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living insights

Published on an occasional basis, *Living Insights* is a source of up-to-date information for followers of the Australasian biotechnology company Living Cell Technologies (LCT)

Message from the CEO

Welcome to this issue of Living Insights.

LCT remains very much focused on increasing value for its shareholders. The next step for the development of NTCELL is to determine if a further clinical trial can be undertaken. Considerations such as study design, site and cost are being actively explored.

We are also progressing two product opportunities licensed from the University of Auckland and are making excellent progress on these projects.

Ken Taylor
CEO

AGM

LCT's AGM will be held on **Thursday 7 November 2019 at 2pm (NZT) Pullman Auckland,** Regatta Room, Lower Lobby Level, Corner Princes Street & Waterloo Quadrant, Auckland City, NZ.
We hope to see many of you there.

NTCELL

In May we released the 24-month follow up data in the Phase IIb study of NTCELL® for Parkinson's disease. Since then, further in-depth analysis has been undertaken of all data from the study.

Such analysis needs to balance interests ranging from patients, investors, expert neurologists versus what NTCELL has been shown to do, based on interpretation of the data from our preclinical studies, clinical study efficacy and safety endpoints as well as longer term patient follow-up data. Most important is understanding what information will be required by regulatory authorities to give marketing approval for NTCELL as well as neurologists who will require compelling data and expert opinion to recommend NTCELL neurosurgical implantation to their patients.

The time we are taking to answer these questions reflects that: there are currently no comparable examples of Parkinson's disease modifying treatments approved for launch; a well-documented placebo response in clinical trials; and the small number of patients in our two clinical trials.

As part of this analysis LCT's Board has consulted with its NTCELL Medical Advisory Board comprising Professor Roger Barker, Cambridge, UK, Dr Patrik Brundin, Michigan, USA, Professor Thomas Foltynie, London, UK, Professor Carolyn Sue, Sydney, Australia and Dr Barry Snow, Auckland, NZ who was also Principal Investigator for the study. These experts have contributed significant background information from their experience in large-scale pivotal clinical studies. The company has also had discussions and advice from Medsafe and the Data Safety Monitoring Board which includes two neurologists, Dr Tim Anderson, Christchurch, NZ and Dr Andrew Hughes, Melbourne, Australia. Statistical analysis has been audited by statisticians with extensive clinical trial experience.

The 18-patient, Phase IIb trial of NTCELL studied three groups of six patients, with two patients from each group having sham surgery, while the active cohorts received 40 microcapsules, 80 microcapsules and 120 microcapsules implanted on each side of the brain.

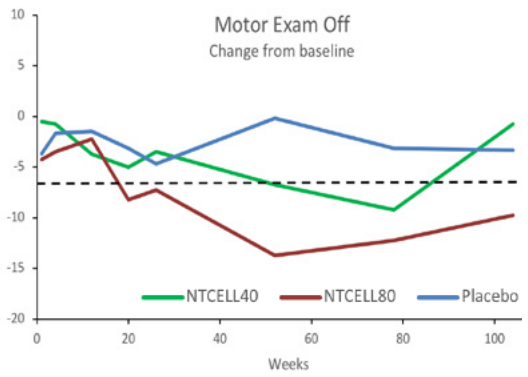
The key parameter used for assessment was motor function in the off state, that is, when recipients were not taking anti-Parkinsonian medications, with the scoring being the Unified Parkinson's Disease Rating Scale standard.

At the initial study endpoint of 26 weeks post-implant there was not a statistically significant difference between the groups who received NTCELL and the placebo group.
At this point it was agreed to unblind the study (patients then knew if they were treated with placebo) and extend the monitoring of the patients out to two years post-implant as per an extended trial protocol.

The one year data showed a statistically significant improvement in the UPDRS Part III in the off state in the patients who received 40 or 80 NTCELL capsules implantated to the putamen on both sides of the brain as compared to the placebo group. No benefit was observed when 120 NTCELL capsules were implanted. There was evidence of inflammation which may have compromised efficacy in this group.

At 18 months post implant, data showed a statistically significant improvement (p = <0.05) in the UPDRS in the patients who received 80 NTCELL capsules as compared to the placebo group.

In May 2019, at 24 months post-implant there was a clinically relevant effect observed (<-6.45 points from baseline) in both the 80- and 40-capsule group. The effect of 80 capsules was greater than that of 40 capsules. When the placebo group was included in the analysis, the treatment effect was clinically relevant at weeks 52-104 for the 80-capsule group, and at week 52 for the 40-capsule group. The fact that the six placebo patients have not shown the expected deterioration in their Parkinson's symptoms over two years has complicated analysis of the results.



Work is underway to complete the final study reports for both the Phase I/IIa and Phase IIb trials. Once these are completed, the patients in both studies will no longer be monitored and will be free to pursue other treatments for their Parkinson's disease.

The future for NTCELL

LCT undertook the additional analysis and investigation after the initial trial results were announced to establish whether it would be worth making an application to Medsafe for provisional consent to market NTCELL as a treatment for Parkinson's disease and whether such an application would be successful.

Complicated by proposed changes to the NZ Medicines Act, Medsafe has advised LCT that the small patient numbers from the Phase I/IIa and Phase IIb studies combined with the lack of compelling efficacy compared to the placebo means there is insufficient data at present to allow conditional approval under the current Medicines Act. This means it is not possible to treat paying patients in NZ, closing that avenue of potential

revenue for the company.

A Phase III clinical study is a large undertaking for a small biotechnology company like LCT. A Phase III study of NTCELL would not likely take place in NZ due to the large patient numbers required. The resources required in manufacturing, regulatory approval and placement of an international study are considerable and require in-depth due diligence. It would be a five-year commitment at least. A further large study would require significant additional capital, which the company does not currently have.

We are in discussions with potential investigators for a Phase III study and hope to get more specific advice through these discussions at the International Congress of Parkinson's Disease and Movement Disorders in Nice, France on 22-24 September.

Our Board Member, Professor Carolyn Sue and Principal Investigator of our clinical trial, Dr Barry Snow, will attend this conference and meet with prospective investigators to discuss trial protocols, patient numbers and appropriate clinical endpoints. A new trial is likely to target either patients earlier on in the course of their Parkinson's disease, when levodopa is still effective, with a view to reducing the rate of disease progression via neuroprotection, or patients at mid to late stage disease in combination with other treatment such as deep brain stimulation.

More specific information on any new study proposed is required for the board to decide whether LCT will undertake a Phase III clinical trial and whether it is able to secure sufficient funding to do so.

Pipeline

We are making good progress on the studies currently underway in partnership with the University of Auckland. Our goal is to complete a Phase I clinical study within one to two years. If such a study proves our novel treatment candidates can be administered once daily they will be attractive candidates for out-licence to big pharma companies due to the very large market potential for treatments for migraine and obesity.

Any biotechnology project depends on high quality pre-clinical science. We are fortunate to be working with Dame Margaret Brimble, whose expertise and reputation in Chemistry is acknowledged by her recent BNZ Supreme Award in the KiwiNet Research Commercialisation Awards 2019. Dame Margaret was recognised for her pioneering work in drug discovery and development.

Dame Margaret's colleague, Professor Debbie Hay is leading the two studies currently underway with the University. Professor Hay is a current James Cook Fellow whose research aims to contribute to the development of medicines to treat migraine, cancer, lymphatic insufficiency, cardiovascular disease, obesity and diabetes, whilst revealing fundamental mechanisms of cell signalling.

Long-acting Pramlintide for obesity

The obesity project targets a single daily injection to achieve significant weight loss in morbidly obese patients.

The project is on track to identify a lead compound, which will be a patented derivative of Pramlintide. Pramlintide is currently on the market as a treatment for diabetes and is known to cause weight loss in patients.

Progress confirms the lead compound candidates can be synthesised. We have developed an analytical method for measuring blood levels. A Phase I safety study, which could take place in NZ, would only need to show that blood levels support a daily dose of long-acting Pramlintide. Moreover, we can measure efficacy after single dosing in a Phase I study. This is a huge advantage compared to the long-term studies required to measure efficacy in Parkinson's disease.

In the course of our research we have identified novel molecularities of action that have supported the filing of a strong patent on 8 May 2019: "Peptide conjugate amylin agonists and uses thereof".

We have also signed a Confidential Disclosure Agreement (CDA) with an interested well-known global pharmaceutical company relating to a novel delivery device to dispense the dose to patients.

During my visits to overseas meetings in the United Kingdom and United States earlier this year I confirmed much interest from global pharma-ceutical business development groups in this project in particular.

This project shows good potential for delivering a return to the company. We anticipate a one to two year out-licensing exit that would create significant shareholder value.

Long-acting Calcitonin Gene-related Peptide (CGRP) for migraine

The chemistry involved in this second project with the University of Auckland is similar, meaning we are efficient with the time and expertise of the chemistry and biology researchers.

Once again, the target is a once-daily dose, this time of a long-acting CGRP antagonist as a treatment for migraine. An advantage of pursuing this target is that there are trial protocols in place for similar products that we can follow. Furthermore, in a Phase I study we can also measure a surrogate efficacy marker after a single dose.

A patent for long-acting CGRP for migraine was published on 9 May 2019: "Peptide conjugate CGRP receptor antagonists and methods of preparation and uses thereof" WO2019087161A1.

Professor Debbie Hay is an expert in this biological area recognised by her presentation of a plenary lecture at the International Headache Congress in Dublin this month. LCT's Chief Operating Officer, Dr Janice Lam is also attending this conference maintaining our contact with prospective global pharma licensing personnel.

Pericyte Protective Agent (PPA)

This study had two milestone goals: to identify a novel active component in NTCELL secretions and identify a neuroprotective mechanism of action for NTCELL. The study did not meet either of these milestones and so the board has elected to terminate this project.

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