Cyclopharm

27 July 2019 Bioshares Conference Queenstown New Zealand James McBrayer, CEO & Managing Director

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All references to dollars unless otherwise specified are to Australian dollars.

TEC€NEGAS[™] Bioshares 2019 Session Brief – "On the Cusp"

- 1. The competitive analysis of lung imaging modalities used to assess Pulmonary Embolism
- 2. The comparison of each imaging technique to include the existing and future competitive advantage of VQ/SPECT and hybrid approaches including with low dose CT.
- 3. Publication strategy to include leveraging recent guidelines
- 4. Update on the USFDA approval process for Technegas

CYCLOPHARM INVESTMENT CASE TECHNEGAS"



Profitable & Growing MedTech underlying business is cash

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business is cash positive and issuing dividends

First in class proprietary product sales to 57 countries with 4.2 million studies to date

Recurring revenue from consumables similar to an annuity model

USFDA approval

set to quadruple the size of the existing PE business and further leverage penetration into the CTPA market

Optionality

into indications beyond PE into chronic respiratory disease management could deliver exponential growth

Company Overview

Technegas is a substantially de-risked commercial proposition with significant upside in the US market

- Technegas revenues generated in 57 countries
- Over 195,000 patient procedures in 2018
- Over **4,200,000 patient procedures** since 1986
- ~1,600 Technegas generators sold globally
- CYC is growing, underlying business is profitable and a dividend paying company
- Stable gross margins of greater than 80%
- Around 80% of historical revenue is recurring consumable sales



Technegas around the world

Technegas was introduced to the medical community in 1986¹

Technegas revenues are generated in 57 countries

via a combination of direct and distributor sales models

Over 4.2 million patient procedures to date

1. Wiebe LI, et al. Current Radiopharmaceuticals 2010; 3(1): 49-59

Available

Coming Soon

What is Technegas?

Particle characteristics

Technegas is composed of Tc-99m cores encapsulated within layers of graphite to form individual hexagonal plate-like particles.¹

These particles agglomerate to reach a dynamic equilibrium with regard to particle size distribution best described as a bell shaped curve with an average size of 100nm.²



Manufacture and Distribution

Technegas is produced on site at the point of patient administration.

Technegas is manufactured by heating Technetium-99m in a carbon crucible within an argon environment for a few seconds at 2,750 degrees Celsius.³

Because of the very small particle size, Technegas is distributed in the lungs almost like a gas and deposited in alveoli by diffusion, providing for SPECT³ ventilation imaging

Particles remain in the lung until they are cleared by ciliary action or phagocytosis⁴.



1. Wiebe Ll, et al. Current Radiopharmaceuticals 2010; 3(1): 49-59 2. Lemb M, et al. Eur J Nucl Med 1993; 20(576-579) 3. Leblanc M, et al. CANM guidelines; Nov 2018: www.canm-acmn,ca/guidelines 4. Möller W, et al. Am J Respir Crit Care Med 2008; 177: 426-432

Pulmonary Embolism

~3 million cases of PE p.a.

> but could be much higher



of pulmonary embolisms are fatal if left untreated

Symptoms

are varied with diagnosis confirmed either through CTPA or a nuclear medicine ventilation-perfusion study



Nuclear Medicine

using 3-D imaging is the most accurate method of diagnosis

Benefits of using Technegas



Superior to competitive nuclear medicine products



Xenon - 133



F

True radioactive gas inhaled with full face mask



Constant inhale -exhale breathing for 15 mins



No 3D images limited to planar imaging resulting in inferior clinical outcomes

Requires special <u>/!\</u> rooms

to contain radioactive gas in the event of a release

DTPA Tc99m



Wet Aerosol impacts efficacy and clinician interpretations



Creates hotspots

in presence of lung diseases, which is a frequent comorbidity in PE

Diagnosing Pulmonary Embolism in the USA



СТРА

High radiation burden

CTPA delivers at least 27 times more radiation to the breast as compared to V/Q SPECT¹

Contraindications

CTPA should not be performed with pregnancy¹⁻², renal impairment³, contrast media allergy³, diabetes⁴

Acute kidney injury (AKI)

AKI occurs in up to 13% of CTPA cases⁵

Lower clinical sensitivity

V/Q planar⁶ = 76% CTPA⁷ = 82% $V/Q SPECT^7 = 93\%$

Availability



Radiology ED services are generally provided 24/7 vs. nuclear medicine after hours on call service

1. Isidoro J, et al. Phys Med 2017; 41: 93-96 2. Bajc M, et al. Eur J Nucl Mol Imaging 2015; 42: 1325-1330

3. Miles S. et al. Chest 2009: 136: 1546-1553

4. Roach PJ, et al. J Nucl Med 2013; 54: 1588-1596 5. Doganay S, et al. Renal Failure 2015; 37(7): 1138-1144

Technegas is not commercially available in the USA.

6. Reinartz P. et al. J Nucl Med 2004: 45: 1501-1508 7. Hess S, et al. Semin Thromb Hemost 2016; 42(8): 833-845

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Nuclear Medicine Imaging Technology Has Evolved Beyond CTPA in Diagnosing PE

1986

Trinary interpretation of V/Q findings³

1. Gutte H, et al. Nucl Med Commun 2010; 31: 82-86

2. Roach PJ et al. Semin Nucl Med 2010; 40:397-407



3. Waxman AD, et al. J Nucl Med 2017; 58: 13N-15N 4. Roach PJ, et al. J Nucl Med 2013; 54:1588–1596

Radiation Dosimetry

A nuclear medicine V/Q scan is Exponentially Lower in dose than CTPA

Technique	Effective dose (mSv/MBq)	Effective dose (mSv)	Breast absorbed dose (mGy)	Lung absorbed dose (mGy)
Ventilation Technegas (20MBq) ¹⁻³	0.015	0.30	0.13	2.2
Ventilation ^{99m} Tc-DTPA (20MBq) ¹⁻²	0.007	0.14	0.04	0.30
Ventilation ¹³³ Xe (800MBq) ¹	0.0014	1.12	0.09	0.89
Perfusion MAA (120MBq) ¹⁻³	0.012	1.44	0.60	7.92
Low dose CT non-contrast ⁴	NA	~ 1.00	-	-
CTPA 16 slice ¹	NA	14.4	10-20	10
CTPA 64 slice ^{1,3}	NA	19.9	22	20

Table: Radiation dosimetry data were sourced from Bajc M et al 2009 ¹; Schembri GP et al 2010 ², Isidoro J et al 2017 ³ and Ling IT et al 2012 ⁴.

1. Bajc M, et al. Eur J Nucl Med Mol Imaging 2009; 36(8): 1356-1370

2. Schembri GP, et al. Semin Nucl Med 2010; 40: 442-454

3. Isidoro J, et al. Phys Med 2017; 41: 93-96
 4. Ling IT, et al. Intern Med J 2012; 42(11): 1257-1261

Nuclear Medicine provides better diagnostic outcomes in Diagnosing PE



Table: Diagnostic ability of V/Q SPECT/CT¹, V/Q SPECT¹, CTPA¹ and V/Q Planar² to detect PE (adapted from Hess and al, 2016¹ and from Reinartz et al, 2004²)

V/Q SPECT and V/Q SPECT/CT have shown that V/Q SPECT/CT is **superior** in most clinical settings with better overall diagnostic performance¹.

In situation of acute PE, chronic PE pregnancy, paediatrics and the COPD population, V/Q SPECT, with or without lowdose CT, can be considered as a first-line investigation to detect PE³ due to:



Its higher accuracy, sensitivity and negative predictive value when compared to CTPA³

Its low radiation and no adverse reactions³

1. Hess S, et al. Semin Thromb Hemost 2016; 42(8): 833-845

2. Reinartz P, et al. J Nucl Med 2004; 45: 1501-1508

3. Leblanc M, et al. CANM guidelines; Nov 2018: www.canm-acmn.ca/guidelines



TECPINEGAS **Coming to America** 0080

Technegas FDA Clinical Trial Process and Design

Study Sites USFDA Clinical trial¹ registered at: https://clinicaltrials.gov/ct2/show/NCT03054870?term=technegas&rank=1 Non-inferiority structural ventilation study comparing Xe133 vs. Technegas¹ Planned 240 patient study at 9 clinical sites **154 Patients** enrolled as at 25 July 2019 Currently compiling a 505(b)2 New Drug Application for submission Clinical Trial enrollment will continue whilst the 505(b)2 submission is being reviewed





1. ClinicalTrials.Gov – A comparison of Technegas and Xenon-133 Planar Lung Imaging in Subjects referred for Ventilation Scintigraphy. https://clinicaltrials.gov/ct2/show/NCT03054870?term=technegas&rank=1

What the guidelines say about Technegas:

Endorsed by the guidelines from the European⁶ and the Canadian⁴ Associations of Nuclear Medicine (EANM & CANM)

- " Using 99m-Tc-Technegas is according to clinical experience better than the best aerosols "
- " Technegas is preferred to DTPA in patients with COPD "
- " For ventilation, 99m-Tc Technegas is the best-aerosol particularly in patients with COPD "
- " Liquid aerosols are inferior for SPECT and should not be used unless Technegas is not available "
- " The best widely available agent for ventilation is 99m-Tc-Technegas "
- " Because of the very small particle size, this agent is distributed in the lungs almost like a gas and deposited in alveoli by diffusion, where they remain stable, thus providing the best possible images for ventilation SPECT "
- " Another advantage is that only a few breaths are sufficient to achieve an adequate amount of activity in the lungs, reducing time and personnel exposure to radiation "
- " Technegas is considered the <u>agent of choice</u> in the COPD population as there is less central airway deposition, better peripheral penetration, and it does not wash out as quickly as traditional aerosols "

^{4.} Leblanc M, et al. CANM 2018; https://canm-acmn.ca/resources/Documents/Guidelines_Resources/MasterDocument_Final_Nov_21_incl-Exec-Sum 6. Bajc M, et al. Eur J Nucl Med Mol Imaging 2009; 36(8): 1356-70; https://eanm.org/publications/guidelines/gl pulm_embolism_part1.pdf

Technegas in the recent literature

- 1. King GG, et al. Dismantling the pathophysiology of asthma using imaging. Eur Respir Rev 2019; 28(152): pii: 1801111
- 2. Yang L, et al. Changes in ventilation and perfusion following lower lobe endoscopic lung volume reduction (ELVR) with endobronchial valves in severe COPD. Clin Respir J 2019; [Epub ahead of print]. 18.
- 3. Kjellberg M, et al. Ten-year-old children with a history of **bronchopulmonary dysplasia** have regional abnormalities in ventilation perfusion matching. Pediatr Pulmonol 2019; 54(5): 602-609
- Paludan JPD, et al. Improvement in image quality of Tc-99m-based ventilation/perfusion single-photon emission computed tomography in patients with chronic obstructive pulmonary disease 20. through pretest continuous positive airway pressure treatment. World J Nucl Med 2019; 18(2): 185–21. 186
- 5. Myc LA, et al. Role of medical and molecular imaging in **COPD.** Clin Transl Med 2019; 8(1): 12
- 6. Ling T, et al. Ventilation/perfusion SPECT/CT in patients with severe and rigid scoliosis: An evaluation by relationship to spinal deformity and lung function. Clin Neurol Neurosurg 2019; 176: 97-102
- 7. Farrow CE, et al. SPECT Ventilation imaging in asthma. Semin Nucl Med 2019; 49(1): 11-15
- 8. Mortensen J, et al. Lung scintigraphy in COPD. Semin Nucl Med 2019; 49(1): 16-21
- 9. Sanchez-Crespo A, et al. Lung VQ SPECT in **infants and children** with nonembolic chronic pulmonary disorders. Semin Nucl Med 2019; 49(1): 37-46
- 10. Bajc M, et al. Ventilation/Perfusion SPECT Imaging Diagnosing other cardiopulmonary diseases beyond PE. Semin Nucl Med 2019; 49(1): 4-10
- 11. Sanchez-Crespo A, et al. Lung scintigraphy in the assessment of aerosol deposition and clearance. Semin Nucl Med 2019; 49(1): 47-57
- 12. Bailey DL, et al. V/Q SPECT Normal Values for Lobar Function and Comparison With CT Volumes. Semin Nucl Med 2019; 49(1): 58-61
- 13. Lawrence NC, et al. Ventilation perfusion single photon emission computed tomography: Referral practices and diagnosis of acute pulmonary embolism in the quaternary clinical setting. J Med Imaging 28. Radiat Oncol 2018; 62(6): 777-780.
- 14. Leblanc M, et al. CANM Guidelines for Ventilation/Perfusion (V/P SPECT) in pulmonary embolism.<u>www.canm-acnm.ca/guidelines</u>
- Hsu K, et al. Endoscopic Lung Volume Reduction in COPD: Improvements in Gas Transfer Capacity Are 30. Associated With Improvements in Ventilation and Perfusion Matching. J Bronchology Interv Pulmonol. 2018; 25(1): 48-53

- 16. Dimastromatteo J, et al. Molecular imaging of pulmonary diseases. Respir Res 2018; 19(1): 17
- 17. Jögi J, et al. Diagnosing and grading heart failure with tomographic perfusion lung scintigraphy: validation with right heart catheterization. ESC Heart Fail 2018; 5(5): 902-910
 - . Waxman AD, et al. Appropriate use Criteria for Ventilation-Perfusion imaging in Pulmonary embolism : Summary and Excerpts. J Nucl Med 2017; 58(5): 13N-15N
- 19. Isidoro J, et al. Radiation dose comparison between V/P SPECT and CT-angiography in the diagnosis of pulmonary embolism. Phys Med 2017; 41: 93-96
- 20. Righini M, et al. Diagnosis of acute pulmonary embolism. J Thromb Haemost. 2017; 15: 1251-1261
- 1. Le Roux PY, et al. New developments and future challenges of nuclear medicine and molecular imaging for pulmonary embolism. Thromb Res 2018; 163: 236-241
- 22. Farrow CE, et al. Peripheral ventilation heterogeneity determines the extent of bronchoconstriction in asthma. J Appl Physiol (1985). 2017; 123(5): 1188-1194
- 23. Tulchinsky M, et al. Applications of Ventilation-Perfusion Scintigraphy in Surgical Management of Chronic Obstructive Lung Disease and Cancer. Semin Nucl Med. 2017; 47(6): 671-679
- 24. Cheimariotis GA, et al. Automatic lung segmentation in functional SPECT images using active shape models trained on reference lung shapes from CT. Ann Nucl Med. 2017; 10: 25-30
- 25. Bajc M et al. Identifying the heterogeneity of **COPD** by V/P SPECT: a new tool for improving the diagnosis of parenchymal defects and grading the severity of small airways disease. Int J Chron Obstruct Pulmon Dis 2017; 12: 1579-1587
- 26. Nasr A, et al. Ventilation defect typical for **COPD** is frequent among patients suspected for pulmonary embolism but does not prevent the diagnosis of PE by V/P SPECT. EC Pulmonology and Respiratory Medicine. 2017; 4(3): 85-91
- Provost K, et al. Reproducibility of lobar perfusion and ventilation quantification using SPECT/CT segmentation software in lung cancer patients. J Nucl Med Technol 2017; 45(3): 185-192
 Metter DF, et al. Current status of ventilation-perfusion scintigraphy for suspected pulmonary embolism. AJR Am J Roentgenol 2017; 208(3): 489-494
- 29. Stubbs M, et al. Incidence of a single subsegmental mismatched perfusion defect in SPECT and planar ventilation/perfusion scans. Nucl Med Commun 2017; 38(2): 135-140
 - El-Barhoun EN, et al. Reproducibility of a **semi-quantitative lobar pulmonary ventilation** and perfusion technique using SPET and CT. Hell J Nucl Med 2017; 20(1): 71-75

Reclaiming and Expanding Pulmonary Imaging

Education

Educating referring physicians to the facts, benefits and capabilities of nuclear medicine will bring back lung imaging to nuclear medicine

Utilizing Available Technology

Leveraging the state of the art techniques to include SPECT, SPECT-CT & Quantification Software

CYC Research Strategy Beyond PE

Exploring new methods and techniques to engage specialists and develop new clinical applications

CYC Publication Strategy Beyond PE

Extending the reach of journal articles beyond the nuclear medicine community.... i.e. Respiratory Medicine, Emergency Medicine & Cardiology



The Canadian Association of Nuclear Medicine Association canadienne de médecine nucléaire



TECANEGAS[™]: Beyond PE



disease?

Clinical Trials Sponsored by Cyclomedica

- Hunter Medical Research Institute (Newcastle, AU): Diagnosis and response to therapy in severe asthma and COPD¹
- Woolcock Institute (Sydney, AU): Diagnosis and response therapy in mild to moderate COPD²
- CHUM (Montreal, CA): Early detection of COPD in asymptomatic smokers³
- Dalhousie (Halifax, CA): Post-lung transplant patients

Clinical Trials Under Discussion with Cyclomedica

- Australia: Clinical utility of Technegas in occupational lung diseases such (e.g. silicosis and coal worker's pneumoconiosis)
- Canada: Lung cancer patients pre and post lung resection

Other Non-Sponsored Clinical Initiatives

- Macquarie University (Sydney, AU): ELVR with endobronchial valves in severe COPD patients
- Macquarie University (Sydney, AU): Bronchial Thermoplasty procedure in asthma patients

1. ACTRN12617001275358 - Can functional lung ventilation imaging identify treatable traits in obstructive airway 2. http://investor.cyclopharm.com/site/PDF/1561 0/BetterDefiningAirwaysDiseasewithTechnegas 3. https://ichgcp.net/clinical-trials-registry/NCT03728712

Building from a strong & well established foundation

Near term opportunities providing significant growth potential beyond PE toward patient management



TEC/NEGAS Three Value Horizons



Technegas is not commercially available in the USA.

*USA Revenue Estimates



Cyclopharm

Thank You

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Appendix Section

FY2018 Results Highlights

Group Sales Revenue

Gross Margin

Net Loss After Tax

Interim Dividend

Underlying Technegas EBITDA¹

FDA Trial expenses

Strong balance sheet²

Guidance Affirmed

\$13.40 million

\$10.85 million

(\$0.04) million including USFDA investment

1.0 cents per share

\$1.90 million

(\$2.96) million

\$9.19 million of cash reserves as @ 31 Jan 2019

The Board expects continuing modest growth in underlying Technegas volumes from existing markets for FY19

Note 1: Underlying Results represent results from the division excluding R&D tax incentive, reversal of contingent consideration, FDA expenses, Pilot Clinical Trial expenses and net expenses for Germany Note 2: Cash reserves as at 31 December 2018 was \$5.85 million

Group Underlying Performance

Solid Underlying Financial Results

Year ended 31 December (\$000's)	2018	2017
Consolidated sales	13,404	13,189
Gross margin	10,855	10,740
Gross margin % sales	81.0%	81.4%
Consolidated EBITDA	655	1,043
Add back:		
CPET / Ultralute [™] division EBITDA	335	457
Reversal of contingent consideration	(314)	-
Unrealised gain on forward exchange contract	(275)	-
Expenses net of writebacks for Germany	410	677
FDA expenses and other pilot trial expenses	3,216	2,855
R&D Tax Incentive	(2,122)	(2,391)
Technegas Underlying EBITDA	1,905	2,641

During the year, CYC continued to implement its strategic priorities, which are to:

- Accelerate the path to regulatory approval to sell Technegas into the world's largest and new highly prospective US market;
- 2. Pursue sales of Technegas in new applications: Chronic Obstructive Pulmonary Disease ("COPD") and Asthma which are significantly larger markets than the Pulmonary Embolism market where CYC traditionally operates;
- Identifying, developing and commercialising complementary innovative technology such as Ultralute[™]; and
- 4. Leveraging our core global regulatory strengths, fiscal discipline, strong balance sheet and welldeveloped expertise in nuclear medicine and pulmonary healthcare to seek out complementary technologies and businesses.

Group Balance Sheet

Financial Foundation to Leverage Growth Strategy

Year ended 31 December (\$000's)	2018	2017
Cash	5,855	8,690
Other current assets	9,600	8,139
Non-current Assets	8,082	6,548
Total Assets	23,537	23,377
Current Liabilities	5,219	5,212
Non-current Liabilities	1,302	916
Total Liabilities	6,521	6,128
Net Assets	17,016	17,249

During the year, CYC continued to implement its strategic priorities, which are to:

- Low debt & cash on hand provides balance sheet and funding flexibility
- Funding used toward USFDA clinical trial enrolment and New Drug Application submission
- Strong financial position supports ongoing investment in R&D and expansion into new markets and indications

Group Cash Position

Cash Position Funding Growth

Year ended 31 December (\$000's)	2018	2017
Operating Activities	(1,107)	(682)
Investing Activities	(1,403)	(1,136)
Financing Activities	(353)	5,828
Net (Decrease) / Increase in Cash	(2,863)	4,010
Opening Cash	8,690	4,591
Foreign Exchange	28	89
Closing Cash @ 31 December (\$000's)	5,855	8,690
Closing Cash @ 30 April 2019 (\$000's)	7,137	

- Capital Raising \$6.59 m June 2017 with 90%
 Shareholder Participation
- Benefited from expanded R&D tax Incentive Program resulting in Other Income of \$2.12 million

Pulmonary Imaging With

TEC€NEGAS™

Hybrid V/Q SPECT/CT

V/Q SPECT provides **functional** information on ventilation and perfusion of the lungs¹⁴⁻¹⁵

Low-dose CT provides anatomical information such as fissures delineation¹⁶

Combination of functional and anatomical information allow for objective results through quantitative software¹⁵⁻¹⁶



Ventilation SPECT





Lobar distribution of ventilation



Percentages, volumes and counts of individual lobes (Images and 3D quantification provided by MMI)

IMPROVES DIAGNOSTIC CAPABILITIES AND OFFERS ANATOMICALLY-BASED QUANTIFICATION OF LOBAR CONTRIBUTION FOR INTERVENTIONAL THERAPIES

- 14. Reinartz P, et al. J Nucl Med 2004; 45: 1501-1508
- 15. King GG, et al. Semin Nucl Med 2010; 40(6): 467-473
- 16. Provost K, et al J Nucl Med Technol 2017; 45(3): 185-192

Treatment response in asthma patient



Images and data were kindly provided by the Woolcock Institute of Medical Research

VENTILATION SPECT/CT TO MONITORE TREATMENT RESPONSE IN PATIENTS WITH LIFELONG ASTHMA

Planning lung volume reduction surgery



CLINICAL HISTORY

Male patient of 64 years old with emphysema

REFERRAL

Assessment of lung ventilation function before planning endoscopic lung volume reduction

PROTOCOL

VQ SPECT/CT imaging with Technegas as ventilation agent



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SAGITTAL FUSION



UPPER LOBES TRANSVERSE FUSION



LOWER LOBES TRANSVERSE FUSION

The ventilation SPECT/CT scan reveals the function of the lower lobes is severely affected. The left oblique fissure is intact so the left lower lobe should be a good target lobe for endobronchial valves insertion.

Assessment for collateral ventilation was confirmed using CHARTIS assessment tool during the procedure.

Decision: 3 valves were inserted into the left lower lobe.

VENTILATION	RELATIVE UP	AKE [%]	
	Right	Left	
UPPER	45%	36%	
MIDDLE	12%	N/A	
LOWER	3%	4%	
TOTAL	60%	40 %	

Lobar 3D quantification provided by Hermes

VENTILATION SPECT/CT AS A TOOL TO ASSIST IN PREDICTING FUNCTIONAL LUNG VENTILATION PRIOR TO LUNG VOLUME REDUCTION