ADMEDUS LTD

Research Note

WELL POSITIONED FOR SIGNIFICANT GROWTH

Investment Highlights

- **Admedus (AHZ) has three business segments: (1) ADAPT – a portfolio of bovine pericardial patches for use in cardiothoracic and vascular surgery; (2) Infusion – a medical products distribution business with a focus on infusion pumps; and (3) Immunotherapies – a clinical stage DNA and RNA vaccine program focusing on herpes simplex virus, type 2 (HSV-2), and human papilloma virus (HPV). This initiation report provides comprehensive research on all of these business segments. We rate AHZ as a BUY.**

- AHZ revenue has been growing steadily over recent years, but this growth has also seen an unsustainable increase in costs, particularly wage and ADAPT manufacturing costs. The new interim CEO, Wayne Patterson, has, in our view, recently put wage and manufacturing costs on a sustainable trajectory with his 'code red' restructure. In the H1/FY17 accounts, selling, general and administration (SG&A) expenses were reduced by 32% on PCP. Gross profit margin for the ADAPT business has improved from 11% to 67% over the same period. We expect gross profit margin for the ADAPT business to rise to 75% during FY19.

- AHZ is trading near its 12 month and 5 year lows. It is adequately capitalised, debt free, and has a new senior management team that have brought costs under control while preserving top line growth. Gross profit margins are also improving significantly. It is undervalued in our opinion. Our valuation of AHZ is $0.50/sh, based on a conservative risk weighting on the Immunotherapies business (HSV-2 application: 8% probability; HPV application: 4%). If these probabilities were doubled from these low bases, it would increase valuation by $0.11/sh, displaying the significant upside if early-stage trials progress well.

- We are of the opinion that AHZ is now poised for significant bottom line growth and this growth potential is yet to be reflected in AHZ's market cap. On the basis of earnings contributions from ADAPT and Infusion alone – i.e., excluding potential upfront licensing fees for one or both of the Immunotherapies clinical assets – we see the Company being profitable by FY19. By FY26, we see AHZ's ADAPT and Infusion business segments generating a combined NPAT in the region of $50m. This implies a CAGR in NPAT of 63%.

- We expect new ADAPT products – CardioCel Neo, VascuCel, and a curved patch – to add to top and bottom line growth from FY18. There are some significant qualitative advantages that AHZ's products have over its competition, accentuated by the fact that competing patches with significant market share have recently been subject to FDA safety recalls and/or negative expert commentary.

- We forecast that CardioCel market share gains will accelerate in FY19 on the back of large, positive data packs (post marketing monitoring, independent observational studies, and clinical results) being available to surgeons and hospital buyers during CY18.

- We expect ADAPT products to start selling in material volumes in the large Indian market during CY18, and the even larger Chinese market in CY20.

- We expect Infusion margins to improve with the opening of the new Royal Adelaide Hospital, scheduled in Q4/CY17. We also think there is a reasonable probability that Infusion will win another large hospital contract over the next 12 months.

- Recent Phase II HSV-2 vaccine interim results were solid, and augurs well for the final results (due H1/CY17), as well as partnering prospects. A HPV-associated head and neck cancer Phase Ib trial is due to start H1/CY17.

7 March 2017

12mth Rating		BUY
Price	A$	0.34
12mth Target Price	A$	0.50
Shares o/s	m	254.8
Market Cap.	A$m	86.63
Net Debt (Cash)	A$m	(14.3)

Valuation:

Methodology		DCF + rNPV
Value per share	A$	0.50

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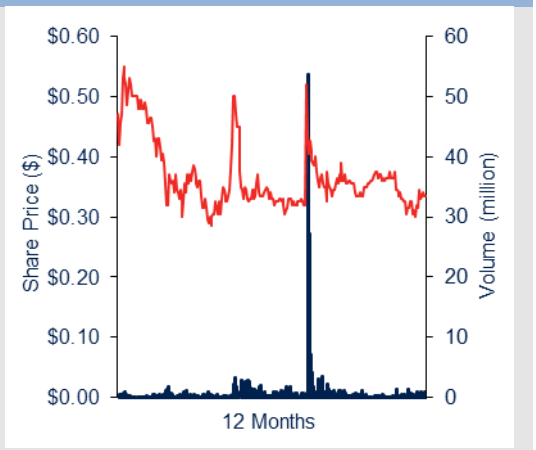
Disclosure: Patersons Securities Ltd acted as Lead Manager and Underwriter to a renounceable Rights Issue that raised A$8.3m at A$0.33/share in September 2016. It received a fee for this service.

12 Month Share Price Performance



Performance %	1mth	3mth	12mth
Absolute	1.52	-6.94	-28.72
Rel. S&P/ASX 300	-2.38	-17.04	-36.10

ADAPT summary

With the 'code-red' restructure putting costs on a sustainable trajectory, we see bottom-line growth from FY18 onwards being driven primarily by increasing sales of high-margin ADAPT products. Sales for the lead ADAPT product – CardioCel – have been increasing by 8-10% a quarter over the last year. We see this c.10% quarter on quarter growth for ADAPT continuing for FY18, but accelerating from FY19. Our rationale for this accelerated ADAPT growth thesis is as follows:

(1) By FY19 we expect the new ADAPT product – VascuCel – to be approved for sale in all markets. We also expect a new curved patch for aortic arch repair (yet to be released) to be approved for sale in all markets by FY19.

(2) We have done a publication analysis of every commercially available ('off the shelf') pericardial patch, and can find no evidence that any other patch presently on the market can match CardioCel in terms of the key performance criteria that cardiothoracic surgeons are looking for.

(3) There have recently been some FDA-mandated product warnings and temporary safety recalls amongst four of CardioCel's key competitors in the US and EU markets. While cardiac surgeons are typically slow movers with respect to the uptake of new products (they typically wait for large, multi-year data sets in the new product), we expect these recalls to nevertheless encourage surgeons to actively look for alternative patches, with CardioCel being the most likely beneficiary.

(4) In CY18, the following important CardioCel data sets will be released: (i) 9-year and 10-year data from a South African Phase II clinical trial; (ii) 5-year post marketing monitoring for hundreds of EU patients; (iii) a 40 patient, 24 month paediatric study conducted at Melbourne Children's Hospital; and (iv) in late CY17 or early CY18, a 4-year CardioCel observational study involving hundreds of patients will be published in a prestigious peer reviewed journal. We expect all of these studies and publications to be unambiguously positive for CardioCel (and, by extension, other ADAPT products), and provide the clear evidence-base that surgeons and hospital buyers require to justify a switch from competing patches.

(5) CardioCel is scheduled to enter the Indian market in CY18 (commercial launch late CY17) and the Chinese market in CY20. While both markets pose considerable challenges for new foreign entrants, we think AHZ has a viable strategy to enter both markets and think they will provide considerable earnings upside potential due to their sheer size.

(6) AHZ's overall marketing strategy for CardioCel has been suboptimal to date, as has been the performance of some of its EU and US sales team. Following 'code red', we are of the opinion that the Company now has a competent sales team in place, backed by a coherent marketing strategy. We expect the new sales team and revamped marketing strategy to bear fruit, especially once the new data sets are in hand.

Infusion summary

The Infusion business ('Infusion') is presently the Company's main top-line contributor. This business segment is growing strongly and sustainably on the back of a number of long-term hospital contracts. Infusion is also AHZ's only profitable business segment at present, generating an FY16 segment profit (= profit before tax) of $783k on revenue of $8.8m. For H1/FY17, this business generated a segment profit of $1.2m on revenue of $8.7m. In our view, it is likely to achieve a 110% year on year segment profit growth in FY17. While we have not assumed it in our DCF model, we also think there is a reasonably high probability that AHZ will win another large hospital contract during CY18. Our cautious optimism regarding new contract wins is due to the fact that many competing infusion pumps have recently been subject to safety recalls.

Immunotherapies summary

We have done a publication analysis of AHZ's DNA vaccines as well as all competing vaccine programs. On the basis of this analysis, we conclude the following:

(1) The 58% decrease in the rate of viral shedding relative to baseline achieved in interim Phase II data for AHZ's HSV-2 vaccine is better than the published data of all competing HSV-2 therapeutic vaccines, albeit in a small (N=20) patient sample.

(2) The shape of the viral shedding curve in the interim Phase II data suggests that even higher rates of viral shedding decrease could be achieved in a longer trial.

(3) The Phase II interim data confirms that AHZ's DNA vaccine technology platform robustly stimulates antigen-specific antibodies in humans, and this augurs well not only for the final Phase II data, but also for the Phase Ib trial in HPV-related head and neck cancer.

(4) There is strong big pharma interest at present for therapeutic vaccines that can be combined with checkpoint inhibitors targeting a range of viral-induced cancers.

(5) A recent HPV therapeutic vaccine, with a similar technology platform to AHZ's, was out-licensed during a Phase I/II trial in a deal worth more than US$700m.

(6) We are cautiously optimistic that both of AHZ's immunotherapies programs – HSV-2 and HPV – will be partnered or receive third party financing during CY18.

(7) Our risk-adjusted net present value (rNPV) for AHZ's Immunotherapy business segment is A$33m.

ADAPT PRODUCT PORTFOLIO: CARDIOCEL, CARDIOCEL NEO, AND VASCUCEL

CardioCel, CardioCel Neo, and VascuCel are the brand names for AHZ's tissue engineered (bovine) pericardial patches. CardioCel was launched in the EU and US in 2014 and is presently approved (CE Mark and FDA 510k) for use in Congenital Heart Defect (CHD) repair in infants and children, as well as paediatric and adult heart valve and annulus repair. CardioCel Neo ('Neo'), a thinner version of CardioCel, is due to start selling in Q1/CY17 and will initially target the neonate market for CHD. VascuCel, for vascular repair, was approved (in the US only at this stage) in October 2016, with first sales occurring in Q1CY17.

Later in CY17, AHZ intends to bring to market a curved patch (shaped for aortic arch repair) and has a TAVR valve (transcatheter aortic valve) under development. In our view, the curved patch and TAVR valve are likely to make material contributions to AHZ's bottom line within the first full year of their launch. The TAVR valve in particular has sales potential that could significantly exceed that of CardioCel. However, due to scarcity of product information at this early stage, uncertain timeframes[1], and analyst conservatism, we do not ascribe any value to the curved patch and the TAVR valve at present and will not comment further on those two products in this note. Instead, we discuss AHZ's market-available products – CardioCel, Neo, and VascuCel – in turn.

CARDIOCEL

In this Section we give an overview of the key indications CardioCel is approved for as well as the approximate number of surgeries performed for each indication in the key markets. We then describe the competitive landscape for CardioCel.

Congenital Heart Defect (CHD)

CHD describes a range of heart defects present at birth. These defects can affect the interior walls of the heart (septal defects), the valves inside the heart, and/or the arteries and veins carrying blood from or to the heart.

Causes

Various combinations of genetic and environmental factors (complex, often controversial, and still poorly understood) are considered causative for around 80% of children born with a CHD. The remaining 20% of CHD sufferers have chromosomal anomalies (in particular Down syndrome and velocardiofacial syndrome), Mendelian syndromes, non-syndromal single gene disorders and teratogens.[2] With respect to the environmental contributions to CHD, maternal exposure during pregnancy to any of the following have all been clinically or observationally linked to CHDs: smoking, excessive air (particulate) pollution[3], alcohol consumption, consumption of selective serotonin reuptake inhibitors (SSRIs –a group of common medications to treat depression, obsessive compulsive disorder (OCD), and biopolar disorder)[4], valproic acid (an

[1] We expect the curved patch to receive FDA 510k approval in mid 2017. We also expect the first prototype of the TAVR valve in mid 2017. However, we think it will be approximately 5 years before TAVR valve is approved for sale.
[2] https://www.mja.com.au/journal/2012/197/3/congenital-heart-disease-current-knowledge-about-causes-and-inheritance
[3] http://ehp.niehs.nih.gov/1307289/
[4] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4183770/

nticonvulsant, also used to treat bipolar disorder)[5], and opioid consumption (for pain relief or in recreational drug use).[6]

Prevalence

CHD is relatively common. Depending on the country and study, CHD affects between 0.4-1.0% of the global population (= between 4 and 10 per 1000 live births). In the US in 2017, around 45,000 babies will be born with CHD.[7] Many children affected by CHD have no, or only minor, symptoms and do not require surgery; but approximately 40-50% of CHD patients do require surgery at some point in their life.[8] In the USA, we estimate approximately 25,000 surgeries (excluding catheter procedures) are performed each year to fix one or more congenital heart defects in babies and young children.[9] We estimate that the EU market for CHD surgeries is around 80% of the US market (20,000 surgeries per year).

Over the coming decade, we expect the rate of CHD in first world countries will stay relatively static and may even decline slightly as increased pre-natal testing for chromosomal abnormalities and a decline of maternal smoking and alcohol consumption is somewhat offset by a modest rise in the consumption of SSRIs and opioid pain killers during pregnancy. In emerging economies in Asia, as well as China and India, where prenatal health care is less advanced, we expect the rate of CHD to increase slightly ahead of population growth. Based on birth rate numbers, we estimate that around 250,000 children are born each year with CHD in China and around 350,000 born in India. We conservatively estimate that the number of CHD surgeries (excluding catheter procedures) performed in the entire ROW market (i.e., all potential CardioCel markets outside of the EU and US) is 125,000 surgeries per year (around 5 times the size of the US market).

CHD surgical procedures

The CHD surgical procedures in which CardioCel is presently used are as follows:

(i) Ventricular septal defect (VSD) repair

(ii) Atrial septal defect (ASD) repair

(iii) Atrio-ventricular septal defect (AVSD) repair

(iv) Tetralogy of Fallot (TOF) repair

(v) Reconstruction of the right ventricular outflow tract (RVOT)

(vi) Aortic root enlargement

(vii) Valve repair

Ventricular septal defect (VSD) repair is by far the most common CHD, with an incidence rate of around 30%. Atrial septal defects (ASD) and TOF repairs are also relatively common, with each having an incidence rate of around 7%. Since its launch in 2014, we estimate that CardioCel has been used successfully in approximately 6,000 CHD surgical procedures (mostly in the EU and US), the majority of which have been the repair of septal defects.

Heart Valve/leaflet and annulus repair in children and adults

The heart has four valves; the tricuspid, the pulmonary, the mitral, and the aortic. Broadly speaking, valvular heart disease (VHD) encompasses three kinds of heart valve problems:

(i) Regurgitation or backflow, which occurs (usually in the mitral valve) if a valve doesn't close tightly;

(ii) Stenosis, which occurs if the leaflets of a valve thicken, calcify, or fuse together. Even in mild cases, stenosis prevents the valve from fully opening.

[5] http://jmg.bmj.com/content/37/7/489.full
[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3835228/
[7] http://circ.ahajournals.org/content/127/1/e6.long
[8] There is little consensus amongst experts as to the % of CHD sufferers requiring surgery. Published estimates range from 25% to 66%. A fairly robust figure confirmed by multiple sources is that 25% of CHD patients are born in a critical condition and have their first surgery before the age of 6 months.
[9] Note that some children undergo multiple surgeries, so the 30,000 surgeries figure is higher than the number of patients operated on.

(iii) Atresia, which is a CHD, and occurs when a valve (usually the pulmonary valve) forms as a solid sheet of tissue instead of a functional valve opening.

When pericardial patches are used in heart valve surgery, they are typically used to repair, augment, or reconstruct the diseased valve or leaflet, as distinct from replacing it completely with an 'off the shelf' mechanical or bio-prosthetic whole valve. The advantage of using pericardial patches over whole valve replacement is that, assuming the patch is of high quality, the patient tends to suffer far less clotting events (and so doesn't require a lifetime of blood thinning medication). Pericardial patches, depending on patch quality, also tend to be accepted by the patient's body more readily, and so have lower infection and rejection rates than mechanical or bio-prosthetic whole valves. The advantage of whole valve replacement over patch repair/augmentation is that replacement valves have long had a reputation of being more robust and long lasting.

With respect to the treatment of specifically *aortic* valve pathologies, whole valve implants are currently used in around 90% of surgeries, with the pericardial patches used in the remaining 10%. With respect to the treatment of *mitral* valve pathologies, whole valve implants are used in around 50% of surgeries, with patch repair/augmentation used in the remaining 50%. (These percentages are somewhat fluid, as surgical trends change over time and next generation materials, such as CardioCel, emerge).

Causes

Like CHDs, there are various genetic, cellular, and micro-environmental contributions to VHD. In addition to CHD, VHD can be caused by Rheumatic fever (uncommon in Western countries). Some valve pathologies can be caused or made worse by high blood pressure. Aging, obesity, and metabolic disorders (affecting cardiovascular health) can all have a degenerative effect on heart valves and contribute to adult VHD.

Prevalence

The overall prevalence of VHD in the USA is around 2.5%, with a wide age-related variation from 0.7% in those aged 18-44, to 13.3% in those aged 75 and older.[10] We estimate that around 8 million children and adults in the USA have mild to significant forms of VHD. We also estimate that around 150,000 corrective VHD surgeries occur each year in the USA (inclusive of whole valve replacements), and 100,000 in the EU. The prevalence of VHD in newborns, children, and young adults is dramatically higher in developing countries such as India.[11]

Annulus Repair

The annulus is a ring shaped piece of fibrous tissue that supports the opening of each valve. The annulus acts as a 'frame' for each of a valve's leaflets. In some people, the annulus can calcify and requires replacement or repair. Annulus calcification often occurs in people with cardiovascular disease; it is also associated with aging.

The annulus can be repaired either with bioprosthetic annuloplasty rings (manufactured by various companies), or reconstructed with pericardial patches.

When repairing or reconstructing a heart valve and/or an annulus using CardioCel, surgeons typically use two sheets (= the sale of two boxes) of CardioCel. Since its launch, we estimate that CardioCel has been used successfully in approximately 500 VHD and/or annulus surgeries, requiring sales of over 1,000 units of CardioCel.

The competitive landscape for CardioCel

Our confidence in CardioCel's growth prospects derives primarily from what we consider to be its unambiguous performance advantages over the competition. Before we describe these specific advantages, it is helpful to understand the general competitive landscape for pericardial patches.

There are basically four kinds of pericardial patch: Synthetic, autologous, allograft, and xenograft (bovine/porcine).

[10] http://heart.bmj.com/content/97/2/91.extract
[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4883659/

- Synthetic patches – such as Gore-Tex, made from expanded polytetrafluoroethylene (ePTFE) – are nowadays considered an inferior product in the context of cardiothoracic surgery because they often cause excessive calcification as well as scarring/fibrosis. And unlike patches made from biological material, they also typically require the patient to take blood thinning drugs for life. For these reasons, we do not consider them a direct competitor to CardioCel (or Neo) and won't discuss synthetic patches further in this section. (Synthetic patches are, however, a competitor to VascuCel in the context of vascular surgery, and will be discussed in the VascuCel section).

- Autologous patches are made by the surgeon from fresh pericardial material sourced from the patient. Their advantage is that they are free of donor-derived pathogens and so don't provoke an immune response. Their disadvantage is that they require considerable time and skill to prepare in the time-constrained operating theatre. They also have a clinically reported tendency to thin, retract and become fibrotic over time.[12] Nevertheless, they are still used today, and provide competition for CardioCel.

- Allograft patches are made commercially (as an 'off the shelf' product) from the pericardial sacs of fresh cadavers.

- Xenograft patches use animal pericardium (typically bovine or porcine) as their source material. CardioCel is a xenograft patch. Its raw material is sourced from bovine pericardium. The majority of patches that CardioCel is competing with are also bovine xenograft patches.

With respect to allograft and xenograft patches, CardioCel has the following 10 competitors for the repair of CHDs, valve repair (VHD), and annulus repair:

(1) **CorMatrix Cardiac Tissue Repair** (porcine), manufactured by CorMatrix. This is currently the best selling patch in the US market for use in CHD and heart valve repair. CorMatrix manufactures a number of different patches. We estimate US sales for this particular patch at US$25-30m pa;

(2) **Peri-Guard** (bovine) patch, manufactured by Baxter Healthcare (Synovis is the name of the business unit);

(3) **PhotoFix** (bovine) patch, which was recently acquired by Cryolife from Sulzer Medica;

(4) **Cryopatch** (allograft), also owned by Cryolife;

(5) **Vivendi** (bovine) patch, manufactured by Labcor and sold mainly in Brazil;

(6) **SJM Pericardial Patch** (bovine), manufactured by St Jude Medical (SJM). SJM was recently acquired by Abbott Laboratories for $25bn[13], so the SJM patch is now an Abbott patch. (NB. The value of the SJM patch would constitute a tiny fraction of this takeover price);

(7) **Bovine Pericardium Patch** (no brand name), manufactured by a Brazilian company called Braile, and sold mainly in the Brazilian market;

(8) **SteriGraft** patch, which along with CryoPatch, is CardioCel's only other allograft competitor,

(9) **Edwards Bovine Pericardial Patch** with XenoLogiX anti-calcification treatment, manufactured by Edwards Lifesciences;

(10) **Edwards Bovine Pericardial patch** with GLX anti-calcification treatment, manufactured by Edwards Lifesciences.

Why and how CardioCel is superior to the competition

During their manufacture, all xenograft patches go through a de-cellularization process to remove any cells, lipids, or nucleic acids that could cause infection (ideally, what remains after this process is pure collagen). Most (but not all) patches then go through a strengthening process. The patch is then preserved in a sterile solution for 'off-the-shelf' packaging. All these processes (decellularization, strengthening, and preservation packaging) are proprietary, and the quality of the patch will depend on the quality/success of these proprietary manufacturing steps.

[12] http://www.diss.fu-berlin.de/diss/servlets/MCRFileNodeServlet/FUDISS_derivate_000000001760/03_1.pdf?hosts=
[13] http://www.bloomberg.com/news/articles/2016-04-28/abbott-agrees-to-buy-st-jude-medical-for-25-billion

Glutaraldehyde

The strengthening process that pericardial patches go through is typically achieved by exposing the patch to a solution that contains glutaraldehyde. Glutaraldehyde significantly improves the tensile strength and durability of decellularized collagen by inducing cross-linking (= a triple helix collagen micro-structure). Compared with untreated tissue, cross-linking stops leakage within a patch, increases its longevity, improves haemodynamics (i.e., facilitates the flow of blood without leakage – critical for heart tissue), and also improves its 'suturability' (i.e., its ability to be sutured without tearing and bleeding along suture lines). However, glutaraldehyde also has three significant drawbacks: (i) it is cytotoxic, and this toxicity increases the probability of inflammation and immune rejection of the patch; (ii) Glutaraldehyde molecules within the structure of the collagen also make the patch more susceptible to calcification and can cause the patch to stiffen or lose elasticity over time (more on calcification in a moment); and (iii), glutaraldehyde residue on the surface of pericardial patches impedes cultivation of endothelial cells on that surface.[14] The latter is significant because endothelial cells are essential for the vascularisation and eventual tissue-graft haemostasis (such that the patient's body treats the patch – or 'bio-scaffold' – as native tissue). This is particularly important for paediatric patients as native tissue formation actually allows the patch/bio-scaffold to grow along with the child's growing body (regeneration).

What is unique about AHZ's proprietary manufacturing process (ADAPT) – what sets it apart from every other pericardial patch manufacturing process – is that it allows the use of gluteraldehyde to gain all the cross-linking (strengthening) advantages that gluteraldehyde confers, while also leaving no gluteraldehyde molecules within the micro-structure or on the surface of the collagen. CardioCel is also preserved in a proprietary sterile solution that is gluteraldehyde-free.[15] We have completed a literature search of all the above-mentioned competing patches, and can confirm that CardioCel is the only *cross-linked* patch on the market that is gluteraldehyde-free at the end of its manufacturing process.

Three of CardioCel's competitors – viz., PhotoFix, CryoPatch, and CorMatrix (the market leader) – use *no* gluteraldehyde during manufacture and so are not cross-linked. The manufactures of these patches have opted to achieve the benefit of no gluteraldehyde (less toxicity, less calcification), but only at the expense of less tensile strength and durability. Thus, as confirmed by FDA recall notices (see below), these patches are prone to rupture, suture line bleeding, and other structural problems as a result of their not being cross-linked. We think the absence of cross-linking in these patches augurs well for CardioCel taking market share.

Calcification

Calcification occurs when calcium-containing extracellular fluid reacts with phosphorus within the patch to generate calcium phosphate deposits (mineralisation) within the patch.[16] Calcification leads to poor haemodynamics and a gradual stiffening and shrinkage of the patch. Calcification typically results in functional failure of the patch and thus patch replacement/re-surgery. It has been clinically confirmed with respect to some of CardioCel's competitors that calcification can begin within two months of surgery.[17]

While calcification is more likely to occur in gluteraldehyde-treated patches, it has in fact been shown to occur in every patch clinically studied to date *except CardioCel*. Specifically, CardioCel has shown zero calcification after 8.5 years implantation in a Phase II paediatric CHD trial (calcification shows up on Magnetic Resonance Imaging, so can be easily assessed). In 2018, AHZ will be able to release data up to 10 years for this trial. To the best of our knowledge, no competing patch, even those which claim to employ "anti-calcification technology,"[18] has gone longer than 2 years without calcifying in a paediatric clinical setting. With respect to being genuinely non-calcifying, then, clinical data suggests that CardioCel represents a paradigm change in pericardial patch performance. We expect CardioCel's non-calcification to also be confirmed in some large observational studies (involving hundreds of patients) which are due to be released late CY17 and also during CY18.

[14] https://www.ncbi.nlm.nih.gov/pubmed/1728078/

[15] Neethling WML, Yadav S, Hodge AJ, Glancy R. Enhanced Biostability and Bio-compatibility of Decellularized Bovine Pericardium, Crosslinked with an Ultra Low Concentration Monomeric Aldehyde and Treated with ADAPT. TM J Heart Valve Di 2008; 17:456-464, Brizard CP, Brink J, Horton SB, Edwards GA, Galati JC, Neethling WM. New engineering treatment of bovine pericardium confers outstanding resistance to calcification in mitral and pulmonary implantations in a juvenile sheep model. The Journal of Thoracic and Cardiovascular Surgery, 2014; 148(6):3194-3201.

[16] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1888152/pdf/amjpathol00157-0140.pdf
[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4473611/
[18] https://www.google.com.au/patents/US7972376 ; also cf., https://www.sjm.com/en/professionals/resources-and-reimbursement/technical-resources/structural-heart/valve-repair/pericardial-patch/sjm-pericardial-patch-with-encap-ac-technology?halert=show&clset=af584191-45c9-4201-8740-5409f4cf8bdd%3ab20716c1-c2a6-4e4c-844b-d0dd6899eb3a

Heat Map

In the context of CHD and VHD repair surgery, CardioCel's competitive advantages can be summarized as follows:

(1) Able to regenerate with native tissue and grow with the patient's heart

(2) No MRI observable calcification after 8.5 years

(3) Has no cytotoxic glutaraldehyde molecules within the structure or on the surface of the patch

(4) Is highly resistant to thrombus (blood clot) formation

(5) Retains tensile strength over time to ensure suture retention, the absence of suture line bleeding, and resistance to tearing or rupture

(6) Retains flexibility and elasticity over time

(7) Is reliably of a consistent thickness 'out of the box' and does not thicken over time

(8) Has excellent haemodynamics – does not allow structural leaks

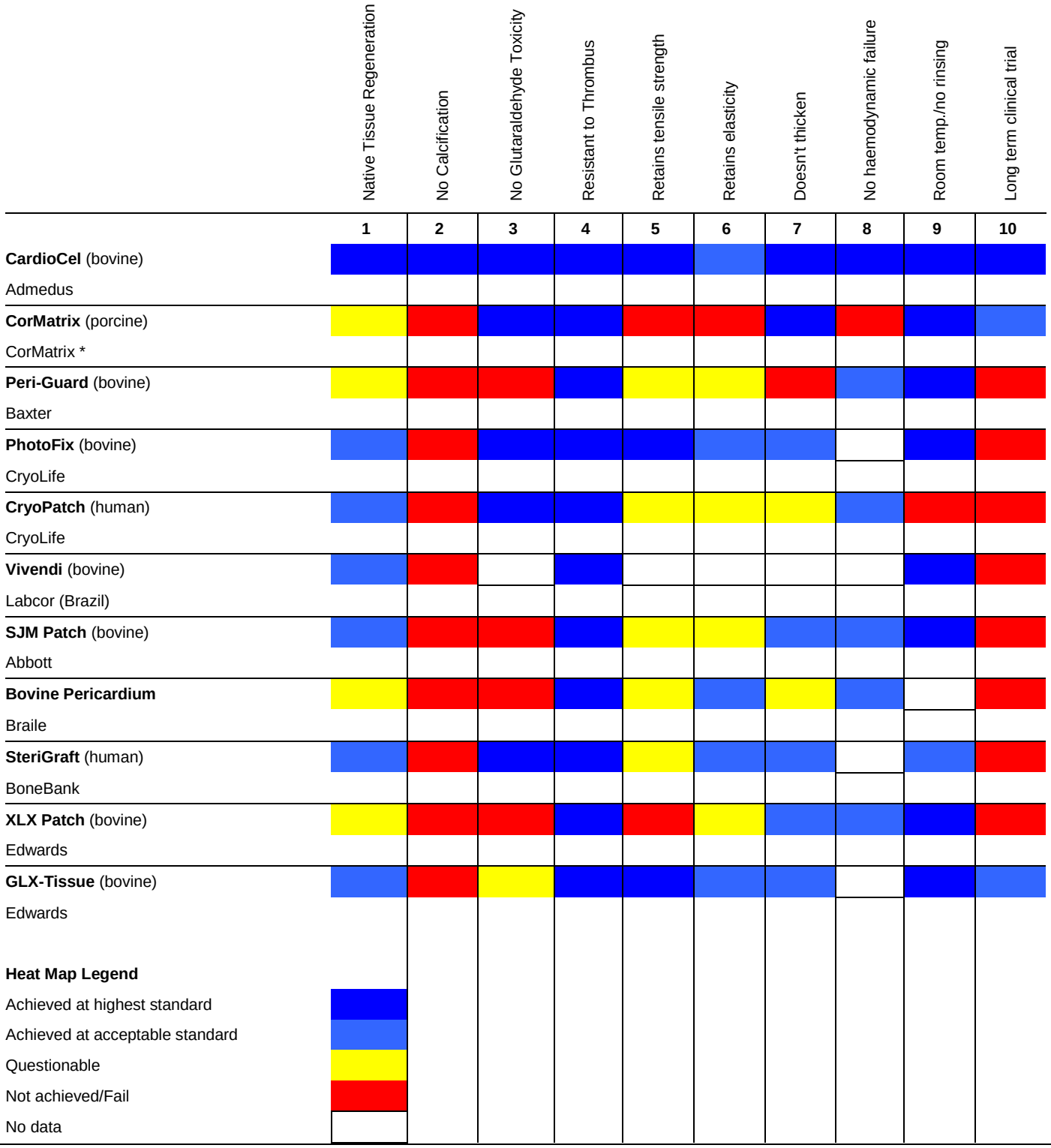
(9) Can be stored at room temperature and requires no rinsing

(10) Is clinically validated with a long term prospective trial for the repair of CHDs and valves[19]

The 10 numbers on this heat map denotes each of the 10 above-mentioned qualities:

[19] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3781795/

Figure 1: Pericardial Patch Heat Map



Source: Patersons Securities Limited, based on company data sheets, FDA recall notices, and published observational or clinical data

** = current best-selling patch in US market*

This heat map shows how all of CardioCel's competitors fail in at least one key performance criterion, whereas CardioCel achieves either the highest standard or an acceptable standard[20] in all performance criteria.

Four of CardioCel's competitors have had recent FDA safety issues or adverse expert commentary

From the perspective of anticipating CardioCel gaining market share over its competitors, it is noteworthy that four competing patches have recently suffered, or been indirectly associated with, FDA safety recalls or adverse expert commentary (reputational damage). The patches in question are Baxter's Peri-Guard, CryoLife's CryoPatch, Edwards' XLX patch, and the CorMatrix Cardiac Tissue Repair patch. Specifically:

- In 2015 and 2016, Baxter's Vascu-Guard patch (a direct competitor to VascuCel), which is made from the same material as Peri-Guard (a competitor to CardioCel), was subject to a Class I FDA recall. Class I recalls are the most serious recalls, and generally mean that use of a product subject to a Class I recall can have deadly consequences. In this instance, the adverse events included life-threatening intraoperative and postoperative bleeding and hematomas.[21]

- In 2014, the CryoPatch SG was subject to an FDA product recall (Class II) due to an infection in human donor pericardial tissue.[22] Other devices made from CryoPatch material have also been subject to Class II recalls in the past.[23]

- In 2012, the Edwards XLX patch was subject to an FDA adverse event report due to dehiscence of the patch after only 3 months. This means that the patch ruptured along its suture line 3 months post operation.[24]

- In 2010, a CorMatrix patch was used in a leaflet repair operation but failed 3 days postop when the sutures pulled through the patch. The patch also leaked and ruptured.[25] A similar event happened to another CorMatrix patch after a valve operation in 2011,[26] and again in 2012 (in a vascular repair setting).[27]

- In 2014, a peer review paper in a prestigious journal was published showing that the CorMatrix patch, when used in valve reconstruction, induced an "intense inflammatory response" and showed that "little or no remodelling to form tissue resembling a … native valve was seen at ≤9 months after implantation."[28]

- In a 2016 peer reviewed animal study, the CorMatrix patch again achieved "suboptimal" results in a trileaflet valve model.[29]

Problems with CardioCel marketing to date

Despite CardioCel's clinically-validated performance advantages over the completion, and despite the above-mentioned product recalls amongst its competitors, CardioCel sales have been underwhelming to date. After two full years of sales in the EU and US, we estimate that CardioCel has a market share of around 2%. In recently entered ROW markets, we estimate that CardioCel's market share is less than 1%. We think this small market share is primarily a function of three issues:

- CardioCel is a new entrant; cardiothoracic surgeons are conservative and pragmatic by nature and thus treat new products with appropriate caution until large data sets are available. Although CardioCel has performed better than any competing patch in the clinic, the number of patients actually treated in a published study setting by CardioCel is still relatively small.

[20] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3781795/
[21] http://www.rxlist.com/script/main/art.asp?articlekey=198032
[22] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRes/res.cfm?ID=124885
[23] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfres/res.cfm?id=98166
[24] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=2655339
[25] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/detail.cfm?mdrfoi__id=1678230
[26] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=2229410
[27] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi__id=2783251
[28] https://www.ncbi.nlm.nih.gov/pubmed/24698560
[29] http://journals.sagepub.com/doi/abs/10.1177/2150135116651113

- Many competing companies have claimed – claims supported by *short* term clinical and post marketing studies – that their pericardial patches have "anti-calcification" technology built in. However, in practice, this has proven to be something of a marketing gimmick, with generally poor patch performance across the board with respect to calcification (see heat map). We suspect that CardioCel's previous 'non-calcification' marketing strategy did not cut through to a critical mass of hospital buyers and surgeons because buyers/surgeons had assumed that CardioCel's non-calcification claim was similar to the misleading 'anti-calcification' claims made by competitors.

- At AHZ's 2016 AGM, it was disclosed that some members of CardioCel's previous US and EU sales teams had had little or no experience in the sector, and were not adequately differentiating CardioCel from the competition.

We think these three issues have been or soon will be addressed. We understand that CardioCel's new post 'code red' sales team includes highly experienced ex-employees from competing pericardial patch companies who better understand what surgeons and hospitals (i.e., bulk buyers) are looking for in a pericardial patch. The new sales team is already selling more than twice the patches per sales employee than the previous team.

With respect to the important, large data sets that surgeons are looking for, the following CardioCel data will be released in CY18: (i) 9-year and 10-year data from the South African Phase II clinical trial; (ii) 5-year post marketing monitoring for hundreds of EU patients; (iii) a 40 patient, 24 month paediatric study conducted at Melbourne Children's Hospital; and (iv) in late CY17 or early CY18, a 4-year Australian observational study involving hundreds of patients will be published in a prestigious peer reviewed journal. We expect all of these studies and publications to be unambiguously positive for CardioCel (and, by extension, other the ADAPT products discussed below), and provide the clear evidence-base that surgeons and hospital buyers require to justify a switch from competing patches.

CARDIOCEL NEO

One common problem that occurs with bovine pericardium patches is significant variations in thickness within the patch. Surgeons will sometimes be unable to use a patch if a section of the patch is thicker than the surrounding tissue it is being sutured into. This problem tends to occur most often in neonate cardiothoracic surgery, where native tissue is thinner.

CardioCel Neo ('Neo') is a uniform, thinner version CardioCel, made from the same bovine pericardium, and undergoing a similar (although not identical) manufacturing process. The average thickness of a CardioCel patch is 0.6mm, whereas the average thickness of Neo is 0.3mm. Neo's competitive advantage is that the ADAPT manufacturing process guarantees that the 0.3mm thickness of the patch is *reliably* uniform (that small variations in thickness are always within acceptable limits).

While Neo is approved for all the uses that CardioCel is approved for, in reality, its use is likely to be limited to the following procedures in patients under the age of 2:

(i) Ventricular septal defect (VSD) repair

(ii) Atrial septal defect (ASD) repair

(iii) Atrio-ventricular septal defect (AVSD) repair

(iv) Tetralogy of Fallot (TOF) repair

(v) Leaflet repair

Unlike CardioCel, Neo's thinness means that is unlikely to be used in the following procedures:

(i) Reconstruction of the right ventricular outflow tract (RVOT)

(ii) Aortic root enlargement

(iii) Valve repair

(iv) Annulus repair

Neo is presently only available in the US market, with the EU and Asian markets likely to follow late in 2017. From the perspective of both regulators and potential buyers, CardioCel's clinical data pack is also applicable to Neo. Based on the above-mentioned uses, when Neo is available in all the markets that CardioCel is available in, we expect Neo to cannibalize around 25% of CardioCel sales (around 75% of present CardioCel sales are for indications in patient groups where Neo would not be advantageous).

While Neo will eventually cannibalize some CardioCel sales, we nevertheless think Neo will be a profitable addition to the ADAPT product line for two key reasons. First, our research indicates that it has only one direct competitor[30] (as of March 2017), viz., the CorMatrix 'Tyke' patch. The CorMatrix Tyke received US FDA 510(k) clearance in February 2016, and sales numbers as well as the results from post-marketing observational studies are not yet publicly available. With Tyke having a minimal head start over Neo, and with the superiority (described above) of ADAPT patches over CorMatrix patches (which are not cross linked and have a tendency to rupture as per the adverse event reports cited in the previous section), we see this emerging neonatal 'thin' pericardial patch market as being wide open for Neo. Second, Neo's premium pricing (average price globally is expected to be A$1,600 per unit versus A$1,200 for CardioCel) should entail a higher gross profit margin relative to CardioCel.

VASCUCEL

VacuCel has an average thickness of 0.4mm and is sold in two sizes (2cm by 8cm and 0.8cm by 8cm). The product is approved in the US only (510k) at this stage for use in vascular repair surgeries.[31] We assume EU (CE Mark) approval in CY18. Most of the major ROW markets base their approval on either FDA 510k approval or CE Mark (or both), and we are expecting a gradual global roll out beginning late CY18. We expect VascuCel to begin selling in the Indian market in CY19 and in the Chinese market during CY20.

'Vascular repair' is a broad term, encompassing many kinds of surgery. However, VascuCel is likely to be used mainly in patch angioplasty. Patch angioplasty involves the use of a patch to repair a disruption of a vessel wall (usually the wall of a major artery) or to repair a vessel after the surgeon has made a longitudinal incision.

The patch angioplasty procedure for which we think VascuCel will be used most often is carotid endarterectomy (CEA). We estimate that, for the foreseeable future, CEA surgeries will account for around 85% of VascuCel sales with our estimate of the sales of VascuCel's other angioplasty uses are as follows:

- Open repair of abdominal aortic aneurysms (AAA) – 5%
- Vascular bypass surgery – 5%
- Arteriovenous (AV) fistula repair – 2%
- Open surgical treatment of thrombotic Vena Cava Occlusion –2%
- Suture line buttressing (general surgery) – 1%

Given the overweight importance of CEA surgery in constituting VasuCel's market for the foreseeable future, we focus on CEA in what follows.

CEA to prevent Thrombotic Stroke

CEA is essentially a surgery to prevent thrombotic stroke. A thrombotic stroke is a stroke (= the blockage of oxygenated blood from entering a region of the brain) caused by a blocked artery. As blood flows through the arteries it sometimes leaves behind cholesterol-laden plaques that stick to the inner wall of the artery. Over time these plaques can increase in size and narrow or block the artery (stenosis), eventually causing stroke.

A CEA involves the removal of these fatty deposits from one of the two main arteries (carotid arteries) in the neck that supply oxygenated blood to the brain. During the procedure, the surgeon makes an incision into the artery, removes the fatty deposits, and then closes the artery with a patch (patch angioplasty). Numerous studies have shown that the patch is a vital part of this surgery, as primary suture closure of the artery (= closure of the artery without a patch) often results in narrowing of the artery (stenosis) post-surgery, which in turn leaves the patient at an unacceptable risk of stroke.

[30] Other companies, such as SJM/Abbott, have a 'thinner' patch available for paediatric use, but only AHZ and CorMatrix have patches especially developed for neonates.
[31] From the FDA approval letter: "VascuCel is indicated as a patch in great vessel repair, peripheral vascular reconstruction and suture line buttressing." http://www.accessdata.fda.gov/cdrh_docs/pdf16/k162579.pdf

The 0.8 by 2cm-sized VascuCel patch has been designed and shaped (based on surgeon feedback) precisely for CEA surgery.

Causes

The dominant causes of (or risk factors for) thrombotic stroke are high blood pressure, atrial fibrillation, poor diet (= a low fibre diet that is high in saturated fats and trans fats), high LDL cholesterol levels in the blood, diabetes/metabolic diseases, physical inactivity, and smoking. Recently, scientists have discovered that air/particulate pollution is also a major short term and long term cause of stroke.[32]

Prevalence

Despite the introduction of statins (cholesterol lowering medication), improved medical care generally, and dramatic falls in the number of people smoking in Western countries over recent decades, the number of people suffering ischemic stroke each year has fallen only slightly. In the US, it is currently around 800k. In the EU, it is around 650k people.[33] The reason why stroke remains a major cause of death and disability in Western countries is mainly due to the continued popularity of sedentary lifestyles combined with low fibre diets that are high in saturated fats and trans fats.

In most middle-income countries, including China and India, the prevalence of stroke is increasing, as Western diets, physical inactivity, particulate pollution levels, and smoking rates all increase. In China, around 2.5m people suffer stroke each year, as do around 1.5m people in India. We estimate that the prevalence of stroke is presently increasing by around 2% per year in China and India. Globally, it is estimated that 15m people per year suffer a stroke.

The competitive landscape for VascuCel

Over the last 20 years, the annual number of CEAs performed in the US has been steadily declining as a less invasive alternative to CEA, endovascular carotid artery repair or carotid artery stenting (CAS), gains in popularity. CAS involves the use of a wire stent that is threaded through an incision in the groin in a catheter until it reaches the carotid artery. Once in place, the cardiologist inflates a balloon inside the stent. This causes the stent to expand, pressing against the fatty deposits and opening up the artery to allow adequate blood flow. CAS typically takes only 90 minutes, and is done under a local anesthetic.

Clinical evidence is clear that CAS and CEA demonstrate clinical equipoise for stroke prevention. And CAS is obviously a preferred treatment for higher surgical risk patients. However, the fact that CAS has similar clinical outcomes to CEA but is less invasive, does not mean that CEA surgery in the US market will decline much from current levels in the foreseeable future. The reason for this is that CEA is unambiguously the preferred option for patients with a 'tortuous' aortic arch or carotid artery.[34] In placing a stent in either carotid artery the cardiologist must pass the catheter through the aortic arch. However, "[s]ignificant tortuosity of the aortic arch or the carotid artery makes it impossible to navigate endovascular catheters to an appropriate location for treatment."[35]

Clinical studies suggest that around 50% of patients at risk of stroke typically have a type II or III aortic arch (= tortuous aortic arch). This percentage is even higher in patients over the age of 80. CEA also may have advantages over CAS in terms of patients performing better on cognitive/neurological tests post procedure, although this point is controversial.[36] In our view, the anatomical presence of tortuous aortic arches and carotid arteries guarantees that demand for vascular patches for CEA surgery will remain robust for the foreseeable future.

We estimate that around 200k patients undergo an aortic revascularisation procedure in the US each year, with around 130k of these being CEA procedures (down from 170k 20 years ago), and 70k CAS procedures.[37] Over the next few years, we expect CEA procedures to fall to around 120k annually in the US, but not fall much further than this due to the high percentage of patients with a tortuous aortic arch.

[32] http://www.thelancet.com/journals/laneur/article/PIIS1474-4422(16)30073-4/abstract
[33] http://www.strokecenter.org/patients/about-stroke/stroke-statistics/
[34] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2588304/
[35] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4757269/
[36] https://www.ncbi.nlm.nih.gov/pubmed/22990503
[37] Our current and forward estimates are extrapolated from a number of sources, including http://circinterventions.ahajournals.org/content/7/5/692.long, and https://www.advisory.com/research/cardiovascular-roundtable/cardiovascular-rounds/2011/08/vascular-productivity-and-procedure-yield-how-do-the-numbers-break-down

In the EU, surgical culture and national health schemes favour CEA surgery over CAS to a higher degree than occurs in the US.[38] We estimate that around 150k CEA surgeries occur each year in the EU, with this being a stable number for the foreseeable future (trending neither higher nor lower).

For the ROW market (including China and India) we are conservatively estimating 350k CEA surgeries per year, and are assuming a 1% annual growth rate for the ROW market as a higher proportion of the ROW population become more susceptible to stroke.

On the basis of the above, we estimate the size of the global patch angioplasty market for use in CEA procedures is currently around US$250mill. We expect zero growth from Western markets. Growth in the global market is expected to come primarily from China and India.

Different kinds of vascular patch

Before we articulate VascuCel's functional advantages relative to the competition, is first necessary to outline the different kinds of vascular patch available for surgeons. As with CardioCel, VascuCel has four types of competitor:

(1) Autologous (vein) patches;

(2) Allograft vascular patches (harvested from fresh cadavers)

(3) Synthetic vascular patches;

(4) Xenograft (bovine or porcine) vascular patches.

With autologous vein patches, the surgeon removes the great saphenous vein in the patient's groin, and then shapes the vein material in such a way that it can be used as a patch to close the carotid artery. While infection/rejection rates are very low with this procedure, autologous patches have a number of significant deficiencies including a clinically validated trend towards increased aneurysm formation and rupture (due to some vein material being thin-walled). Both of these deficiencies are potentially fatal.[39] Autologous patches are also labour intensive for the surgeon and increase the duration of surgery, which also carries additional risk for the patient. The popularity of vein patches is waning as next generation biomaterials become more reliable. We see vein patches providing only minimal competition to VascuCel.

Allograft Cryolife manufacture the only commercially available allograft vascular patch.[40] The Cryolife patch is manufactured from cryogenically preserved human tissue and is decelluarized to minimize the likelihood of a recipient immune response. We estimate that Cryolife presently holds around 5-7% of the US market. Because their manufacture depends on the availability of fresh donor cadavers, Cryolife patches are not widely available and are expensive; each Cryolife patch is 4 to 5 times the price of a VascuCel patch. As noted in the CardioCel section, Cryolife patches also have a tendency to calcify over time.

Synthetic patches have been used in CEA procedures since the 1970's. Relative to autologous patches, synthetic patches are strong, long-lasting, cheap, and reduce surgery times (since they are available 'off the shelf'). Their key drawbacks are increased risk of infection/rejection/inflammatory response, increased rates of suture line bleeding, and increased risk of hematomas (the leakage of blood outside the wall of the artery). Up until the turn of this century, synthetic patches held around 90% of the vascular patch (CEA) market, but now collectively account for less than 40%.[41] The main synthetic vascular patch brands still on the market today are:

- Maquet, Hemacarotid
- B-Braun
- Labcor
- Gore Tex
- VascuTek

[38] Alan Dardik (ed), *Vascular Surgery: A Global Perspective*, Springer International Publishing, Switzerland, 2017. 176-178.
[39] https://www.researchgate.net/publication/42256339_Patches_of_different_types_for_carotid_patch_angioplasty
[40] Other companies, such as Lifenet Health, offer whole vessel allograft bio-implants, but not patches.
[41] Pattersons estimate

- InSitu
- Perouse

In the late 1990's the first xenograft vascular patches were introduced to the market, and have been gradually gaining market share ever since. We estimate that the three best-selling xenograft brands collectively hold approximately 55% of the US vascular patch market. These brands are:

- LeMaitre, XenoSure (bovine) 25% market share in the US and EU
- Baxter's Vascu-Guard (bovine) 20% market share in the US (prior to recent recall)
- CorMatrix (porcine) 10% market share in the US

Xenograft vascular patches are typically around 20% more expensive than synthetic patches, but have nevertheless gained significant market share at the expense of the synthetic vascular patches. The reason for the increasing popularity of xenograft patches is that clinical and post market observational studies over the last decade have confirmed that xenograft vascular patches, relative to synthetic patches, are:

(i) equivalent in strength,

(ii) have superior biocompatibility,

(iii) facilitate superior native tissue ingrowth, and

(iv) have far lower rates of infection

Xenograft patches are also superior to autologous patches, since they allow the preservation of the great saphenous vein in the patient's groin.

How VascuCel compares to the competition

Advantages

VascuCel, like CardioCel, is a xenograft patch, and thus confers all the advantages described above that other xenograft patches have over synthetic patches. However, we think VascuCel is also superior to each of the three above-mentioned xenograft rivals with respect to the following:

(1) *Advantage over XenoSure and Vascu-Guard*: Because of the ADAPT manufacturing process, VascuCel is the only vascular patch on the market that has all the cross-linking (strengthening) advantages that gluteraldehyde confers, while also leaving no toxic gluteraldehyde molecules within the micro-structure or on the surface of the collagen. By contrast, XenoSure and Vascu-Guard are not gluteraldehyde-free. They are therefore both theoretically prone to gluteraldehyde toxicity and thus an inflammatory response by the patient.

(2) *Advantage over Vascu-Guard*: as noted in the CardioCel section, Baxter's Vascu-Guard was subject to a serious Class I FDA recall in 2016. According to the FDA issue notice, Vascu-Guard caused three patient deaths shortly after CEA surgery due post operative bleeding and hematomas.[42]

(3) *Advantage over CorMatix Vascular Patch:* As also noted in the CardioCel section, CorMatrix patches, including its vascular patch, are not cross-linked and have been subject to at least 3 FDA adverse event reports for rupturing (in each case, patients required an emergency re-operation). By contrast, VascuCel patches are cross-linked and so are structurally stronger than CorMatrix patches.

Disadvantage

VascuCel is a new product and AHZ has released no clinical or post marketing studies yet. We understand that the first of these studies will be published early CY18.

[42]https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm518852.htm

VascuCel's likely market share

There is presently a marked trend in vascular surgery away from the use of synthetic patches towards biologic patches. This trend has been going on for nearly 20 years, but we expect it to accelerate over the next 5 years to the point where synthetic patches become largely obsolete, and thus gradually removed from the market.

We measure the size of the global vascular repair market at around US$300m (with CEA constituting around US$250m of this market). At present, synthetic patches constitute around US$120m worth of the global market, with biological patches making up the remainder. However, within 5-7 years the US$300m global market for vascular patches will, in our view, likely be shared *only* amongst xenograft and allograft patches.

How much of this US$300m market VascuCel will capture is a function, like CardioCel, of; (i) its functional advantages relative to competing patches used in angioplasty; (ii), the speed in which AHZ is able to introduce VascuCel into major markets (it is presently only available in the US); (iii) the results of most marketing studies, and (iv); and most importantly, the skill of AHZ's sales team in being able to translate these competitive advantages into substantial sales.

VascuCel has only just (February 2017) been released in the US – so sales in FY17 will be modest. Nevertheless, we are forecasting 50%+ CAGR for VascuCel from FY18 to FY27 on the back of Baxter's Vascu-Guard FDA recall and supportive VascuCel post marketing studies being released next year. Within 10 years, we are forecasting that VascuCel will capture around 17% of the global market. We assume that gross profit margins will be the same as CardioCel (around 67% now, rising to 75% in FY19).

INFUSION (DISTRIBUTION BUSINESS)

AHZ's Infusion business ('Infusion') essentially involves marketing and reselling a number of high-end European manufactured medical devices and related consumables, as well as post sale support and maintenance in Australia and New Zealand. Infusion has both product and customer diversity, which minimises risk. It is not a sexy business (it owns no IP), but it is a growing, profitable business. In our view, it is likely to achieve year on year segment profit growth of 110% in FY17. We expect growth beyond FY17 to be more moderate.

Infusion adds new or synergistic products from time to time. The complete list of products this business currently distributes is as follows:

- Arcomed AG Infusion System
- Arcomded Consumables
- V-Set Infusion Systems
- AmbiT Infusion Pumps
- DOSI-FUSER Portable Pumps
- Springfusor Disposable Pump/tubing
- Eldor Fenestrated Catheter
- Amnicot Finger Cot
- O'Neil Urinary Catheters

The business's range of electronic and portable (or spring-loaded) infusion pumps and related consumables constitute over 95% of sales. Infusion pumps allow for the controlled release of medication and fluids directly into a patient's veins (IV administration). Lightweight, portable pumps are used in non-critical situations to allow patient mobility. Electronic pumps are used in more critical situations. They can be programmed in various ways to deliver various doses at different times. Historically, infusion pumps have been associated with a "high rate of recalls and adverse events, resulting patient injuries and deaths,"[43] and Australian and

[43] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4549602/

New Zealand hospitals are presently going through a cycle of updating their pumps to improve safety outcomes.[44]

AHZ has recently won a large 5-year contract to supply Swiss-made Arcomed Chroma infusion pumps, related consumables (disposable tubing, reservoirs, cartridges, etc.), and technical support to the Royal Adelaide Hospital (RAH). We think there is a high probability that this contract will be extended well beyond 5 years. Each electronic infusion pump has a life span of around 10-12 years before reaching technological obsolescence, and, given staffing familiarity with the Chroma pumps[45], we think there is a high probability that the RAH will place another similar-sized order with AHZ in around 10 years.

At the AGM, AHZ management said that they are bidding for other infusion pump hospital contracts – including SA Health. We note that there are a number of hospitals larger than the RAH in Australia. Potentially, if AHZ was to win a contract for one of these larger hospitals, annualised revenue from the new contract could substantially exceed the $5-6mill pa generated from the RAH contract.

While this is a competitive space (see below), and while Arcomed products are higher priced than most (but not all) of its competitors, Arcomed products nevertheless have a 'Swiss-Made' reputation for quality and reliability. Reliability/quality rather than cost is arguably the more important consideration for hospitals, given the social and monetary costs of medical negligence/error.

Arcomed's competition has suffered product recalls

Arcomed's key competitors in the Australian and New Zealand infusion pump market are as follows:

- CareFusion
- Fresenius Kabi
- B-Braun
- Baxter
- Hospira (recently bought by Pfizer)

It is noteworthy, we think, that most of these competitors have recently suffered product recalls. Specifically, on the 10th of February 2017, the FDA issued a worldwide recall (including Australia) for an infusion pump manufactured by CareFusion.[46] This is the 9th Class 1 product recall for this product since 2010.[47] Further, in 2016, the TGA issued an Australian Class II recall for a pump manufactured by Fresenius Kabi.[48] Also in 2016, ECRI (a highly respected not for profit consulting group that examines healthcare products) found that the B-Braun Infusomat Space Infusion System had "unclear" indications/alerts and that "the pump's workflow is…limited by its small screen."[49] Between 2010 and 2016, a number of Baxter-branded infusion pumps were subject to either Class I or Class II recalls.[50] Finally, in 2015, the FDA issued a security warning on Hospira infusion pumps, stating that they were vulnerable to cyber attackers taking control of the pumps and changing medication doses, timeframes etc.[51] Hospira pumps have also been subject to a number of recalls since 2012.[52]

Unlike the above-mentioned competitors, we can find no evidence that Arcomed infusion pumps have ever been issued with a product recall (Class I or Class II), and can find no negative commentary or opinion on the pumps from experts. On this basis, and given that AHZ has already won one major hospital contract, we think there is a reasonable probability that AHZ will pick up other hospital infusion pump contracts over the next 12-24 months. Like the RAH, all these contracts tend to be front loaded, with most of the revenue associated with the delivery of the pumps, followed by a moderation of revenue with delivery of consumables throughout the life of the contact.

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[44] Better quality next gen pumps, such as Chroma pumps, deliver the required doses of medication over the required time period with a significantly higher degree of accuracy relative to older pumps or lower quality pumps. They also have clear digital displays that significantly reduce the risk medical practitioner error and alert staff to tube blockages, air pockets etc.
[45] There are safety risks associated with changing pump manufacturers as the change introduces unfamiliarity and requires additional training.
[46] http://www.fda.gov/MedicalDevices/Safety/ListofRecalls/ucm540609.htm
[47] http://www.fiercebiotech.com/medical-devices/carefusion-recalls-its-alaris-infusion-pump-franchise-s-9th-class-1-recall-since
[48] http://www.tga.gov.au/SARA/arn-detail.aspx?k=RC-2016-RN-00053-1
[49] http://www.qmed.com/news/why-b-braun-spat-over-infusion-pump-ratings
[50] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfRes/res.cfm?ID=150017, also see: http://articles.chicagotribune.com/2014-05-01/business/chi-baxter-recall-20140501_1_infusion-pumps-sigma-spectrum-baxter-healthcare-corp
[51] http://www.reuters.com/article/us-hospira-fda-cybersecurity-idUSKCN0Q52GJ20150731
[52] http://www.in-pharmatechnologist.com/Regulatory-Safety/Slew-of-recalls-Form-483-shake-Hospira

IMMUNOTHERAPIES (72.8% OWNED BY AHZ)

If AHZ's immunotherapy business achieves clinical success, it will undoubtedly become the Company's most valuable asset. Like all early stage immunotherapy programs, the statistical probability of success (for regulatory approval) at present is low. Nevertheless, we think this business has already achieved enough, preclinically and clinically, to warrant a risk-adjusted Net Present Value (rNPV) of $33m.[53]

AHZ's immunotherapy business consists of four programs; two pre-clinical, and two clinical. The two pre-clinical programs, which we will not discuss in this note, both target cancers related to the human papilloma virus (HPV). With respect to the clinical programs, the most advanced is a Phase II therapeutic vaccine[54] (called COR-1) to treat genital herpes, or herpes simplex virus type 2 (HSV-2). The second clinical program, which is about to start a Phase Ib trial, is a therapeutic vaccine (presently unnamed) to treat human papilloma virus (HPV) associated head and neck cancer.

HSV2

HSV-2, or genital herpes, while significantly less common than HSV-1 (orolabial herpes/ 'cold sores'[55]), is nevertheless one of the most common diseases in the world, affecting approximately 530m worldwide between the ages of 14 and 49.[56] The virus initially infects skin cells, but then spreads to nerve cells where it persists for life. While there are regulator-approved antiviral medications and topical creams to reduce the symptoms (outbreaks) of HSV-2, there is no cure at present. Of these 530m people, most suffer only one or two outbreaks, with no further symptoms (such that many are not even aware they carry HSV-2). However, approximately 20m-40m people worldwide suffer multiple outbreaks every year. Outbreaks can last from 2 to 20 days.

Apart from being physically uncomfortable or painful, HSV-2 can have a debilitating long-term psychological effect on its sufferers (and their partners), particularly those that suffer from multiple outbreaks. HSV-2 infected individuals are also more likely to acquire other sexually transmitted diseases. Of particular concern is a 3 fold higher risk for acquiring HIV (human immunodeficiency virus).[57] Neonatal herpes (HSV-2 passed from mother to child through vaginal birth) is a horrific, painful, and often fatal condition for the baby (because neonates have undeveloped immune systems). Amongst children that survive neonatal herpes, there is a high probability that it will cause permanent brain damage.[58] In the USA, the incident rate of neonatal herpes is approximately 4 cases in 100,000 live births.[59] Globally, the incidence rate of neonatal herpes is approximately 10 cases in 100,000 live births. In Africa, the incidence rate is 15 cases per 100,000 live births.[60] Given all of the above, there is an enormous unmet medical need for a therapeutic vaccine that could provide a practical cure for HSV-2.

Market Size

We choose to define the market for an effective therapeutic vaccine not by the number of people that carry HSV-2, but by the number of people who are *aware* that they carry HSV-2 and who are thus motivated to actively seek treatment. On this basis, we conservatively estimate that the global demand for a successful therapeutic HSV-2 vaccine would presently be in the region of 50m people. In the USA, we estimate that around 4m people are presently aware they have HSV-2, with around 2m of these people suffering severe/recurrent HSV-2 outbreaks. Furthermore, each year 776k people acquire a new HSV-2 infection in the USA.[61] Of these 776k people, we estimate that around 100k 'new sufferers' would actively seek a therapeutic vaccine each year. Depending on how many booster shots are required and over what time period, we estimate that the size of the USA market for a successful therapeutic HSV-2 vaccine would be in the region of $2b-$5b pa. Globally, we estimate that a successful therapeutic HSV-2 vaccine would create an $8b-$20b pa market for a period of approximately 12 years. After 12 years, in our estimation, a highly successful therapeutic HSV-2 vaccine would begin to materially shrink its own market as significantly fewer and fewer people become infected each year.

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[53] This is the value to AHZ (72.8% ownership). We value 100% of the Immunotherapies business at $45m.
[54] *Therapeutic* vaccines are used to treat people with an existing condition. By contrast, *prophylactic* vaccines (which AHZ is not developing) prevent people from acquiring a future pathogen.
[55] The WHO estimates some 3.4bn people under the age of 50 have HSV-1. See http://www.who.int/mediacentre/news/releases/2015/herpes/en/
[56] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2649511/
[57] https://www.ncbi.nlm.nih.gov/pubmed/16327322/
[58] http://www.thelancet.com/journals/langlo/article/PIIS2214-109X(17)30047-5/fulltext
[59] https://www.ncbi.nlm.nih.gov/pubmed/18157062/
[60] http://www.thelancet.com/journals/langlo/article/PIIS2214-109X(16)30362-X/fulltext?rss=yes
[61] CDC estimate

COR-1

AHZ's COR-1 vaccine is a glycoprotein D (gD2) based DNA vaccine. gD2 is a structural component of the external envelope of the HSV-2 virus, and plays an essential role in allowing the virus to enter host cells and spread. In the COR-1 vaccine, gD2 functions as an antigen.[62] A DNA vaccine (sometimes referred to in the literature as a polynucleotide vaccine or as a "third generation" vaccine) is a non-live, subunit vaccine containing genetically engineered DNA. With respect to COR-1, part of this genetic engineering involves 'codon optimization', where the genetic code in the DNA has been artificially modified according to a patent protected algorithm. COR-1 contains a 1:1 mixture of 2 plasmids[63] which carry codon-modified gene sequences. The first plasmid encodes the full-length (i.e., every amino acid) of gD2. The second plasmid encodes an *ubiquitin*-fused truncated version of gD2. (We explain ubiquitination more fully below). The scientific rationale behind this 1:1 mixture of different genetic antigen presentations is that each plasmid will stimulate a different immune response and the combined effect will be a stronger, more balanced immune response (=stronger T-cell responses and stronger antibody induction).[64]

Once COR-1 is injected into its 'host' (i.e. the HSV-2 positive patient), the patient's own cells take up the DNA such that the patients own cells (harmlessly) produce both the full length and ubiquitin-fused versions gD2. Thus, unlike earlier generation vaccine platforms, with DNA vaccines the host's cells act as kind of bioreactor to produce the vaccine. The vaccine is then released from the cells and, over time, naturally spreads throughout the body's immune system, thus achieving – assuming success – long-term immunity to HSV-2.

gD2 has been used previously as an antigen in a number of large pharma, late stage trials for an HSV-2 *prophylactic* vaccine. All these trials essentially failed; or, more specifically, while the vaccines did successfully produce an immune response (confirming that gD2 is indeed a valid antigen), the response was not strong enough to act as a functional cure for HSV-2 or sufficiently prevent seronegative partners from HSV-2 infection. The scientific rationale behind sticking with gD2 as the antigen with COR-1 is that these earlier trials failed because the vaccines only induced high antibody titrers. The vaccine technologies used in the earlier trials did not produce a *cellular* response. By contrast, DNA vaccines are uniquely able to generate both a strong cellular and antibody response – thus conferring both cellular and humoral immunity.

What is distinctive about COR-1?

There are presently two other competing, gD2, codon modified DNA HSV-2 therapeutic vaccines in Phase II clinical development (see below). In our view, there is a solid scientific rationale to expect COR-1 to ultimately be more successful than competing DNA vaccines in this space. AHZ owns the patents for a technique of encoding DNA for *ubiquitinated* proteins. No other competing vaccine company can attempt to encode DNA for ubiquitinated proteins without infringing on AHZ's IP. What is the significance of this? Ubiquitin is a protein the body's immune system uses to first 'flag' foreign entities that need to be destroyed by an immune response. Thus, before macrophages and the like 'know' that they need to destroy a foreign antigen, the body's immune system must first stamp that antigen with an ubiquitin protein. And sometimes this does not occur, or does not occur with sufficient critical mass, which partly explains why some antigens do not elicit a strong immune response. As we noted above, half of the plasmids in COR-1 are proprietary encoded in such a way that they instruct the host body's cells to produce gD2 that is *already ubiquitinated*. That is, unlike competing DNA vaccines, some of the gD2 that is produced by COR-1 is produced with a protein 'flag' attached to gD2 that reliably instructs (or signals to) the body's immune system to produce an antibody response. Ubiquitination sets AHZ's vaccine technology platform apart from all other vaccine platforms and adds significant value in our view.

COR-1 Trial Results

In an early encouraging animal study, COR-1 was shown to be 100% protective for mice against an otherwise lethal dose of HSV-2. Indeed, for 70% of infected mice at the higher dose, COR-1 had *completely cleared* HSV-2 from the mice by 62 days post vaccination. This study also confirmed that the mice were protected because they produced anti-gD2 antibodies.[65]

In a Phase I clinical trial on 20 HSV-1 and 2 seronegative healthy individuals, COR-1 was found to be safe and well tolerated. Unlike the mouse study, anti-gD2 antibodies were not detected in any of the subjects, however 19 of the 20 subjects (95%) did produce a dose dependent T-cell response. COR-1 was thus shown

[62] An antigen is any substance in the body which induces an immune response. In vaccine development, it is hoped that the antigen contained in the vaccine will safely lead to the production of antigen-specific antibodies.
[63] A plasmid carries gene sequences in a cell that are distinct from the cell's chromosomal DNA.
[64] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5215501/
[65] http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0076407

in this trial to be immunogenic in humans. It was speculated in the publication of the trial results that the lack of anti-gD2 antibodies was probably due to the relatively low dose of the vaccine given during the trial.[66]

In October 2016, AHZ released interim results on the first 20 patients (15 in the study arm, 5 placebo) for an ongoing Phase II trial involving 36 patients. All patients in the study have now completed vaccinations (intradermal delivery) and there have been no safety issues relating to COR-1. With respect to efficacy, there was a 58% decrease in viral shedding (i.e., the expulsion and release of HSV-2 viral progeny – often asymptomatically – on the surface of the skin) compared to baseline in those receiving COR-1. Further, the lesion rate (the visible herpes ulcers on the skin) was reduced by 52% post vaccination compared to baseline. Also, both anti-gD2 antibodies and T-cell responses were generated in the vaccine group. Importantly, no patient receiving the placebo generated an immune response.

The competitive landscape for COR-1

COR-1 is competing against other HSV-2 vaccine candidates, as well as existing approved frontline treatments for HSV-2. With respect to existing treatments, there are three antiviral drugs approved to treat the symptoms of HSV-2. These are acyclovir (Zovirax, GSK), valacyclovir (Valtrex, GSK), and famciclovir (Famvir, Novartis). These antivirals are all taken in daily pill form. Some patients take them daily for 2-10 days only during outbreaks, other patients take these antivirals daily all year round as a suppressive treatment.

COR-1's competing therapeutic vaccine candidates are:

- GEN-003, a glycoprotein D, DNA vaccine (Genocea, USA). GEN-003 has completed a large Phase IIb. Genocea has stated its intention to start a phase III in Q4/CY17.
- Vaxfectin (ViCal, USA), glycoprotein D, DNA vaccine, completed Phase II.
- Theravax (Rational Vaccines, USA), live attenuated vaccine to treat both HSV-1 and HSV-2. Competed a small Phase I.

Sanofi also has a live, replication-disabled prophylactic vaccine in Phase I development. Clinicaltrials.gov lists the status of this phase 1 as "ongoing, but not recruiting participants."

The COR-1 Phase II interim results in context

In order for COR-1 to attract the funding or out-license partner required to proceed further in the clinic, the relevant expert decision makers will likely need to be satisfied that there is a reasonable probability that COR-1 has some safety or efficacy advantage and no safety or efficacy inferiority with respect to the acyclovir antivirals as well as competing therapeutic vaccines.

Common side effects associated with the acyclovir antivirals include nausea, diarrhoea, vomiting, abdominal pain, and tiredness. With respect to safety, it is the scientific consensus that all DNA vaccines, including COR-1, will be safer and considerably more convenient than the acyclovir antivirals (which need to be taken daily). It is too early in the clinical trial process to make meaningful safety or adverse event distinctions between COR-1 and the competing DNA vaccines mentioned above – although the safety profile of COR-1 is excellent at this stage. However, in theory, DNA HSV-2 vaccines will be safer (for both medical staff and patients) than Theravax's live attenuated HSV-2 vaccine.

For the purposes of this note, the comparative efficacy measure we will focus on, and which we expect potential COR-1 partners to focus on, is the reduction in viral shedding. The lesion rate, while psychologically significant for the patient, is a subjective measure (based on a daily visible assessment of lesions, usually by patients themselves). Because it is subjective, we consider it an unreliable efficacy measure for comparative purposes. By contrast, the viral shedding rate is not a subjective measure, but is scientifically measured from skin swabs using standard PCR technology. In essence, a reduction in the viral shedding rate from a baseline reliably tells clinicians that the number of viral proteins on the surface of the skin has been reduced by a specific percentage. Patients can be asymptomatic of HSV-2 lesions but still shed the virus (and thus be contagious). If the number of viral proteins on the surface of the skin, over a given time period, is reduced to zero or near zero (=100% reduction in the rate of viral shedding), the patient will not be contagious for HSV-2 during unprotected sex during that time period. A functional cure for HSV-2, in our opinion, would not necessarily need to induce the complete elimination of the virus from the host's nerve cells, but would entail a durable reduction in viral shedding close to 100%.

[66] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5215501/

As noted above, in interim results from a small patient sample (N=15), COR-1 achieved a reduction in viral shedding rate of 58% relative to baseline. By comparison, COR-1's competitors have achieved the following reductions in viral shedding loads:

- Acycolvir antivirals: reductions between 76% and 82% compared to baseline in phase III trials
- GEN-003 DNA vaccine: a reduction of 40% compared to baseline in a 131 patient phase IIb trial[67] (This is an encouraging result because of the size of the trial).
- Vaxfectin DNA vaccine: a reduction of 19% compared to baseline (placebo achieved a 45% reduction!) in a phase 1/2 trial.[68] (This is a poor result, and we would be surprised if Vaxfetin progresses much further in the clinic).
- Theravax live vaccine, yet to start phase II, so viral shedding rate yet to be measured

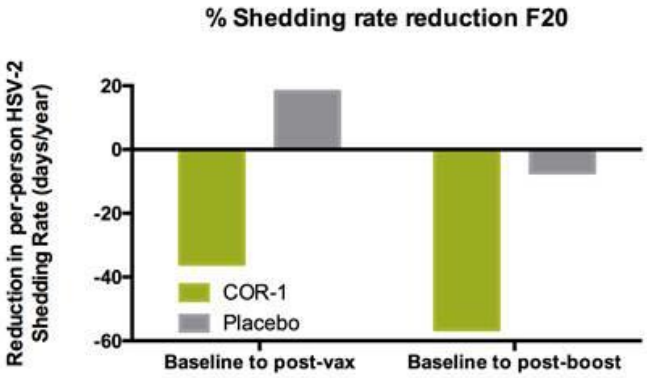
On this basis, and at face value, COR-1 is less efficacious than existing frontline antiviral therapy, but potentially more efficacious than any of the competing vaccines (where data is available). In our view, in order to be commercially successful as a mono-therapy therapeutic vaccine, a future trial of COR-1 would need to achieve a reduction in viral shedding rate of at least 75%. At this level of shedding reduction, COR-1 could usurp the existing antiviral market as COR-1 would have none of the gastro side effects associated with antivirals, and patients would prefer to take a few injections of a therapeutic vaccine rather than daily antivirals for life.

Even at the present 50-60% reduction in viral shedding, especially if this proved durable over years, there would, in our view, be a market for COR-1 taken in combination with antivirals. The scientific rationale here is that the combination of the therapeutic vaccine and the antivirals may reduce viral shedding to a level where patients are reliably non contagious.

Can COR-1 achieve a reduction in viral shedding rate above 58%?

The graph AHZ attached to the interim results is cause for cautious optimism, in our view.

Figure 2: % Shedding Rate Reduction F20



Source: Admedus Limited

The green (study arm) bars show the start of curve of increased viral shedding reduction over a 12-month period. By contrast, the placebo arm is 'noisy', showing an increase and then a small decrease – reflecting the natural variation in viral shedding that occurs amongst HSV-2 positive people not on medication. What is encouraging about this curve is that it suggests that additional 6-month boosters could lead to further reductions in viral shedding.

[67] https://globenewswire.com/news-release/2016/09/29/875656/0/en/Genocea-s-Genital-Herpes-Immunotherapy-GEN-003-Demonstrates-Significant-Reduction-of-Viral-Shedding-in-Phase-2b-Clinical-Trial.html
[68] http://www.vical.com/investors/news-releases/News-Release-Details/2015/Vical-Reports-Top-Line-Results-From-Phase-12-Trial-of-Therapeutic-Genital-Herpes-Vaccine/default.aspx

After 12 weeks from the initial inoculation, study arm patients went from a 38% reduction in viral shedding to a 58% reduction over an additional 9 months and after 2 boosters. If that trend was to continue over an additional year (= 2 additional 6 month boosters), the viral shedding rate would fall another 20% to 78%. At this level of reduction, COR-1 would be able to usurp the long-term antiviral market. And if the trend indicated with this curve was to continue over two years (=4 additional boosters), COR-1 would get to the status of a practical cure for HSV-2, with a reduction in viral shedding of 98%.

There is a scientific rationale to expect DNA vaccines to confer greater immunity over longer time periods, although this rationale is untested in the clinic. To a greater extent than traditional vaccines, DNA vaccines could be expected to increase their efficacy over time as the cellular responses that are unique to effective DNA vaccines play an essential role in producing a long-lasting memory response. However, this cellular response itself can take time (and boosters) to achieve its maximum immunological impact; the antigen-carrying genetic code needs to be transmitted to cells throughout the body and then to all the different parts of the immune system. Furthermore, studies have shown that the time to maximum immunity and the duration of immune responses induced by DNA vaccines can be affected by "(i) the mode and site of gene delivery, (ii) the dose of plasmid and (iii) the administration of booster injections and the interval between immunisations."[69]

With respect to the mode and site of gene delivery, we note that there have recently been a number of promising studies showing that electroporation delivery of DNA vaccines can significantly increase the immune response and decrease the time to that response.[70] We would expect future trials of COR-1 to potentially involve different delivery technologies, delivery sites, and possibly higher dosing regimes. Further, a potential partner for future COR-1 trials could well be the owner of an optimal delivery technology.

In our opinion, AHZ management made a strategic error in not planning for a 1 year extension to the current Phase II trial. Had they done this, they would have been able to confirm (at relatively low cost and in the shortest period of time) whether the encouraging trend on the 12-month viral shedding curve would continue. As things stand with the interim Phase II data, we attribute a rNPV to COR-1 of $25m (8% probability of success). Should COR-1 achieve a reduction in viral shedding close to 75% in the context of a Phase II trial, our probability of success for COR-1 rises to 25%, and our rNPV to $100m+. So there is significant value attached to any future increases in the rate of viral shedding reduction relative to baseline.

Given that it has achieved the best viral shedding reduction of any therapeutic HSV-2 vaccine to date, COR-1 is arguably the most promising HSV-2 therapeutic vaccine candidate in the world at present. However, this claim should be qualified with the recognition that COR-1's Phase II trial is relatively small and incomplete, and that COR-1's competition is not particularly advanced or numerous. AHZ does not have a sufficient cash cushion to conduct a longer, larger Phase IIb trial for COR-1 in the near term.

Given the blockbuster potential of an HSV-2 therapeutic vaccine, the scientific pedigree behind COR-1, young patents, and assuming the viral shedding trend established with the Phase II interim data is confirmed with the final data (due in Q2/CY17), we think COR-1 has good prospects for attracting a third party funding partner (or out licensee) for a Phase IIb trial to begin in H1 2018.

Immunotherapy for HPV associated head and neck cancer

AHZ has announced that it will soon (1H/CY17) begin a Phase Ib trial to test a DNA therapeutic vaccine to treat c.20 patients with human papilloma virus (HPV) associated head and neck cancer. The (presently unnamed) DNA vaccine in this trial uses the same proprietary, ubiquitinated, codon-optimised technology platform as COR-1. For the purposes of this note, we shall call this HPV therapeutic vaccine 'COR-2'.

The DNA encoded in COR-2 produces two antigens: E6 and E7. E6 and E7 are viral proteins produced by a cancer causing strain of HPV (genotype 16). When wild-type HPV16 infects host cells, E6 and E7 are coexpressed and, under the right circumstances (such as the additional presence of oxidative stress and a number of other factors that are too complex to articulate here), E6 and E7 can transform the infected host cell into a cancer cell. Every HPV16 associated cancer cell contains the E6 and E7 proteins.

With COR-2, the cancer-causing properties of E6 and E7 have been 'turned off' by the introduction of carefully designed mutations in the DNA genetic sequences. Furthermore, codon optimization techniques have been employed to ensure that the antigens in COR-2 cannot recombine with wild-type E6 and E7 to become cancer causing.

[69] http://www.sciencedirect.com/science/article/pii/S222116911530366X, https://www.ncbi.nlm.nih.gov/pubmed/18425596
[70] See Lambricht et al., "Clinical potential of electroporation for gene therapy and DNA vaccine delivery," in *Expert Opinion on Drug Delivery*, Vol. 13, 2016, issue 2. Also see: http://www.inovio.com/technology/electroporation-delivery/electroporation-devices/

Cancer cells typically have none of the DNA modifications necessary for the body's immune system to be able to recognise and destroy the cancer cells. The scientific rationale behind COR-2 is that by introducing these 'flagged' (i.e., ubiquitinated) antigens (E6 and E7) into the body's immune system, COR-2 will 'train' the immune system to target and destroy cancer cells expressing wild-type E6 and E7 proteins. In particular, what clinicians (and potential partners) will be looking for upon the conclusion of this Phase Ib trial is that COR-1 has generated antigen-specific CD8 + T cell responses in a majority of patients.

Head and Neck Squamous Cell Carcinoma (HNSCC)

Head and neck cancer (HNSCC) accounts for more than 550k cancer cases or 6% of cancer cases worldwide each year (= the 6th most common malignancy worldwide). Globally, the main cause of HNSCC is cigarette smoking, followed by alcohol consumption. In a minority of cases (25%) HPV is the cause (where HPV is transmitted mainly through oral sex). However, in advanced western countries, where smoking is rapidly declining and oral sex is widely practiced, HPV now accounts, at least according to some studies, for up to 90% of new HNSCC cases each year.[71] According the CDC, around 15k (3k female, 12.5k male) new HNSCC cases are caused by HPV in the USA each year.[72]

HNSCC generally carries a poor prognosis. The median overall survival for recurrent or metastatic HNSCC in western countries is less than 1 year.

Treatment Options for HPV associated HNSCC

Standard chemotherapy, radiation therapy, and surgical options can be effective in early stage HNSCC. For recurrent or metastatic HNSCC, standard treatment options have minimal benefit.

Some (but not all) tumour cells evade immuno-surveillance by exploiting inhibitory checkpoint pathways that suppress anti-tumour T-cell responses. For recurrent/metastatic HNSCC, new checkpoint inhibitor immunotherapy approaches have recently shown promise in the clinic. In late 2016, the FDA approved two checkpoint inhibitors for the treatment of patients with advanced HNSCC: Keytruda (Merck) and Opdivo (Bristol-Myers Squibb).

Both Keytruda and Opdivo showed significant benefit for this hard to treat population group. However, the response rate (the percentage of HNSCC patients actually having a positive response to the drug) was only 16% for Keytruda,[73] and 13.3% for Opdivo.[74]

Clinicians as well as big pharma active in the checkpoint inhibitor space are looking for other drugs, oncolytic viruses, and therapeutic vaccines that can combine with checkpoint inhibitors to increase response rates, efficacy and safety. DNA vaccines, which boost antitumor immunity (by antigen specific immunisation), may 'prime' the immune system to be more receptive to checkpoint inhibition (relative to checkpoint inhibitor monotherapy) by first undermining native immune tolerance to cancer cells.

COR-2 pre-clinical results

In a mouse study, COR-2 was shown to be immunogenic and able to induce both hormonal and cell-mediated immunity which protected 100% of mice in a solid tumour challenge. Tumour growth was completely prevented in immunised mice. This immune response was still detectable 5 months after immunisation.[75]

In another mouse study, COR-2 was combined with an anti-PD-L1 checkpoint inhibitor.[76] In this study, 6 of 8 mice (75%) survived tumour burden up to 60 days, with 3 of 8 mice completely clearing the tumour (complete response).[77]

[71] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3287051/
[72] https://www.cdc.gov/cancer/hpv/statistics/cases.htm
[73] https://www.cancer.gov/news-events/cancer-currents-blog/2016/fda-pembrolizumab-hnscc
[74] https://www.ncbi.nlm.nih.gov/pubmed/27718784
[75] http://journals.lww.com/immunotherapy-journal/Fulltext/2017/02000/DNA_Vaccine_Encoding_HPV16_Oncogenes_E6_and_E7.3.aspx#P81
[76] PD-L1 on the surface of a tumour cell combines with PD-1 on T-cells to block T-cells from attacking the cancer cell. By blocking PD-L1, T-cells are better able to recognize cancer cells as foreign.
[77] http://journals.lww.com/immunotherapy-journal/Fulltext/2017/02000/DNA_Vaccine_Encoding_HPV16_Oncogenes_E6_and_E7.3.aspx#P81

The significance of this Phase Ib trial for investors

In August 2015, AstraZeneca's MedImmune subsidiary paid for exclusive rights to Inovio's Phase I/II DNA cancer vaccine INO-3112. The deal involved US$27.5m up front, US$700m in potential milestone payments, funding of all development costs, and a double-digit royalty on sales. Also included in the deal was an agreement to collaborate on some preclinical cancer vaccine candidates.[78] The clinical results Inovio had reported at the time of this deal was that INO-3112 had generated, in the context of an open label Phase I/II, a significant antigen-specific CD8 + T cell response in three of four patients with head and neck cancer associated with HPV. In other words, on the basis of solid results in a tiny patient sample, MedImmune was willing to sign onto a large (albeit back-ended) deal to exclusively license a promising early stage therapeutic vaccine.

As noted above, in the context of checkpoint inhibitor combination therapy, there is strong demand at present for effective therapeutic cancer vaccines. If COR-2 can generate solid results in its Phase Ib, we think there is a reasonable probability that AHZ could ink a similar deal to Inovio with one of the many large pharma companies now active in cancer immunotherapy. If AHZ can ink an identical deal to Inovio, COR-2 would, according to our model, immediately attract a rNPV in excess of $110m. (Inovio presently has a market cap of around US$530m).

On the basis of the outstanding COR-2 pre-clinical results and the fact that COR-1 is unambiguously generating an antigen-specific immune response for HSV-2 patients, we are cautiously optimistic that this Phase Ib will be successful. And if successful, we think that COR-2 has good prospects of being partnered early.

VALUATION

We think fair value for AHZ is $126m or 50c per share. This is also our 12-month price target.

Methodology

AHZ has two distinct business types in its portfolio: revenue-generating medtech (viz., ADAPT and Infusion) and early clinical stage biotech (Immunotherapies). Each of these business types demands a slightly different valuation methodology. For AHZ's medtech business segments we use a 10-year discounted cash flow (DCF) model, assuming a discount rate of 12.8%. For Immunotherapies, we use a risk-adjusted net present value (rNPV) method to discount future cash flows over 10 years. Again, our discount rate is 12.8%. In arriving at our unrisked Immunotherapies NPV, we use biotech industry experience combined with an analysis of competing companies/technologies to estimate the size and timing of milestone payments, peak sales, and royalties. We then adjust our unrisked NPV by a series of conditional probabilities. Specifically, we estimate the probability of: (i) attracting third party financing; (ii) clinical success if financing is secured; and (iii) FDA approval if clinical success achieved. The sum of these conditional probabilities gives us an effective probability of success for each immunotherapy programme.

The key assumptions behind our Immunotherapies rNPVs are as follows:

- COR-1: A$30m upfront licensing fee, licensee to cover all costs from CY18 onwards, A$20m milestone payment at conclusion of a successful Phase III, A$40m milestone payment at registration, 12% royalty on sales, effective probability of success (= probability of FDA approval) at this early stage: 8%.

- COR-2: A$30m upfront licensing fee, licensee to cover all costs from FY19 onwards, A$100m milestone payment at conclusion of successful Phase III, A$100m milestone payment at registration, 14% royalty on sales, effective probability of success (= probability of FDA approval) at this early stage: 4%

[78] http://www.genengnews.com/gen-news-highlights/medimmune-licenses-inovio-cancer-vaccine-for-up-to-727-5m/81251607

Figure 3: AHZ sum of the parts valuation		
COR-1 HSV2 (rNPV)	A$'000	25,315
COR-2 HPV (rNPV)	A$'000	7,666
CardioCel/Neo (NPV)	A$'000	74,133
VascuCel (NPV)	A$'000	34,330
Infusion Products (NPV)	A$'000	24,456
Taxation	A$'000	(49,770)
Value of Tax Losses	A$'000	10,155
Valuation	A$'000	**126,285**
Shares on issue		254,796,534
Valuation/share (A$)		**0.50**

Source: Patersons Securities Limited

Commentary

We note that our rNPV of 100% of Immunotherapies is A$45m (AHZ owns 72.8%), which is less than half the enterprise value (EV) of Genocea Biosciences Inc (Nasdaq: GNCA). Genocea has a similar technology and is focusing on the same indications as AHZ Immunotherapies, yet has an EV of US$75m (A$100m). Genocea has completed a large Phase II study, but, as noted earlier, the headline results were slightly less promising that COR-1's interim data. We think Genocea's DNA vaccine IP is less scientifically attractive than AHZ's. Another relevant comparator, which has a larger clinical program than AHZ, is Inovio (Nasdaq: INO). Inovio presently has an EV of around US$400m.

We think it likely that, once one or both of the clinical stage assets in Immunotherapies has secured third party funding, Immunotherapies will be spun out of AHZ and listed as a separate company, potentially creating a significant value inflection point for AHZ shareholders.

Sensitivity and risk analysis

We see Immunotherapies as the key variable in our valuation over the next 12 months. Should COR-1 (Phase II) and COR-2 (Phase Ib) both achieve positive clinical results in their current trials, and assuming no significant change in the viral shedding rate released with the COR-1 interim results, our valuation rises to 58c/share. With respect to downside risk, should both clinical programs fail, we would ascribe a zero value to Immunotherapies (at least until such time as the two HPV pre-clinical programs enter the clinic), and our valuation would fall to 39c/share.

We also note that the cancer immunotherapy market is very crowded. In particular, there are hundreds of clinical trials going on at present looking at a range of drugs, oncolytic viruses, and vaccines to be used in combination with checkpoint inhibitors. With so much competition, the risk of technological obsolescence for the HPV vaccine, even with positive clinical trial data, remains real. The HSV-2 vaccine market is significantly less competitive, which is advantageous for COR-1's partnering prospects.

Another variable over the next 12-18 months is whether or not Infusion receives another large hospital contract. Our model assumes no additional large hospital contract wins over the next 18 months. Nevertheless, a win of any reasonable size provides upside risk.

Over the medium term, our model assumes that AHZ introduces its full range of ADAPT products into the large Indian and Chinese markets, starting with India in 2H/FY18 and China in FY20. Our model also assumes that VascuCel will get EU approval next year. A significant delay with respect to VascuCel in the EU, or any ADAPT product with respect to India and China, would have a material negative impact on our valuation.

Figure 4: *Income Statement (excludes Immunotherapies[79])*

	FY17	FY18	FY19	FY20	FY21	FY22	FY23	FY24	FY25	FY26	FY27
REVENUE											
CardioCel/Neo	7,893	13,410	23,826	35,132	44,707	52,050	59,129	67,213	72,630	76,659	78,743
VascuCel	442	1,412	4,078	8,135	14,952	25,225	34,294	39,694	44,650	48,411	50,054
Infusion	14,162	15,176	15,893	16,669	21,444	20,951	22,129	23,737	25,468	27,388	29,459
Total	**22,498**	**29,998**	**43,797**	**59,935**	**81,103**	**98,226**	**115,552**	**130,644**	**142,766**	**152,458**	**158,256**
COGS											
CardioCel/Neo	(2,605)	(4,425)	(7,863)	(11,593)	(14,753)	(15,615)	(17,739)	(20,164)	(18,158)	(19,165)	(19,686)
VascuCel	(146)	(466)	(1,346)	(2,685)	(4,934)	(7,568)	(10,288)	(11,908)	(11,162)	(12,103)	(12,514)
Infusion	(8,639)	(8,347)	(8,741)	(9,168)	(11,794)	(11,523)	(12,171)	(13,055)	(14,017)	(15,063)	(16,202)
Total	**(11,390)**	**(13,238)**	**(17,949)**	**(23,446)**	**(31,481)**	**(34,706)**	**(40,198)**	**(45,128)**	**(43,337)**	**(46,331)**	**(48,402)**
Gross Profit	11,108	16,760	25,848	36,490	49,621	63,521	75,354	85,517	99,429	106,127	109,854
OPEX	(24,513)	(24,428)	(24,598)	(26,660)	(28,490)	(29,969)	(31,133)	(31,757)	(32,346)	(32,895)	(35,246)
Pre-Tax Profit	(13,405)	(7,669)	1,250	9,830	21,132	33,551	44,222	53,759	67,082	73,232	74,609
Tax Expense							(3,651)	(16,128)	(20,125)	(21,970)	(22,383)
NPAT	**(13,405)**	**(7,669)**	1,250	9,830	21,132	33,551	40,571	37,632	46,958	51,262	52,226

Source: Patersons Securities Limited

[79] This income statement includes $2m of Immunotherapies costs in FY17, $500k in FY18, but no Immunotherapies costs beyond FY18.

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