Chief Executive Officer's review of performance

The decision we have recently taken to focus our in-house activities on our retinal disease and exosome-based programmes provides the Company with significant near-term opportunities to deliver value-enhancing data and commercial partnerships.

"During the period under review, and subsequent to it, we have continued to generate encouraging positive efficacy data from the ongoing US Phase 2a clinical trial of our hRPC cell therapy candidate in retinitis pigmentosa.

Olav Hellebø
Chief Executive Officer

12 August 2020

Review of clinical programmes

hRPC (human retinal progenitor cells) for retinal disease

During the period under review, and thereafter, we have made significant progress with our ongoing clinical programme targeting retinitis pigmentosa (RP). RP is a group of hereditary diseases of the eye that lead to progressive loss of sight due to cells in the retina becoming damaged and eventually dying.

The ongoing Phase 1/2a clinical trial is an open-label study to evaluate the safety, tolerability and preliminary efficacy of our hRPC stem cell therapy candidate in patients with advanced RP. The Phase 2a segment of the study, which uses a cryopreserved hRPC formulation, enrols subjects with some remaining retinal function and, thus far, has been conducted at two clinical sites in the US – Massachusetts Eye and Ear in Boston and Retinal Research Institute in Phoenix, Arizona.

In April 2019, initial data from the first cohort of three patients in the Phase 2a segment of the study were presented at the sixth annual Retinal Cell and Gene Therapy Innovation Summit in Vancouver, Canada. The data demonstrated a sustained improvement in visual acuity compared with baseline in these patients, as measured by the number of letters read on the ETDRS chart (the standardised eye chart used to measure visual acuity in clinical trials).

In October 2019, further positive efficacy data from the study were presented at the American Academy of Ophthalmology Annual Meeting (AAO) in San Francisco. At this point, 22 patients had been treated in the study, consisting of 12 patients in the Phase 1 segment of the study and 10 patients in the Phase 2a segment of the study. Eight out of the ten Phase 2a patients treated had reached at least the one month follow up time point. The visual acuity data presented at the AAO conference from the patients treated in the Phase 2a segment of the study continued to show the hRPC therapy's ability to deliver clinically meaningful signals of efficacy in a patient population where inexorable disease progression is the norm.

We announced further updates regarding the Phase 2a study in February 2020 and, more recently, in June 2020. This latest update summarised data gathered from patients at six, nine, twelve and, for the first patient treated, 18 months follow-up. The latest data continue to demonstrate the efficacy of the therapy, with a clinically meaningful benefit being observed at all time-points. The results announced in February 2020 excluded two subjects who experienced sight loss in the treated eye as a result of complications arising from the surgical procedure. In the June update, we reported that one of these two patients has now recovered their vision and is back to at least baseline at one year post treatment.

Also in June 2020, we announced that the Group had received regulatory approval from both the FDA and MHRA to expand the ongoing Phase 2a clinical

study to treat patients with RP at a higher dose level, at clinical sites in both the US and the UK. We intend to open the ongoing study to a highly experienced UK clinical site, the Oxford Eye Hospital, with Professor Robert MacLaren, a world-renowned leader in the treatment of retinal diseases, as Principal Investigator. These approvals will enable the treatment of up to a further nine patients in the Phase 2a extension segment of the study (beyond the ten Phase 2a patients already treated).

We expect to commence treating patients shortly in both the US and the UK under the revised approved study protocol, subject to a continued easing of COVID-19 related restrictions at the relevant clinical sites. On this basis, and as announced in June, we expect to present further data from the expanded Phase 2a clinical trial during the next twelve months and we expect to have sufficient data from the study to enable the Group to seek approval in the second half of 2021 to commence a single pivotal clinical study with our hRPC cell therapy candidate in RP.

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 designation provides eligibility for an accelerated approval and priority review process by the FDA.

Exosome and iPS cell technologies

Our exosome technology is being exploited as a novel vector for delivering third party biological drugs. We have developed exosomes derived from our CTX human neural stem cell line that have a natural ability to cross the blood brain barrier and can thus be used to deliver therapeutics for diseases of the brain. These exosomes can be produced through a fully qualified, xeno-free, scalable process and the clinical-grade source cell-line ensures consistent exosome product. The exosomes can be loaded with a diverse range of potential therapeutics, such as siRNA/mRNA/miRNA, CRISPR/Cas9, antibodies, peptides and small molecules.

In July 2019, we announced the grant of a number of key patents in Europe, Japan, China and South Korea covering our exosomes and their methods of production. In August 2019, we announced a new grant-funded collaboration with the European Cancer Stem Cell Research Institute at Cardiff University to develop novel systems to enable the delivery of therapeutic nucleic acids across the blood brain barrier using our exosomes.

In April and June 2020, we announced separate commercial collaboration agreements to explore the potential of our exosomes to deliver therapeutic agents to the brain. The first of these agreements, with a major pharmaceutical company, focuses on the use of our exosomes for the delivery of novel gene silencing therapeutics. The second, with a major US biotechnology company, focuses on the use of the exosomes to deliver the US biotechnology company's neuroscience therapeutic candidates.

Further collaborations with pharmaceutical/biotechnology companies are anticipated to commence over the coming months. In response to COVID-19, we have also developed a proprietary exosome displaying the SARS-CoV-2 spike protein with the objective of out-licensing it for the potential delivery of COVID-19 vaccines.

In October 2019, we presented new data demonstrating the stability and scalability of new stem cell lines derived from our CTX human neural stem cells following re-programming to an embryonic stem cell-like state (induced pluripotent stem cells, or iPSCs). This means that we are able to take our CTX neural stem cells back to being stem cells that are able to differentiate into any other type of stem cell, including bone, nerve, muscle and skin. Further, we showed that the new stem cell lines generated could be grown at scale by virtue of the Group's conditional immortalisation technology, enabling the efficient production of clinical-grade, allogeneic ("off-the-shelf") cell therapy candidates.

As a result of the above findings, we are exploring the potential of our iPSC technology to be utilised to develop further new, immortalised allogeneic cell lines of varying types as potential therapeutic agents in diseases of unmet medical need for subsequent licensing to third parties. For example, the production of allogeneic haematopoietic stem cells from our iPSCs could potentially provide an alternative approach to those cancer immunotherapies currently in development that rely on the use of the patient's own T-cells. The iPSC-derived cell populations can also be utilised for the production of exosomes with specific tissue targeting, thus providing further scope for a wide range of industry partnerships.

CTX for stroke disability

During the period, we continued to progress the clinical development of our CTX cell therapy candidate for stroke disability, via our PISCES III clinical study, a randomised, placebo-controlled, Phase 2b clinical trial being undertaken in the US. Patients in the study are treated between six and 24 months after their stroke and are randomised to receive either CTX therapy or placebo treatment. The primary end-point of the PISCES III study is the proportion of patients showing a clinically important improvement (at least one point) on the modified Rankin Scale (mRS) at six months post-treatment compared with baseline. The mRS is a global

Chief Executive Officer's review of performance

measure of disability or dependence upon others in carrying out activities of daily living and is accepted by regulatory authorities as an appropriate end-point for marketing approval in stroke disability.

In February 2020, we announced that positive data from the PISCES II Phase 2a clinical trial of CTX in stroke disability had been published in the Journal of Neurology, Neurosurgery, and Psychiatry. PISCES II was a single arm, open-label study in patients living with significant disability resulting from ischaemic stroke. A total of 23 stable stroke patients with moderate to severe disability were treated with a single dose of 20 million CTX cells a median of seven months post-stroke. Clinically meaningful improvements in disability scales were measured out to 12 months post-implantation.

In June 2020, we announced that, following a review of programme priorities and resource requirements, we intended to focus the Group's resources on our retinal disease programme and our exosome and induced pluripotent stem cell (iPSC) research platforms. Consequently, we have suspended the PISCES III clinical trial in the US and our stroke disability programme will now continue through regional partnerships. Fosun Pharma, our exclusive licensing partner in China, will develop the CTX cell therapy candidate for stroke disability in the licensed territory (Greater China including Hong Kong, Macao and Taiwan) where the Company has the potential to benefit from future operational and regulatory milestones under this out-license agreement. Clinical trial applications have recently been filed by Fosun Pharma to open clinical sites in the licensed territory to build on the clinical data already generated in the US. Patient recruitment in the PISCES III study, which has been on hold due to COVID-19 related restrictions, will remain suspended in the US for the foreseeable future; clinical trial sites will be kept open and patients already treated will be followed up over time in line with the clinical trial protocol.

As part of the June 2020 programme update, we announced that our CTX cell therapy candidate would be made available for licensing in stroke disability outside China. We further announced that the CTX cell therapy candidate would be available for licensing in other indications where the candidate might have the potential to address the deficits in those indications. As an illustration of this potential, in May 2020 we announced the publication of new positive data relating to our CTX cell therapy candidate in the journal Stem Cells. The new data showed for the first time that our CTX human neural stem cell line can rescue deficits associated with an accepted animal model of Huntington's disease, a progressive genetic brain disorder.

Other activities

In April 2019, we announced the signing of an exclusive licence agreement with Fosun Pharma for the development, manufacture and commercialisation of both our CTX and hRPC cell therapy programmes in the People's Republic of China. Under the terms of the licence agreement, Fosun Pharma will fully fund the development of our CTX and hRPC cell therapy programmes in China, including clinical development and subsequent commercialisation activities. Fosun Pharma has also been granted rights to manufacture the licensed products in China. In return, ReNeuron received £6.0 million (before withholding tax) on entering into the agreement and will receive up to £6.0 million in near-term operational milestones and up to £8.0 million in future regulatory milestone payments. In addition, ReNeuron will receive post-launch profit threshold milestone payments derived from the licensed products, leading to total estimated milestone payments of £80.0 million provided all milestones and profit thresholds are successfully met, as well as tiered royalties at rates between 12% and 14% on sales of the licensed products in the Chinese market.

We continue to work closely with Fosun Pharma as it pursues the development, manufacture and commercialisation of our cell therapy programmes in the People's Republic of China, with the CTX programme for stroke disability being the initial focus of activities.

Summary and outlook

During the period under review, and subsequent to it, we have continued to generate encouraging positive efficacy data from the ongoing US Phase 2a clinical trial of our hRPC cell therapy candidate in retinitis pigmentosa. We are pleased to have recently received regulatory approvals in both the US and the UK to pursue this study in further patients at a higher dose level and we look forward to presenting further data from this extended study in due course.

Additionally, we have been very encouraged to see the potential of our exosome and iPS cell technologies emerge during the period, with further collaboration agreements expected in the near term to complement the agreements we have already signed with major pharmaceutical/biotechnology companies regarding our exosome programme.

The decision we have recently taken to focus our in-house activities on our retinal disease and exosome-based programmes provides the Group with significant near-term opportunities to deliver value-enhancing data and commercial partnerships. Our stroke disability programme will continue through regional partnerships and we are pleased to be working with Fosun Pharma as our partner for China, following the signing of the exclusive licence agreement for both our CTX and hRPC programmes in that territory during the period.

Olav Hellebø
Chief Executive Officer