EDISON

ReNeuron Group

Re-initiation of coverage

Rebranding in exosome targeted drug delivery

Pharma and biotech

ReNeuron is a UK-based stem cell research company now strategically re-focused on the development of its exosome drug delivery technologies. Recent encouraging preclinical proof-of-concept data demonstrated the potential of ReNeuron's exosomes to deliver complex therapeutic payloads with high tissue specificity. Drug delivery remains a major challenge in both central nervous system (CNS) and cell and gene drug development, and we view these as key markets for ReNeuron to offer differentiation. Positive preclinical data have led to the signing of substantial licensing deals within the exosome market which, if acquired, would represent a significant catalyst for the share price. To date, the company has established seven discovery stage collaborations with pharma, biotech and academic institutions, through which its proprietary exosome platform is being investigated for application in targeted drug delivery. We value ReNeuron at £47.3m or 83p per share.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
03/21	0.3	(13.4)	(0.29)	0.0	N/A	N/A
03/22	0.4	(11.1)	(0.17)	0.0	N/A	N/A
03/23e	0.8	(11.0)	(0.17)	0.0	N/A	N/A
03/24e	0.9	(12.0)	(0.18)	0.0	N/A	N/A

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

Strategic refocus on exosomes

In January 2022 ReNeuron announced it would halt clinical development of its human retinal progenitor stem cell (hRPC) programme with the intention of completing the clinical data package and identifying out-licensing partners. The decision came as management believed future investigations would not be in the best interests of shareholder value. With the company now fully focused on resourcing development of its exosome platform we view this as a positive strategic pivot to maximise the potential opportunity in the targeted drug delivery market.

Strengthened management team

Following the departure of Olav Hellebø in CY Q122, ReNeuron appointed Catherine Isted as chief executive officer (previously chief financial officer) while also appointing Dr Randolph Corteling, a global expert in therapeutic exosomes, as chief scientific officer. We see these changes as a sensible strategic decision and a positive indicator that ReNeuron is well positioned to execute its newly developed strategy.

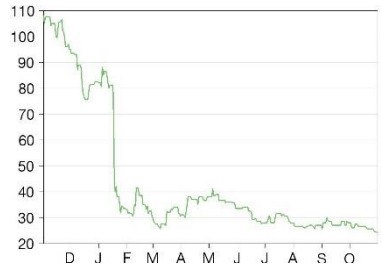
Valuation: £47.3m or 83p per share

We value ReNeuron at £47.3m or 83p per share, based on a risk-adjusted net present value (rNPV) of two assumed preclinical exosome programmes and the out-licensed cortex (CTX) stem cell therapy programme to Fosun Pharma in stroke disability. At end-March 2022, the company had a gross cash position of £14.5m, which we estimate will fund operations to end FY Q124 (June 2023).

2 November 2022

Price	**24p**
Market cap	**£14m**
	£:US$1.10
Gross cash (£m) 31 March 2022	14.5
Shares in issue	57.1m
Free float	99.7%
Code	RENE
Primary exchange	AIM
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(14.3)	(13.5)	(78.7)
Rel (local)	(16.8)	(8.4)	(77.3)
52-week high/low		113p	24p

Business description

ReNeuron Group is a UK biotech focused on the development of its stem cell-derived exosome drug delivery platform (CustomEx). The company operates as a contract research and development organisation and has established partners which are progressing the preclinical development of exosome-based therapeutics, utilising ReNeuron's CustomEx technology.

Next events

Expansion of exosome partnerships	FY24
Fosun CTX manufacturing initiated	FY24

Analysts

Soo Romanoff +44 (0)20 3077 5700

Dr Adam McCarter +44 (0)20 3077 5700

healthcare@edisongroup.com

Edison profile page

Investment summary

Company description: A stem cell-derived exosome company

ReNeuron is a UK-based stem cell research company focusing on the development of exosomes, a new class of emerging drug delivery platform, which aims to address challenges associated with existing delivery systems including safety, target specificity and therapeutic payload diversity. The company has reported encouraging preclinical data, demonstrating its exosome technology as potential vehicles for targeted drug delivery to the brain and the enhanced cellular specificity and drug delivery capabilities (siRNA) of its exosome technologies over conventional HEK exosomes. Should clinical utility be demonstrated, these unique properties could offer market differentiation over existing drug delivery methods, in our view. Additionally, the application of the exosome platform in difficult to treat CNS diseases, as well as for the delivery of cell and gene therapies, may represent a potentially significant market opportunity, in our view. However, we note that preclinical results are not necessarily a reliable indicator for clinical success.

ReNeuron currently operates as a contract research and development organisation model on a fee-for-service basis, establishing partnerships in which its exosome platform can be utilised as a drug delivery vehicle for third-party therapies. The company has, so far, established seven preclinical collaborations with industrial and academic partners in progressing exosome-based assets towards the clinic. The group has longstanding expertise in stem cell development and process scale up, having progressed its hRPC programme to Phase II clinical trials and is currently undertaking the technology transfer of its CTX cell line manufacturing to Fosun Pharma. Following a strategic refocus in January 2022, the reshaped management team is prioritising development of its stem cell-derived exosome platform, CustomEx, and, additionally, it intends to identify licensing partners for its legacy cell lines (hRPC and CTX) outside of greater China where they are licensed to Fosun Pharma. The company's new strategy is focused on establishing further developmental partners with the goal of out-licensing its exosome programmes while progressing with its own internal exosome pipeline. With extensive experience in stem cell research and multiple shots on goal with established partners, we see ReNeuron's exosome technology as well positioned, in our view, to deliver clinical assets.

Valuation: £47.3m or 83p per share

We value ReNeuron Group at £47.3m or 83p per share. Our valuation is based on an rNPV calculation for the clinical success of two of ReNeuron's exosome programmes in CNS indications (combined rNPV £27.2m or 47p per share) and the launch of the group's CTX programme in China through Fosun (rNPV £5.7m or 10p per share), and incorporates a gross cash and near cash of £14.5m at end-March 2022. We have assumed the two exosome programmes will target CNS indications, specifically Alzheimer's disease (AD) and Parkinson's disease (PD), and that a full licensing deal for the two exosome programmes is attained in mid-2025 and mid-2026. With the preclinical assets we apply a discount rate of 15.0% and a 12.5% discount rate for the out-licensed Fosun CTX programme. We note that ReNeuron's shares are currently trading only modestly above cash value, dented previously by the halting of the hRPC programme.

Financials: Development funded to FY Q124

At end-March 2022, the company had cash and near cash of £14.5m and no debt. R&D expenses decreased in FY22 due to the discontinuation of clinical activities associated with the Phase II hRPC trial; however, we anticipate these will increase as the company looks to ramp up its exosome developmental activities. Based on our projected burn rates (operating cash outflow FY23e: £9.5m, FY24e: £10.2m) we estimate a cash runway to end Q124 (end-June 2023), in line

with management's guidance. We anticipate that ReNeuron will need to raise c £15m in FY24, which we view as sufficient to fund operations to mid-2025, when we forecast the company will engage in a global licensing deal, receiving an upfront payment of £36m with a milestone payment of £9m in FY26 as the exosome programme progresses into the clinic. We assume an additional licensing deal will be signed in FY26 with a further upfront payment of £36m. In the absence of a licensing deal, we expect the company will need to raise c £15m in FY24 (shown as illustrative debt in our model) with an additional £20m in FY25 to fund operations into H226.

Sensitivities: Early-stage preclinical assets

ReNeuron is subject to the regular risks associated with drug research and development. As the company currently operates as a contract research and development organisation, it will be affected by the development delays or failures, regulatory risks and competitor successes of its partners' preclinical or clinical assets. The group itself may also be exposed to partnering setbacks and financing risks. The largest development sensitivities relate to the company's preclinical exosome pipeline. The exosome platform is still in the early stages of development; therefore, the most prominent near-term risk lies in failure to progress partner programme assets into the clinic. Additionally, due to contractual obligations, ReNeuron is unable, currently, to disclose the details of its established exosome partnerships, making the target markets and indications challenging to predict. Management has communicated that the nature of these collaborations may become more transparent following positive data readouts; however, this may not be realised until clinical progression, the timing of which cannot be easily predicted. The exosome therapeutic market is also significantly underdeveloped, with no FDA approved exosome-based drugs, meaning there is a high degree of uncertainty around future drug pricing and market dynamics.

ReNeuron: A strategic reset to targeted drug delivery

There have been significant changes at ReNeuron in FY22 both in terms of newly developed strategy and management structure. Previously, the company had focused on the clinical progression of its Phase IIa (NCT02464436) hRPC stem cell therapy programme to treat retinitis pigmentosa. The initial patients treated in the study demonstrated a statistically significant improvement in visual object recognition after 12 months (mean 9.9 letter improvement versus baseline in ETDRS letter score); however, the 24-month data collected showed a drop off in efficacy. Additionally, patients treated in the dose expansion arm of the trial experienced complications during the surgical procedure of administration. To further investigate these findings the company would have had to initiate a further Phase II clinical study to identify the suitable patient sub-population that would benefit more from treatment. Following a review with the group's scientific advisory board, management made the decision to halt clinical development of the hRPC study with the intention of identifying out-licensing partners for the existing data package. While this news was disappointing, we see the decision as sensible considering the additional financing the company would have required to fund clinical development and the potentially dilutive nature of future capital raises. Furthermore, the decision has allowed ReNeuron to fully focus on the development of its exosome technology platform which, in our view, represents a significant opportunity in the drug delivery market.

Fresh management structure

Following the change in corporate strategy, ReNeuron appointed Catherine Isted as the group's new chief executive officer (CEO), having previously held the role of chief financial officer (CFO). In her role, Isted brings with her invaluable experience gained from her time at the leading viral vector company Oxford Biomedica, where she was head of corporate development and part of the finance leadership team. During her time at Oxford Biomedica she was part of the team that helped steer

the company during its significant growth period where it entered the FTSE 250. Additionally, Dr Randolph Corteling has been appointed as chief scientific officer (CSO) and will lead ReNeuron's exosome research programmes. Dr Corteling has 24 years' experience in medical research and drug discovery, spanning academia, biotechnology and the pharmaceutical industry. Dr Corteling was responsible for establishing the first exosome programmes at ReNeuron over a decade ago before moving to Evox Therapeutics, a privately listed exosome company, leading the Disease Biology and Exosome Payloads teams. He re-joined ReNeuron in March 2022, heading up research activities as vice president of research before being appointed CSO. Additionally, the company has appointed Simon Dew, who also joins ReNeuron as chief business officer and brings with him extensive experience in the exosomes field. Dew is a senior healthcare executive with significant experience in business development and corporate strategy and formerly worked at Evox, where he played a key role in the pencilling of preclinical licensing deals for Evox with Eli Lilly and Takeda worth up to c $2bn in value. In our opinion, these appointments provide ReNeuron with the management capabilities required to execute the company's strategic expansion into exosome therapeutics.

Exosome partners established

ReNeuron's exosome developmental programme currently consists of seven discovery stage collaborations with both industrial and academic partners, Exhibit 1. The programmes are investigating the use of ReNeuron's proprietary exosome platforms as targeted delivery vehicles across a range of drug types, primarily focused on CNS diseases. The therapeutic payload diversification across its programmes represents an important differentiator for the company's exosome technology, in our view. While the nature of these collaborations remains undisclosed, we anticipate the existing partnerships may have the potential to translate into larger licensing opportunities.

The group has a smaller internal pipeline that it is looking to obtain proof-of-concept data from and, should positive results be achieved, it will explore out-licensing opportunities prior to progression into the clinic.

Exhibit 1: ReNeuron's development pipeline

Source: ReNeuron annual report and accounts 2022

Drug delivery not an afterthought

Clinical investigators continue to make steps in developing the next generation of leading pharmaceutical products; however, there is a risk that the true therapeutic potential of many drugs goes unrealised. This is largely due to the inability to deliver them to their site of action in the body. This is particularly true for CNS diseases, such as PD and AD, which require drugs to target the brain. Targeted delivery to the brain is extremely challenging with c 98% of newly discovered small molecule drugs unable to cross the blood brain barrier (BBB) and we see CNS diseases as key indications in which ReNeuron may offer differentiation with its exosomes platform. Additionally, efforts to improve drug safety profiles remains paramount as it is estimated that almost one in three FDA approved drugs exhibit post market safety issues. New delivery systems must therefore not only demonstrate efficacy but also the ability to safely distribute drugs in patients. With the evolution and development of more complex therapies, such as cell and gene, there is a continued need to develop new drug delivery platforms to address these clinical challenges, in our view.

Delivery platforms in the clinic today

Conventional drug dosage forms such as solutions or immediate-release mechanisms often face difficulties when administered to patients such as non-specific tissue distribution and dosing control. To address these pitfalls the development of more sophisticated drug delivery platforms has made significant headway in recent years. Today, the most clinically advanced technologies can be split into two main categories, viral vectors and non-viral vectors (primarily lipid nanoparticles), Exhibit 2. In contrast, exosomes represent an emerging drug delivery platform that is beginning its transition into the clinic; however, we note that the technology is still very much in its clinical infancy.

Exhibit 2: Selected drug delivery technologies

Drug delivery platform	How it works	Advantages	Disadvantages	Selected FDA approved therapies
Viral vectors	Uses modified, inactivated, versions of viruses to introduce gene-based therapies (DNA or RNA) into target cells	Highly efficient in delivering DNA or RNA High target specificity Can induce effective immune responses	Limited to gene therapy payloads Mutagenic safety concerns with certain vector technologies May trigger adverse immunogenic responses and toxicity Issues with re-dosing due to immune response inhibiting efficacy	Imylgic (gene therapy, oncology) Zolgensma (gene therapy, rare disease) Luxturna (gene therapy, ophthalmology)
Lipid nanoparticles (LNP)	Synthetic nanometre-sized particles, consisting of lipids, which encapsulate and deliver therapies to target cells	Potentially improved safety profiles over viral vectors Enhance bioavailability and efficacy of non-water-soluble drugs Allows for controlled, sustained release of lower doses of drugs	Non-specific tissue distribution of drug Can accumulate in certain tissues including the liver and spleen Technology challenges associated with scale-up manufacturing	Patisiran/ONPATTRO (gene therapy, metabolic disorders) Comirnaty (mRNA vaccine, immunology) Spikevax (mRNA vaccine, Immunology)
Exosomes	Nano-sized extracellular particles, naturally produced by all cells, that can be manipulated to incorporate therapies and target cells with high specificity	Potential to deliver drugs across the BBB Can carry a range of therapeutic payloads Can be used for highly specific, targeted drug delivery with or without modifications Naturally found in the body, which means it is inherently non-immunogenic and offers improved safety profiles	Controlled drug release may provide challenges Mechanism of drug delivery and biology not fully elucidated Technology still in its clinical infancy	No existing therapies

Source: Edison investment research

Viral vector platforms

Viral vectors use modified versions of viruses to deliver genetic material (DNA or RNA) into target cells to illicit a therapeutic response. In a clinical context, they have been utilised in the development of cell and gene therapies. To date, the FDA has approved eight viral vector-based cell and gene therapies, four of which have been approved for direct administration (in vivo) to patients. In recent years, the most notable use of the technology has been the discovery of the Oxford/AstraZeneca COVID-19 vaccine. However, concerns over patient safety have meant the vaccine is yet to receive approval by the FDA. Potential toxicity issues highlights what we see as one of the significant limitations of viral vector therapies. A number of recent clinical incidents, particularly around Adeno-associated virus vectors, have brought viral vector safety into further question. These include trial pauses for both Pfizer and Astella's muscular gene therapy treatments and Novartis's FDA approved Zolgensma, which is being further reviewed for potential liver toxicity. While viral vector therapies are expected to share a significant portion of the drug delivery market, particularly for cell and gene therapies, high-profile adverse patient events and increased regulatory scrutiny may hinder overall clinical uptake, in our view.

Non-viral platforms: Lipid nanoparticles

The most common class of FDA approved non-viral delivery platforms are lipid-based nanomedicines. These formulations use lipid structures to encapsulate drugs with the aim of

improving their physicochemical properties. While lipid-based drugs have been in clinical development for c 30 years, earlier therapies suffer from off-target specificity and unfavourable safety profiles. Advancements in the clinic have seen a new subset of lipid technologies appear called lipid nanoparticles (LNPs). LNPs have advantages over earlier lipid formulations such as improved stability and drug bioavailability. These more sophisticated platforms have found use in the development of gene therapy treatments (DNA or RNA). The FDA approval of Patisiran (ONPATTRO) in 2018 represented a clinical breakthrough for LNPs as the first RNA therapy-delivering nanoparticle. More recently, the COVID-19 pandemic marked a further milestone for LNP technology, acting as critical delivery systems for both the Pfizer-BioNTech and Moderna mRNA vaccines. However, tissue specificity remains a drawback for LNPs and the technology struggles to deliver therapies to tissues in the body other than the liver, inhibiting its application for treating CNS diseases.

Exosomes 101

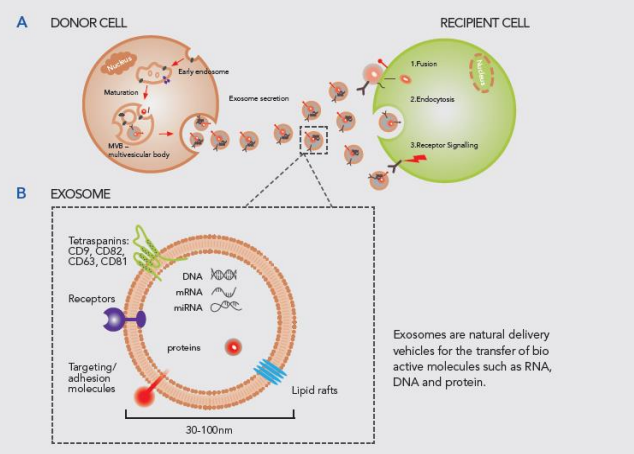
In our opinion, the limitations associated with existing technologies provide an opportunity for new delivery platforms to address these clinically significant challenges. Exosomes represent a new class of drug delivery system, which aims to overcome the drawbacks associated with viral vector and LNP platforms. We see the potential market differentiators of exosomes being:

- Ability to specifically target a range of different tissues
- Ability to improve safety profiles
- Ability to cross a range of biological barriers, particularly the blood brain
- Ability to protect encapsulated therapies from immune system degradation
- Ability to incorporate multiple therapeutic payloads

Exosomes: Harnessing the cellular postmen

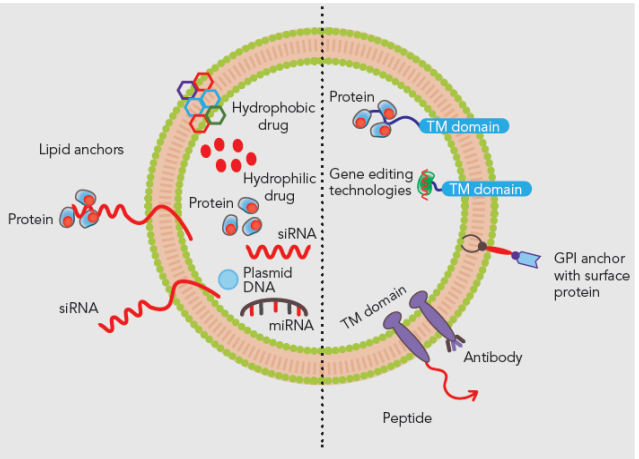
Exosomes are small, membrane bound compartments naturally produced and released by all cells in the body, functioning as transporters of materials (nucleic acids, proteins, lipids) between cells. Once released, they can travel to local tissue cells or through the body to reach more distant sites where they can deliver their biomolecules, playing a critical role in cell-cell communication. The cells from which exosomes originate impart a specific surface marker profile on the exosome, which is recognised specifically by the recipient cells, much like a hand fitting into a glove, Exhibit 3. This natural affinity between exosomes and specific cells has led to significant clinical research investigating exosomes as potential vehicles for targeted drug delivery. Notably, exosomes can be engineered to incorporate a range of therapeutics and their targeted drug delivery capability enhanced through the modification of proteins on the exosome surface, Exhibit 4.

Exhibit 3: How exosomes work



Source: ReNeuron annual report

Exhibit 4: Potential exosome therapy incorporation



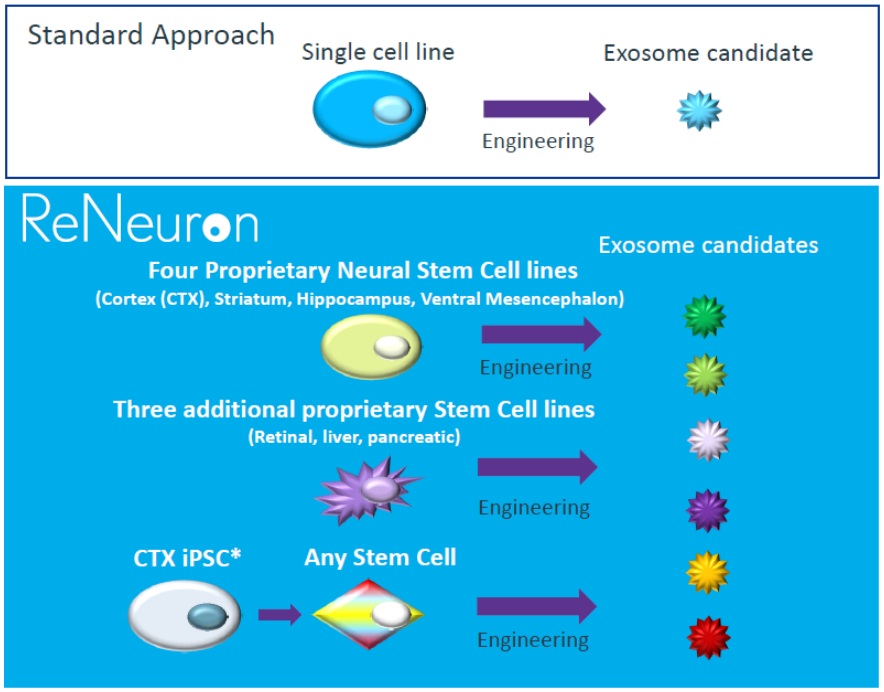
Source: ReNeuron annual report

ReNeuron's exosome approach

Multiple cell lines the differentiator

ReNeuron's exosomes are derived from the group's seven proprietary stem cell lines, four neural stem cell (NSC) lines (Cortex, Striatum, Hippocampus and Ventral Mesencephalon) and three stem cell lines from areas outside of the brain (retinal, liver and pancreatic), Exhibit 5.

Exhibit 5: ReNeuron's exosome platform



Source: ReNeuron corporate deck

Each stem cell line can produce exosomes that have a natural tissue targeting ability based on the parent cell line they are derived from, for example striatum stem cells will produce exosomes that target striatum tissue cells. Additionally, ReNeuron's technology platform allows for stem cell lines to be engineered that can produce exosomes incorporated with therapeutic payloads. The exosomes

may be further engineered through surface modifications to enhance their overall cellular targeting ability.

Exhibit 6: Exosomes competitor analysis

Company	Stem cell line	Advantages	Disadvantages	Targeted indications	Stage
Codiak	HEK293	Scalable production Can be manipulated easily	Difficulty in targeting brain Single cell line only producing single exosome, limiting tissue targeting diversity	Solid tumours and myeloid rich cancers	Two active Phase I clinical programmes (NCT05375604, NCT04592484)
Evox	HEK293	Scalable production Can be manipulated easily	Difficulty in targeting brain Single cell line only producing single exosome, limiting tissue targeting diversity	Rare diseases	Preclinical
ReNeuron	Neural	Can target the brain Low immunogenicity Multiple cell lines offer exosome tissue targeting diversity	Potential scale up challenges	CNS diseases	Preclinical

Source: Derived from Kim et al

The most advanced exosome therapies in the clinic are currently derived from HEK293 stem cell lines, Exhibit 6. While initial data have provided clinical validation of HEK293-derived exosomes as platforms for drug delivery, the use of a single cell line to produce a single type of exosome limits the tissues which they can target. This may result in significant challenges when designing exosomes to target difficult to reach tissues such as crossing the BBB to treat CNS diseases. In our view, ReNeuron's diversification in stem cell lines and ability to produce exosomes with enhanced natural tissue targeting affinity, particularly neural stem cell lines to target CNS indications, currently offers market differentiation against single cell line competitors.

Further potential with iPSCs

In addition to the seven proprietary exosome producer stem cell lines, the company's cortex derived induced pluripotent stem cells (CTX-iPSC) may also offer future upside potential. The CTX-iPSC platform provides an opportunity to generate any stem cell type and, ultimately, any type of tissue-specific exosome. While the technology could significantly enhance the group's exosome platform into new indications and targets, we note that utilisation of the CTX-iPSC cell line to generate exosomes is still in the early stages of preclinical development. However, the group is also progressing the development of the CTX-iPSC cell line as a platform in its own right. ReNeuron has established a collaboration with the University College London, investigating the use of CTX-iPSC in the production of Schwann cells for peripheral nerve damage repair and in the generation of CAR-T and CAR-NK cells. The breadth of diverse exploratory investigations being conducted further highlights the potential utility of the CTX-iPSC platform.

Technology guarantees consistent exosomes

A major challenge faced during exosome production is the need to produce consistent stem cell lines to generate consistent exosomes. Multiple rounds of cell manufacturing (passaging) can often result in changes to the underlying cell lines, resulting in exosomes with varying compositions. The selective tissue targeting ability of exosomes is dictated by their biological structure making it critical to maintain uniformity during production. ReNeuron's patented conditional immortalisation c-mycER technology provides a scalable method to ensure consistent, stable producer cell lines that can generate uniform exosomes. The technology can be applied across each of the group's exosome-producing stem cell lines, working through an on/off switch mechanism where the addition of a chemical stimulator (4-OHT) allows cells to replicate without undergoing changes in cellular composition. Of note, the CTX-cell line can be scaled under good manufacturing practice (GMP) conditions, allowing exosomes to be produced in volumes suitable for late-stage clinical studies. ReNeuron does not currently possess in-house GMP-accredited exosome production facilities for its cell lines – these typically require significant capital expenditure; however, investment or

outsourcing may be options management can consider for expansion. The company's technological know-how, reproducible exosome manufacturing capabilities and experience in scale-up manufacturing, make ReNeuron an attractive developmental partner within the therapeutic exosome market, in our view.

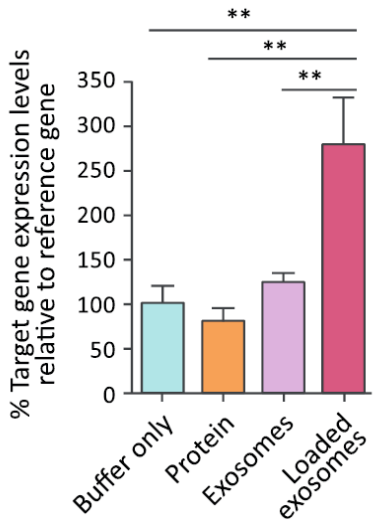
Robust IP position

Management attests that ReNeuron boasts the third largest global patent portfolio in the field of exosomes (Exhibit 6) and we see the true value centring around two main patent families. The first (WO2013150303) provides the company with exclusivity around using any type of neural stem cell to generate therapeutic exosomes. The patent has been granted in the EU and a US application is currently pending. The second (WO2014125277) surrounds the group's proprietary c-mycER conditional immortalisation technology. The protection covers both the production of stem cells through the c-mycER chemical switch mechanism and the use of a conditionally immortalised cell line to produce exosomes. The latter patent covers a range of cell types to generate therapeutic exosomes including the iPSC cell lines which, owing to their exosome diversification potential, we view as of significant importance. With extensive protection across its conditionally immortalised stem cell lines and patent lives extending beyond 2030, this provides ReNeuron with a distinct competitive advantage and the ability to leverage its intellectual property (IP) position to secure future licensing deals and create longer term value, in our opinion.

Preclinical encouragement

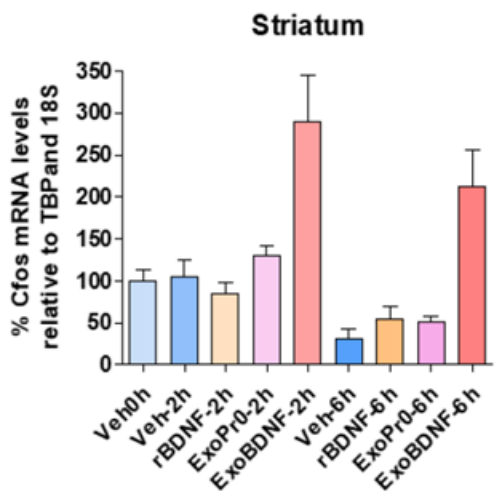
ReNeuron continues to work with its partners to progress its exosome platforms towards the clinic; however, the company has already reported encouraging preclinical proof-of-concept data demonstrating the technology's unique targeting ability and potential clinical utility. In a preclinical mouse model, NSC-derived exosomes were loaded with a therapeutic protein on their surface called brain derived neurotrophic growth factor (BDNF). BDNF is a neurotransmitter modulator that plays an important role in neural cell survival, growth and neuronal plasticity by activating the mitogen-activated protein kinase (MAPK) pathway. The mouse model data highlighted that those mice treated with BDNF engineered, NSC-derived exosomes experienced increased levels of gene expression associated with the MAPK pathway, Exhibit 7. The response was not observed in mice treated with BDNF or exosomes alone demonstrating the improved delivery of a functional protein to the brain when incorporated into tissue targeting exosomes.

Exhibit 7: Gene activation by therapeutic exosomes



Source: ReNeuron corporate presentation

Exhibit 8: Gene activation of striatum cells after two and six hours



Source: ReNeuron corporate presentation

Of note, a sustained response (up to six hours) was observed selectively in the striatum with only a transient response (up to two hours) in the hippocampus and no responses in any other areas of the brain, Exhibit 8. Neuropathological changes in striatal cells have been associated with diseases such as PD and Huntingdon's, so this highlights the potential clinical utility of ReNeuron's platform. Additionally, this targeted delivery was achieved by lumbar puncture (administration into spinal fluid) and did not require direct injection into the brain, providing a potentially safer and cheaper method for patient dosing.

In October 2022 ReNeuron announced positive results from a further preclinical study in which it demonstrated the enhanced cellular specificity and drug delivery capabilities of its exosome technologies over conventional HEK exosomes. ReNeuron's exosomes displayed a minimum 10-fold increase in cellular uptake across three cell types (endothelial, neural and epithelial) versus HEK-derived exosomes, with an 18-fold increase observed in endothelial cells. Additionally, when loaded with a therapeutic payload (small interfering RNA, siRNA), a 600% improvement in delivery to the target cell was recorded versus HEK exosomes. These results therefore not only provide encouraging signs for the clinical progression of ReNeuron's exosomes but may also provide a distinct competitive advantage against HEK competitors, in our view.

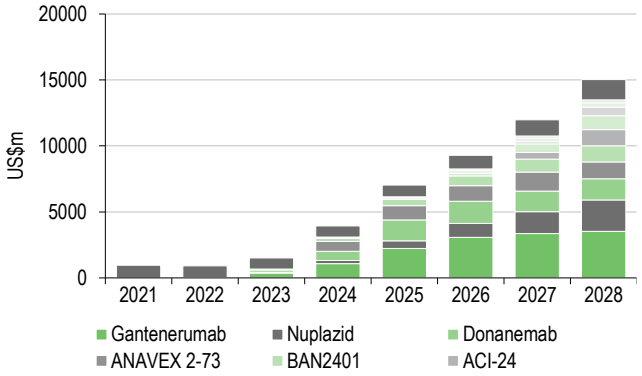
Notably, the study was able to demonstrate the effective delivery of siRNA, a new class of complex drug modality, in which targeted drug delivery is a significant challenge and overcoming first-pass liver metabolism remains a developmental issue. The RNA therapeutic pipeline is poised to deliver further drug candidates, so we view this market as a potential opportunity for ReNeuron to target. However, we recognise that results from these early-stage preclinical studies may not necessarily translate into the clinic.

CNS diseases an obvious target

While exosomes have the potential to target a range of indications, in our view, CNS indications are key markets in which ReNeuron's exosomes could offer a competitive advantage with regards to safety and neural targeting ability. AD and PD are currently two of the most sizeable markets in the CNS space and ones in which much clinical research is concentrated. EvaluatePharma estimates that the markets for AD and PD treatment will reach $15.0bn and $7.8bn by 2028 respectively, with both markets being highly fragmented. We believe this provides opportunities for companies

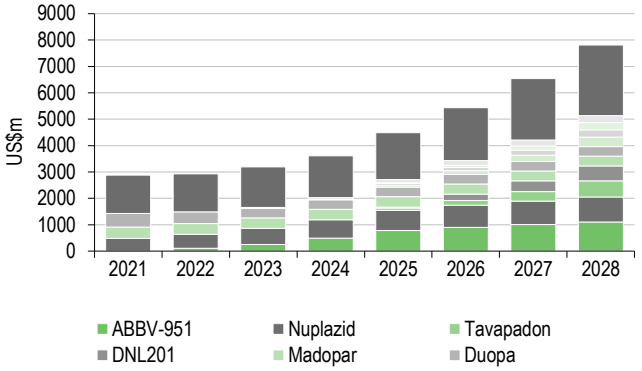
addressing these indications as they may be able to garner significant market share. Additionally, there are currently no approved disease modifying therapies (drugs treating the underlying cause of the disease not just symptoms) to tackle PD and only one for AD (Aduhelm). In particular, the trend for AD clinical trials is moving to treat earlier-stage symptoms of the disease and, in our view, the next generation of therapies which will begin to appear from the clinic will focus on disease modification as opposed to symptomatic treatments. Such therapies are likely to be more complex than traditional small molecules, examples include RNA therapeutics, a pipeline which is poised to deliver future drug candidates. With its encouraging siRNA preclinical data and neural targeting ability, ReNeuron's exosomes may be uniquely positioned to incorporate such modalities to tackle large CNS indications with unmet need. However, we acknowledge that exosomes are still in the very early stages of development and may take significant time before clinical success is realised.

Exhibit 9: Estimated AD treatment market to 2028



Source: EvaluatePharma

Exhibit 10: Estimated PD treatment market to 2028



Source: EvaluatePharma

Exosomes pencilling preclinical deals

While therapeutic exosomes may still be in their clinical infancy there have been a handful of licensing agreements secured amongst leading exosome research companies. The most substantial of these have involved Codiak, Evox and PureTech Health, which have amassed combined deal values worth up to c $3.4bn to develop exosome-based therapeutics, Exhibit 11. Additionally, Codiak's GMP exosome production facilities were recently acquired by Lonza in a deal that will see Codiak receive c $65m of manufacturing services in kind. Notably, these partnerships have been established during early drug development indicating the potential value and upside that can be realised through demonstrating robust preclinical proof-of-concept data. With its seven established partnerships, we view ReNeuron's pipeline as being uniquely positioned for potential future out-licensing opportunities, should positive data be generated. Monetisation of its preclinical exosome assets is a key focus for management, deals of which would represent a significant catalyst for the share price. However, a breadth of statistically significant preclinical data will have to be generated before such deals could be realised.

Exhibit 11: Exosome licensing deals

Exosome company	Deal partner	Indication	Phase	Upfront milestone payments ($m)	Total potential deal value ($m)
Codiak	Jazz Pharmaceuticals	Multiple cancers	Preclinical	56	276
Codiak*	Sarepta	Neuromuscular disease	Preclinical	Undisclosed	72.5
Evox	Takeda	Rare diseases	Preclinical	44	882
Evox	Eli Lilly	CNS indications	Preclinical	20	1,200
Evox	Boehringer Ingelheim	Undisclosed	Preclinical	Strategic partnership	Undisclosed
PureTech Health	Roche	Immunological disorders	Preclinical	36	1,000
			Median	40	c 180/asset

Source: Edison Investment Research. Note: *Deal terminated.

A leading developmental partner the ultimate end goal

ReNeuron currently operates as a contract research and development organisation, generating early-stage revenue streams through its exosome research services. However, management's longer-term ambitions lie in becoming a key developmental partner, establishing multiple partner programmes with licensing agreements consisting of upfront milestones related to development and back-end royalties on sales. The key differentiator that ReNeuron's business will drive growth and derive value from is its technology-enabling CustomEx platform which limits the possibility of switching to competitive technologies, something that may be possible with conventional HEK derived exosomes. Unlike CDMOs such as Oxford Biomedica, the company does not currently foresee becoming a large-scale GMP-accredited manufacturing partner. Instead, the group will focus more on smaller scale manufacturing capabilities for preclinical and potentially early-stage clinical requirements and will look to outsource larger scale production to third parties. The company has significant technology transfer experience having previously tech transferred the manufacturing of it clinical stage stem cell programmes to CMOs. We see this as a sensible strategy for ReNeuron that removes the risk of conducting large capital expenditure programmes requiring significant investment.

Creating value from legacy assets

With ReNeuron now fully committed to the development of its exosome platforms, management intends to monetise its legacy CTX and hRPC stem cell clinical programmes by pursuing out-licensing deals. A primary focus for the company will be to continue to work with its established partner, Fosun Pharma, while identifying further out-licensing opportunities in geographies outside of China.

Fosun: A key strategic partner

ReNeuron entered into a licensing agreement with Fosun Pharma in 2019 for the development, manufacture and commercialisation of both its CTX and hRPC stem cell therapy programmes in China. ReNeuron received an initial payment of £6m as part of the deal and is eligible to receive future, post-launch, operational and regulatory milestone payments estimated by management to be worth up to £80m as well as double-digit (12–14%) tiered royalties on sales. The deal terms are constituted from both the hRPC and CTX programmes; however, Fosun has prioritised the development of the CTX programme aimed at treating post stroke rehabilitation. In July 2022, the supplemental terms for an additional technology transfer and supply agreement was signed whereby ReNeuron will provide its CTX cell bank line and scale-up expertise. The deal will see the company potentially receive up to an additional c £6m in total (£1m over 24 months and £5m in the medium to long term). Additionally, Fosun is expected to complete construction of a new GMP-regulated facility to manufacture CTX, with completion aimed for Q123, underpinning Fosun's commitment to the programme. Notably, ReNeuron has previously demonstrated the efficacy of its CTX stem cell to treat patients suffering from stroke disability as part of its Phase II (PISCES II) study. The study's primary endpoint was for a minimum of two patients to exhibit a minimum two-point improvement in the Action Research Arm Test, three months post treatment. Three patients achieved this up to 12 months after treatment. This clinical proof of concept data will be significant in attracting interest from potential future partners outside of China, in our view.

Phase II hRPC setback shifts focus to out-licensing

As part of its strategic refresh, ReNeuron is seeking to capitalise on its hRPC cell therapy programme, following the results of its Phase IIa study in retinitis pigmentosa. While no serious

adverse events were recorded and promising 12-month efficacy data in certain patients observed, efficacy waned after 24 months in treated patients and additional clinical studies were required to identify those patient sub-populations that would benefit most from treatment. Management is currently completing the existing data package, expected in Q422, with the intention of out-licensing it to a third party. In our view, the encouraging initial data reported from the study provides a licensing partner with a robust platform to refine future study scopes and progress development.

Sensitivities

ReNeuron is subject to the regular sensitivities associated with drug research and development. The company's prospects will be affected by development delays or failures, regulatory risks, competitor successes, partnering successes and financing risks. As ReNeuron's developmental pipeline is comprised purely of preclinical assets, the most near-term risk for the company would be the failure to progress its exosomes programmes into the clinic. Additionally, the company's undisclosed pipeline also provides significant challenges with regards to assessing the potential target markets, competitive landscape and valuation. Future clinical progression may allow additional transparency, which would further refine the overall market opportunity and investment case. While exosomes may offer advantages over existing technologies, viral vectors and LNPs are well established drug delivery platforms with approved therapies. The clinical infancy of exosomes may result in longer timescales before such therapies are launched into the market. However, we note that a number of preclinical exosome companies are looking to progress their exosome platforms into the clinic, achievement of which would provide further confidence in the clinical utility of exosomes.

Valuation

We value ReNeuron Group at £47.3m or 83p per share. Our valuation is based on an rNPV calculation for the clinical success of two of ReNeuron's exosome programmes in CNS indications (combined rNPV £27.2m or 47p per share), the launch of the group's CTX programme in China through Fosun (rNPV £5.7m or 10p per share) and incorporates a gross cash position of £14.5m at end-March 2022. With the preclinical assets we apply a discount rate of 15.0% and a 12.5% discount rate for the out-licensed Fosun CTX programme. A breakdown of our valuation assumptions can be found in Exhibit 12. We note that ReNeuron's shares are currently trading only modestly above cash value, dented previously by the halting of the hRPC programme; however, there is clear upside from the potential of the exosome platforms, albeit ascribed little value by the market due to their preclinical status.

For the purposes of our model, we have selected AD and PD as indications that ReNeuron's exosomes may find clinical application for the following reasons:

- These CNS diseases are the focus of intense clinical research with almost no approved disease modifying therapies.
- More complex therapies (such as RNA) are likely to be developed to target these diseases, requiring more sophisticated drug delivery technologies.
- There remain significant challenges in developing new drugs crossing the BBB.
- ReNeuron's neural stem cell-derived exosomes dovetail targeting CNS indications.

Exhibit 12: rNPV assumptions

Indication	Assumptions
Exosome programme 1 (AD)	■ **Target market**: We assume one of ReNeuron's prospective exosome partners will develop drugs targeting AD and we model our patient population using relevant statistics for this indication. Our assumptions are based on targeting AD patients with mild cognitive impairment, which represents 50% of patients diagnosed with AD. We assume the partner will achieve a peak penetration of 5%.
	■ **Pricing and licensing**: Based on the initial price per patient per year for Aduhelm of $56k we assume a target price of $56k per patient per year in the US, with a 50% discount in the EU5. We assume that ReNeuron will secure a licensing deal for its first exosome programme in 2025 receiving up to $40m (£36m) in upfront payments, a further $140m (£127m) in developmental and sales milestones and low double-digit royalties on net sales.
	■ **Trial timelines and R&D cost:** £4.2m in FY23, £4.6m in FY24 and £5.1m in FY25 to fund preclinical development. Assuming a licensing deal is secured in FY25 we expect the licensee to assume all subsequent development and commercialisation costs and the initiation of clinical studies in FY26.
Exosome programme 2 (PD)	■ **Target market**: We assume one of ReNeuron's prospective exosome partners will develop drugs targeting PD and we model our patient population using relevant statistics for this indication. We assume a prevalence of PD of 0.3% in the US and 0.35% in the EU.. We assume that the partner will achieve a peak penetration of 1%
	■ **Pricing & Licensing**: Based on the price per patient per year for Nuplazid of $40k (Evaluate Pharma) we assume a target price of $40k per patient per year in the US, with a 50% discount in the EU5. We assume that ReNeuron will secure a licensing deal for its second exosome programme in 2026 receiving up to $40m (£36m) in upfront payments, a further $140m (£127m) in developmental and sales milestones and low double-digit royalties on net sales.
	■ **Trial timelines and R&D cost:** £4.2m in FY23, £4.6m in FY24, £5.1m in FY25 and £5.6m in FY26 to fund preclinical development. Assuming a licensing deal is secured in FY25, we expect the licensee to assume all subsequent development and commercialisation costs and the initiation of clinical studies in FY27.
Fosun Pharma CTX stroke programme (China)	■ **Target market**: We assume an incidence rate of stroke in China of 0.003%. Of these, we assume 70% suffer an ischemic stroke, 80% of patients survive and 30% of patients who survive are left severely disabled and would be eligible for treatment. We assume a peak market penetration of 2%
	■ **Licensing:** Based on an estimated average price per patient per year cost of Brilinta ($53k) and Radicava ($94k) for acute ischemic stroke and a discount of 60% for being included in the Chinese National Reimbursement Drug List (NRDL), we assume a price for the CTX stem cell therapy of $28k per patient per year in China.
	■ **Trial timelines and R&D cost:** Fosun will fund all future development and commercialisation costs for the CTX programme. We assume clinical development will progress into Phase III studies in FY26 with an estimated market launch in China in FY28.

Source: Edison Investment Research

ReNeuron is currently unable to disclose details of the indications being targeted in collaboration with its existing developmental partners so our valuation may be significantly altered should additional details of the target markets, mechanism of action and drug modalities be revealed.

In our model we assume that for our selected target market of AD, a conservative peak penetration of 5% is achieved by one of ReNeuron's developmental partners, for which ReNeuron will be entitled to tiered royalties on sales. We assume approval of the AD exosome-based therapy in 2031 and estimate global peak sales of $7,631m (£6,875m) in 2037. Our estimated price of $56,000 per patient per year is based on the per patient initial price set by Biogen for Aduhelm, the first FDA-approved disease modifying AD therapy.

In our second selected exosome programme, for PD, we assume regulatory approval will be achieved in 2032 with a conservative peak penetration of 1% and global peak sales in 2038 of $682m (£614m). Our estimated price of $40,000 per patient per year is based on the cost per patient per year for Nuplazid (c $40,000, EvaluatePharma), for the treatment of hallucinations and delusions associated with PD.

Our timelines for clinical development are based on the clinical progression of Onpattro, the first RNAi LNP technology to be launched into the market, entering the clinic in 2012 before receiving FDA approval in 2018. As the exosome programmes are still in very early stages of development, we have assigned a PoS of 2%. We will revisit these assumptions upon clinical progression and on disclosure of further details of the indications.

For the Fosun CTX programme we have assumed that the total potential deal value (£80m, $105m at the time of securing in January 2019), assuming successful launch, is split equally between both the hRPC and CTX programmes for regulatory and milestone payments. We have assumed Fosun will prioritise clinical development of the CTX programme with a product launch in FY28. Our estimated price for the CTX therapy is based on the average price of two marketed drugs to treat acute ischemic stroke, Brilinta ($53k per patient per year) and Radicava ($94k per patient per year).

Drug pricing in China is governed by inclusion on the Chinese NRDL, which significantly discounts drug prices by up to 60%. We therefore assume a price of $28k per patient per year in China. The CTX cell represents a clinical asset that has already demonstrated clinical proof-of-concept from the Phase II PISCES study; however, we note that Fosun's clinical development strategy for the CTX programme is still undisclosed, so we assign a PoS of 5%.

Exhibit 13: ReNeuron rNPV breakdown

Product	Launch	Peak	Peak sales (£m)	Value (£m)	Probability (%)	rNPV (£m)	rNPV/share (p)
Exosome Programme 1 (AD)	2032	2037	6,875.4	644.7	2	22.5	39
Exosome Programme 2 (PD)	2033	2038	614.4	68.2	2	4.7	8
Fosun Pharma CTX Programme	2028	2033	377.0	100.4	5	5.7	10
Gross cash at 31 March 2022 (including bank deposits)				14.5	100	14.5	25
Valuation				**822.9**		**47.3**	**83**

Source: Edison Investment Research

According to our model, a combined 57% of value is derived from the two exosome programmes (47% in AD and 10% in PD), 12% from the CTX Fosun programme and 31% from the company's gross cash position at 31 March 2022. In our valuation we assume clinical success will be achieved from two of the seven existing exosome partnerships and that licensing deals for each are found in FY25 and FY26, at which point partners will assume full development and commercialisation costs. In line with previous preclinical exosome deals (Exhibit 8) we assume the two licensing deals will be worth up to c £160m (180m) in value, with ReNeuron receiving c £36m ($40m) in upfront payments and £127m ($140m) in sales, regulatory and developmental milestones. We have also assumed that as part of any future licensing deal ReNeuron will be subject to low double-digit royalties on net sales. This is in line with a precedent transaction pencilled by Evox and Eli Lilly, utilising Evox's exosome platform as part of a CNS drug development programme.

Financials

As part of the technology transfer and supply agreement signed with Fosun Pharma the company received an upfront payment of £0.32m in January 2022, which we anticipate will be recognised in FY23. ReNeuron is set to receive a further £0.68m over the next two years with potentially an extra £5m in the medium to long term for provision of its CTX cell bank vials. The company is subject to future milestone and royalty payments from Fosun Pharma as it develops the CTX programme; however, additional details on timelines, clinical strategy and route to market need to be communicated before these can be factored into our model.

In FY22 ReNeuron recorded revenues of c £0.4m (FY21: c £0.25m) associated with research services (c £0.3m) and royalties (c £0.1m, c 30% y-o-y growth) from one of the company's legacy stem cell lines. The company has stated its ambitions to grow its revenue base through additional partnerships, building upon its seven existing research collaborations. Overall, we anticipate revenue to increase to £0.8m in FY23 and £0.9m in FY24 as a result of Fosun payments, contract revenue from customers and existing royalties. We anticipate a further milestone payment of £1.8m in FY25 as the technology transfer with Fosun is completed and Fosun initiates CTX stem cell production.

The group is eligible to receive R&D tax credits at 14.5%, for which the company received £1.4m in FY22. The company's total operating expenses were £11.6m (FY21: £13.2m) consisting of £8.1m in R&D expenses (FY21: £9.5m) and £3.5m (FY21: £3.7m) in general and administrative costs, resulting in operational losses for the period of £11.2m (FY21: £12.9m). The reduction in R&D costs was primarily driven through the cessation of clinical activities for the hRPC programme. We expect

R&D expenses to increase as the company produces data to grow and enhance the CustomEx exosomes platform and proprietary products and forecast R&D expenses of £8.1m in FY23 and £8.9m in FY24. Overall, we estimate operating losses for ReNeuron in FY23 and FY24 to be £11.1m and £12.0m, respectively.

At end-March 2022 the company reported a net cash and near cash of £14.5m and no debt. ReNeuron reported operating cash burn of £7.4m for FY22, which we estimate will increase to £11.4m in FY23e and £10.2m in FY24e providing a cash runway to end FY Q124 (ie to mid-June 2023). For the purpose of our model, we anticipate that ReNeuron will need to raise c £15m in FY24 which we view as sufficient to fund operations to mid-2025, when we assume in our model that the company will engage in a global licensing deal, receiving an upfront payment of £36m with a milestone payment of £9m in FY26 as the exosome programme progresses into the clinic. We assume an additional licensing deal will be signed in FY26 with a further upfront payment of £36m. In the absence of a licensing deal, we expect the company will need to raise c £15m in FY24 with an additional £20m in FY25, which will fund operations into H226. We include this in our model as illustrative debt.

Exhibit 14: Financial summary

Accounts: IFRS, Yr end: March 31, GBP(£):000s	2021	2022	2023e	2024e
PROFIT & LOSS				
Total revenues	335	403	799	906
Cost of sales	0	0	0	0
Gross profit	335	403	799	906
Total operating expenses	(13,249)	(11,631)	(11,890)	(12,892)
Research and development expenses	(9,503)	(8,068)	(8,149)	(8,964)
SG&A	(3,746)	(3,563)	(3,741)	(3,928)
Operating income (reported)	(12,914)	(11,228)	(11,091)	(11,986)
Finance income/(expense)	(496)	170	50	(3)
Exceptionals and adjustments	0	0	0	0
Profit before tax (reported)	(13,410)	(11,058)	(11,040)	(11,988)
Profit before tax (normalised)	(13,410)	(11,058)	(11,040)	(11,988)
Income tax expense (includes exceptionals)	2,063	1,369	1,601	1,738
Net income (reported)	(11,347)	(9,689)	(9,439)	(10,250)
Net income (normalised)	(11,347)	(9,689)	(9,439)	(10,250)
Basic average number of shares, m	39.1	57.0	57.0	57.0
Basic EPS	(0.29)	(0.17)	(0.17)	(0.18)
Adjusted EPS	(0.29)	(0.17)	(0.17)	(0.18)
Dividend per share	0.00	0.00	0.00	0.00
BALANCE SHEET				
Tangible assets	213	288	250	167
Intangible assets	186	186	186	186
Right-of-use assets	473	373	298	239
Other non-current assets	0	0	0	0
Total non-current assets	872	847	735	592
Cash and equivalents	22,203	14,548	2,781	7,119
Current tax receivables	1,832	1,392	1,601	1,738
Trade and other receivables	444	536	563	591
Other current assets	0	0	0	0
Total current assets	24,479	16,476	4,945	9,448
Non-current loans and borrowings	0	0	0	0
Non-current lease liabilities	562	416	254	106
Long term debt	0	0	0	15,000
Total non-current liabilities	562	416	254	15,106
Accounts payable	5,727	6,873	4,811	4,571
Illustrative debt	0	0	0	0
Current lease obligations	157	146	165	165
Other current liabilities	0	0	0	0
Total current liabilities	5,884	7,019	4,976	4,736
Equity attributable to company	18,905	9,888	449	(9,802)
	0	0	0	0
CASH FLOW STATEMENT				
Operating income	(12,914)	(11,228)	(11,091)	(11,986)
Depreciation and amortisation	380	324	412	442
Share based payments	764	649	0	0
Other adjustments	6,025	1,788	1,392	1,601
Movements in working capital	(307)	1,056	(2,089)	(269)
Cash from operations (CFO)	(6,052)	(7,411)	(11,375)	(10,211)
Capex	(25)	(302)	(300)	(300)
Acquisitions & disposals net	0	0	0	0
Other investing activities	27	26	73	14
Cash used in investing activities (CFIA)	2	(276)	(227)	(286)
Capital changes	16,265	23	0	0
Debt Changes	(154)	(157)	(165)	(165)
Other financing activities	(7,500)	2,500	5,000	0
Illustrative Debt	0	0	0	15,000
Cash from financing activities (CFF)	8,611	2,366	4,835	14,835
Cash and equivalents at beginning of period	12,625	14,703	9,548	2,781
Increase/(decrease) in cash and equivalents	2,561	(5,321)	(6,767)	4,338
Effect of FX on cash and equivalents	(483)	166	0	0
Cash and equivalents at end of period	14,703	9,548	2,781	7,119
Net (debt)/cash	14,703	9,548	2,781	(7,881)

Source: Edison Investment Research, ReNeuron company accounts

Contact details	Revenue by geography
ReNeuron Pencoed Business Park, Pencoed, Bridgend, CF35 5HY United Kingdom +44 (0) 203 819 8400 https://www.reneuron.com/	N/A

Management team

CEO: Catherine Isted ACMA	Chief scientific officer: Dr Randolph Corteling
Catherine Isted was appointed CEO in September 2022, having joined ReNeuron's board and been CFO since October 2021. Isted was previously part of the finance leadership team at Oxford Biomedica, a global leading cell and gene therapy company, heading up the corporate development and IR teams and helping the business grow over 800%, enter the FTSE250 and pass through £1bn market capitalisation.	Dr Randolph Corteling was appointed chief scientific officer in September 2022, after re-joining ReNeuron as vice president of research in March 2022. Dr Corteling has 24 years' experience in medical research and drug discovery, spanning academia, biotechnology and the pharmaceutical industry. He gained his PhD in medical and surgical sciences at Nottingham University, followed by three years as a heart and stroke foundation postdoctoral fellow at the University of Calgary, Canada. Prior to joining ReNeuron, Dr Corteling led the disease biology and exosome payloads teams at Evox Therapeutics.
CFO: John Hawkins	
John Hawkins was appointed CFO in September 2022. Hawkins joined ReNeuron in October 2014 as financial controller and was appointed company secretary in June 2021. Prior to joining ReNeuron Hawkins worked in the financial services sector where he specialised in business partnering, helping to drive growth and profitability. During this time, he played a lead role in a number of acquisitions and played a key role in the $1bn sale of a division of Standard Chartered Bank to The Lloyds Banking Group.	

Principal shareholders	(%)
Griffiths (Richard Ian)	11.46
Obotritia Capital KGaA	7.83
Octopus Investments Ltd	5.86
Rosetta Capital Ltd	5.63
Arix Capital Management Limited	5.25
The Invus Group, LLC	3.73
Schroder Investment Management Ltd. (SIM)	3.60

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Frankfurt +49 (0)69 78 8076 960
Schumannstrasse 34b
60325 Frankfurt
Germany

London +44 (0)20 3077 5700
280 High Holborn
London, WC1V 7EE
United Kingdom

New York +1 646 653 7026
1185 Avenue of the Americas
3rd Floor, New York, NY 10036
United States of America

Sydney +61 (0)2 8249 8342
Level 4, Office 1205
95 Pitt Street, Sydney
NSW 2000, Australia