



Vitamin E champion

NSX: VTL

Sector: Life Sciences

8 June 2021

Azure Health Technology Limited, trading as VGI Health Technology (VTL), went public on the National Stock Exchange of Australia (NSX) after an IPO that raised \$2.5m at 20 cents per share and capitalised the company at \$27.5m post-money. VTL is the result of a June 2020 merger between Azure Health Technology, previously listed on the ASX but since delisted, and an unlisted biopharmaceuticals company called Invictus BioPharma Ltd. The merged group raised \$3.5m in a pre-IPO placement to sophisticated investors in mid-2020. This Initiation Report evaluates the technology behind VTL and the market potential of those products.

A nutraceuticals to prescription drug play

VTL is a Sydney-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. VTL has developed two nutraceutical products delivering tocotrienols from Vitamin E based on a third delivery platform, called 'MELT3', designed for nutraceuticals only. VTL 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, VTL 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 developing high-value prescription-only products.

A valuable natural products play

The Independent Experts Report prepared by PKF for a previous transaction which was not completed (an RTO between Azure Health Technology and Invictus while Azure was listed on the ASX) 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 of A\$43.6-A\$54.7m.



Source: Company



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Executive summary

VGI Health Technology Ltd (VTL) 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. VTL's first application of TransT3 are two nutraceutical products delivering tocotrienols from Vitamin E using a delivery platform, MELT3[®], which is designed for nutraceuticals. VTL 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, VTL 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.

VTL's drug delivery platforms can be company-making

VTL'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 drugs¹. 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 VTL.

VTL can quickly grow shareholder value following this IPO. VTL's first two nutraceutical products, nE1-Elite[®] and nE1-Heart[®], are being launched in the US now. We believe the combination of marketed products, the two Phase 2 clinical data readouts and data around Tocotrienol ProDrugs, can add significant shareholder value immediately post completion of this IPO.

VTL 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 Pharmaceuticals². The independent non-executive Chairman of VTL, Lou Panaccio, is also a director of Sonic Healthcare and ASX-listed biotechs Avita Medical and Rhythm Biosciences. The President and CEO of VTL'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. VTL'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 Australia and has put 40 new pharmaceutical products on the market during his 30 years at Roche. On the Scientific Advisory Board and responsible for the pancreatic cancer program is US-based, world-renowned cancer physician and research scientist Professor Richard Pestell AO. VTL as a company is young, but the Board, Scientific Advisory Board and management are seasoned operators in biotech, nutraceuticals and pharmaceuticals.

¹ Crit Rev Ther Drug Carrier Syst. 2008;25(5):449-84.

² Developer of a new anesthetic with the potential to replace propofol – see drawbridgepharmaceuticals.com.au.



Ten reasons to look at VTL

- 1) **VTL 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 VTL has obtained on nE1-ElitE[®] and exercise endurance suggests the potential for a particularly successful launch.
- 2) **VTL 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) **VTL 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, VTL 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) **VTL may have a low-toxicity pancreatic cancer drug**, with clinical and pre-clinical evidence suggesting that tocotrienol therapy could work in this cancer, particularly when delivered using either VTL's TransT3 or TPD technologies. This bodes well for VTL's IVB002 and IVB004 drug candidates.
- 5) **VTL can become a late stage clinical company within two to three years**. IVB001 could potentially be Phase 3-ready for NAFLD by 2023, since the measurement window to show that a drug can reduce liver fat is narrow.
- 6) **With TPD, VTL can go after 'composition of matter'**. VTL'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, strengthens VTL's intellectual property position. Instead of formulation and method of use patents, VTL would be using composition of matter patents that protect the prodrug molecule as a New Chemical Entity.
- 7) **Tocotrienols can help VTL 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 VTL with its products (in this case Vitamin E) and ambitions.
- 9) **The IPO 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 2021 and read out data by 2023.
- 10) **VTL 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 of a the ASX-listed biotech Avita Medical and Rhythm Biosciences). Renowned cancer researcher Professor Richard Pestell AO leads the pancreatic cancer program.

IVB001 could potentially be Phase 3-ready for NAFLD by 2023



VTL 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 supplements³. What these consumers value is the Vitamin as an antioxidant⁴, mainly to prevent cardiovascular disease⁵. There is also a strong body of opinion that Vitamin E supplements will help reduce cancer risk⁶. 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 1922⁷, but the tocotrienols were only discovered in 1965⁸. 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 properties⁹. Tocotrienols possess powerful neuroprotective¹⁰, anti-cancer¹¹ and cholesterol lowering¹² capability that the tocopherols just don't have¹³. VTL 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. 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 level¹⁴. The reason, it is believed, is a widely noted 2005 study from researchers at Johns Hopkins¹⁵ indicating that high doses of Vitamin E could increase mortality. VTL 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 2008¹⁶, off the back of re-evaluations

Vitamin E is a large market opportunity

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 neutralised. 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.

¹⁶ Kantor et. al., op. cit.



of the available data showing no serious mortality issues¹⁷. We argue that tocotrienol nutraceuticals like those which VTL 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 tocotrienols¹⁸.

VTL 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[®] may be a new adjunct to the statins. VTL 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 reductase¹⁹, as do the statins²⁰. 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 statins²².
- 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.

VTL 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 VTL’s recent clinical work there was little evidence of a similar effect in humans²⁴. When research conducted in the laboratory of Professor Michael Mathai (a friend of Glenn Tong’s) at Victoria University confirmed that tocotrienols improved exercise endurance in rats²⁵ 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 and so as far as he was concerned this direct delivery had to happen without the use of needles

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

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.

²⁵ See PLoS One. 2016 Apr 8;11(4):e0152562.



**nE1-Elite reduces
Delayed Onset Muscle
Soreness**

or surgical implants. This was where Tong started his work on TransT3. VTL has also investigated the ability of its tocotrienols to promote muscle recovery after exercise.

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 informative²⁶. 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 VTL'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 cycle²⁷. 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. (VTL'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 medalist has signed on as one of the first brand ambassadors.

TransT3: VTL develops tocotrienols as therapies

VTL's TransT3 technology represents a new way to deliver tocotrienols transmucosally. VTL 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 annatto²⁸, 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 literature²⁹ and the technology platform involved the transmucosal delivery of T3, Tong called his technology for tocotrienol formulation TransT3. There are now patents granted in the US, the European Union, Japan, China, Australia, New Zealand, Singapore, South Africa and a Notice of Allowance issued in Canada based on this invention. VTL is currently working on two drug candidates from TransT3, IVB001 for Non-Alcoholic Fatty Liver Disease

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.



(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 liver³⁰. 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 minutes³¹. The classic case of transmucosal efficiency is Actiq, a transmucosal formulation of fentanyl from Cephalon³² that can go to work as a painkiller in five minutes as opposed to 30-45 minutes for standard short-acting oral opioids³³. VTL believes that with TransT3 it has a very efficient delivery system for tocotrienols, allowing low doses to be used in a therapeutic setting.

IVB001 could potentially be Phase 3-ready for NAFLD by 2023. As we note below, tocotrienols have been shown by various groups to be able to reduce the liver fat volume of patients with NAFLD. VTL'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 has commenced preparations for a proof-of-concept Phase 2 clinical study which is expected to commence recruitment of patients and dosing later in 2021. VTL is conducting a randomised, double blind, placebo-controlled trial recruiting NASH patients and comparing the effects on liver structure as measured by ultrasound and MRI. By 2023 VTL could therefore have one of the few drugs in the world in Phase 3 for NAFLD/NASH.

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 treatment³⁴. 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). VTL 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 those 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 patents³⁵. That said, if high daily dosages are not required, VTL 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.

VTL 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 VTL for the TransT3 drug

IVB003 may have utility in pancreatic cancer.

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. After 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.

³⁵ Since the T3s themselves occur naturally and these molecules are therefore not patentable.



candidates IVB001 for NAFLD/NASH and IVB003 for pancreatic cancer. The FDA also agreed with VTL's proposition that IVB001 and IVB003 could potentially adopt an abbreviated drug development pathway known as the FDA 505(b)(2) pathway. Drugs on 505(b)(2) can hit the market quicker than drug candidates going through the normal unabbreviated development pathway. VTL expects in 2021 or 2022 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.

TPDs: VTL moves into the NCE space

VTL's Tocotrienol ProDrug (TPD) technology takes tocotrienols to the next level. As well as the TranST3 delivery platform, VTL has in-licensed a delivery technology developed in the laboratory of Professor Chris Porter at Monash University in Melbourne. VTL 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), VTL 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.

VTL can go after large market therapeutic indications with TPDs. VTL 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, VTL will target NAFLD with a TPD called IVB002, and pancreatic cancer with a TPD called IVB004.

The next stage for VTL's TPDs. VTL 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 VTL 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. VTL is currently working on lead optimisation, pre-clinical safety and toxicology studies before taking a lead candidate into a Phase 1 clinical study in 2022.

How VTL intends to move into the 'Big League'

Can VTL 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 VTL.

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

*A TPD from VGI Health
Technology could
enter the clinic in 2022*



Natural products have been coming back into favour in modern medicine

the willow tree³⁶; the antibiotic penicillin came from an ordinary mould called *Penicillium chrysogenum*³⁷; and the cancer drug Taxol came from the Pacific yew tree, *Taxus brevifolia*³⁸. 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 libraries³⁹.

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.

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 products⁴⁰.
- **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 supplements⁴¹. It has been estimated that out-of-pocket spending on complementary alternative medicine in the US totaled some US\$30bn in 2012, roughly 8% of all out-of-pocket healthcare spending⁴².
- **The Cannabis revolution.** Beginning around 2015 there has been a boom in drug development related to compounds available in *Cannabis indica*, reversing a decades-long period of neglect of this plant due to its being the source of illicit psychoactive substances⁴³.
- **The unexpected commercial success story of the prescription omega-3 products.** These days a significant percentage of Western world populations takes omega-3 supplements⁴⁴ because a large body of knowledge around the cardiovascular benefits⁴⁵. What is less well known is how high-purity omega-3 products became prescription-only blockbuster products. This was largely the work of a US company called

³⁶ Br J Haematol. 2017 Jun;177(5):674-683. Epub 2017 Jan 20.

³⁷ Emerg Infect Dis. 2017 May; 23(5): 849–853.

³⁸ Semin Oncol Nurs. 1993 Nov;9(4 Suppl 2):2-5.

³⁹ 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.

⁴⁰ Nat Rev Drug Discov. 2015 Feb;14(2):111-29. Epub 2015 Jan 23.

⁴¹ Clarke et. al., Natl Health Stat Report. 2015 Feb 10;(79):1-16.

⁴² For a summary of the data see the NCCIH press release dated 22 June 2016 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.

⁴³ Mayo Clin Proc. 2018 Dec;93(12):1842-1847.

⁴⁴ 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.

⁴⁵ 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.



**America's Orphan
Drug Act favours
natural product
development**

Reliant Pharmaceuticals⁴⁶, 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 Amarin⁴⁷, FDA approved in 2012, and Epanova, from AstraZeneca⁴⁸, FDA approved in 2014. Other companies have contemplated market entry⁴⁹. Interestingly, Lovaza is long off-patent but that hasn't prevented Vascepa and Epanova from growing sales based on new indications⁵⁰.

- **The commercial success prompted valuations to follow.** BASF acquired Pronova, the original developer of Lovaza, in 2013 for US\$845m. Amarin in early 2020 was a US\$6.5bn company⁵¹ before it experienced an adverse ruling in a US court related to a Vascepa generic in March 2020⁵².

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 VTL 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 VTL intends to explore this route with the FDA. In fact, VTL 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.

⁴⁶ 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.

⁴⁷ A product made up almost entirely of EPA – see Am J Cardiovasc Drugs. 2014 Dec;14(6):471-8.

⁴⁸ A mixture of polyunsaturated free fatty acids, not just EPA and DHA – see Am J Cardiovasc Drugs. 2014 Oct;14(5):393-400.

⁴⁹ Acasti Pharma (TSX-V: ACST), a Montreal-based company, was until recently developing prescription drugs using omega-3 fatty acids derived from krill oil. Acasti's lead product candidate from this programme, called CaPre (omega-3 phospholipid) was studied in two Phase 3 studies for severe hypertriglyceridemia. In each case there were strong reductions in triglyceride levels but the results did not achieve statistical significance. For background here see the 31 August 2020 Acasti press release headlined 'Acasti Pharma Reports Topline Triglyceride Results from Phase 3 TRILOGY 2 Study of CaPre in Patients with Severe Hypertriglyceridemia'. Previously, on 18 February 2020, Acasti had a market cap on TSX-V of C\$64m.

⁵⁰ 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.

⁵¹ 18 February 2020 close on Nasdaq.

⁵² See the Amarin press release dated 30 March 2021 headlined 'Amarin comments on ruling in Vascepa ANDA litigation'.



Tocotrienols address large market opportunities

Even a cursory glance at the literature shows the potential of Tocotrienol ProDrugs to do for VTL 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 activity⁵³. Tocotrienols have been shown to have pro-apoptosis properties⁵⁴, work against the epithelial-to-mesenchymal transition⁵⁵, suppress VEGF tumour angiogenic pathways⁵⁶, induce an anti-cancer immune response⁵⁷, render cancer more sensitive to chemotherapy⁵⁸ and act against cancer stem cells⁵⁹. For all these reasons it's reasonable to expect tocotrienols to have activity in a wide variety of cancers. We expect that once VTL 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. VTL expects its first cancer indication will be pancreatic cancer.
- **Fibrosis.** Tocotrienols have known anti-fibrotic properties⁶⁰. 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. VTL 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 VTL's future development. We noted above that tocotrienols have a similar mode of action to statins in that they inhibit the biosynthesis of HMG CoA Reductase. In that light, it's worth remembering 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 to develop over time in therapeutic areas as diverse as anti-inflammatories, neuroprotection and bone metabolism once a future VTL product helps the field to be taken seriously as a source of potential prescription medicines⁶¹.

Tocotrienols have known anti-fibrotic properties

⁵³ Biofactors. 2014 Jan-Feb;40(1):49-58. Epub 2013 Jun 27

⁵⁴ Cell Prolif. 2013 Apr;46(2):203-13.

⁵⁵ Cell Prolif. 2016 Aug;49(4):460-70. Epub 2016 Jun 21.

⁵⁶ J Agric Food Chem. 2009 Sep 23;57(18):8696-704.

⁵⁷ Cancer Genomics Proteomics. 2011 Jan-Feb;8(1):19-31.

⁵⁸ PLoS One. 2015 Apr 7;10(4):e0122712.

⁵⁹ Int J Cancer. 2011 May 1;128(9):2182-91.

⁶⁰ See, for example, Inflamm Bowel Dis. 2011 Mar;17(3):732-41.

⁶¹ See Nutr Metab (Lond). 2014; 11: 52 for a good review.



An important opportunity in pancreatic cancer

Survival for pancreatic cancer has improved, but not by much

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 now the fourth-worst cancer killer.

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 resection⁶², 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 1980s⁶⁴. 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 uncommon⁶⁵.
- 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-FU⁶⁶.
- Abraxane⁶⁷, a Celgene drug⁶⁸ 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 combination⁶⁹.

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 chemoresistance⁷⁰, in part because of K-Ras mutations, which, occur in over 90% of cases⁷¹. In addition, pancreatic cancer tends to be poorly vascularised. A recent example of a promising pancreatic cancer agent that failed was Jakafi⁷², the JAK Kinase inhibitor from Incyte that seemed to work in a subgroup of patients in Phase 2⁷³. That company shut down its pancreatic cancer programme for Jakafi in February 2016.

Why VTL'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

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.

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 Pancreatolgy. 2005;5(4-5):403-9. Epub 2005 Jun 28.



Vitamin E can be effective against pancreatic cancer. Population studies have also suggested an inverse relationship between Vitamin E intake and pancreatic cancer risk⁷⁶. Vitamin E is known to work against pancreatic cancer by inhibition of NF-κB activity⁷⁷, regulation of the cell cycle, modulation of the Ras–Raf–MEK–ERK pathway, and the induction of apoptosis⁷⁸. We noted above the work of the Malafa laboratory at the Moffitt Cancer Center on delta tocotrienol, and another group found similar results in conjunction with gemcitabine using gamma tocotrienol⁷⁹. The Malafa lab reported promising results from a Phase 1 clinical study of delta tocotrienol in pancreatic ductal neoplasia in 2015⁸⁰. That study⁸¹ 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 tocotrienol⁸² 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 market⁸³. 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. 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 steatosis⁸⁵. 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 literature⁸⁶. That said, 30%-or-so of the US population has this condition⁸⁷, and there are comparable figures in other Western world jurisdictions⁸⁸. The reason NAFLD can be regarded as serious 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 kind⁸⁹, 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 NASH⁹⁰, and that

30% of the US population may have fatty liver

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.

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.



large patient population has fueled heavy research interest in NASH from pharma companies, including two major transactions⁹¹, so that today there are four agents in Phase 3⁹².

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 NASH⁹³. 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 fibrosis⁹⁴. 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:

- 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 patients⁹⁵.
- 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 steatohepatitis⁹⁶.
- 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 group⁹⁷.
- 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 fibrosis⁹⁸.

VTL 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.

Tocotrienols appear to inhibit lipid accumulation in the liver

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 VTL

Independent valuation range A\$44-55m. The Independent Experts Report related to an earlier RTO (which was not completed) when VTL was listed on the ASX 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.

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 available⁹⁹ 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. VTL's prescription products are commencing Phase 2 clinical studies in the case of the TranST3-based drug candidates (IVB001 and IVB003) and pre-clinical studies 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 VTL

We see the following developments helping to grow VTL's value after the IPO:

- 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;
- *In vivo* studies relating to the TPDs establishing proof of concept for bioavailability and efficacy;
- Progress of Phase 2 Proof of Concept clinical studies in NAFLD and pancreatic cancer (including a clinical data read out for NAFLD in 2023)



- 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 VTL

Figure 2: Companies to watch⁹⁹

Company	Location	Code	Market cap	
			(USDm)	Web
Clearside Biomedical	Alpharetta, Ga	Nasdaq: CLSD	160	www.clearsidebio.com
Milestone Scientific	Livingston, NJ	OTCQB: MLSS	141	www.milestonescientific.com
Celsion	Lawrenceville, NJ	Nasdaq: CLSN	101	www.celsion.com
IntelGenX	Saint-Laurent, Qc	TSX-V: IGX	72	www.intelgenx.com
Acerus Pharmaceuticals	Mississauga, On.	TSX: ASP	58	www.aceruspharma.com
InMed Pharmaceuticals	Vancouver, BC	TSX: IN	29	www.inmedpharma.com
Titan Pharmaceuticals	South San Francisco, Ca	OTCBB: TTNP	27	www.titanpharm.com
Midatech Pharma	Abingdon, UK	LSE: MTPH	25	www.midatechpharma.com
GB Sciences	Las Vegas, Nv.	OTCQB: GBLX	17	www.gbsciences.com
Crescita Therapeutics	Mississauga, On.	TSX: CTX	14	www.crescitatherapeutics.com

Source: Pitt Street Research

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 VTL.

- **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 the product is currently in under investigator-sponsored development for several cancer indications. 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.
- **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 refiled in May 2021.

⁹⁹ Market caps for 3 June 2021 on Nasdaq and elsewhere.



- **Crescita Therapeutics.** This dermatology company's main product is an enhanced formulation of Pliaglis, a lidocaine/tetracaine cream used as a local anaesthetic on the US market since 2008. Crescita's formulation was licensed in 2017 to the generic drug company Taro Pharmaceutical Industries.
- **GB Sciences.** This company develops drugs based on plant extracts, including 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 rizatriptan product, called Rizaport, gained its first European Marketing Authorisation in 2015. It received Complete Response Letters from the FDA in April 2019 and March 2020. 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 DFIG (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 buprenorphine implant for the treatment of opioid addiction that was marketed for a while until Titan decided to develop other indications, such as a nalmefene implant.



Appendix I – Capital structure

Figure 3: Azure Health Technology proposed capital structure

	Shares on issue
Pre-IPO shares	105,037,167
Shares issued on conversion of notes	19,844,943
Shares raised in the IPO	12,485,000
Shares after IPO	137,367,110
Market cap at offer price	\$27,473,422

Source: Company

Appendix II - A VGI Health Technology 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 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. An IND is a request filed with the FDA for authorisation 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.

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

NASH – Short for Non-Alcoholic SteatoHepatitis, a liver disease in which the fat buildup of NAFLD is accompanied by damaging liver inflammation, leading to fibrosis and from there, in some instances, to cirrhosis. Perhaps 3% of the US population has NASH¹⁰⁰.

nE1-Elite[®] – An VTL dietary supplement for exercise endurance.

nE1-Heart[®] – An VTL dietary supplement for cardiovascular health.

New Chemical Entity (NCE) – A new drug, generally synthetic, 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 trial 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 – VTL’ platform that allows transmucosal drug delivery of tocotrienols

¹⁰⁰ NASH (Dig Dis. 2010;28(1):155-61. Epub 2010 May 7.



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 – VTL’s intellectual property

VTL’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.

VTL (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 (PPAR δ) agonist¹⁰¹ that is in Phase 3 in Primary Biliary Cholangitis (PBC) and Phase 2 in NASH. The drug has been shown to be able to bring about significant reductions of serum alkaline phosphatase, a surrogate marker for disease progression¹⁰². CymaBay put the Seladelpar programme on hold in November 2019 after ‘atypical histological findings’ showed up during a Phase 2b in NASH. However in July 2020 the programme was revived after an independent experts panel found that the drug wasn’t causing liver injury¹⁰³.

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 condition¹⁰⁴.

Genfit. This company’s lead compound, another PPAR agonist called Elafibranor, failed in Phase 3 in NASH in July 2020, even though the in Phase 2 the drug met its primary endpoint of NASH resolution without worsening of fibrosis¹⁰⁵. Elafibranor remains in Phase 3 in Primary Biliary Cholangitis with first data expected to be available in early 2023.

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-LPS¹⁰⁶ 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 biomarkers¹⁰⁷. Immuron has chosen not to take IMM-124E forward in NASH

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 See the Cymabay press release dated 23 July 2020 and headlined ‘FDA Lifts All Clinical Holds on Seladelpar’.

¹⁰⁴ Where that cirrhosis occurred without esophageal varices, that is abnormal, enlarged veins in the tube that connects the throat and stomach.

¹⁰⁵ 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’.

¹⁰⁶ Lipopolysaccharide is a bacterial endotoxin implicated as a driver of liver inflammation. See, for example, Lab Anim. 2015 Apr;49(1 Suppl):37-46.

¹⁰⁷ See the Immuron market release dated 8 March 2018 and headlined ‘Immuron reports positive results in NASH clinical trial’.



but is instead has focused the product on travelers' diarrhea and, since early 2020, on Covid.

Intercept Pharmaceuticals. This company's foundation product is Ocaliva, which targets the farnesoid X receptor (FXR), highly relevant in inflammatory disorders and fibrotic disease¹⁰⁸. The drug gained its first approval in May 2016 for the treatment of PBC. Ocaliva had Phase 3 success in NASH after a Phase 2 demonstrated improved liver histology in 45% of the treated patients versus 21% in the placebo group¹⁰⁹. In a Phase 3 study called REGENERATE, for which topline data became available in early 2019, the drug achieved a statistically significant improvement in liver fibrosis without worsening of NASH at 18 months ($p=0.0002$)¹¹⁰. However in June 2020 the drug received a Complete Response Letter from the FDA¹¹¹, citing uncertainty as to whether reduction in liver fibrosis would result in patient benefit.

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 undecanoate¹¹², completed Phase 3 and in late 2020 received tentative FDA approval to launch in the generic market when exclusivities expire in March 2022¹¹³. LPCN 1144, an oral androgen, is in Phase 2 as a NASH treatment on the understanding that low testosterone contributes to increased liver fat¹¹⁴.

Madrigal Pharmaceuticals. This company's Remetirom drug (MGL-3196) 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 placebo¹¹⁵. 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 and degenerative cervical myelopathy. 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. A second Phase 2 trial in NASH is being prepared and a Phase 2 trial in IPF is enrolling.

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

¹⁰⁸ Generic name obeticholic acid. Ocaliva is a synthetic bile acid agonist of the farnesoid X receptor.

¹⁰⁹ Lancet. 2015 Mar 14;385(9972):956-65. Epub 2014 Nov 7. Ocaliva was granted Breakthrough Therapy Designation by FDA for the treatment of NASH with liver fibrosis in January 2015.

¹¹⁰ See the Intercept press release 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'.

¹¹¹ See the Intercept press release dated 29 June 2020 and headlined 'Intercept receives Complete Response Letter from FDA for Obeticholic Acid for the treatment of fibrosis due to NASH'.

¹¹² Traditionally lacking in oral bioavailability.

¹¹³ The product received Complete Response Letters in May 2018 and November 2019 which were subsequently overcome.

¹¹⁴ Cardiovasc Endocrinol. 2015 Sep 1;4(3):83-89.

¹¹⁵ 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'.



($p < 0.01$) while 91% of patients in this group saw a $>30\%$ reduction in liver fat¹¹⁶.

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 ACOX1¹¹⁷. Currently the lead indication for Masitinib is Amyotrophic Lateral Sclerosis¹¹⁸.

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, did well in Phase 1b in pancreatic cancer¹¹⁹.

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 initial 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 ($p=0.034$)¹²⁰.

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 Disease¹²¹. 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 rates¹²². The thinking with pamrevlumab is that by attacking the connective tissue of the tumour, unresectable tumours can become resectable.

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 ifosfamide into its cancer-killing form. Such a product has potential in pancreatic cancer, where a PharmaCyte programme is in Phase 2.

¹¹⁶ 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'.

¹¹⁷ Ann Oncol. 2015 Jun;26(6):1194-200. Epub 2015 Apr 9.

¹¹⁸ Amyotroph Lateral Scler Frontotemporal Degener. 2019 Jul 7:1-10. [Epub ahead of print]

¹¹⁹ See the ChemoCentryx press release dated 22 January 2018 and headlined 'ChemoCentryx Announces Positive Overall Survival Results with CCR2 Inhibitor CCX872 for Locally Advanced/Metastatic Pancreatic Cancer'

¹²⁰ 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'.

¹²¹ The drug stimulates red blood cell production by inhibiting an enzyme called hypoxia-inducible factor-prolyl hydroxylase.

¹²² 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'.



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 inhibitor¹²³, has completed Phase 2 in pancreatic cancer, where it has FDA Orphan Drug designation.

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 trials¹²⁴.

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.

¹²³ Extracellular proteases play a key role in tumour cell invasion – see Clin Chim Acta. 2000 Feb 15;291(2):113-35

¹²⁴ 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 VTL

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

- Funding risk. There is the risk that VTL, being a small cap NSX-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 VTL's products may not reach their primary endpoint.
- Regulatory risk. There is the risk that VTL may take not be able to gain registrations for its products.
- Commercial risk. There is the risk that VTL 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 VTL 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 VTL.



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 research franchises in other sectors such as property and resources.

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