Clinical Trials Update

Open Briefing interview with MD & CEO Andrea Grant

Living Cell Technologies Limited
Level 3, Suite 302, 70 Pitt Street
Sydney, New South Wales 2000

In this Open Briefing®, Andrea discusses:

- Progress on DIABECELL Phase IIb trial
- Status of DIABECELL Phase III trial
- Update on NTCELL Phase I trial

Record of interview:

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Living Cell Technologies (ASX LCT) in November last year announced the start of a Phase IIb clinical trial of its diabetes treatment DIABECELL in Argentina. Can you provide an update on how that trial is progressing?

MD & CEO Andrea Grant
It's progressing really well. We've recruited all 20 of the patients for the trial, and we've performed the first implant in the initial eight patients. Each patient has to be monitored for three months from the time of recruitment before we do the first implant. The purpose of that monitoring period is to establish the patient's baseline data such as their HbA1c readings, glucose lability and unaware hypoglycaemic events. We need the baseline data from those three months in order to compare with any improvements we observe after the implant.

As we announced, the first patient was recruited on 22 November, so their three-month assessment was completed on 23 February and that was the date we gave them their first implant. From there, we've kept rolling the patients through and are carrying out implants at a much faster pace than we ever have before.

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Previously, you've indicated that a Phase III trial of DIABECELL would commence this calendar year in New Zealand and/or Germany. What is the status of this trial and has there been any change to your initial plan to complete the clinical trials of DIABECELL by 2015 and launch a commercial product by 2016?

MD & CEO Andrea Grant
In short there is no change in our target of launching a commercial product by 2016, provided the trials are successful.. We've determined that a 30-patient study with a combined endpoint of reduction in unaware hypoglycaemic events and no increase in HbA1c is a sufficient study for registration. We call this 30-patient study our "registration study" or Phase III.

The first 20 patients for this study will come from the Argentinean IIb study which is well underway. We're expecting the next 10 patients to come from New Zealand and we have a clinical trial application, with exactly the same protocol as the Argentinian IIb study, in preparation to submit to Medsafe, the New Zealand regulator. As long as this application in New Zealand is approved, we'll have the 30 patients that we need, and effectively both trials "convert" to a Phase III trial, or as we prefer to say, registration study.

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The Argentinean Phase IIb trial is an “adaptive trial”. How does the design of the trial differ from an ordinary Phase II trial?

MD & CEO Andrea Grant
We've taken the data from our three previous clinical studies of DIABECELL and together with Otsuka and our external statisticians, determined a trial design which, if it's successful, should be sufficient to achieve registration of DIABECELL in New Zealand. The most critical part of that design is to get the clinical endpoints correct so you can show that your product is clinically useful and safe, but also to design the trial so you're confident you have sufficient patient numbers in the trial, i.e. the n number, to meet those endpoints. We've determined from prior trial data that a trial with 30 patients should be sufficient to achieve our endpoints.

The adaptive trial design allows us to go into the data at a pre-specified time point in order to check our calculations of the required n number are correct. If at this point we see a large amount of variability in the data or spread of the data we can increase the n number of the trial if we need to.

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What are the endpoints of your DIABECELL study?

MD & CEO Andrea Grant
It's a 30-patient study in two countries - Argentina and New Zealand. The participants are those people with type 1 diabetes who despite receiving intensive insulin therapy, which is standard of care, still experience unstable glucose control. All 30 participants will receive two implants of 10,000 islet-equivalent per kilogram of body weight, with the second implant three months after the first. The patients will be followed for 12 months after the second implant and the primary endpoint is a composite endpoint, where patients must show both a reduction in unaware hypoglycaemia and no increase in HbA1c.

The significance of that endpoint is that unaware hypoglycaemia can be life threatening for a person with type 1 diabetes. It occurs when a patient’s blood glucose falls to a dangerous level without the patient having any sign or symptom that it’s happening. People who have normal blood glucose control would sweat and feel faint, but many patients with type 1 diabetes can be unaware that their blood glucose is falling. If glucose is not given immediately, the patient is at risk of losing consciousness and in worse cases can die. So for patient themselves and for their families unaware hypoglycaemic events are very distressing, dangerous and patients tend to limit their activity because of their fear of having one. Some people with type 1 diabetes won’t drive alone or sleep alone, so clearly the quality of life is severely affected.

The reason we have a composite endpoint of both a reduction in unaware hypoglycaemia and no increase in HbA1c is that you can reduce unaware hypoglycaemic events by reducing insulin dose but the problem with doing that is that your HbA1c level rises as well as your glucose level. We want to demonstrate that the reduction in unaware hypoglycaemia is not due to a worsening of the patient's overall diabetes control, so we need both measures in our primary endpoints.

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Will this registration study be adequate for registration in the major markets of Europe and the US without a formal Phase III trial?

MD & CEO Andrea Grant
We’ve had some really constructive recent discussions with regulators in Europe which indicate that they would most likely want us to run at least one trial in Europe before applying for market approval. As you know, we're well ahead of the field, having progressed a therapy of this kind into the clinic, and none of the major regulators have yet had first-hand

experience of approving a product like ours for commercial use. So it makes sense the regulators would want a clinical trial before giving approval.

On the positive side, there's a great deal of cooperative enthusiasm from both the European principal investigators we plan to work with and the regulatory teams in the major markets. That's because there's still a significant unmet need for treatments for people with type 1 diabetes and it's clear to those clinicians and regulators that DIABECELL has the potential to address that unmet need. We feel we're in good stead in relation to registration in those markets.

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The DIABECELL trials are being funded by Diatranz Otsuka Limited (DOL), your 50:50 joint venture with Otsuka Pharmaceutical Factory Inc (OPF). OPF invested A$25 million in DOL, which was expected to be adequate to fund DIABECELL's development through to market approval. What is your strategy with regard to commercialisation of DIABECELL in the major markets?

MD & CEO Andrea Grant
The initial DOL funding has been and will continue to be critical to us being able to step up our work with the regulators in major markets and preparing for trials and launching there. But equally important as the dollars is the partnership, global reach and expertise that OPF brings to the table to support that expansion. The priority for us is to ensure that DOL keeps hitting its milestones, in particular the milestone of commercialising DIABECELL in 2016, and that will ensure the partnership can only become stronger and the path for DIABECELL to expand into the bigger markets will become easier.

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You'd previously flagged the start in April of a Phase I trial of NTCELL in Parkinson's disease. NTCELL is a choroid plexus cell implant that has been shown in the laboratory to be effective against degenerative diseases. Has there been a delay in starting the trial and will it have a significant impact on NTCELL's targeted registration in 2018?

MD & CEO Andrea Grant
There has been no major delay, but a few technical issues have slowed us down by a few weeks. The trial is underway and we're expecting the first patient to be consented in the next week or so. After that, the patient will have to undergo baseline assessments over a period of eight weeks, before travelling to Vancouver for a PET scan. We still expect their implant, i.e. the actual transplant of cells, to occur during the third quarter of this calendar year.

The target registration date is a moving feast, mainly because it's so early in the clinical development program. A lot depends on the first trial, which is a first-in-man safety trial, as well as the efficacy of the product in later trials. What we can say is that if the product is as effective in humans as we observed in our monkey studies, then a registration of 2018/2019 via a fast-tracked development program should be achievable. But I must emphasise that there are many unknowns in that estimate.

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Under an agreement signed with OPF in December for the co-development of NTCELL, LCT will receive an additional upfront payment of A$2 million once the first patient is safely transplanted in the Phase I trial. What other conditions are attached to this payment and when are you likely to receive it?

MD & CEO Andrea Grant
We still anticipate receiving this towards the end of the September quarter or early in the December quarter. There are no other conditions attached, but it's worthwhile explaining what is involved in demonstrating that "the first patient has been safely transplanted". As this is a first-in-man study and therefore primarily a safety study, the trial has been designed so the first patient will receive their implant and then be assessed for two months before any

further patients are implanted. This two month “stand down period” is a safety measure to ensure there's no serious adverse event and therefore it's safe to proceed with the subsequent implants in the next three patients.

The decision on whether it's safe and appropriate to proceed is made independently of LCT by the Data Safety Monitoring Board (DSMB) for the trial. So, provided the DSMB agree at two months after the first patient implant that the trial is OK to proceed, we'll receive the further A$2 million option payment from OPF.

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As at 31 March, LCT had A$4.91 million in cash reserves, after having received the initial A$3.00 million option fee under the NTCELL co-development agreement during the March quarter. How are you positioned to fund your planned R&D and other activities over the short to medium term?

MD & CEO Andrea Grant
At this point in time, the cash required for R&D and other activities which aren't already funded by either DOL or OPF is relatively low at A$1.2 million per annum. So, we currently have around four years' runway, which could extend to almost seven once the A$2 million option is paid. So, I describe us as relatively low risk with exciting upside!

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Thank you Andrea.

For more information about Living Cell Technologies, visit www.lctglobal.com or call Andrea Grant on (+64 9) 276 2690.

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