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Cyclopharm Ltd.

FDA approval is last piece of the puzzle

Share Price: A$1.46

ASX: CYC

Sector: Healthcare Equipment & Services

1 March 2022

Cyclopharm's (ASX:CYC) core radiopharmaceutical product, Technegas, is used in functional lung ventilation imaging, particularly for the diagnosis of pulmonary embolism (PE). Technegas produces a gas-like substance that is inhaled by the patient and distributed throughout the lungs. This mechanism of action allows a gamma camera to create an image of functional ventilation of the lungs. Technegas offers a safer and more effective alternative radioactive compound. Its sensitivity, specificity and accuracy are equivalent to alternative imaging technologies while diagnosing PE even at sub-segmental levels. Moreover, Technegas involves a minimal radiation dosage and can be administered to patients without any exclusion criteria.

US FDA approval expected early 2023

Technegas is already being sold in over 60 countries and management is now trying to expand its presence in the US, which is the largest market for nuclear medicine. The company is in the final stages of the FDA approval for Technegas and expects to receive approval early in 2023 at the latest. It is believed that the size of the US addressable market for PE alone is ~US$90m annually in the medium term and this can further expand to US$180m annually in the long term. In our view, Cyclopharm should be able to capture the US growth opportunities because of its superior technology, global footprint and significant support it receives from Key Opinion Leaders. Further, one of the key complications of COVID-19 is PE and Technegas is safer and easier to use in such cases and clinically superior compared to competing technologies.

COPD market is 30x larger than the PE market

The bigger opportunity in the long term will be applications of Technegas beyond PE. CYC is targeting new applications through clinical studies that are focussing on diagnosis of Chronic Obstructive Pulmonary Disease (COPD), asthma and other respiratory diseases, like Long-Covid. The COPD market is 30x larger than PE! It is already working on research projects with leading universities on this front and has invested over A$500,000 during 2019–2020 to fund these initiatives.

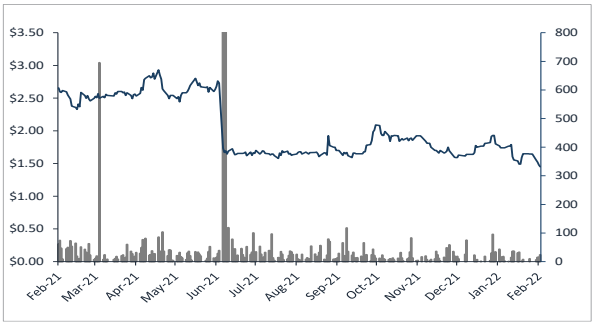
Valuation range of A$2.74–3.33 per share

We have valued Cyclopharm using a DCF approach, which highlights that the company is currently highly undervalued, even excluding opportunities beyond PE. It seems investors are not factoring in the full potential of Technegas in the near and long term. A key share price catalyst will be US FDA approval if and when received.

Market cap. (A$ m)	130.3
# shares outstanding (m)	89.6
# shares fully diluted (m)	89.6
Market cap full. dil. (A$ m)	130.3
Free float	31.8%
52-week high/low (A$)	2.95 / 1.43
Avg. 12M daily volume ('1000)	36.7
Website	www.cyclopharm.com

Source: Company, Pitt Street Research

Share price (A$, l.h.s.) and avg. daily volume (k, r.h.s.)



Source: Refinitiv Eikon, Pitt Street Research

Valuation metrics	
Fair valuation range (A$)	2.74–3.33
WACC	10.1%
Assumed terminal growth rate	3.0%

Source: Pitt Street Research

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Disclosure: Pitt Street Research / Stocks Down Under directors own shares in CYC.

Please refer to page 16 for key investment risks.

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Introducing Cyclopharm, ASX:CYC

Incorporated in 2005 and headquartered in Kingsgrove, New South Wales, Australia, Cyclopharm (ASX:CYC) is a nuclear medical device company operating in the field of diagnostic lung imaging. Cyclopharm's core radiopharmaceutical product, Technegas, is used in functional lung ventilation imaging, particularly for the diagnosis of pulmonary embolism (PE). Technegas produces a gas-like substance, which when inhaled by the patient, coats the inside of lungs and is delivered anywhere oxygen is delivered into the lungs. Thus, it acts as a replica of how ventilation is performed by lungs. Once the radioactive compound expands through the pathways of the lungs, it allows a gamma camera to create an image of the lungs. Technegas not only offers a safer, but also a more effective alternative radioactive compound.

Technegas is already sold in 60 countries

Cyclopharm has clinically delivered Technegas to over 4.4 million patients across 60 countries around the globe. The company has also made a foray into molecular imaging in 2006 and is currently partnering with ANSTO, Cyclotek and Macquarie University in this area. This business will produce radiopharmaceuticals to be used by physicians in the detection of cancer, neurological disorders and cardiac diseases.

US market entry will be the primary near-term catalyst

Although Technegas is available in large parts of the world, it is not yet available in the US, which is the largest market for nuclear medicine. The nuclear medicine ventilation imaging market in the US for PE alone is around ~US$180m annually. Currently, 65% of Technegas revenues are generated in Europe with France being the single largest market in that region.

Once it receives FDA approval, Cyclopharm is well positioned to expand rapidly in the US

Cyclopharm submitted a New Drug Application (NDA) for Technegas with the US FDA in 2021 and management is expecting to receive FDA approval in early 2023 at the latest. While the company has faced a setback in not being able to achieve its previous goal of receiving FDA approval by mid-2021, it is important for investors to understand that the FDA has not asked for any additional clinical trials and there is a finite list of issues/queries that management now needs to respond to. Further, the company has been receiving tremendous support from Key Opinion Leaders in the US, which reinforces our belief that it is a matter of time before Technegas will receive FDA approval.

Once FDA approval is secured, Technegas will be reimbursable by health insurers from day one making its adoption easier for hospitals. Moreover, the company plans to supply Technegas generators to US hospitals through a service model rather than an upfront sale of generators. This revenue model should help build a recurring revenue base in the US very quickly.

'Beyond PE' initiatives to provide blue ocean opportunities

Total addressable market will expand considerably if Technegas can be successfully applied to other respiratory diseases

Currently, the primary use case for Technegas is PE, but the company has already commenced investing in trials and supporting clinicians to expand the use of Technegas beyond PE, into Chronic Obstructive Pulmonary Disease (COPD), asthma and other respiratory disease states. The company estimates the global COPD market to be about 30 times of the size of the PE market!

Global COPD market is 30x larger than PE

It is currently involved in several 'Beyond PE' clinical research projects using Technegas via collaborations with leading academic institutions and has invested over A$500,000 in clinical trials during 2019–2020 in this direction.

Ten reasons to look at Cyclopharm

1) **Cyclopharm's flagship product Technegas, offers not only a safer but also a more effective alternative radioactive compound.** Its sensitivity, specificity and accuracy are equivalent to alternative imaging technologies, while diagnosing PE even at sub-segmental levels. At the same time, Technegas involves minimal radiation dosage and can be administered to almost all patients without any exclusion criteria. Furthermore, while delivering Technegas is a quick and simple process, it does not compromise the diagnostic imaging quality.
2) The company has a **natural moat as it is a supplier of both the drug and equipment.** It is not just providing consumables. Further, the company also earns revenue through after-sales services of the devices. Thus, this combination of solutions helps the company in generating multiple revenue streams from the Technegas product offering.
3) **Cyclopharm has a presence in 60 countries, with Europe and Canada currently being its primary markets.** Also, Technegas recently renewed its CE mark under the new European Medical Device Regulations. The global footprint of the company places it in a strong position to leverage the growth potential in the addressable markets.
4) **Cyclopharm's primary near-term growth catalyst is entry into the US market,** which has half of the world's nuclear medicine departments. As a first step, the company aims at capturing ~50% of the US nuclear medicine market (estimated to be US$90m) in 2-3 years and up to 80% of the market in 5-7 years. The second stage of the strategy will aim at increasing the PE diagnostic market imaged through nuclear medicine from 15% to 30% (this will expand the market by another US$90m).
5) **In the final stages of FDA approval.** Management is expecting to receive FDA approval for Technegas early in 2023 at the latest. To facilitate a smooth entry into the US market, the company is already building up its inventory, sales capabilities and infrastructure. Moreover, the company plans to supply Technegas generators through a service model rather than an upfront sale of generators. Under the service model, Cyclopharm will continue to retain ownership of its generators over their lifecycle. But it will provide consumables, generator maintenance and operator training to hospitals and earn recurring service fees and consumables sales.
6) **Strong growth drivers for PE diagnostic imaging.** PE is associated with substantial morbidity and mortality, accounting for over 50,000 deaths per year in the US alone. **Further, PE has been identified as a major clinical challenge since the beginning of the COVID-19 pandemic,** as one of the complications of COVID-19 is blood clots in lungs. We believe that the incidence of PE is likely to remain elevated driven by lifestyle diseases, smoking, longer life expectancy and more sensitive diagnostic tests.
7) **'Beyond PE' initiatives.** Cyclopharm is working on extending Technegas into new applications, such as the diagnosis and monitoring of COPD, asthma and other respiratory diseases, which will create opportunities to expand the market for Technegas. The company has already invested over A$500,000 on these initiatives over the past two years, and it believes that these new applications have the potential to dwarf its current PE market.
8) **Well-funded for growth.** The company successfully raised A$33m in equity capital in February 2021, which includes an institutional placement of A$30m and a retail share purchase plan of about A$3m. It plans to use

this capital to support commercialisation of Technegas in the US, once it gets through the FDA approval process, and to support its 'Beyond PE' initiatives.

9) Cyclopharm has a **highly experienced management team.** The CEO, James McBrayer, has been working in the field of nuclear medicine for over 30 years and is a trained Nuclear Pharmacist. We think the leadership team's combined experience has been key in the company's strategy to grow globally and explore applications beyond PE.

10) **We believe Cyclopharm is undervalued at its current market value.** We value the share in a range of A$2.74–3.33, which is significantly higher than its current market value. In our view, the stock should re-rate to our valuation range once the company receives FDA approval and enters the US market.

Evolution of Cyclopharm/Technegas

Technegas was discovered in the mid-80s and was registered as a drug in Europe in 1996. 2001 marked the commencement of the Phase III study for Technegas' submission to FDA. During 2003–2005, Technegas achieved a major breakthrough by entering the Canadian market and securing an agreement with the Australian National University to continue research into liquid Technegas.

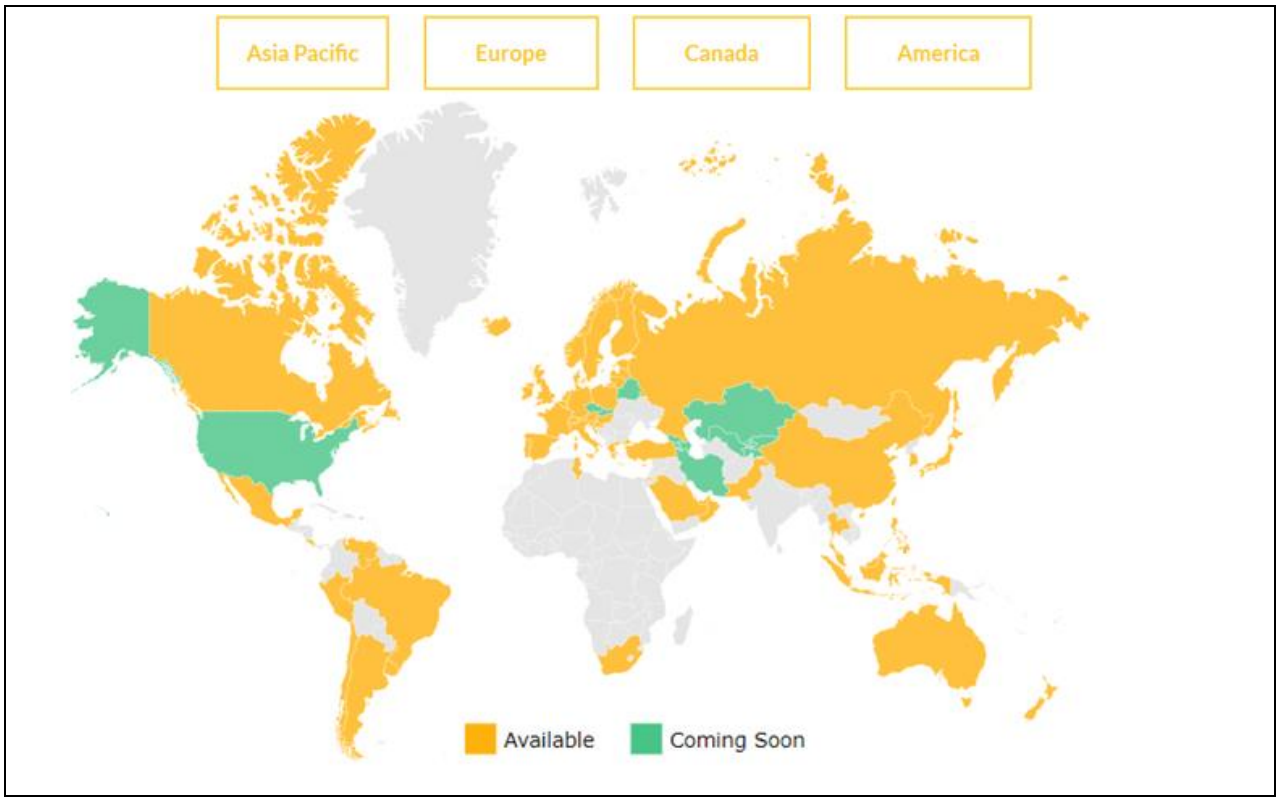
Cyclopharm went public on ASX in 2007

Cyclopharm was incorporated in 2005 as an unlisted public company and it completed the acquisition of the Technegas System business from Vita Life in May 2006 via a share exchange. Subsequently, Cyclopharm went public in 2007 and started trading on the ASX. The company also secured sites in North Ryde, Sydney, Kensington and Melbourne for positron emission tomography (PET) pharmacies.

During 2010–2013, Cyclopharm expanded its presence to 55 countries and began sales of the Technegas generator in Japan.

In April 2013, the company started development of Ultralute, a patented nuclear medicine technology to extend the useful life of its generators by 50%. Further, in 2014, the company began trials in China for the use of Technegas in the diagnosis and treatment of COPD.

Figure 1: Cyclopharm's global presence



Source: Company

During 2017–2018, Cyclopharm acquired Inter Commerce Medical BVBA (Belgium) and Medicall Analys AB (Sweden). By 2020, the company had penetrated 60 countries (Figure 1). Europe is currently the largest market in terms of revenue contribution (~70% of group sales in 2020), followed by Asia Pacific (16%) and Canada (14%).

Cyclopharm is now aiming to enter the US market and replicate its success in the Canadian market. It is in the final stages of the FDA approval process for Technegas and is all set for commercialisation once it secures the approval.

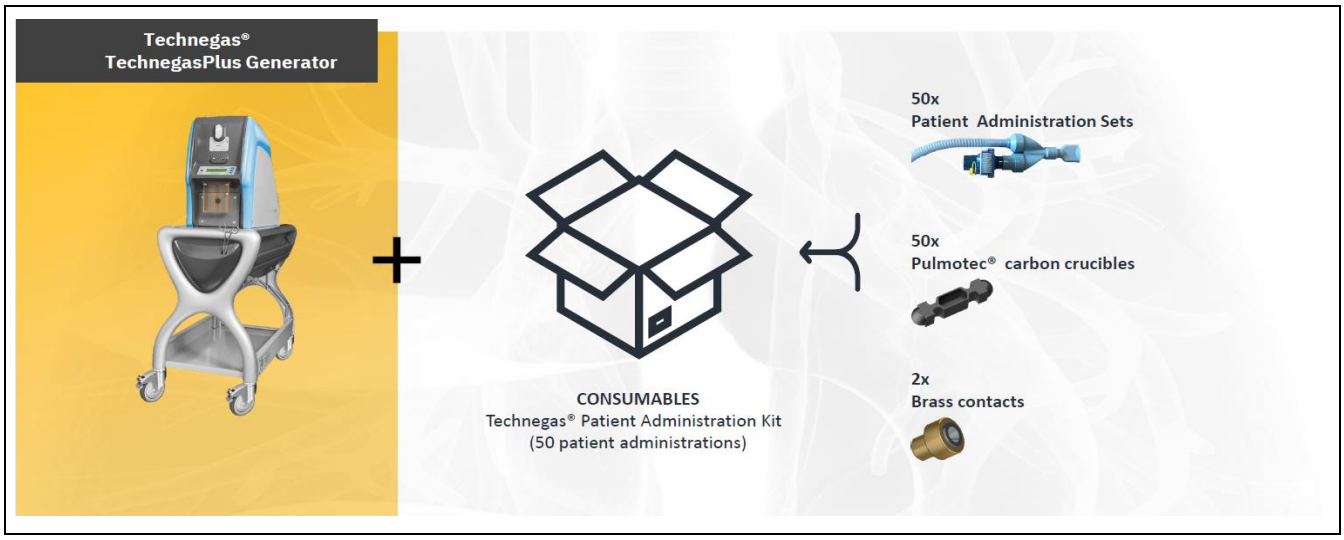
Technegas – Cyclopharm's flagship product

The Technegas technology entails a structured, ultra-fine dispersion of radioactive labelled carbon, produced by using dried Technetium-99m (Tc-99m) in a carbon crucible, micro furnaced for a few seconds at around 2,700^0 C. The resultant gas-like substance is inhaled by the patient (lung ventilation) via a breathing apparatus, which then allows multiple views and tomography imaging under a gamma or single photon emission computed tomography (SPECT).

Cyclopharm's technology includes both equipment and consumables

To produce Technegas, an electrically powered medical device called TechnegasPlus Technegas Generator is used (Figure 2). This device produces hydrophobic Tc-99m-labelled carbon particles, which is dispersed as an aerosol. Tc-99m is an isotope commonly used in a number of medical diagnostic imaging scans. It is also used as a radioactive tracer in nuclear medicine.

Figure 2: Technegas solution includes generators along with consumables

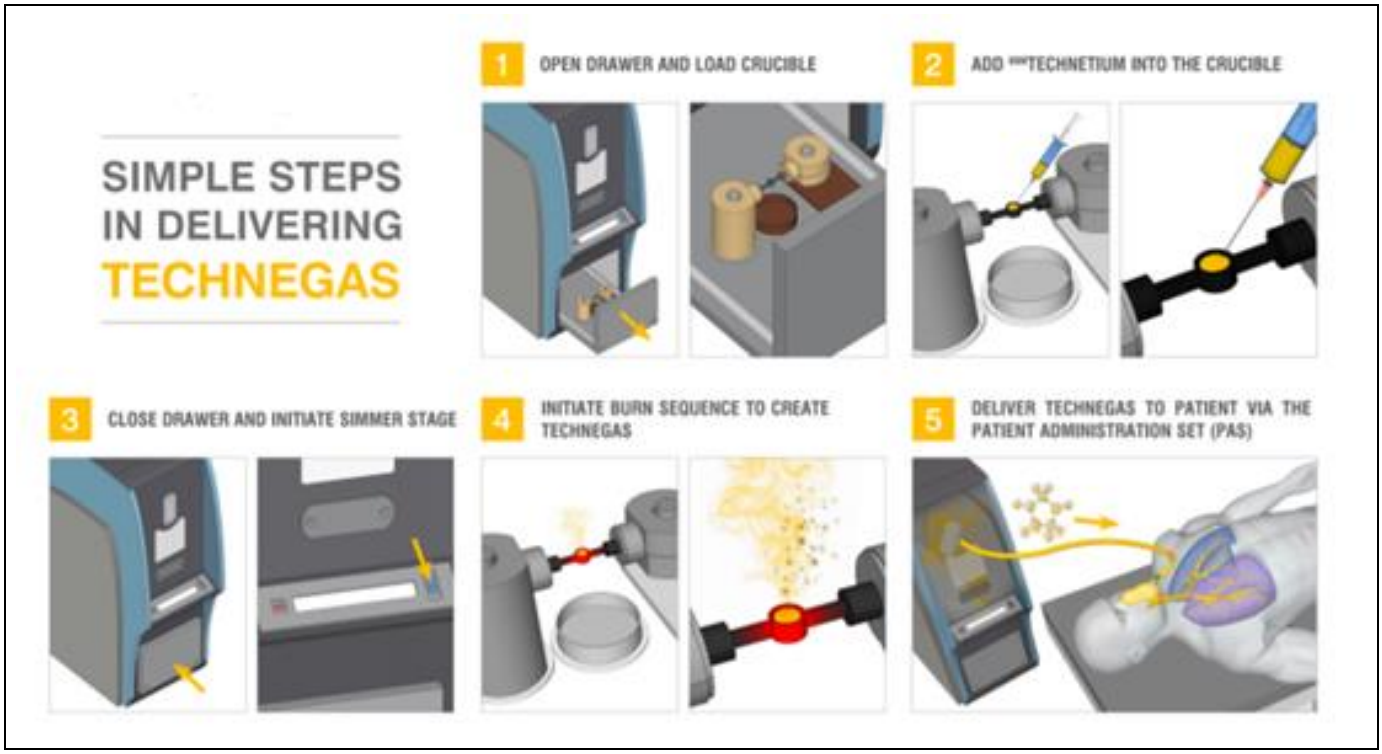


Source: Company

Technegas provides ideal characteristics for gaseous behaviour and alveolar deposition in the lungs owing to its hydrophobic properties and nanoparticle size, in turn facilitating gamma-ray imaging of the functional ventilation distribution for diagnosing pathological processes.

Post infusion of Technegas and gamma camera imaging or SPECT or SPECT/CT (Computed Tomography), the technologist/clinician can deliver planar or 3D images providing information relating to lung function and pulmonary physiology (Figure 3).

Figure 3: Technegas generation and delivery process



Source: Company

Benefits of V/Q SPECT with Technegas

Overall, Technegas offers not only a less damaging but also a more effective alternative radioactive compound. The several critical benefits of this technology are described below:

- **Diagnostic accuracy:** Sensitivity, specificity and accuracy are equivalent to computed tomography pulmonary angiogram (CTPAs), while diagnosing PE even at sub-segmental levels.
- **3D images:** The gas-like behaviour of Technegas along with the ideal energy of Tc-99m allows excellent penetration to peripheral areas of the lungs. As a result, images can be captured in multiple projections facilitating image interpretation.
- **Low radiation burden:** V/Q SPECT with Technegas has a 27 to 36 times lower radiation dosage being administered to a patient compared with CTPA.
- **Quick and simple:** Rapid and easy administration of Technegas (3–4 breaths by patients) enables accurate and immediate decision-making even in case of lung obstructive disease. Only a few breaths of Technegas particles are required.
- **Minimal exclusion criteria:** Technegas can be administered to almost all patients, including ones with renal impairment, iodinated contrast allergy and chronic lung obstruction disease. It can also be administered to pregnant women.
- **Non-invasive:** Technegas is easy to inhale and hence aids in patients' comfort and compliance. Also, it uses SPECT technology, which is a well-established, non-invasive technique, for quantitative assessment of

V/Q SPECT with Technegas has a low radiation burden as compared with CTPA while allowing high-quality diagnostic imaging

regional lung ventilation and perfusion distribution in both children and adults.

In comparison with Technegas, other agents and technologies used in lung imaging have certain drawbacks that are listed below (Figure 4).

Figure 4: Drawbacks of alternative lung imaging technologies

Xenon 133 (Xe-133) used in nuclear ventilation imaging	DTPA (diethylene-triamine-pentaacetate acid) Tc-99m used in nuclear ventilation imaging	Imaging modalities via CTPA
It is a heavy radioactive gas which is inhaled with a full-face mask.	Wet aerosol impacts efficacy, bronchospasm and acts as a COVID-19 carrier.	CTPA delivers at least 27 times more radiation to the breast as compared to V/Q SPECT.
Constant breathing for 15 minutes increases the risk of COVID-19 exposure.	DTPA requires 3–5 minutes of periodic administration to deliver the target dose.	CTPA should not be performed on pregnant women, and people with renal impairment, contrast media allergy and diabetes.
It does not provide 3D images and is limited to planar imaging, resulting in inferior clinical outcomes.	Creates hotspots in presence of small airway lung diseases, a frequent comorbidity in PE and impacts clinician interpretations.	Acute kidney injury occurs in up to 13% of CTPA cases.
Requires special rooms to contain radioactive gas in the event of a release.		It has lower clinical sensitivity.

Source: Company, Pitt Street Research

The US is the largest market for nuclear medicine

We believe the near-term growth driver for Cyclopharm will be entry into the US market. The US is expected to see a growing number of cases of PE driven by lifestyle diseases, smoking, longer life expectancy and more sensitive diagnostic tests.

US has half of the world's nuclear medicine departments and has the potential to become the largest market for Technegas

As per the American Heart Association's 2018 statistics, PE was a factor in more than 36,000 deaths[1]. As per an article published in Essential Echocardiography in 2019, PE is associated with substantial morbidity and mortality, accounting for over 50,000 deaths per year in the US[2]. Furthermore, PE has been identified as a major clinical challenge since the beginning of the COVID-19 pandemic.

In the US, about four million diagnostic procedures are conducted each year on PE patients. Out of all these diagnostics tests being conducted, 15% are based on nuclear medicine imaging and 85% of them are CTPA. These 600,000 nuclear medicine ventilation procedures being conducted every year represent a market opportunity of ~US$90m.

[1] See *Pulmonary embolism is common and can be deadly, but few know the signs* by Michael Merschel, American Heart Association, 23 November 2021.
[2] Elsevier 2019, 'Pulmonary Embolism', *Essential Echocardiography: A Companion to Braunwald's Heart Disease*, 369—375.

Significant addressable market for Technegas in the US

The target market for Technegas in the US equates to ~480,000 patient procedures of the total ~600,000 nuclear medicine ventilation procedures being conducted annually[3]. We believe, based on Cyclopharm's experience in the Canadian market, Technegas can achieve a 50% share of the US market over 2–3 years and an 80% share achievable over a 5 to 7-year period.

In the first stage of its US market entry strategy, Cyclopharm plans to address the existing market of US$90m. The second stage of the strategy aims at increasing the PE diagnostic market imaged through nuclear medicine from 15% to 30%. This is expected to expand the addressable market by an additional US$90m.

CYC is well-positioned to capture a large part of the US market

The US nuclear medicine market is likely to increasingly adopt the 3D imaging technique (SPECT) that provides superior outcomes to both planar imaging and CTPA in the diagnosis of PE[4]. Based on the global experience of reliability of imaging outcomes using Technegas, 3D SPECT imaging using Technegas will be clinically superior and safer than CTPA.

In our view, Cyclopharm is well placed to leverage the growth opportunities in the US driven by its superior technology, real-world evidence from 60 countries and significant support of Key Opinion Leaders. Moreover, Technegas is safer from a COVID-19 perspective as compared to competing nuclear medicine products, such as DTPA Tc-99m.

In the final stage of getting US FDA approval

The primary near-term catalyst for the company is US entry and for this, the company needs to secure FDA approval. Cyclopharm's Phase 3 trials to support its FDA application to permit entry in the US market were confirmed to have met their primary and secondary efficacy endpoints in September 2020.

The FDA then conducted a Pre-Approval Inspection (PAI) of Cyclopharm's manufacturing facility at Kingsgrove, New South Wales, in March 2021. Thereafter, a Complete Response Letter (CRL) was received in June 2021. The CRL highlighted points relating to better definition, validating production, delivery of Technegas particles and other aspects of crucible manufacturing and dosimetry that needed to be addressed before the NDA could be approved. This development meant that management could not achieve its previous goal of receiving FDA approval by mid-2021.

Management is expecting to receive FDA approval in early 2023 at the latest

However, it is important for investors to understand that the FDA has not asked for any additional clinical trials and there is a finite list of issues/queries that management now needs to respond to. As per the latest update, the company is expected to submit its formal and complete response to the FDA in Q3 2022. Post that, USFDA would have 6 months to complete its review. Once approved, the company will be in a position to commercialise Technegas in the US.

US physicians have asked the FDA to expedite the approval of Technegas

It is also important to note that between 2020 and 2021, several nuclear medicine physicians and technologists have written to the FDA requesting to expedite approval of Technegas for the use in the US market. The physicians are in support of the observation that Technegas has a superior safety profile in relation to COVID-19 when compared to its alternatives. We believe this is a key testimonial to the company's growth potential in the US and it will be a matter of time before the company will make inroads into this market.

[3] See Cyclopharm's Investor Update release, dated 10 November 2021 and headlined 'Investor Update Bell Potter HealthCare Conference'.
[4] See *US Market entry and sales model in Annual Report 2020* by Cyclopharm Limited, 29 March 2021.

US market entry model

While Cyclopharm is awaiting US FDA approval, management has been doing groundwork to ensure a hassle-free entry and rapid expansion post Technegas' approval. To promote a rapid roll out, the company has taken the following steps:

Service model for US sales will help build a recurring revenue base very quickly

- It is maintaining a certain level of inventory for the US market and is pursuing agreements for third-party distribution, service and installation as well as administrative support.
- Management has ensured that Technegas will be reimbursable by health insurers from day one making its adoption easier by patients and hospitals.
- For expansion in the US, the company plans to supply Technegas generators to US hospitals through a service model rather than an upfront sale of generators. Through this model, the company will retain ownership of the generators over their lifecycle and charge an ongoing annual fee attributed to preventative maintenance, training and product support. This approach will result in accelerated consumables revenue and provide a more predictable revenue base over the generators' lifecycle.

Substantially more upside beyond PE

The existing market for nuclear medicine ventilation imaging in the US for PE alone is estimated to be over US$180m. In our view, while the primary use case for Technegas is currently PE, the blue ocean opportunities will be provided by applications beyond PE.

The global COPD market is 30x larger than the PE market

Cyclopharm is investing in new applications through clinical studies that are focussing on diagnosis and monitoring of COPD, asthma and other respiratory disease states. The company estimates that the global COPD market is approximately 30 times the size of the PE market and over 500 million patients suffering with COPD and asthma can benefit from the use of Technegas.

Chronic Obstructive Pulmonary Disease (COPD)[5,6]

V/Q SPECT/CT with Technegas can be used as an effective monitoring tool in a range of conditions such as COPD, asthma and CTEPH

Guidelines from the Canadian Association of Nuclear Medicine (CANM), published in 2018, and the European Association of Nuclear Medicine (EANM), published in 2019, confirm superior outcomes from the use of Technegas for imaging in patients with COPD. For ventilation, 99mTc-Technegas was observed to be the best radio-aerosol, particularly in patients with COPD.

As per the CANM guidelines, liquid aerosols produced in nebulizers – such as 99mTc-DTPA – are inferior for SPECT and should not be used unless Technegas is not available. In situations of COPD, up to 31% of patients may have PE and up to 10% may die. Even those patients who have an abnormal chest X-ray can undergo V/P SPECT. Technegas is considered the agent of choice in the COPD population as there is less central airway deposition, better peripheral penetration, while Technegas does not wash out as quickly as traditional aerosols.

[5] See *CANM Guidelines for Ventilation/Perfusion (V/P SPECT) in Pulmonary Embolism Executive Summary* by CANM, November 2018.
[6] See *EANM guideline for ventilation/perfusion single-photon emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond* by EANM, Springer, 13 August *2019.*

Early detection of lung disease[7]

Technegas can be effective in the early detection of lung disease, often caused by cigarette smoking, including chronic bronchitis and emphysema. This was substantiated by a Canadian study, published in 2013 by Rhem, J. et al., which focussed on the detection of lung dysfunction using ventilation and perfusion SPECT in a mouse model of chronic cigarette smoke exposure. In this study, researchers from the McMaster University and the Firestone Institute for Respiratory Health at St. Joseph's Healthcare in Ontario, Canada demonstrated that Technegas detected changes in lung ventilation and perfusion before structural changes in the lungs were detected by CT scans. The study concluded that V/Q imaging utilising Technegas could detect early changes to the lung caused by cigarette smoke exposure.

Asthma[8,9]

The primary functional abnormality in asthmatic airways is presumably the generalised narrowing in response to a variety of inhaled irritants. A SPECT lung scan takes around 20 minutes. Therefore, the inhaled substance must enter the lungs and remain in situ for at least 20 minutes while the scan is being developed. Technegas is currently the only known imaging isotope used for ventilation that has these properties. Technegas can provide the clinician the ability to visualise and quantify lung ventilation by region.

Chronic Thrombo-Embolic Pulmonary Hypertension (CTEPH)[10]

Technegas has demonstrated superior predictive value for detection of CTEPH in clinical tests as compared to other technologies

A study was conducted at Charles Sturt University, Australia in September 2020, aimed at evaluating the performance of different ventilation methods in detecting CTEPH. Out of the 64 positive cases for CTEPH, CTPA was positive in only 18 cases while the V/Q was positive in all the 64 cases.

Compared to Tc-99m DTPA aerosol, Technegas demonstrated superior positive predictive value, sensitivity and specificity with comparable negative predictive value and accuracy, thereby concluding that in suspected CTEPH, a high/intermediate V/Q report is consistent with a positive diagnosis.

The use of Technegas for ventilation improves the positive predictive value and sensitivity over aerosol ventilation. This was an important finding as CTEPH is a potentially treatable condition.

Potential applications of V/Q SPECT (/CT) in other indications[11]

- Diagnosis and follow-up of Pulmonary Hypertension.
- Preoperative assessment of homogeneous Endoscopic Lung Volume Reduction (ELVR) candidates.
- Preoperative assessment of lung resection candidates with borderline pulmonary reserve.
- Planning radiation therapy to target tumours while preserving functional lung zones.
- Diagnosis and monitoring of COVID-19 patients. The Technegas ventilation procedure is faster and improves compliance and hence decreases the risk of room and staff contamination. The apparatus is single-use without recirculation and poses no contamination risk between patients[12].

[7] See *Cyclopharm's Technegas has potential for early detection of lung disease,* Proactive, 2 May 2013.
[8] See *Bioshares 2017 Biotech Summit* by Cyclopharm Limited, 22 July 2017.
[9] See *Investigation of airway closure in asthma using Technegas and simultaneous emission/transmission SPECT*, Australian National University, January 2019.
[10] J. Nucl. Med. Radiol. Radiat. Ther.2020; DOI: 10.24966/NMRR-7419/100020.
[11] See *Beyond PE applications of V/Q SPECT(/CT)* in Cyclopharm's Investor Update Bell Potter HealthCare Conference, 10 November 2021.
[12] See *Lung Imaging and COVID-19 Impact*, Cyclomedica.

Cyclopharm's investment in 'Beyond PE' trials[13]

The company has tie-ups with several leading universities for its 'Beyond PE' projects

In its quest to develop Technegas applications beyond PE, the company has invested over A$500,000 in clinical trials during 2019–2020 to substantiate the different cases. It has several research projects in its pipeline (Figure 5) that are being conducted in collaboration with leading academic institutions. These projects were impacted due to the COVID-19 pandemic as recruitment of patients slowed down, but this is now expected to pick up pace.

Figure 5: Cyclopharm's 'Beyond PE' research projects

Study/Institution	Indication	Status: February 2021
CYC-009	Ventilation comparison – Technegas vs. Xe133	Primary and secondary endpoints met. Results reported in September 2020
HMRI	Asthma/COPD	Fully recruited 100 patients. First publication pending
McMasters University	Lung resection surgery	Recruitment resumed. 19 of 115 patients recruited
McMasters University	COVID-19 related lung ventilation and perfusion injury	Recruiting - 25 of 92 patients recruited
CHUM	COPD	Recruitment resumed - 4 of 30 patients recruited
Woolcock Institute	Asthma/COPD	5 of 70 patients recruited
Dalhousie University	Lung transplant complications	Recruitment resumed - 12 of 30 patients recruited

Source: Company

[13] See *Expand the use of Technegas™ – Beyond PE in Annual Report 2020* by Cyclopharm Limited, 29 March 2021.

Highly experienced leadership

Cyclopharm's top management is highly experienced with extensive knowledge in the healthcare space. The leadership team's combined experience has been key to the company's strategy to grow globally and explore applications beyond PE. The current leadership team's composition is as below (Figure 6).

Figure 6: Board and management team members

Name	Designation	Affiliations (Current and Past)
David Heaney	Non-Executive Chairman	Colorpak Ltd, National Australia Bank
James McBrayer	Managing Director and CEO	Lipa Pharmaceuticals, Brambles Cleanaway, Syncor
Dianne Angus	Independent Non-Executive Director	Imagion Biosystems, Neuren Pharmaceuticals, Alterity Therapeutics, Florigene Ltd

Source: Company

David Heaney has over 40 years' experience in the field of wholesale banking and finance, handling senior executive roles in National Australia Bank Ltd and subsidiaries. Mr. David was appointed to the board in November 2006 and served as the Chairman of the Audit and Risk Committee until 28 February 2019.

James McBrayer joined the board in June 2008 as Managing Director and was appointed as the Company Secretary on March 2011. He has been working in the field of nuclear medicine for over 30 years and is a trained Nuclear Pharmacist. Prior to joining Cyclopharm, Mr. James served as the Managing Director at Lipa Pharmaceuticals.

Dianne Angus has extensive experience in the field of biotechnology, corporate strategy and product development. Ms. Dianne was appointed to the board in August 2021. She is a registered patent attorney and holds a Master's degree in Biotechnology, Bachelor of Science and a Graduate Diploma in Intellectual Property Law.

Valuing Cyclopharm

We have valued Cyclopharm using a DCF approach based on the following key assumptions:

- Revenue streams: The key revenue streams assumed in our model include sale of generators and consumables as well as service revenue.
- US entry: We are assuming entry into the lucrative US market by H1 2023, and growth to accelerate thereafter over the next 4-5 years.
- Base vs. Bull case: Under our base case, we expect the group revenue for Cyclopharm to grow at a CAGR of 21.9% over 2021-2026. This is all organic growth, to be achieved without the aid of any acquisition. In our bull case, we forecast a higher group CAGR of 24.2% in the same period – again all organic.
- Discount rate: We have applied a discount rate of 10.1%, appropriate in our view for a 'Medium' risk rating[14].
- Capital structure: It has been assumed that the company will remain heavily reliant on equity funding for its US growth, in line with its capital raising in February 2021.
- Terminal growth rate: We have assumed this as 3.0% keeping in mind the US growth plans and the uniqueness of the company's technology.

Entry into US should drive the company's valuation

Our DCF model yields a value of A$2.74–3.33 per share (Figure 7). We believe this is a conservative estimate as we have not factored in any benefits from the potential growth in the addressable market for PE diagnosis beyond 5 years as well as the 'Beyond PE' initiatives of Cyclopharm.

Figure 7: DCF valuation – Base and Bull case

BASE CASE

Cyclopharm (A$m)	
Enterprise value	221.0
Net debt (cash)	(24.7)
Minority Interest	-
Other Investments	-
Equity value	**245.8**
Share outstanding (Diluted, million)	89.6
Implied price (A$)	2.74
Current price (A$)	1.48
Upside (%)	85.4%

BULL CASE

Cyclopharm (A$m)	
Enterprise value	273.4
Net debt (cash) (m)	(24.7)
Minority Interest (m)	-
Other Investments (m)	-
Equity value	**298.1**
Share outstanding (Diluted, million)	89.6
Implied price (A$)	3.33
Current price (A$)	1.48
Upside (%)	124.9%

Source: Pitt Street Research

[14] For a relevant discount rate, we use varying WACCs depending on the risk for Life Science companies. We start with an RFR of the Australian ten-year bond rate (1.7%) and an ungeared beta of 1.1 but use a variable MRP of 7.5-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies). Ordinarily we regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.

Key share price catalysts

Cyclopharm's stock is currently trading below our base case valuation. We think the stock can re-rate to our valuation range based on positive news flow around the FDA approval, signing of major partnership or distribution deals, value-enhancing acquisitions and better-than-expected results from Europe and Canada.

Figure 8: Key financial data

Year to December (AUD)	2020	2021	2022F	2023F	2024F	2025F	2026F
Group Revenue (m)	17.7	20.1	23.7	29.9	36.6	44.8	54.2
YoY growth	3.8%	13.9%	17.7%	26.1%	22.4%	22.3%	21.1%
EBITDA (m) Adjusted	(4.7)	(3.5)	0.2	2.7	6.2	10.9	15.0
Net Profit (m) Adjusted	(6.0)	(5.0)	(1.0)	1.2	3.6	6.8	9.7
EBITDA Margin (%)	NM	NM	0.9%	8.9%	16.9%	24.3%	27.8%
RoA (%)	NM	NM	NM	2.1%	6.1%	10.4%	13.0%
Net Gearing (%)	16.5%	-57.4%	-48.7%	-43.0%	-40.0%	-39.5%	-40.6%
EPS before extr. & amort.	(7.9)	(5.6)	(1.1)	1.3	4.0	7.6	10.8
EPS (cents)	(7.9)	(5.6)	(1.1)	1.3	4.0	7.6	10.8
DPS	NA	NA	NA	NA	NA	NA	NA
Price	2.50	1.64	1.48	1.48	1.48	1.48	1.48
M-Cap (m)	191.5	146.9	132.6	132.6	132.6	132.6	132.6
Net Debt (cash) (m)	2.8	(24.7)	(20.5)	(18.6)	(18.7)	(21.2)	(25.7)
Non-controlling interest (m)	NA	NA	NA	NA	NA	NA	NA
Provisions (m)	NA	NA	NA	NA	NA	NA	NA
EV (m)	194.3	122.2	112.1	114.0	113.8	111.4	106.8
EV/Sales	11.0x	6.1x	4.7x	3.8x	3.1x	2.5x	2.0x
EV/EBITDA	NM	NM	525.1x	42.8x	18.4x	10.3x	7.1x
P/E	NM	NM	NM	1.1x	0.4x	0.2x	0.1x

Source: Pitt Street Research

Key investment risks

The main risks that we see to our investment thesis include:

- **Execution risk:** The majority of future growth for the company is expected to come from the US market. Any interruption or delay in receiving the FDA approval will delay commercial progress and consequently jeopardise investor sentiment.
- **Competition:** As the global diagnostic imaging market expands, the larger (both regional and global) service providers will also try to increase their presence in niche segments. Cyclopharm will have to counter their financial and technological prowess to retain its market leadership.

Comparable companies

Cyclopharm has a unique technology proposition and currently there are no directly comparable competitors. However, in order to provide a sense of related entities in the market, we have compiled a list of firms in developed markets that are operating in the nuclear medicine field, but are not large-cap entities (Figure 9).

Figure 9: Comparable firms in nuclear medicine

Company	Code	Location	Market Cap (US$m)	Website
Lantheus Holdings Inc	NasdaqGM:LNTH	Massachusetts, US	2,018	www.lantheus.com
China Isotope & Radiation Corp	SEHK:1763	Beijing, China	957	www.circ.com.cn
Broncus Holding Corp	SEHK:2216	Zhejiang, China	286	www.broncus.com
Positron Corp	OTCPK:POSC	New York, US	14	www.positron.com
Curium Pharma	Private firm	Paris, France	NA	www.curiumpharma.com
Jubilant DraxImage	Private firm	Montreal, Canada	NA	www.draximage.com
Cyclopharm Ltd	ASX:CYC	New South Wales, Australia	100	www.cyclopharm.com

Source: S&P Capital IQ, Pitt Street Research

Lantheus Holdings develops, distributes and commercialises diagnostic image agents and products. It provides Definity, a microbubble ultrasound enhancing agent used in ultrasound exams of the heart; TechneLite, a technetium generator for nuclear medicine; Xe-133 to assess pulmonary function; Neurolite to identify the area within the brain where blood flow has been blocked or reduced due to stroke; Cardiolite, an injectable Tc-99m-labeled imaging agent; and Relistor for opioid-induced constipation.

China Isotope & Radiation Corp engages in the research and development, manufacture and sale of diagnostic and therapeutic radiopharmaceuticals and radioactive source products for medical and industrial use in China. It operates through four segments — Pharmaceuticals, Radioactive Source Products, Irradiation and Independent Clinical Laboratory Services.

Broncus Holding Corp operates in the field of interventional pulmonology, providing lung solutions in China and internationally. The company markets LungPoint Virtual Bronchoscopic Navigation, a computer-assisted image-based navigation software system; LungPoint Plus, a system that provides real-time navigation within the airways for lung biopsy and other procedures; and LungPro, a virtual bronchoscopy navigation product.

Positron Corp specialises in the business of cardiac positron emission tomography (PET) imaging in the US. It offers PET molecular imaging systems, clinical and support services, automated radiopharmaceutical systems as well as radiopharmaceuticals and radioisotope processing and production.

Curium Pharma specialises in the production and supply of radioactive tracers used in nuclear medicine. Its products aid in early diagnosis of cancer as well as heart, brain and bone diseases. With manufacturing facilities across Europe and US, Curium Pharma supports over 14 million patients around the world with SPECT, PET and therapeutic radiopharmaceuticals.

Jubilant DraxImage, doing business as Jubilant Radiopharma, develops, manufactures and commercialises radiopharmaceuticals. One of its product offering is Draximage DTPA, which is a widely-used nuclear medicine imaging agent that has been witnessing expanding indications for lung ventilation assessments. Draximage DTPA is essentially a kit for the preparation of Tc-99m pentetate injection.

Appendix I – Glossary

Chronic Obstructive Pulmonary Disease (COPD): COPD is a chronic inflammatory lung disease which includes chronic bronchitis and emphysema; it is a long-term lung disease that that causes obstructed airflow from the lungs. Symptoms include breathing difficulty, cough, mucus (sputum) production and wheezing.

Chronic Bronchitis: Coughing, shortness of breath and mucus that lingers at least three months for two years in a row, are symptoms of having chronic bronchitis. Hair-like fibres, called cilia, line the bronchial tubes and help move mucus out. When a person has chronic bronchitis, they lose the cilia. This makes it harder to get rid of mucus, which makes the patient cough more, creating more mucus.

Chronic Thrombo-Embolic Pulmonary Hypertension (CTEPH): CTEPH refers to high blood pressure in the lungs' arteries. It is a rare and progressive form of pulmonary hypertension (PH). CTEPH is caused by blood clots that do not dissolve in the lungs. These clots cause scar-like tissue that clogs up or narrows the small blood vessels in the lungs.

Computed Tomography (CT): A CT scan combines a series of X-ray images taken from different angles around the body and uses computer processing to create cross-sectional images (slices) of the bones, blood vessels and soft tissues inside your body. CT scan images provide more-detailed information than plain X-rays.

Computed Tomography Pulmonary Angiogram (CTPA): A CT pulmonary angiogram (or CTPA) is a CT scan that looks for blood clots in the lungs. A CT pulmonary angiogram takes pictures of the blood vessels that run from the heart to the lungs (the pulmonary arteries).

Emphysema: This results from damage to the lungs' air sacs (alveoli) that destroy the walls inside them and causes them to merge into one giant air sac. Damaged alveoli can make the lungs stretch out and lose their springiness. Air is trapped in the lungs and one cannot easily breathe under such circumstances.

Pulmonary Embolism (PE): Pulmonary embolism is caused when a blood clot (thrombus) becomes lodged in an artery in the lung and blocks blood flow to the lung. Pulmonary embolism usually arises from a thrombus that originates in the deep venous system of the lower extremities; however, it rarely also originates in the pelvic, renal, upper extremity veins, or the right heart chambers.

Single Photon Emission Computed Tomography (SPECT): SPECT is a nuclear imaging scan that integrates computed tomography (CT) and a radioactive tracer. The tracer is what allows doctors to see how blood flows to tissues and organs. It is an imaging test that shows how blood flows to tissues and organs. It may be used to help diagnose seizures, stroke, stress fractures, infections, and tumours in the spine.

Single Photon Emission Computed Tomography Ventilation/Perfusion (SPECT V/Q) imaging: Single photon emission computed tomography (SPECT) provides high contrast 3D images of the regional distribution of a radiotracer. SPECT is a widely used technique in pulmonary investigations of the ventilation (V) and perfusion (Q) in the adult patient, mainly in the diagnosis of pulmonary embolism. A VQ scan consists of two parts. In the first part, radioactive material is breathed in and pictures or images are taken to look at the airflow in the lungs. In the second part, a different radioactive material is injected into a vein in the arm, and more images taken to see the blood flow in the lungs.

Technetium (Tc-99m): Technetium (chemical symbol Tc) is a silver-grey, radioactive metal. It occurs naturally in very small amounts in the earth's crust, but is primarily man-made. Tc-99m is produced as Mollybdenum-99 (Mo-99) decays. Mo-99 is produced in via nuclear fission from enriched Uranium. Tc-99m It has a short life (6 hours) and does not remain in the body or the environment for long.

Tc-99m DTPA (diethylene-triamine-pentaacetate acid): It is one of the technetium radiopharmaceuticals used in renal imaging and primarily used to measure the glomerular filtration rate (GFR). When placed in a nebulizer and inhaled in can also be used to image the lungs.

Xenon 133 (Xe-133): Xe-133 is a radioactive isotope of a noble gas. It can be inhaled into the lungs and washes out quickly in a normal lung, although there is persistent activity (gas trapping) in parts of the lung affected by airway disease, such as asthma or COPD. It may also be used to assess cerebral blood flow.

Appendix II – Capital Structure

Class	In millions	% of fully diluted	Note
Quoted Securities			
Ordinary shares on issue	93.37	100.0%	
Unquoted			
Options and performance rights	-	0.0%	
Fully diluted shares	**93.37**		

Source: Company

Appendix III – Major Shareholders

The company has seven key shareholders, many of them institutional investors:

- Anglo Australian Christian and Charitable Fund, Endowment Arm (14.1%).
- Barings Acceptance Ltd (12.3%).
- Australian Ethical Investment Ltd (9.9%).
- Chemical Trustee Ltd (9.8%).
- Karst Peak Capital (9.5%).
- CVC Ltd (7.1%).
- James McBrayer (Managing Director and CEO, 5.5%).

Appendix IV – Analysts' Qualifications

Stuart Roberts 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 speciality 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 over 2015–2016 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 Sciences 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 Sciences companies.
- Since 2018, Stuart has led Pitt Street Research's Resources Sector franchise, spearheading research on both mining and energy companies.

Marc Kennis has been an equities analyst since 1996.

- Marc obtained an MSc in Economics from Tilburg University, Netherlands, in 1996 and a post graduate degree in investment analysis in 2001.
- Since 1996, he has worked for a variety of brokers and banks in the Netherlands, including ING and Rabobank, where his main focus has been on the technology sector, including the semiconductor sector.
- After moving to Sydney in 2014, he worked for several Sydney-based brokers before setting up TMT Analytics Pty Ltd, an issuer-sponsored equity research firm.
- In July 2016, with Stuart Roberts, Marc co-founded Pitt Street Research Pty Ltd, which provides issuer-sponsored research on ASX-listed companies across the entire market, including technology companies.

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