Analysis of Living Cell Technologies Limited

ASX:LCT; OTCQX:LVCLY.

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Prepared by
Pacific Channel Limited

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EXECUTIVE SUMMARY

Background

Living Cell Technologies (LCT) is an Australasian biotechnology company that is focused on discovering, developing and commercialising cell-based therapies. LCT has access to a breed of disease-free pigs, known as the Auckland Island pig, which is uniquely suitable for transplantation into humans.

LCT was founded to develop a type I diabetic treatment. This treatment uses islet cells from Auckland Island pigs encapsulated in IMMUPEL®. Through a series of transactions, LCT sold its interest in this technology to Otsuka Pharmaceutical Co., Ltd.

LCT is currently focused on developing treatments for Parkinson's disease (Parkinson's). LCT's enabling platform technology is IMMUPEL®, an alginate-coated capsule that enables the xenotransplantation of cells. LCT leverages this technology with the world-leading xenotransplantation advantages of Auckland Island pigs. For its Parkinson's treatment, NTCELL capsules contain clusters of neonatal porcine choroid plexus cells from the Auckland Island pigs encapsulated in IMMUPEL®. After transplantation into the brain, NTCELL produces factors which promote new central nervous system growth and repair disease-induced nerve degeneration.

On 23 July 2019, LCT announced that its Phase IIb trial of NTCELL was a success as all the primary outcomes were met and a clinically relevant effect was observed for both the NTCELL 40 and 80 capsule groups. The NTCELL 80 treatment showed sustained efficacy and clinical relevance from 52 until 104 weeks, when compared against the placebo group. LCT's expected next step will be to complete a Phase III trial to confirm NTCELL's ability to halt the progression of Parkinson's disease.

NTCELL trial results and implications

Pacific Channel has reviewed LCT's NTCELL phase I/IIa and phase IIb trial data. Pacific Channel's view is that a Parkinson's disease treatment does not need to improve patient health compared to baseline; it need only prevent further decline in their health. Given the small patient numbers it is remarkable that improvement in patients was statistically significant at 12, 18 months and remains clinically relevant at 24 months for NTCELL 80 compared to patients treated with a placebo. NTCELL is the only therapeutic asset that we have been able to identify globally that has shown clinically relevant improvements in patient health for Parkinson's Disease.

Pacific Channel has reviewed the design of the Phase I/IIa and Phase IIb trials. It is Pacific Channel's assessment that the Phase I trial is designed to determine safety and tolerability, while in LCT's own words the Phase IIb is "designed to confirm the most effective dose of NTCELL, define any placebo component of the response and further identify the initial target Parkinson's disease patient sub-group."
It is our view that the trial has indicated the efficacy of NTCELL 80 and its ability to halt Parkinson's disease, while meeting all its primary outcomes.

LCT's next steps should be to design a Phase III trial to demonstrate a significant improvement in patients in the larger numbers required to give regulators and medical community more confidence. We expect that such a trial would require 30-100 patients to be treated at the preferred dosage (this being within the range of patient numbers in other phase III Parkinson's studies) and is likely to be at the low end of this range given that efficacy has been already demonstrated with a smaller trial.

In LCT's Phase I/IIa trial, at 4 years post treatment, only 3 of 4 patients remained in the trial. Patient 1 had a "clinically significant improvement" from their entry score, while Patients 2 and 4, showed no substantial change from their entry score. We believe this is a positive outcome for LCT.

The Phase IIb trial has confirmed NTCELL 80 bilaterally as two implants spaced to the putamen as the most effective dose of NTCELL, at certain timepoints has enabled LCT to define efficacy and placebo contribution, and has identified the initial target Parkinson's disease patient sub-group as patients who do not respond to symptomatic treatment, and that are candidates for Deep Brain Stimulation (DBS). At 24 months, NTCELL continues to show a benefit.

Clinical analysis of the Phase IIb trial supports that NTCELL 80 can improve the health of Parkinson's disease patients at 12, 18 and 24 months, when compared to patients who received a sham treatment. Additionally, at 24 months following treatment NTCELL 40 and 80 were able to improve patients compared to baseline when assessed with Unified Parkinson's Disease Ration Scale (UPDRS), which is an industry standard measure for Parkinson's disease progression.

We believe that NTCELL 80 has met its endpoints in its Phase IIb trial, and therefore should be considered a promising therapy to treat and reduce the symptoms of Parkinson's disease.

Based on company disclosures we assume that LCT has provided data from its clinical trials to New Zealand's regulatory body, MedSafe. LCT asserts that it has met the 3 critical questions set by MedSafe to qualify for conditional approval. Given LCT's earlier announcements that it expected MedSafe to advise it on the regulatory pathway for NTCELL by May 2019 and our inference from LCT's 23 July 2019 announcement, it is likely in our view that MedSafe has not accepted LCT's filing for conditional approval, probably due to the small sample size of its successful Phase IIb study.

As Pacific Channel takes the view that NTCELL has met its endpoints in its Phase IIb trial, we assert that NTCELL should now be considered a phase III-ready asset. Mitigating this view, it should be noted that the Phase IIb trial was unblinded at the six-month mark. MedSafe will therefore need to make its own assessment about the quality of 18 and 24-month data. Assuming that the 24-month data does not contain any unannounced issues, in our view MedSafe is likely to consider NTCELL phase III ready. We also believe that is likely that an additional larger, confirmative Phase III trial, if successful, will achieve MedSafe approval of NTCELL as a Parkinson's treatment. However, LCT may not have the capability to communicate its progress and plans to capital markets as required to support a capital raise to fund a phase III trial.

Concerns

It is Pacific Channel's view that NTCELL trial data has not been adequately communicated to the market. Jargon-rich technical analysis, including graphs with non-intuitive scales are provided to shareholders. On these graphs, a decreasing slope can illustrate patient improvement, which is not clearly explained. Furthermore, there has been insufficient analysis provided in shareholder updates to explain the failure of the highest dose, NTCELL 120, in the Phase IIb trial. Patients who received the 120-dose had increased damage on the region of the brain that is involved in movement. Put simply, it appears the volume of cells in the NTCELL 120 dose causes inflammation. Accessing an explanation of this part of the trial - a recently-released scientific journal article - necessitated a subscription or one-off payment to a scientific journal database. We believe a clear explanation should be made to all shareholders and that this should not be limited to those able to access and interpret a scientific article.

We are concerned that the scientific analysis and interpretation of NTCELL trial data has been left to academic scientists and trial clinicians who have a function to assess science without clearly addressing the 'plain' outcome and potential commercial biotechnology impact. Experienced commercial biotechnology director(s) would be better suited to determining and communicating to capital markets whether NTCELL is a compelling commercial opportunity.

Despite our concerns, we commend LCT for achieving the recent trial results. However, we are concerned that LCT has neither announced the outcome of the clinical trial Phase IIb clearly enough, nor produced a clear plan to scale up production and commercialise NTCELL. Additionally, LCT has not communicated a clear plan to seek further funding, nor its vision to drive growth and ultimately increase shareholder value.

We note that LCT has licensed 4 small molecule assets for development. However, it is unclear how these assets fit into LCT's strategic plan or leverages its key competencies as they are unrelated both to its cell therapy platform technology or to LCT's current and past disease foci of Parkinson's disease and diabetes. From a technology perspective, the small molecule actives are a separate category of therapy, which represents a significant departure from the cell therapy approach that LCT has pursued over its 31-year history. With NTCELL's promising results, we question whether the license of these assets is a distraction, both in focus and financially, that does not leverage LCT's core competency of cell therapy development. While we acknowledge the desirability of a technology pipeline, we question why LCT has not sought to in-license or internally develop other cell therapies or associated assets such as cell encapsulation.

Specifically, we are aware that LCT has chosen to not explore another potential application of NTCELL with strategic parties, which, if pursued, could have been done at low cost to the company and had the potential in our view to create significant value for shareholders. We understand from the offeror, who is expert in the field of application, that LCT received an offer in 2017 to support the company to complete a clinical trial of transplantation of NTCELL to validate it as a treatment for a non-neurology related application that has a current overall treatment market of $US4.9b per annum. We understand that MedSafe would allow a Phase II study and that there is a large global unmet need for such a potential treatment for the targeted application.

PACIFIC CHANNEL'S ASSESSMENT

Pacific Channel has a long-standing interest in LCT as it has recognised the commercial potential for NTCELL. Pacific Channel is currently a shareholder through its own evergreen investment fund, Pacific Channel Holdings. Additionally, members of its staff hold shares in LCT. These interests represent over 1% of LCT's shares outstanding. Pacific Channel also has an interest in NZeno, which is a potential supplier to LCT as it believes in the commercial potential of Auckland Island pigs as a tissue source for xenotransplantation. Pacific Channel is currently a shareholder in NZeno through its own evergreen investment fund, Pacific Channel Holdings. Additionally, members of its staff hold shares in NZeno.

Pacific Channel's view is that Living Cell Technologies has poorly reported progress to shareholders over the past 17 months, which has not enabled financial investors to form an accurate assessment of the value of the company. Pacific Channel has released this report to provide the market with its views on the current status and potential of LCT and outline upcoming challenges that in our view have not been fully addressed by LCT's board. We believe that, with guidance from a reconfigured board of directors, LCT could, assuming continued positive clinical results, successfully commercialise NTCELL as a Parkinson's disease therapy. We aim for this document to help inform and precipitate what we believe are necessary changes to LCT to achieve this goal.

Pacific Channel's assessment is that LCT's board and management team has adequate corporate governance and academic scientific capability and have been effective stewards of the execution of the Phase I/IIa and Phase IIb NTCELL trials. However, with what we believe are questionable commercial and reporting decisions it is our view that LCT's board would benefit from the addition of further expertise in biotechnology commercialisation, capital markets, and investor relations. In particular, the new board member(s) need(s) to be well-known to specialist industry investors and investment banks to assist LCT in seeking additional capital to commercialise NTCELL. Pacific Channel has joined with other large shareholders to make a recommendation to the board that it appoint a new director with this expertise. These interests represent over 15% of shares in LCT. Despite discussions with the board, there has been limited engagement or any action from the LCT board transparent to shareholders to make any timely material changes. It is our view that LCT's directors have been delinquent in their responsibility to report clinical progress in a clear and timely way. For example, on 13 May 2019, LCT advised that the 4 patents who received 80 capsules all continued to show at 24 months a benefit greater than the 2 placebo group patents from that section of the trial. LCT also further advised that it is seeking further advice from both its statistician and advisory panel to help interpret the data. In our view the board is delinquent to have made such announcement without completed sufficient statistical analysis to be able to clearly describe its results; and then to not provide an updated analysis until over 10 weeks later.

Parkinson's disease

Parkinson's disease is caused by the gradual breakdown and death of neurons (nerve cells) in the 3 dopamine levels in the brain. This decrease causes abnormal brain activity and leads to the onset of symptoms such as tremors, slowed movement, rigid muscles, impaired posture and balance, loss of automatic movements, speech and writing changes. End-stage Parkinson's is extremely debilitating and sufferers require full-time care, often experiencing non-motor symptoms such as incontinence, insomnia and dementia. Ailments caused by it are often fatal and patients are understandably anxious to lessen the effects of Parkinson's through treatment.

The progression of Parkinson's disease is typically measured by the UPDRS, which assesses both motor and non-motor symptoms associated with the disease. The progression of Parkinson's measured with UPDRS shows a deterioration on average of 4-5 points each year.

Parkinson's disease is the second most common age-related neurodegenerative disorder after Alzheimer's disease. It is estimated that 7-10 million people worldwide suffer from Parkinson's disease.1 The incidence of the disease generally increases with age and it is 1.5 times more likely to affect men. Currently, Parkinson's medication typically costs USD2,500 per year (over a lifetime) and surgery cost related to deep brain stimulation can cost up to USD100,000 per patient.

NTCELL

NTCELL is a biocompatible capsule containing clusters of porcine choroid plexus cells. These cells secrete large volumes of cerebrospinal fluid that contains multiple neurotrophins, anti-oxidants, and molecular chaperones which have been seen to maintain and regenerate neural tissues and potentially re-establish damaged neuronal circuitry. The effects of these secretions are expected to be the protection and regeneration of dopamine producing neurons. The recent results of NTCELL trials have shown a halt in the progression of Parkinson's over a 4-year study period. This halt in progression has been indicated by no change in the patients UPDRS score since beginning the trial when one would expect to see a ~16-20-point score increase.

NTCELL utilizes a process to encapsulate the choroid plexus cells called IMMUPEL™. IMMUPEL™ aims to protect cells from the patient's immune system.

Pacific Channel believes that if the Phase III trial confirms the halt of progression of Parkinson's, patients seeking NTCELL treatment will not be price sensitive.

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1 https://parkinsonsnewstoday.com/parkinsons-disease-statistics/

ANALYSIS OF NTCELL CLINICAL TRIALS

Pacific Channel has reviewed data and statistical analysis provided by LCT through its public announcements. Pacific Chanel has not received individual patient data and therefore has not conducted its own statistical analysis. It is possible that the analysis provided by LCT may contain inaccuracies.

Please note the following trial analyses contains graphs that have been vertically flipped from their original form for illustrative purposes only, so that the results may be more easily interpreted by a non-technical reader. A reader should see an upswing in these graphs as showing patient improvement.

Phase I/IIa trial

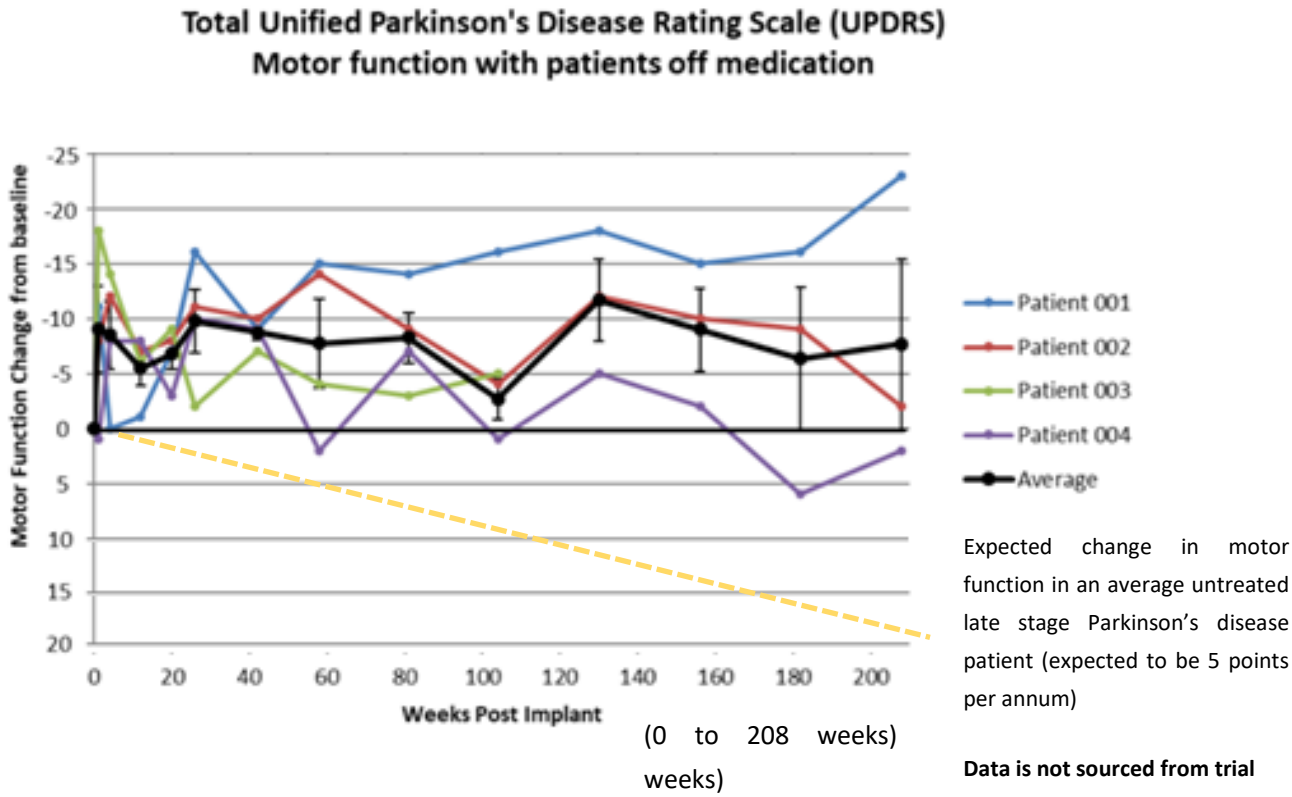
This trial involved four patients listed for DBS treatment, who received implants of 40 NTCELL capsules unilaterally i.e. into one hemisphere only (i.e. ¼ the preferred dosage of NTCELL 80 in the phase IIb study), into the putamen (the part of the brain responsible for regulating movement). These patients have severe Parkinson's disease and LCT reported that these patients were no longer responding to all available existing medications.

a) Phase I/IIa 4-year trial data – positive results

- The NTCELL Phase I/IIa Parkinson's trial update shows that patient data 4 years after implantation demonstrates safety and indicates efficacy.
- At the four year follow up only 3 of the 4 patients remained active in the trial.
- Ken Taylor (CEO) stated that Patient 1's data showed "clinically significant improvement" in Parkinson's disease symptoms. The patient's Parkinson's UPDRS score improved during the course of the study. This implies that their disease progression was not only halted but reversed. As there is only one sample, we cannot validate the statement 'clinically significant improvement', however, the magnitude of the improvement was substantial.
- Patients 2 and 4 showed no substantial change from their entry score. Pacific Channel views this as a real improvement, as their disease did not progress over this 4-year period. As a patient's Parkinson's disease progresses, they deteriorate on average by approximately 4 to 5 points each year. Notwithstanding patient to patient variability, one would expect their UPDRS score to otherwise deteriorate by 16-20 points over the 4-year trial period.[2]
- Patient 3 withdrew from the trial after 2 years and requested DBS treatment.

[2] Holden, S. K., Finseth, T., Sillau, S. H., & Berman, B. D. (2018). Progression of MDS‐UPDRS Scores Over Five Years in De Novo Parkinson Disease from the Parkinson's Progression Markers Initiative Cohort. *Movement disorders clinical practice*, *5*(1), 47-53.

- In all patients, the primary endpoint of this study, safety, was met.
- There is currently no treatment available for late stage Parkinson's disease. Trial data suggests NTCELL could be effective in these late stage patients.
- Only 4 patients were in this trial so one cannot confidently infer efficacy from the data.



(0 to 208 weeks)

Expected change in motor function in an average untreated late stage Parkinson's disease patient (expected to be 5 points per annum)

Data is not sourced from trial

Phase I/IIa clinical trial data at 4-year follow-up

Phase IIb Trial

- This study dosed 40, 80 and 120 cell implants bilaterally, i.e. as 2 implants per patient into the putamen. The three groups were treated separately, along with a placebo group for each section, in approximately 2015, 2016 and 2017 respectively.
- Trial patients were on their optimum medication for Parkinson's and were likely to list for DBS in the future. These patients are significantly less progressed than the patients in the Phase I/IIa trial.
- For statistical analysis, data from treated patients are compared to:

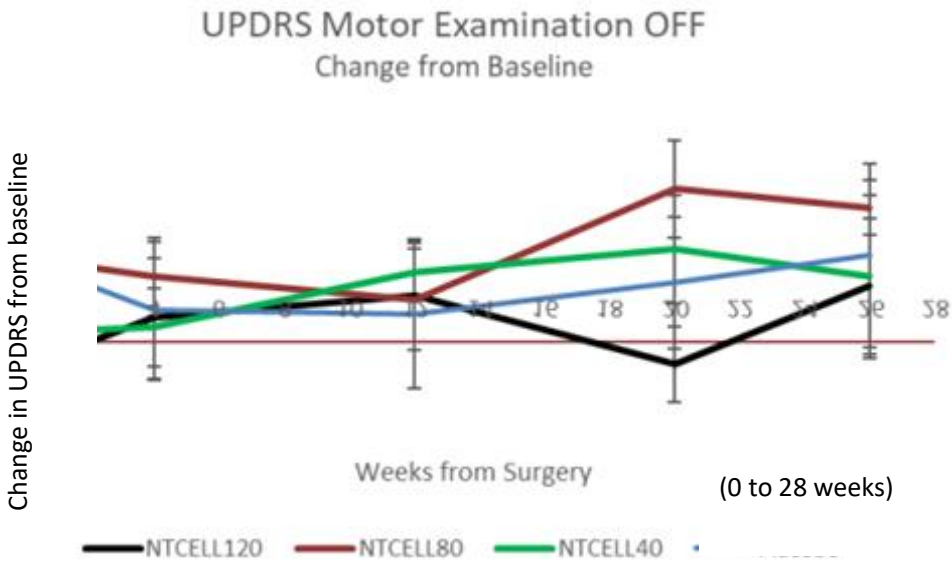
- A placebo group - this is a group of patients that receive a sham therapy that has no therapeutic benefit; or
- Baseline

b) Phase IIb 26-week trial data – inconclusive results

- NTCELL Phase IIb interim 26-week trial data. The data presented suggested the trial did not demonstrate statistically significant efficacy
- Due to the result, its presentation and lack of full explanation from LCT, the share price plummeted from AU$0.25 to AU$0.03, an 88% decrease, which resulted in a loss of over $100m of shareholder value. Without accompanying explanation, many shareholders concluded that NTCELL had failed. It was also unclear whether the trial was to continue.
- In contrast, our assessment of the results was that NTCELL produced a meaningful improvement to Parkinson's patients. However, the data from patients receiving NTCELL did not meet a statistical threshold due to the placebo (i.e. sham therapy) group also improving, which is counter to the expected trend of untreated Parkinson's patients declining in health.

- It is possible that this was the "placebo effect", where patients receiving a sham therapy improve due to psychological reasons.
- The placebo effect is well-known and common in clinical trials.
- At this timepoint, due to the short timeframe since commencement of the trial it could be expected that the placebo effect would be a factor in the improved health of the placebo group compared to the average Parkinson's disease patient. Our conclusion at this timepoint was that NTCELL remained a promising theory, and that the trial should continue for results to be assessed at a later stage after the placebo effect ceased being a factor.
- Therefore, we believe that the trial design should not have required the 26-week trial data to be unblinded and released, as it was a reasonable expectation the placebo effect would be present and make it difficult to assess a therapeutic benefit. LCT's lack of explanation of the data presented further highlights its inability to adequately communicate the company's results and development.

- Positive results from the 78-week and for the NTCELL 80 group 104 week data supports our assessment that conclusions made at 26 weeks were premature.
- We believed the company could improve the timing and the context of its reporting.



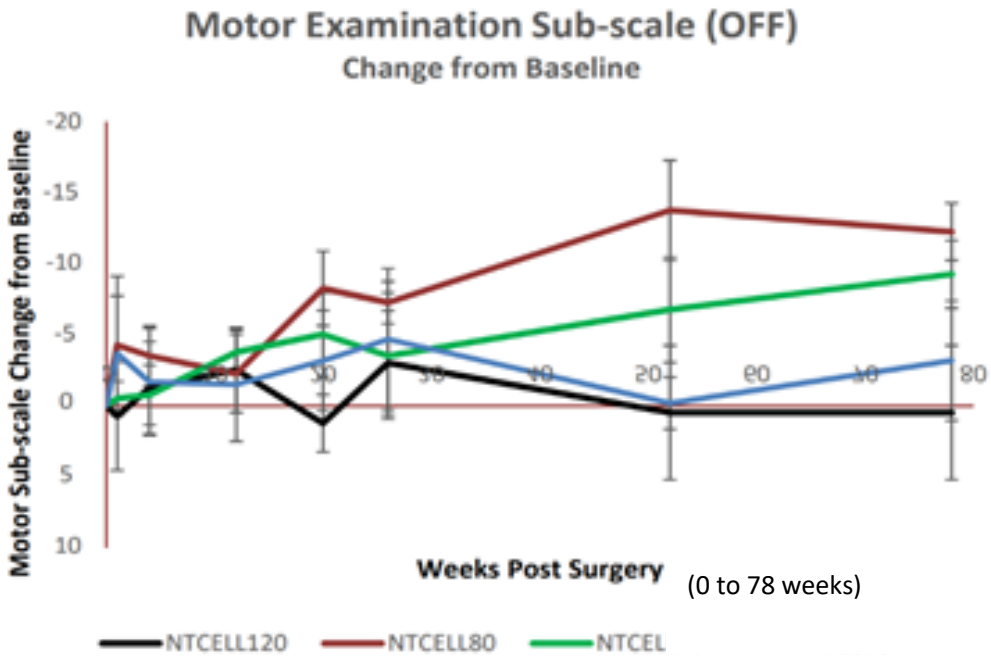
c) Phase IIb 78-week data release – positive results:

- Concluded that NTCELL 80 is the optimal dose and indicated benefit in the treatment of Parkinson's.
- The NTCELL 40 dose provided benefit to patients, although to a lesser degree than NTCELL 80.
- The improvements in patients were expected to be smaller than the Phase I/IIa trial as the patients participating in this trial were less advanced in their Parkinson's progression. However, the data demonstrates that treatment produced a strong improvement in patient health, which is therefore remarkable.
- The data does not suggest nor deny the presence of non-responders in NTCELL 40 and 80.
- Professor Robert Elliot, scientific founder and director orally stated in LCT's annual meeting of shareholders in November 2018 that all patients treated with NTCELL 40 and NTCELL 80 did not deteriorate.
- NTCELL 120 was not tolerated and provided no benefit to patients.
- LCT has previously announced its plan to seek advice on the regulatory pathway for NTCELL 80 from MedSafe post the successful conclusion of its Phase IIb study at 24 months. Given LCT's earlier announcements that it expected MedSafe to advise it on the regulatory pathway for NTCELL by May 2019 and our inference from LCT's 23 July 2019 announcement, it is likely in our view that MedSafe has not accepted LCT's filing for conditional approval, likely due to the small sample size of its successful Phase IIb study.
- LCT states that the results from the NTCELL 120 group did not produce any patient benefit. LCT maintains that this is due to inflammation associated with the large dose, impacting its

tolerability. Patients who received the 120-dose had increased lesioning on the region of the brain which is involved in movement. This lesioning may have worsened motor symptoms of the NTCELL 120 patients. Due to this lesioning, it is impossible to ascertain whether the 120 group were non-responders or responders as the effect of NTCELL may have been masked.

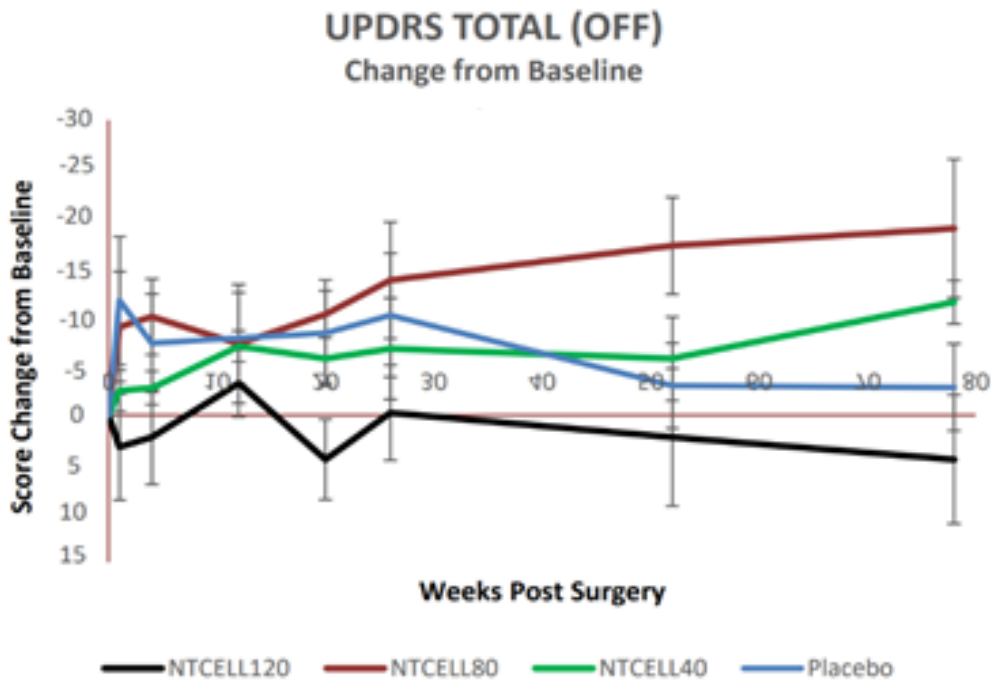
- Despite the issues associated with the 120-dose there was a strong rationale to trial the dose. The NTCELL Phase IIb trial was designed to be a dose-ranging study to determine the maximum tolerable dose; NTCELL 120 was determined as intolerable, and therefore NTCELL 80 is, from the 3 doses applied, is the maximum tolerable dose. Dose-ranging or dose-escalation studies are routinely used in this way in Phase II trials.
- We do not believe the NTCELL 120 result should become an insurmountable barrier for NTCELL 80 to receive regulatory approval for clinical use. As LCT stated that it "was a phase IIb, randomised, double-blind, placebo-controlled, stepped dose investigation of the safety and efficacy of NTCELL® in patients with PD."[3]
- The publicly available data for this trial did not provide an individual breakdown by patient. When considering NTCELL 40 and NTCELL 80 dose groups as a whole, both groups improved.

Results of trial:



- NTCELL 80 – 12-point benefit vs. baseline at 18 months post-implant (p=0.01)

- NTCELL 80 dosage had a 12-point benefit vs baseline in the motor examination subscale, which was statistically significant (p=0.01); this means that there is only a 1% chance that the result was produced by chance, therefore we can have a high level of confidence on these results.



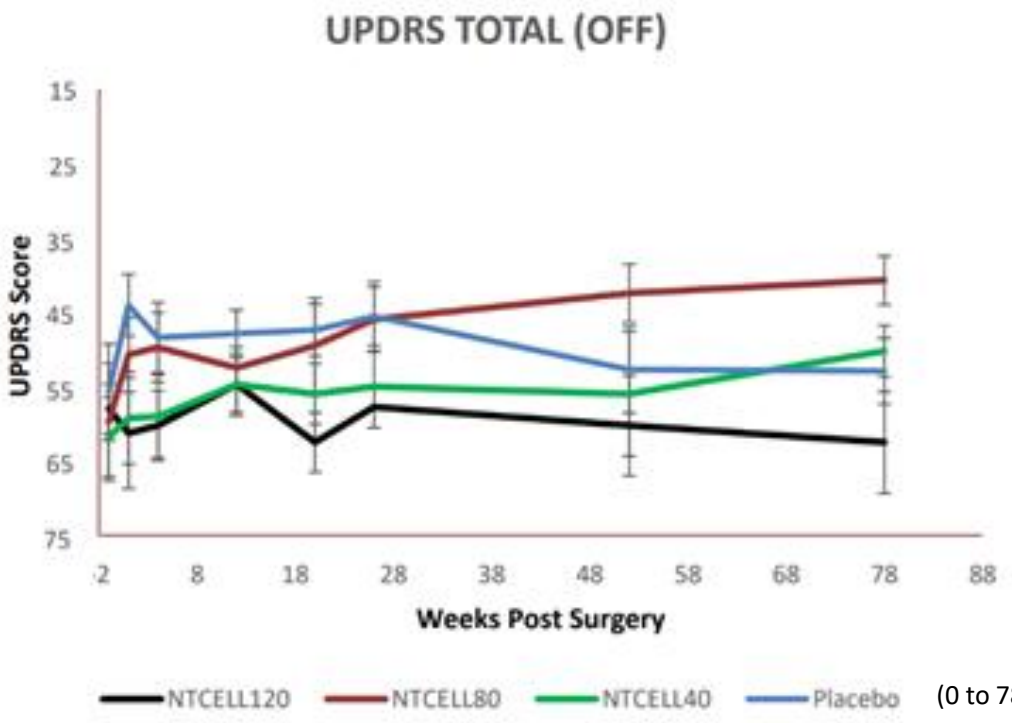
(0 to 78 weeks)

NTCELL 80 – 20-point benefit vs. baseline at 18 months post-implant (p=0.07)

NTCELL 40 – 12-point benefit vs. baseline at 18 months post-implant (p=0.01)

- NTCELL 80 had an average 20-point benefit vs. baseline in the UPDRS scoring. Statistical analysis shows that there is a 7% probability (p=0.07) that the data was produced by chance. This is above the 5% 'chance' threshold that is commonly used in scientific analysis which suggests that the level of confidence on the results of this set of data is slightly less than we would have if a p-value less than 0.05 was obtained.

- The NTCELL 40 group had a 12-point benefit vs. baseline in the UPDRS scoring. This reached statistical significance (p=0.01), as there is only a 1% chance that the data was produced randomly. Therefore, we can have a high level of confidence on these results.
- Regardless of the statistical analysis, the magnitude of improvement a dose response between NTCELL 40 and NTCELL 80.



(0 to 78 weeks)

NTCELL 80 – 15-point benefit vs. 2-point benefit in placebo at 18 months post-implant (p=0.04)

- Over 78 weeks NTCELL 80 had a 15-point benefit vs. a 2-point benefit in the placebo group. Statistical analysis shows that there is only a 4% probability (p=0.04) that the data was produced from random chance. Therefore, we can have a high level of confidence on these results.

d) Phase IIb 104-week data release - successful trial outcome

"NTCELL® Parkinson's trial – 2-year data analysis shows successful outcome"

The Phase IIb 104-week patient data continues to support PCL's contention that there has been a successful outcome to this trial. Both NTCELL 40 and 80 treatments were determined to produce a clinically relevant outcome using the UPDRS scale with a -6.45 point move away from the UPDRS baseline.

NTCELL 80's treatment was determined to be superior to NTCELL 40. As NTCELL 80 treatment showed sustained efficacy and clinical relevance from 52 until 104 weeks, while NTCELL 40 only appears clinically

relevant at 52-week. This result suggests that NTCELL 80 is likely to be the optimum dose for halting Parkinson's disease. The graph provided, in the most recent update, appears to confirm that NTCELL 80 treatment slows the loss of motor skills in moderate to severe Parkinson's patients.

Overall, the primary outcomes required for a successful Phase IIb trial were met; safety and dose-responsive efficacy.

Next Steps

We believe the next step for NTCELL will be a larger Phase III study to reconfirm the results of the Phase IIb trial. In the absence of announced plans from LCT, we researched the potential size and cost of a Phase III confirmative trial and estimate that it would likely be sufficient to have a sample size of at least 30 patients per arm. The trial would require 2 arms, placebo (control) and NTCELL 80 treatment, resulting in a minimum 60 patients total.

We assume it will take 3-4 years for this Phase III trial to be completed, as it will likely take 1 year to establish the trial, another 2 years to complete it, an additional 6 months for trial data analysis and 6 months for regulatory approval.

We have developed an estimated cost for this 4-year period, this assumes that the corporate costs per year are AU$1m, NTCELL manufacture as AU$4m, trial cost per patient as AU$50k per patient, additional trial site costs as AU$5m and AU$2m contingency for any stability or inter-batch QA/QC testing needed and/or manufacturing difficulties. Over this 4-year period, it will likely require AU$18m to complete these activities. Assuming that LCT currently has AU$4.9m in cash or cash equivalents and that it is able to gain further non-dilutive grants of AU$5m (we note that LCT has secured more grant funding than this to date on the basis of less developed clinical proof), we anticipate that additional funds of ~AU$8.1m are needed.

Important Note: The NTCELL manufacture costs assume the use of existing internal and external infrastructure, including NZeno's pig facility (formerly LCT's) and contract cell processing, i.e., no new capital expenditure on manufacturing.

Estimated Costs	**Yearly Cost (AUD)**	**Cost Over 4 Years (AUD)**
Corporate Costs	$1m/year	$4m
NTCELL Manufacture	$4m overall	$4m
Cost of Trial per Patient	$50k/patient	60 patients x $50k = $3m
Trial Site Costs (2yrs)	$500k/year/clinic	5 clinics x 2 yrs x $500k =$5m

Contingency	$500k/year	$2M
Total cost		**$18m**
Current Cash	$4.9m	
Non-dilutive Grants	$5m	
Total Raise		**AUD$8.1m**

Assuming that LCT carries out its Phase III trial in Australasia, we anticipate that the cost, per enrolled patient, of the initial surgery plus patient care throughout the trial, will be AU$50k. However, as LCT has completed studies previously in Argentina and Russia, there is a possibility that it may complete its Phase III trial in such lower cost countries, potentially including China, which we expect to cost one-third less (AU$34k) than in Australasia.

Our estimated costs for Phase III trial may be impacted by unexpected costs associated with getting NTCELL to market of which we have no knowledge.

Trial data

- Up until the end of that 24 month period we understand that NCELL 40, 80 and 120 were each dosed 12 months apart. LCT has released its analysis of the 24 month data for all patient groups in its phase IIb trial, which required waiting until May 2019 for the data from the 120 group to be provided.
- We understand the scientific rationale for not releasing data earlier during the course of the 24 month study to avoid potential biases, given that up until the end of each group's 24 month period patients were blinded from whether they were on the trial therapy or a sham therapy.
- However, now that the patient blinded study period has been completed for all groups, we would believe it would be in LCT's best interest to release its 24 month data for the NTCELL 40 and 80 groups to at least the same level of detail as in the 12 & 18 month data releases.
- Further, we encourage LCT to release information on each individuals UPDRS baseline against their respective 24 month data measurements.

VALUATION

Valuation Methodology

Pacific Channel has not prepared a formal valuation of LCT. However, medical therapies can be broadly categorized by their phase of clinical development, which have distinct risk profiles. Pacific Channel has outlined what it views as the risk mitigated towards achieving commercial sales and the common valuation ranges at each phase for an Australasian-based therapeutic venture.

NEXT PHASE	RISK MITIGATED AS PHASE COMMENCES[3]	INDICATIVE VALUATION RANGE (AU$)
PHASE I/IIA	20%	5m - 10m
PHASE IIB	30%	15m - 30m
PHASE III	67%	100m - 250m
US FDA REGISTRATION	81%	400m - 700m
AT FDA APPROVAL	100%	500m – 1b

Please note that the US FDA does not have a regulatory framework for approval of a cell xenotransplantation therapy and it is unlikely in our view to approve unless LCT "humanizes" its cell therapy. We have also included market validation of identified competitors, where known, in the competitors section below. However, this includes mainly Europe and US-based companies that typically attract higher valuations than Australasian-based companies.

Consequent to the LCT Announcement 23 July 2019 we take the view that:

- NTCELL has reached its endpoints with its Phase IIb trial that would allow for it to enter Phase III.

[3] Sourced from: Pharmaceutical Manufacturing and Research Association and FDA FY 2000 Performance Report to Congress for the Prescription Drug User Fee Act

We observe that:

Pacific Channel's assessment of the data at 12 month (52 weeks), 18 months (78 weeks), and what can be derived from the 23 July 2019 announcement of the 24 month (104 week) results, supports that NTCELL met its stated endpoints: "Two years after NTCELL implantation, the criteria of a successful Phase IIb trial were met: safety and dose responsive efficacy compared to a placebo group." This is supported by statements in a presentation made by LCT to the PHAR-EAST conference on 20 March 2019 and the interim announcement of 104 week results; and subsequent 23 July 2019 announcement.

- *'The trial endpoints address the 3 questions raised by the Ministry of Health to qualify for conditional (fast track) consent to market:*
  - *Define efficacy and any placebo contribution:*
    - *Clinical significant effect at 12 and 18 months in both UPDRS total and motor sub-scale measurements.*
  - *Define optimal dose of NTCELL implantation:*
    - *80 capsules bilaterally as 2 implants spaced to putamen,*
    - *LCT advised that the 4 patients who received 80 capsules all continued to show a benefit greater than the 2 placebo group patients from that section of the trial.*
    - *LCT further advised that it is seeking further advice from both its statistician and advisory panel to help interpret the data further.*
  - *Define initial target Parkinson's disease patient subgroup:*
    - *Patients failing symptomatic treatment, candidates for DBS*
  - *Safety:*
    - *No safety issues up to 80 capsules bilateral'*

e) Valuation Comparison

As Pacific Channel takes the view that as reported NTCELL has met its endpoints in its Phase IIb trial, we believe that NTCELL should now be considered a Phase III ready asset; that at the preferred NTCELL 80 dose has also shown indicative efficacy. Comparable pre-revenue biotechnology companies are typically valued only on the basis of their lead therapeutic asset. A Phase III ready Australasian therapeutic asset without any known US regulatory difficulties is typically valued in the range of AU$100-250m. Please note that the US FDA does not have a regulatory framework for approval of a cell xenotransplantation therapy and it is unlikely in our view to approve NTCELL unless LCT "humanises" its cell therapy.

Given that we expect difficulties with the US market, which typically represents approximate half of given global market value we apply a discount of 50% from the indicative valuation range for a Phase III asset (ie. AU$50-125m). We further assume a valuation at the lower end of this range given that we believe that LCT faces challenges to scale up its supply chain in order to deliver commercial product relative to other more readily manufacture-scalable products. On the basis of owning a Phase III ready asset and

taking into account discounts described above this would suggest a valuation of ≥AU$50m (relative to its current market cap of ~AU$16.57m). However, capital markets apply a premium for good governance, management, reliable results and clear reporting; and conversely discount value where it believes these factors are missing. Pacific Channel believes that given the value of its Phase III ready therapeutic asset, LCT is significantly undervalued and would be revalued higher if these corporate issues were addressed.

We have also included market valuation of identified competitors, where known, in the competitors section below. We note that this includes mainly U.S.-based companies, which typically attract higher valuations than Australasian based comparables, so we have not taken these into consideration for valuation purposes

f) Valuation Observations

We note that on 16 October 2018, which was prior to LCT's announcement of the 26-week Phase IIb results, LCT's share price peaked at AU$0.26 per share, which implied a market capitalization of AU$148.57m. The share price declined to AU$0.03 per share after LCT announced that its 26-week trial results did not meet its "efficacy endpoint "(as the trial is not designed to demonstrate statistically significant efficacy, we interpret this to mean indicative efficacy).

We believe this implies that significant re-rating of the company is possible should the market be appraised that NTCELL has met its safety, and patient group identity and dose definition in the Phase IIb trial; plus has shown indicative efficacy; and if LCT successfully can address the corporate issues identified above.

g) Impact on Valuation of MedSafe Conditional Approval

We believe that a phase III trial will be required for entry into a major market outside of New Zealand. However, if LCT is able to secure conditional approval from MedSafe to undertake limited commercial sales in NZ, this would enable LCT to undertake a phase III equivalent trial in NZ that is paid or partly paid by patients. This would reduce capital requirements and risk, and therefore potentially increase the valuation range from AU$50-125m to AU$80-200m. In this scenario, we again assume a valuation at the lower end of this range, at AU$80m to AU$100m, as we believe that LCT faces challenges to scale up its supply chain in order to deliver commercial product relative to other more readily manufacture-scalable products.

h) Valuation on capital raising to support a Phase III trial

In our assumed case, if MedSafe declines to provide conditional approval and LCT is required to undertake a phase III trial to support NZ approval and it can address its corporate issues described above and delivers a market-standard corporate communications and investor relations effort, we believe it could raise additional capital at a valuation in the range of AU$40-60m to fund those trials.

ANALYSIS OF LCT'S STRENGTHS AND WEAKNESSES:

Strengths

1. 'Approved' virus-free pigs

    - LCT has access to a unique breed of high health status pigs. NZeno Limited is the only other company that has access to these pigs. They are unlike other pig herds that commonly have diseases, such as porcine retroviruses. Porcine retroviruses have been a significant concern to regulatory bodies for porcine to human xenotransplantation. Isolated on the Subantarctic Auckland Islands since the early 1800s, LCT's pigs are considered to have undergone 'genetic purging.' Genetic purging is the reduction in frequency of deleterious alleles (disease-producing genes) within a population caused by increased efficiency of natural selection prompted by inbreeding. They are an ideal source of cells for xenotransplantation because of their low viral load (arising from their isolation) and because they are not capable of secreting porcine endogenous retroviruses, which is otherwise a significant infection concern following transplantation.

    - Auckland Island pigs are exclusively held by LCT and NZeno Limited. There are pigs that remain on the Auckland Islands itself, however obtaining these would require approval from the Department of Conservation, which manages access to the Auckland Islands; and the Southern Heirlooms Breeds Trust, which manages access to the pigs.

    - LCT built a designated pathogen-free facility to maintain the high health status of the pigs. This facility is located in Kumeu and was built to accommodate initial NTCELL trials. The facility is where the pigs are bred to produce piglets that are euthanized to be used as a source of porcine choroid plexus cells for transplant. Each sow produces 2 litters of 5 to 6 piglets per annum. These piglets are harvested for transplant at 6-15 days old. Each piglet produces choroid plexus cells to treat 5-10 patients.

    - This breed of high health status pigs has been approved as a tissue source for human transplantation trials by New Zealand's MedSafe in consultation with the US FDA and the Centre for Disease Control. LCT's access to this breed is a key value point for the company and its operations. We are unaware of any other Parkinson's treatments that have access to these high health status pigs. Additionally, LCT has significant know-how and records surrounding the breeding of pigs, and data to characterize the resultant pigs for the suitability for transplant and for evidence of disease-free status. We believe this provides LCT with at least a 3-year advantage over another party should it receive access to the Auckland Island pigs.

2. NTCELL® Parkinson's trial – 2-year data analysis shows successful outcome

- NTCELL 80 treatment showed sustained efficacy and clinical relevance from 52 until 104 weeks, this result suggests that NTCELL 80 is likely to be the optimum dose for halting Parkinson's disease.

The graph provided in the most recent update, appears to confirm that NTCELL 80 treatment slows the loss of motor skills in moderate to severe Parkinson's patients.

- Overall, the primary outcomes required for a successful Phase IIb trial were met; safety and dose-responsive efficacy.

3. Ability to develop biocompatible encapsulation system – IMMUPEL™

    - IMMUPEL™ allows foreign material to be transplanted into the body without eliciting an immune response. Implanting foreign material into patients requires immuno-suppressant drugs to prevent rejection of the foreign material. However, this reduces immunity and increases susceptibility to infection, as well as damaging the cells implanted into the body. IMMUPEL™ rules out the need for immuno-suppressant drugs in many foreign cell implant cases, which will positively affect transplant outcomes.

4. Potential approval for NTCELL's use in NZ from MedSafe

    - At the PharEast conference (March 2019), LCT presented and stated that the Phase IIb NTCELL trial endpoints address the 3 questions raised by the Ministry of Health to qualify for conditional (provisional) consent to market. This statement improves Pacific Channel's medium-term outlook on LCT.

    - If LCT gains conditional approval it is likely that treatment would be limited to a finite number of patients and would require ongoing patient monitoring and reporting.

    - In June 2019 LCT announced that it intends to file for Section 29 regulatory approval in NZ.

    - This approval may enable LCT to establish operating clinics in NZ that can carry out the NTCELL treatment. This may permit medical tourism to NZ for Parkinson's treatment.

    - As noted earlier, given LCT's earlier announcements that it expected MedSafe to advise it on the regulatory pathway for NTCELL by May 2019 and our inference from LCT's 23 July 2019 announcement, it is likely in our view that MedSafe has not accepted LCT's filing for conditional approval, likely due to the small sample size of its successful Phase IIb study.

    - Medical centres in New Zealand have indicated that they are capable and willing to carry out the procedure. If LCT gains MedSafe approval for NTCELL it is expected that additional New Zealand medical centres/clinics will have interest in providing the therapy.

    - A private hospital in Auckland believes it can have up to 2 surgeons performing 4 operations each per day.

    - Parkinson's sufferers globally will want access to this treatment and interested recipients will initially have to travel to New Zealand to receive it. We believe NZ is well positioned to receive these patients.

5. Population need and ability to pay

    - There is currently no Parkinson's treatment proven to work in the long-term (end stage). Existing treatments become less effective as the disease progresses.

    - The current treatments on the market for Parkinson's are combined and manipulated as the disease progresses. The treatment often becomes ineffective in slowing the progression of the disease or reducing the symptoms.

    - While there are existing treatments in the early to mid-stage, there are no competing late/end-stage Parkinson's treatments. The current treatments are designed to treat symptoms and disease progression is inevitable. Whereas NTCELL aims to repair the damaged site. If NTCELL succeeds in halting progression, it can be expected to capture the majority of the early to mid-stage market. Existing end stage patients would also be expected to seek treatment.

    - Current treatment for Parkinson's includes dopamine producing drugs (levodopa), dopamine agonists, MAO B inhibitors, COMT inhibitors, anticholinergics, and amantadine. However, these drugs become ineffective over time as the disease progresses and can have significant negative side effects. Most patients require multiple drugs to ensure that their symptoms are controlled.

    - During the Phase IIb trial of NTCELL, patients were able to continue their other Parkinson's treatment. Parkinson's patients have a strong trend of using combination therapy. We have not identified reasons as to why these indirect competition treatments could not work in combination with NTCELL. We do not believe this detracts from NTCELL as a Parkinson's therapy as any therapy of combination or therapies that are able to arrest and/or reverse the symptoms of Parkinson's in end stage patients will be strongly received by the market.

    - As Parkinson's disease is the most prevalent in older males, it is expected that initial patients would have the ability to pay a significant price for an effective treatment for such a debilitating disease.

6. Diabetes royalties

    - It is our understanding that LCT has an exclusive license to use the diabetes treatment (DIABECELL) in New Zealand, Australia and Argentina if US FDA approval is achieved by Otsuka Pharmaceutical.

7. Medical Advisory Board

    - It is our view that has the core of a world-class advisory board to inform NTCELL's development, regulatory applications and market entry (as key opinion leaders) is required.

Weaknesses:

1. Xenotransplantation regulatory barriers

    - Few developed countries have a regulatory framework for approval of a cell xenotransplantation therapy.

    - Initial market therefore likely to be limited to New Zealand and countries that are developing new regulatory frameworks for cell therapy including cell xenotransplantation therapy such as Japan and China.

    - Conventional therapeutic development acquisition and funding sources including large pharmaceutical companies are unlikely to support NTCELL given the difficulty of entering established major medical markets such as the US and Europe. LCT may need to "humanize" its cell therapy approach to enter such markets. Stem cell technology required to achieve this is still under development globally.

2. Small patient numbers in NTCELL trials (22 in total)

    - A large response from patients is required to gain statistical significance. However, given this, it is remarkable that improvement in patients was statistically significant for at 18 months NTCELL 80 compared to patients treated with a placebo. Furthermore, it is compelling that all patients in the NTCELL 80 group continue to show a benefit greater than the 2 placebo group patients from that section of the trial.

    - Due to the small patient numbers, MedSafe may require a larger trial with more patients prior to approval

3. Weak board with limited experience in commercialization of biotechnology and associated specialist capital markets

    - Professor Bernard Tuch (Chairman): Has extensive academic research experience, specialising in diabetes and cell therapy, where he also has a separate commercial interest. However, he has no apparent experience in getting a treatment to market.

    - Professor Robert Elliot (Founder): Has extensive experience with clinical care and research, start-up technology companies including successfully commercializing biotechnology as a founding scientist for A2 Corporation (NZX:A2) and Somnaceutics, which returned >100x and >10x respectively for their seed investors.

    - Laurie Hunter: Has extensive oil industry experience in stockbroking, investment banking and corporate investing. Has input into finances and investment strategy for LCT.

    - Robert Willcocks: Holds a Bachelor of Laws degree from Australian National University and a Master of Laws degree from the University of Sydney. Willcocks has been a director of a number of Australian Securities Exchange (ASX) listed companies.

- Dr Ken Taylor (CEO): Has a strong background in pharmacology and experimental small molecule therapeutics in academia and pharmaceuticals. No evident experience prior to LCT in cell therapy, getting a product to market or public capital markets. Successfully led a $6.3m placement into LCT in 2016. We note that Dr Taylor did not put his name to the Announcement dated 23 July 2019.

- Prof Carolyn M. Sue (appointed 7 May 2019) has a strong background in neurological science and medicine. She is the Head of Neuroscience Research at the Kolling Institute at Sydney's Royal North Shore Hospital, and Director of Neurogenetics, Director of the National Centre for Adult Stem Cell Research and a Senior Staff Specialist in the Department of Neurology at the Kolling Institute. She is also a Professor at Sydney Medical School.

LCT's Board announced in May 2019 that it is now considering the possibility of appointing another non-executive Director, with relevant commercial expertise. Mr Laurie Hunter, who has served on the LCT Board since August 2006, has indicated that he does not intend to offer himself for re-election at the AGM in November 2019, and will be stepping down from the Board at the expiration of his term.

Pacific Channel strongly agrees that LCT's board could benefit from further expertise. Specifically, someone who has both a commercial and scientific background, who has been a CEO or director of a biotechnology company that has secured capital, taken a product to market and created significant shareholder value through that process. Such a person would complement the CEO's skills and experience; and allow for board oversight, guidance and where appropriate assistance in these areas. We have made several written recommendations to the LCT board in this regard during 2019 and are pleased that it appears to now be considering such an appointment.

Pacific Channel believes that the LCT board has been delinquent in its responsibility to report its clinical progress in a clear and timely way. Given this, the corporate issues described above and the lack of progress in the appointment of a new commercial director, Pacific Channel - together with other large shareholders, with interests representing collectively over 15% of shares in LCT – intends to make a formal request for a resolution at the AGM to appoint one to three new directors.

4. Pipeline

- LCT has licensed 4 small molecule assets for development. We have not reviewed these assets other than to note that they have been licensed from a reputable university and have world leading lead researchers. These assets are in our view a major diversion from their current and prior focus on cell therapy (i.e. NTCELL and DIABECELL). The rationale for licensing these assets remains undisclosed by LCT. LCT may have acquired the rights to these small molecule assets as a risk mitigation strategy in case NTCELL is not successful. We agree with the requirement for a risk mitigation strategy but would argue that this could be better achieved through the development of assets arising from LCT's core competency in cell therapy. We note that experimental small molecule therapeutics aligns with Dr Taylor's (CEO) R&D management

experience. However, we question whether LCT holds any comparative advantage or significant expertise in this field, and whether this development effectively utilizes the core competencies developed by LCT through its 31-years' experience in cell therapy.

- Pacific Channel views LCT's small molecule pipeline as a distraction from its core competencies; and believes LCT would be better to focus on developing additional cell-based therapies e.g. a well regarding New Zealand medic has proposed to Pacific Channel the potential for an ophthalmological treatment using LCT's cell therapy capabilities.

5. Board and management have not advised a clear plan to; scale up production and commercialise NTCELL, to seek further funding, nor its vision to drive growth and ultimately increase shareholder value , and when questioned by the shareholders are not responsive:

   - Numerous shareholders publicly claim that the management and board are 'reactive' when they should be 'proactive' in creating value from IMMUPEL and NTCELL.

   - Press releases and clinical data are lacking in detail and can be hard to interpret for those who are not scientifically literate.

   - Shareholders appear to be increasingly frustrated with the board. They claim to have not received detailed up to date information regarding LCT and its progress; and that many queries and concerns receive no response.

   - Current directors have no obvious mandate or significant shareholding.

6. Scale up preparedness

   - LCT plans to go to market in 2020. However, there is no evidence to suggest that LCT is in a position to scale up for commercial provision of NTCELL within the next 12 months

     - LCT's last reported current cash and cash equivalents are $4,907,957, which is expected to last until December 2020. Considering the recent positive trial results for NTCELL, LCT should be considering how to secure further funding to allow scale up, commercialisation, or further trials (if necessary) of NTCELL.

   - Many factors will challenge NTCELL's ability to get to market by 2020. establishing a sustainable pig herd, expanding facilities for a larger pig herd and developing an organ harvesting and cell encapsulation manufacturing facility.

   - Establishing a sustainable pig herd:

     - We have not seen a scale-up plan that sees LCT achieve their target to reach market within the next 12 months. We see the biggest hurdle as the number of pigs required and how they plan to develop their breeding programme in order to reach the number of pigs required.

- NTCELL requires the provision of piglets for choroid plexus cells to be extracted at 6-15 days old. The culling of piglets for harvesting cells will need to be balanced against the expansion of the herd.

- We anticipate LCT will require a herd of at least 100 healthy and suitable pigs to ensure a sustainable supply of NTCELL before going to market. It is currently unclear how many healthy and suitable pigs LCT currently holds, and the length of time that would be required to reach 100 pigs. We anticipate it may require in excess of two years to establish such a herd. Given that LCT's pigs are a key asset and limitation to its scale up, we would expect LCT to provide herd information in its quarterly guidance to shareholders.

- Auckland Island sows can produce 5-6 piglets per pregnancy, twice per annum. As LCT scales it its herd, the timeline may need to account for sows that are incapable of holding pregnancies to term, and piglets that are not viable for xenotransplantation.

- Assuming LCT has access to a limited number of pigs with a narrow gene pool, it should consider the possibility of recurrent inbreeding. The pigs will become increasingly inbred with each subsequent generation, which might affect the quality of the herd and its suitability for xenotransplantation. However, Auckland Island pigs are already highly inbred, therefore they may have already genetically purged negative traits related to inbreeding. If this is the case, continued inbreeding may have no effect.

- Mitigating these risks, NZeno Limited is a private New Zealand company that has secured access to Auckland Island pigs, and has established a herd in a separate and larger specific pathogen free facility. It may be in LCT's interest to expand the base of its herd through collaboration with NZeno.

- Expanding pig facilities:

  - Auckland Island pigs are the only breed of pigs approved for medical use due to their high health status. If LCT chooses to expand its herd, it may require a new specific-pathogen free facility to house pigs. This facility will need to be compliant with the regulations of each market it intends to provide its therapy. LCT should consider building the facility in an isolated area that is remote from a current or previous piggery to reduce potential exposure to pathogens. Pigs should be housed within separate units to avoid cross-contamination, and the facility should incorporate effective waste disposal systems, temperature control, autoclaves, feed and water control as well as allow for extensive staff protocols.

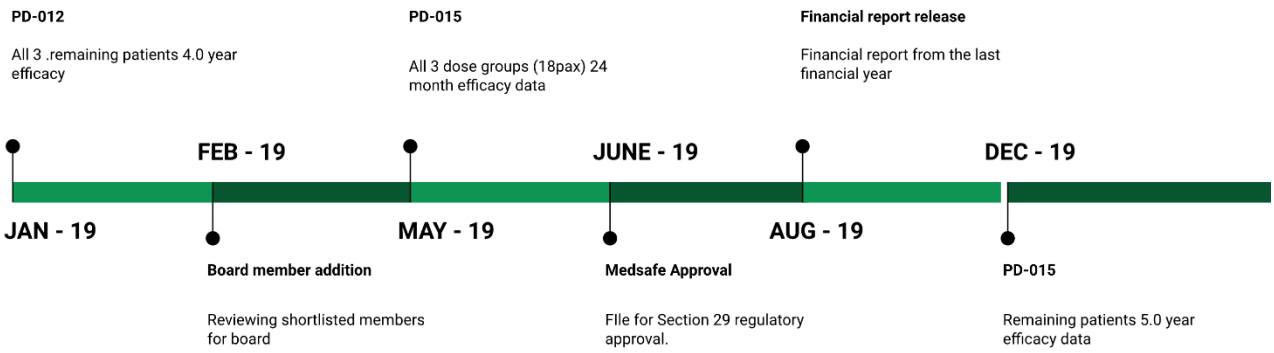
  - LCT should consider its production plan, to determine whether it intends to transport pregnant sows, piglets or harvested tissue to a cell encapsulation manufacturing facility.

If LCT chooses to send tissue, then a pig housing facility may also require surgical facilities, which would need to meet strong quality and hygiene protocols.

- LCT should consider the requirements for a cell encapsulation facility. As Xenotransplantation of encapsulated porcine choroid plexus cells is novel, and there are no established manufacturers that can produce NTCELL for LCT.
- The process will require identification of a suitable site, design, approvals, identification of suitable construction contractors, construction and certification.
- Due to these factors, the process of developing a pig facility could take two or more years. LCT's belief that it will take less than a year to go to market appears optimistic and indicates in our view that it has not sufficiently considered scale-up planning.

- Manufacture scale up risk:
  - As LCT scales up its manufacturing process, it may be required to modify the process used to create the NTCELL product. Any alterations from the processes used to product NTCELL for trials may require bioequivalence testing and additional approvals.

LCT Key Dates



Patent landscape

The following patents have been identified related to LCT's technology:

- Swine population having low levels of porcine endogenous retrovirus and uses thereof
  - US8088969
  - Protects *LCT's* method of breeding disease free pigs.
  - Current assignee: Diatranz Otsuka Ltd
  - Priority date: 2005/04/15

- Applications in Mexico, Korea, South Africa, and New Zealand,
- Granted patent in USA, Australia, Canada, and China.
- We note there is no application or granted patents in the EU or Russia
- Diatranz Otsuka has ownership of this patent which protects the method of breeding of LCT's disease free pigs. It is unclear whether LCT has a license to use this patent. If a license to this patent is not needed, LCT should clearly communicate this to the market.

- Treatment of CNS disease with encapsulated inducible choroid plexus cells
  - US20160361365A1
  - Covers LCT's proprietary process to treat central nervous system diseases through encapsulated choroid plexus cells.
  - Current assignee: Living Cell Technologies New Zealand Ltd
  - Priority date: 2015/05/15
  - Applications in Australia, Europe, Canada, United States, Korea, Japan, Israel, Mexico, and Brazil. No patent applications have yet been granted.
- Pericyte protective agents for neurological disorders including neurodegenerative diseases, central nervous systems diseases and others
  - PCT/US2018/58797

Regulatory changes

Recently, Japan and especially China have codified and streamlined the regulatory process surrounding cell therapies. This may allow LCT to access these large markets directly within a reasonable timeframe.

COMPETITION:

The following is a non-exhaustive list of new and emerging Parkinson's disease treatments.

Direct Competition – Neuroprotective treatment:

i) Phase I clinical trials:

Medgenesis Therapeutics

Medgenesis Therapeutics is developing glial cell line-derived neurotrophic factor (GDNF) direct infusion therapy that has shown some promising effects. However, the data gained from this trial showed no significant difference between the placebo group and the group receiving the treatment. Meaning that the positive effects of the treatment could be a result of the placebo effect. This treatment requires an indwelling catheter implanted deeply into the patient's brain. The patient then receives monthly infusions of GDNF. The idea behind this treatment is that scientists believe that GDNF will "regenerate dying brain cells and even reverse the condition." However, there are significant risks attached to an indwelling catheter, such as infection and potential strokes. We believe the science behind the treatment is promising and may be effective, as GDNF is a factor present in NTCELLs' secretion. However, we believe the method of delivery is sub-optimal given that the infusions were not continuous unlike NTCELL and the damage done during implantation of the catheter could have further impeded the data. The data gained from this trial showed no significant difference between the placebo group and the group receiving the treatment. Meaning that the positive effects seen in the treatment group could be a result of the placebo effect.

NTCELL supplies not only GDNF but also Nerve growth factor (NGF), Vascular endothelial growth factor (VEGF), Brain-derived neurotrophic factor (BDNF) and possibly others which all contribute to cell regeneration and the prevention of disease progression. NTCELL has the advantage of being a one-off treatment not requiring an invasive, long-term and life-risking ongoing intermittent infusions

This treatment still requires a lot more development and is not likely to reach the market before NTCELL.

Metabolic Solutions Company

Metabolic Solutions Company is repurposing an already FDA approved insulin sensitiser (MSDC- 0160), which was originally intended to treat type 2 diabetes. However, it has been recognised to have potential to treat Parkinson's. There is increasing research that supports the idea that mitochondrial dysfunction is a key feature in Parkinson's patients. MSDC-0160 works to reduce mitochondrial dysfunction via regulating mitochondrial pyruvate carriers in Parkinson's patients.

Affiris

Affiris is developing Affitope, a vaccine treatment for Parkinson's disease. Affitope promotes the production of α-Syn-targeting antibodies to prevent the clumping of α-Syn or reduce its production in the brain to prevent the progression of Parkinson's disease. Their pilot Phase I trial showed that their doses were locally and systematically well-tolerated, however, there is no data present that suggests its effects on Parkinson's progression.

j) Phase III clinical trials:

Voyager Therapeutics Inc

Voyager (NASDAQ: VYGR) is developing a gene therapy for Parkinson's disease, VY-AADC, that is current in Phase 2 trials.

Parkinson's disease is characterized by a loss of dopamine and its function. Dopamine is a chemical "messenger" that is produced in the brain and is involved in the control of movement. Some chemicals, like dopamine, are made from other chemicals by proteins called enzymes. Dopamine is made in the brain when the enzyme AADC (Aromatic l-amino acid decarboxylase) converts the chemical levodopa to dopamine. Levodopa, AADC, and dopamine are each present at normal levels in healthy people.

When dopamine levels decrease in the brain and there is no longer enough to control movement, the motor symptoms of Parkinson's disease including tremors, slow movement or loss of movement, rigidity, and postural instability, may occur. When this happens, a doctor may prescribe a levodopa medication, which is converted into dopamine by the enzyme AADC in the same way that naturally occurring levodopa is converted to dopamine.

As Parkinson's disease worsens, there is less AADC enzyme in parts of the brain where it is needed to convert levodopa to dopamine. Therefore, the amount of dopamine that is produced from each dose of levodopa medicine may be reduced. When this happens, patients' motor function may worsen with a less predictable response to medications.

Voyager Therapeutics' investigational gene therapy is designed to put the AADC enzyme into brain cells where it can convert levodopa to dopamine. To do this, the AADC gene is delivered inside a transporter called "adeno-associated viral vector" (AAV), much like a letter that carries the instructions the brain needs to make the AADC enzyme with the AAV as the envelope that carries the letter.

Voyager is valued at USD900m. Voyager has disclosed 4 other gene therapies that are at a preclinical stage.

Indirect competition – symptomatic treatment

k) Phase I clinical trials

Apitinyx Inc.

Aptinyx (NASDAQ: APTX) is developing NYX-458, an NMDA receptor modulating small molecule for the treatment of cognitive impairment associated with Parkinson's disease. NYX-458 has been evaluated in a Phase 1 clinical study

While motor symptoms are the principle symptoms of Parkinson's disease, many people with Parkinson's also suffer from cognitive impairment. Aptinyx refers to the belief that the loss of dopamine neurons and the associated downstream changes, including dysregulation and dysfunction of NMDA receptors, leads to impairments in multiple cognitive domains. NYX-458 may have the potential to correct the function of NMDA receptors and address the cognitive symptoms in people with Parkinson's disease.

Aptinyx is valued at USD130m. In addition to Parkinson's disease, Aptinyx has three assets currently in Phase 2 trials.

l) Phase II clinical trials:

Novartis

Novartis (NYSE: NVS) is developing Nilotinib is a protein kinase inhibitor that blocks the activity of a protein kinase which is linked to several mechanisms in the brain, such as oxidative stress and α-synuclein-induced neurodegeneration, which are seen to play critical roles in Parkinson's and other brain disorders.

Novartis is a large diversified pharmaceutical company valued at USD190b

Anavex Life Sciences

Anavex (NASDAQ: AVXL) is developing Anavex 2-73 as a treatment for Parkinson's Disease dementia.

Anavex 2-73 is expected to be able to restore the function of damaged nerve cells and significantly improve motor function. Anavex is undertaking a 120 patient phase 2 trial for Anavex 2-73, to evaluate its efficacy and safety as a treatment for Parkinson's disease dementia. The trial is halfway through recruitment.

Annavex is valued at USD150m. Aside from Parkinson's disease, Anavex 2-73 is recruiting for Phase 2 for Rett syndrome, and has completed phase 2a for Alzheimer's.

resTORbio

resTORbio (NASDAQ: TORC) is undertaking a phase 1b/2a trial of RTB101, an orally administered, small molecule, inhibitor of target of rapamycin complex 1 (TORC1) alone or in combination with sirolimus to treat Parkinson's disease (PD). The trial will assess safety and tolerability. Phase 1b/2a trial data is expected to be reported in 2020.

Selective and broad inhibition of TORC1 has been shown to ameliorate neurodegenerative disease in several preclinical studies across multiple species, including models of Parkinson's Disease

TORC1 inhibition with RTB101 in combination with sirolimus, may provide a therapeutic benefit to Parkinson's disease patients to clear protein aggregates in neurons.

resTORbio is valued at USD295m. The company's lead indication for RTB101 is for respiratory tract infections. It is currently in Phase 2 trials.

m) Phase III clinical trials:

ND0612L and ND0612H by NeuroDerm

ND0612L and ND0612H are the first formulations of levodopa and carbidopa to be administered subcutaneously to achieve steady state levodopa plasma levels. These formulations will be continuously delivered through a belt pump. They have been designed for moderate and severe Parkinson's disease. The severe treatment has shown to reach higher levodopa steady plasma levels,[4] indicating that it may provide an effective alternative to current treatments requiring surgery, such as deep brain stimulation and LD/CD Intestinal Gel.

IPX-203; carbidopa and levodopa by Amneal Pharmaceuticals

IPX-203 is an extended release oral capsule formulation of carbidopa and levodopa (CD-LD), that is considered to be a potential treatment for Parkinson's disease. It is designed to have an onset of effect similar to immediate-release CD-LD while providing a longer duration of effect compared to other oral levodopa products available.

n) Approved:

Acorda Therapeutics

Acorda Therapeutics (NASDAQ: ACOR) has developed Inbreja, an inhaled drug designed to rapidly deliver a precise dose of levodopa in a dry powder form to the lungs. Inbreja is used as a 'quick fix' to rapidly relieve motor symptoms. Inbreja was approved by the FDA in December 2018.

[4] N. Giladi, Y. Caraco, T. Gurevich, et al. Presentation: O2114 -Pharmacokinetic profile of ND0612 (levodopa/carbidopa for subcutaneous infusion) in Parkinson's Disease (PD) patients with motor fluctuations: results of a Phase IIa dose finding study , Eur J Neurol. 2015 Jun; 22 Suppl 1: p.66.

Acordia is valued at USD580m. In addition to Inbrija, Acordia has an FDA approved treatment for multiple sclerosis.

Adamas Pharmaceuticals

Adamas Pharma (NASDAQ: ADMS) has developed Gocovri, a treatment for a side effect caused by a commonly prescribed Parkinson's drug. A majority of patients diagnosed with Parkinson's are treated with levodopa, whose use often leads to involuntary movements that are non-rhythmic, purposeless and unpredictable.

Gocovri Adamas asserts that Gocovri is the first drug cleared by the FDA to control levodopa-induced dyskinesia (LID).

Adamas is valued at USD172m. The company's value peaked at USD1.15b 6 months after FDA approval, however, its share price has been negatively affected by poorer than expected sales.

ACADIA Pharmaceuticals Inc.

ACADIA (NASDAQ: ACAD) has developed NUPLAZID, which it asserts is the first and only medication approved by the FDA for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. Acadia is valued at USD3.86b. NUPLAZID is Arcadia's only approved product. The same active is in phase 3 trials for three indications, and phase 2 trials for two indications.