells (e.g. by blocking PD-L1) or by sustaining the T-cells' attacks on the tumour cells (e.g. by blocking LAG-3) (see p.8).

   It is important to note that there could be *multiple* Affimers incorporated into a single AfDC (e.g. AVA021 – Avacta's proprietary bispecific combining PD-L1 and LAG-3 inhibitors), to enhance the support given to the patient's immune response.

2) **The cytotoxin**

   This is essentially a potent anti-cancer drug, also known as a 'warhead', that is used in chemotherapy. Once the AfDC reaches the tumour mass, the warhead is activated, causing a massive pro-inflammatory response as it attacks various cells within the tumour mass. The inflammatory response enables the patient's immune system – which will have been on the periphery of the tumour mass – to enter the tumour itself and also attack the tumour cells. This in turn causes the immunotherapy component of the AfDC (i.e. the Affimers) to kick in, as the tumour has turned from 'cold' to 'hot'. This enhances and sustains the attack of the immune system.

3) **The linker**

   Tufts' proprietary linker is a fibroblast activation protein alpha ('FAPα') substrate. The linker is cleaved by FAPα enzymes that are only upregulated (i.e. found in large, concentrated quantities) within the tumour microenvironment. Once the linker is cleaved, the chemo-warhead component of the AfDC is activated. This ensures that the warhead targets only the tumour mass, and not healthy tissue.

In summary then:

- The Affimer-drug conjugate is comprised of three components: Affimer(s), chemo-warhead, and linker.
- The Affimer's targeting ability takes the AfDC to the tumour mass.
- On the journey to the tumour, healthy tissues are unharmed, as the warhead component of the AfDC is inactive (FAPα enzymes capable of cleaving the linker are in very low concentration in healthy tissue).
- Upon reaching the tumour mass, FAPα enzymes that are present in high concentration in the tumour mass are activated and *cleave* the linker.
- At this point, the warhead becomes active. A major inflammatory response within the tumour mass occurs, as the powerful cytotoxins attack cells within the tumour mas. The 'cold' tumour becomes 'hot'.
- The T-cells of the patient's immune system are now able to identify the tumour as unhealthy; infiltrate it; and attack the tumour cells.
- The Affimer component of the AfDC (be it a monotherapy or a bispecific) enhances and sustains the attack of the immune system.

To our knowledge, the AfDC is the *only* drug class in existence that combines immunotherapy with targeted chemotherapy in a single drug molecule. We will examine this in more detail in the next section.

The linker – animal studies to date

In H1 2019, Avacta carried out in-vivo studies (using mice) to demonstrate the effectiveness of the FAPα substrate. Given that it is a key component of an entire new class of drug that the Company intends to develop, these studies were of course of critical importance.

In order to simplify the development of the AfDC as a whole, the Company has opted to initially test the linker not as part of an AfDC, but with a single, well-established chemotherapy – doxorubicin.

Doxorubicin has been the standard-of-care for over 40 years for patients with advanced soft tissue sarcoma such as breast cancer. Although an extremely effective drug, patients must be taken off treatment with doxorubicin due to irreversible heart damage once the cumulative dose reaches a certain level – even if they are experiencing clinical benefit. This is because standard doxorubicin is not targeted to the cancer. Accordingly, the exposure of healthy tissue such as the heart to the drug is the same as the exposure of the tumour. As a result, patients cannot be dosed for long enough to achieve a better median progression-free survival than approximately 6 months, with median overall survival of 12-15 months.

In the H1 2019 in-vivo studies, the Company compared the safety and efficacy of standard doxorubicin and a novel, proprietary form of doxorubicin targeted to the tumour using the FAPα substrate. Avacta has named it *pro-doxorubicin* (or 'AVA6000').

In mice, standard doxorubicin was distributed between the tumour and heart with a 1:1 ratio. This caused severe cardiotoxicity (damage to the heart), as is seen in humans.

However, the pro-doxorubicin was distributed between the tumour and heart with an 18:1 ratio.

The maximum tolerated dose ('MTD') for the animals treated with pro-doxorubicin was thus substantially greater – six times, in fact – than the MTD for the animals treated with the standard doxorubicin.

In the study, all animals treated with standard doxorubicin (MTD of 2mg/kg) died before Day 60. Conversely, all animals treated with pro-doxorubicin (MTD of 12mg/kg) *survived* to Day 60.

Fast-tracking pro-doxorubicin (AVA6000) into Phase I human trials in 2020

Following the successful animal studies, the Company is in the process of completing IND ('Investigational New Drug') studies and intends to file regulatory applications at the end of this month. This will enable a Phase I human trial for pro-doxorubicin to commence in Q3 2020. It will be a dose escalation study involving 15-20

patients with a wide range of tumours at sites in Europe and North America. Initial data are expected towards the end of this year.

As with the animal studies, the purpose of the Phase I trial is to demonstrate significantly reduced cardiotoxicity for patients treated with pro-doxorubicin, in comparison to those treated with standard doxorubicin. This would enable patients to be dosed for longer with pro-doxorubicin, which should ultimately result in improved overall survival rates.

The significance and potential commercial value of the pre|CISION™ linker technology

If the Phase I human trial for pro-doxorubicin replicates the successes of the animal study, it would be immediately transformational for Avacta. Firstly, it would be a colossal step towards bringing the Company's first TMAC drug into the clinic – which in itself would be the first of a novel, first-in-class drug class that would be well positioned to take a substantial share of both the global chemotherapy and immuno-oncology markets. We explore this in the next section. Secondly, it would open up *another* enormous – and significantly, *near-term* – commercial opportunity for Avacta, namely reformulated (i.e. enhanced) chemotherapies.

Doxorubicin is a circa $1bn drug (that is to say, annual global sales of the drug amount to ~$1bn). This is expected to increase to circa $1.4bn by end 2025. The drug is *generic* – it is no longer patent-protected. Thus, doxorubicin can be labelled and marketed – or indeed *reformulated* – by anyone (with the approval of the relevant regulatory bodies, of course).

Let us assume that Avacta's pro-doxorubicin is successful in Phase I. If it is, management has suggested that the doxorubicin market as a whole could increase by 3-5x its current size. We believe that this is a reasonable assumption: after all, the vast majority of cancer patients only cease chemotherapy because of the damage that their healthy tissues (crucially, their hearts) have sustained in the process.

That would transform doxorubicin into a $4bn drug overnight. Now, the incremental $3bn is 100% dominated by pro-doxorubicin (elsewise it would not exist). We could also reasonably assume that the pro-doxorubicin would very rapidly take a large majority share of the *existing* market. Let us say 75%.

That would equate to a $3.75bn product for the owner – or licensee – of an approved pro-doxorubicin. That could be closer to $5.0bn by 2025.

Avacta's management has stated in recent interviews that it intends to have a heads-of-terms ('HoT') in place with a major pharmaceutical company, for a development and licensing agreement for pro-doxorubicin, *prior to* the completion of the Phase I trial. Assuming a successful Phase I, the pharma partner would fund pro-doxorubicin through the Pivotal Phase II trial, and thereafter into commercialisation.

If the results from the trial (expected later this year) are positive, this HoT agreement would be executed. Management has alluded to such a deal being in the region of $50m in upfront / near-term (i.e. within one year) milestone payments, with a further $300m to $500m in clinical / commercial milestone payments.

Royalties on future product sales would also be due. As the partner would be picking up the tab for all development and commercialisation costs after Phase I, we would expect it to be a single digit royalty – let us assume 5%. After the 20% royalty owed to Tufts (our own estimate), that would still generate net annual royalty payments to Avacta, using our suggested total sales figure for 2025, of circa $200m.

Avacta has also stated that it has identified fifteen *other* chemotherapies that could likewise be reformulated with its FAPα linker technology. The Company has already synthesised nine of these, the most advanced of which (a FAP-activated proteasome inhibitor (AVA3996)) is only circa 12 months away from an IND regulatory filing.

For Avacta, positive results in Phase I this year could mean that the Company would never again have to raise funds through the capital markets. An executed licensing agreement for pro-doxorubicin would unlock a substantial amount of non-dilutive funding. This would enable Avacta to fund all its other programmes, including the landmark maiden Affimer human trial in 2021.

Therapeutics Division: 3) TMAC Platform

Please see the previous section for an examination of the TMAC platform and the mechanism of Affimer-drug conjugates ('AfDC').

TMAC platform: lead AfDC programme – AVA004/100

AVA004/100 is Avacta's first AfDC under development. The conjugate is comprised of an Affimer PD-L1 checkpoint inhibitor; the FAPα linker; and a cytotoxin warhead called I-DASH – a chemo-warhead molecule for which Tufts University has already generated substantial pre-clinical and clinical anti-tumour data.

In January this year, Avacta announced that it had successfully demonstrated initial proof-of-concept for the TMAC platform – using AVA004/100 – in an animal study.

In the study, AVA004/100 outperformed Bavencio, which is a marketed monotherapy (specifically, a PD-L1 antibody inhibitor) developed by Merck and Pfizer. Animals treated with AVA004/100 showed a *significant reduction* in the rate of tumour growth compared to those treated with Bavencio. Moreover, a considerably higher level of the released I-DASH warhead was measured in the tumours compared with very low levels in the blood.

In short, the study demonstrated that both key concepts of the AfDC work well (in mice, at least). The powerful chemo-warhead is targeting the tumour mass only; and the dual therapy (immunotherapy and chemotherapy working in tandem) is more effective than the existing standard-of-care immunotherapy.

The implications of this are astonishing: AVA004/100 combines immunotherapy and chemotherapy in a single drug molecule, which is much more effective than existing IO monotherapies. However, it does *not* have the side effects (most crucially, cardiotoxicity) that existing chemotherapies are notorious for. As such, the maximum tolerated dose for AVA004/100 will be *substantially* greater than existing chemotherapies. This will ultimately increase survival rate amongst cancer patients.

AVA004/100 cannot enter Phase I human trials until each of the linker and the Affimer technology have completed separate Phase I trials. As we have discussed in previous pages, the linker is entering the clinic (in the form of pro-doxorubicin, AVA6000) this year, with data readout due before Christmas. The first Affimer will then go into the clinic in next year, as the monotherapy AVA004 (the PD-L1 inhibitor). Assuming success in both trials, we expect that the first AfDC – AVA004/100 – will enter Phase I human trials in 2022.

The competition: antibody-drug conjugates ('ADC')

There has been significant interest in (and funds spent on developing) drug conjugates utilising antibody technology (as opposed to Affimers in AfDCs) in recent years. From 2011 to end 2018, over $5bn had been invested in the development of ADCs. The US FDA has approved seven ADCs to date, with over 200 more investigational ADCs currently in pre-clinical or clinical trials. It has been estimated that by 2025, the global ADC market will have reached ~$10bn.

In a similar manner to AfDCs, ADCs utilise the dual-targeting mechanism of a monoclonal antibody and a linker to target a chemo-toxin to the tumour. However, a key advantage that Avacta's AfDCs enjoy over ADCs is the dual therapeutic action of both chemotherapy *and* immunotherapy. Besides its tumour-targeting attribute, the Affimer component of an AfDC provides an *immunotherapeutic* action. The monoclonal antibody component of the ADC does not provide this.

In addition to this major *therapeutic* advantage, AfDCs would also be substantially cheaper to produce than ADCs (see p.3 for the differences in Affimer and monoclonal antibody production).

Assuming the AfdC molecule is viable in man, not only would we expect the novel drug class to take a significant share of the $10bn ADC market, but, as we explain on pp.23-24, its total addressable market could be many multiples larger.

Therapeutics Division: Roadmap

Proprietary programme	IND submission	Phase I trial
AVA6000 (pro-doxorubicin)	Q2 2020	H2 2020
AVA004 (monotherapy – PD-L1 inhibitor)	Q4 2020	H1 2021
AVA004/100 (TMAC molecule)	H2 2021	H1 2022
AVA021 (bispecific therapy – PD-L1 & LAG-3 inhibitors)	2022	2022

Notes

- AVA6000 Phase I trial is fully funded out of the Company's existing cash resources.
- If the AVA6000 trial is successful, management believes that it will be in a position to secure a licensing deal for the drug before end 2020. This would include upfront and near-term (within 12 months) milestone payments of something in the region of $50m.
- This sum would be sufficient to cover all of the Company's financing requirements until well into 2023, including the three Phase I trials pencilled in for 2021 and 2022. By that stage we believe additional licensing agreements would have been established, such that there is a reasonable possibility that Avacta would never have to raise money again via the equity markets.
- A successful AVA6000 trial would likely fast-track other reformulated chemotherapies developed by the pre|CISION platform – notably AVA3996, the FAP-activated proteasome inhibitor. We believe that it could even leapfrog the intended AVA004 and AVA004/100 trials noted above, given the nearer term opportunity for commercialisation.

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Therapeutics Division: Commercial Collaborations

The importance of partnerships

Avacta founded its Therapeutics division in 2015 precisely as a result of being approached by Moderna, a global leading mRNA company, and the resulting licensing and option agreement that they entered into. Although Moderna paid an upfront cash sum of $0.50m, the potential for milestone payments amounting to "several tens of millions of dollars" for each therapeutic Affimer candidate that Moderna licensed, persuaded Avacta of the commercial opportunity in moving into the therapeutics space.

The business model for the Therapeutics division is founded upon securing licensing agreements: in return for yielding majority ownership and/or rights of products that it has developed in-house, the Company will avoid having to self-fund the substantial capital expenditure required to complete Phase II and Phase III human trials. Moreover, in developing multiple products with partners simultaneously, Avacta will be in receipt of a steady flow of milestone payments, and ultimately will build out a diversified portfolio of royalty bearing assets.

It is important to note that, so long as the Affimer technology remains at a pre-clinical stage (i.e. it has not successfully completed a Phase I human trial), upfront payments will be in the region of 1% to 2% of the total potential value of the collaboration. However, once the first Phase I human trial has been completed – which fundamentally proves the safety profile of the platform technology – upfront payments will increase to 10% to 15% of the total potential value of collaborations.

A we examine below, Avacta's major commercial collaborations are all *fully funded* by the partner in question. All research and development costs that Avacta would otherwise expend are reimbursed to them. We believe that these reimbursements from the four ongoing major collaborations could amount to many hundreds of thousands of pounds per annum.

Another critical aspect of collaborations is the development of *intellectual capital*. The partnerships might focus on the usage of Affimer technology in different modalities (immunotherapy, gene therapy, etc.), but they are all contributing to the Company's ever-growing knowledge and understanding of the Affimer protein scaffold as a whole.

When a new commercial partnership is formed, the terms of the exclusivity over the Affimer technology are narrowed down as much as possible. The modality in which Affimers are being utilised (gene therapy, mRNA, etc.), the number of Affimer candidates per modality, regions, etc. – all of these are highly specified in each collaboration. This ensures that there's an almost boundless amount of licensing possibilities for Avacta, regarding its Affimer technology.

Over the past 16 months, Avacta has entered into four major commercial collaborations with high calibre partners. We expect that further major partnerships will continue to be formed going forward.

Moderna Therapeutics

In May 2015, Avacta entered into a collaboration, licensing and option agreement with Moderna Therapeutics. Moderna is the world leader in drug discovery and drug development based on mRNA. The company creates synthetic mRNA that can be injected into patients to help them create their own therapies. Moderna has raised circa $3bn in equity financing since its inception only a decade ago, including $604m upon its NASDAQ IPO at the end of 2018, and a further $500m last month. Its current market capitalisation is $9.6bn.

The agreement provided Moderna with exclusive access to Affimers against certain targets, and the option to enter into exclusive license agreements with Avacta for selected therapeutic Affimer candidates for clinical development. Moderna made an upfront payment of $0.5m and would be obliged to pay up to "several tens of millions of dollars" in various milestone payments for each Affimer candidate that it licensed.

In February 2019, Moderna exercised its option to enter into an exclusive licensing agreement with respect to certain Affimers against a single potential therapeutic target that had been part of the ongoing research

collaboration since 2015. No details have been given on the specific target, or on the potential financial implications for Avacta other than that the Company "*may receive undisclosed payments upon future clinical development milestones and royalties in connection with future product sales*."

From the limited detail given in the two announcements made by Avacta concerning the collaboration with Moderna, we can glean that:

- In exercising its option to license certain Affimers, Moderna is endorsing the technology platform as a whole. Given Moderna's sterling reputation, this will be a major positive for others in the pharma industry who have been watching, or indeed in talks with, Avacta.
- Avacta is likely to receive $30m to $50m in cash payments, from this year onwards, relating to the first chosen target that Moderna is licensing Affimers against.
- This chosen target is likely to be brought into clinical trials (i.e. Phase I human) by Moderna as early as *this year*. Regardless of the efficacy of Moderna's novel drug, the trial could generate good human safety data for the Affimer platform. As we have previously discussed, this would be a critical value inflection point for Avacta.

LG Chem Life Sciences

In December 2018, the Company formed a major, multi-target, Affimer therapeutics development alliance with LG Chem Life Sciences ('LG Chem'), a business division of South Korean multinational conglomerate LG Group. LG Chem focuses on three key core therapeutic areas, namely: Immunology; Oncology; and Metabolic Diseases (specifically, diabetes).

As with the Moderna collaboration, much of the detail of this alliance has not been disclosed. Avacta has been required to generate, and carry out early stage optimisation of, Affimer drug candidates against multiple undisclosed targets. The Company has achieved this first phase, having successfully generated a large number of Affimer proteins that bind to the first drug target nominated by LG Chem. These candidate Affimer molecules are now being optimised by Avacta, for LG Chem to then carry out pre-clinical development.

In November 2019, following Avacta's successful work on the first nominated drug target, LG Chem expanded the collaboration by nominating two further drug targets. Avacta is presently carrying out the discovery programmes for Affimer binders to those new targets.

For each of these three nominated drug targets, LG Chem and Avacta will collaborate to progress them through to drug candidate selection. Thereafter, LG Chem will be responsible for pre-clinical and regulatory studies, clinical development and worldwide marketing of any resulting products.

The commercial terms of the alliance are extremely attractive for Avacta:

- The agreement provides for upfront ($2.5m) payments, near-term milestone payments and longer-term clinical development milestones payments of up to $180 million.
- A further $130m in the same form of payments could be due to Avacta, if LG Chem were to nominate additional drug targets (it has already expanded the collaboration to include two additional targets. In total, we believe that the $310m covers up to six potential drug targets).
- Avacta will receive royalties (percentage not specified – we assume low to mid-single digits) on any future product sales.
- LG Chem will cover all of Avacta's research and development costs associated with the collaboration.

ADC Therapeutics

In October 2019, Avacta entered into a collaboration and option agreement with Swiss biotech company, ADC Therapeutics ('ADC'). ADC develops highly potent and targeted antibody-drug conjugates for patients suffering from haematological malignancies and solid tumours. The agreement is to develop Affimer-drug conjugates combining Avacta's Affimer technology with ADC's pyrrolobenzodiazepine ('PBD')-based warhead and linker technologies.

As part of the multi-target collaboration, Avacta will generate and optimise Affimer binders against three undisclosed cancer targets and provide these to ADC to target its proprietary cytotoxic warheads to the site of the tumour. ADC will carry out pre-clinical research and development programmes to evaluate each of the Affimer-drug conjugates with a view to generating clinical candidates.

The agreement provides ADC with options, on a target by target basis, to obtain exclusive licenses to the Affimer proteins for clinical development and commercialisation.

The terms of the collaboration are very similar to those of the LG Chem alliance. Avacta will receive upfront, near-term and long-term milestone payments, as well as a single digit royalty on sales of any products successfully developed and commercialised. ADC will also pay for all of Avacta's R&D costs associated with the collaboration.

It is worth noting that all of this R&D work carried out by Avacta will also assist in developing the Company's overall intellectual capital regarding this novel drug class, Affimer-drug conjugates. After all, given its enormous potential commercial value, successfully developing and commercialising its proprietary Affimer-drug conjugate platform, TMAC, should be, in our view, Avacta's ultimate goal.

With regard to the potential total amount that Avacta might receive in upfront and milestone payments, we believe that it is in the region of $150m (based on the $310m, six-target LG Chem collaboration).

ADC was founded in 2011. Its PBD technology was licensed from British-Swedish multinational pharmaceutical and biopharmaceutical company, AstraZeneca – which holds a 7% equity stake in ADC. The company currently has five drugs in human trials. ADC intended to list on NASDAQ in September 2019, seeking to raise $200m in new equity at a pre-new money valuation of $1.8bn – but postponed the listing, citing adverse market conditions.

Daewoong Pharmaceutical

In January this year, Avacta formed a joint venture with Daewoong Pharmaceutical Co Ltd ('Daewoong'), a leading Korean pharmaceutical company. The JV company has been named AffyXell Therapeutics ('AffyXell'): it has been established to develop the next generation of cell and gene therapies. These are two overlapping fields of biomedical research. *Cell* therapy is therapy in which cellular material – usually intact, living cells – is injected, grafted or implanted into a patient for the treatment of disease. *Gene* therapy can be defined as the use of genetic material (usually DNA) to manipulate a patient's cells for the treatment of disease.

Cell therapy has been around since the 1940s – the most common type now being bone marrow transplantation. Bone marrow transplantation is the treatment of choice for many kinds of leukaemia and lymphoma and is also used to treat many inherited disorders. Gene therapy was introduced in the late 1970s – although the first therapy was only approved by the US FDA in 2017 (there are now approximately 20 that have been granted marketing approval).

Mesenchymal stem cells ('MSC') are promising agents for the treatment of autoimmune and inflammatory diseases. They enable "allogeneic cell therapy", which is when the donor is a different person to the recipient of the cells. AffyXell's first area of focus is in cell therapy – specifically in developing a new class of MSCs that are primed to produce Affimer proteins.

Avacta and AffyXell have already entered into a collaboration and licensing agreement: Avacta will develop Affimer proteins against a range of targets which, when produced by MSCs, are intended to inhibit inflammatory and autoimmune pathways and improve the overall efficacy of MSCs.

Daewoong's role will be to provide AffyXell with access to its proprietary technology for generating the MSCs themselves. This technology facilitates the development of cell therapies as 'off-the-shelf' products, as it enables the generation of MSCs from a dingle donor (in effect, a renewable supply) that can then be used to treat a large number of patients.

The initial focus for AffyXell's novel MSC treatments will be on inflammatory and autoimmune diseases such as inflammatory bowel diseases, multiple sclerosis and chronic obstructive pulmonary disease. Autoimmune and inflammatory diseases affect over 50 million people worldwide: in the EU and USA alone, healthcare costs relating to these diseases amount to over $150bn per annum.

In the longer term, there is potential for AffyXell to address oncology uses for these Affimer-enabled cell (and potentially gene) therapies.

The collaboration differs from the first three that we have detailed, in that it is not a licensing deal based on milestone payments. Rather, Avacta owns 45% of the JV company, AffyXell, and Daewoong holds the balance. Consequently, the upside for Avacta in the longer term is potentially much greater. Moreover, *all* costs incurred by AffyXell (R&D, overheads, commercialisation costs, etc.) will be covered by Daewoong.

AffyXell will combine two first-in-class platform technologies, namely Avacta's Affimer technology and Daewoong's proprietary 'MSC-generator' technology, with the intention of creating the next generation of stem cell therapies.

Given the length of time it took for Avacta to successfully generate Affimer proteins for the first drug target in the LG Chem partnership, we estimate that the first Affimer proteins for AffyXell's MSCs will be ready at around the end of this year.

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Valuation analysis

Earl stage biotech and pharma companies are notoriously difficult to value, as a result of their idiosyncratic products under development. We will not attempt to calculate a fair value for each asset via detailed intrinsic and relative analysis and derive a sum-of-the-parts valuation for Avacta. Instead, we shall simply highlight relative valuations (both publicly listed comparable companies, and precedent transactions) and total addressable markets for certain of the Company's products under development. In doing so we hope to paint a broad picture of how we think Avacta could and should be valued over the coming years.

Diagnostics division

As detailed on p.5, AIM peer Bioventix is an ideal publicly listed comparable for Avacta's Diagnostics division. To recap, Bioventix manufactures and supplies high affinity sheep monoclonal antibodies for use in diagnostic applications such as clinical blood testing. In short, it does exactly what Avacta's Diagnostics division does, but with antibodies.

Bioventix's current market capitalisation is £192m. The shares trade on a trailing PSR of 20.6x, and a trailing PER of 30.6x. Using consensus market forecasts, the shares trade on a 2020 PSR of 19.0x, and a 2020 PER of 29.6x.

Given that Avacta's Diagnostics division is lossmaking at present, only Bioventix's PSR metrics are relevant.

In the 12-month period to end July 2019, combined revenues and order intake for the Diagnostics division amounted to £1.2m. This was an increase of 130% year-on-year ('YoY'), from £0.52m in 2018.

If we assume that Diagnostics' revenue growth rate in FY 2020 were to decelerate by half – to 65% YoY growth – the division would be still be generating circa £2m in sales.

On Bioventix's PSR ratios, Avacta's Diagnostics division could be valued at between **£24.7m** and **£38.0m**.

Therapeutics division

There are a plethora of assets and operations addressing a broad range of therapeutic modalities within this division, which renders it extremely challenging to derive a fair value for it. We shall talk through the three proprietary platforms individually, analysing individual assets and then the platform technology as a whole.

i) Affimer platform

As we explained on pp.8-9, as a result of the already saturated market, Avacta's two leading monotherapies – the PD-L1 inhibitor AVA004, and the LAG-3 inhibitor AVA017 – do not hold much commercial value as standalone assets. For that reason, we believe that only the former will be brought to clinic. A successful Phase I human trial will demonstrate the efficacy – and crucially, the safety profile – of the Affimer technology as a whole. This is of fundamental importance, as it will allow the Company to proceed with the development of higher value novel drugs within its in-house pipeline. It will also validate the technology's viability to existing and potential partners.

- **AVA021 (bispecific therapy)**

The bispecific therapy AVA021 (comprised of both the PD-L1 and LAG-3 inhibitors) is Avacta's lead high-value drug on the Affimer platform. As we highlighted on pp.9-10, bispecific immunotherapies are a newer subclass of drug, and consequently the competition in the space is, at least for the present, less intense.

In 2018, the global market for immune checkpoint inhibitor therapies amounted to $17bn. 83% of that was attributable to antibody-based monotherapies that targeted PD-1 / PD-L1 checkpoints. [The leading monotherapy by global sales in 2018 was Merck's Keytruda, at $7.2bn.] *Bispecific* immune checkpoint inhibitor

therapies have proved to have a higher efficacy in animal models than immune checkpoint inhibitor *monotherapies*: consequently, assuming successful human trials, it would be reasonable to envisage that the more potent bispecific therapies will rapidly carve out for itself a significant share of the market. Moreover, bispecific therapies could also substantially *expand* the immune checkpoint inhibitor global market. Firstly, the subclass of treatment could be used on cancer patients who have hot tumours but do not respond to simple monotherapy treatments. Secondly, it could be used on patients who have relapsed following monotherapy treatment.

The most advanced bispecific therapy under development is an antibody-based version of AVA021, owned by F-star Biotechnology (see p.10). It is in the final stages of completing its Phase I human trial. Although the commercial deal has now been cancelled, Merck had been willing to commit over €1bn in upfront and milestone payments to F-star for exclusive commercial rights over five of F-star's pre-clinical drugs, including its lead candidate, FS118.

Importantly, Avacta's AVA021 isn't far off on the development pathway than where FS118 was, when Merck and F-star entered into the pre-clinical €1bn deal. Furthermore, as we explained on p.9, an Affimer-based bispecific therapy would enjoy several key advantages over an antibody-based one such as F-star's SS118 (notably greater ease of formatting, and much lower cost of manufacturing).

- **The Affimer technology itself**

Affimers are based on the naturally occurring human protein, stefin A: they constitute a 'protein scaffold' and are an alternative to antibodies (known as an 'antibody memetic').

The Affimer platform is a therapeutic platform: it has the capacity to create a novel class of immuno-oncology (and other) drugs that are based on Affimers, as opposed to the market standard, *antibodies*. As Affimers possess a number of key technical advantages over antibodies, the platform also has the capacity to *improve on* already existing antibody-based drugs. Given that antibodies currently dominate global drugs markets worth over $125bn – and forecast to exceed $200bn by 2023 – there is evidently a colossal commercial opportunity for Avacta, if the Company can successfully prove the efficacy and safety profile of Affimer-based therapies in first-time-in-human trials.

The true commercial value of such a platform resides in the owner's – or licensee's – ability to operate freely in a market that is extraordinarily guarded by patents. An antibody memetic platform can be used to recreate existing antibody-based drugs that are under patent, and then patent and commercialise the proprietary, non-antibody-based versions.

Big Parma has demonstrated that it is more than willing to pay Big Money for alternative protein scaffolds.

In June 2018, global pharmaceutical company Sanofi acquired Ablynx for ***a total equity value of €3.9 billion***, paid in cash. Ablynx owned an antibody memetic platform, named Nanobody®, that – as with the Affimer technology – possesses a number of key advantages over standard antibodies. At the time, Ablynx was utilising its Nanobody platform to develop over 45 treatments, both in-house and via collaborations, for a broad range of therapeutic indications including across: haematology, inflammation, infectious disease, autoimmune disease, oncology and immuno-oncology. Its lead drug Caplacizumab, a treatment for a rare blood clotting disease, had passed its Phase III trial in late 2017. It has an estimated market opportunity of circa €800m. Caplacizumab gained FDA approval in the US in February 2019.

Within the Takeover Bid document was stated the reasons for the bid by Sanofi. We believe that it is highly relevant to understanding the blue-sky potential value of Avacta's Affimer platform technology, and so have copied it in, verbatim, below:

"*Sanofi and Ablynx had already entered into a collaboration to discover and develop certain multi-specific nanobodies against selected targets.*

Sanofi's R&D model and priorities are focussed on technology platforms such as Ablynx's Nanobody platform. Sanofi has particular interest in Ablynx's platform, since it has led to promising results within the framework of the collaboration agreement and it would provide Sanofi with an important strategic and competitive advantage in drug discovery.

The acquisition of Ablynx will enhance the Sanofi Group's strategy by contributing to sustaining leadership in rare diseases thanks to caplacizumab, Ablynx's most advanced product candidate.

Further, Ablynx's expertise will allow Sanofi to make great progress in the prevention and treatment of diseases Sanofi has been developing antibodies for.

Sanofi has a global footprint and a large R&D scale, which should allow Sanofi to accelerate the development and maximize the commercial potential of Ablynx's ongoing programmes, and to further leverage the platform with the introduction of new programmes.

The acquisition of Ablynx is expected to significantly broaden Sanofi's Specialty Care portfolio and its long-term R&D capabilities.

Thanks to its Nanobody platform and the quality of products currently in development, Ablynx constitutes a unique opportunity for Sanofi to accelerate its portfolio reshaping, sustain R&D innovation, and therefore enhance growth at Sanofi Group level."

Of course, Ablynx was several years ahead of Avacta with regard to platform development, at the time it was acquired. Avacta is yet to put an Affimer into a Phase I trial, whilst in contrast Ablynx had completed a Phase III trial for a drug that utilised its Nanobody technology. Nevertheless, it is clear from the above Takeover Bid statement why other pharma conglomerates might also wish to lay their hands on antibody memetic technologies, such as the Affimer platform.

Indeed, at this juncture it is crucial to highlight another matter regarding the Sanofi-Ablynx takeover. Three weeks before Sanofi tabled its bid, in January 2018, Denmark's Novo Nordisk – another tier 1 multinational pharmaceutical company – had made a €2.6 billion offer for Ablynx, which was rejected. This demonstrates that there is at least one other player in Big Pharma that is on the look-out for an antibody memetic platform. If we were to guess at other potential suitors, our first choice would be British-Swedish multinational pharmaceutical and biopharmaceutical company, AstraZeneca. It has significant equity holdings in two of Avacta's major partners (namely Moderna and ADC) and has a major interest in both immuno-oncology and drug conjugates – two areas that as we have highlighted in this paper, Affimer technology could significantly enhance.

Besides Ablynx, we briefly highlight below three other companies that have developed alternative protein scaffolds, to be utilised in drug development. For the sake of brevity, we will not detail the mechanics of each platform, but recommend viewing p.26 of Avacta's January 2020 corporate presentation (hosted on the Company's website), which compares the key attributes of each platform against the Affimer technology.

i) Molecular Partners (SIX listed, mkt cap: $459m)
The Swiss-based company is developing the DARPin platform, with its lead multi-specific candidate in Phase II trials.

ii) Bicycle Therapeutics (NASDAQ listed, mkt cap: $243m)
The company has used its eponymously named platform to develop various IO therapies. The first two – both being novel drug conjugates – are presently in Phase I trials. Last week, Bicyle entered into a strategic collaboration with Genentech – a member of multinational pharmaceutical conglomerate, Roche Group – to discover, develop and commercialise novel Bicycle-based IO therapies. Bicycle will receive a $30m upfront payment, and additional payments based on potential discovery, development, regulatory and commercial milestones that could total up to $1.7 billion.

iii) Pieris Pharmaceuticals (NASDAQ listed, mkt cap: $176m)
Pieris proprietary platform is its Anticalin technology, which it using to developing therapies focussed on two areas, namely IO and respiratory disease. In its IO division, its lead candidate is a bispecific compound that is currently in Phase I human trials.

The commencement of human trials is evidently a major value inflection point for developers of antibody memetic platforms, with successful completion of each trial catalysing further step changes in value. Bicycle and Pieris, whose lead candidates are in Phase I trials, have market capitalisations that are 4.7x and 3.4x that of Avacta's, respectively. Molecular Partners, whose lead candidate has already successfully passed through its Phase I trial and is now in its Phase II trial, is valued at 9.0x Avacta.

Of course, this is hardly a fair relative valuation methodology, as all of the companies have various other assets and operations that must be taken into account. However, the market capitalisations in the peer group do provide at least some indication of how investor interest in Avacta might build as its first Affimer molecule commences Phase I trials (likely to be AVA004 in H1 2021).

ii) pre|CISION platform

- **AVA6000 (pro-doxorubicin)**

On p.13, we set out some basic illustrative figures to demonstrate the potential commercial value to Avacta of a successfully commercialised pro-doxorubicin. To summarise:

- Upfront cash payment due to Avacta on positive data readout from Phase I trial, in Q4 2020: circa $50m
- Milestone cash payments due to Avacta in 2021-2025+: $300m to $500m
- Doxorubicin market size, 2019: circa $1bn
- Pro-doxorubicin market size, 2025: circa $5bn
- Gross royalty due to Avacta: 5%
- Net royalty due (after 20% royalty due to Tufts): 4%
- Net royalty due per annum (once peak sales are achieved): circa $200m

It is important to note that as AVA6000 is merely a reformulation of an existing, approved drug (doxorubicin has been the standard-of-care for many types of tumour for over four decades), it need only successfully pass a Phase I trial and then a Pivotal Phase II trial. [A novel drug must do 3-4 trials, including 1-2 much larger and more expensive Phase III trials.] This means that a partner that were to license AVA6000 in the event of a successful Phase I trial at the end of this year, could begin work on the Phase II trial early next year, and have it completed by 2023, with marketing approval granted by the end of that year. In other words, there is a reasonable possibility that Avacta could start to receive royalties from product sales as early as 2024.

- **Pipeline of other reformulated chemotherapies**

If AVA6000 is successful in Phase I, Avacta has a further *nine* pro-chemotherapies in the pipeline that it has already synthesised – the most advanced of which (a FAP-activated proteasome inhibitor named AVA3996) is only circa 12 months away from an IND regulatory filing.

The global chemotherapy market is forecast to reach $56.5bn by 2024. Clearly, *if* the pre|CISION technology works in man, this forecast could increase substantially. And if it does, Avacta – as the exclusive licensee of the platform technology from Tufts – and its partners would be perfectly positioned to seize a *major* share of this enlarged market.

iii) TMAC platform

The first of Avacta's novel Affimer-drug conjugates ('AfDC') will not likely enter the clinic until 2022. Each of the pre|CISION and Affimer technologies must be first successfully tested in humans in standalone trials (this year and next year, respectively). Realistically then, the first AfDC will not receive FDA marketing approval until 2028/29 at the earliest. It is difficult to forecast what the total addressable market ('TAM') might look like then, given the continuously evolving state of the cancer therapy market.

It has been estimated that by 2025, the global market for antibody-drug conjugates ('ADC') will have reached ~$10bn. That is a useful starting point for us in considering what the absolute base case TAM for Avacta's AfDCs might be. However, as we explained on p.11-14, Avacta's AfDCs are (theoretically, at least) far superior to conventional ADCs as they enable both chemotherapies and immunotherapies to work simultaneously, and complementary to one another. Accordingly, one could reasonably argue that the TAM for AfDCs could encompass a significant portion of the global immunotherapy market *and* the aforementioned *expanded* global chemotherapy market.

Indeed, the Company has alluded to such an expanded TAM in recent presentations. It quotes the following:

- By 2025, there will be ~350k patients treated by immunotherapies per annum worldwide
- Average reimbursement rate for treatment of $13k per month, or $156k pa
- Therefore the global market would be circa $55bn pa
- However, circa 1.75m new cancer patients are diagnosed pa in the EU and USA alone
- Only 20% - 30% of these (i.e. 350k to 525k patients) respond to monotherapies
- There are thus 1.2m to 1.4m cancer patients worldwide who could benefit from Avacta's AfDCs
- Assuming an equivalent reimbursement rate of $156k pa, this would amount to a further $187bn to £218bn in global sales pa
- 1% penetration of the overall expanded market would equate to $2.4bn to $2.7bn in global sales pa

Valuing such a platform at its current stage is virtually impossible; but it would be fair to say that, in light of the above quoted potential TAM for AfDCs, a successfully developed and commercialised TMAC platform would offer blue-sky valuation potential to its owner.

Most importantly, for the here and now, management has stressed that there is "significant commercial interest" in the TMAC platform and the AfDC concept. It is of course extremely early stage, but it is not difficult to perceive that a successfully developed TMAC platform could be nothing short of game-changing for cancer treatments. That is why we believe there is an immense inherent value in the TMAC platform, even at its current pre-clinical stage.

iv) Commercial collaborations

It is challenging to ascribe accurate valuations to each of the four major collaborations that Avacta has entered into, owing to the lack of detail provided (that is invariably the reality of most collaborations in the pharma and biotech business). Upfront payments are not (usually) known; milestone payments could ultimately be spread out over as long as a decade; royalty terms are unknown, etc.

What we do know is that all four major partners are covering Avacta's R&D costs in the respective collaborations.

Furthermore, from the details provided about the first three collaborations (namely with Moderna, LG Chem and ADC), we can calculate that for each therapeutic target against which a partner selects and licenses an Affimer candidate, said partner will pay Avacta approximately $50m, split across upfront and milestone payments.

To our knowledge, the number of therapeutic targets that the collaborations are working on are as follows:

Moderna: 1 target (with options over an undisclosed number of further targets)
LG Chem: 3 targets (with options over 3 further targets)
ADC: 3 targets

Once the Affimer technology has been validated in human trials, we anticipate a material increase in the ~$50m-per-licensed-candidate figure, in future collaborations. Additionally, upfront payments as a percentage of the total potential deal value will increase from 1% to 2%, to 10% to 15%.

The sporadic payments from each the collaborations, as well as Avacta's R&D costs being paid by the partners, will increasingly assist in offsetting the Company's cash burn going forward.

- **AffyXell Therapeutics (JV company with Daewoong Pharmaceutical Co Ltd)**

Avacta's collaboration with its fourth major partner, Daewoong, follows the same operational format as those above: Daewoong has selected certain targets; Avacta will generate a range of Affimer proteins against those targets; Daewoong will then incorporate the Affimers into their own therapeutics, etc.

However, in *corporate* format, the collaboration differs from the others. Whilst Avacta's first three collaborations are based on licensing deals, Avacta and Daewoong have created a new joint venture company, named AffyXell (Avacta holds a 45% equity stake).

Although the JV is only at an embryonic stage, it is interesting to observe how other early stage biotech companies specialising in gene and/or cell therapies have attracted dizzying valuations in recent years:

- In October 2018, Allogene Therapeutics listed on NASDAQ at a post-new money valuation of $2.1bn, raising $324m in new equity in the process. Allogene is a biotech business pioneering the development of allogeneic cell therapies for cancer (similar to Daewoong's platform technology, Allogene's platform enables it to develop 'off-the-shelf' therapies). At the time of IPO, the company had one drug candidate in Phase I clinical trials, with the remainder at pre-clinical stages.

- In July last year, Japan's multinational pharmaceutical conglomerate, Takeda Pharmaceutical Co, acquired Belgium-based TiGenix for €520m. TiGenix has a proprietary allogeneic stem cell platform technology which it is utilising for the treatment of autoimmune and inflammatory diseases. At the time of the acquisition, it had three lead drugs: the first in a Pivotal Phase III trial, the second in a Phase II trial, and the third in Phase I.

- In August last year, Germany's Bayer (one of the world's largest pharmaceutical companies) acquired the remaining 59.2% equity that it did not already own in BlueRock Therapeutics for up to $600m in cash. The deal valued BlueRock at circa $1bn. BlueRock is a US-based biotechnology company focussed on developing engineered cell therapies in the fields of neurology, cardiology and immunology, using its proprietary stem cell platform.

- In September last year, NASDAQ-listed Vertex Pharmaceuticals acquired Semma Therapeutics for $950m in cash. Founded only five years previously in 2014, Semma has developed a breakthrough stem cell technology which it is initially using to generate a curative cell therapy for type 1 diabetes.

- In February this year, Massachusetts-based Beam Therapeutics raised $170m in new equity in its NASDAQ IPO, at a post-new money valuation of $844m. Having been founded in only 2017, Beam develops gene editing technologies for the treatment of diseases. The Company has 12 programmes in development – all of which are pre-clinical.

Both Avacta and Daewoong believe that a combination of their proprietary technologies could create the "*next generation of cell therapies*", superior to existing types of therapies in the marketplace.

If the companies are correct in their belief, then there is no reason to think that AffyXell could not achieve the sort of valuations highlighted above, in just a few short years (even whilst at a pre-clinical stage).

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The Investment Thesis for Avacta Group

At the current share price of 22.75p, Avacta's market capitalisation is £40.0m. In this note, we have set out our rationale as to why we believe that there is a genuine possibility of Avacta becoming a billion-pound company within three years, if not sooner. Crucially, we believe that there is also a reasonable possibility that Avacta will not be required to return to the market to raise additional capital for the foreseeable future. This is as a result of the first pre|CISION therapeutic going into Phase I trials this year, and the licensing deal that we think the Company will secure on the back of it. An upfront cash payment of $50m would be sufficient to fund Avacta's activities over the next two years, during which time revenues in the Diagnostics division should grow rapidly and milestone payment receipts form the Therapeutics division should increase in size and frequency.

We have demonstrated, via publicly listed comparators, how Avacta's Affimer platform alone could potentially be worth several hundred million dollars by the end of next year; and, via the Sanofi-Ablynx transaction, how it could potentially be worth several *billion* dollars by the end of this decade. The true value of the platform resides in its capacity to provide the owner (or licensee) with *freedom to operate*. Almost any drug that is antibody-based can be remade using the Affimer protein scaffold. Indeed, as we have explained in this note, Affimers offer numerous advantages (such as cost of manufacture and ease of formatting) over antibodies in the development of drug molecules. Even if an antibody-based drug is still on patent, the owner / licensee of the Affimer technology could create an equivalent drug that has almost identical therapeutic effects, and yet not be infringing on the patent of the existing antibody-based drug. Drugs markets worth in excess of $125bn would be fair game.

We have also portrayed how the Diagnostics division alone could command a valuation of between £24.7m and £38.0m (or between 14.0p and 21.6p per share for Avacta), using the most relevant publicly listed comparator, Bioventix. Whilst of secondary importance to our investment thesis, the division nevertheless plays an important role in underpinning much of Avacta's existing valuation.

However, in our view the investment thesis for Avacta was totally transformed with the signing of the deal with Tufts in 2018, which granted Avacta with exclusive access to the pre|CISION platform. Firstly, it offers the potential for a major cash windfall for the Company *this year*. Secondly, as a standalone platform it could then be used to reformulate at least a dozen *other* existing chemotherapies, and in doing so *substantially* expand the global chemotherapy market that is estimated to reach $55bn by 2025. Crucially, as the process is only a *reformulation* of generic drugs, the development pathway for a pro-chemotherapy would consist of only Phase I and Pivotal Phase II trials – in other words, Avacta (and its partner) could take a chemotherapy from a pre-clinical stage to FDA approved status, in only 3-4 years.

Thirdly, and in our opinion most significantly of all, access to the pre|CISION platform has provided Avacta with the opportunity to combine it with its own Affimer technology to create a third, hybrid platform: TMAC. We believe that the Affimer-drug conjugates that the TMAC platform can generate have the potential to change the landscape of cancer treatment in the years ahead. An immunotherapy-chemotherapy drug, linked together in a single molecule, working in tandem with one another to destroy cancer cells – and critically whilst not causing any unwanted side effects associated with standard chemotherapies – is an astonishing concept. The total addressable market for such a class of therapy could be in the hundreds of billions of dollars.

A vital aspect of the investment thesis is the fact that all three platforms have performed successfully – both with regard to efficacy and to safety profile – in pre-clinical animal studies. Whilst this in no way guarantees success in Phase I human trials and beyond, it is a very good start. With regard to the more established Affimer platform at least, the fact that four major pharmaceutical companies have licensed the technology for a cumulative sum that could ultimately far exceed $500m – *even in its current pre-clinical stage* – is hugely reassuring for us as investors.

Turning to corporate matters. The shareholder register is highly impressive for an AIM-listed, £40m company. 59.8% of the share capital is held by the top nine institutional investors. They have been extremely supportive when Avacta has sought to raise cash over the past five years (a total of ~£42m across three equity placings).

On a less impressive note, the board of directors between them hold less than 1% of the share capital. Their participations in the last two placings have been minimal. To offset this, the résumés of the directors and senior management are first class, with substantial cumulative experience in tier 1 multinational pharmaceutical companies. The CEO, Alastair Smith, having listed Avacta in 2006, has been responsible for raising circa £70m for the Company in new equity (the dilutionary effect of which largely explains his now very modest equity holding).

In our opinion, Avacta must dispose of, or close down, its legacy Animal Health division with all due haste. It is a cash drain on the wider business (losing circa £0.5m per annum) and a distraction to senior management. We hope to see this carried out in 2020.

Moving on to valuation. It should be apparent to readers by now that Avacta really does possess 'blue-sky potential'. Why, then, is it presently valued at only £40m? We believe there are several reasons for this. There is a plethora of varying workflows being progressed simultaneously within Avacta. Some of the therapeutic programmes involve entirely novel concepts, whilst the platforms themselves are quite complex. It is thus challenging for investors to understand them in an instant, and consequently to truly appreciate their potential commercial value. Following on from this, the *UK* investment community for some unknown reason tends to attribute significantly less value to early stage biotech than does its cousins across the pond. The valuations of comparable peers listed on NASDAQ verify this.

We feel that the UK market is in fact pricing in far too great a probability of failure in the upcoming pro-doxorubicin Phase I human trial, and the PD-L1 monotherapy trial next year. Phase I human trials have on average a success rate of 70% to 80%. Even if only one of the two trials were to succeed, Avacta should enjoy a material rerating in its valuation.

To achieve the billion-pound valuation, however, it is vital that the pro-doxorubicin trial is successful, as it will validate the pre|CISION platform, create an immediate cash windfall, and most significantly of all, potentially unlock what we consider to be Avacta's Holy Grail – the TMAC platform and its Affimer-drug conjugates.

To achieve the *multi*-billion-pound valuation, Avacta must complete a successful Phase I trial for its first AfDC (likely to be in 2022). If that were to occur, we would expect suitors to come knocking quickly. The acquirer of Avacta would gain control of:

- A first-in-class antibody memetic platform that would enable it to operate freely in its drug development programmes, without a concern for infringing on antibody-based drug patents;
- A targeted chemotherapy platform, that can be used to reformulate existing chemotherapies;
- A platform that can generate an entirely novel class of drug (that combines immunotherapy with targeted chemotherapy in a single drug), which could reshape the landscape for cancer treatment.

Certainly, there is significant risk for investors to consider, as is invariably the case in early stage biotech. However, our investment thesis for Avacta is founded on our view that at its current market capitalisation of £40m, the risk / reward ratio is quite simply wrong. Very wrong. We believe that the wider market has not perceived the inherent value already within the Company, and its relatively near-term blue-sky potential.

We will end our paper with this:

Were the Phase I human trial for pro-doxorubicin later this year to be successful, it is not difficult to imagine that Avacta would hit mainstream global news. A well-known, established chemotherapy has been reformulated so that it no longer causes horrible side-effects; and, critically, can now be used for many more cycles (as it no longer harms the heart), thus giving it a much great chance of destroying the patient's cancer? Interest in the Company, both from within the pharmaceutical industry and from the international investment community, would explode. A billion-pound valuation wouldn't just be pie in the sky then.

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Disclosure

The author of this paper, Myles McNulty, is a private investor. He and his family hold 1.0% of the ordinary shares of Avacta Group.

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