EDISON

ReNeuron Group

Strategic update

Focus on retinal therapy, out-licensing of stroke

Pharma & biotech

ReNeuron has changed its focus to concentrate on cell therapy for retinal disorders. The Phase I/II has FDA clearance to use a higher dose and a new UK trial site in Oxford has been added. A pivotal study may start in H221. The CTX cell line for stroke will now be out-licensed. Internally, it will be used to produce exosomes, an emerging new area. Preclinical exosome technology might be used for therapeutic delivery to the brain and in vaccination or treatment of SARS-CoV-2 infections. Our indicative value is adjusted to £107m, formerly £197m, pending full FY20 results due in July.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
03/18	0.9	(21.0)	(55.66)	0.0	N/A	N/A
03/19	2.7	(17.2)	(45.34)	0.0	N/A	N/A
03/20e	6.1	(22.8)	(60.33)	0.0	N/A	N/A
03/21e	3.1	(30.8)	(83.69)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

hRPC cell-based therapy might treat any RP patient

Retinitis pigmentosa (RP) is an inherited, degenerative eye disease caused by one of over 100 different gene mutations. ReNeuron's human retinal progenitor cell (hRPC) therapy could potentially treat any RP patient, giving a big potential commercial advantage; competing gene therapies only treat specific mutations. ReNeuron has regulatory permission from the FDA to move to a higher dose level in its US Phase /IIa US trial (NCT02464436). The 12-month data on eight patients are due by late 2020. Data from February showed rapid gains in the treated eye followed by a stable gain in mean visual acuity. In the UK, a new trial site in Oxford has been approved. A pivotal hRPC study is being planned to start in H221. Running a US trial may require a US partner. We use an unchanged 25% probability of success for hRPC therapy but extend launch to 2024.

Stroke and Huntington's therapies to be partnered

Edison has always assumed that the stroke CTX cell therapy would be eventually out-licensed. The decision not to invest further in this project means that partners will be required without a large data set. This cuts our estimate of the royalty rate from 30% to 12.5%. It also extends the time to market from 2024 assumed to at least 2027 and, due to partnering, reduces the probability from 30% to 15% (Phase I). The current partner in China, Fosun, is unaffected by the decision so its value is unchanged. Preclinical data in June on improving motor ability in Huntington's disease were promising but any development will be run and funded by partners.

Valuation: Now £107m

The changes above reduce our indicative value to £107m (formerly £197m). The stroke indication was 49% of the pre-cash value. We will reassess the hRPC valuation as data emerge. Exosome deals are promising but the projects are preclinical and cannot be realistically assessed yet. The hRPC launch is now assumed in 2024. Cash on 31 March 2020 is estimated to be about £8m pending the year-end results due in July. We envisage a further funding need in FY21.

23 June 2020

Price	**132.5p**
Market cap	**£42m**
	$1.32/£
Cash (£m) at 30 September 2019	21.3
Shares in issue	31.6m
Free float	99.7%
Code	RENE
Primary exchange	LSE
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	(12.3)	60.6	(35.7)
Rel (local)	(16.3)	31.6	(24.8)
52-week high/low	275.0p		75.5p

Business description

ReNeuron Group is a UK biotech company developing allogeneic cell therapies. Human retinal progenitor cells are also being studied for retinitis pigmentosa (in Phase I/IIa). There is a strong preclinical technology base in exosomes.

Next events

Further hRPC Phase I/IIa data	Ongoing
FY20 results	July 2020
hRPC Pivotal study start	H221

Analyst

Dr John Savin +44 (0)20 3077 2500

healthcare@edisongroup.com

Edison profile page

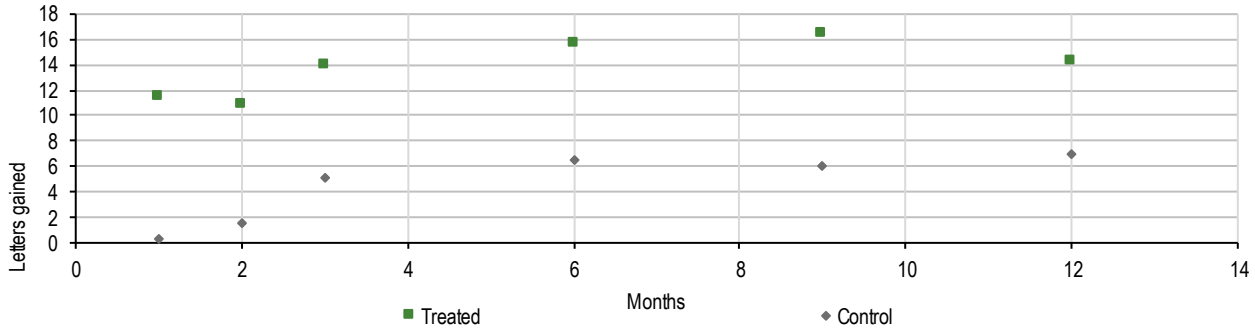
Detailed RPC data to 12 months, US and UK expansion

The January 2020 data update on the US Phase I/IIa US trial (NCT02464436) is shown in Exhibit 1 based on eight treated patients who had successful surgery. At 12 months, there were three patients reported. By the end of 2020, there will be 12 months of data on eight patients, giving a better view of the long-term response. By then, there will also be some 18-month vision data. The trial has a two-year final endpoint. The reported patients were each dosed with one million cells.

In an amended protocol submitted to the FDA, now approved, nine extra patients will be added to the 21 planned and the dose will be raised to two million cells. In addition, a wider range of pre-treatment baseline visual acuity in patients will be eligible and the trial endpoints will be expanded to include microperimetry testing to measure and detect spatial changes in retinal sensitivity. The trial currently runs at two US centres.

The UK MHRA regulatory agency has approved a UK site trial at the Oxford Eye Hospital. Professor Robert MacLaren, a recognized leader in the treatment of retinal diseases, will be principal investigator.

Exhibit 1: Visual mean acuity gain in treated and untreated eyes with hRPC



Source: ReNeuron (Edison graphic)

The exact 12-month mean data in Exhibit 1 are less important as the numbers will change as much more patient data is acquired at the higher dose level. According to management, the planned pivotal study is now due to start from H221. We have no indication of timeline or design. The valuation assumption was formerly of sales from 2023, which is still potentially feasible – just – if enough patients can be enrolled quickly and approval is fast-tracked. However, with the extended Phase I/II study and a start later in 2021 than anticipated, we prudently now assume a 2024 launch.

This is now ReNeuron's key project. As in previous notes, we have valued it on a partnered basis with a 30% royalty. This level assumes that ReNeuron funds the project itself, so we have added an extra year of R&D costs. However, there have been a number of deals in the genetic eye diseases area, for example Nightstar was acquired for $800m by Biogen in 2019. Hence partnering based on expanded Phase II data is possible and could be significantly value enhancing. Alternatively, this type of specialist retinal therapy (subretinal implantation of hRPC) would only be expected to be carried out by a limited number of a specialists, potentially allowing direct sale by ReNeuron – this will require future investment in a small salesforce.

CTX therapy

The intention now announced is to use regional partnerships to progress the use of the CTX cell platform in stroke and possibly in Huntington's disease. ReNeuron has announced that 'patient recruitment in the PISCES III Phase 2b study with CTX in stroke disability, which has been on hold due to COVID-19 related restrictions, will remain suspended in the US for the foreseeable future'. A recent publication summarised data from the prior PISCES II study showing improvement in upper limb function so long as some function was present at the time of cell implantation.

We have therefore left the Fosun deal value in place and assumed further deals on CTX in stroke with no further R&D costs. The use of regional partnerships might be problematic as deals could be hard to close outside the US and there are no scale effects to clinical studies. We therefore reduce the probability to 15% (from 25%) and cut the expected royalty rate from 30% to 12.5% given the potentially major clinical costs and risks. Due to the current hold on the PISCES III study and the need for deals, the expected launch date outside China is pushed out to 2027 (formerly 2024).

A paper in June on a preclinical Huntingdon's disease showed that CTX cells showed stable engraftment and connection of the transplanted cells into the brains (of mice), which gave improved motor skills in a disease model.

Exosomes

The main future internal use of the CTX line is to generate exosomes. Exosomes are tiny lipid (oil) vesicles about 100nm in diameter. They are secreted by cells, especially by mesenchymal stem cells (MSCs), the basis of CTX. Exosomes carry proteins and RNA messages between cells and may be responsible for the modification of the local immune response by MSCs. They have relatively robust membranes making them potentially delivery vehicles.

ReNeuron announced in 2018 at an R&D day that it had a method to scale up exosome production under GMP conditions which should allow a clinical study. The main preparation method in research laboratories is ultracentrifugation, which gives tight size ranges but is laborious and small scale.

Exosomes can be loaded once isolated with short RNA sequences and/or small therapeutic proteins or drugs. The membrane can be modified to enable the exosomes to target specific cell types or be produced from specific cell lines giving inherent targeting to that tissue. ReNeuron notes that it can add the SARS-CoV-2 spike protein, for example, which could make the exosomes appear like viral particles. This is a possible SARS-CoV-2 vaccine candidate. Exosomes also appear to pass though the blood/brain barrier, as shown by literature reports of down regulation of brain proteins by exosomes injected into mice.

The ability to load and modify/target exosomes is very important as, when produced inside MSCs, exosomes will contain an assorted variety of RNA and proteins. To ensure a consistent product therefore, isolation, exosome loading and possible targeting would appear necessary. For a therapeutic product, consistency and scale are essential.

So far, ReNeuron has entered into a collaboration agreement with a US-based biopharmaceutical company to explore the use of exosome technology to deliver synthetic oligonucleotides for gene therapy. It is also in active discussions with other companies on potential collaborations. Currently, there are no disclosed timescales and we note that the COVID-19 vaccine area is already crowded.

We are aware of only one very small academic trial with exosomes so far. There are also some emerging specialist companies like Evox Therapeutics, based in Oxford, UK. Evox announced a deal with Takeda in 2020 worth up to €803m (over several years and assuming successful

development) to develop exosomes for rare diseases, showing the commercial potential of this area. Exosomes are therefore a highly promising area but at an early stage generally.

Valuation: Revised and rebased

In the previous valuation, CTX for stroke was about 50% of the pre-cash valuation. Adjusting the probability, royalty rate and extending the timescale reduces this from £87m to £6m. The discount period has been rebased to 2020 from 2019, giving some automatic uplifts of the projects. However, we have also extended the hRPC timescale and increased the cost forecast accordingly. Overall, this reduces the estimated enterprise value pre-cash from £176m to £99m.

Our estimate of end-FY20 (31 March) cash is £8m, down from £21m in September 2019. Cash use in the second half of CY20 might be lower than previously expected due to reduced trial activity and cessation of CTX patient recruitment, initially due to COVID-19 and later due to the new strategy. We retain our previous assumption that up to £30m might be raised in H2 CY20 to allow for expansion of hRPC studies and exosome developments.

The revised value basis is shown in Exhibit 2. This gives an overall value including estimated March 2020 cash of £107m, equal to 336p per share with about 32m shares in issue currently.

Exhibit 2: Revised valuation estimate

Product	Setting	Status	Launch	NPV (£m)	Peak sales ($m)	Probability of success	Royalty rate	rNPV (£m)		rNPV per share (p)
								Dec-19	Jun-20	
CTX	Stroke disability	Phase II	2027	59	1,388	15%	12.5%	87	6	20
hRPC	CRD	Phase I/II	2024	63	185	20%	30%	11	11	36
hRPC	RP	Phase I/II	2024	206	691	25%	30%	55	64	201
Fosun Partnership	N/A	N/A	N/A	31	N/A	N/A	N/A	23	17	53
Portfolio total				328				176	99	311
Cash								21*	8**	25
Overall valuation								197	107	336

Source: Edison Investment Research. Note: *Reported 30 September 2019. **Estimated amount for 31 March 2020.

Our financial estimates are unchanged pending the publication of FY20 results in July. They are shown in Exhibit 3.

Exhibit 3: Financial summary

£'000s	2018	2019	2020e	2021e
Year end 31 March	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS				
Revenue	897	2,720	6,094	3,094
Cost of Sales	0	0	0	0
Gross Profit	897	2,720	6,094	3,094
R&D expenses	(16,657)	(16,240)	(24,685)	(28,634)
SG&A expenses	(4,616)	(4,779)	(5,078)	(5,586)
EBITDA	(20,222)	(17,915)	(23,448)	(30,965)
Operating Profit (before amort. and except.)	(20,376)	(18,299)	(23,575)	(31,032)
Intangible Amortisation	0	0	0	0
Exceptionals	0	0	0	0
Operating Profit	(20,376)	(18,299)	(23,575)	(31,032)
Other	0	0	0	0
Net Interest	(591)	1,064	792	240
Profit Before Tax (norm)	(20,967)	(17,235)	(22,783)	(30,792)
Profit Before Tax (FRS 3)	(20,967)	(17,235)	(22,783)	(30,792)
Tax	3,352	2,887	3,579	4,152
Profit After Tax (norm)	(17,615)	(14,348)	(19,204)	(26,640)
Profit After Tax (FRS 3)	(17,615)	(14,348)	(19,204)	(26,640)
Average Number of Shares Outstanding (m)	31.6	31.6	31.8	31.8
EPS - normalised (p)	(55.66)	(45.34)	(60.33)	(83.69)
EPS - FRS 3 (p)	(55.66)	(45.34)	(60.33)	(83.69)
Dividend per share (p)	0.0	0.0	0.0	0.0
BALANCE SHEET				
Fixed Assets	912	1,522	1,682	1,959
Intangible Assets	186	186	186	186
Tangible Assets	726	632	792	1,069
Other	0	704	704	704
Current Assets	41,706	29,988	11,684	15,849
Stocks	0	0	0	0
Debtors	1,285	834	834	834
Cash and deposits	37,411	26,386	8,082	12,247
Other	3,010	2,768	2,768	2,768
Current Liabilities	(5,949)	(7,402)	(7,402)	(7,402)
Creditors	(5,949)	(7,261)	(7,261)	(7,261)
Short term borrowings	0	0	0	0
Short term leases	0	(141)	(141)	(141)
Other	0	0	0	0
Long Term Liabilities	0	(864)	(864)	(30,864)
Long term borrowings	0	0	0	(30,000)
Long term leases	0	0	0	0
Other long-term liabilities	0	0	0	0
Net Assets	36,669	24,108	5,965	(19,593)
CASH FLOW				
Operating Cash Flow	(14,887)	(11,947)	(18,808)	(25,733)
Net Interest	383	342	792	242
Tax	0	0	0	0
Capex	(235)	(239)	(287)	(344)
Acquisitions/disposals	0	0	0	0
Financing	0	0	0	0
Dividends	0	0	0	0
Other	0	0	0	0
Net Cash Flow	(14,739)	(11,844)	(18,304)	(25,835)
Opening net debt/(cash)	(53,061)	(37,411)	(26,380)	(8,076)
HP finance leases initiated	0	0	0	0
Other	(911)	813	0	0
Closing net debt/(cash)	(37,411)	(26,380)	(8,076)	17,759

Source: ReNeuron accounts, Edison Investment Research

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