e-therapeutics

Enhancing siRNA drug discovery with LLMs

e-therapeutics is a biotech leveraging its validated computational biology platform to identify novel, liver-associated targets and expand its internal pipeline of short interfering RNA (siRNA or RNAi) therapeutics. In addition to the advantages of focusing on a single cell type (hepatocytes), the company's recent strategic commitment to large language model (LLM) technologies has the potential to provide accelerated access to effective new drugs. RNAi medicines are a rapidly evolving drug class, with five drugs currently that use this technology. We view RNAi as a key growth market for e-therapeutics. At end-January 2023, the company had a net cash position of £31.7m, supported by a capital raise of £13.4m (net proceeds) in September 2022.

A differentiating approach in hepatocytes and RNAi

To our knowledge, e-therapeutics' computational biology platform is the only application of artificial intelligence (AI) in the industry that combines hepatocyte-centric disease biology modelling with novel RNAi development. There continues to be a diverse range of hepatocyte-associated disease indications (not restricted to diseases of the liver) with untapped, novel targets, providing scope for new treatments to have a unique offering. Additionally, global sales of RNAi drugs are projected to reach c $14bn by 2028 (EvaluatePharma), representing an attractive opportunity for new RNAi therapies to garner market share.

Partnering strategy to maximise value retention

e-therapeutics intends to leverage its computational biology and RNAi platforms to develop novel RNAi treatments, progressing selected assets into early clinical studies (Phase I) before seeking non-dilutive partnership transactions for its RNAi/liver centric candidates. It has multiple preclinical programmes across haematology and cardiovascular indications as well as non-alcoholic steatohepatitis (NASH). While management has not yet provided guidance on timings, we see the initiation of clinical trial programmes as the next major catalyst for investor attention.

Cash runway to support strategy execution

At end-January 2023, e-therapeutics had a net cash position of £31.7m, aided by a £13.4m capital raise (net proceeds) in Q3 CY22. At the FY23 underlying operating cash burn rate of £9.6m, this would provide a cash runway into H1 CY26. While operational costs may increase as the company progresses its RNAi assets into clinical studies, management asserts that with its computationally enabled and potentially expedited development strategy, operational costs should be significantly lower than those incurred by traditional drug development programmes.

Historical figures

Year end	Revenue (£m)	PBT (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
01/21	0.3	(4.5)	(0.99)	0.0	N/A	N/A
01/22	0.5	(9.5)	(1.65)	0.0	N/A	N/A
01/23	0.5	(9.8)	(1.54)	0.0	N/A	N/A

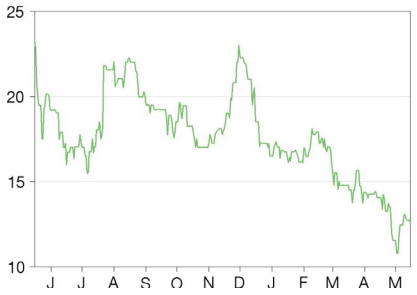
Source: Company accounts. Note: *EPS is diluted.

Pharma and biotech

16 May 2023

Price	12.6p
Market cap	£73m

Share price graph



Share details

Primary code (secondary code)	ETX (ETXPF)
Primary exchange (secondary exchange)	LSE (OTCQX)
Shares in issue	582.7m
Net cash at end-January 2023	£31.7m

Business description

e-therapeutics is a UK biotech using its proprietary computational biology and RNAi platforms to discover novel disease targets and therapies. The company is specifically focused on leveraging its expertise to design treatments targeting one cell type in the liver, hepatocytes. e-therapeutics is currently progressing multiple preclinical programmes in haematological, cardiovascular diseases and NASH.

Bull

- Platform approach has potential to identify novel disease targets with little market competition.
- To our knowledge, it is the only platform approach in the market combining hepatocyte focused disease modelling with RNAi discovery.
- RNAi therapies have potential to be developed against any disease-associated gene.

Bear

- Risk associated with early-stage preclinical pipeline.
- Failure to clinically validate the RNAi platform would affect partnering opportunities.
- Increased costs associated with clinical development may require additional funding.

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Overview: A computational focus on hepatocytes

Founded in 2003, e-therapeutics is a UK-based biotech leveraging its computational biology platform (called HepNet) to discover novel hepatocyte-associated therapeutic targets, and develop novel RNAi medicines using its RNAi platform (called GalOmic). The company has previously partnered with large pharmaceutical companies such as Merck and Novo Nordisk, which have used e-therapeutics' capabilities as part of early-stage drug discovery programmes in small molecule and disease target identification. Additionally, the company has collaborated with mid-size biopharma partners Galapagos and iTeos (still in progress), across a variety of therapeutic areas, helping generate milestone revenue payments and providing validation of e-therapeutics' platform approach.

Over the last two years, e-therapeutics has focused on developing a proprietary liver-targeting RNAi platform approach and filed patent applications to protect its novel GalNAc and RNAi stabilisation chemistry. The company has also further developed its computational biology capabilities (HepNet) by focusing on one cell type in the liver – hepatocytes. The strategy of understanding biology as a first principle and doing so in hepatocytes enables e-therapeutics to train its deep learning algorithms and functional tools on comprehensive hepatocyte-specific data resources. This potentially provides more accurate disease/biological process modelling, novel target identification and the ability to predict the behaviours of potential targets, as opposed to computational approaches applied to broader or more systemic disease approaches, in our view.

In addition to disease biology modelling, the company is also utilising its RNAi liver platform (GalOmic) to expedite the design and production of novel therapies. RNAi-based therapeutics are a rapidly evolving commercial-stage category of new drugs showing promise as treatments for disease pathways and targets previously considered 'undruggable' through conventional small molecule medicines. Unlike small molecules, which often target disease associated proteins, RNAi products aim to stop the production of these proteins altogether by targeting the root cause of the problem, that is the expression of the underlying genes that make them (gene silencing), much like targeting the roots of a weed. Such treatments have now been clinically validated, with the FDA having, to date, approved five RNAi therapies. The company's preclinical pipeline consists of multiple programmes in haematology, cardiovascular indications and NASH, which management claims are assessing novel disease targets. Should any of these programmes deliver clinical candidates, this would represent a significant catalyst for investor attention, in our view. Management also states that it has a large portfolio of additional target ideas that are being continuously discovered and assessed. With an approach that puts the identification of novel gene targets associated with hepatocyte disease biology at the forefront and a focus on discovering and bringing next-generation RNAi medicines into the clinic, e-therapeutics is positioning itself to potentially create value from its platform approach and differentiate itself in the market, in our view.

Financials: R&D spending designed to support growth

e-therapeutics reported total operating losses for FY23 of £10.2m, with R&D expenses totalling £7.2m, 18% y-o-y higher than FY22. These costs were associated with increased outsourced contract research organisation expenses related to the development of the company's computational biology and RNAi discovery platforms, as well as IP related expenses. This translated to an underlying operating cash burn of £9.6m for FY23, with the company reporting a year-end cash and cash equivalents position of £31.7m. In September 2022, the company announced a capital raise of £13.4m (gross £13.5m less related costs and commissions of £0.1m) through a share issue subscription by funds managed by M&G Investment Management.

Sensitivities: Clinical validation of RNAi drug candidates

e-therapeutics is subject to all the regular sensitivities associated with drug research and development. The company's prospects may be affected by development delays or failures, regulatory risks, competitor successes, partnering setbacks and financing risks. As the company is in the preclinical stages of drug development, the largest development sensitivity relates to validation of the company's computational biology platform by producing RNAi clinical candidates. While e-therapeutics has previously validated its computational biology platform through successful small molecule and target identification partnerships, the company is yet to progress its internally developed RNAi assets and hepatocyte targeting programmes into clinical studies. In our view, AI platforms are heavily assessed by their ability to deliver clinical candidates. Therefore, failure to deliver novel hepatocyte targeting RNAi therapies into the clinic represents a significant near-/medium-term risk and may affect the company's ability to secure future partnership opportunities, a key element of e-therapeutics' strategy and a potentially significant source of future revenue.

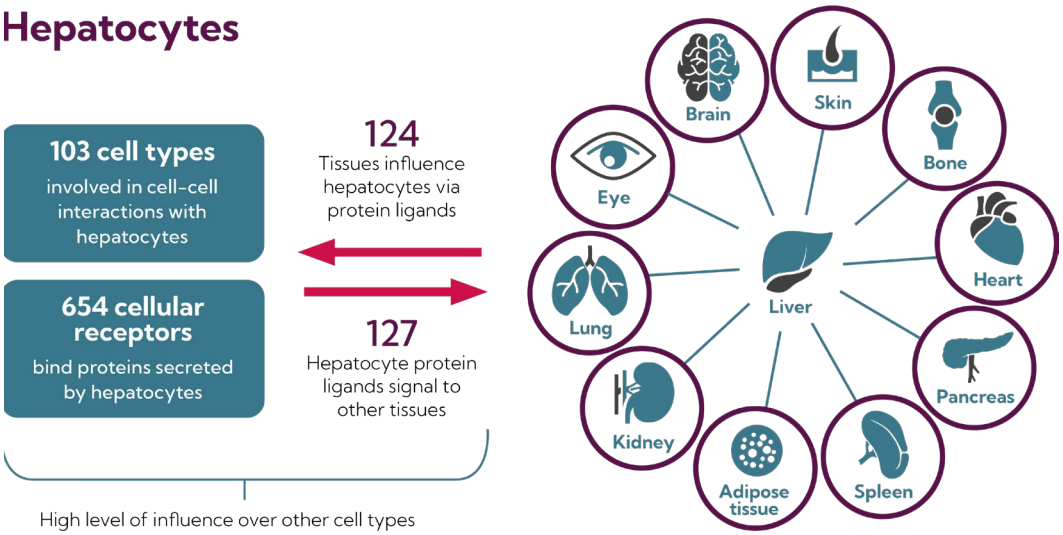
e-therapeutics: Leveraging AI in drug discovery

The application of AI platforms in the pharmaceutical industry has evolved significantly and has matured to a stage where the first purely AI generated candidates have entered clinical trials (as discussed in our recent note about machine learning). This validation of AI is further supported by evidence suggesting that the use of computational platforms can expedite drug discovery timelines and reduce developmental costs. We believe that platforms capable of designing novel, effective drugs and capable of identifying new disease targets will offer an advantage over competitors.

A deeper dive into HepNet

In e-therapeutics' 2023 annual report, it emphasised the centrality of the proprietary HepNet computational platform to ongoing activities. Management describes HepNet as a comprehensive hepatocyte-centric data resource and analytical engine that provides disease-relevant insights across a multitude of hepatocyte-linked processes in multiple tissues and organ systems (Exhibit 1). Within HepNet, e-therapeutics is now integrating the power of LLMs (such as OpenAI's GPT-4) to mine and interpret vast amounts of 'unstructured' information, leveraging the reasoning capabilities of this technology to extract additional non-obvious insights across disparate data domains.

Exhibit 1: HepNet – enabling insights across multiple disease-relevant domains



Source: e-therapeutics annual report 2023

LLMs, such as GPT-4 (released in March 2023), are advanced AI systems that can understand and generate human language. They are capable of encoding and decoding complex information and have advanced reasoning capabilities, as they are trained on large volumes of data and consequently have comprehensive static knowledge. Recent enhancements have transformed the capabilities of LLMS, and include:

- marked advancements in reasoning ability and base knowledge due to the size of the models;
- the ability to process and generate modalities such as images and text;
- the possibility of fine-tuning proprietary data and content to generate domain expert models;
- live connection to the internet to enable interaction with web content via browsing;
- plug-ins for access to real-world information and specialised proprietary functionalities such as symbolic maths engines; and
- the ability to write and execute computer code and database queries, and utilise the outputs.

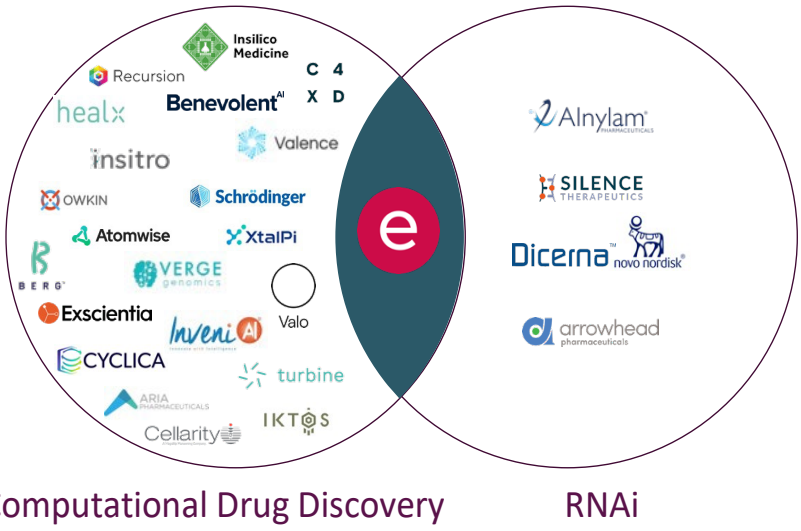
e-therapeutics is working to mine, structure, summarise, integrate and interpret large volumes of 'unstructured' textual and image information related to hepatocyte-centric disease using this technology. It expects these efforts to enable the discovery and leveraging of additional insights that arise from non-obvious complex associations across large and disparate data domains, or that are otherwise inaccessible due to the significant work that would be required to perform analogous tasks manually. The company plans to integrate these capabilities into the existing data and analytical abilities of the HepNet platform. Management also believes that LLMs may become the primary way in which users interact with HepNet, with the possibility of streamlining a drug discovery workflow from exploratory concept to drug design, experimental planning, data analysis and report generation, through to the accelerated development of new medicines.

Standing out from the crowd: AI hybridised with RNAi

Based on the current macro pressures and funding challenges in the biotech drug development industry, there is likely to be heightened interest from development-stage biotech companies in new technologies that claim to de-risk development and avoid costly late-stage clinical failures. With this, the AI drug discovery market is becoming an increasingly competitive landscape and there are a number of companies now applying proprietary AI technologies to progress drug discovery. While these platforms may be at different stages of maturity and validation, there are currently two main limitations associated with existing AI techniques, in our view. Firstly, most AI is being applied purely towards the discovery of small molecule therapies. Secondly, existing computational platforms often take broader or more systemic approaches to disease/biological process modelling as opposed to focusing on a specific disease area or cell type.

To our knowledge, e-therapeutics is the only company applying a platform approach specifically focusing on combining hepatocyte disease biology modelling with RNAi development, providing a unique offering (Exhibit 2).

Exhibit 2: e-therapeutics' market interface between AI and RNAi developers



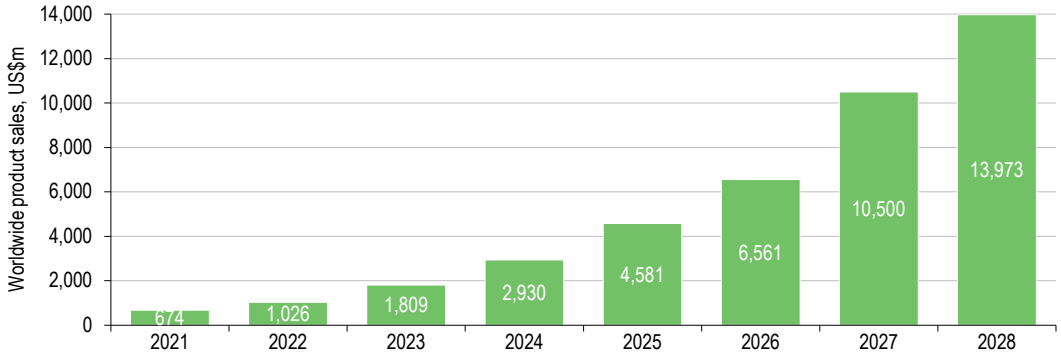
Source: e-therapeutics corporate deck

This single cell type approach potentially creates a platform that can model liver-associated diseases with greater accuracy, compared to more holistic modelling approaches, and may better support the selection of novel hepatocyte targets that have the greatest impact on disease pathology.

RNAi therapies represent a rapidly evolving new drug class aiming to overcome some of the issues faced by conventional medicines. One of the major advantages of RNAi medicines is their ability to potentially target almost any disease associated gene, including targets that may be considered 'undruggable' by small molecules or antibodies. Additionally, it takes roughly three to five years for a small molecule to progress from initial validation against a disease target to being a fully optimised preclinical candidate. This lengthy process means costs for the optimisation of the small molecule alone can be up to c US$400m. e-therapeutics attests that it can leverage its computational biology platform to design and produce a single RNAi therapy ready for animal studies in six months at a cost of c $500k; however, this is yet to be validated. The FDA, to date, has approved five RNAi therapies, providing clinical validation for the therapeutic approach. Relative to small molecules and antibody therapies, RNAi technologies are still gaining traction in the pharmaceutical industry.

The instability of RNAi drugs requires the use of specialised delivery systems, such as lipid nanoparticles (LNP) for the encapsulation of the RNAi therapeutic or GalNAc conjugation to the RNAi therapeutic. However, these approaches still have challenges in delivering RNAi treatments to areas of the body outside of the liver, and this lack of tissue specificity and liver accumulation can potentially lead to hepatotoxicity. Further, the delivery of LNP-RNAi drugs can require frequent intravenous infusions coupled with steroid pre-medications. The discovery of conjugating RNAi drugs to a GalNAc moiety was a material advancement. Using this delivery mechanism, it is now possible to silence a target gene for longer periods of time, compared to LNP-RNAi drugs, with a simple subcutaneous injection and without the need for a steroid pre-medication. With advancements in this field receiving increasing scientific and commercial validation, we believe the RNAi pipeline is poised to deliver many further drug candidates. Furthermore, with a market projected by EvaluatePharma to grow to c $14bn by 2028, in our view, this provides a significant opportunity for e-therapeutics (Exhibit 3).

Exhibit 3: Estimated RNAi technology market to 2028



Source: EvaluatePharma

RNAi therapeutics: A validated new drug class

RNA interference (RNAi) is a naturally occurring biological process that takes place within our cells to regulate gene expression and protein synthesis. In recent years, this process has been harnessed to silence the expression of disease-associated genes through the development of short interfering RNA (siRNA or RNAi) therapeutics. An RNAi therapy is a synthetic RNA molecule designed to inhibit the production of a disease-associated protein by targeting the gene leading to its formation. This differs from traditional small molecule or monoclonal antibodies (mAbs), which are typically designed to recognise and engage with a disease-associated protein after it has been produced. The rise of biological drugs such as mAbs have played an important role in reshaping the existing therapeutic landscape, offering enhanced target selectivity and significantly improved safety profiles over small molecules in some instances. Despite these advantages, one of the major obstacles faced by mAbs is their inability to cross cell membranes and target intracellular proteins, somewhat limiting their interaction to extracellular targets. Additionally, due to the complex spatial conformation of certain proteins produced by cells, the design of small molecules and mAbs with high affinity, specificity and selectivity to such proteins can be challenging. As such, it is estimated that c 85% of all human proteins are considered 'undruggable' using conventional small molecule or mAb approaches. With the potential to circumvent such issues by targeting the genetic source of a disease-associated protein, RNAi technologies may allow access to novel gene targets, which, if knocked down, offer a more effective way to interrupt a disease's biological mechanism. However, we caveat that with existing RNAi delivery technologies these genetic targets are primarily constrained to cells located in the liver.

RNAi treatments require the use of sophisticated drug delivery platforms to effectively transport the RNAi payload to the desired cells, otherwise they would break down as soon as they are administered. The first FDA-approved RNAi therapy (Onpattro) utilises LNPs as a delivery vehicle to hepatocytes; however, for liver disease targets, these first-generation LNP technologies have now been largely replaced by small and simpler GalNAc-siRNA conjugates. The use of GalNAc (a type of sugar molecule) is designed to enable the highly precise delivery of RNAi therapeutics specifically to hepatocyte cells. This specificity arises from the high binding affinity between the GalNAc moiety and a protein abundantly expressed on the surface of hepatocytes called asialoglycoprotein receptor (ASGPR). Additionally, GalNAc constructs have been shown to offer improved safety and efficacy profiles over LNP delivery systems as well as more efficient drug loading capabilities. The administration of GalNAc-RNAi drugs is also a more straightforward process, compared to LNP-RNAi drugs, with simple subcutaneous injections and no need for steroid pre-medications. Of the five FDA-approved therapies, four to date have utilised GalNAc as a delivery method, which we view as a key indicator for the clinical validation of this approach (Exhibit

4). With its focus on targeted delivery of RNAis to hepatocytes, e-therapeutics is prioritising its efforts on utilising a GalNAc targeting strategy.

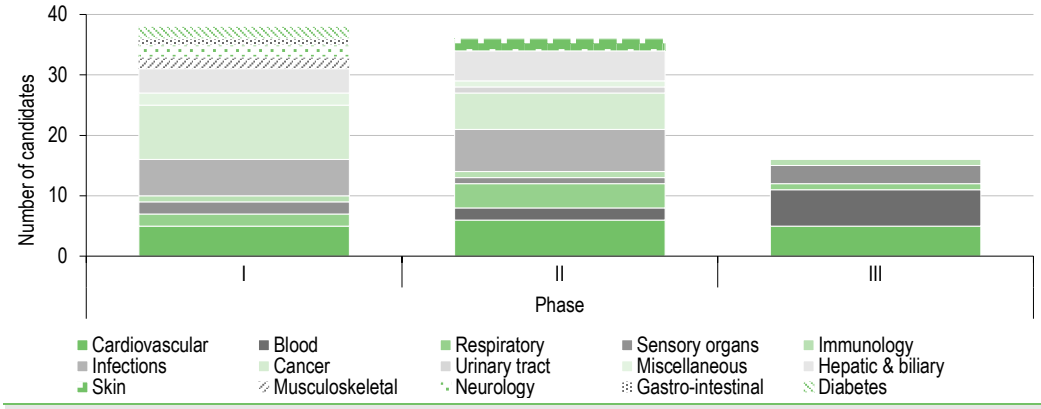
Exhibit 4: Approved RNAi therapies and projected sales according to Evaluate Pharma

Company	Drug (approval date)	Delivery/mechanism	Estimated sales 2028	Indication(s)
Alnylam	Onpattro (Aug 2018)	LNP-siRNA	$1.6bn	Hereditary transthyretin-mediated amyloidosis
Alnylam	Givlaari (Dec 2019)	GalNAc-siRNA	$580m	Acute hepatic porphyria
Alnylam	Oxlumo (Dec 2020)	GalNAc-siRNA	$364m	Primary hyperoxaluria type 1
Novartis	Leqvio (Jun 2021)	GalNAc-siRNA	$2.6bn	Heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease
Alnylam	Amvuttra (Jul 2022)	GalNAc-siRNA	$2.9bn	Hereditary transthyretin-mediated amyloidosis

Source: EvaluatePharma

With only five FDA-approved drugs, relative to small molecules and mAbs, the RNAi therapeutics market may still be considered to be in its infancy. However, the technology is gaining significant interest, exemplified by the number of RNAi drugs in the clinical drug development pipeline (Exhibit 5). Additionally, RNAi therapies are being developed across a multitude of indications demonstrating the diversity of treatment applications for the drug class.

Exhibit 5: RNAi therapeutic pipeline and indications



Source: EvaluatePharma

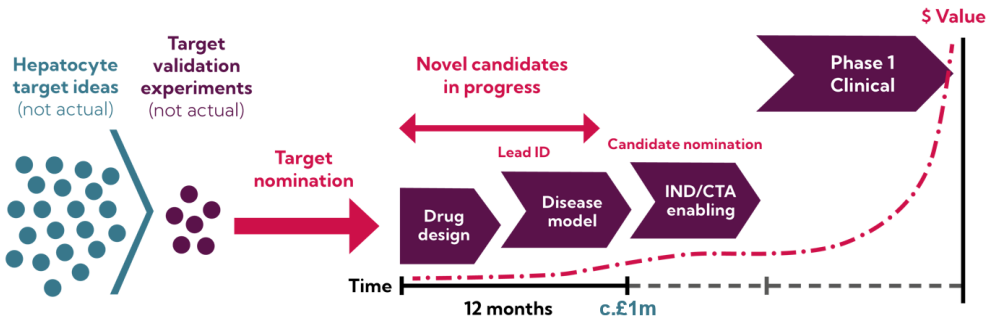
A strategic pivot to maximise value

A common model adopted by biotechs with proprietary AI platforms is to monetise their technologies through early-stage partnering, often as tools in small molecule drug discovery and target identification programmes. This approach can help provide important validation for a platform while also generating nearer-term revenues; however, being at the early drug discovery stage, the value of such projects is often lower than preclinical/clinical-stage asset deals. An example of this is e-therapeutics' partnership with mid-size pharmaceutical company Galapagos, which was announced in June 2020 and concluded in H1 CY22. e-therapeutics successfully leveraged its computational biology platform and know-how to identify hit compounds (small molecules) and novel targets for the treatment of idiopathic pulmonary fibrosis (IPF) and potentially other fibrotic indications. The two-year collaboration successfully concluded with e-therapeutics receiving a total of c £1m, comprising upfront payments and the achievement of all milestones under the agreement. Importantly, the partnership provided third-party validation of the company's computational biology platform and its application in the discovery of new disease targets.

Having developed its proprietary technology, e-therapeutics has made a strategic decision to move away from small molecule drug discovery to focus on developing its internal RNAi pipeline. The company intends to strike a balance between partnering preclinical-stage assets and assets it intends to progress first into early (Phase I) clinical studies. By pivoting from early-stage discovery collaborations, e-therapeutics looks to benefit from higher-value non-dilutive sources of funding or revenue from partnerships that can be obtained further along the drug development process.

Notably, the company believes it can utilise its computational biology and RNAi platforms to generate RNAi constructs for animal testing studies in around six months (Exhibit 6) following target identification.

Exhibit 6: e-therapeutics' value creation model



Source: e-therapeutics annual report 2023

RNAi therapies have secured deals even at the preclinical stages of development; however, clinical-stage deals have extracted significantly higher-value licensing terms, as shown by the deals in Exhibit 7. Securing a validating partnership for liver-centric RNAi candidates forms a key part of the company's near-term strategy. Overall, we view e-therapeutics' strategic refocus as a positive indicator as the company attempts to extract maximum value from its computational biology platform and in-house RNAi chemistry capabilities.

Exhibit 7: Selected RNAi preclinical and clinical deals

Licensee	Licensor	Deal date	Status on deal date	Upfront payment (US$/asset)	Deal value (US$/asset)
Horizon Therapeutics	Arrowhead Pharmaceuticals	21/06/2021	Preclinical	40m	700m
Amgen	Arrowhead Pharmaceuticals	29/09/2016	Preclinical	17.5m	337m
Alexion (AstraZeneca)	Dicerna (Novo Nordisk)	24/10/2018	Preclinical	6m	114m
Roche	Dicerna (Novo Nordisk)	31/10/2019	Phase I	200m	1,670m
GSK	Arrowhead Pharmaceuticals	22/11/2021	Phase I/II	120m	1,030m
Johnson & Johnson	Arrowhead Pharmaceuticals	04/10/2018	Phase I/II	175m	1,850m
Average preclinical deals				21m	383m
Average early clinical deals				165m	1,517m

Source: Evaluate Pharma

Targeting more than purely liver diseases

The liver is one of the most important organs in the body, playing a critical role in many essential biological processes such as metabolism, detoxification and inflammation. Despite only representing c 2–3% of overall bodyweight, the liver receives c 25% of cardiac output, a relatively high percentage of overall blood circulation. It is this intimate relationship with the bloodstream that makes the liver an extremely popular therapeutic target, not just for diseases that affect the liver directly but also diseases that primarily affect other parts of the body such as cardiovascular and haematological diseases. This is because certain proteins formed in the liver are transported through the blood to other tissues and organs where they then carry out a function. While the liver is comprised of many different cell types, the most common cells targeted by therapies are the non-structural liver cells: hepatocytes. Hepatocytes perform many of the liver's critical roles, listed above, and are responsible for making key proteins essential for the continued maintenance of both liver and non-liver cells. The dysregulation of the production of specific protein(s) in hepatocytes caused by certain genetic variations can therefore lead to significant health consequences and, as such, make them attractive cellular targets for potentially treating a myriad of diseases.

The e-therapeutics computational biology approach

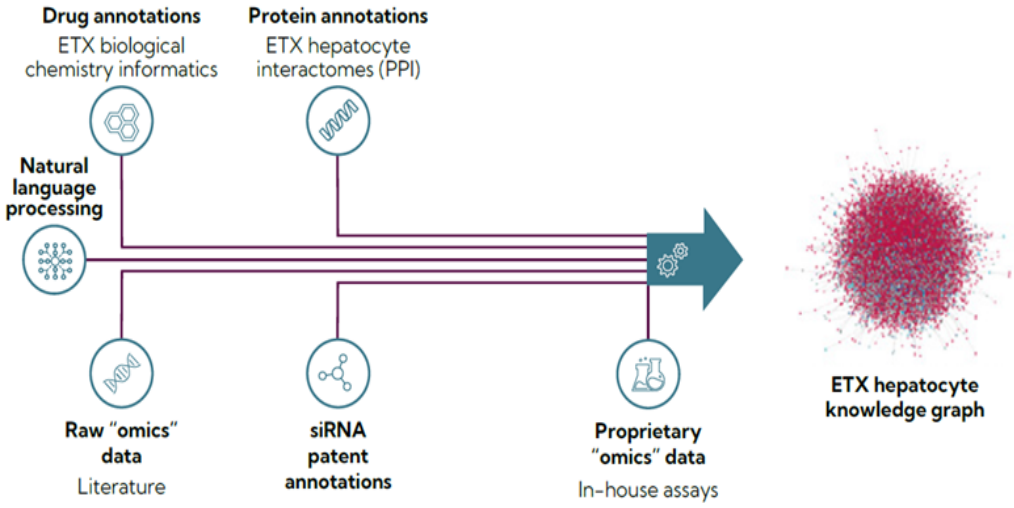
In our view, one of the biggest challenges faced in identifying novel targets in drug discovery is the complexity of human diseases. Once a protein or gene target is drugged, it can potentially cause a ripple effect that affects many other proteins or genes that form part of the disease mechanism of action by preventing them from interacting. Understanding this potential domino effect is crucial to identify novel targets that are most critical in the overall functioning of a disease network. However, building up this picture of human diseases and protein/gene interdependencies is extremely complex. This is one of the reasons the market becomes saturated with 'me-too' drugs, with many companies preferring to pursue existing clinically validated targets perceived to be somewhat already de-risked. This also leads to the approval of drugs that, in some cases, only provide marginal improvements in efficacy over existing standard-of-care treatments. e-therapeutics is taking a disease biology first approach, aiming to use its computational biology platform (HepNet) to build deeper insights into human diseases to help uncover the most effective targets, while also de-risking, and potentially aiding the discovery of highly specific, efficacious RNAi treatments using its RNAi platform (GalOmic).

An industry-leading deep hepatocyte knowledge base

Human diseases are underpinned by vast degrees of biological complexity and, as such, it is extremely challenging to have a single computational biology platform capable of accurately processing and modelling every kind of disease state. e-therapeutics is taking a more tailored approach with its hepatocyte-centric focus. The company asserts that this clear strategy on hepatocyte biology allows it to develop a computational biology platform with disease modelling capabilities possessing greater depth and predictive accuracy by focusing on the collation and analysis of data specific to one cell type.

The company builds its novel mechanistic disease biology models using computation to extract information from a wealth of public and in-house generated proprietary hepatocyte data sources (Exhibit 8). These sources include literature, patents, clinical data and industry news as well as hepatocyte specific 'omics' data, such as genomics (genetic data), proteomics (protein data), transcriptomics (RNA data) and metabolomics (metabolite data). A risk that all AI platform developers that utilise public data face is that competitors could potentially replicate a similar computational approach using the same available data. However, one of the major issues with public data is that it can contain significant amounts of noise and bias. e-therapeutics' innovative platform is designed to filter and cleanse public data through natural language processing before enriching it with machine learning predictions combined with the company's proprietary hepatocyte data generated from in-house cell based and animal studies. This helps the company create an ever-growing, extensive, and unique hepatocyte-centric database – HepNet. Management believes that this is the largest and deepest hepatocyte resource in the industry, and considers it to be like a comprehensive search engine for this cell type.

Exhibit 8: e-therapeutics' approach to building hepatocyte biology networks



Source: e-therapeutics annual report 2022

e-therapeutics can utilise this platform to group different data sets together in various ways to create a hepatocyte knowledge base, from which it can begin to predict the most effective targets to pursue. The knowledge base is essentially a way of arranging all the hepatocyte data to create a network that e-therapeutics believes most accurately represents a disease's biological mechanism, highlighting all the processes that are involved, including protein-protein interactions, drug-protein interactions and cell-cell/tissue interactions. It can more loosely be thought of as a display of information flowing through a network. Importantly, the knowledge base can help identify the most important of these information flows within the disease; for example, it may reveal a single protein that, if perturbed, would disrupt the entire protein-to-protein network and have the greatest impact or ripple effect. This methodology could allow the company to prioritise and test millions of hypotheses using computation to identify better therapeutic targets with higher confidence, prior to conducting costly experimental programmes. Additionally, with its cloud-enabled computational biology platform, e-therapeutics expects to reduce this target analysis time from months to hours. In our view, e-therapeutics' approach, which aims to analyse the complexity of disease biology at the earlier stages of drug discovery, has potential to unlock new opportunities and de-risk the development of new therapeutic RNAi modalities against novel, unexplored disease targets. The company has also been actively engaged across the last six months in the use of advanced computational language models to capture all hepatocyte-related knowledge and information from scientific papers, clinical trial data and patents, ensuring it is up to date on all recent developments in the field.

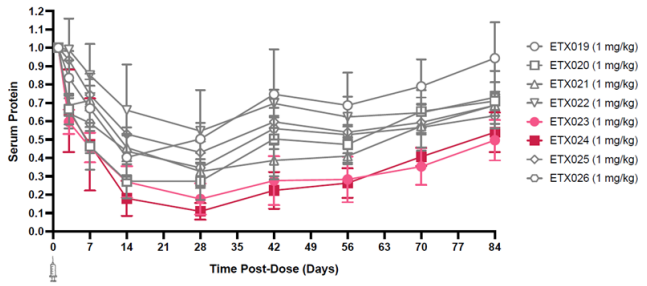
On the way to a clinically validated RNAi platform

Having established a grounding in computational biology for expedient target identification, e-therapeutics has spent the last two years strengthening its capabilities through the development of its RNAi discovery platform – GalOmic. The RNAi platform leverages computation to optimise the construct design of the company's proprietary hepatocyte-targeting GalNAc-siRNA scaffolds by predicting sequence efficacy and drug properties. In doing so, it aims to accelerate the design component of drug development by minimising the number of in vitro (test tube) studies required prior to in vivo (living organism) testing. Management has stated that once a target gene has been selected, it can develop a lead scaffold in just six months at a cost of c $500k. By using computational biology (for target identification), integrated with an RNAi approach (for drug design), the company has generated a library of novel RNAi constructs.

In order to validate e-therapeutics' strategy, proprietary GalNAc-siRNA constructs were benchmarked against an approved RNAi treatment (undisclosed by e-therapeutics) developed by

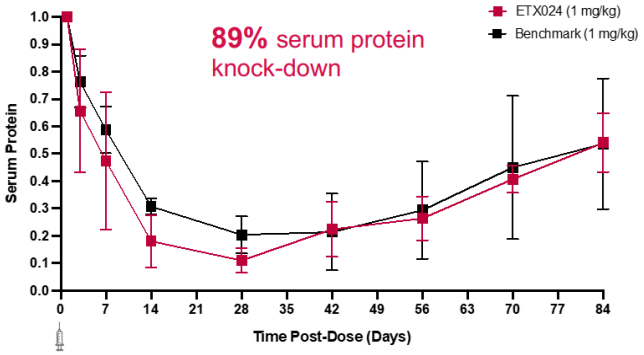
Alnylam. GalNAc-siRNA analogues were screened against the known associated gene target (but undisclosed) in the liver and identified the ETX024 candidate as having an equivalent gene knockdown profile to the benchmark (Exhibit 9). Notably, ETX024 demonstrated greater potency than a best-in-class RNAi competitor therapy, with treatment resulting in gene silencing that triggered an 89% knockdown in serum protein production (Exhibit 10). Additionally, the treatment response was sustainable, achieving gene knockdown for three months from a single dose, with a safety profile equivalent to that of the competition, according to the company. We note that these validation studies were conducted on non-human primates (NHPs), which is particularly encouraging as NHPs represent one of the most advanced forms of preclinical animal testing, with biology that closely resembles that of humans. While we see these data as a positive step towards further validating e-therapeutics' platform, we acknowledge that preclinical results are not necessarily a reliable indicator of clinical utility. We also note that the specifications of the benchmark RNAi treatment and associated gene target were undisclosed, so we must view with caution any direct comparisons between competitive treatments until such details are publicly disclosed.

Exhibit 9: GalNAc-RNAi constructs tested



Source: e-therapeutics annual report

Exhibit 10: Benchmarking of ETX024



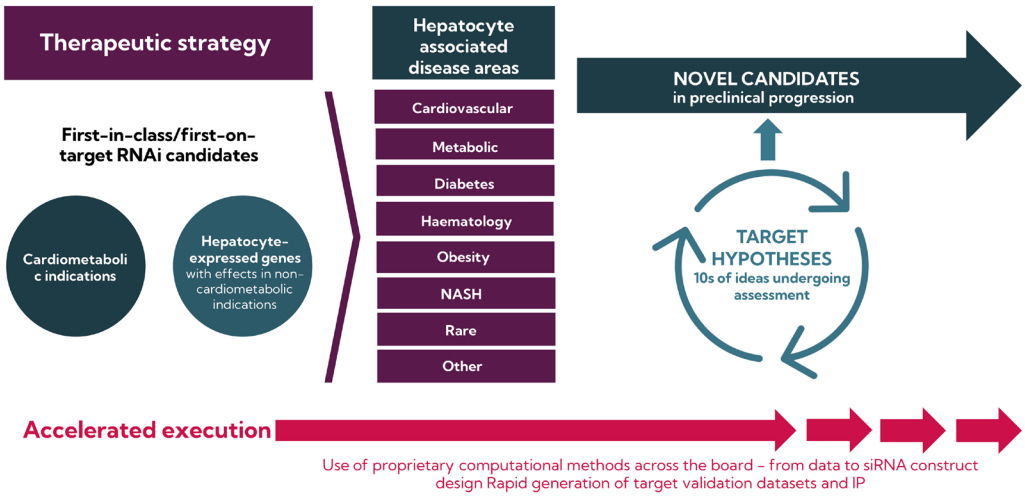
Source: e-therapeutics annual report

With the potential to drug almost any genetic target (in the case of e-therapeutics, provided there is significant distribution in the liver), and with a rapid, adaptable and cost-effective development process, RNAi therapies are now a clinically validated drug class with significant scope to disrupt the existing conventional therapeutic landscape, in our view. However, the technology still faces potential challenges such as liver toxicity and unfavourable immunogenic responses in some instances. The next milestone we see for e-therapeutics will be clinical validation of its computational biology/RNAi discovery platform by delivering novel RNAi assets into first-in-human studies.

Breaking the conventional RNAi target mould

With a platform approach capable of joining up computationally driven novel hepatocyte target identification and AI-enhanced GalNAc-siRNA design, e-therapeutics is now executing preclinical development of its in-house RNAi pipeline, generating data packages that it intends to use to support first-in-human studies. The company is evaluating multiple novel gene targets in late-stage experimental and in vivo studies (Exhibit 11).

Exhibit 11: e-therapeutics pipeline overview



Source: e-therapeutics annual report 2023

Two gene targets are being investigated in haematological indications, one in cardiovascular disease and one in the aggressive fatty liver disease NASH. An important feature of e-therapeutics' active programmes is that all the gene targets being investigated, according to the company, are novel for the associated indication. Currently, there is a significant degree of RNAi target overlap from studies being undertaken by some of the industry's leading RNAi companies (Exhibit 12). With this landscape, the identification of novel genetic targets is critical to develop treatments with potentially material gains in efficacy and to offer differentiation in a competitive market. In our view, e-therapeutics is potentially well positioned to generate novel RNAi gene targeting programmes. The company has multiple ongoing programmes (across haematology and cardiovascular indications and NASH). In addition to this, more than 20 additional target ideas are being assessed computationally and in experimental validation studies, offering further opportunities.

Exhibit 12: RNAi competitor gene targets

Target Genes	HBV	LP(a)	AAT	PCSK9	TTR	HSD	XDH	C3
Alnylam	✘		✘	✘	✘	✘	✘	
Dicerna	✘	✘	✘					✘
arrowhead pharmaceuticals	✘	✘	✘			✘	✘	✘
SILENCE THERAPEUTICS		✘						✘
IONIS	✘	✘		✘	✘			

Source: e-therapeutics corporate presentation

A sizable opportunity remains in NASH

While further details of the haematological and cardiovascular indications e-therapeutics is investigating are yet to be disclosed, one of the major indications the company is pursuing is NASH, a potentially life-threatening metabolic disorder. NASH is the most aggressive form of non-alcoholic

fatty liver diseases (NAFLD) and is characterised by the build-up of fat deposits in the liver that can lead to inflammation (hepatitis), scarring (fibrosis), advanced scarring (cirrhosis) and, ultimately, liver failure. The disease is one of the most common forms of chronic liver disease and individuals with obesity, high cholesterol or type 2 diabetes are at higher risk of developing the condition. The development of new medicines to treat NASH has proven to be extremely challenging, with many notable studies failing to meet their histological endpoints. Such setbacks include Intercept's Phase III REVERSE study of Ocaliva in cirrhosis due to NASH, Gilead's Phase II ATLAS study in NASH induced fibrosis and Boehringer Ingelheim's discontinuation of BI 1467335 following a failed Phase IIa readout. To date, there are no approved therapies in the United States or EU for the treatment of NASH. Following positive results from its Phase III MAESTRO-NASH trial, Madrigal and Roche's resmetirom could potentially be the first NASH treatment to market, with a number of other candidates in later-stage clinical studies (Exhibit 13).

Exhibit 13: NASH late-stage clinical development pipeline

Drug	Company	Phase	Trial dosing	Technology	Target	Notes
Resmetirom/ MGL-3196	Madrigal/ Roche	Phase III	Daily	Small molecule	Thyroid hormone receptor β agonist	Phase III MAESTRO-NASH trial (n = 950) hit both primary endpoints in the two dose groups, 80mg and 100mg daily doses. 26% of patients (80mg) and 30% of patients (100mg) achieved primary endpoint of reduction in NASH activity score and 24% (80mg) and 26% (100mg) achieved second primary endpoint of at least one stage improvement in fibrosis.
Semaglutide (Ozempic)	Novo Nordisk	Phase III	Weekly	Peptide therapy	GLP-1 receptor agonist	Ozempic currently approved for type II diabetes being repurposed against NASH. Phase II study did not meet primary endpoint with 10.6% of patients observing improvement in liver fibrosis vs 29.2% on placebo. Phase III ESSENCE trial to report interim data in 2024.
Ocaliva	Intercept	Phase III	Daily	Small molecule	Bile acid receptor agonist	Mixed data from Phase III REGENERATE trial in NASH-caused liver fibrosis met primary endpoint of improving liver fibrosis but only 6.5% resolution of NASH vs 3.5% for placebo. Failed Phase III REVERSE study in cirrhosis due to NASH.
Lanifibranor	Inventiva/ Sino	Phase III	Daily	Small molecule	PPAR regulator	Phase III NATiV3 trial to report interim results in 2024. Phase IIb study met primary and key secondary endpoints with no worsening of fibrosis, improvement of fibrosis with no worsening of NASH as well as resolution of NASH. 49% of patients achieved primary endpoint of reduction in reduction of the Steatosis Activity Fibrosis score vs 27% placebo.
Belapectin	Galectin	Phase II/III	Bi-weekly	Small molecule	Galectin-3 inhibitor	Phase II/III NAVIGATE trial in NASH cirrhosis to report in 2024. Phase IIb study displayed statistically significant reduction in : Hepatic Venous Pressure Gradient (HPVG) vs placebo and reduced emergence of varices.
Aramchol	Galmed	Phase III	Daily	Small molecule	Stearoyl-CoA desaturase 1 regulator	Phase III ARMOR trial currently suspended as Galmed reformulates Aramchol to Aramchol Meglumine. Results from a Phase IIb study demonstrated a statistically significant reduction in liver fat without worsening fibrosis with NASH resolution in 19.2% of patients in the 600mg dosage arm vs 7.5% in placebo.
Cotadutide	AstraZeneca	Phase IIb/III	Daily	Peptide therapy	Glucagon & GLP-1 receptor agonist	Readouts from Phase IIb/III PROXYMO-ADV study anticipated in 2023. A Phase IIb study in obese patients with Type 2 diabetes and met coprimary endpoints but side effects of nausea occurred in 35% of patients.
MSDC-0602K	Cirius	Phase III	Daily	Small molecule	Mitochondrial target of thiazolidinediones regulator	Phase III study in patients with pre-type 2 diabetes or type 2 diabetes and NASH or non-alcoholic fatty liver disease (NAFLD) to report in 2024.

Source: EvaluatePharma

Global sales of NASH drugs are projected to reach $6.7bn by 2028 (EvaluatePharma), with Madrigal's small molecule resmetirom contributing $1.1bn to this figure (EvaluatePharma). Despite what appears to be a competitive landscape, there remain significant opportunities for new treatments to differentiate in the market. The majority of late-stage assets are small molecule therapies that would require daily dosing of treatment. RNAi therapies may elicit more sustained and durable responses compared to small molecules or antibodies with some GalNAc–siRNA treatments showing in other indications that they can offer quarterly or twice-yearly administration. Additionally, the NASH target landscape is highly diverse, with no two late-stage candidates sharing the same mechanism of action, allowing scope for novel first-in-class treatments to be established.

There are currently only a handful of RNAi therapies in early clinical development for the treatment of NASH (Exhibit 14).

Exhibit 14: NASH RNAi clinical pipeline

Drug	Company	Phase	Technology	Target	Notes
ND-L02-s0201 (BMS-986263)	Nitto Denko (Bristol Myers Squibb)	Phase II	LNP-siRNA	HSP47	Bristol Myers Squibb (BMS) licensed drug in October 2016 for the treatment of advanced liver fibrosis, with upfront payment of $100m, and has option in idiopathic pulmonary fibrosis, which has completed Phase II studies. Results are still to be announced.
ALN-HSD	Alnylam/Regeneron	Phase II	GalNAc-siRNA	17β-HSD13	Preliminary results from Phase I study demonstrated safety and tolerability of treatment. Robust target knockdown and lower liver enzyme and biopsy derived NAFLD activity score (NAS) achieved over six months, although study not designed to achieved statistical significance on these endpoints.
GSK4532990 (ARO-HSD)	GSK (Arrowhead pharmaceuticals)	Phase II	GalNAc-siRNA	17β-HSD13	Phase I study results demonstrated safety and tolerability with 90% reduction in hepatic HSD17B13 mRNA in patients treated at 200mg dose. Treatment was out-licensed to GSK in November 2021 for an upfront fee of $120m and which it has progressed development into Phase II studies.
AMG 609	Amgen	Phase I	Undisclosed	PNPLA3	Targeting a variant allele of PNPLA3 called PNPLA3 I148M.

Source: EvaluatePharma

There is little publicly available clinical data related to BMS (BMS-986263) and Amgen's (AMG 609) RNAi treatments; however, encouraging safety and tolerability profiles have been reported from Alnylam and Regeneron's ALN-HSD and GSK's in-licensed GSK4532990 (formerly ARO-HSD). Additionally, both drug candidates have demonstrated early indications of target engagement and knockdown, with the caveat that conclusive efficacy assessments cannot be confidently drawn based on the design of these early-stage studies. However, these results set an encouraging precedent and provide clinical validation for the use of RNAi therapies (specifically those using GalNAc-siRNA technology) in the treatment of NASH. An important point to note is that both ALN-HSD and GSK4532990 are targeting the protein coding gene 17β-HSD13, while e-therapeutics is addressing a novel (undisclosed) gene target in its ongoing preclinical NASH programme.

Should e-therapeutics deliver a clinical asset from its NASH programme, we believe this may garner significant interest from potential licensing partners due to the potential advantages RNAi therapies possess over conventional treatment (eg durability of effect), the less crowded RNAi clinical pipeline and the potential novel first-in-class NASH target.

An expanding patent portfolio

While e-therapeutics' proprietary AI-based technologies are protected by trade secrets, the company is executing a proactive patent strategy, having filed multiple patent applications across its GalNAc-siRNA platform. In 2021, 11 patent applications were filed with a further eight filed in August 2022. The patent applications cover, in total, 13 inventions related to novel disease targets as well as novel GalNAc-siRNA construct designs derived from the company's computational RNAi platform. More recently, in February 2023, e-therapeutics announced the filing of an additional four new patent applications, which cover novel target innovation and siRNA chemistries. While we acknowledge patent applications do not necessarily translate into patent approvals, the volume of filings in the timeframe serves as a positive indicator for the pace at which e-therapeutics is progressing with R&D activities, in our view.

Sensitivities

With a strategic refocus on progressing its internal RNAi therapies, e-therapeutics is subject to the regular sensitivities associated with drug research and development. The company's prospects may be affected by development delays or failures, regulatory risks, competitor successes, partnering setbacks and financing risks. The primary development sensitivities relate to the

company's preclinical RNAi pipeline. The company's GalNAc-siRNA conjugates are still in the early stages of development; therefore, the most prominent near-term risk lies in the company failing to clinically validate its RNAi platform, which may affect potential licensing values and opportunities. While RNAi therapies have been validated as new treatment approaches in certain indications, to date, only five have received FDA approval and concerns still exist over potential liver toxicity and off-target effects associated with the technology. Such concerns need to be addressed before the technology sees more widespread use in broader disease indications.

While we do not anticipate any immediate funding requirements, e-therapeutics' new development strategy is likely to see costs increase as the company progresses assets through preclinical and clinical studies. This has already been exemplified with the company's increased cash burn in H123 and contrasts with the previous business model of early-stage, less capital-intensive discovery programmes. Consequently, the company will need to raise additional capital to fund its development objectives. The company aims to secure partnership transactions for its RNAi/liver-centric candidates as a means of non-dilutive funding; however, should capital need be raised through an equity offering, this could result in significant dilution of existing shareholders.

Financials

At end-January 2023, e-therapeutics had a net cash position of £31.7m, supported by a £13.4m capital raise (net proceeds) in Q3 CY22 which, at the current underlying operating cash burn rate (excluding the R&D tax credit and working capital changes) of £9.6m, should provide a cash runway into H1 CY26. However, operating costs are likely to increase as the company ramps up R&D activities in line with its strategic priorities, which may affect the current runway.

As part of its early target and small molecule discovery partnerships, e-therapeutics recorded revenues of £0.5m in FY23 (FY22: £0.5m). This consisted of upfront and milestone-related payments of £0.3m for the small molecule discovery agreement with iTeos, along with a final milestone payment of £0.2m on successful completion of the collaboration with Galapagos. As e-therapeutics moves away from small molecule discovery, we do not anticipate that the Galapagos or iTeos (once concluded) partnerships will generate material recurring revenue. While e-therapeutics is not actively seeking new small molecule partnerships, we believe that if it can demonstrate the utility of its RNAi platform through the delivery of clinical-stage candidates, it may result in future licensing opportunities and related revenue.

Operating losses for FY23 amounted to £10.2m (FY22: £9.6m), with R&D expenses totalling £7.2m (FY22: £6.1m). The increase in R&D expenditure was attributed to higher outsourced contract research organisation costs associated with the development of e-therapeutics' HepNet computational platform and IP-related expenses (a total of 17 patents were filed by end FY23). The company reported an FY23 operating cash outflow of £9.6m, up from the operating cash burn of £8.9m in FY22. However, management has communicated that it expects cash burn to increase materially in H223 and FY24 as e-therapeutics progresses its R&D activities and enhances its internal infrastructure to support business growth. The company's cash balance for FY23 benefited from the receipt of a £1.5m R&D tax credit.

At end-January 2023, the company reported cash and cash equivalents of £31.7m. In September 2022, e-therapeutics announced a capital raise of £13.5m through a share issue subscription from funds managed by M&G Investment Management, an institutional investor and existing shareholder of the company.

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