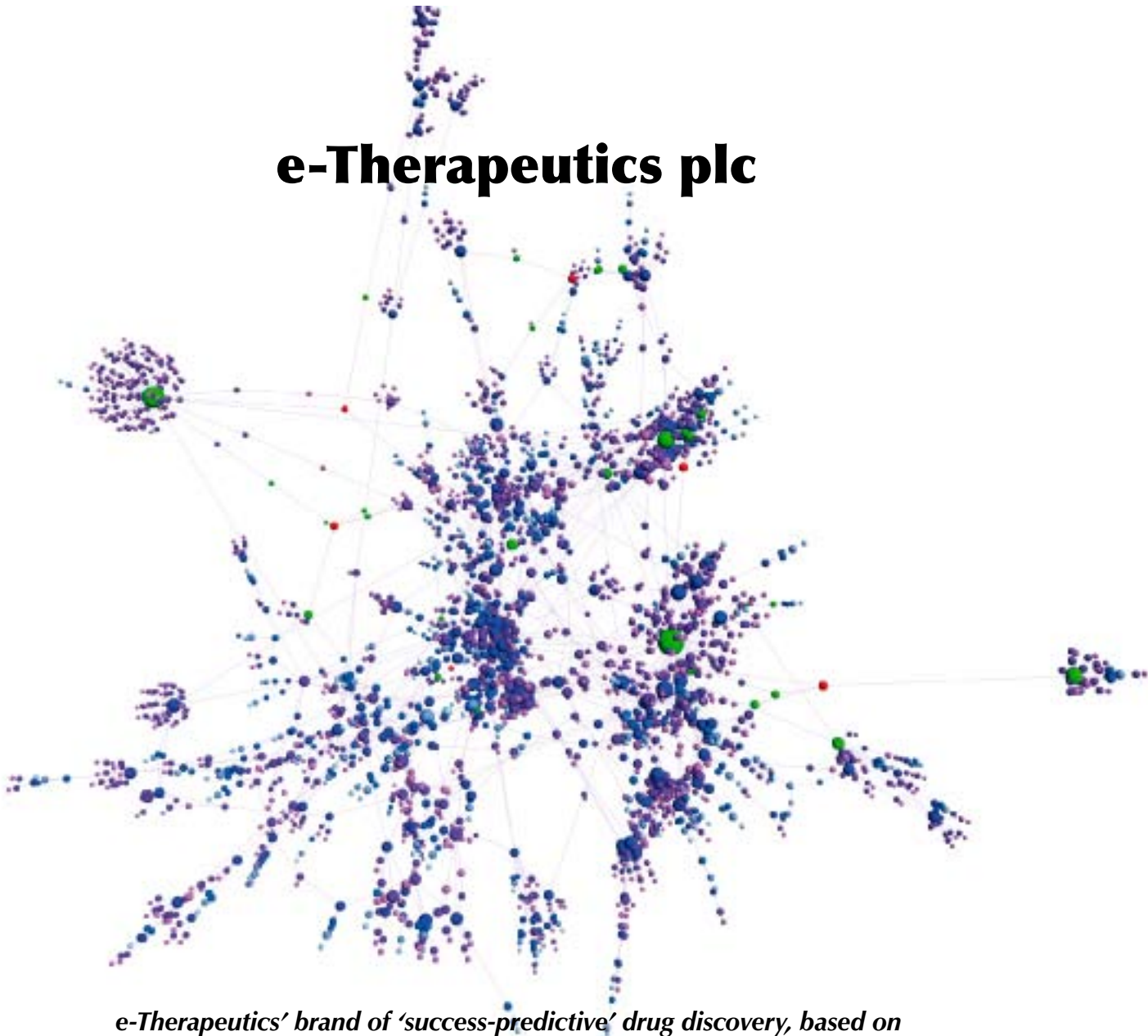


e-Therapeutics plc



e-Therapeutics' brand of 'success-predictive' drug discovery, based on bioinformatics and the analysis of complex biological systems, holds the potential, if clinically validated, to open up entirely new horizons in the treatment of complex, intractable or poorly treated diseases

Executive Summary

For the full report please visit:

<http://www.ObjectiveCapital.co.uk/etherapeutics.pdf>

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Initiation Report

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I certify that this report represents my own opinions.

Steven Zimmer, *Analyst*
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Key Points

18 November 2008

Price: 37.5p

e-Therapeutics' brand of 'success-predictive' drug discovery, based on bioinformatics and the analysis of complex biological systems, holds the potential, if clinically validated, to open up entirely new horizons in the treatment of complex, intractable or poorly treated diseases.

- ***If e-Therapeutics has its way, the last frontiers of therapeutic medicine are about to fall*** – The treatment of complex, intractable or poorly treated disease remains one of the richest sources of un-mined blockbuster areas of modern therapeutic medicine. e-Therapeutics' predictive drug discovery platform is aimed at providing a solution.
- ***Drug development failure rates remain high despite advances in biology*** – Only 2-3% of drugs identified as therapeutically relevant eventually make it to market. e-Therapeutics' drug discovery technology is aimed at identifying drugs that circumvent the uncertainties of drug development by identifying drug candidates that offer efficacy and safety.
- ***Identification of low-redundancy targets with minimal extraneous interactions are the key*** – e-Therapeutics uses powerful computers, integrated databases and sophisticated scientific approaches to overcome the pitfalls of searching for a 'needle in a haystack' in large, complex, 'noisy' data systems. The result is a 'predictive' system that looks for drugs that avoid 'leakiness' in efficacy and tolerance/side-effect interactions with healthy pathways and tissues.
- ***The current focus is on re-positioned compounds*** – e-Therapeutics has opted to focus first on re-positioning drugs developed for other applications. This represents the 'low hanging fruit' for this technology as it throws up drugs with full regulatory monographs and therefore much shorter development times.
- ***Clinical validation and the road to glory*** – As with all highly innovative pharma development science, the proof of the pudding remains successful clinical trials that are confirmatory of the predictions of the system. In the end, only clinical outcomes that match the predictions of the system in both efficacy and safety will give this approach the credibility that is needed for e-Therapeutics to become a perceived 'player' in the pharma discovery game.
- ***First 'Proof of Principle' trials should give early indications*** – The small PoP asthma and depression trials should provide some early insights as to safety and some indication as to whether the predicted efficacy parameters are confirmed. The trials are not statistically powered for efficacy but should give sufficient data to feed into potential licensees.
- ***Valuation is indicative and preliminary only*** – The valuation work presented here is illustrative in nature. But, should the clinical outcomes match the predictions, what is now highly speculative could rapidly transition into a goldmine of opportunity. Investors, watch this space!

Price chart (p)



Current fair value of equity

Expected value	US\$119.8m
Value per share	US\$2.15 (£1.33)
Optimistic scenario	US\$176.4m
Value per share	US\$3.17 (£1.96)

Company details

Quote

Shares	
- London AIM	ETX
- Berlin	3AQ.BE
Hi-Lo last 12-mos. (p)	70 - 18
Shares issued (m)	55.7
Fully diluted (m)	61.9
Market Cap'n (£m)	22.3
Website:	www.etherapeutics.co.uk

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Overview

e-Therapeutics' black box – a potential disruptive technology

e-Therapeutics plc is a UK-based drug discovery and development company with its head office in Newcastle. Its discovery platform derives from the application of Complex Systems Science, a science that involves the study of interactions within complex biological networks. Massive biological databases containing information about the genes, proteins and metabolites that make up these complex systems are translated into computer-usable information using mathematics and computational algorithms. These data can then be processed via powerful computers, yielding models that can be used to identify important network junctions that have biological relevance in diseased cells and tissues. In turn, these biological 'circuit breakers' can then be used to identify drugs that block them thereby blocking or enhancing a desired biological function.

A pioneer in the application of Network Analysis in Systems Biology

e-Therapeutics is one of several pioneers in the field of Systems Biology as applied to drug discovery and development. The approach it has taken to date has focused on the identification of key network nodes that have the ability to shut down targeted sections of the networks that are active in a particular diseased cell.

Once a data model for a diseased cell has been derived, key system nodes are selected computationally in relation to their ability to shut down the targeted network function and resolve the malfunction that triggered the disease state. e-Therapeutics' analytical system then selects compounds that interact with the key system nodes, but **do not interact** with key nodes in **non-target** cell-types, therefore yielding drug candidates that are **predicted** to be both safe and effective.

A strong pipeline of single and combination compounds tackling major diseases

This approach has yielded a promising pipeline of potential drug candidates in diverse areas such as anti-infectives, anti-depressants and treatments for asthma and cancer. It either yields a single or a combination of compounds depending on whether a single compound has the binding affinities required to effectively and selectively shut down a sub-network.

To start, 'repositioned' is the name of the game.

In its first phase of development, e-Therapeutics has focused on identifying potential drug candidates with clinical regulatory monographs for a particular application that could be repositioned as a treatment for a completely different disease than that originally indicated. These drugs fall into two categories:

- those that have full regulatory safety data that has been validated by a regulator but have failed to show efficacy in either proof of concept or, preferably, in subsequent pivotal trials for a different target indication;
- those already in the market but which are at the end of or beyond their initial composition of matter patent life.

In the field of 'repositioned' drug candidates, the need for intelligent drug formulation and creative patent strategies is a fundamental driver to the business. While in broader terms, Systems Biology offers the potential to identify *new* drug candidates that are 'de-risked' in terms of tolerance and safety, not all elements of de-risking are necessary for re-positioned ones, since their safety profile is already known.

Nevertheless, repositioned drugs bring with them other challenges which include creating new IP that can hold its ground against potential challenge; formulation of the new drug or drug combination to find an optimal dosing regime; and in the case of combination drugs, overcoming any regulatory barriers that creating such a novel entity might entail.

Some early PoC trials with early promising results

e-Therapeutics has risen to the challenge of this novel type of drug discovery/development workflow. Two pipeline candidates have completed their first phase of clinical testing:

- **ETX 9101** is an oral, long-acting anti-asthmatic drug based on the synergistic combination of a repositioned anti-histamine and NSAID¹ both of which are currently marketed and beyond their initial patented life;
- **ETS 6103** is a generic pain medication and is being repositioned for the treatment of depression in SSRI²-refractory MDD³ patients.

The results of the ETX 9101 trial have just been announced which, although of a very preliminary nature, show signs of efficacy and safety that encourage further clinical testing.

The ETS 6103 Phase IIa PoP pilot study (controlled versus amitriptyline) was halted half way through as a significant reduction in depression symptoms was observed.

This drug is intended to be a once daily formulation and is an orally active repositioned compound developed under the hypothesis that in a significant percentage of depressed patients, non-symptomatic pain is involved in the underlying aetiology⁴ of the disease (which is probably why SSRIs do not work in such a large number of depressed patients), so that both mechanisms of central mood and of central pain need to be treated. Hence the development of this drug target was aimed at specific pathways known to be involved in pain and mood. The results of this trial should be announced shortly.

Other candidates all directed at un- or poorly met clinical needs

e-Therapeutics also has:

- a combination drug under development for the treatment of MRSA/VRE/C.difficile⁵ (**ETX 1153**);
- a single agent developed originally for metastatic melanoma (**ETS 2101**) but under investigation as a tumoricidal agent for a wide variety of tumours;
- a combination for the treatment of fibromyalgia⁶ (**ETS 6218**);
- various candidates (**ETS 6107 & ETS 6114**) for the treatment of hypercholesterolaemia but with a view to blocking atherosclerosis⁷ and multiple cardiovascular risk factors as well.

Corporate development activities are in full swing with partnerships in the works

e-Therapeutics is engaged in a wide variety of discussions across the industry to partner the drugs in this pipeline and move them further through clinical development. However, in the near term, the results of its two self-funded Phase IIa trials should provide the evidence needed to validate the company's approach.

¹ Anti-histamines for allergies and NSAID's or non-steroidal anti-inflammatory drugs are used to treat pain and inflammation such as in pre-menstrual syndrome and rheumatoid arthritis amongst many others.

² Selective Serotonin Reuptake Inhibitors of which Prozac was the first and most illustrious member. Patients that are refractory are resistant to treatment.

³ Major Depressive Disorder.

⁴ Aetiology is a medical term from the underlying cause or pathology of a disease. Molecular aetiology would refer to the underlying molecular mechanisms of a disease.

⁵ MRSA or methicillin-resistant *Staphylococcus aureus*, VRE or vancomycin-resistant enterococci and C.difficile or *Clostridium difficile* are all difficult to treat bacterial infections that are associated with very high mortality.

⁶ A chronic musculoskeletal condition involving chronic pain.

⁷ Atherosclerosis is a disease affecting arterial blood vessels. It involves a chronic hardening of the arteries, ultimately leading to the formation of multiple plaques and a narrowing (or stenosis) of the artery.

Valuation

As with most early stage drug development companies, it is easy to get carried away and end up with a great disparity between stock price and valuation. As we have said elsewhere, companies listed on the AIM market are now suffering from a significant change in investor appetite for risk which is reflected in the average 40-60 percent drop in stocks in this sector (and in other similar sectors). In valuing the assets of e-Therapeutics, we have tried to take a very cautious approach to projecting market penetrations in what are very large, and for the most part, established therapeutic markets. As we have discussed further on in this report, we believe that the pricing of drugs will come under increasing scrutiny in the coming years and this has also been reflected in our revenue models.

The current business model of the company is to take compounds through a Proof of Concept or PoC Phase II trial as the basis for inking partnership deals with third parties. We have constructed from our discussions with management and from our own views on the matter, a series of pipeline timelines that drive our model for upfront and milestone payments as well as royalties in our model. As is usual, the set of financial assumptions that underlie our model are depicted in the graphic on the accompanying valuation pages. We have used the standard diMasi probability of success model of the industry with added discounts/premiums wherever appropriate. ETX 9101 and ETS 6103 are estimated to be at Phase II stage with a premium based on the extensive safety data available for these drugs. ETX 6218 and ETS 6103 are not yet in clinical trial but are considered to be a blend of Preclinical and Phase II so end up at a significant premium to preclinical but at a discount to Phase II.

The profile of the drugs being developed, if translated into clinical and regulatory success, would result in the introduction of drugs into the marketplace that could garner significant market shares. Nevertheless, we have refrained from estimating such large penetrations for two reasons:

1. We remain to be convinced that this sort of drug (not generic and not NCE-based proprietary) will trigger partnership deals with the largest pharma companies that have the greatest marketing muscle.
2. These are large highly competitive markets where entrenched positions will put up a vigorous fight to keep new entrants out.

Still, we believe that a clean safety and tolerance profile combined with a highly effective drug could, in the hands of an aggressive regional or specialty pharma company, garner a significant share of each market. We have allowed for two scenarios: one basic, core scenario and the other one more aggressive (primarily in market penetration). In each model, we have taken publicly available data on incidence and prevalence of each disease and calculated the total number of patients that would benefit from these therapies discounted to take into account the precise disease population target. Pricing has been targeted to the market leader or average price of medication and in some cases discounted further to reflect an aim to garner as much market share as possible with a mid-size pharma partner.

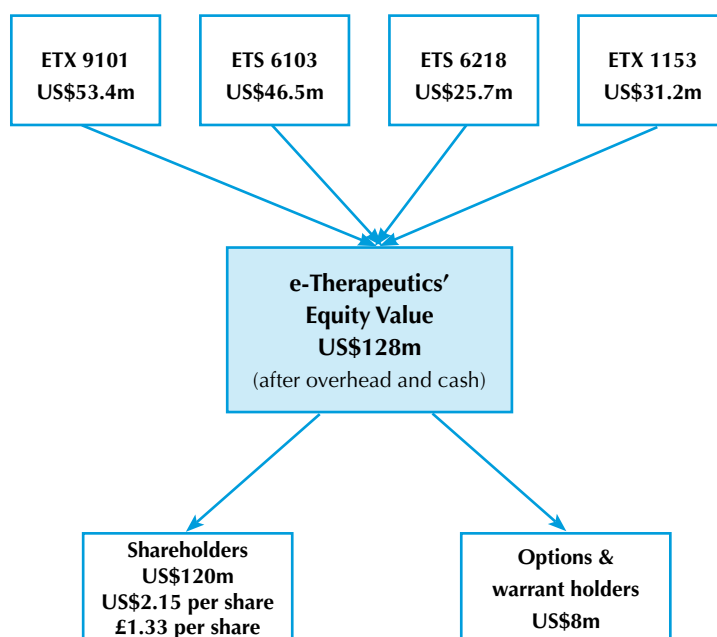
The result is a core valuation of £1.33 and a more optimistic one at £1.96. This is to be compared to a stock price now at 37p, still a long ways away.

Fair value summary (US\$m)

Scenario	Core	Optimistic
Development drugs		
- ETX 9101	53.4	87.3
- ETS 6103	46.5	60.9
- ETS 6218	25.7	27.4
- ETX 1153	31.2	41.7
Less: overhead	32.2	32.2
Expected value of pipeline	124.6	185.1
Add: other assets	0.0	0.0
Add: starting cash + new funds	3.2	3.2
Total current value for firm	127.8	188.2
Less: Bank & other debt	0.0	0.0
Total value to equity claims	127.8	188.2
Less: warrants & options	8.0	11.8
Ordinary equity holders	119.8	176.4
Value per share (US\$)	2.15	3.17
Value per share (£)	1.33	1.96

Components of e-Therapeutics' entity value

If the e-Therapeutics' model works its development portfolio could currently be worth ...



Drug portfolio

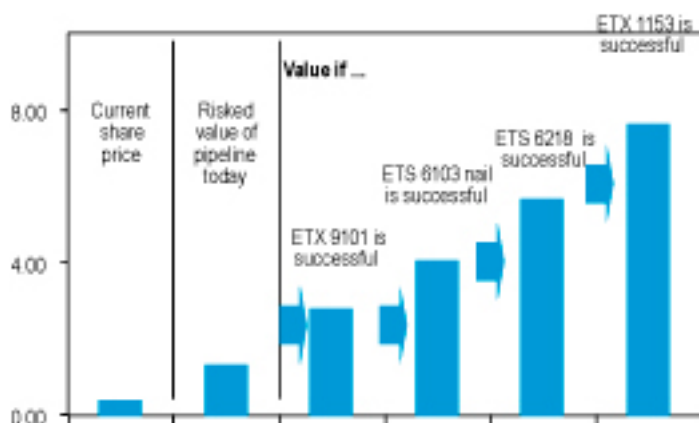
Summary of core drug valuations (US\$m)

Drug	ETX 9101	ETS 6103	ETS 6218	ETX 1153
Royalty revenue				
EV of royalties	271.5	234.5	258.2	316.1
Likelihood of success (PoS)	26%	26%	14%	14%
EMV of royalties	71.7	61.9	35.4	43.3
Add: EMV of upfront payments	2.0	2.0	0.6	0.6
Add: EMV of milestone payments	2.5	2.5	0.8	0.7
less: EMV of dev costs	0.0	0.0	0.1	0.1
EMV	76.3	66.5	36.7	44.5
per share (\$ ps)	1.37	1.19	0.66	0.80
per share (£ ps)	0.85	0.74	0.41	0.49
After tax EMV	53.4	46.5	25.7	31.2
Detailed valuation on page	43	46	49	39

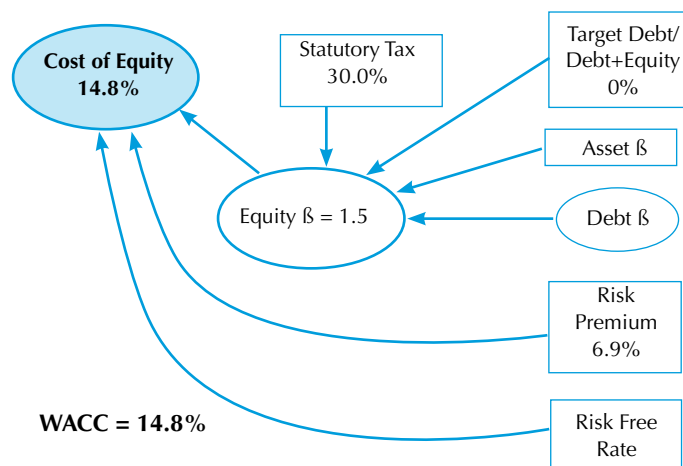
Summary of optimistic drug valuations (US\$m)

Drug	ETX 9101	ETS 6103	ETS 6218	ETX 1153
Royalty revenue				
EV of royalties	454.8	312.0	275.6	425.4
Likelihood of success (PoS)	26%	26%	14%	14%
EMV of royalties	120.1	82.4	37.7	58.3
Add: EMV of upfront payments	2.0	2.0	0.6	0.6
Add: EMV of milestone payments	2.5	2.5	0.8	0.7
less: EMV of dev costs	0.0	0.0	0.1	0.1
EMV	124.7	87.0	39.1	59.5
per share (\$ ps)	2.24	1.56	0.70	1.07
per share (£ ps)	1.39	0.97	0.43	0.66
After tax EMV	87.3	60.9	27.4	41.7
Detailed valuation on page	43	46	49	39

Current EMV and value if pipeline is successful (£ps)



Weighted cost of capital



Key Risks

Inability to deliver clinical outcomes that match the system-predicted safety/efficacy profiles

Validation of the discovery technology rides completely on attaining the predicted safety/efficacy profiles that are the predicted basis for the value of each of the company's pipeline candidates. This is a decisive process which, formulation and regulatory issues aside, will determine the perceptions, both of investors and potential pharma partners, as to the credibility of this approach. The science is plausible and it does deliver candidates; the question that must be answered is whether these candidates pass muster in clinical terms.

Formulation of combination drugs

The ability to formulate a single drug with a known pharmacokinetic profile can be difficult enough. Formulating combination drugs where the pharmacokinetic profile in one application (let alone multiple applications) may or may not be transportable to the re-positioned one poses its own challenges. It is unclear at this time (mostly because it is too early to say) whether this will be easily achievable for each of these candidates.

Safety of novel combination drugs

While individually safe with many years of administration, repositioned drugs in combination may or may not display additive safety. The potential for drug/drug interactions will in some cases need to be vetted to satisfy any regulatory concerns. Initial testing of the asthma-directed oral combination underlying ETX 9101 appears to be safe in the preliminary PoP test the company conducted in India. However, there can be no assurances that this will be the case of other current (ETX 1153 as an antimicrobial for example) or future combinations.

Regulatory uncertainties

While there are significant re-positioned drugs that have passed regulatory scrutiny (Rogaine or minoxidil for hair growth and Viagra for erectile dysfunction are most famous for this), the regulatory climate for drug approvals, particularly in complex, chronic and severe conditions, has tightened up considerably (viz. the Vioxx debacle). The safety profiles of the repositioned compounds being pursued by the company, all drug/drug interaction issues aside, are not in doubt. Despite the availability of section 505 (b) (2) in the US for drugs with legacy safety monographs, the regulatory impediments to market for these drugs remain to be tested particularly as they pertain to novel combination drugs. The expectation that drugs derived from this sort of development workflow will lead to shorter development timelines remains to be tested and confirmed.

IP integrity of the pipeline

The patent position for e-Therapeutics' pipeline remains untested at this time. The company's proprietary data search capabilities do put it in a strong position to identify new applications with no prior art. Nevertheless, until these claims are challenged by third parties, uncertainties will remain as to the strength of these patents.

Profit & Loss					
Year ending Jan (£000's)	2007A	2008A	2009E	2010E	2011E
Revenues					
Projects for third parties	—	64	137	110	88
Upfront payments	—	—	—	4,849	32,326
Milestone payments	—	—	—	—	—
Licensing/royalty revenues	—	—	—	4,076	9,555
Net revenues	—	64	137	9,035	41,969
Development costs					
Development costs	—	—	—	323	—
Other development costs	—	—	—	—	300
Other cost of sales	—	24	99	227	700
Gross profits	—	40	38	8,808	41,269
Gross margins	<i>NM</i>	63%	28%	97%	98%
Other operating income	—	82	—	—	—
Administrative expenses	1,158	2,399	2,024	2,205	2,324
Depreciation	27	31	91	148	149
Amortisation	—	—	—	—	—
Wages and staff costs	827	1,020	1,071	1,178	1,296
Share-based payments	125	8	9	9	10
AIM flotation costs	—	472	—	—	—
Other costs	179	868	853	870	870
Profit from operations	(1,158)	(2,277)	(1,986)	6,603	38,945
Interest income	10	52	20	195	929
Interest expenses	(1.00)	—	—	—	—
Pretax income	(1,149)	(2,225)	(1,966)	6,798	39,874
Net tax	—	(259)	(485)	(120)	11,842
Net income	(1,149)	(1,966)	(1,481)	6,918	28,032
Ending shares outstanding (000's)	1,530	55,710	55,710	55,710	55,710
Average Shares Outstanding (000's)	1,530	55,710	55,710	55,710	55,710
EPS (p)	(75.1)	(3.5)	(2.7)	12.4	50.3

Balance Sheet					
Year ending Jan (£000's)	2007A	2008A	2009E	2010E	2011E
Non-current assets					
Property plant & equipment	78	56	165	267	268
Goodwill	—	—	—	—	—
Other intangible assets	51	72	122	172	222
Total	129	128	287	439	490
Current assets					
Trade and other receivables	143	613	100	200	300
Cash & equivalents	150	1,977	745	7,432	35,320
Total	293	2,590	845	7,632	35,620
Total assets	422	2,718	1,132	8,071	36,111
Current liabilities					
Other trade payables	98	154	51	50	50
Other payables	—	75	65	79	79
Total	98	229	116	129	129
Net assets	324	2,489	1,016	7,942	35,982
Shareholders' equity	324	2,489	1,016	7,942	35,982

Cashflow					
Year ending Jan (£000's)	2007A	2008A	2009E	2010E	2011E
Operating loss	(1,158)	(2,277)	(1,986)	6,603	38,945
Depreciation and amortisation charges	27	31	91	148	149
Loss on sale of PPE	—	80	—	—	—
Share-based payments expenses	125	8	8	8	8
Income tax/credit	—	259	485	120	(11,842)
Net cash from operations	(1,006)	(1,899)	(1,402)	6,879	27,259
(Increase)/Decrease in trade and other receivables	(99)	(470)	513	(100)	(100)
(Decrease)/Increase in trade and other payables	52	131	(113)	13	—
Net cashflow from operations	(1,053)	(2,238)	(1,002)	6,792	27,159
Cashflow from investing					
Property plant & equipment sales	—	66	—	—	—
Property plant & equipment purchases	(47)	(155)	(200)	(250)	(150)
Purchase of intangible fixed assets	(5)	(21)	(50)	(50)	(50)
Net interest received	10	52	20	195	929
Net cash from investing activities	(42)	(58)	(230)	(105)	729
Cashflow from financing activities					
Issue of ordinary shares	1,100	4,123	—	—	—
Interest paid	(1)	—	—	—	—
Net cash from financing	1,099	4,123	—	—	—
Net increase (decrease) in cashflow	(4)	1,827	(1,232)	6,687	27,888
Opening cash equivalents	154	150	1,977	745	7,432
Closing cash equivalents	150	1,977	745	7,432	35,320

Source: Objective Capital

Professor Malcolm Young

Chief Executive

Malcolm is a scientist by background. He has recently been Director of the Complex Systems Group, Director of the Institute for Neuroscience, Provost of the Faculty of Science, Agriculture and Engineering, and Pro-Vice Chancellor for Strategic Development at Newcastle University, after having been a Royal Society Research Fellow at the RIKEN Institute in Japan, and at Oxford University. His research expertise lies in complex systems analysis and informatics, and recent outputs of his group include six publications in Nature and Science and twelve in Proceedings and Philosophical Transactions of the Royal Society. The main goals of his research have been to understand how biological function arises from structural aspects of complex biological systems. His recent research funding exceeds £11 million, and includes programme and project grants for research on complex systems from the Wellcome Trust (the world's largest medical research charity), EU Framework programmes, the Human Frontiers Science Programme Organisation, DEFRA, BBSRC, EPSRC and DTI e-Science. He is one of eighteen scientists worldwide nominated by the Sunday Times as the "Brains behind the 21st Century". All this scientific experience and expertise is now dedicated to delivering safe and effective new medicines through e-Therapeutics. Professor Young founded e-Therapeutics, and has led its development since.

Dr Royston Drucker

Chief Medical Officer

Royston is a medical doctor, with a great deal of experience of the pharmaceutical industry. He originally joined the European R&D organisation of Sterling Drug Inc. as a medical adviser, and was promoted to be responsible for clinical pharmacology, drug metabolism and bioanalysis in Europe. In 1986, he moved to the Upjohn company, subsequently Pharmacia & Upjohn, Inc, where he held a range of international responsibilities. His positions there included Director, Marketing with responsibility for worldwide marketing of cardiovascular products; Executive Director, European Community Affairs and Business Systems; and Vice-President, Drug Development, with global responsibility, in multiple therapeutic areas, for clinical drug development. A graduate of the Harvard Business School Advanced Management Program and Member of the Securities Institute, Roy managed Technomark Consulting Services, including a corporate finance operating unit, BioCorp Securities, which is the European leader in crossborder transactions in the pharmaceutical contract research industry, before joining e-Therapeutics.

Johnny Cordiner

Finance & Commercial Director

Johnny is an experienced investment banker who specialised in life sciences. Johnny is a graduate chemist, a member of the Institute of Chartered Accountants for Scotland, and a member of the Securities Institute. He gained 15 years' business experience in a number of financial roles, including working in industry, management consulting and offshore banking before entering investment banking. Johnny has been instrumental in the commercialisation of e-Therapeutics, having worked with Malcolm and Royston for more than three years to place the company in a sound financial and strategic position for rapid development.

Professor Oliver James

Non-executive Chairman

Oliver has been a non-executive director of BUPA since 1999 and was a non-executive director of Goldsborough Health Care plc from when it floated on the main market in 1995 until it was acquired by BUPA in 1997. He has also been a non-executive director of the Newcastle upon Tyne Hospitals NHS Foundation Trust since 2006. Oliver qualified as a physician in 1975 and practised until 2004 when he became head of the medical faculty at Newcastle University. He was senior vice president of the Royal College of Physicians from 1997 to 1999 and has also been a member of a number of national and governmental medical-related boards and committees. Oliver joined the company as a non-executive director in November 2007.

We are pleased to bring you this report on **e-Therapeutics plc**.



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Gabriel Didham, CFA
Objective Capital

Steven Zimmer, M. Sc. (Molecular Biology)
Steven has more than 25 years experience in analysis, corporate finance and as a portfolio manager in biotech and pharma including working for DLJ, CSFB and Robert Fleming in London, NY and Switzerland.

About our relationship with e-Therapeutics plc

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