AVACTA GROUP LTD

UPDATE III: PART I

12.10.2020

Ticker:	**AVCT.L**
Price (p):	**182.0**
Shares in issue (m):	**252.6**
Market cap. (£m):	**459.8**

Introduction

This Update Note should be read in conjunction with our previous commentary on Avacta Group. All notes viewable here:

https://aimchaos.com/

Since we published the final instalment of our last Update Note on 24 June, Avacta Group ('Avacta') has grown considerably as a business, rapidly progressing multiple, significant workstreams. It is developing (or co-developing) at least six COVID-19 related products, some of which are at the point of commercialisation. We believe that the Company is now on the cusp of a critical value inflection point.

The global pandemic, which had tapered off somewhat in the Northern Hemisphere during the summer months, has returned in full force to much of Europe and North America in a second wave – which really was an inevitability. Daily new cases worldwide over the past week have been at record highs, and lockdown measures are now firmly back in play. In the absence of an effective – and then very widely distributed – vaccine, it has now become widely acknowledged by governments and health bodies across the globe that regular testing on a mass scale could be humanity's best hope of curbing the spread of COVID-19.

This is the first instalment of a two-part Update Note on Avacta. In this instalment, we focus entirely on Avacta's SARS-CoV-2 lateral flow test ('LFT'). We first examine its current status, and its probable routes to market. We then analyse the requirements for a high quality LFT that could be used for point-of-care professional use; and, more significantly, for at-home, consumer use. Subsequently, we explain why we believe that Avacta's Affimer technology provides the Company with a real chance of producing a first-in-class LFT, globally. Finally, we briefly comment on the potential market for a high quality LFT, as well as on competing tests.

In the second instalment, we will examine the other COVID-19 products under development, including:

- BAMS test
- ELISA test
- Microtox PD – wastewater detection system
- Microtox BT – personalised breath test
- Neutralizing Affimer therapy

We will then consider the potential impact on Avacta's activities from the successful development of a vaccine, and from the possibility of herd immunity.

We shall also discuss the recent progress made by the wider (non-COVID-19-related) Diagnostics division, and by the Therapeutics division.

Corporate matters – including the potential timing and impact of a NASDAQ listing – will be considered.

Finally, we shall revisit and update our Investment Thesis for Avacta – which has improved dramatically since we published our initial Thesis on 1 March this year.

Current Status

Since we published our last note on 24 June, Avacta has made considerable progress in the development of its Affimer-based antigen lateral flow test ('LFT'). On the same day of our publication, the Company also announced that it had generated "*positive initial data*" from the first LFT prototypes:

"*These data show that the test strips detect the spike protein in model samples at concentrations within the clinical range found in saliva of patients with COVID-19.*"

Over the following six weeks, Avacta and Cytiva then worked to "*optimise its performance and get the best detection limit possible in order to generate the highest sensitivity in the final rapid test product.*"

On 6 August, Avacta announced that it had appointed BBI Solutions ('BBI'), part of BBI Group, as lead manufacturing partner for the LFT. BBI is a developer and manufacturer of raw materials and finished test products for the in-vitro diagnostics market, with manufacturing sites in the UK, US, South Africa, Germany and China.

The 'technology transfer' process, which had commenced before 6 August, is still underway. This involves scale up of the manufacturing process, and subsequently optimisation of the performance of the devices manufactured with the scaled-up process. The supply of the raw materials – namely the nitrocellulose strip from Cytiva, and the Affimer reagents from Avacta – should not be a limiting factor; neither should be the supply of plasticware, including casing, saliva collection tube and pipette. However, we believe that the difficulty in achieving mass scale production will be in the test kit assembly. Aspects of this simply cannot be automated and will thus rely on manual production lines – involving very large workforces.

We expect the tech transfer process to be completed in the coming weeks. However, with previous timeframes having been suggested and subsequently missed by the Company, we note that management (in our view, wisely) is no longer providing the market with any detailed timeline, other than to state that tech transfer will be completed at some point in Q4 2020. Recently, numerous sub-par antigen tests for SARS-CoV-2 have been rushed to market around the world, only to stall or even fail at clinical validation or point of commercialisation. Avacta's management is intent on developing, validating, commercially launching, and manufacturing its LFT methodically and meticulously, in order to minimise risk further down the line. If it has missed out on being first to market, then so be it. As we discuss on p.15, the total addressable market for Avacta going into 2021 will essentially be unlimited: a handful of large competitors will make no difference to the commercial opportunity.

On 2 September, Avacta announced that it had signed up another UK-based manufacturing partner for its LFT, namely Abingdon Health. Abingdon is Europe's largest contract manufacturer of LFTs and has two production sites in the UK. Tech transfer to Abingdon is also ongoing – although it will essentially be mimicking the process that Avacta and lead manufacturer, BBI, are now establishing.

Between BBI and Abingdon, we believe that current manufacturing capacity for Avacta' LFT is in the region of 7-8 million per month, although we understand that this could be significantly increased over the coming months (our estimation is by 2-3x).

Clinical Validation and CE Marking

Within the EU (or more specifically, within the European Economic Area), clinical validation of an in-vitro diagnostic ('IVD') medical device ('MD') can only be conducted on devices made using the finalised, scaled-up manufacturing process. "CE marking" is a self-certification process by the manufacturer – a declaration that the product meets EU standards for health, safety, and environmental protection. It is mandatory for certain IVD MDs (including LFTs) to be CE marked before they can be marketed for professional use within the EU.

"Professional use" means that a trained healthcare professional must administer the test to the patient. There are 10 health and social care professional bodies in the UK, whose qualified members could administer an IVD MD – thus providing an already sizeable addressable market for a professional use only test.[1] In the case of Avacta's LFT, it would permit the test to be used in hospitals, GP surgeries, testing stations, and locations such as care homes and airports that have trained healthcare professionals on-site.

Attaining CE marking for consumer use, i.e. "self-testing", is an altogether much more difficult task. Whilst self-certification for professional use can be achieved through a clinical validation process that uses only several hundred patient samples in the hospital setting, clinical validation for a *consumer use* IVD MD must be carried out using *thousands* of samples. This "lay user study" involves lay persons (i.e. random individuals from the general population) using the LFT (likely to be on a regular basis), and evaluates the usability of the test to ensure that it can be carried out successfully and safely, by anyone.

Consumer use CE marking of an IVD MD cannot be self-certified, but must be granted by the notified body of the manufacturer of the device. A notified body is an organisation that has been designated by an EU member state to assess whether manufacturers and their medical devices meet the requirements set out in legislation. The Medicines and Healthcare Products Regulatory Agency ('MHRA') is the notified body in the UK.

Following completion of tech transfer from Avacta and Cytiva to BBI, an initial batch of 10,000 LFTs will be manufactured. These will be used to run the two studies – professional use clinical validation, and the lay user study – in parallel. The former will likely be run in several hospitals across the UK. Assuming priority access to patient samples is granted over other IVD MDs being clinically validated, it could be completed in less than two weeks. The lay user study, on the other hand, will likely take at least one month to complete, in our view.

With regards to securing approval for marketing in the US, we believe that Avacta could be granted Emergency Use Authorization ('EUA') by the FDA, on the back of securing CE marking for each of professional use and consumer use following its UK-based studies. It is, in our opinion, highly likely that dialogue between the Company and the FDA has already commenced.

[1] https://www.professionalstandards.org.uk/what-we-do/our-work-with-regulators/find-a-regulator

Production Strategy

Avacta intends for as much of its manufacturing capacity as possible to be UK-based. In addition to BBI and Abingdon, it has also been reported in the UK press that Avacta and fellow AIM peer, Omega Diagnostics, have held preliminary discussions with a view to Omega becoming yet another UK-based manufacturing partner.[2] We believe that this is a highly probable outcome and expect confirmation of a manufacturing agreement from both companies shortly. Another potential manufacturing partner for Avacta is CIGA Healthcare, a member of the UK Rapid Test Consortium ('UK-RTC') along with BBI, Abingdon, Omega and Oxford University. Indeed, we feel that ultimately, the lion's share of the UK-RTC's total manufacturing capacity will be assigned to Avacta's LFT.

Between those four UK manufacturers, we estimate that there is existing capacity to produce perhaps 15-20 million LFTs per month. Given the scale of the UK Government's plans for Project Moonshot (which we discuss in detail on p.15), this capacity will have to be ramped up substantially in the coming weeks and months.

However, to achieve an output of *many tens* (and indeed, *hundreds*) of millions of units per month, Avacta will require manufacturing partners overseas as well. To that end, management has disclosed that it is already in talks with manufacturers in South East Asia. These manufacturers would cover the shortfall in the UK market of the domestic manufacturers; and thereafter supply Avacta's LFT to international markets (with priority markets being US, EU, India and Latin America (especially Brazil), in our view).

The reality is that the demand for Avacta's test will be – for all intents and purposes – unlimited. If Avacta actually manages to achieve its implied goal of producing 100m+ LFTs per month, this will be gobbled up instantly. We think 400m tests per month would likewise be snapped up. It is almost impossible, in our view, that Avacta will ever achieve that second number: but the point is that demand for the LFT – at least from an investment perspective – is essentially uncapped.

It is significant to note that in addition to expanding its own Affimer production facilities in Wetherby (for which it earmarked £5m of the fundraise carried out in June), the Company is now in discussions with contract manufacturers to *also* produce Affimers. This suggests that the anticipated demand for the LFT (and other Affimer-based diagnostic products under development, both in-house and by third parties) has now increased *considerably*, from the level of demand that the Company had thought realistic as recently as June.

Finally, Avacta is putting plans in place to expand Affimer-based LFT production through third party developers. The rationale is simple: if the global market for SARS-CoV-2 detecting LFTs is half a billion or more units per month (in fact, we consider it to be much larger than this), there is simply no way that Avacta will ever be able to meet this demand. Why not then lease out the Affimer technology to major IVD players, for them to use instead of monoclonal antibodies ('mAb') in their own-manufactured, branded and distributed LFTs?

As we examine on pp.11-14, we believe that Avacta's Affimers offer several distinct advantages over mAbs when used as reagents in IVD medical devices – and especially in LFTs. One of these is not so much an advantage as a critical differentiator: *specificity*. When Affimer-based, SARS-CoV-2 targeting IVD assays have completed clinical validation (with the BAMS test due in the coming weeks, followed by the LFT in the coming months), we strongly believe that the global diagnostics industry will really wake up to the superiority of Affimers over mAbs.

In the presentation that accompanied its recent interim results, Avacta has already alluded to this strategy of leasing out its SARS-CoV-2 binding Affimers. It stated:

"There is significant additional third-party commercial interest in spike protein Affimer binders (including from several global IVD companies, bioprocessing companies and research reagents suppliers)."

[2] https://www.yorkshirepost.co.uk/business/consumer/avacta-set-momentous-milestones-it-prepares-launch-covid-19-test-2985152

We believe that besides securing additional manufacturing partners for its own-branded LFT both at home (Omega, CIGA) and abroad (manufacturers in South East Asia), Avacta could shortly announce partnerships with major IVD players. The partnerships would likely consist of Avacta supplying Affimer binders to these companies, for them to use the Affimers to replace the mAb-based reagents in their own-branded LFTs. Potential partners could be companies such as Danaher Corporation (the parent company of Avacta's existing development partner, Cytiva); Thermo Fisher Scientific; Abbott Laboratories; Roche, etc. All companies that have market leading capabilities in lateral flow immunoassay development and production – but all of whom use mAb reagents.

Such partnerships would remove the development risk for Avacta itself, as well as commercialisation costs. Instead, the Company would receive royalties on each and every LFT sold, regardless of the branding. The ultimate goal for Avacta is simply to ensure that its Affimers are used in as many models of LFTs as possible.

Think ARM processing chips in numerous different makes of smartphones and tablets. Think Mercedes or Ferrari engines being used by multiple Formula 1 racing teams.

Distribution Strategy

Given that the CE marking for professional use and consumer use are likely to be as much as a couple of months apart, Avacta will have two distinct distribution strategies in place for each market.

We retain our view that the UK Government is highly likely to purchase the entirety of Avacta's output – be it 10m per month or 50m per month – for *at least* the first several months. We discuss the Government's much touted Project Moonshot in more detail on p.15.

Besides the Government purchasing, the other key areas for a professional use only LFT are in airports, ports, care homes and in the workplace (especially for large corporations). As we stated in our first Update Note in April (p.10):[3]

"*In 2019, it was almost unimaginable that the lockdowns now in place across many of the world's most democratic countries could have ever occurred. In light of the unprecedented measures taken to battle the pandemic, it would now be entirely reasonable to suggest that airlines across the world may insist on all passengers taking a point-of-care ('POC') antigen test before boarding. With the test only taking 5-10 minutes, the extra admin would hardly be prohibitive. We imagine that queuing for flights could be split into two segregated areas, with passengers only permitted into the second area once they have submitted their completed tests (which they would collect upon entrance to the first area).*

In just this example of how POC antigen tests could be used at strategic checkpoints, it is noteworthy that circa 4.3 billion passengers were carried on scheduled flights in 2018.

Another example of POC antigen checkpoint testing could be corporations only permitting entry to the office to their employees once they have submitted a POC test, at the office door. It may be that a test is only required of each employee on a weekly basis (Monday morning being the obvious choice)."

We are unsure how Avacta will target the consumer use market. The Company already has in place a global, exclusive, direct-to-consumer ('DTC') sales and marketing agreement with Medusa19 Ltd ('Medusa'), an IVD MD distribution company recently launched by the founders of boohoo, the affordable fashion clothing giant.[4]

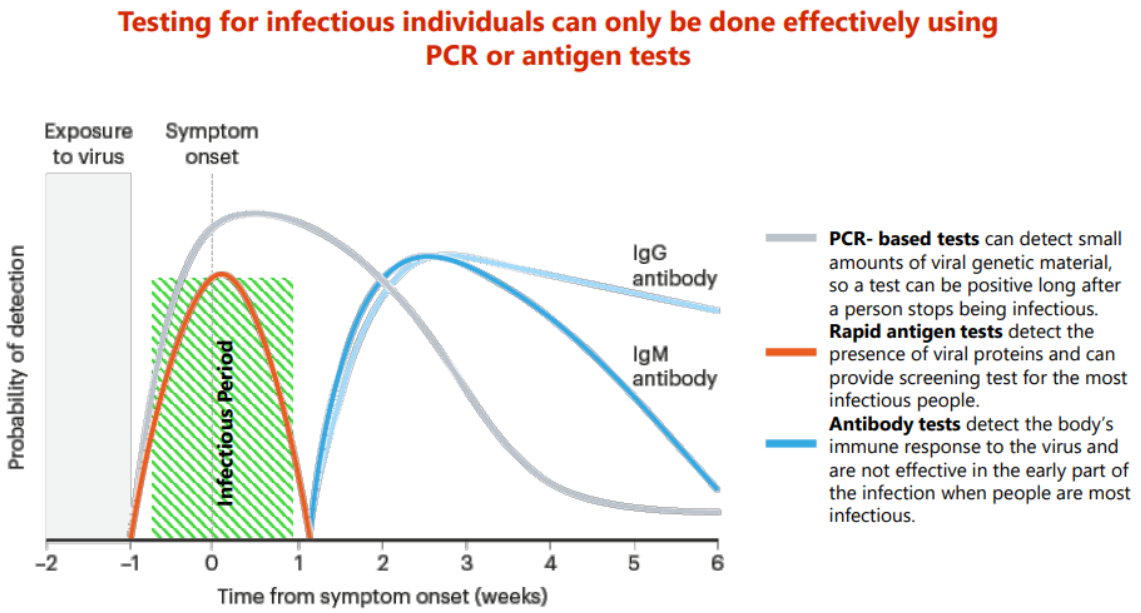
However, we increasingly believe that the UK Government may well decide to take DTC distribution in the UK into its own hands. A wholesale population testing programme using a high quality antigen-based LFT, could be as effective as – and arguably, even more so than – a vaccination programme (we will be examining this in Part II of this Update Note). As such, the Government could seek to secure the entire supply of Avacta's LFTs – not just for the NHS but for DTC distribution as well – for *significantly* longer than the first several months of production.

With regards to international sales, we expect that commercial distribution partners will be announced in due course.

[3] https://aimchaos.files.wordpress.com/2020/04/avacta-group-update.pdf
[4] https://aimchaos.files.wordpress.com/2020/05/avacta-group-update-ii-part-i.pdf - see p.8 for Avacta's exclusive DTC distribution agreement with Medusa

LFT Requirements for Point-of-Care and At-Home Testing

We wrote in detail of how an antigen test works, and of its benefits over RT-PCR testing for SAR-CoV-2, in our Update Note dated 15.04.2020.[5] To summarise: whilst antigen tests will, in general, be less sensitive than PCR tests (they do not employ the amplification technique that is used in PCR), they are suitable for identifying the majority of *infectious* patients. Moreover, for the purposes of mass population screening, due to the amplification technique it uses PCR testing can in fact be *too* sensitive, in that it detects *infected* patients who are no longer *infectious*. In effect, they can generate another sort of false positive result. The slide below, extracted from Avacta's Interim Results presentation, demonstrates this:



At this juncture, we will explain in more detail the importance of test sensitivity and specificity, and what would be required for an effective rapid antigen test for point-of-care ('POC') and/or wholesale population screening.

In medical diagnosis, test *sensitivity* is the ability of the test to correctly identify those with the disease, i.e. the percentage of sick people who are correctly identified as having the disease. It is the extent to which 'true positives' are not overlooked. An incorrect result – a result that indicates a person does not have the disease, when in fact they do – is referred to as a false negative.

Test *specificity* is the ability of the test to correctly identify those without the disease, i.e. the percentage of healthy people who are correctly identified as being healthy. It is the extent to which 'true negatives' are not overlooked. An incorrect result – a result that indicates a person does have the disease, when in fact they do not – is referred to as a false positive.

In the case of SARS-CoV-2, the perfect test would have 100% sensitivity, meaning that all infectious individuals would be correctly identified as infectious; and 100% specificity, meaning that no healthy individuals would be incorrectly identified as infectious.

Unfortunately, qualitative diagnostic tests (i.e. a test that simply indicates whether a particular substance is present in the specimen) such as LFTs tend to lack the high sensitivity that quantitative tests (i.e. a test that indicates *how much* of a particular substance is present in the specimen) enjoy. This is primarily due to having to sacrifice accuracy for the sake of improving speed of result.

[5] https://aimchaos.files.wordpress.com/2020/04/avacta-group-update.pdf

Attempting to increase the sensitivity of an LFT also invariably results in the specificity of the test declining – and vice-versa. Accordingly, there is usually a trade-off between the two – and the one that is given higher priority is dependent on the intended use case of the test in question.

For rapid, POC testing for SARS-CoV-2, governments and health bodies around the world have articulated that *specificity* should be given priority over sensitivity. For example, the UK Government updated its guidance last month for POC rapid antigen tests for SARS-CoV-2: its minimum sensitivity is >80%, and minimum specificity, >95%. Its *desirable* performance characteristics are sensitivity >97% and specificity >99%.[6]

Similarly, in its Interim Guidance dated 11 September, the World Health Organization ('WHO') suggested that the minimum performance requirements for POC rapid antigen tests should be at least 80% sensitivity and at least 97% specificity.[7]

In the case of regular screening where the purpose of the test is to identify any and all infectious persons, whether pre-symptomatic, symptomatic or asymptomatic – such as point-of-entry (e.g. airport) testing; or crucially, *at-home*, wholesale population testing (which by definition would require a rapid, self-administered test such as an LFT) – an even higher specificity is necessary. To quote the WHO's Interim Guidance (p.3):

"*Use of antigen-detecting rapid diagnostic kits ('Ag-RDT') is not recommended in settings or populations with low expected prevalence of disease (e.g. screening at points of entry, blood donation, elective surgery), especially where confirmatory testing by RT-PCR is not readily available. Such use will not be possible until there are more data from high quality studies confirming high specificity (>99%) of one or more of the commercialized Ag-RDT test kits.*"

We shall now explain why it is critical that POC and/or at-home tests for SARS-CoV-2 must have an exceptionally high specificity.

Firstly, it is important to note what is occurring across the world with regards to testing for SARS-CoV-2. Centralised testing – comprised of the highly sensitive and specific PCR tests that currently return results to patients within 24 to 48 hours, as samples must be sent to laboratories for machine-based processing – is already at breaking point. PCR machines are running at maximum capacity, as ever greater numbers of people request tests because they are showing symptoms or have been in contact with a confirmed infected person. There are also chronic shortages worldwide of both testing reagents and swabs.

Regular, at-home, wholesale population testing using LFTs is not only a potential solution to easing the burden on centralised testing, but in fact a potential solution to suppressing the pandemic itself. It would work as follows:

- The majority of the population self-administers a cheap, disposable test – at their own homes, say on a Monday morning. Individuals log their results on a mobile phone App (Government-backed and linked to the national health body / track-and-trace system).

- Those individuals who record positive results, isolate at home. They then use a second LFT on Tuesday or Wednesday morning, to validate the positive result of the first test. [Taking multiple tests *substantially* reduces the probability of recording a false negative or false positive.]

- Individuals who test positive could also apply for a PCR test, after the first (or more likely second) positive LFT result – for the purpose of validation.

- Individuals who have been confirmed as positive (i.e. infectious) continue to isolate at home, and self-test again with an LFT every 3-4 days, until they are no longer infectious.

[6] https://www.gov.uk/government/publications/how-tests-and-testing-kits-for-coronavirus-covid-19-work/target-product-profile-point-of-care-sars-cov-2-detection-tests
[7] https://www.who.int/publications/i/item/antigen-detection-in-the-diagnosis-of-sars-cov-2infection-using-rapid-immunoassays

- In this manner, infectious individuals are removed from circulating within the wider, healthy population. Theoretically, this should ensure that the virus dies out through lack of available hosts. Of course, the virus could re-enter the country through infectious individuals travelling into the country from abroad; but this could be mitigated by strict LFT testing (and confirmatory PCR testing) at airports, ports and border crossings.

Why should specificity take priority over sensitivity in an LFT for SARS-CoV-2 detection? Most would *assume* that for governments and health bodies, high sensitivity is of greater importance than high specificity. After all, a test with high sensitivity will ensure that the least number of individuals are given a false negative result. [False negative results would usually cause infected individuals to believe that they are healthy, and therefore to mix with the wider population and consequently to inadvertently spread the virus.] The answer to this apparent lack of regard for human life lies in a combination of two key matters:

1) The LFT *must* be highly specific, in order to ease the burden on centralised testing across the world; and, even more significantly, to unlock economies and societies by enabling people to go out and about with a very high degree of confidence that they are not infectious (as the LFT will yield only a minute percentage of false positives).

2) The LFT doesn't *have* to be extremely highly sensitive, given that antigen testing tends to detect only the *infectious* period (and not the entire period of infection) that patients experience anyway.

We shall expand on 1) first. A test with lower *specificity* would mean that a greater number of false positives would be recorded. As winter approaches in the Northern Hemisphere, other coronaviruses will become increasingly prevalent. There are in fact *seven* known coronaviruses that infect humans. The other six besides SARS-CoV-2 are:

1) Human coronavirus 229E (HCoV-229E)
2) Human coronavirus HKU1 (HCoV-HKU1)
3) Human coronavirus NL63 (HCoV-NL63)
4) Human coronavirus OC43 (HCoV-OC43)
5) Middle East respiratory syndrome-related coronavirus (MERS-CoV)
6) Severe acute respiratory syndrome coronavirus (SARS-CoV-1)

The first four of the above are estimated to cause 10-15% of common cold cases worldwide.[8]

A SARS-CoV-2 diagnostic test with a low specificity might bind to one or more of the above coronaviruses, thus recording a false positive. Such a test used en masse would result in many non-infectious people thinking they were infectious: they would isolate unnecessarily, causing further damage to the economy and to society. This would be the very inverse of what a mass screening programme would be striving to achieve: reopening societies and economies and returning life to 'normal', in which freedom of movement is a given once more.[9]

Furthermore, uninfected individuals who had received false positive results would then swamp the already overstretched health services and central testing capacity, in search of (unnecessary) medical assistance and confirmatory PCR tests.

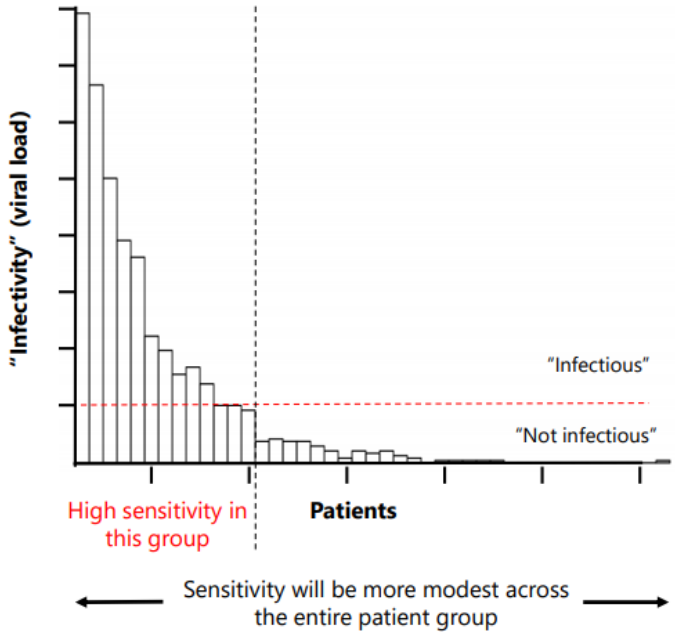
With regards to 2) above: the diagram on p.7 illustrates perfectly why the sensitivity of a rapid antigen test that has been designed for mass population testing need not be perfect.

The incubation period for SARS-CoV-2 averages around one week (but can vary from as little as two days to as much as two weeks). For several days following exposure to the virus, an individual will be infected but not infectious. During that period, infectious material rapidly builds up in the upper respiratory tract (i.e. the nose

[8] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7125703/
[9] https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30453-7/fulltext

and throat) of the individual: at around two to three days before onset of symptoms, the material is present there in sufficient enough quantities as to make the individual infectious (through shedding viral particles into their surroundings). This high viral load that makes an individual infectious lasts for approximately a week *after* onset of symptoms. As such, an individual is *infectious* for around ten days on average.

The purpose of the antigen-based LFT when used in point-of-entry settings or in wholesale population screening is to prevent transmission of the virus by extracting infectious individuals from circulating within the wider, healthy population. Accordingly, it must be sensitive enough to detect this period of infectiousness, but not beyond that. The illustration below (again taken from Avacta's Interim Results presentation) demonstrates this.



To support this view, we note that PCR tests with extremely high sensitivity can detect infected individuals who are no longer infectious (as demonstrated by the illustration on p.7). Although impossible to determine, enforced isolation of infected but not infectious individuals (and consequently, unnecessary isolation) has likely occurred many millions of times already worldwide this year, owing to overly sensitive PCR testing. This would have caused incalculable damage to societies and economies.

Furthermore, regular, repeat testing using LFTs is a fundamental component of the mass testing programmes being planned by governments. *Repeat* testing will ensure that infectious cases are very rarely missed for more than a few days (assuming willing participation in the mass testing programme by the population).

To summarise: mankind does not yet have the technological capability to produce an LFT to detect SARS-CoV-2 that has 100% sensitivity, 100% specificity and a 15-minute turnaround. Ultimately, as in almost all diagnostics scenarios, there is a trade-off decision to be made in LFT testing. Sensitivity has to be partially sacrificed to afford a rapid test with extremely high specificity. There will be missed cases, certainly – a test with anything other than 100% sensitivity is going to result in false negatives. However, these false negatives will almost all relate to cases of infection, but not *infectiousness*. That is a sacrifice that health authorities and governments across the world seem willing to make – and for very good reason, in our view.

So then, the ideal lateral flow test (within the realms of possibility!) for detecting SARS-CoV-2 is a test that gives a result in less than 15 minutes, has at least 99% specificity, and at least 95% sensitivity for infectious cases.

The Potential Quality of Avacta's LFT

We are confident that Avacta is now near to completing the development of what will be a first-in-class rapid antigen LFT for detecting SARS-CoV-2. Our confidence is founded upon the superiority of Avacta's proprietary technology, Affimers, over monoclonal antibodies, when used in reagents for IVD MDs.

Avacta has two very similar Affimer scaffolds, based on protein conformations, that each have substantial protein libraries. The first is of human origin, based on the naturally occurring human protease inhibitor Stefin A, and is ideal for therapeutic applications. This was developed by Dr Paul Ko Ferrigno at the University of Leeds: Avacta secured the commercial rights to it via the acquisition of Aptuscan Ltd (a spin-out from the university) for £1.5m in early 2012. The second Affimer scaffold is based on a consensus sequence of Cystatin A from a number of plant species and is ideal for use in reagents and diagnostics. This second scaffold was developed subsequent to the first, by Dr Darren Tomlinson and Professor Mike McPherson at the University of Leeds, with the priority date for the family of patents being in February 2013. Affimer binders derived from this second protein library are being used in Avacta's various diagnostic products – not least those focussed on the detection of SARS-CoV-2.

So: what are the advantages of Affimers over mAbs, when used in reagents in in-vitro diagnostic medical devices? We believe that there are five advantages of note – although, particularly with regards to an LFT designed for mass population screening for SARS-CoV-2, one of these five is the critical differentiator, namely *specificity*. The other four advantages we believe that Affimers hold over mAbs are:

- *Potentially* higher sensitivity
- Ease of manufacturing (and thus easier to produce at mass scale)
- Robustness (and thus greater durability throughout the distribution supply chain, as well as longer shelf-life)
- Rapid development (which would ensure that, in the case of a severe mutation of the SARS-CoV-2 emerging that the existing Affimers being used do not bind to, Avacta could develop – in just a few short weeks – additional Affimers for new reagents to be installed on its LFTs).

We shall first examine that critical differentiator, specificity, in tandem with sensitivity.

Numerous factors can affect the sensitivity of a diagnostic test. One of these is binding affinity. Binding affinity is the strength of the binding interaction between a single biomolecule (in this case, the Affimer protein) to its binding partner (in this case, the SARS-CoV-2 spike protein). Essentially, affinity is a measure of the tightness with which these two molecules bind together. *Generally* speaking, the higher the affinity of the antibody (or in this case, antibody mimetic – the Affimer) in the reagent, the higher the sensitivity of that reagent.

Affimers have a high binding affinity. This is due to their small size, which ensures that their numerous binding sites constitute a high ratio of their total surface area. Miss Joe Jackson summarised it succinctly in her 2017 PHD:[10]

"*The use of Affimers in immunohistochemistry and microscopy techniques may also allow for greater sensitivity of these techniques when compared to antibodies due to increased number of binding events, resulting from the reduced size of the Affimer verses the antibody.*" (p.68)

"*As previously mentioned… the small size of Affimers compared to their antibody counterparts may allow them to be employed to increase the sensitivity of imaging techniques. This is due to the potential increase in binding events resulting from decreased stearic hindrance.*" (p.69)

[10] http://etheses.whiterose.ac.uk/19759/1/Zoe%20Jackson%20SMCB%202017.pdf

"*The main functional improvements made when considering the design of non-antibody binding proteins is to reduce or eliminate the number of cysteine residues, this simplifies the basic structure of the Affimer and ensures there are no homodimer formations. Furthermore, it also increases the binding affinity to the target molecule as well as decreasing the size of the binding protein, reducing the redundancy seen in many antibodies. This is because only a small region is involved in the binding with the target protein relative to the size of the antibody. The reduction in size of the binding protein also lends the reagents to be used in different molecular biology applications where conventional antibody size poses a direct challenge, for example as detection reagents in super resolution microscopy… The production of a non-antibody reagent for the use in LFTs should result in an improvement in time-to-result as well as sensitivity of the test, as a direct result of the reagent being able to move through the device components at a faster flow rate.*" (p.102)

Moreover, there is a further aspect of the Affimer technology that could potentially improve the sensitivity of a reagent in which it is utilised. In its announcement of 11 May 2020, Avacta announced that it had made another important discovery during its research into its newly discovered Affimers that bind the SARS-CoV-2 spike protein:

"…there are Affimer reagents that can work in pairs, both binding to the spike protein at the same time. This allows tests to be developed that detect both the intact virus particle and the detached spike proteins which become separated from the virus particle during the development of the COVID-19 disease, which may also be important in monitoring disease progression…. This means that we should have the best possible COVID-19 antigen test."

In our view, this is a hugely positive development: it will ensure an even higher level of sensitivity for Avacta's test, as well as a lower (i.e. improved) limit of detection. This technique was in fact referenced as early as 2017, in a research paper on Affimers: [11]

"*Whilst our screening strategy identifies monoclonal reagents, these can also be combined to generate polyclonal reagents that may improve sensitivity for certain in vitro applications.*"

Miss Jackson also alluded to this possibility in her PHD three years ago:

"*A multiplex system can also be employed to include a number of Affimers binding to different epitopes of one protein as it is unlikely that a mutation would occur at the covered epitopes at the same time, hence prolonging the life of the device during an outbreak.*" (p.180)

However, it is the high – or, as Avacta refers to it, 'exquisite' – *specificity* of Affimers that sets them apart from the competition that is antibodies and other mimetics. Affimer proteins are generated via in-vitro screening of a pre-existing phage display library, comprising approximately ten billion molecules. Each of these molecules has differentiating binding capabilities: multiple repeats of the screening process of the library ensure that only *absolutely specific* Affimers to the desired target are identified.

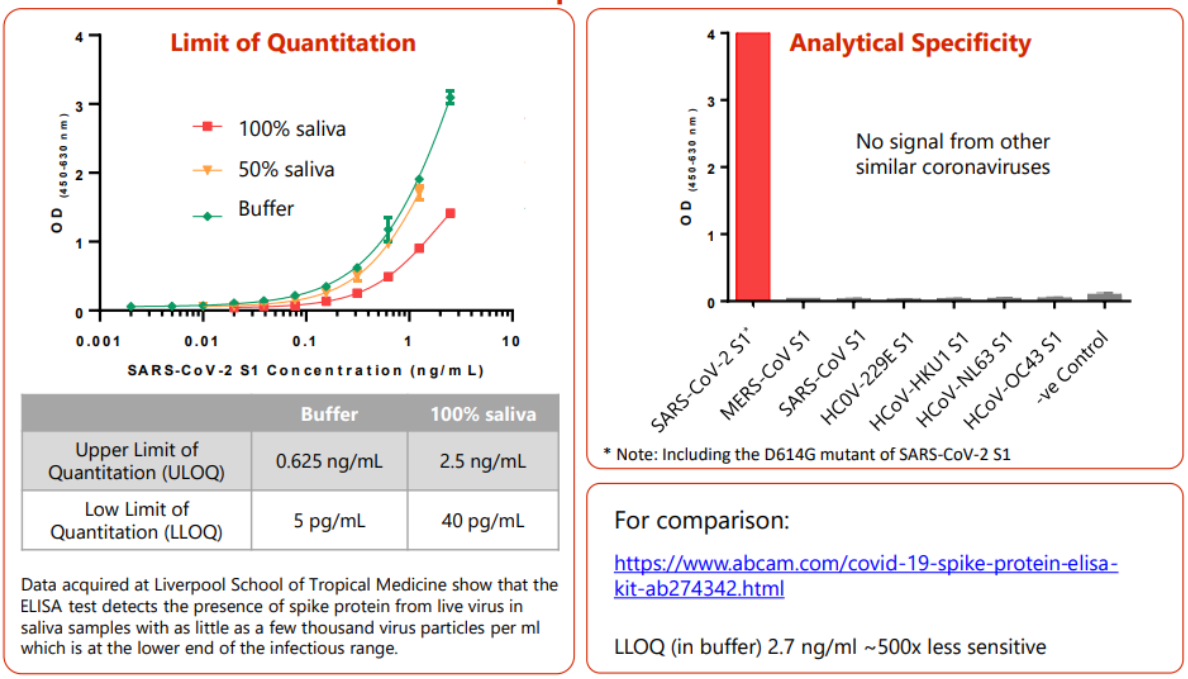
In contrast, generation of specific antibodies commonly requires the immunisation of an animal, and then purifying the antibodies from the animal's blood. Not only does this take significantly longer than Affimer generation (many months as opposed to a few weeks), but it means that antibodies cannot be subsequently optimised to maximise their specificity, as Affimers can be (which is simply a process of methodically scouring the pre-existing library for those Affimers that have absolute specificity to the target).

On 7 September, Avacta announced that it was launching an enzyme linked immunosorbent assay ('ELISA') for SARS-CoV-2, for research use only. Subsequently, on 30 September, the Company also launched its BAMS test for research use only. We shall be examining both tests as standalone products in greater detail in Part II of this Update Note; but for now, the information that the Company has released on them thus far (in RNSs and in presentations) is highly useful as a read-across to the possible performance of the LFT.

[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5487212/

The highly specific Affimers to SARS-CoV-2 that Avacta generated back in April, and that it is using in each of the ELISA and BAMS tests, are those same Affimers that are being used in the reagent in its LFT. The read-across should be apparent to all – and management has stated this on multiple occasions in recent RNSs and presentations.

Excellent sensitivity and specificity in ELISA bodes very well for lateral flow test performance



	Buffer	100% saliva
Upper Limit of Quantitation (ULOQ)	0.625 ng/mL	2.5 ng/mL
Low Limit of Quantitation (LLOQ)	5 pg/mL	40 pg/mL

Data acquired at Liverpool School of Tropical Medicine show that the ELISA test detects the presence of spike protein from live virus in saliva samples with as little as a few thousand virus particles per ml which is at the lower end of the infectious range.

For comparison:

https://www.abcam.com/covid-19-spike-protein-elisa-kit-ab274342.html

LLOQ (in buffer) 2.7 ng/ml ~500x less sensitive

Of course, the LFT will not have the sensitivity nor specificity of those tests; but as we have detailed earlier in this note, its intended use case does not demand that. What the read-across *does* suggest – particularly in light of comparison made between Avacta's and Abcam's ELISA tests (with Abcam's test being ~500x less sensitive) – is that an Affimer-powered LFT could *significantly* outperform a mAb-powered LFT, both in terms of sensitivity and specificity.

In fact, we would go as far as to suggest that a primary motive for launching the ELISA test was so that the Company could openly publish the performance of these Affimers, without breaking the probable numerous NDAs that have kept the analytical performance of the LFT under wraps to date. In doing so, we think management has sought to reassure the market that the LFT will indeed be first-in-class, whilst this current 'holding period' endures until the tech transfer process from Avacta and Cytiva to BBI completes.

We consider it dangerous to predict the potential sensitivity and specificity of Avacta's LFT before the clinical validation has been completed. However, we will highlight management's own views on what constitutes a high quality antigen test for SARS-CoV-2; as well as what it considers to be the *minimum* sensitivity and specificity required for an LFT intended to be used for general population screening.

CASE 1: Testing by airlines to allow travel, or testing by employers to allow safe return to work

Target Group: General public – low prevalence (<2%)

Test Requirements: High NPV (low FN) to provide the best possible protection from the disease being spread and ideally minimise the number of false positives because that would lead to potential claims for not being allowed to travel or lost business days for employers.

Group	Prevalence	SENS	SPEC	Real Cases (P)	Non-cases (N)	TP	FP	TN	FN	PPV	NPV
High Performance Test											
1000	2%	95%	98%	20	980	19	20	960	1	48.7%	99.9%
Mid Performance Test											
1000	2%	85%	90%	20	980	17	98	882	3	14.8%	99.7%

Prevalence of the disease in the target group influences the minimum necessary performance criteria of a COVID-19 antigen test for different use cases

- Sensitivity and specificity are useful for comparing the performance of different tests because these parameters do not change with the prevalence of a condition.
- Positive and negative predictive values are what end-users find most useful but they are dependent upon the prevalence of the condition in the group being tested.
- For COVID-19 testing a high negative predictive value (NPV) is required which means that there is a high level of confidence in a negative result being correct.
- Guidance from regulators on the target performance for antigen tests is emerging with a minimum sensitivity of 80%.
- We are aiming to have the highest possible test performance but, in our view, the minimum hurdles for a rapid antigen test for use in the general population are a sensitivity > 90% and specificity > 95%.

Group	Prevalence	Real Cases (P)	Non-cases (N)	SENS	SPEC	TP	FP	TN	FN	PPV	NPV
1000	2%	20	980	90%	95%	18	49	931	2	26.9%	99.8%

The above two slides taken from the 23 June presentation, coupled with what the Company has relayed to the market already regarding the exceptionally high quality of the ELISA and BAMS tests, leads us to believe that Avacta's LFT will at least meet the sensitivity and specificity that it sets out in its 'High Performance Test' parameters (first slide above). Concerning specificity, we also think it probable that the test will meet the UK Government's and the WHO's desired parameters of >99% (see p.8).

Beyond sensitivity and specificity, the other benefits that we referenced on p.11 are extremely important. Rapid scaling of Affimer production will not be an issue (in contrast to mAbs, the production of which could be a potential bottleneck). Likewise, the robustness of Affimers (including being resistant to high and low temperatures) should ensure Avacta's LFT has a long shelf-life and does not require special treatment throughout the supply chain.

Target Market and Competing Tests

In previous notes, we have suggested that the global market for a high quality LFT (that is of high enough sensitivity and specificity to be used for general population screening) could be several billion units per annum. In recent months, it has become apparent that, on a worldwide basis, demand could *significantly* exceed our initial estimate. The UK's Project Moonshot, for example, is aiming to test up to 10 million people *per day* by early next year. Now consider that the UK population equates to less than 0.9% of the global population.

Avacta itself has been more conservative and suggested that the UK market (alone) could be 120 million tests per month. It is now being reported in the UK press that Avacta's LFT will play a central role in Project Moonshot.[12] Last week, a document posted on the UK Parliament website also validated the rumour that the Government is interest in both Avacta's LFT and BAMS test.[13] It is thus entirely reasonable to assume that the 120m per month target market that the Company has suggested in recent presentations, has been guided by what the UK Government itself has requested Avacta to manufacture.

In light of our assumptions set out in our 24.06.2020 Update Note of £10 per test and a profit before tax margin of 30% (which we still stand by), it is understandable why Avacta is currently valued at £460m, despite not having commenced sales of any COVID-19 focussed products.

If Avacta successfully completes the tech transfer to BBI, and clinical validation is in line with management's expectations, then the *global* market for such an LFT (namely, one that is accurate enough to be effective for at-home use) would be multiples of the UK market. And, *if* the tech transfer is successfully completed, that would signify that a manufacturing blueprint has been created, that could then be rolled out to multiple more manufacturers, in the UK and overseas.

With regards to competition, we feel that the total addressable market is so vast that a *dozen* high quality LFTs could all thrive and record substantial sales over the next 1-2 years. As such, our investment thesis for Avacta (specifically with regards to its SARS-CoV-2 LFT) is absolutely not impacted by emerging LFTs from other diagnostics players. As it stands, however, there remain very few quality LFTs in existence.

Of note, only Abbott Laboratories and Access Bio have received Emergency Use Authorisation ('EUA') from the US FDA.[14] It is significant that both tests (which are for professional use only) were clinically validated using samples from patients that already showed symptoms. Both tests are (for now, at least) only intended for use on patients showing symptoms.

Swiss giant Roche is launching an LFT imminently, which does look of higher quality than those of Abbott and Access. Yet it still will be a professional use only diagnostic product.[15]

Sona Nanotech's LFT has, in our view, certainly not met the requirements for a consumer use product.[16] It has still not been granted FDA EUA for professional use. We no longer consider the company to be a viable competitor to Avacta.

We would also highlight that NASDAQ-listed OraSure Technologies, which is at a similar stage to Avacta in its product development, in August announced that it had abandoned its attempts to produce a saliva-based LFT:

[12] https://www.thisismoney.co.uk/money/markets/article-8801981/STOCK-WATCH-Martin-Sorrell-set-blockbuster-deal.html
[13] https://post.parliament.uk/the-latest-in-covid-19-testing-developing-new-technologies/
[14] https://www.fda.gov/medical-devices/coronavirus-disease-2019-covid-19-emergency-use-authorizations-medical-devices/vitro-diagnostics-euas#individual-antigen
[15] https://www.roche.com/media/releases/med-cor-2020-09-01b.htm
[16] https://sonanano.com/sona-nanotech-announces-clinical-evaluation-study-results-for-its-covid-19-antigen-test/

"*Although originally intended for use with oral fluid, this test has been modified to employ an easily and comfortably self-collected lower nostril sample in order to achieve the best possible accuracy.*"[17]

To our knowledge, this places Avacta's LFT as the only high quality LFT in development, *globally*, that is using saliva as its sample of choice. It is the simplest of tasks to comprehend how saliva is infinitely preferable to nasopharyngeal swabbing, *especially* for population-wide, at-home testing. Just consider that enormous sub-population of almost entirely asymptomatic cases – children.

All of the above-mentioned competitors are using mAb-based reagents in their LFTs. Only Avacta is using Affimers – and only Avacta is pressing ahead with saliva sampling. This speaks volumes about the superiority of Affimers over mAbs in in-vitro diagnostics.

And to remind readers: Avacta has, through its patent protection programme, global, exclusive rights over the usage of Affimers in IVD medical devices into well into the 2030s. We close this instalment by repeating our words from earlier in the note:

Avacta is putting plans in place to expand Affimer-based LFT production through third party developers. The rationale is simple: if the global market for SARS-CoV-2 detecting LFTs is half a billion or more units per month, there is simply no way that Avacta will ever be able to meet this demand. Why not then lease out the Affimer technology to major IVD players, for them to use instead of monoclonal antibodies in their own-manufactured, branded and distributed LFTs?

Such partnerships would remove the development risk for Avacta itself, as well as commercialisation costs. Instead, the Company would receive royalties on each and every LFT sold, regardless of the branding. The ultimate goal for Avacta is simply to ensure that its Affimers are used in as many models of LFTs as possible.

Think ARM processing chips in numerous different makes of smartphones and tablets. Think Mercedes or Ferrari engines being used by multiple Formula 1 racing teams.

[17] https://orasure.gcs-web.com/news-releases/news-release-details/orasure-technologies-inc-announces-2020-second-quarter-financial

Disclosure

The author of this paper, Myles McNulty, is a private investor. He and his family hold 0.9% of the ordinary shares of Avacta Group.

This paper is non-independent research. It has not been prepared in accordance with legal requirements designed to promote the independence of investment research and is not subject to any prohibition on dealing ahead of the dissemination of the investment research.

This paper is designed for information purposes only and does not constitute a personal recommendation, offer or invitation to buy or sell any investment referred to within it. Investors should form their own conclusions and/or seek their own advice to determine whether any particular transaction is suitable for them in the light of their investment objectives, the benefits and risks associated with the transaction and all other relevant circumstances.

The views expressed in this paper are those of Myles McNulty. They are based on information sourced entirely from the public domain, which is believed to be reliable. However, no warranty or representation, express or implied, is made about the accuracy or completeness of this information, which may be subject to change without notice. Any opinion given reflects Myles McNulty's judgement as at the date of this paper's publication. Any or all statements about the future may turn out to be incorrect.

Myles McNulty has no business relationship with Avacta or with any other company mentioned in this paper, and has received no compensation from any party for writing it.

Twitter: @MylesMcNulty