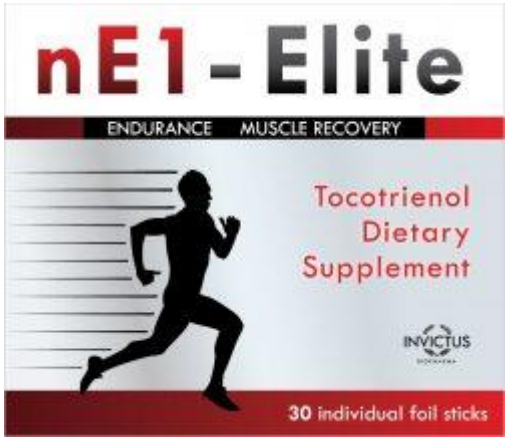
Vitamin E champion

ASX: AZT
Sector: Life Sciences
24 February 2020

Azure Health Technology Limited (ASX: AZT) is a listed shell company which announced on 8 November 2019 its intention to acquire Invictus BioPharma Ltd in a Reverse Takeover (RTO) transaction. After the RTO the merged group will raise $7-10m in a placement of new shares to develop the Vitamin E-based products currently being worked on by Invictus. Azure Health Technology believes this transaction can be completed in early-to-mid-2020. Post-money it will value Azure Health Technology at $28-31m. This report evaluates the technology behind AZT and the market potential of those products.



A nutraceuticals to prescription drug play

Invictus BioPharma is a Melbourne based drug developer being built around two drug delivery technologies called 'TransT3' (which allows transmucosal drug delivery for direct delivery of the drug to target tissues and organs) and 'Tocotrienol ProDrug' (TPDs) which allows a drug to be orally administered but at the same time delivered more effectively to target tissues and organs without passing through the liver first. AZT has developed two nutraceutical products delivering tocotrienols from Vitamin E based on a third delivery platform, called 'MELT3', designed for nutraceuticals only. AZT believes that the true health benefits of Vitamin E lie in the tocotrienol fraction of Vitamin E, and that the company's products can reactivate the historically large market for Vitamin E supplementation. Longer term, AZT believes that TransT3 and TPD can be used to develop a wide range of drugs targeting indications with unmet needs and that ultimately the company can transition to the development of high value prescription-only products.

A valuable natural products play

The Independent Experts Report related to the RTO contains an attachment headlined 'Independent Valuation Report of Intellectual Property owned by Invictus BioPharma Limited'. In that attachment, expert Dr David Randerson of Acuity Technology Management postulates a valuation range for Invictus BioPharma of A$43.6-A$54.7m. We consider that valuation range reasonable.

Subscribe to our research HERE

Analyst: Stuart Roberts

Tel: +61 (0) 447 247 909

Stuart.roberts@pittstreetresearch.com

Table of Contents

Executive summary

The new Azure Health Technology Ltd (ASX:AZT) is an Australian drug developer being built around two drug delivery technologies called 'TransT3' (which allows transmucosal drug delivery for direct delivery of the drug to target tissues and organs) and 'Tocotrienol ProDrug' (TPDs) which allows a drug to be orally administered (swallowed like a pill) but at the same time delivered more effectively to target tissues and organs without passing through the liver first. AZT's first application of TransT3 are two nutraceutical products delivering tocotrienols from Vitamin E using a delivery platform, MELT3®, which is designed for nutraceuticals. AZT believes that the true health benefits of Vitamin E lie in the tocotrienol fraction of Vitamin E delivered directly to target tissues and organs, and that the company's products can reactivate the historically large market for Vitamin E supplementation. Longer term, AZT believes that TransT3 and TPD can be used to develop a wide range of drugs targeting indications with unmet needs and that ultimately the company can transition to the development of high value prescription-only products.

Azure Health Technology (ASX: AZT) is currently completing a Reverse Takeover transaction. Azure on 8 November 2019 announced its intention to acquire Invictus BioPharma in a Reverse Takeover transaction. After the RTO the merged group will raise $7-10m in a placement of new shares to develop the Vitamin E-based products currently being worked on by AZT. We describe the RTO in Appendix I of this report.

AZT's drug delivery platforms can be company-making

AZT's transmucosal (TransT3) and TPD drug delivery platforms can be company-making. In transmucosal drug delivery, the patient simply places a tablet, a lozenge or powder/granules under their tongue, and as it melts the drug slips through the oral-mucosal layer of the mouth and from there into the bloodstream. Transmucosal drug delivery has obvious advantages in terms of patient convenience for the 4% of adults with difficulties swallowing. It is also known as one of the fastest ways to deliver drugs[1]. Importantly, it is a *non-invasive* way of delivering drugs directly to target tissues and organs which gives it clear advantages over invasive direct delivery methods such as injections. We believe there is room in the market for a transmucosal drug delivery play like AZT.

AZT can quickly grow shareholder value following the RTO. AZT's first two nutraceutical products, nE1-ElitE® and nE1-Heart®, will be launched in the US this year. We believe the combination of marketed products, and data around Tocotrienol ProDrugs, can add significant shareholder value immediately post completion of the RTO.

AZT has seasoned biotech leadership. Managing Director and CEO, Dr Glenn Tong, has been involved in biotech ventures for many years, including stints as CEO of the Molecular Plant Breeding CRC and Executive Director of Drawbridge Pharmaceuticals[2]. Tong's fellow director, the independent non-executive Chairman of AZT, Lou Panaccio is also a director of Sonic Healthcare and a couple of ASX-listed biotechs such as Avita Medical. The President and CEO of AZT's US subsidiary, Invictus Nutraceuticals, Inc. is Richard Estalella who is a proven senior executive in the US sports nutrition market having overseen a 167% growth in international sales over 4 years in a US sports nutrition company called MusclePharm Corp. AZT's clinical development program is led by Chief Scientific Officer and Chair of the Scientific Advisory Board, Dr David Kingston, who was formerly the Medical Director for Roche

[1] Crit Rev Ther Drug Carrier Syst. 2008;25(5):449-84.
[2] Developer of a new anesthetic with the potential to replace propofol.

Australia and has put 40 new pharmaceutical products on the market. On the Scientific Advisory Board and responsible for the pancreatic cancer program is US-based, world-renowned cancer physician and research scientist Dr Richard Pestell AO. The Company is young, but the Board, Scientific Advisory Board and management are seasoned operators in biotech, nutraceuticals and pharmaceuticals.

Ten reasons to look at AZT

1) **AZT has an early-stage revenue opportunity in the MELT3® products**, two nutraceutical products which are now being brought to market in the US. The data that AZT has obtained on nE1-ElitE® and exercise endurance suggests the potential for a particularly successful launch.
2) **AZT may be able to deliver on the therapeutic potential of Vitamin E**, with its TransT3 and TPD technologies allowing efficient delivery of the tocotrienols, which are in turn widely regarded as the more effective of the Vitamin E isotypes.
3) **AZT may have one of the world's first drugs for Non-Alcoholic Fatty Liver Disease**. With tocotrienols having been shown to be effective in reducing the level of fat in the liver, AZT believes that either its IVB001 or its IVB003 drug candidate can be among the first in the world to represent an effective NAFLD drug treatment. 30% of the US population may have NAFLD, so an effective drug has blockbuster potential.
4) **AZT may have a low-toxicity pancreatic cancer drug**, with clinical and pre-clinical evidence suggesting that tocotrienol therapy could work in this cancer. This bodes well for AZT's IVB002 and IVB004 drug candidates.

IVB001 could potentially be Phase 3-ready for NAFLD by 2021

5) **AZT can become a late stage clinical company within two to three years.** IVB001 could potentially be Phase 3-ready for NAFLD by 2021, since the measurement window to show that a drug can reduce liver fat is narrow.
6) **With TPD, AZT can go after 'composition of matter'**. AZT's Tocotrienol ProDrugs use Monash-developed technology to deliver tocotrienols into the blood stream without first going through the liver. This technology, because it uses novel chemicals derived from tocotrienols rather than formulations of tocotrienols, allows AZT to go beyond formulation and method of use patents, notably strengthening its intellectual property position through composition of matter patents that protect the prodrug molecule which is a New Chemical Entity.
7) **Tocotrienols can help AZT build a pipeline**, with clinical and pre-clinical evidence from numerous groups showing that tocotrienols are effective in many disease states, including cancer, fibrosis and cardiovascular disease.
8) **Omega-3 has strengthened the investment case for companies working on 'supplements as therapies'**. The story of GSK's Lovaza and its competitor drugs, in developing the Rx market for Omega-3, provides a roadmap for companies like AZT with its products (in this case Vitamin E) and ambitions.
9) **The current funding round can potentially deliver a serious valuation uplift,** with a Proof of Concept Phase 2 for IVB-001 in for NAFLD patients expected to commence in FY20 and read out data in FY21.
10) **AZT has a capable management team and Board**, led by the seasoned biotech executive Dr Glenn Tong and including Dr David Kingston (an ex Roche Australia Medical Director who has put 40 new pharmaceutical products on the market), Richard Estalella (an experienced US executive

who was the President of MusclePharm Corp), and Lou Panaccio (non-executive director on a number of ASX-listed biotech Boards such as Avita Medical Ltd). Renowned cancer researcher Dr Richard Pestell AO leads the pancreatic cancer program.

AZT is helping to 'rehabilitate' Vitamin E

Vitamin E is a major dietary supplement. Vitamin E is a vitamin one can get from consuming wheat germ oil, egg yolk, and leafy vegetables, but roughly one third of US adults regularly take Vitamin E supplements[3]. What these consumers value is the Vitamin as an antioxidant[4], mainly to prevent cardiovascular disease[5]. There is also a strong body of opinion that Vitamin E supplements will help reduce cancer risk[6]. The trouble is people may be getting the wrong type of Vitamin E.

There's tocopherol Vitamin E, and there's tocotrienol Vitamin E. The latter is better. Vitamin E is not a single molecule, but rather a family of eight molecules, of which four are called 'tocopherols' and four 'tocotrienols'. In each case the molecule has a Greek letter, either α, β, γ or δ. Vitamin E was first identified in 1922[7], but the tocotrienols were only discovered in 1965[8]. That four-decade head start explains why most commercially available Vitamin E supplements today are tocopherol-based. The most commonly used tocopherol is α-tocopherol, since that was the first isoform to be identified and is available in large quantities in most sources of Vitamin E such as soybeans. We now know that the ideal Vitamin E supplement would be a tocotrienol one, since the tocotrienols have much greater antioxidant properties[9]. Tocotrienols possess powerful neuroprotective[10], anti-cancer[11] and cholesterol lowering[12] capability that the tocopherols just don't have[13]. AZT with its TransT3 technology has now developed a transmucosal tocotrienol-only product which, in a Phase 1a Clinical Study conducted in 2015, has been demonstrated to have good bioavailability (which does not depend on having a fatty meal unlike orally administered tocotrienols), has a linear dose response (that is, treatment effect rises with increasing dose), and is easy to take, palatable and well tolerated.

Vitamin E is a large market opportunity

Vitamin E is a large market opportunity. Tocotrienols can help realise that opportunity. In 1999, US consumers spent over US$800m on Vitamin E supplements, but by 2008 sale were down around 60% on the 1999 level[14]. The reason, it is believed, is a widely noted 2005 study from researchers at Johns Hopkins[15] indicating that high doses of Vitamin E could increase

[3] See Kantor et al., JAMA. 2016 Oct 11;316(14):1464-1474.

[4] A prominent feature of the complementary medicine scene since the 1980s has been the recommended use of antioxidants as prophylactics or therapeutics for various diseases. When we breathe, the oxygen taken in by our bodies is processed to produce energy, however in the process various 'free radicals' are created including 'reactive oxygen species', that is, molecules with an oxygen component where there are unpaired electrons. A free radical must combine with a complementary molecule to achieve chemical stability. If it bonds with a positively charged molecule, its charge is neutralized. If not, the oxygen component of the free radical can damage cells in the body in a process called oxidative stress. Reactive oxygen species are widely believed to cause or aggravate various diseases such as neurodegenerative diseases, cancer and stroke. Antioxidants are assumed to counteract the oxidative stress involved

[5] Since Vitamin E is known to inhibit oxidative modification of LDL cholesterol, thereby reducing the risk of atherosclerosis - See J Nutr. 1998 Oct;128(10):1593-6.

[6] Cancer Prev Res (Phila). 2012 May;5(5):701-5. Epub 2012 Apr 3.

[7] By two researchers at the University of California Berkeley, Herbert Evans (1882-1971) and his assistant Katherine Bishop. See Science. 1922 Dec 8;56(1458):650-1.

[8] Nature. 1965;201:521–522.

[9] Pharmacol Ther. 2016 Jun;162:152-69. Epub 2015 Dec 17.

[10] Neuropharmacology. 2004 Nov;47(6):904-15.

[11] Biofactors. 2016 Mar-Apr;42(2):149-62. Epub 2016 Mar 7.

[12] Curr Pharm Des. 2011;17(21):2147-54.

[13] Life Sci. 2006 Mar 27;78(18):2088-98. Epub 2006 Feb 3.

[14] See *Will Ginkgo Sales Continue to Slip Following Recent JAMA Study?,* Nutrition Business Journal, 5 January 2010.

[15] Ann Intern Med. 2005 Jan 4;142(1):37-46. Epub 2004 Nov 10.

mortality. AZT would note that supplements evaluated in the 2005 analysis contained mostly tocopherol and not tocotrienols. That said, Vitamin E use seems to have stabilised anyway after 2008[16], off the back of revaluations of the available data showing no serious mortality issues[17]. We argue that tocotrienol nutraceuticals like those which AZT is preparing to launch could, with the help of new data, bring the market back to its 1999 levels, particularly in the light of evidence that the tocopherols may hinder the effect of the tocotrienols[18].

AZT has developed two tocotrienol-based dietary supplement products using a delivery platform they have called MELT3®, one for cardiovascular health called nE1-Heart® and one for exercise endurance and prevention of muscle soreness called nE1-Elite®. MELT3® is a technology platform where a tablet or powder is first 'melted' (in fact, it is dissolved rather than melted) in the mouth and then swallowed.

nE1-Heart could serve as a useful adjunct to the statins

- nE1-Heart® may be a new adjunct to the statins. AZT believes that many consumers who would be attracted to Vitamin E for cardiovascular health would buy nE1-Heart®, particularly after a 60-subject Phase 1a clinical study which was led by David Kingston showed 20-25% better bioavailability than orally administered tocotrienols. It is noteworthy that nE1-Heart® has a similar mode of action to statins, which are the 'gold standard' prescription medicines for hyperlipidaemia. Specifically, tocotrienols inhibit the biosynthesis of an enzyme called HMG-CoA reductase[19], as do the statins[20]. nE1-Heart® would obviously not replace the statins, where typically LDL cholesterol can come down by 30%[21], but could serve as a useful adjunct or alternative for patients not yet ready to go on statins[22].
- nE1-Elite® reduces muscle soreness after exercise and can improve exercise endurance in humans, with the company having demonstrated these claims clinically. Given that a substantial percentage of Western world populations exercise daily and take dietary supplements as part of their exercise regime, this product could have particularly strong market appeal.

AZT has two other tocotrienol delivery systems in the works, one called TransT3 and one called TPDs. We explore these platforms in two subsequent sections of this report, after we look in more detail at the potential of nE1-Elite®.

nE1-Elite®: Data-supported claims

Tocotrienols have novel properties in promoting exercise endurance. This has long been known *in vivo* (in rats)[23] but until Invictus' recent clinical work there was little evidence of a similar effect in humans[24]. When research conducted in the laboratory of Professor Michael Mathai (a friend of Glenn Tong's) at Victoria University confirmed that tocotrienols improved exercise

[16] Kantor et. al., op. cit.
[17] See Curr Aging Sci. 2011 Jul;4(2):158-70. Some would argue that the jury is still out on the safety of high dose Vitamin E – for example one 2014 study suggested that Vitamin E increased the risk of prostate cancer (J Natl Cancer Inst. 2014 Mar;106(3): djt456. Epub 2014 Feb 22).
[18] J Nutr. 1996 Feb;126(2):389-94; Asia Pac J Clin Nutr. 1997 Mar;6(1):36-40; Atherosclerosis. 2002 Mar;161(1):199-207.
[19] J Biol Chem. 1993 May 25;268(15):11230-8.
[20] J Cell Mol Med. 2001 Oct-Dec;5(4):378-87.
[21] JAMA. 1997 Jul 23-30;278(4):313-21.
[22] J Clin Hypertens (Greenwich). 2012 Feb;14(2):121-32. Epub 2012 Jan 17
[23] Eur J Appl Physiol. 2009 Nov;107(5):587-95. Epub 2009 Aug 25.
[24] One relatively disappointing study is reported in J Sports Sci Med. 2006 Dec 15;5(4):629-39.

endurance in rats[25] Glenn Tong theorised that direct delivery of tocotrienols to the target tissues could improve the efficacy for this and other indications in humans. But there was one hitch – Tong had a great fear of needles so as far as he was concerned this direct delivery had to happen without the use of needles or surgical implants. This was where Tong started his work on TransT3. AZT has also investigated the ability of its tocotrienols to promote muscle recovery after exercise.

nE1-Elite reduces Delayed Onset Muscle Soreness

nE1-Elite® can reduce muscle soreness after exercise and improve exercise endurance. The results of a double-blind, placebo-controlled study of its tocotrienol formulation in 17 subjects conducted at the University of Mount Union in the eastern Ohio town of Alliance in May 2016 were very informative[26]. The Mount Union investigators showed that the product worked against Delayed Onset Muscle Soreness, with a marked reduction in whole-body muscular pain compared to a control group 24 hours after a particularly challenging weight training session (p=0.02). The product also reduced swelling and microtrauma. There were strong trends towards statistical significance in terms of a reduction in 'hanging arm angle' (p=0.05), as well as peak power on an exercise bike the day after damaging exercise (p=0.056). These observations confirmed the results of AZT's internal research and supported specific claims including: reduced muscle soreness after exercise, improved muscle recovery after exercise and improved maintenance of peak muscle power. Dietary supplements with specific claims which are supported by clinical data and protected by patents are few and far between, which arguably makes nE1-Elite® stand out from the crowd.

The commercial potential of this product is strong. Around 5% of the US population are physically active every day of the week, including ~30 million people who run or jog and 25 million people who cycle[27]. There are, however, very few dietary supplements which are effective for the treatment of muscle soreness after exercise. One of the key ways that Invictus Nutraceuticals, Inc. (AZT's US subsidiary) will be promoting the dietary supplement products in the US will be through sports heroes and heroines. A celebrity US track and field athlete and six-time Olympic medallist has signed on as one of the first brand ambassadors.

TransT3: AZT develops tocotrienols as therapies

AZT's TransT3 technology represents a new way to deliver tocotrienols transmucosally. Invictus originated from Glenn Tong's 2012 invention of a transmucosal delivery system for tocotrienols. Since tocotrienols are lipophilic (that is, fat soluble, not water soluble) the conventional wisdom held that they couldn't be delivered through the aqueous oral-mucosal layer, that is, the mucous membrane which lines the inside of the mouth. Tong proved that such transmucosal delivery was possible by taking δ and γ tocotrienols from a plant extract called annatto[28], and experimenting with various formulation systems until he found one that worked sub-lingually. He filed for patent protection over his approach, which allowed high plasma levels of tocotrienol for over 12 hours. Since tocotrienol is often called 'T3' in the literature[29] and the technology platform involved the transmucosal

[25] See PLoS One. 2016 Apr 8;11(4):e0152562.
[26] See the press release dated 2 May 2016 and headlined '*Gordagen reports top-line results of US human research (clinical) study for muscle recovery supplement*'.
[27] Source: The Sports and Fitness Industry Association, 2013 Sports, Fitness and Leisure Activities Topline Participation Report.
[28] Annatto comes from the seed of the achiote tree, *Bixa orellana*. It is most often used as a condiment and food colouring.
[29] Since there are three 'enols' in the molecules, enols being alkenes where there is a hydroxyl group attached to one end of the double bond that characterises alkenes.

delivery of T3, Tong called his technology for tocotrienol formulation TransT3. AZT is currently working on two drug candidates from TransT3, IVB001 for Non-Alcoholic Fatty Liver Disease (NAFLD)/Non-Alcoholic SteatoHepatitis (NASH) and IVB003 for pancreatic cancer.

Transmucosal delivery of drugs is highly efficient. Since the oral mucosa is rich in blood vessels, drugs that are absorbed through this membrane enter the bloodstream directly, bypassing the gastrointestinal tract and first-pass metabolism in the liver[30]. This can lead to rapid onset of action compared to conventional pills – transmucosally delivered drugs typically appears in blood within one minute, with peak blood levels achieved within 10 to 15 minutes[31]. The classic case of transmucosal efficiency is Actiq, a transmucosal formulation of fentanyl from Cephalon[32] that can go to work as a painkiller in five minutes as opposed to 30-45 minutes for standard short-acting oral opioids[33]. Invictus believes that with TransT3 it has a very efficient delivery system for tocotrienols, allowing low doses to be used in a therapeutic setting.

IVB001 is could potentially be Phase 3-ready for NAFLD by 2021. As we note below, tocotrienols have been shown by various groups to be able to reduce the liver fat volume of patients with NAFLD. AZT's IVB001 formulation has completed a Phase 1a clinical study and met all the primary endpoints, showing it is safe, non- toxic, palatable and easily absorbed. IVB001 is Phase 2-ready and a proof of concept Phase 2 clinical study is planned for H2 of 2020. AZT envisages a randomised, double blind, placebo-controlled trial recruiting NASH patients and comparing the effects on liver structure as measured by ultrasound and MRI. By 2021 AZT could therefore have one of the first drugs in Phase 3 in the world for NAFLD/NASH.

IVB003 may have utility in pancreatic cancer.

IVB003 may have utility in pancreatic cancer. There is an emerging body of knowledge showing tocotrienols to be effective in pancreatic cancer. Probably the most important study to date has come from the laboratory of Dr Mokenge Malafa at the Moffitt Cancer Center in Tampa, Fl., which found that delta tocotrienol could act synergistically with gemcitabine in a pancreatic tumour model, halving tumour volume over 34 days of treatment[34]. In that study raw tocotrienols were administered to rats by gavage, which is expected to imitate what happens when tocotrienols are administered orally (swallowed like a pill or capsule). AZT expects over the next twelve months to see if TransT3 tocotrienols can work better.

TransT3 can generate multiple products. Given that there are four tocotrienols and multiple potential indications for tocotrienols it is reasonable to expect more products to emerge from the TransT3 platform. TransT3 has two main limitations – there is a limit to the dose size the technology can handle, and the intellectual property protection centers around formulation and method-of-use patents, since the T3s themselves occur naturally and these molecules are therefore not patentable. That said, if high daily dosages are not required, AZT can move quickly with TransT3 products - the Active Pharmaceutical Ingredient is a natural product with a well-established safety and toxicology profile in humans and has GRAS status from the FDA.

[30] Clin Pharmacokinet. 2002;41(9):661-80

[31] J Control Release. 2009 Nov 16;140(1):2-11. Epub 2009 Aug 6.

[32] Actiq was launched in the US market in 2001, grew from US$15m in sales that year to US$580m in global sales in 2006 prior to US patent expiry. Post 2006 Cephalon's sales of branded and generic Actiq plus a related product called Fentora (buccal tablets rather than 'lozenges') meant that this franchise was still worth US$353m in sales in 2010.

[33] J Natl Cancer Inst. 1998 Apr 15;90(8):611-6.

[34] Mol Cancer Ther. 2011 Dec;10(12):2363-72. Epub 2011 Oct 4.

AZT has strong clinical development expertise. A formal Pre-IND consultation process was completed with the US FDA in June 2019 and the FDA broadly endorsed the manufacturing, preclinical and clinical development plan which was developed by AZT for the TransT3 drug candidates IVB001 for NAFLD/NASH and IVB003 for pancreatic cancer. The FDA also agreed with AZT's proposition that IVB001 and IVB003 could potentially adopt an abbreviated drug development pathway (known as the FDA 505(b)(2) pathway) which would mean these products could hit the market quicker than drug candidates going through the normal unabbreviated development pathway. AZT expects to undertake a formal Pre-IND consultation process with the US FDA for the TPD drug candidates IVB002 and IVB004 for NAFLD/NASH and pancreatic cancer respectively in late 2020.

TPDs: AZT moves into the NCE space

AZT's Tocotrienol ProDrug (TPD) technology takes tocotrienols to the next level. As well as the TransT3 delivery platform, AZT has in-licensed a delivery technology developed in the laboratory of Professor Chris Porter at Monash University in Melbourne. AZT expects that one of its next products will be a tocotrienol that can be taken orally (as in, a pill that is swallowed) but at the same time avoid first pass metabolism in the liver. The Porter group's Prodrug technology facilitates transport from the gut into the blood stream, markedly improving the bioavailability and therefore efficacy of the delivered drug. The beauty of the Porter Group technology is twofold:

- Since prodrugs are New Chemical Entities (NCEs), AZT has the potential to file for composition of matter patents which protect the actual prodrug molecule rather than a formulation of the prodrug or a method of use or treatment.
- Prodrugs have great dosage flexibility, potentially allowing large, gram-scale quantities of tocotrienols to be delivered, as against the 50-60mg maximum doses of the TransT3 platform.

AZT can go after large market therapeutic indications with TPDs. AZT believes that its TPDs would allow high enough levels of tocotrienol dosing to treat cancer, fibrosis and hyperlipidaemia (ie high cholesterol), all multi-billion-dollar market opportunities. Initially, AZT will target NAFLD with a TPD called IVB002, and pancreatic cancer with a TPD called IVB004.

An AZT TPD could enter the clinic in 2021

The next stage for AZT's TPDs. AZT announced in August 2018 that a rat pharmacokinetic study conducted in collaboration with the Porter lab had found strong oral bioavailability, comparable to what one could expect from tocotrienols especially emulsified for improved oral delivery. A lead candidate was identified through this study and AZT is now working with the Porter lab on a TPD with optimal delivery properties. This will be followed by assessing the efficacy of the chosen TPD in select indications such as cancer and fibrosis in validated animal models. AZT intends to spend 2020 on lead optimisation, pre-clinical safety and toxicology studies before taking a lead candidate into a Phase 1 clinical study in 2021.

How AZT intends to move into the 'Big League'

Can AZT build a large company from natural products? A common belief among Life Science investors is that the days of building billion-dollar drug development companies from natural products are over. We believe, by contrast, that the evolution of the Life Sciences sector since the 1980s now favours companies such as AZT.

Many former blockbusters started life as natural products. A large number of the drugs used in modern medicine have their origin in natural products. To name just three examples: the original source of aspirin was the bark of the willow tree[35]; the antibiotic penicillin came from an ordinary mould called *Penicillium chrysogenum*[36]; and the cancer drug Taxol comes from the Pacific yew tree, *Taxus brevifolia*[37]. Since pre-history nature has proved a treasure trove of new drug candidates, firstly because there are so many compounds available, secondly because of the historical tendency of medical practitioners to experiment with what was available, and thirdly because of the availability of large natural product libraries[38].

Why natural product companies went out of favour for a while. We think the biotech revolution of the 1980s temporarily pushed natural products to one side. The great advances in understanding of drug targets, and in the kinds of synthetic drugs that would hit those targets better than known natural products, increased the scope of drug discovery while allowing notionally more secure intellectual property protection based on 'composition of matter' patents protecting the drug molecule itself, rather than a formulation or a method of use or treatment. As a consequence fewer drug development companies went public that had natural products at their core.

Natural products have been coming back into favour in modern medicine

Why natural products have been coming back. More recently bio-entrepreneurs have started to rediscover natural products, for four main reasons:

- **The realisation that natural products were in many ways superior to synthetic products.** It turned out that the structural diversity and complexity to be found in nature was often better at binding targets than a randomly assembled collection of molecules. This insight, combined the increasing sophistication of high-throughput screening tools, led pharma companies to give more priority to natural products[39].
- **The rise of complementary medicine.** In the US today one third of US adults regularly use complementary medicine approaches in managing their health, with around one in five using nonvitamin, nonmineral dietary supplements[40]. It has been estimated that out-of-pockets on complementary alternative medicine in the US totalled some US$30bn in 2012, roughly 8% of all out-of-pocket healthcare spending[41].
- **The Cannabis revolution.** Beginning around 2015 there has been a boom in drug development related to compounds available in *Cannabis indica*,

[35] Br J Haematol. 2017 Jun;177(5):674-683. Epub 2017 Jan 20.
[36] Emerg Infect Dis. 2017 May; 23(5): 849–853.
[37] Semin Oncol Nurs. 1993 Nov;9(4 Suppl 2):2-5.
[38] To date, 35,000-70,000 plant species have been screened for their medicinal use – See J Adv Pharm Technol Res. 2012 Oct-Dec; 3(4): 200–201.
[39] Nat Rev Drug Discov. 2015 Feb;14(2):111-29. Epub 2015 Jan 23.
[40] Clarke et. al., Natl Health Stat Report. 2015 Feb 10;(79):1-16.
[41] For a summary of the data see the NCCIH press release dated 22 June 2916 and headlined '*Americans spent $30.2 billion out-of-pocket on complementary health approaches*'. There have been higher estimates – see, for example Natl Health Stat Report. 2009 Jul 30;(18):1-14.

reversing a decades-long period of neglect of this plant due to its being the source of illicit psychoactive substances[42].

- **The unexpected commercial success story of the prescription Omega-3 products.** These days a significant percentage of Western world populations takes Omega-3 supplements[43] because a large body of knowledge around the cardiovascular benefits[44]. What is less well know is how high-purity Omega-3 products became prescription-only blockbuster products. This was largely the work of a US company called Reliant Pharmaceuticals[45], which in 2004 gained FDA approval for what became Lovaza. Reliant was acquired by GlaxoSmithKline in 2007 for US$1.65bn primarily for Lovaza and by 2012 Lovaza's sales had peaked at US$960m. Lovaza's success spawned two main competitors, Vascepa, from Amarin[46], FDA approved in 2012, and Epanova, from AstraZeneca[47], FDA approved in 2014. Interestingly, Lovaza is long off-patent but that hasn't prevented Vascepa and Epanova from growing sales based on new indications[48].
- **The commercial success prompted valuations to follow.** BASF acquired Pronova, the original developer of Lovaza, in 2013 for US$845m. Amarin today is a US$6.53bn company[49].

Patents are less of an issue for drug development these days. Two important pieces of US legislation work in favour of natural product developers like Azure where obtaining composition-of-matters patents is more difficult – the Orphan Drug Act of 1983 and the Waxman-Hatch of 1984.

- An Orphan Drug in the US is one that notionally serves less than 200,000 patients p.a. The Orphan Drug Act grants the developer of such a drug seven years of market exclusivity regardless of the IP position around the product. Pancreatic cancer is an orphan indication and AZT intends to explore this route with the FDA. In fact, AZT has already held discussions with a US CRO which has successfully gained orphan status for another company's pancreatic cancer drug candidate.
- Under Waxman-Hatch a 'New Clinical Investigation' of an existing drug can gain three years of exclusivity regardless of market size or patent protection.

So, the path across the Rx divide for any number of natural products or dietary supplements could simply be a matter of search the literature and running the studies suggested by it. A great example of a natural product blockbuster that started as an Orphan Drug was Allergan's Botox, which gained FDA approval in 1989 as a treatment for a rare eye disorder called blepharospasm.

[42] Mayo Clin Proc. 2018 Dec;93(12):1842-1847.
[43] The Omega-3 polyunsaturated fatty acids are found in oil from certain types of fish, vegetables, and other plant sources. These fatty acids are not made by the body and must be consumed in the diet – see Postgrad Med. 2009 Nov;121(6):148-57.
[44] Data from America's 2012 National Health Interview Survey indicate that 7.8% of U.S. adults and 1.1% of U.S. children use supplements containing fish oil, omega-3s, and/or the DHA or EPA omega-3 components.
[45] The first highly purified, prescription Omega-3 with high concentrations of EPA and DHA was Omacor, developed in Norway by a company called Pronova in the 1980s and launched on the European market in 1996. Reliant Pharmaceuticals licensed the Omacor product from Pronova.
[46] A product made up almost entirely of EPA – see Am J Cardiovasc Drugs. 2014 Dec;14(6):471-8.
[47] A mixture of polyunsaturated free fatty acids, not just EPA and DHA – see Am J Cardiovasc Drugs. 2014 Oct;14(5):393-400.
[48] Vascepa gained FDA approval in December 2019 for its use in with high triglyceride levels who have multiple risk factors such as heart disease and diabetes, but where the triglyceride levels are less extreme than in the original approved indication.
[49] 18 February 2020 close on Nasdaq.

Tocotrienols address large market opportunities

Even a cursory glance at the literature shows the potential of Tocotrienol ProDrugs to do for AZT what Omega-3 did for GSK:

- **Cancer.** Tocotrienols are well known to inhibit tumour cell growth and viability, and not just because they have antioxidant activity[50]. Tocotrienols have been shown to have pro-apoptosis properties[51], work against the epithelial-to-mesenchymal transition[52], suppress VEGF tumour angiogenic pathways[53], induce an anti-cancer immune response[54], render cancer more sensitive to chemotherapy[55] and act against cancer stem cells[56]. For all these reasons it's reasonable to expect tocotrienols to have activity in a wide variety of cancers. We expect that once AZT and the Porter Group at Monash have optimised their technology, the company can move towards *in vitro* studies, beginning with high throughput screening on multiple cell lines, with a view to picking which cancer types would be most interesting to pursue. AZT expects its first cancer indication will be pancreatic cancer.

Tocotrienols have known anti-fibrotic properties

- **Fibrosis**. Tocotrienols have known anti-fibrotic properties[57]. Fibrosis is a significant factor in the pathogenesis of a range of disease conditions, however it has only been in the last decade or so that the pharmaceutical industry has been working on new anti-fibrotic agents, driven in part by the success of Roche's Esbriet drug for the treatment of Idiopathic Pulmonary Fibrosis. The approval of the first drug for the treatment of Non-Alcoholic Steatohepatitis (NASH[58]) is now on the cards after the February 2019 announcement by America's Intercept Pharma that its Ocaliva drug had improved liver fibrosis in NASH patients in a Phase 3 study[59]. Ocaliva gained FDA approval in 2016 for the treatment of Primary Biliary Cholangitis. The PDUFA date[60] for Ocaliva's NASH liver fibrosis indication is 26 March 2020. New NASH drugs are likely to increase this interest in new anti-fibrotics. AZT intends to evaluate drug candidates based on both TransT3 and TPD platforms in Non-Alcoholic Fatty Liver Disease as its first fibrosis indication.
- **Cholesterol**. As we noted above, the Omega-3 drugs are good at knocking down triglycerides. However, as we noted above, the tocotrienols are clearly good at lowering cholesterol, which would make them a contender to augment the statin class at some point in AZT's future development. We noted above that tocotrienols have a similar mode of action to statins in that they inhibit the biosynthesis of HMCG CoA Reductase. In that light, it's worth remembering here that Pfizer's Lipitor statin drug enjoyed peak sales of close to US$13bn in 2006.
- **Other indications**. It's reasonable to expect research interest in tocotrienols developing over time in therapeutic areas as diverse as anti-

[50] Biofactors. 2014 Jan-Feb;40(1):49-58. Epub 2013 Jun 27
[51] Cell Prolif. 2013 Apr;46(2):203-13.
[52] Cell Prolif. 2016 Aug;49(4):460-70. Epub 2016 Jun 21.
[53] J Agric Food Chem. 2009 Sep 23;57(18):8696-704.
[54] Cancer Genomics Proteomics. 2011 Jan-Feb;8(1):19-31.
[55] PLoS One. 2015 Apr 7;10(4):e0122712.
[56] Int J Cancer. 2011 May 1;128(9):2182-91.
[57] See, for example, Inflamm Bowel Dis. 2011 Mar;17(3):732-41.
[58] Non-Alcoholic Steatohepatitis sees the fat buildup of NAFLD accompanied by damaging liver inflammation, leading to fibrosis and from there, in some instances, to cirrhosis. Perhaps 3% of the US population has NASH (Dig Dis. 2010;28(1):155-61. Epub 2010 May 7).
[59] See the Intercept Pharma announcement dated 19 February 2019 and headlined *'Intercept announces positive topline results from pivotal Phase 3 REGENERATE study of Obeticholic Acid in patients with liver fibrosis due to NASH'*.
[60] A drug's PDUFA date is the day by which the FDA seeks to review an NDA under the Prescription Drug User Fee Act, which allows the agency to charge drug makers for the review process.

inflammatories, neuroprotection and bone metabolism once a future AZT product helps the field to be taken seriously as a source of potential prescription medicines[61].

An important opportunity in pancreatic cancer

Pancreatic cancer incidence is small but rising. Around 50,000 Americans and 80,000 people in the EU will be diagnosed with pancreatic cancer this year. Incidence is steadily rising, and the cancer is now high on the list of cancer killers – in America it is the now the fourth-worst cancer killer.

Survival for pancreatic cancer has improved, but not by much

Survival for pancreatic cancer has improved, but not by much. In the 2000s in the US the five-year survival rate for pancreatic cancer was only 6%, with survival post diagnosis tending to be ~8-9 months after diagnosis and only 20% of patients alive after 12 months. For the 10-15% of patients eligible for surgical resection[62], the five-year survival rate improves, but only to ~20%[63]. 6% five-year survival may be small but that compares to 2% in the mid-1970s and 4% in the late 1980s[64]. In recent years there have been three important developments in pancreatic cancer.

- Better surgery, as more surgeons have mastered the 'Whipple pancreaticoduodenectomy'. This difficult procedure was first devised in the 1930s but traditionally came with double-digit perioperative mortality. Such outcomes are now uncommon[65].
- Gemcitabine, which gained FDA approval in pancreatic cancer in 1996 with median Overall Survival of 5.7 months as a monotherapy, 1.3 months better than 5-FU[66].
- Abraxane[67], a Celgene drug[68] which gained FDA approval for use in pancreatic cancer in conjunction with gemcitabine in September 2013. In Phase 3 Abraxane increased median overall survival by another 1.8 months, from 6.7 months for gemcitabine alone to 8.5 months for the gemcitabine/Abraxane combination[69].

Why most drug candidates haven't worked in pancreatic cancer. The reason that pancreatic cancer has traditionally been a graveyard for novel oncology agents is that pancreatic cancer cells have more chemoresistance[70], in part because of K-Ras mutations, which, occur in over 90% of cases[71]. In addition, pancreatic cancer tends to be poorly vascularised. A recent example of a promising pancreatic cancer agent that failed was Jakafi[72], the JAK Kinase inhibitor from Incyte that seemed to work in a subgroup of patients in Phase

[61] See Nutr Metab (Lond). 2014; 11: 52 for a good review.
[62] In America around 9% of all pancreatic cancer is local at the time of diagnosis and 24% is regional (see J Gastrointest Surg. 2006 Nov;10(9):1212-23; discussion 1223-4). For an estimate of the resection-eligible population see Surgery. 1996 Oct;120(4):680-5; discussion 686-7 and Med J Aust. 2012 May 7;196(8):511-5.
[63] See Ann Surg. 2008 Mar;247(3):456-62 and World J Surg. 2003 Mar;27(3):324-9. Epub 2003 Feb 27.
[64] See Ann Surg. 1987 Sep;206(3):358-65.
[65] See Am Surg. 1999 Sep;65(9):889-93.
[66] See Burris et. al., J Clin Oncol. 1997 Jun;15(6):2403-13.
[67] Generic name nab-paclitaxel, see www.abraxane.com.
[68] Abraxane was first FDA-approved in 2005, for breast cancer. Celgene paid US$2.9bn in mid-2010 in order to buy Abraxis Bioscience, primarily because of Abraxane.
[69] See N Engl J Med. 2013 Oct 31;369(18):1691-703. Epub 2013 Oct 16..
[70] A good parallel can be made here to primary liver cancer. No drug was successful here until the Bayer/Onyx drug Nexavar (sorafenib) in 2007 (see See N Engl J Med. 2008 Jul 24;359(4):378-90), but Sirtex's SIR-Spheres brachytherapy had a long track record of success in this indication stretching back to the late 1990s.
[71] See Science. 2008 Sep 26;321(5897):1801-6. Epub 2008 Sep 4.
[72] Generic name ruxolitinib, see www.jakafi.com.

2[73]. That company shut down its pancreatic cancer programme for Jakafi in February 2016.

Why AZT's products could work in pancreatic cancer. There has been evidence in the literature for some time, both *in vitro*[74] and *in vivo*[75], that Vitamin E can be effective against pancreatic cancer. Population studies have also suggested an inverse relationship between Vitamin E intake and pancreatic cancer risk[76]. Vitamin E is known to work against pancreatic cancer by inhibition of NF-κB activity[77], regulation of the cell cycle, modulation of the Ras–Raf–MEK–ERK pathway and the induction of apoptosis[78]. We noted above the work of the Malafa at the Moffitt Cancer Center on delta tocotrienol, and another group found similar results in conjunction with gemcitabine using gamma tocotrienol[79] The Malafa lab reported promising results from a Phase 1 clinical study of delta tocotrienol in pancreatic ductal neoplasia in 2015[80]. That study[81] was notable for significant levels of apoptosis in pre-operative patients and the fact that no dose-limiting toxicities were achieved even when the daily tocotrienol doses had reached the gram level. Malafa has sought patent protection for delta tocotrienol[82] but, as we noted above, both TransT3 and TPDs are different from raw Vitamin E material.

The market opportunity is a multi-billion dollar one. Gemcitabine has been generic in the US since 2010, however the Abraxane+gemcitabine combination can reimburse at >US$12,000/month in that market[83]. This suggests a US plus Europe market opportunity of at least US$4-5bn at pricing of only US$35,000 p.a.[84]. It's fair to say that any agent with strong survival data would almost certainly be a blockbuster.

Opportunity in Non-Alcoholic Fatty Liver Disease

30% of the US population may have fatty liver

30% of the US population may have fatty liver. When fat molecules build up inside liver cells, to the point where more than 5% of the liver by weight is fat, the result is Non-Alcoholic Fatty Liver Disease (NAFLD), also called hepatic steatosis[85]. The 'Non-Alcoholic' means that the fat buildup isn't primarily the result of drinking. The presence of fat in the liver may be almost asymptomatic in most cases, which is why it took until 1980 for it to be first described in the literature[86]. That said, 30%-or-so of the US population has this condition[87], and there are comparable figures in other Western world

[73] See the Incyte press release dated 21 August 2013 and headlined *'Incyte provides top-line results from Phase II proof-of-concept trial of ruxolitinib in patients with refractory metastatic pancreatic cancer'.*

[74] J Surg Res. 2000 Jan;88(1):23-5.

[75] Pancreatology. 2005;5(4-5):403-9. Epub 2005 Jun 28.

[76] Med Sci Monit. 2015 May 1;21:1249-55.

[77] NF-κB is known to assist the accumulation of pro-inflammatory cytokines at the sites of tumours, helping the cancer to grow and metastasize as the inflammation damages tissue and DNA – for a review see Cancer Immunol Res. 2014 Sep;2(9):823-30.

[78] Adv Nutr. 2015 Nov 13;6(6):774-802. Print 2015 Nov.

[79] Cancer Res. 2010 Nov 1;70(21):8695-705. Epub 2010 Sep 23. The group was led by Bharat Aggarwal at the MD Anderson Cancer Center in Houston, Tx. It needs to be noted that a number of Aggarwal's papers have been retracted due to allegations of scientific fraud. This paper has not been retracted.

[80] EBioMedicine. 2015 Nov 14;2(12):1987-95.

[81] See NCT00985777 at clinicalTrials.gov.

[82] See US Patent 8,846,653, *Delta-tocotrienol treatment and prevention of pancreatic cancer*, granted in September 2014. The priority date for this patent is 27 June 2006.

[83] Med Oncol. 2016 May;33(5):48. Epub 2016 Apr 11.

[84] Should an agent show the kind of survival brought about by Folfirinox versus gemcitabine, priced at US$100,000 for a year's worth of treatment. Folfirinox is 5-FU, leucovorin, irinotecan and oxaliplatin. In a 2011 study in 342 patients it beat gemcitabine as a first-line treatment in pancreatic cancer by 4.3 months, with median Overall Survival of 11.1 months versus 6.8 months for gemcitabine (see N Engl J Med. 2011 May 12;364(19):1817-25). In recent years the cost-per-QALY threshold in US healthcare seems to have lifted to US$100,000 or more to account for healthcare inflation (N Engl J Med. 2014 Aug 28;371(9):796-7).

[85] From the Greek word stéar, meaning 'fat'.

[86] Mayo Clin Proc. 1980 Jul;55(7):434-8.

[87] Am J Epidemiol. 2013 Jul 1;178(1):38-45. Epub 2013 May 23.

jurisdictions[88]. The reason NAFLD can be regarded as a serious disease condition is that, over a couple of decades, the fibrosis caused by the fat will see perhaps one in eight NAFLD patients develop severe liver disease of some kind[89], most notably NASH or liver cancer. NASH sees the fat buildup of NAFLD accompanied by damaging liver inflammation, leading to fibrosis and, from there, in some instances, to cirrhosis. Perhaps 3% of the US population has NASH[90], and that large patient population has fueled heavy research interest in NASH from pharma companies, including two major transactions[91], so that today there are four agents in Phase 3[92].

Vitamin E has shown some benefit in fatty liver. There's plenty of clinical evidence showing that Vitamin E supplementation can improve liver function and bring about some favourable histologic changes in patients with both NAFLD and NASH[93]. Vitamin E has, however, yet to go all the way because the underlying fibrosis isn't affected. For example, a 247-patient study reported in 2010 found that 800 International Units per day could significantly improve the histologic features of NASH (43% vs 19%; p = 0.001) but not move the dial on fibrosis[94]. What data that exists on Vitamin E fractions and NAFLD has suggested that tocotrienols are where the action is at.

The evidence on the therapeutic power of tocotrienols in fatty liver is starting to emerge:

Tocotrienols appear to inhibit lipid accumulation in the liver

- A group at Ohio State University Medical Center in Columbus, Oh. showed in 2012 that tocotrienol supplementation in patients on the liver transplantation list could reduce the level of disease severity in 50% of all patients, whereas the same effect was only registered in 20% of tocopherol-supplemented patients[95].
- A group at the University of Tokyo demonstrated in 2013 that tocotrienols inhibits lipid accumulation, inflammation and fibrosis in the liver in this rat model of steatohepatitis[96].
- A 2013 double-blind, placebo-controlled clinical study of tocotrienol supplementation in NAFLD patients in Malaysia showed two thirds of the subjects in the supplemented group recording significant lowering of fatty liver, as measured by ultrasound. 50% of the subjects had complete remission. The results were statistically significant ($p < 0.05$) compared with the control group[97].
- In September 2018 a group at the University of Nebraska-Lincoln found *in vivo* that gamma tocotrienol was able to reduce both hepatic inflammation and fibrosis[98].

AZT could develop the first truly effective NAFLD drug - one that improves liver function, reduces liver fat, *and* reduces fibrosis. Even at modest pricing, such a drug could reasonably be expected to become a blockbuster.

[88] Hepatology. 2016 Jul;64(1):73-84. Epub 2016 Feb 22.
[89] J Hepatol. 2017 Dec;67(6):1265-1273. Epub 2017 Aug 10.
[90] Dig Dis. 2010;28(1):155-61. Epub 2010 May 7.
[91] Allergan bought Tobira Therapeutics in July 2016 for US$1.7bn while Gilead Sciences paid US$400m upfront and agreed to US$800m in milestones in April 2016 to acquire the NASH programme of Nimbus Therapeutics.
[92] Elafibranor (Genfit), obeticholic acid (Intercept Pharmaceuticals), selonsertib (Gilead), and cenicriviroc (Allergan)
[93] Nutrition. 2015 Jul-Aug;31(7-8):923-30. Epub 2014 Dec 24.
[94] N Engl J Med. 2010 May 6;362(18):1675-85. Epub 2010 Apr 28.
[95] J Nutr. 2012 Mar;142(3):513-9. Epub 2012 Feb 1.
[96] J Clin Biochem Nutr. 2013 Mar;52(2):146-53. Epub 2013 Mar 1.
[97] Nutr J. 2013 Dec 27;12(1):166.
[98] Mol Nutr Food Res. 2018 Sep 5 [Epub ahead of print]

Valuing AZT

Independent valuation range A$44-55m. The Independent Experts Report related to the RTO contains an attachment headlined '*Independent Valuation Report of Intellectual Property owned by Invictus BioPharma Limited*'. In that attachment, expert Dr David Randerson of Acuity Technology Management postulates a valuation range for Invictus BioPharma of A$43.6-A$54.7m. We consider that valuation range reasonable and encourage readers of this report to carefully scrutinise Randerson's work.

Reasonable probability weights. We regard Discounted Cash Flow analysis to be an appropriate tool for valuing Life Science ventures, so long as the DCF valuation is weighted by the probability of success. The chances of a new drug candidate just starting out in the clinic are about one in five. Drug development is risky, and many drug candidates fail either at pre-clinical, in the various clinical stages of development (Phase 1, 2 and 3), or at the regulatory stage when agencies have to make the decision to approve or not approve a drug. For clinical stage drug candidates, there are databases available[99] stretching back to the 1960s that have allowed researchers to estimate the probability of success at various stages of development. One such estimate is shown in Figure 1. AZT's prescription products are Phase II ready in the case of the TransT3-based drug candidates (IVB001 and IVB003) and pre-clinical in the case of the TPD based drug candidates (IVB002 and IVB004). Therefore, we think that Acuity's probability weighting of 5.0%-12.2% for TransT3 candidates for cancer and NASH respectively, and 2.9%-8.3% for TPD technologies fits within this accepted framework.

Figure 1: Historical probabilities of success in drug developments

	SMALL MOLECULES	LARGE MOLECULES
Phase I	63%	84%
Phase II	38%	53%
Phase III	61%	74%
Filing for approval	91%	96%
Phase I to approval	13%	32%

Source: Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3.

Increasing shareholder value at AZT

We see the following developments helping to grow AZT's value after the RTO:

- Publications by various groups demonstrating the therapeutic potential of tocotrienols;
- Growing the sales of nE1-Heart® and nE1-Elite® products and endorsement by high profile brand ambassadors;
- Announcement of various distribution arrangements related to the products;

[99] Most notably from the Center for the Study of Drug Development at Tufts University in Medford, Ma. (see csdd.tufts.edu).

- *In vivo* studies relating to the TPDs establishing proof of concept for bioavailability and efficacy;
- Commencement of Phase II Proof of Concept clinical studies in NAFLD and preclinical studies for pancreatic cancer including Pre-IND meetings with the FDA;
- Patent grants related to TransT3 and new patent filings relating to TPDs.

Reasonable valuation windows. Acuity has used 2034 as a final year for estimated cash flows from prescription products, this being the notional end of market exclusivity. In reality patent extension usually kicks in for successful drugs, sometimes for fresh patent coverage but often just because of the usual patent terms extension rules that apply to compensate for the time lost in clinical trials.

Reasonable sales estimates. Acuity has used product selling prices which are based on the cost of available drugs for NASH and cancer chemotherapy, and used only seven markets (the US, Japan, and five large European markets) in estimating payoffs.

Comparable companies to AZT

Two relevant companies for the medium term. In addition to the broader peer group (Figure 2), we believe two companies are comparable to the post-RTO Azure, one for the medium-term potential, another for the long-term:

- **Acasti Pharma (TSX-V: ACST)**. This Montreal-based company is developing prescription drugs using omega-3 fatty acids derived from krill oil. Acasti's lead product candidate, called CaPre (omega-3 phospholipid) is in Phase 3 for severe hypertriglyceridemia. Topline results from this study became available in January 2020 and showed a 31% and 37% reduction in triglyceride levels, compared with baseline, among patients receiving CaPre at 12 and 26 weeks respectively. Acasti is currently capitalized at C$64m on TSX-V.

Figure 2: Companies to watch

Company	Location	Code	Market cap (USDm)	Web
Clearside Biomedical	Alpharetta, Ga	Nasdaq: CLSD	117	www.clearsidebio.com
Milestone Scientific	Livingston, NJ	OTCQB: MLSS	113	www.milestonescientific.com
InMed Pharmaceuticals	Vancouver, BC	TSX: IN	42	www.inmedpharma.com
IntelGenX	Saint-Laurent, Qc	TSX-V: IGX	40	www.intelgenx.com
Celsion	Lawrenceville, NJ	Nasdaq: CLSN	30	www.celsion.com
Titan Pharmaceuticals	South San Francisco, Ca	OTCBB: TTNP	20	www.titanpharm.com
Midatech Pharma	Abingdon, UK	LSE: MTPH	17	www.midatechpharma.com
Crescita Therapeutics	Mississauga, On.	TSX: CTX	15	www.crescitatherapeutics.com
GB Sciences	Las Vegas, Nv.	OTCQB: GBLX	10	www.gbsciences.com
Acerus Pharmaceuticals	Mississauga, On.	TSX: ASP	8	www.aceruspharma.com

Source: Pitt Street Research

- **Amarin (Nasdaq: AMRN).** As we noted above, this company developed the Omega-3 product Vascepa, which gained FDA approval in 2012. Amarin is now a US$6.5bn company on Nasdaq.

Other companies to watch. Companies working at an early stage on repurposing natural products are generally not public companies. We chose ten companies in the drug delivery and drug reformulation spaces that we think provide good proxies for AZT. We have included some a couple of the less-well-known Cannabis-based companies in the list given the multiple uses to which this natural product can be put[100].

- **Acerus Pharmaceuticals.** This company gained FDA approval for a testosterone replacement gel called Natesto in 2014. The product is also available in Canada and South Korea. Natesto's point of difference with other testosterone replacement products is its delivery system, which is via an intranasal 'no-touch' dispenser with a metered dose pump.
- **Celsion.** This company's original technology involved heat-sensitive liposomes that deliver conventional chemotherapy drugs to cancer cells, for activation by an external heating device. Celsion's original Phase 3 trial of ThermoDox, which is heat-activated doxorubicin, missed its primary endpoint of PFS in primary liver cancer, however a new Phase 3 treating a sub-group identified in the earlier study is now underway. Celsion's second technology, called 'TheraPlas', is a polymer-based gene delivery system. The first candidate from this technology is GEN-1, which delivers interleukin 12 for localised anti-cancer immunotherapy. That product is in Phase 1/2 in ovarian cancer. Suprachoroidal Space (SCS) Microinjector.
- **Clearside Biomedical.** This company's technology allows drugs to be delivered to the suprachoroidal space at the back of the eye, allowing potential in-office treatments for eye diseases without the need for surgery. An initial application of the technology is Xipere, a formulation of the corticosteroid triamcinolone acetonide that in Phase 3 was able to successfully treat macular edema associated with uveitis. Clearside licensed the North American rights to this product to the eye care major Bausch in October 2019. After a Complete Response Letter related to the delivery Clearside intends to refile for FDA approval this year.
- **Crescita Therapeutics.** This dermatology company's main product is an enhanced formulation of Pliaglis, a lidocaine/tetracaine cream used as a local anaesthetic that has been on the US market since 2008. Crescita developed the new product and in 2017 licensed it to the generic drug company Taro Pharmaceutical.
- **GB Sciences**. This company develops formulations of chemicals extracted from the Cannabis plant. The furthest developed products are being indicated for neuropathic pain and Parkinson's disease.
- **InMed Pharmaceuticals.** This company's technology allows microbial-based biosynthesis of any of the more than 100 known cannabinoids that may be therapeutically useful. InMed has applied its technology to drug produce candidates in the skin condition Epidermolysis Bullosa as well as glaucoma and orofacial pain.
- **IntelGenX.** This company's VersaFilm oral film technology has helped to create a range of formulations for buccal or sublingual delivery such as the migraine drug rizatriptan and a buprenorphine/naloxone combination. The ritzatriptan product, called Rizaport, gained its first European Marketing Authorisation in 2015. It received a Complete

[100] Market caps at for close on 18 February 2020 and elsewhere.

Response Letter from the FDA in April 2019 but IntelgenX is working to address the issues raised by the Agency. Other VersaFilm products are tadalafil (generic Cialis) for erectile dysfunction, loxapine for schizophrenia, and montelukast, once a blockbuster asthma drug, being repurposed into a drug for the treatment of degenerative diseases of the brain.

- **Midatech Pharma.** This company's technologies allow cancer drugs to be formulated for sustained release as well as solubility and targeted delivery. MTD201 is a sustained-release formulation of Octreotide for the treatment of carcinoid cancer and acromegaly while MTX110 is a soluble form of panobinostat for the pediatric brain cancer DPIG (Diffuse Intrinsic Pontine Glioma).
- **Milestone Scientific.** This company's CompuFlo computer-controlled drug -delivery injection system has been adapted to epidural and intra-articular injections. Cosmetic surgery and ophthalmic applications are planned.
- **Titan Pharmaceuticals.** This company's ProNeura technology allows the delivery for chronic disease conditions of low-dose, non-fluctuating medication levels for up to one year in a single procedure. ProNeura encapsulates the drug to be delivered in a small, solid rod made from a mixture of ethylene-vinyl acetate. The technology has been used to develop a now-marketed buprenorphine implant for the treatment of opioid addiction

Appendix I – The 2020 AZT RTO

Azure Health Technology is currently an ASX-listed shell with ~180 million shares on issue. As foreshadowed in the 8 November 2019 ASX announcement, Azure Health Technology will consolidate its shares on issue down to 70 million and then acquire Invictus BioPharma for 35 million shares, after which it will place 35-50 million shares at $0.20 per share to raise $7-10m (Figure 3). Shareholders will vote on the acquisition on 6 March 2020.

Figure 3: Azure Health Technology proposed capital structure

	Minimum subscription	Maximum subscription	Note
Ord. shares on issue	179,998,454	179,998,454	
Ord. shares on issue after 2.57 to 1 share consolidation 2.57 to 1	70,000,000	70,000,000	
Issued to Invictus shareholders	35,000,000	35,000,000	
Placement at 20 cents per share	35,000,000	50,000,000	
Total shares on issue post raising	140,000,000	155,000,000	
Employee options to be issued	6,081,228	6,081,228	Exercisable at $0.477
Fully diluted shares on issue	146,081,228	161,081,228	
Market cap undiluted at offer price (A$m)	28.0	31.0	

Source: Company

Appendix II - An AZT glossary

Active Pharmaceutical Ingredient (API) – The part of a drug with pharmaceutical activity as opposed to a mere 'support' role.

Antioxidants – Substances that neutralise oxygen in free radicals, which can damage cells in the body. Various vitamins including Vitamin E have antioxidant properties.

Apoptosis – 'Programmed' cell death, that is, death that is naturally-occurring. Cancer cells tend to avoid apoptosis.

Bioavailability – The quantity of a drug that is able to make it to its target once inside the body. High bioavailability is an important component in a drug's prospects for commercial success.

Blockbuster – A pharmaceutical drug with more than US$1bn in annual sales.

Cholesterol – A lipid produced by the liver with many functions including the metabolism of fat soluble vitamins and the production of sex hormones. Too much cholesterol, however, is bad for cardiovascular health. There are two types of cholesterol, LDL and HDL. LDL (low-density lipoprotein) is 'bad' cholesterol because it can be deposited in the arteries, increasing the risk of heart attack or stroke.

Composition of matter – A patent that covers the chemical make-up of a drug.

Dietary Supplement – see 'Nutraceutical'.

Fibrosis – Scarring and thickening of tissue, thereby weakening tissue function.

First pass metabolism – Metabolism of drugs before entering the systemic circulation.

Gavage – Force feeding through a tube inserted through the mouth or nose into the stomach.

GRAS – Short for 'Generally Regarded as Safe'.

IND – Short for Investigational New Drug application. It is a request filed with the FDA for authorization to conduct human trials of a new drug or biological product in the United States.

In vitro – Latin for 'in glass', referring to data obtained through testing in a test tube.

In vivo – Latin for 'in life', referring to data obtained through testing in live organisms including animal models and humans.

Liver – An organ in the abdominal cavity that has a number of responsibilities. It plays an important role in metabolism, not least through its production of bile; it stores glycogen, a carbohydrate the body converts to glucose for energy purposes when required; and it helps detoxify certain poisons.

Lymph – A clear fluid that acts as a key part of the body's filtering and drainage system. The lymphatic system drains directly into the blood without passing through the liver.

MELT3 – An AZT technology allowing drugs to be dissolved in the mouth before swallowing.

NASH – Short for Non-Alcoholic SteatoHepatitis, a liver disease characterised by buildup of fat in the organ, accompanied by liver inflammation. NASH can lead to liver fibrosis and from there to cirrhosis.

nE1-Elite – An AZT dietary supplement for exercise endurance.

nE1-Heart – An AZT dietary supplement for cardiovascular health.

New Chemical Entity (NCE) – A drug that has yet to gain regulatory approval.

Non-Alcoholic Fatty Liver Disease (NAFLD) – A range of liver disorders characterised by too much fat in the liver. Probably the best known NAFLD is NASH.

Nutraceutical – A food or part of a food that provides health or medicinal benefits, including the prevention or treatment of a disease.

Oral mucosa – The mucous membrane which lines the inside of the mouth.

Pancreas – A gland organ located in the abdomen that produces various enzymes and hormones, including insulin.

Pharmacokinetics (PK) – The study of the time course of a drug's absorption, distribution, metabolism, and excretion from the body.

Phase – A stage of the clinical trialling process for a drug candidate. Phase 1 tests for safety. Phase 2 tests for efficacy in a small sample. Phase 3 tests for efficacy in a large sample.

Prodrug – A drug that is administered in an inactive form and then metabolised into an active drug. Prodrugs are useful in targeting therapies to the right place in the body.

p-value – A measure of statistical significance. Generally, a p-value below 0.05 is considered 'statistically significant'.

Rx – A medicine that is available by prescription only. Rx comes from the Latin word 'recipe' meaning 'to take'.

Statistical significance – The probability, measured by the 'p-value', that an observed outcome of an experiment or trial is due to chance alone. Generally, p-values below 0.05 are taken as markers of statistical significance.

Supplement – see "Nutraceutical".

Tocotrienol – A form of vitamin E.

TPD – Short for Tocotrienol ProDrug, a technology that allows tocotrienols to be orally administered without first-pass metabolism.

TransT3 – AZT's platform that allows transmucosal drug delivery of tocotrienols

Triglycerides – The major form of fat consisting of three molecules of fatty acid combined with the alcohol glycerol. High levels of triglycerides are linked to heart disease and atherosclerosis.

Vitamin E – A vitamin best known for its antioxidant properties. Tocopherols and tocotrienols are two kinds of Vitamin E.

Appendix III – AZT's intellectual property

AZT's intellectual property (held in its wholly-owned subsidiary Invictus Biotechnology Pty Ltd) is covered by a single patent application: *Transmucosal delivery of tocotrienol,* WO/2014/075135, priority date 13 November 2012, invented by Glenn Tong. This patent application covers the TransT3 platform.

AZT (through its wholly-owned subsidiary Invictus Biotechnology Pty Ltd) has been granted rights to the TPD platform through a licensing arrangement with Monash University.

Appendix IV – Companies to watch in fatty liver

CymaBay Therapeutics. This company's lead compound is Seladelpar, an orally active peroxisome proliferator-activated receptor δ (PPARδ) agonist[101] that was being studied in Primary Biliary Cholangitis (PBC) and NASH. The drug has been shown to be able to bring about significant reductions of serum alkaline phosphatase, a surrogate marker for disease progression[102]. However CymaBay put the Seladelpar programme on hold in November 2019 after 'atypical histological findings' showed up during a Phase 2b in NASH.

Galectin Therapeutics. This company is being built around carbohydrate-based drugs that bind to proteins called galectins, known to play a role in fibrosis. Galectin's Belapectin (GR-MD-02) compound, a galectin-3 inhibitor, is in Phase 3 in NASH cirrhosis, having shown in Phase 2 that it could bring about a clinically meaningful improvement in this condition[103].

Genfit. This company's lead compound, another PPAR agonist called Elafibranor, is in Phase 3 in NASH after the drug's Phase 2 met its primary endpoint of NASH resolution without worsening of fibrosis[104]

Immuron. This company has been built on various enriched immunoglobulin preparations delivered from colostrum. IMM-124E, an oral, three-times-daily preparation of polyclonal anti-LPS[105] immunoglobulins, performed well in a Phase 2 study in NASH patients in terms of reducing LPS-related inflammation, taking down serum ALT, among other liver-related biomarkers[106].

[101] PPAR is Peroxisome proliferator-activated receptor. PPARs are of nuclear receptor proteins that function as transcription factors and play an important role in metabolism. Elafibranor targets PPAR alpha and delta – see Hepatology. 2013 Dec;58(6):1941-52. Epub 2013 Oct 29.
[102] Lancet Gastroenterol Hepatol. 2017 Oct;2(10):716-726. Epub 2017 Aug 14.
[103] Where that cirrhosis occurred without esophageal varices, that is abnormal, enlarged veins in the tube that connects the throat and stomach.
[104] But only after adjusting for baseline severity and site heterogeneity - see the Genfit press release dated 26 March 2015 and headlined 'Genfit announces topline results from the Golden-505 trial in NASH'.
[105] Lipopolysaccharide is a bacterial endotoxin implicated as a driver of liver inflammation. See, for example, Lab Anim. 2015 Apr;49(1 Suppl):37-46.
[106] See the Immuron market release dated 8 March 2018 and headlined *'Immuron reports positive results in NASH clinical trial'*.

Intercept Pharmaceuticals. We noted above that this company has had Phase 3 success with Ocaliva[107], a drug which in Phase 2 demonstrated improved liver histology in 45% of the treated patients versus 21% in the placebo group[108]. In a Phase 3 study called REGENERATE the drug achieved a statistically significant improvement in liver fibrosis without worsening of NASH at 18 months (p=0.0002). Ocaliva was granted Breakthrough Therapy Designation by FDA for the treatment of NASH with liver fibrosis in January 2015. The drug, which targets the farnesoid X receptor (FXR), highly relevant in inflammatory disorders and fibrotic disease, gained its first approval in May 2016 for the treatment of PBC.

Lipocine. This company's Lip'ral platform allows for solubilisation of water insoluble drugs through various excipients which optimally present the drug to the intestinal absorption site. The company's Tlando product, an oral prodrug of testosterone containing testosterone undecanoate[109], completed Phase 3 but received Complete Response Letters in May 2018 and November 2019. LPCN 1144, an oral androgen, is in Phase 2 as a NASH treatment on the understanding that low testosterone contributes to increased liver fat[110].

Madrigal Pharmaceuticals. This company's MGL-3196 drug is an orally administered, small-molecule, thyroid hormone receptor beta agonist. In a Phase 2 study in NASH patients MGL-3196 brought about a highly significant (P<0.0001) 37% reduction in liver fat at week 36 compared to 9% for placebo[111]. The product is now in Phase 3 in this indication.

MediciNova. This company's lead compound is MN-166, which has MediciNova has completed Phase 2 for MN-166 (ibudilast) in MS and ALS and has moved to Phase 3 in ALS. MN-001 (tipelukast), a leukotriene receptor antagonist, was studied in Phase 2 in NASH and NAFLD patients with hypertriglyceridemia (high triglyceride levels). The study terminated early due to positive interim data, which was released in April 2018. The positive outcome, however, related to reduced serum triglyceride levels (260.1 mg/dL to 185.2 mg/dL after eight weeks, p=0.00006) rather than reduced liver fat.

Viking Therapeutics. This drug developer has a focus on drugs for metabolic and endocrine disorders. VK2809, a liver-selective thyroid receptor beta agonist, reduced LDL cholesterol and liver fat content over 12 weeks in patients in a Phase 2 study in NAFLD patients where those patients had elevated LDL-C. The reduction in fat content was 60% for the once daily group (p<0.01) while 91% of patients in this group saw a >30% reduction in liver fat[112].

[107] Generic name obeticholic acid. Ocaliva is a synthetic bile acid agonist of the farnesoid X receptor.

[108] Lancet. 2015 Mar 14;385(9972):956-65. Epub 2014 Nov 7.

[109] Traditionally lacking in oral bioavailability.

[110] Cardiovasc Endocrinol. 2015 Sep 1;4(3):83-89.

[111] See the Madrigal press release dated 31 May 2018 and headlined *'Madrigal's MGL-3196 Achieves Liver Biopsy Endpoints in Patients with Non-alcoholic Steatohepatitis (NASH) at 36 Weeks in Phase 2 Clinical Trial'*.

[112] See the company's 18 September 2018 press release headlined '*Viking Therapeutics Announces Positive Top-Line Results from Phase 2 Study of VK2809 in Patients with Non-Alcoholic Fatty Liver Disease (NAFLD) and Elevated LDL-Cholesterol*'.

Appendix V – Companies to watch in pancreatic cancer

AB Science. This company's Masitinib product, a tyrosine kinase inhibitor, is in Phase 3 in various indications including pancreatic cancer. Phase 3 data from 2015 identified that the product seemed to provide a survival benefit in patients that expressed a biomarker called ACOX1[113]. Currently the lead indication for masitinib is Amyotrophic Lateral Sclerosis[114].

Celyad. This company, a player in CAR-T therapy for cancer, has as its lead CAR-T construct one that expresses NKG2D, an activating receptor found on the surface of Natural Killer cells and which has ligands on a wide variety of tumour types, both solid and liquid. Pancreatic cancer is one of several early indications of interest for this CAR-T. The product is in Phase 1.

ChemoCentryx. This company, whose focus is drugs that act via chemokines, has successfully completed Phase 3 with Avacopan, a drug which targets a complement receptor and which is initially indicated for a rare inflammatory disorder of the blood vessels called anti-neutrophil cytoplasmic auto-antibody-associated vasculitis (ANCA Vasculitis). A CCR inhibitor called CCX872, designed to knock down myeloid derived suppressor cells in the tumour microenvironment, is in Phase 1b in pancreatic cancer.

Erytech Pharma. This company's technology allows therapeutic drugs to be encapsulated inside red blood cells, which allows them to remain inside the body longer. The company's lead product, Eryaspase, is encapsulated L-asparaginase, an enzyme that is sometimes used in the treatment of Acute Lymphoblastic Leukemia. Erytech's Phase 2/3 with Eryaspase is in pancreatic ductal adenocarcinoma. In Phase 2b as a second line treatment, Eryaspase increased Overall Survival from 19 weeks to 26 (p=0.034)[115]. This indication has now moved to Phase 3.

FibroGen. This company's lead product, for which FibroGen has now filed for FDA approval, is Roxadustat for the treatment of anemia associated with Chronic Kidney Disease[116]. Pamrevlumab, an antibody to Connective Tissue Growth Factor, is in Phase 3 in pancreatic cancer, where pamrevlumab has demonstrated a dose-dependent improvement in one-year survival rates[117]. The thinking with pamrevlumab is that by attacking the connective tissue of the tumour, unresectable tumours can become resectable.

Five Prime Therapeutics. This company has been built on a proprietary library of human extracellular proteins which the company screens looking for new targets. The company's Cabiralizumab monoclonal antibody targets the tumour-associated macrophages known to suppress an anti-cancer immune response. Cabiralizumab is being trialled in Phase 2 in combination with Bristol-Myers Squibb's Opdivo PD-1 inhibitor in various cancers including pancreatic, where the thinking is that the two drugs will potentiate standard-of-care chemotherapy.

Pharmacyte Biotech. This company's cellulose-based live cell encapsulation technology allows cellular therapies to be implanted in patients protected from the patient's immune system. One application of this technology is live human cells that produce an enzyme designed to convert the cancer prodrug

[113] Ann Oncol. 2015 Jun;26(6):1194-200. Epub 2015 Apr 9.

[114] Amyotroph Lateral Scler Frontotemporal Degener. 2019 Jul 7:1-10. [Epub ahead of print]

[115] See the Erytech press release dated 27 March 2017 and headlined '*Erytech reports positive Phase 2b data for eryaspase for the treatment of metastatic pancreatic cancer*'.

[116] The drug stimulates red blood cell production by inhibiting an enzyme called hypoxia-inducible factor-prolyl hydroxylase.

[117] See the FibroGen press release dated 31 May 2014 and headlined '*FibroGen Announces Results of Phase 2 Study of FG-3019 Indicating Positive Activity Against Pancreatic Cancer*'.

ifosfamide into its cancer-killing form. Such a product has potential in pancreatic cancer.

RedHill Biopharma. This company, which markets several prescription products for gastrointestinal disorders, has a pipeline of mostly gastrointestinal drugs including a combination antibiotic therapy for Crohn's disease that has successfully completed Phase 3. RHB-107, a protease inhibitor[118], has completed Phase 2 in pancreatic cancer.

Tyme Inc. This company is in Phase 2 with a drug combination called SM-88, which comprises a tyrosine derivative plus phenytoin, methoxsalen, and sirolimus. The tyrosine derivative is designed to interfere with tumour cell metabolism. SM-88 is now in Phase 3 in pancreatic cancer. In a Phase 2 study of SM-88 in third-line patients survival was more than double when compared to the median expected survival of third-line pancreatic patients in historical trials[119].

Verastem. This company gained FDA approval in September 2018 for Copiktra, a PI3K inhibitor indicated for refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Verastem's Defactinib candidate, an inhibitor of the Focal Adhesion Kinase (FAK) pathway, is in Phase 2 in various cancers including pancreatic cancer, in conjunction with the Merck & Co. immune-oncology drug Keytruda.

[118] Extracellular proteases play a key role in tumour cell invasion – see Clin Chim Acta. 2000 Feb 15;291(2):113-35

[119] See the Tyme press release dated 18 January 2019 and headlined *'TYME's novel metabolic-based cancer therapy, SM-88, improves survival in Phase II study of patients with advanced pancreatic cancer'.*

Risks related to AZT

Risks specific to AZT. We see five major risks for AZT as a company:

- Funding risk. There is the risk that AZT, being a small cap ASX-listed biotech company, may find it more difficult to raise capital than would be the case for larger cap companies which are publicly traded and with better liquidity.
- Clinical risk. There is the risk that any clinical studies related to AZT's products may not reach their primary endpoint.
- Regulatory risk. There is the risk that AZT may take not be able to gain registrations for its products.
- Commercial risk. There is the risk that AZT may fail to gain adequate sales for nE1-ElitE® and nE1-Heart® even if the product is deemed safe and effective in various clinical studies and gain further registrations.
- Timing risk. There is the risk that AZT may take longer to develop its potential that the timing we have suggested in this report.

Risks related to Life Science companies in general.

Biotechnology and medical device companies without large revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.

The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

Caveat emptor. Investors are advised to be cognisant of the abovementioned specific and general risks before making an investment in any biotechnology and medical device company, including AZT.

Analyst qualifications

Stuart Roberts, lead analyst on this report, has been an equities analyst since 2002.

- Stuart obtained a Master of Applied Finance and Investment from the Securities Institute of Australia in 2002. Previously, from the Securities Institute of Australia, he obtained a Certificate of Financial Markets (1994) and a Graduate Diploma in Finance and Investment (1999).
- Stuart joined Southern Cross Equities as an equities analyst in April 2001. From February 2002 to July 2013, his research specialty at Southern Cross Equities and its acquirer, Bell Potter Securities, was Healthcare and Biotechnology. During this time, he covered a variety of established healthcare companies such as CSL, Cochlear and Resmed, as well as numerous emerging companies. Stuart was a Healthcare and Biotechnology analyst at Baillieu Holst from October 2013 to January 2015.
- After 15 months in 2015 and 2016 doing Investor Relations for two ASX-listed cancer drug developers, Stuart founded NDF Research in May 2016 to provide issuer-sponsored equity research on ASX-listed Life Science companies.
- In July 2016, with Marc Kennis, Stuart co-founded Pitt Street Research Pty Ltd, which provides issuer-sponsored research on ASX-listed companies across the entire market, including Life Science companies.
- Since 2018 Stuart has led Pitt Street Research's reseracg franchises in other sectors such as property and resources.

General advice warning, Disclaimer & Disclosures

Terms & Conditions

The information contained herein ("Content") has been prepared and issued by Pitt Street Research Pty Ltd ACN 626365615 ("Pitt Street Research"), an Authorised Representative (no: 1265112) of BR Securities Australia Pty Ltd. ABN 92 168 734 530, AFSL 456663. All intellectual property relating to the Content vests with Pitt Street Research unless otherwise noted.

Disclaimer

The Content is provided on an as is basis, without warranty (express or implied). Whilst the Content has been prepared with all reasonable care from sources we believe to be reliable, no responsibility or liability shall be accepted by Pitt Street Research for any errors or omissions or misstatements howsoever caused. Any opinions, forecasts or recommendations reflect our judgement and assumptions at the date of publication and may change without notice. Pitt Street Research will not accept any responsibility for updating any advice, views, opinions or recommendations contained in this document.

No guarantees or warranties regarding accuracy, completeness or fitness for purpose are provided by Pitt Street Research, and under no circumstances will any of Pitt Street Research officers, representatives, associates or agents be liable for any loss or damage, whether direct, incidental or consequential, caused by reliance on or use of the Content.

General Advice Warning

The Content has been prepared for general information purposes only and is not (and cannot be construed or relied upon as) personal advice nor as an offer to buy/sell/subscribe to any of the financial products mentioned herein. No investment objectives, financial circumstances or needs of any individual have been taken into consideration in the preparation of the Content.

Financial products are complex, entail risk of loss, may rise and fall, and are impacted by a range of market and economic factors, and you should always obtain professional advice to ensure trading or investing in such products is suitable for your circumstances, and ensure you obtain, read and understand any applicable offer document.

Disclosures

Pitt Street Research has been commissioned to prepare the Content. From time to time, Pitt Street Research representatives or associates may hold interests, transact or hold directorships in, or perform paid services for, companies mentioned herein. Pitt Street Research and its associates, officers, directors and employees, may, from time to time hold securities in the companies referred to herein and may trade in those securities as principal, and in a manner which may be contrary to recommendations mentioned in this document.

Pitt Street Research receives fees from the company referred to in this document, for research services and other financial services or advice we may provide to that company. The analyst has received assistance from the company in preparing this document. The company has provided the analyst with communication with senior management and information on the company and industry. As part of due diligence, the analyst has independently and critically reviewed the assistance and information provided by the company to form the opinions expressed in the report. Diligent care has been taken by the analyst to maintain an honest and fair objectivity in writing this report and making the recommendation. Where Pitt Street Research has been commissioned to prepare Content and receives fees for its preparation, please note that NO part of the fee, compensation or employee remuneration paid will either directly or indirectly impact the Content provided.