e-Therapeutics plc (LON:ETX)

Undervalued Stock with a Unique Approach to Drug Discovery

KEY INVESTOR MESSAGES

1. e-Therapeutics (LON:ETX) focuses on the discovery of new drugs in a more efficient and effective way and aims to be a valued partner to address the productivity challenge that the pharma industry faces.

2. e-Therapeutics (LON:ETX) has developed a novel and unique in-silico approach to drug discovery: starting from the analysis of complex interactions between proteins in biological systems (networks), they apply advanced computational techniques to identify new drug candidates.

3. This approach was labeled Network-driven Drug Discovery (NDD) and has been validated across several therapeutic areas (cancer, central nervous system, auto-immunity, infectious diseases) and molecular pathways.

4. e-Therapeutics (LON:ETX) discovery platform has generated three drug candidates for multiple cancer indications which are ready to be out-licensed to pharma partners for their further development.

5. We estimate e-Therapeutics intrinsic value to be roughly 3x higher than current market capitalisation. The latter doesn't reflect the commercial potential of e-Therapeutics' most advanced drug candidates and of the platform itself.

6. e-Therapeutics ability to finalise a co-development or licensing agreement in the near term will represent a key inflection point for its stock re-rating.

A BRIEF OVERVIEW OF DRUG DEVELOPMENT AND R&D PRODUCTIVITY

e-Therapeutics addresses in a unique and differentiated way a well known and pressing problem in the quest for new drugs: the very high failure rate of new drug candidates during their decade-long development path, despite the huge investments made in time and dollar terms.

Essentially new drugs are brought to patients through a lengthy (10-15 years) and costly (from hundreds of million to over a billion dollar) process, which hasn't changed that much over last few decades.

Figure 1: Time from patent filing to drug launch

Source: Lifetime trends in biopharmaceutical innovation, QuintilesIMS Institute, 2017

PHARMA AND BIOTECH

25/10/2017

SHARE PRICE	52 WEEK LOW
10.63p	6p
MARKET CAP	52 WEEK HIGH
£28.5m	13.12p
INDEX	NET CASH
AIM	£12.4m

MAJOR SHAREHOLDERS

1)	Invesco:	31.99%
2)	Richard Griffiths:	21.15%
3)	Woodford IM:	17.7%
4)	Lombard Odier:	12.13%
5)	Octopus Group:	4.2%

Shares in Issue	268.47m
Avg Trading Volume	245,461
Primary index	AIM
EPIC	LON.ETX
Next Key Announcement	-
Sector	Pharma and Biotech

SHARE PRICE CHART

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Moreover, medicines for the most obvious "druggable" targets have already been produced, making the development of incrementally beneficial drugs increasingly hard.

We also note that payers are increasingly asking for clinical trials that show a clear benefit compared to available therapies (outcome-based reimbursement), raising the bar for the commercialization of new drugs, or at least limiting the addressable patients population.

As such returns on every dollar invested in R&D have been steadily declining, despite favourable demographic trends and pricing environment, at least in the US.

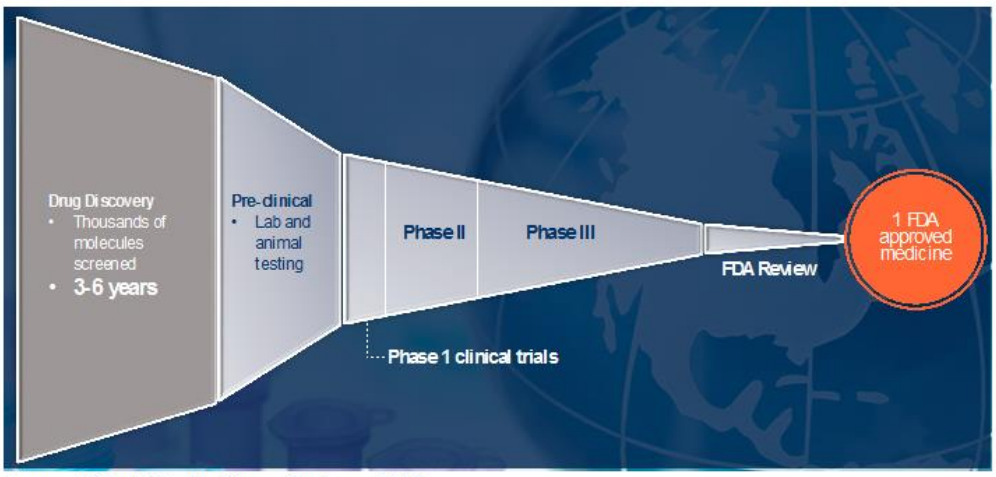
Figure 2: R&D expenses tend to grow faster than revenue

	2016	2015	% change
Public company data			
Revenues	139.4	130.3	7%
R&D expense	45.7	40.6	12%
Net income	7.9	16.3	-52%
Market capitalization	862.5	1,041.2	-17%
Number of employees	203,210	178,690	14%
Public company data			
Public companies	708	680	4%

Source: Beyond orders, Ernst & Young 2017

To simplify, the approval of a new medicine requires four sequential phases: discovery, pre-clinical development, in-human clinical trials (clinical stage development), and regulatory review.

Figure 3: Drug development steps



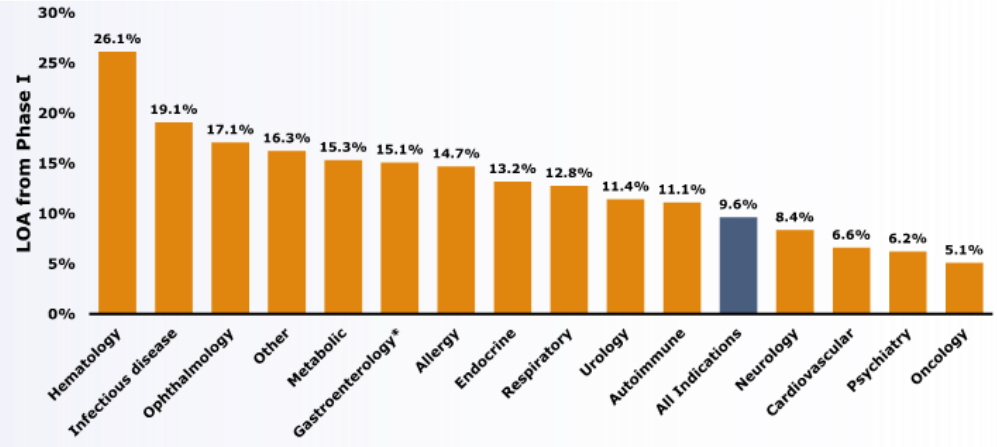
Source: CB Insights, Healthcare Horizons, 2017

What mostly hurts returns on R&D investments is the last part of the development process, i.e. the large phase 3 trials that regulators require in order to give green light to a new drug. Although each phase 3 trial enrolment size depends on the therapeutic indication and other factors, these late-stage clinical studies tend to include large patient populations and end up representing around 80-90% of the total drug development cost. In fact they are designed to be the last barrier before a drug can be widely prescribed to the public, as such they are powered to detect drugs' efficacy and safety with a much higher sensitivity than earlier stage phase 1 and phase 2 clinical trials.

Although from a patient's perspective it is a good sign that many drugs fail in the late stages of development (i.e. useless or dangerous drugs never reach the market), this represents an enormous problem for pharmaceutical companies and biotech investors in general.

As shown in Figure 4, only 10% of drugs that enter the in-human development stage, ultimately end up receiving a regulatory approval.

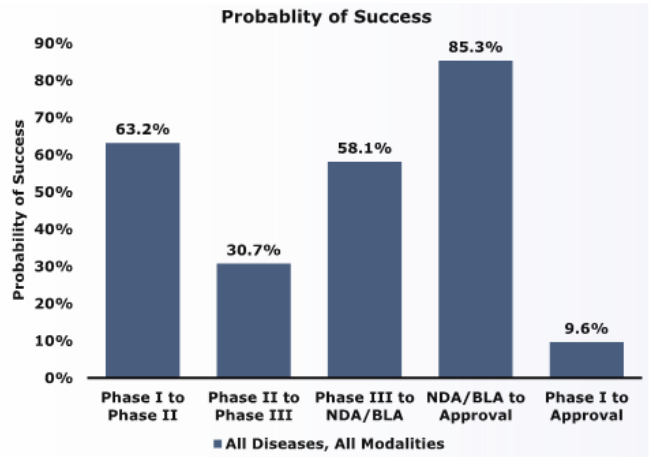
Figure 4: probability of regulatory approval from phase 1, by therapeutic area



Source: D. W. Thomas et al., Clinical Development Success Rate 2006-2015, Biomedtracker, Biotechnology Innovation Organization (BIO), Amplion

The highest attrition rate usually occurs in phase 2, when new drug candidates are required for the first time to show a proof of clinical efficacy (proof-of-concept data).

Figure 5: probability of moving on to next development phase



Source: D. W. Thomas et al., Clinical Development Success Rate 2006-2015, Biomedtracker, Biotechnology Innovation Organization (BIO), Amplion

It should also be noted that the statistics shown above include clinical trials for both new drugs and for additional indications of already approved drugs: the actual probability of success of truly innovative, first-in-class, new molecules are likely to be significantly lower than the averages described above.

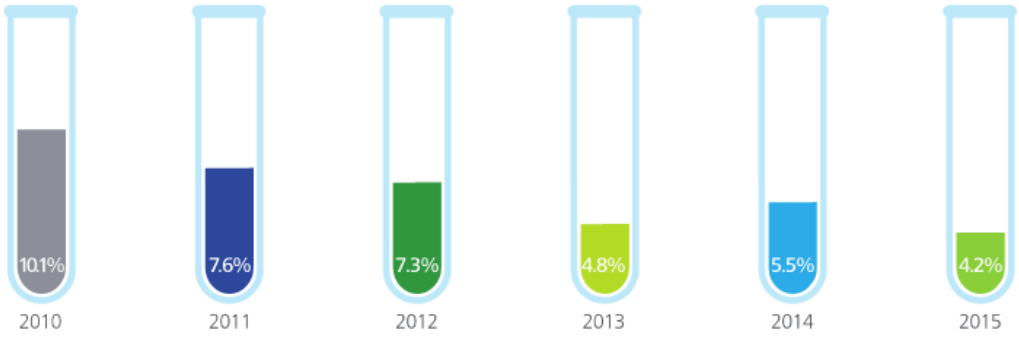
As we briefly discussed, the costs of bringing a new drug to the market are rising fast, and the revenue generated by these new drugs tend, on average, to be lower than in the past.

Figure 6: development costs vs new drugs sales

Source: Measuring the return from pharmaceutical innovation 2015, Deloitte Centre for Health Solutions, 2015

This leads to the need of new solutions to address the decreasing returns on R&D investments, and here is where new drug discovery methodologies come into play.

Figure 7: Declining R&D returns



Source: Measuring the return from pharmaceutical innovation 2015, Deloitte Centre for Health Solutions, 2015

A new approach that could help addressing R&D attrition is represented by the application of artificial intelligence (AI) techniques to the earlier stages of the drug development, i.e. to the discovery phase.

It's hard to describe briefly what AI is, but in essence it can be defined as a software-on-steroids that can learn to do things, without being explicitly programmed to do them. This usually happens after a "trial" period where the system has been properly trained to do so. As an example, AI can be used to recognize images of animals when fed with a larger dataset of random images. For the readers who wish to dig deeper into AI and its branches, amongst the multiplicity of freely available sources we would recommend the following as an introduction.

AI-driven drug design represents the application of machine learning techniques to drug discovery, with the aim of speeding up and make more efficient the whole process of developing new medicines.
The discovery phase is the first stage of drug development: it is meant to produce "lead candidates", or molecules ready to be tested in pre-clinical in-vitro and in-vivo models.

The discovery phase can be broken down in two parts: i) the generation of "hits", or molecules with an acceptable level of the desired activity, via an initial screening process and ii) the optimization of "hits" into "leads" or drug candidates with a sufficient level of biological activity, pharmacokinetic and safety properties in order to be progressed to the pre-clinical development stage.

In traditional drug discovery hits generation is done through *in vitro* assays of large compound libraries. The subsequent lead optimization happens through sequential DMTA (Design-Make-Test-Analyze) cycles.

In vitro assay can typically screen libraries of 10^6 molecules and take about a year to set-up whereas *in silico* screening ramps up to 10^{13} compounds. To put this into perspective the whole druggable chemical space is estimated to be in the 10^{63} order of magnitude.

Figure 8: Traditional vs AI-driven drug discovery

	Traditional	AI driven
Hit generation	*In vitro*	*In silico* (software)
Screening capacity	10^6	10^{13}
Time to "hit"	Over two years	Less than a year
Lead optimization	DMTA cycles	DMTA cycles

Source: public data, A. Davis et al. (2017), CN analysis

A recent paper on drug discovery [Andrew M. Davis et al., Directing evolution: the next revolution in drug discovery, *Nature Reviews Drug Discovery 2017*] estimates the duration of the discovery phase at about 4-5 years for a US$ 14-25mil cost. Furthermore they estimate an attrition rate for the discovery phase at 50% or higher and then up to 97% from lead candidate to the launch of a new drug in the market.

We finally note that Vasant Narasimhan, the recently appointed CEO of Novartis, has declared that the increased use of digital technology (data analytics and AI) could lead to a 10-25% reduction of drug development costs.

E-THERAPEUTICS' NETWORK-DRIVEN DRUG DISCOVERY (NDD)

e-Therapeutics has developed its own differentiated approach to drug discovery.

The company has created a unique and powerful computer-based drug discovery platform and uses a specialised approach to network biology.
Their main claim is that novel network-driven drug discovery methodology allows them to discover new and better drugs in a more efficient and effective way.

Their discovery process (represented in the figure below) is based, first, on a fundamental understanding of the biological basis of disease which e-therapeutics are able represent as a collection of complex protein networks. Their approach is driven using very comprehensive datasets, including all know protein-protein interactions, multi-omic data, patient tissue sample data and compound-protein bioactivity footprints.

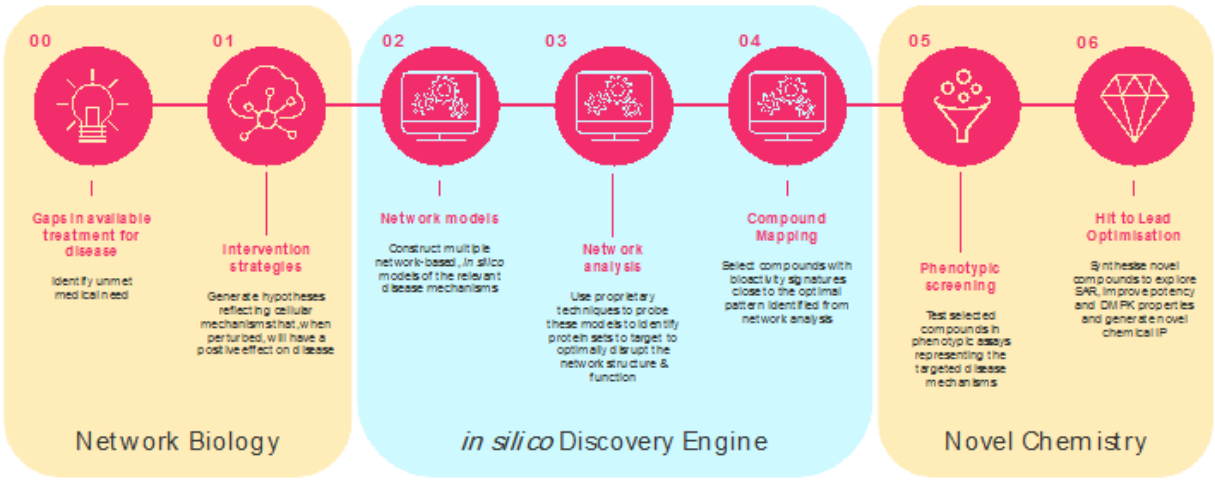
The NDD approach has been enabled by recent advancements in big biological data, network science, computational power, advanced analytical methods and techniques such as machine learning and AI.

e-Therapeutics then uses a variety of sophisticated and often proprietary computational techniques to identify and analyse which protein sets to target to optimally perturb the diseased state. In-silico screening (compound mapping) of millions of compounds leads to the selection of compounds with bioactivity signatures close to the optimal pattern that should interact with the disease networks and restore their physiological status. e-therapeutics then takes the identified compounds and tests them in disease-relevant cell or tissue- based phenotypic assays. The proportion of compounds that have activity at levels of <10 micromolar is highly impressive and several orders of magnitude higher than high throughput techniques. Another advantage is that the NDD approach can identify several different chemotypes to drive subsequent medicinal chemistry.

Another key advantage is that because e-therapeutics interrogates biology in a fundamentally different way they have been able to discover drugs with novel mechanism of action, which can lead to first-in-class drugs which may have advantages in the clinic.

In traditional pharma discovery, this process ("hits" generation) is usually done through in-vitro screening of large libraries and takes several years. e-Therapeutics digital approach was able to reduce the time required to generate new hits to about 9 months or less.

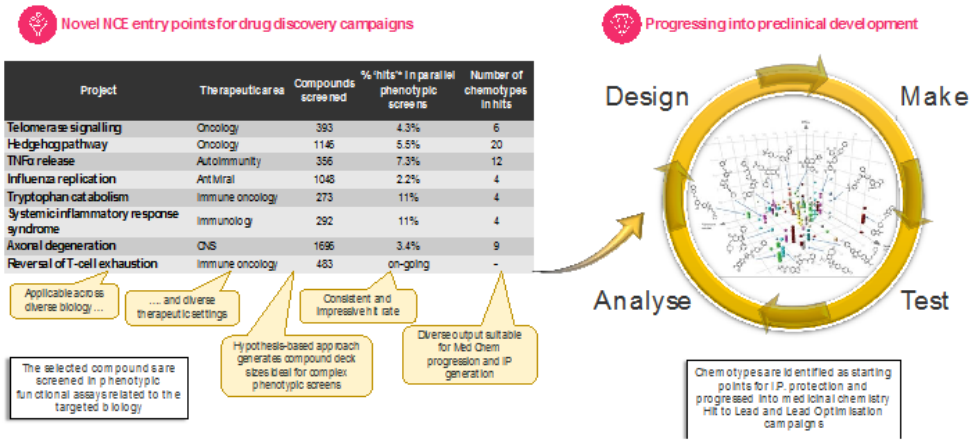
Figure 9: e-Therapeutics Network-driven Drug Discovery (NDD)



Source: Company presentation

Finally, the lead optimization phase proceeds through Design-Make-Test-Analyze (DMTA) cycles, as in traditional drug discovery.

Figure 10: Hits generation followed by DMTA



Source: Company presentation

E-THERAPEUTICS KEY ASSETS

e-Therapeutics NDD platform has led to the identification of several promising programs over the last few years.

Following a recent strategic review meant to assess each molecule potential, and taking into account currently available resources for their further development, the company has decided to focus on three key candidates, described in the table below.

Figure 11: Focus on three key projects

Project	Therapeutic area	Description	Status
Checkpoint modulation	Cancer	Increase the anti-cancer activity of the immune system (T-cells), with new MoA (not A2A or CTLA-4)	Ongoing DMTA and data-package preparation. Ready to be actively out-licensed from 1Q 2018
Tryptophan catabolism	Cancer	Prevent the suppression of T-cell anti-tumor activity by reducing tryptophan catabolism through novel MoAs (not IDO or TDO inhibitor)	Ongoing DMTA and data-package preparation. Ready to be actively out-licensed from 1Q 2018
Hedgehog modulation	Cancer	Hedgehog pathway modulators designed to overcome resistance to currently used vismodegib and sonidegib	Ready to be out-licensed. No further internal funding of the program.

Source: Company data, CN analysis

Out of those three assets, based on current research and deal-making trends, we are of the view that the checkpoint modulation program is the one with the highest commercial attractiveness.

COMPETITION

As diminishing R&D productivity represents a pressing issue in the bio-pharma industry, new drug discovery methodologies are certainly a hot and highly competitive area.

Given the breadth of the problem, we would not expect that a single company would dominate this space. On the contrary, we believe that several different approaches may lead to successful drug discovery across therapeutic areas.

One such area is the application of AI to drug discovery. However it should be noted that e-therapeutics use AI as a tool in their suite of technologies rather than as the fundamental technology itself.

Figure 12: Selected AI drug discovery companies

Company	Location	Funding	Stage	Collaborations
Atomwise		$6.4mln	Pre-clinical	Merck, Monsanto
BenevolentAI	UK	$140mln	Clinical	J&J
BERG	US	n/a	Clinical	AstraZeneca
e-Therapeutics	UK	*$40mln	Pre-clinical	n/a
Exscientia	UK	n/a	Pre-clinical	Sanofi, GSK
Insilico Medicine	US	$10mln	Pre-clinical	GSK, Novartis
Nimbus	US	n/a	Clinical	Gilead, Celgene, Genentech
NuMedii	US	$5.5mln	Pre-clinical	Astellas, Allergan
Numerate	US	$40mln	Pre-clinical	Takeda
Recursion	US	$75mln	Pre-clinical	n/a
twoXAR	US	$3.4mln	Pre-clinical	Santen
Verge	US	$4mln	n/a	n/a

*Source: CN analysis from various publicly available sources, *Market Capitalization*

What really matters for companies such as e-Therapeutics is to have a well defined and differentiated approach compared to their competitors. On this respect we note for many players AI/machine learning represents the starting point and core of their platform, whereas e-Therapeutics puts a strong emphasis on the deep comprehension of biologic systems (networks). This in turn represents the starting point for the application of AI techniques for the identification of drug candidates that could fix "broken" protein networks responsible for the development of diseases.

VALUATION

We are not aware of any straightforward, widely accepted methodology to value an innovative drug discovery platform; and whilst there aren't truly comparable companies publicly trading on a stock market, valuations of VC-backed private companies are hard to come by.

Anecdotally, we note that BenevolentAI, a UK-based AI healthcare company, was reported to have raised US$100mln at a valuation of US$1.78bn, although this occurred after they had licensed out two drug candidates for Alzheimer's to an unnamed pharma company with a deal valued up to $800mln.

Earlier this year Exscientia, another UK-based, AI-driven drug discovery company, signed a collaboration agreement with Sanofi, a French big pharma, worth EUR250 million. Then more recently Evotec, a German pharma CRO, acquired a minority stake in Exscientia via a EUR15 million investment.

Other in-silico drug discovery companies have raised amounts in the US$4-50mln range from Venture Capital investors.

Two important factors appear to affect the valuation of AI-driven discovery platforms: i) the development stage reached by the drugs they have produced and ii) the finalization of a licensing deal with a global pharma company that bought into their technology.

In this respect, e-Therapeutics appears to be in a peculiar situation. As a listed company, it is subject to market forces, i.e. its market capitalization is also dependent on market factors (liquidity, risk appetite, institutional investors' mandates etc.), unrelated to the merits of its technology.

Furthermore, up to now, e-Therapeutics has not yet signed any collaboration with a larger pharma company and its leading projects are still completing the discovery phase.

As such we believe that the most appropriate way to estimate E-Therapeutics intrinsic value is to break it down into several components:

1. The three most advanced discovery projects (hedgehog, tryptophan, checkpoint)
2. The proprietary network-driven discovery platform
3. Cash on hand
4. R&D tax credits

Discovery projects

We have built a simplified model to estimate the present value of a hypothetical licensing deal worth £250mln, with a £25mln upfront payment and the balance in milestones payments spread over a 20-year period.

Future milestones have been risk-adjusted and discounted using a 15% discount rate, which we believe to be in line with industry standards for this kind of projects.

Should e-Therapeutics sign a deal of this kind within the next 12 month, we estimate it would be worth £67mln (present value).

However, as it is still far from certain that such deal will be finalized in the near term, we show in the table below the present value of this hypothetical deal, adjusted for different probabilities of this deal actually happening.

Table 1: Adjusted-present value of an hypothetical £250mln licensing deal

Deal probability	100%	40%	30%	20%
Present value	£67mln	£27mln	£19mln	£12mln

Source: CN analysis

Given the relative commercial attractiveness of the checkpoints, tryptophan and hedgehog projects we used these assumptions to value these assets. That is of course equivalent to say that we estimate a 40%, 30%, and 20% probability that a deal for each one of these three programs will occur in the near future.

Table 2: Key e-Therapeutics projects valuation

Deal probability	40%	30%	20%
Value	£27mln	£19mln	£12mln
Asset	Checkpoint	Tryptophan	Hedgehog

Source: CN analysis

Network-driven Discovery Platform

Whilst it is hard to attribute a precise a value to an early stage drug discovery platform as e-Therapeutics NDD, it is undeniable that such a unique, proprietary platform has a significant value.

Still using as a base our theoretical deal illustrated above, assuming that e-Therapeutics will be able to generate two lead candidates per year in calendar 2019, 2020 and 2021, this would equate to a cumulative present value of about £50mln. This represents the value we currently attribute to e-Therapeutics discovery platform.

Cash on hand

Based on a net cash position of £12.4 million at the end of July, we estimate a cash position of approx. £11mln at the end of October 2017.

R&D tax credit

Based on our forecast for R&D expenses in fiscal year to January 2018, e-Therapeutics would be entitled to a £1.5mln cash reimbursement in fiscal year 2019.

Dilution discount

Given e-Therapeutics cash runaway, we acknowledge that investors may factor in a discount to reflect the fact that a dilutive fundraising in the medium term can't be ruled out. As such we apply our SOTP valuation at a 30% discount, which we believe adequately reflects the risk of a dilutive capital increase taking place in the next couple of years.

As shown below, our valuation methodology yields an intrinsic value approx. 3x higher than current market capitalisation, despite our conservative assumptions.

Figure 13: e-Therapeutics SOTP valuation

e-Therapeutics SOTP valuation (£ mln)	
Checkpoint modulation	27
Tryptophan catabolism	19
Hedgehog modulation	12
Advanced programs	**58**
Discovery platform	**50**
Cash*	**11**
Tax receivable on FY 2017 R&D	**2**
SOTP total value	**120**
Potential dilution discount	*30%*
ETX Intrinsic value	**84**
ETX current market capitalization	29

**CN estimate at 31 October 2017*

Source: CN analysis

KEY FINANCIALS

Our model doesn't include any recurrent or non-recurrent income from potential licensing agreements that e-Therapeutics may sign over the coming months or years.

We focus on the ongoing operating expenses necessary to support the generation of further drug candidates, which we expect to be in the £7-8 million range in the next few years.

Our cash flow projection also take into account that the company receives cash tax credits worth approx. 1/3 of their R&D expenses.

As such, based on our forecast, e-Therapeutics has sufficient funds to support their ongoing discovery activities into the first half of calendar year 2019 (fiscal year ending Jan. 2020).

Figure 14: e-Therapeutics summary financials

Summary Financials *Year to 31 January (GBPm)*	2016 A	2017 A	2018 E	2019 E	2020 E	2021 E
Revenue	-	-	-	-	-	-
Growth	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
Gross profit	-	-	-	-	-	-
Gross margin	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*	*n/a*
R&D	*(10.0)*	*(10.9)*	*(5.5)*	*(5.6)*	*(5.8)*	*(6.0)*
SG&A	*(1.6)*	*(2.6)*	*(2.1)*	*(2.2)*	*(2.3)*	*(2.4)*
EBIT	***(11.6)***	***(16.3)***	***(7.5)***	***(7.8)***	***(8.1)***	***(8.4)***
Earnings pre-tax	***(11.3)***	***(16.2)***	***(7.5)***	***(7.7)***	***(8.1)***	***(8.4)***
Net income	***(8.8)***	***(13.1)***	***(4.5)***	***(6.2)***	***(6.4)***	***(6.7)***
EPS (GBp)	*(3.3)*	*(4.9)*	*(1.7)*	*(2.3)*	*(2.3)*	*(2.4)*
Net cash	***24.8***	***14.0***	***8.8***	***4.0***	***(2.5)***	***(9.3)***

Source: Company data, CN analysis

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