Chief Executive Officer's review of performance

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Chief Executive Officer

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Review of clinical programmes

hRPC (human retinal progenitor cells) for retinal disease

The hRPC therapeutic candidate is currently undergoing Phase 2a clinical evaluation for the treatment of the inherited blindness-causing disorder retinitis pigmentosa (RP). The study uses a cryopreserved hRPC formulation, enrols subjects with advanced RP with some remaining central vision and, prior to 2021, has been conducted at two clinical sites in the US. Having received regulatory approvals in the UK and in Spain, the Company now has three clinical sites in the US, one in the UK and one in Spain.

In June 2020, we announced an update regarding the ongoing Phase 2a study of our hRPC cell therapy candidate in RP patients. The data at that point continued to demonstrate the efficacy of the therapy, with a clinically meaningful benefit being observed at all time-points. In January 2021, we confirmed that all patients in the study had reached 6 months follow-up post-treatment, eight patients had reached 9 months follow-up, seven patients had reached 12 months follow-up and two patients had reached 18 months follow-up. Following the commencement of the high dose extension of this Phase 2a study, we look forward to presenting further data from this study later in Q4 2021.

In January 2021, the Company announced the completion of dosing of the first cohort of three subjects in the Phase 2a extension segment of the study. This segment of the study is treating up to nine subjects with RP at a higher dose level than the first 10 subjects already treated in the study. In line with the clinical trial protocol, the Data & Safety Monitoring Board for the study

has reviewed the short-term safety data from this first cohort and gave its approval for the study to proceed to dosing the next cohort.

Also in January 2021, the Company was pleased to report that a subject had been dosed in the study at a new US site, the prestigious Casey Eye Institute, Oregon Health & Science University. The Principal Investigator at this new site is Mark Pennesi, MD, PhD, Associate Professor of Ophthalmology, Kenneth C. Swan Endowed Professor and Chief, Paul H. Casey Ophthalmic Genetics Division.

We have previously announced that we have received regulatory approval to expand the Phase 2a study in the UK and regulatory approval has also been received to expand the Phase 2a study in Spain. The Company has activated two new sites in the UK and in Spain (The Oxford Eye Hospital and The Institut de la Màcula, Barcelona) to expand the Phase 2a extension study outside the US, thus representing a total of four active sites worldwide.

In early June 2021, we announced that unfortunately, following a successful surgical procedure, the most recently enrolled subject presented with a presumed bacterial intraocular infection in the treated eye which impacted their vision, and was treated initially with an appropriate regimen of antibiotics, to which they responded with clinical improvement. Systemic anti-inflammatory therapy was subsequently added, and the subject continues to improve on this regimen.

As a precaution we temporarily suspended the dosing of further subjects in the study while we undertook an investigation into the cause of the event. The origin of the presumed infection is not clear however investigations have shown no evidence of a causal link to the drug product. The conclusions of the investigation were submitted to the Data & Safety Monitoring Board (DSMB) and the DSMB agreed that the study may proceed. The study has reopened for enrolment in the US and regulatory filings are being made to reopen the study in the UK and Spain. It is anticipated that this process will conclude in August and if so this would allow dosing to resume in all three territories.

There is a pipeline of subjects in screening which gives the Company confidence that following the impending re-start of the Phase 2a study, all subjects will be treated within the next quarter. Data from the earlier cohorts of subjects indicate that 3-month data have been a good predictor for 12-month data and the plan is to present a minimum of 3-month data for the subjects from the extension segment of the Phase 2a study.

The Company anticipates that, subject to the sufficiency of this expanded Phase 2a data, it will be able to seek regulatory approval to commence a pivotal clinical study in the second half of 2022 with its hRPC cell therapy candidate in RP. The pivotal study will be designed to demonstrate further the safety and efficacy of this treatment and, assuming a successful outcome, enable ReNeuron to seek marketing approvals for its hRPC cell therapy candidate in RP in selected major markets.

Our hRPC cell therapy candidate offers a number of potential advantages over alternative approaches to the treatment of RP. Firstly, our cell therapy candidate is independent of the many specific genetic defects that collectively define RP as a disease, thereby allowing a much broader potential patient population to be eligible for the treatment. Secondly, the cells are cryopreserved, enabling on-demand shipment and use at local surgeries and hospitals. Finally, the cells are injected directly to the site of retinal degeneration, allowing a greater chance of anatomic restoration of photoreceptor function.

Our RP clinical programme has been granted Orphan Drug Designation in both Europe and the US, as well as Fast Track designation from the FDA in the US. Orphan Drug Designation provides the potential for a significant period of market exclusivity once the therapy is approved in those territories. Fast Track designated products may also be eligible for accelerated approval and priority review processes at FDA.

During the period, we were pleased to announce that the US Patent and Trademark Office (USPTO) had completed its examination of the Company's patent application (14/379,239), entitled "Phenotype profile of human retinal progenitor cells", and the patent was granted in September 2020 (patent number 10,758,572). The allowed patent protects the composition of our hRPC cell therapy candidate for retinal diseases and adds further intellectual property protection to the hRPC technology, which already has patent protection in a number of other major territories including Europe, Japan and Australia.

Read more

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Chief Executive Officer's review of performance

Exosome platform

ReNeuron is developing its exosome platform in collaboration with pharmaceutical, biotechnology and academic partners as a novel delivery vehicle for third party therapeutic agents targeting the brain and other parts of the body. The Company's proprietary cell lines produce a panel of distinct exosome drug delivery candidate tools with commercial potential, and the Company's iPSC programme provides an opportunity to generate additional bespoke tissue-specific exosomes. This extensive repertoire of exosome candidates has the potential to target a variety of indications and tissues. Exosomes produced by the Company's neural stem cell line, CTX, can be manufactured through a fully qualified, xeno-free, scalable process and loaded with a variety of payloads, such as nucleic acids (including siRNA, mRNA and miRNA), proteins (such as Cas9, antibodies and peptides) as well as small molecules. These exosomes have also been shown to exhibit a natural ability to cross the blood brain barrier.

ReNeuron is exploring multiple strategies for loading exosomes and has signed a further four separate research collaboration agreements with major pharmaceutical/biotechnology companies on these projects during the period.

These collaborations have demonstrated efficient loading of nucleic acid payloads in the Company's exosomes and functional payload delivery, in vivo, to the brain and peripheral tissues via systemic administration.

Specifically, target knockdown by exosome candidates was assessed in multiple brain regions and in key peripheral tissues including the heart, the kidney and the skeletal muscle. Evidence of target knockdown was observed in each of these organs suggesting these exosomes have the potential to deliver payloads to therapeutically-meaningful levels to a variety of tissues. These studies have also anticipated that exosomes are well-tolerated, laying the foundation for expansion to functional delivery studies.

The Company has initiated two additional collaborations with leading academic institutions in the UK and mainland Europe. One key aim of these studies is to consolidate data from a recent pilot study which showed that exosome-loaded growth factors can engage target receptors in the CNS. Confirmation of these findings will enable further studies examining functional delivery of growth factors by the Company's exosomes.

In addition to exploiting natural exosome tissue specificity, ReNeuron has also now successfully decorated the surface of its neural stem-cell derived exosomes with a specific tissue-targeting peptide. This proprietary peptide was modified to enhance binding to the exosome surface, resulting in a several fold increase in surface binding compared with unmodified peptide. This complex has been shown to be stable, enabling the next phase of this collaboration, which aims to confirm that the peptide promotes exosome targeting to additional tissues in vivo. This peptide platform has the potential to generate further targeting peptides that would rapidly expand the therapeutic reach of ReNeuron's exosome candidates.

Further data across these collaborations are expected during the course of the next six months, which, if positive, will enable subsequent potential out-licensing deals with the Company's exosome platform.

Induced Pluripotent Stem Cell (iPSC) Platform

During the period, we have also progressed our CTX cell-based iPSC technology in a number of potential applications. We are deploying this technology to develop new, immortalised allogeneic cell lines of varying types as potential therapeutic agents in diseases of unmet medical need for subsequent licensing to third parties.

Our CTX-iPSCs can be differentiated into hematopoietic stem cells, lymphoid progenitors and, of great interest for cancer immunotherapy, NK and killer T-cells. We are currently collaborating with a commercial third party to explore the possibility of large-scale in vitro expansion of CTX-iPSC-derived hematopoietic stem cells and discussions are ongoing with other interested parties in the immunotherapy field.

We have also produced pancreatic progenitor cells from our CTX-iPSCs and from these, insulin-producing ß-islet cells. We are currently scaling up this process prior to phenotype analysis and confirmation of the glucose responsiveness of these derived, mature ß-islets.

Other activities

During the period, we announced that, following a review of programme priorities and resource requirements, we intended to focus the Company's resources on our retinal disease programme and our exosome and iPSC platforms. As a result, we have closed down the PISCES III clinical trial of our CTX cell therapy candidate for stroke disability in the US and our stroke disability programme will now only continue through partnerships, as it is our stated intention to license out the CTX cell therapy candidate in other indications.