EDISON

e-Therapeutics

FY17 results

Right place, right time

Pharma & biotech

e-Therapeutics offers public market investors a unique opportunity to gain exposure to a proprietary, cutting-edge *in silico* drug discovery platform that has already attracted significant investment and has been fully operational since 2014. This second-generation platform has generated new chemical entities (NCEs) in several different disease areas and, under a new CEO, is on the cusp of commercial validation. The priority for the company is securing deals to provide external validation of this approach. e-Therapeutics' strength is its discovery capability, particularly in complex disease; it also has six internal discovery projects with the prospect of more to come. The CEO's business review will determine the focus of internal investment and business development activities.

Year end	Revenue (£m)	PBT* (£m)	EPS* (p)	DPS (p)	P/E (x)	Yield (%)
01/16	0.0	(11.1)	(3.3)	0.0	N/A	N/A
01/17	0.0	(13.4)	(3.9)	0.0	N/A	N/A
01/18e	0.0	(8.9)	(2.6)	0.0	N/A	N/A
01/19e	0.0	(9.0)	(2.7)	0.0	N/A	N/A

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

The premise

e-Therapeutics carries out early discovery work *in silico,* structuring and analysing its proprietary disease networks using network science and computational optimisation to identify effective protein target sets and compounds with matching multi-point footprints. The principle is that this approach identifies biologically active lead compounds (>10% of candidates from the platform have the desired activity profile in phenotypic screens), which should improve drug discovery productivity and influence the probability of success downstream in Phase II and III trials.

The priorities

The key priority is obtaining external pipeline and discovery platform validation via securing licensing or collaboration deals. The 2016 strategic review rationalised the existing discovery pipeline, focusing resources onto the six most advanced programmes (in medicinal chemistry phase) and into the platform and the discovery process to further enhance its internal capabilities. The CEO's review will determine the level and specific focus of investment and set business development priorities.

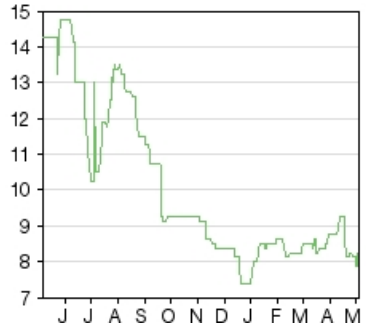
Financials and valuation: Cash into 2019

The restructuring and strategic review meant there were several non-recurring P&L items in FY17. Cash and equivalents of £14m at end-January coupled with potential tax credits (up to £5.8m) and reduced operating costs post-review should provide sufficient runway into 2019 without additional cash inflow. Cash burn will be affected by future priorities/spending plans to be determined by the CEO's review, as well as the longer-term balance between internal investment and partnering of programmes. Licensing deals, partnerships and collaborations – particularly for the immuno-oncology programmes – will be pivotal in driving the value of the platform.

5 May 2017

Price	**8.25p**
Market cap	**£22m**
Net cash (£m) at end January 2017	14.0
Shares in issue	268.4m
Free float	59%
Code	ETX
Primary exchange	AIM
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(5.7)	(4.4)	(42.1)
Rel (local)	(5.6)	(6.2)	(51.2)
52-week high/low		14.8p	7.4p

Business description

e-Therapeutics is a UK-based drug discovery company that has developed a proprietary network-driven drug discovery platform. Its focus is now on commercialisation: securing collaborators and/or partners for its platform, discovery and development projects.

Next events

H118 results	September 2017
Preclinical data	H217/H118
Partnering deal(s)	2017 onwards

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Investment summary

Company description: Network-driven drug discovery

e-Therapeutics is a UK-based drug discovery company built around a proprietary network-driven *in silico* drug discovery platform, which has to date been validated in 17 different discovery programmes. The company was founded in 2003 as a technology spin-out from Newcastle University and listed on AIM in 2007, but the current incarnation of the platform has been in operation since 2014. Secondary offerings in 2011 and 2013 totalling £57m facilitated the development, strengthening and industrialisation of its network analysis platform from prototype to a "fully operational, highly engineered and efficient discovery engine". A dedicated drug discovery hub opened in 2012 in Oxford to expand its drug discovery capabilities; e-Therapeutics employs 21 staff and is recruiting three bio-informaticians. The 2016 strategic/operational review focused the company onto further development of the discovery platform and the six most advanced discovery assets to maximise its chances of securing commercial deals with pharma partners (for the platform and/or product leads) to progress these assets into the clinic and beyond. Dr Raymond Barlow joined as CEO in April 2017 and is carrying out a full review of the company; the outcome will inform the future strategic direction.

Valuation: Well-positioned to secure valuable deals

The discovery platform and early-stage NCE lead candidates are the two main sources of value creation. The first deal, an important de-risking event, is yet to be secured; there is no benchmark for potential terms, nor any firm indication of deal format. IP is in the process of being secured on its programmes ahead of embarking on business development activities. Analysis of disclosed out-licensing deal metrics for preclinical/research-stage assets (BioCentury) indicates that average upfront payments since 2014 are >$20m, although the range is broad ($500k to $90m; $10m median). The focus of e-Therapeutics' discovery programmes will have a bearing on potential terms; with its platform and existing immuno-oncology projects it appears to be well positioned to benefit from the technology 'land grab' in the immuno-oncology space (average upfront payments >$30m with 63% of immuno-oncology asset deals struck at the research or preclinical stage).

Financials: Flexibly funded into 2019

FY17 P&L included several non-recurring items, ie £2.8m of intangible impairment and board restructuring costs. FY17 pre-exceptional operating loss was £13.5m (FY16: £11.6m) with reported operating loss of £16.3m. Cash and equivalents of £14m at end-January 2017, coupled with receipt of up to £5.8m in potential R&D tax credits in the next two years and reduced operating costs post-strategic review should provide sufficient runway into 2019 without additional cash inflow. Cash burn will be affected by future priorities and spending plans to be determined by the CEO's review. Forecasts include discretionary spend on top of the c £5m core business cost; investment timing/magnitude is likely to vary in response to the strategic priorities, number of active discovery programmes, rate of preclinical development progress, results generated and deal timings.

Sensitivities: Deal execution is key

e-Therapeutics' key near-term sensitivity is execution risk in relation to securing commercial deals. Its strategy is centred on securing partner(s) for its preclinical drug candidates or discovery platform collaborations, which will be critical for future revenue generation through upfront payments, downstream milestones and royalties. Increased focus on business development activities, coupled with a new CEO with considerable commercial and business development expertise, should add impetus to deal making, although timing of the first deal remains uncertain. Conversely, an absence of deals in the next 24 months may mean that e-Therapeutics will have to raise additional funds.

Outlook: Building on foundations

e-Therapeutics offers public market investors a unique opportunity to gain exposure to a cutting-edge *in silico* drug discovery platform that has already attracted significant investment, enabling it to be fully operational since 2014. This platform has generated new chemical entities (NCEs) in several different disease areas and, under a new CEO, is on the cusp of commercial validation.

e-Therapeutics' approach combines data mining (of both public and proprietary sources), big data network analysis, and machine learning with highly skilled employees to analyse and interpret biomedical data to generate novel insights, intellectual property and NCEs for potential commercialisation. This network-driven drug discovery approach encompasses the complexity of biological systems, which is often not a consideration in traditional single-target drug discovery.

Unlike e-Therapeutics, other companies focused on the application of artificial intelligence techniques to drug discovery are private and many come from a software engineering approach to solve 'problems', rather than having biology at the centre of the technological process. e-Therapeutics also explicitly considers the curation, processing and analysis of data, which enables it to uncover new insights into biology and novel mechanisms of action, which is outside the capabilities of companies that are more concerned with pattern recognition in aggregated data.

Emerging from a year of change

e-Therapeutics is emerging from a year of change and is now better positioned to focus on generating value from its proprietary network-driven drug discovery platform and discovery pipeline. During FY17 (12 months to January 2017), the company underwent a strategic operational and scientific review and management restructuring following the departure of the founder CEO. The primary outcome of this initial review was announced in September, in tandem with the H117 results: rationalisation of the 17-programme discovery portfolio to focus resources onto the six most advanced assets. This decision increased e-Therapeutics' flexibility and improved resource allocation to the core business: these promising pipeline programmes and the discovery platform.

A cash balance of £14m at end-January 2017, coupled with potential tax credits of up to £5.8m, provides e-Therapeutics with resources into 2019 to both support its core business and deliver on its business strategy. This strategy involves leveraging its differentiated drug discovery platform to discover NCEs in commercially attractive areas of unmet medical need and collaborating with industry partners to unlock shareholder value.

New CEO to refine strategy

The appointment of Dr Raymond Barlow, who joined as CEO in April 2017, has prompted further refinement of e-Therapeutics' strategy. Dr Barlow is currently in the process of a bottom-up business review, the outcome of which will be articulated to the market once it is completed. We continue to expect that key priorities for e-Therapeutics will be the commercial validation of pipeline and platform through deals in 2017 and beyond. Alongside this, we expect continued investment in the platform and the discovery process to further enhance its internal capabilities, as well as in the next wave of discovery work. Dr Barlow's review should determine investment level and focus, and the longer-term balance between internal investment and partnering of programmes. With significant expertise in R&D and business development (gained at Amgen, J&J/Crucell and AstraZeneca), we expect Dr Barlow to commercially orient the company and unlock the innate value in the discovery platform/assets. Partnership opportunities include industry collaborations or licensing of existing (and future) discovery projects. The company will embark on active business development once IP for existing programmes is secured (patents currently being filed/pending). The most advanced oncology asset is close to being marketed. First deals will provide important commercial validation for an approach that has already been technically validated.

Right place, right time

The high cost and high attrition rates of pharmaceutical R&D have presented the industry with significant challenges in recent times. Various strategies have been employed to boost productivity and innovation; e-Therapeutics' drug discovery platform is one such novel approach that integrates the rapid growth in biomedical (proteomic/genomic) data with computing power and modern big data analysis and machine learning techniques and applies this to complex disease. The premise is that new insights and better understanding of the underlying disease mechanism will increase the probability of clinical success of drug leads targeting complex diseases (such as cancer), thus reducing expensive failures in late-stage trials. It also, through leveraging knowledge of both drug properties and the drug targets, allows the discovery of improved compounds with potentially novel targets. At present, e-Therapeutics' platform allows for shorter development timelines with all projects having generated tractable chemical hits with activity in relevant biological screens within nine months of project initiation. As such project initiation to lead selection occurs in 24 months rather than the typical three to five years.

In an environment with intensifying payer pressures there is also a persuasive argument that innovation and value in the pharma industry will increasingly stem from the discovery end of the development process. With reimbursement decisions centred on value-based healthcare economics assessments, drug companies are increasingly expected to provide real world evidence to prove that new drugs are more effective/safer than existing therapies. First-in-class drugs with novel mechanisms of action, or highly efficacious drugs targeting specific patient populations are more likely to have a profile that justifies premium pricing.

The whole is greater than the sum of the parts

Biological networks have evolved to be both resilient and robust in order to continue to enable healthy function in spite of continual internal and external pressures. In common with many other types of highly optimised, large-scale networks, biological networks have the property of attack tolerance. This makes interventions intended to change their behaviour both challenging and non-intuitive. e-Therapeutics builds network models of disease mechanisms and manipulates them computationally to see the outcomes. By using a multi-point bioactivity footprint incorporating functional assay data, rather than a more standard 'reductionist' single binding target approach, it seeks to determine which are the most critical proteins for a particular disease, and ultimately identify highly potent molecules with the optimal chemical-biology 'footprint' that are able to modulate the multiple proteins that are central to the disease network. The aim is to discover molecules that will prove to be more effective than traditional therapies by having more optimal effects on the structural integrity of disease networks, as well as uncovering novel biological insights into complex diseases.

e-Therapeutics' current platform, its second generation, has been operational since 2014 and has benefited from the investment gained in the last funding round. It has two important differences over the previous incarnation in relation to its applications, although the core underlying concept of multi-point interventions remains the same. These differences are:

- a focus on NCE discovery rather than repurposing (unless serendipitous or driven by partner interest) and;
- a more statistical approach to compound generation and screening computational outputs to acknowledge and deal with incomplete and noisy data.

There has also been an important shift in mindset to recognise the collective importance of network effects rather than the identification of high-value nodes, so that the whole is now considered greater than the sum of its parts.

Why is e-Therapeutics different?

The biopharmaceutical industry typically employs a 'reductionist' approach to drug discovery based on understanding the function and interactions of a drug on an individual protein. This discovery approach often aims to manipulate a complex phenotype by binding a single protein target without a full understanding of the downstream consequences of that binding. The binding target may be validated by genetic knockdown experiments, but these do not inform whether the effect will be optimal in the context of the disease. e-Therapeutics' network-driven drug discovery approach explicitly incorporates the inherent complexity of biology as it recognises that the cellular phenotype (diseased or normal) emerges from the interaction of several proteins acting in complex networks.

Based on in-depth biological insights, e-Therapeutics' scientists build network models of disease mechanisms and create an 'intervention strategy' to computationally manipulate (perturb) these networks to see the outcomes. These network models are based on databases of protein-protein interactions, signalling pathway information and analyses of scientific literature, and contain up to 1,000s of interacting proteins relevant to the disease state, which are tested *in silico* with millions of compounds. Around half of these compounds have known bioactivity data, while the rest have activity information predicted by machine learning: this adds in an additional layer of proprietary knowledge. Data to date have shown that over 10% of predicted hits from its drug discovery platform have the desired activity profile when tested in phenotypic screens.

Over the past four years e-Therapeutics has taken advantage of the opportunity presented by both the expansion and increased access to biologically relevant data and the advances in *in silico* modelling and data analysis techniques, and their application across broader search strategies for NCEs. Its strength is its discovery capability, particularly in application to complex diseases, since its network approach explicitly considers biological complexity during the compound discovery stage. This also means that the platform has potential utility in addressing industry challenges such as overcoming drug resistance and also expanding into personalised therapeutics.

Artificial intelligence (AI), in particular machine learning, approaches to drug discovery are being used by an increasing number of companies, most of which are private (unlike e-Therapeutics), to uncover new and actionable insights from big health data (eg demographics, protein interactions, multi-gene interactions, environmental effects). In many cases it allows software engineers to 'solve problems' related to drug discovery, rather than only scientists, as evidenced by the bio-subsidiaries set-up by the likes of Alphabet (Google), IBM (Watson) and Microsoft. AI has the benefit of being a faster process vs traditional lab-based drug discovery, is agnostic (predictions are based on statistical modelling with less human bias), is comprehensive (working with varied data sources), scalable (able to process datasets of any size/complexity), and can incorporate 'noisy' data. This latter point is of particular importance as source data determine the quality of the output as much as the methods used to analyse it.

Various companies look at different aspects of data, eg curation, processing, analysis; e-Therapeutics does all three in the context of mechanistic modelling of disease, and this context is the biggest differentiator. e-Therapeutics consolidates aggregated data and carries out its own data mining, as well as structuring and subsequently analysing its proprietary disease networks *in silico*, using network science and optimisation theory to identify effective protein target sets, ie compounds with a target footprint based on a multi-point target set. This process has the ability to uncover novel mechanisms of action, which is outside the capabilities of companies that are more concerned with pattern recognition in aggregated data. Importantly, e-Therapeutics is able to employ both knowledge-driven (science-driven) and data-driven analyses. The closest peers, in our view, are outlined in Exhibit 1 overleaf. As these are predominantly privately held, and their IP includes algorithms and significant know-how, disclosures are limited.

Exhibit 1: Selected Artificial Intelligence/Machine Learning drug discovery companies

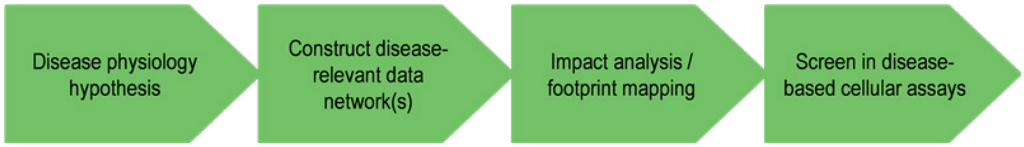
Company (founded)	Market cap/ private investment (latest round)	Proprietary technology description	Disease area	Repurposing/ NCEs	Partnerships	Most advanced programme
AtomWise (2012)	$6.35m (2015)	AtomNet: deep learning neural network technology for structure-based small molecule drug design and discovery.	Metabolic; infectious diseases; neurology; cancer	NCEs	Numerous academic /health institute collaborations; Merck & Co.	Discovery
BenevolentAI (2013)	$100m (2015)	Judgement Augmented Cognition System (JACS): deep learning technology and natural language processing to analyse scientific research data for drug discovery.	Inflammation; neuro-degeneration; orphan diseases (ALS); rare cancers.	Both	Undisclosed US pharma ($800m deal for Alzheimer's' targets). Janssen (J&J) exclusive licence to series of novel clinical drug candidates.	Phase IIb trials for J&J candidates to start mid-2017
BERG Health (2008)	Undisclosed	Interrogative Biology platform: combines disease-relevant patient data and AI analytics to model protein networks for drug and diagnostics discovery, biomarker identification and monitoring of patient responses to therapy.	Cancer; metabolic disease; neurology.	Both	Numerous academic/health institute collaborations	BPM31510 (Phase II): pancreatic cancer ongoing; squamous cell carcinoma complete
Cloud Pharmaceuticals (2012)	$3.35m (2016)	Quantum Molecular Design: utilisation of AI and cloud computing to search the virtual molecular space to identify and reverse engineer novel drug candidates that bind to druggable targets with a low probability of off-target effects	Cancer, inflammation, metabolic, CNS and rare diseases	NCEs	Undisclosed	Undisclosed – announced completion of 17 new drug discovery projects (February 2016)
ExScientia (2012)	Undisclosed	Proprietary cloud-based drug design platform that can leverage machine learning models, molecular shape and structural biology data to automatically design ligands for single-target and bispecific drug discovery projects. Its phenotypic design platform extracts key performance markers from high-dimensional phenotypic readouts using these to generate and optimise new iterations of compounds.	Immuno-oncology, metabolic, CNS	NCE	Evotec (immuno-oncology); Sumitomo Dainippon (CNS); Sunovion ($4.8m CNS deal); Janssen R&D, and two undisclosed large pharma	Preclinical
InSilico Medicine (2014)	$10m (2017)	DeepPharma: deep learning approach to analysis of multi-omics data and extensive tissue-specific pathway activation profiles obtained using proprietary methods.	Cancer; age-related diseases	Both	Academic and industry, including Novartis and L'Oréal	Undisclosed
Nimbus Therapeutics (2009)	$72m (2015)	Computational chemistry platform built in partnership with co-founder, Schrödinger, Inc to develop machine learning algorithms to iterate and optimise leads using a variety of next-generation, physics-based technologies.	Metabolic disease; cancer; inflammation	NCE	Charles River Labs, Gilead (Acetyl-CoA Carboxylase inhibitor programme acquired for $400m upfront, and up to $800m in milestones - $200m received to date), Genentech; Monsanto.	NDI-010976 (Gilead's GS-0976) Phase II ongoing in non-alcoholic steatohepatitis (NASH)
NuMedii (2008)	$5.35m (2015)	Big Data Discovery technology: proprietary biological network-based machine learning algorithms to discover drug-disease connections and biomarkers that are predictive of efficacy.	Undisclosed	Both	Undisclosed large pharma; Astellas; Allergan	Undisclosed
Numerate (2007)	$17.4m (2014)	Numatix: proprietary cloud-scale machine-learning algorithms to generate *in silico* small molecule drug leads for specific disease targets using virtual libraries and virtual assays.	Metabolic; cardiovascular; neuro-degeneration	NCE	Gladstone Institutes (Alzheimer's disease); Merck (cardiovascular); Boehringer Ingelheim	Discovery
Pharnext (2007; IPO 2016)	€94m (Euronext)	Pleotherapy R&D platform for synergistic combinatorial medicine	Neuro-degeneration	Repurposing	N/A	PXT3003 Phase III (Charcot-Marie-Tooth disease)
Recursion Pharma (2013)	$24.3m (2017)	Computationally Intelligent Phenotypic Platform: parallel analysis of automated high-throughput screening data from human cell assays using statistical and machine learning approaches to identify new drug-disease combinations.	Rare genetic diseases	Both	Sanofi Genzyme; two undisclosed partners	Pre-IND
TwoXar (2014)	$3.5m (2015)	DUMA drug discovery platform: biological data extraction from public and proprietary datasets to generate drug-disease models and identify and rank high-probability drug-disease matches using machine learning.	Disease agnostic	Both	Numerous academic collaborations; Santen (glaucoma)	Preclinical

Source: Edison Investment Research, company websites

The discovery platform and process

Post-IPO equity rounds in 2011 and 2013 provided the resources for e-Therapeutics to accelerate and strengthen its discovery capabilities and infrastructure. Advances have been made across all three of the key areas of disease network construction, disease network analysis and compound discovery. Exhibit 2 summarises the discovery workflow. e-Therapeutics' approach has several key differences to both target-driven drug discovery employed by large pharma and the pattern recognition applied by many machine learning/analytics companies.

Exhibit 2: e-Therapeutics discovery work flow



Source: e-Therapeutics

While the exact process depends on the project and data available, e-Therapeutics will typically start with knowledge about the disease mechanism and may apply either a 'guilt by association' (ie if proteins are known to have an effect on disease, look at what they interact with) or a 'hypothesis-free' approach where patterns are sought from the data. Data come from a variety of sources, including current biological and pathophysiological data relevant to the disease to build a database of observed cellular interactions (the 'interactome'), and identify what happens in the disease state by comparing genomics from disease tissue with healthy tissue to construct networks (which potentially includes patient segmentation and clustering) and seeking the component(s) that perturbs the network via impact analysis and footprint mapping. Compound(s) which map to this footprint are identified from proprietary databases (currently of c13m compounds) constructed from both empirical evidence (around 4m have existing experimental data) and evidence from machine learning models. 'Enriched actives' that emanate from the statistical output are then tested in cell-based phenotypic assays. This analysis stage is, as far as we are aware, unique to e-Therapeutics, as while other companies use network biology for biomarker discovery, no one uses it as a discovery target for a multi-point target set to discover compounds that have the desired target footprint.

Partnerships to provide validation and unlock value

Securing commercial partnerships will be the most significant near-term value driver. We expect first deals to be centred on mutually beneficial, discovery-stage collaborations with e-Therapeutics providing access to its platform and capabilities. In addition to providing important external validation of the discovery approach and generating first revenues, such deals may also enhance the discovery process after the *in silico* phase by offering access to proprietary data not in the public domain. New data sources would increase the scientific robustness of e-Therapeutics' network models, potentially translating into lower downstream technical risk and/or a broader field of application. In our view, partnerships/collaborations are most likely to be one of two structures:

- **Discovery collaborations:** earlier-stage collaborations could include assay development; access to in-house genomic/proteomic data; and/or access to in-house compound libraries. Screening of e-Therapeutics' compound outputs is currently limited to assays available at clinical research organisations (CROs), while application of the discovery platform to in-house pharma databases could unlock hidden value by identifying promising candidates in areas of unmet medical need. The latter deals would likely involve a licence fee for technology access and resource expertise, coupled with success-based milestones and likely partners would be large pharma or biotechnology drug discovery units.

- **Preclinical out-licensing:** potential partners for the core discovery assets would likely have existing development capabilities in the underlying disease area, with a longer-term aim of either self-commercialisation or entering into a downstream commercialisation deal depending on their size, geography and capabilities. Typical economics incorporate an upfront payment, development (and potentially sales) milestones, plus sales royalties.

A partnership would unlock the inherent value in the discovery platform and projects, and cash inflows from potential deals would bring e-Therapeutics closer to becoming sustainably funded. This would also provide resources to invest into additional discovery projects and the further development of the platform to enhance and expand its capabilities into areas that have not been accessible to traditional drug discovery approaches.

Ongoing platform enhancements

The underlying discovery platform is not static; one of the core elements of the 2016 strategic review was that ongoing investment into the platform would further improve its functionality, including via development of additional modules. The intention is to enhance critical parts of the discovery and preclinical development process, potentially speeding up the process, broadening the scope of the platform and also improving the chance of a compound successfully transitioning to the next stage of early development. Discussions with potential partners are part of this strategy.

Past investment into, and enhancement of, the platform enabled e-Therapeutics to embark on a second wave of NCE drug discovery to exploit higher-value partnering opportunities in a variety of disease areas. Ahead of future deals, the company has also sought to consolidate its ownership of key network analysis IP: the rationale behind the £2.32m acquisition of Searchbolt in 2016. To date, platform development has been heavily focused on network construction (into broader disease domains) and compound mapping. Experience has driven the former, enabling refinements in technique and the algorithm with increasing gains with data use.

The new CEO will be responsible for determining the strategic direction of future e-Therapeutics development work, both in relation to the discovery pipeline and platform capabilities. For the latter, there are a variety of avenues that could be pursued in enhancing the discovery platform. The nearer-term opportunity is in improving the existing platform by developing the computational power and broadening and enriching the sources of data/knowledge inputs. New capabilities could additionally be developed to apply e-Therapeutics' discovery approach into novel potential areas that are not amenable to more traditional discovery approaches. In order to pursue these, the company would need to expand into other mechanistic areas of biology: examples include targeting gene regulation/transcription factors and patient segment-specific discovery (with particular relevance to cancer subtypes).

Current pipeline: Close to seeking partners

e-Therapeutics' six core programmes (five of which are disclosed in Exhibit 3) are in the medicinal chemistry phase of the discovery process. A key driver of the discovery pipeline is commercial opportunity and unmet medical need underpinned by scientific knowledge. Tissue-based or pathological classifications of disease are not intuitive for drug discovery. e-Therapeutics' systems based approach is different as it focuses on the underlying mechanisms of disease to identify differentiated and potentially disruptive assets (including with new mechanisms of action), which should be attractive to partners. These include immuno-oncology and antivirals.

The latest management disclosure indicates that one oncology project is close to completing *in vivo* testing, with patents pending ahead of active promotion to potential partners. Three other discovery programmes, which have contributed to technically validating the platform from hypothesis to lead compound, will complete discovery prior to initiating partnership discussions. Importantly, e-Therapeutics has demonstrated that its discovery engine has the ability to progress from a project

concept to hit confirmation in less than nine months. Finally, the company intends to invest additional internal resources into progressing two lead immuno-oncology projects to a later stage of preclinical development, with the aim of securing more attractive commercial terms.

Exhibit 3: e-Therapeutics' disclosed preclinical assets from proprietary platform

Asset	Target	Comment
ETS2300	Haematological cancers: telomerase inhibition	ETS2300 aims to disrupt as many aspects of telomerase activity as possible.
ETS3100	Inflammation: anti-TNFα	Small molecule that could potentially avoid issues with biologic therapies (eg inconvenience of administration, development of drug-resistance).
ETS2400	Cancer: hedgehog pathway inhibition	Hedgehog pathway inhibitors with nanomolar potency, with and without binding the SMO protein, thus potentially addressing drug resistance issues by rescuing existing SMO inhibitors (approved for basal cell carcinoma) from therapeutic resistance, or displacing them.
ETS2500	Cancer: tryptophan catabolism	The enzyme IDO catabolises the amino acid tryptophan in tumour tissue; IDO inhibition may be beneficial in solid cancer treatment.
ETS5200	Broad-spectrum antivirals	Novel small molecule programme initially focused on influenza: active against multiple rather than single strains. Potential to extend platform to other high-profile viruses with high unmet medical need, eg Zika, Ebola, John Cunningham Virus.

Source: e-Therapeutics, Edison Investment Research

We expect that the assessments and the judgements from the initial scientific review, overlaid by commercial considerations, will continue to apply to future pipeline decisions. Pipeline progress will be assessed on an ongoing basis, and target areas will continue to be reviewed ahead of restarting new discovery projects during 2017. e-Therapeutics expects to phase its pipeline investment, both into existing assets and the next generation of discovery.

Legacy business: Line drawn under clinical development

Prior to the 2016 scientific review, e-Therapeutics pursued a strategy that aimed to maximise its chances of success with a broad pipeline of many programmes, in the hope that one or more would be successful in attracting a partner. However, the review concluded that while all 17 discovery programmes were scientifically robust, they could not be funded to the preclinical stage with current financial and internal scientific resources; consequently, 12 early-stage assets were placed on hold.

Early discovery efforts, associated with a previous iteration of the platform, also generated a legacy clinical pipeline of repurposed assets. No further internal spend is anticipated on the two remaining clinical legacy assets (ETS2101 and ETX6103) with the exception of FY18 costs (c £40k per month) associated with the two remaining patients in the ETS2101 Phase I/II cancer study, which is in the process of winding down.

Sensitivities

The usual risks associated with drug discovery and development companies apply to e-Therapeutics, including development delays/failures, IP protection, regulatory risks, competition, and financing and commercial risks. However, e-Therapeutics' key near-term sensitivity is execution risk in relation to securing commercial deals. Its strategy is centred on securing partner(s) for its preclinical drug candidates or discovery platform collaborations, which will be critical for future revenue generation through upfront payments, as well as downstream milestones and royalties. An increased focus on business development activities, coupled with the appointment of a new CEO with considerable commercial and business development expertise, should add impetus to deal making although timing of the first deal remains uncertain. A deal should provide important validation for the network-driven drug discovery platform and may catalyse additional partnerships. Our financial model currently excludes potential deal economics: clarity on these should increase comfort regarding the attainability of our indicative valuation. An absence of deals in the next 24 months may mean that e-Therapeutics would have to raise additional funds.

Valuation

e-Therapeutics' main sources of value creation are its discovery platform and discovery assets. With significant historic investment into and development of the discovery platform, the strategy has shifted emphasis onto commercialising this platform and new product candidates. Priorities for the business in this respect will be determined by the CEO's review, although platform validation through execution of collaborations will be a key focus. The first deals are yet to be secured; thus there is no existing benchmark for potential deal terms, nor any firm indication of deal format. In our view, simple preclinical asset out-licensing, a discovery collaboration (coupling a partner's compound library with e-Therapeutics' discovery engine) or a technical JV are likely.

Analysis of disclosed out-licensing deal metrics for preclinical/research stage assets as collected by BioCentury indicates that average upfront payments have increased to >$20m since 2014, whereas upfront payments were typically mid-teen million dollars between 2009 and 2013. Nevertheless, the range of upfront values is broad: stripping away the outliers, upfront payments since 2014 have ranged from $500k to $90m, although $5m to $30m is more typical, with a median of $10m. The disease focus of e-Therapeutics' discovery programmes will also have a bearing on potential terms, and in this respect, the immuno-oncology projects could be lucrative. A Defined Health analysis in 2016 revealed that average upfront payments for immuno-oncology (IO) assets is >$30m with 63% of immuno-oncology asset deals having been struck at the research or pre-clinical stage. This is likely attributable to both the earlier-stage of their development vs non-IO oncology assets and also the technology 'land-grab' that is taking place as industry players position themselves in IO. With its platform and existing assets, e-Therapeutics appears to be well positioned to benefit.

The first deal would represent an important de-risking event. It would also unlock the potential for execution of deals at a faster pace, or with larger upfront payments (particularly with respect to competitively attractive targets). Additional deals would unlock upside as this commercial strategy is highly scalable. As we gain greater visibility on the pathway for the lead projects and deal economics, we will refine our valuation methodology accordingly.

Financials

e-Therapeutics' FY17 pre-exceptional operating loss was £13.4m (FY16: £11.3m) excluding share-based payments; the reported FY17 operating loss of £16.23m included £2.8m of intangible impairment (£2.1m good will write off connected to Searchbolt and £0.7m of IP impairment relating to clinical development candidates). Both admin (+£1m) and R&D (+£0.9m) expenditure in FY17 increased by a similar absolute amount. The increase in admin costs (FY17: £2.6m vs FY16: £1.6m) was largely a result of the £0.7m cost of the board restructuring; while R&D spend continued to reflect the shift towards investment in discovery rather than development. Drug discovery costs increased to £7.6m (FY16: £4.4m), with £5.1m of external costs incurred as various active discovery projects have progressed into lead optimisation/lead compound selection. Wind down of the ETS2101 Phase Ib trial resulted in development spend falling to £3.3m (FY16: £5.6m).

Receipt of a £2.6m tax credit (relating to FY16) in June 2016 offset some of the operating loss, which including the £1.5m cash cost of the Searchbolt acquisition, meant lower cash burn of £10.9m. Cash and equivalents stood at £14m at end-January 2017 (vs £19.9m at end-July 2016 and £24.8m as of 31 January 2016). This current funding position, coupled with receipt of up to £5.8m in potential R&D tax credits in the next two years (an application is pending for £2.8m) and the reduced operating costs post-strategic review should allow e-Therapeutics to operate into 2019 without a need to generate additional cash on our current forecasts. However, management have stated that they intend to "seek commercial sources" of funding in the near future.

The outcome of the new CEO's business review will determine future priorities and spending plans, on both existing projects and potential new programmes in addition to the *in silico* platform. Ahead of the conclusion of this review, we broadly maintain existing forecasts for FY18 and publish FY19 forecasts for the first time. We continue not to include potential deal revenue in our model at this stage given the current uncertainty regarding timelines and deal structure. However, we expect that business development activities will gain momentum once the CEO has outlined company strategy. Our R&D forecast for FY18 and FY19 is £7.5m; this figure is lower than FY17 given the portfolio rationalisation and wind down of the ETS2101 clinical trial (incurring costs of c £40k per month; we anticipate completion in FY18). Our assumed annual G&A spend of c £1.5m reflects the ongoing cost of the business post-restructuring. On this basis, our forecast normalised loss before tax for FY18 is £8.9m and for FY19 £9.0m; we assume receipt of £1.8m in tax credits in both years. However, we highlight that future cash burn will be affected by various factors to be determined by the CEO's review and understand that the annual cost of supporting and maintaining the core business in its current form is c £5m. Our forecasts include an element of discretionary spend; timings and magnitude of investment are likely to vary in response to the strategic priorities, the number of active discovery programmes, the rate of preclinical development progress, results generated and deal timings.

Exhibit 4: Financial summary

£'000s	2015	2016	2017	2018e	2019e
Year ending 31 January	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	0	0	0	0	0
R&D	(8,549)	(9,965)	(10,911)	(7,500)	(7,500)
G&A	(1,520)	(1,375)	(2,614)	(1,475)	(1,531)
EBITDA	(9,997)	(11,267)	(13,469)	(8,895)	(8,951)
Operating profit (pre GW and except.)	(10,069)	(11,340)	(13,525)	(8,975)	(9,031)
Intangible amortisation	0	0	(2,805)	0	0
Exceptionals/special Items	0	0	0	0	0
Share-based payment	(106)	(215)	(99)	(250)	(250)
Operating profit	(10,175)	(11,555)	(16,429)	(9,225)	(9,281)
Net interest	357	271	132	110	40
Profit before tax (norm)	(9,712)	(11,069)	(13,393)	(8,865)	(8,991)
Profit before tax (as reported)	(9,818)	(11,284)	(16,297)	(9,115)	(9,241)
Tax	2,041	2,464	3,073	1,800	1,800
Profit after tax (norm.)	(7,671)	(8,605)	(10,320)	(7,065)	(7,191)
Profit after tax (as reported)	(7,777)	(8,820)	(13,224)	(7,315)	(7,441)
Average number of shares outstanding (m)	264.3	264.4	267.1	268.4	268.4
EPS - normalised (p)	(2.9)	(3.3)	(3.9)	(2.6)	(2.7)
EPS - as reported (p)	(2.9)	(3.3)	(5.0)	(2.7)	(2.8)
Dividend per share (p)	0.0	0.0	0.0	0.0	0.0
EBITDA margin (%)	N/A	N/A	N/A	N/A	N/A
Operating margin (before GW and except) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed assets	733	804	207	312	417
Intangible assets	637	740	156	251	346
Tangible assets	96	64	51	61	71
Current assets	37,424	28,783	17,724	11,838	4,577
Stocks	0	0	0	0	0
Debtors	3,602	3,941	3,749	2,549	2,549
Cash	33,822	24,842	13,975	9,289	2,028
Other	0	0	0	0	0
Current liabilities	(1,133)	(1,156)	(1,951)	(1,951)	(1,951)
Creditors	(1,133)	(1,156)	(1,951)	(1,951)	(1,951)
Other creditors	0	0	0	0	0
Short-term borrowings	0	0	0	0	0
Long-term liabilities	0	0	0	0	0
Long-term borrowings	0	0	0	0	0
Deferred taxation	0	0	0	0	0
Other long-term liabilities	0	0	0	0	0
Net assets	37,024	28,431	15,980	10,199	3,043
CASH FLOW					
Operating cash flow	(10,942)	(11,204)	(11,711)	(7,695)	(8,951)
Net interest	642	329	194	121	75
Tax	1,087	2,027	2,570	3,073	1,800
Capex	(31)	(6)	(22)	(50)	(50)
Purchase of intangibles	(158)	(138)	(143)	(135)	(135)
Acquisitions/disposals	0	0	(1,768)	0	0
Financing	77	12	13	0	0
Dividends	0	0	0	0	0
Other	0	0	0	0	0
Net cash flow	(9,325)	(8,980)	(10,867)	(4,686)	(7,261)
Opening net debt/(cash)	(43,147)	(33,822)	(24,842)	(13,975)	(9,289)
HP finance leases initiated	0	0	0	0	0
Other	0	0	0	0	0
Closing net debt/(cash)	(33,822)	(24,842)	(13,975)	(9,289)	(2,028)

Source: Edison Investment Research, e-Therapeutics accounts

Contact details	Revenue by geography
17 Blenheim Office Park Long Hanborough Oxfordshire, OX29 8LN United Kingdom +44 (0) 1993 880000 www.etherapeutics.co.uk	N/A

Management team

CEO: Dr Raymond Barlow	Finance director and interim COO: Steve Medlicott
CEO since April 2017, having most recently been executive director of corporate development at Amgen. Previously held scientific, business and corporate jobs at AstraZeneca, Crucell and Johnson & Johnson, as well as a post-doc at McGill University. Holds a BSc in chemistry (Leeds University) and PhD in chemistry (Manchester University).	Finance director since April 2014, having previously advised the company in its £40m fund-raising in 2013. Previously held key business development and sell-side industrial analyst roles with Peel Hunt, N+1 Singer, Altium Capital and Williams de Broe; he was finance director at Waste2Tricity and trained as a chartered accountant with PwC. He co-founded Blueprint Advisors in 2012.
Non-executive Chairman: Iain Ross	
Chairman since January 2016. 35-year track record in life sciences, M&A and financing transactions. Prior management roles include CEO of Celltech (instrumental in sale to Lonza), Quadrant Healthcare (pre-IPO through to Elan buyout) and Allergy Therapeutics (also chairman, involved in restructuring prior to IPO), and chairman of Silence Therapeutics. Currently non-exec chairman of Biomer Technology and Redx Pharma; non-exec director of Anatara Lifesciences, Novogen and Premier Veterinary Group. He is a qualified chartered director, and vice chairman of Royal Holloway, London University.	

Principal shareholders (April 2017)	(%)
Invesco Asset Management	32.0
Woodford Asset Management	17.7
Aviva	15.8
Lombard Odier	10.3
Malcolm Young	8.9
Octopus Group	4.2

Companies named in this report

AtomWise, Benevolent AI, BERG Health, Cloud Pharmaceuticals, ExScientia, InSilico Medicine, Nimbus Therapeutics, NuMedii, Numerate, Pharnext, Recursion Pharma, TwoXar