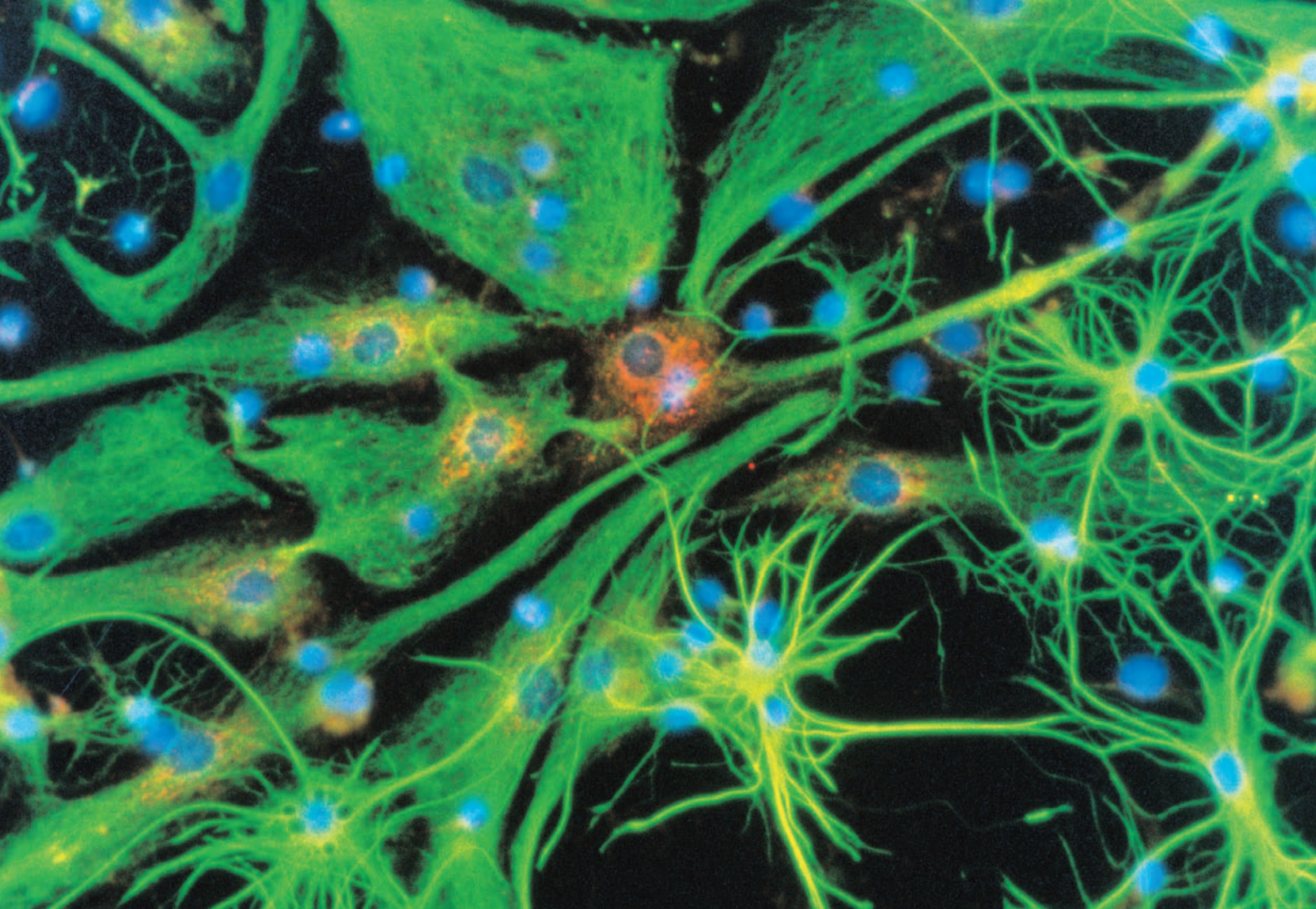


## CeNeS Pharmaceuticals (CEN)



*CeNeS is at a pivotal point with the likely initiation of its post-operative pain drug (M6G) into the regulatory process. The profile of this morphine metabolite looks extraordinarily promising with all of the cost, side-effect and efficacy characteristics pretty much known at this juncture. Failure would be very surprising indeed.*

Objective Capital Limited  
Token House  
11-12 Tokenhouse Yard  
London EC2R 7AS  
Tel: +44-(0)870-080-2965  
Fax: +44-(0)870-116-0839  
US toll-free: 1-888-802-7215  
editor@objectivecapital.com

# Initiation Report

Corporate: [www.ObjectiveCapital.com](http://www.ObjectiveCapital.com)  
Research: [www.ObjectiveCapital.co.uk](http://www.ObjectiveCapital.co.uk)

---

## Contents

Key Points	3
Overview	4
Valuation	6
Key Risks	8
CeNeS Company Overview	9
Drug Portfolio Analysis: the end game	13
Financials	26
Appendix 1: News flow and dev. timeline	28
Appendix 2: M6G drug profile	29
Appendix 3: CNS 5161 drug profile	32
Appendix 4: CNS 7056X drug profile	35
Appendix 5: COMT inhibitors drug profile	38
Appendix 6: Management	42

---

We certify that this report represents our own opinions.

Steven Zimmer, *Analyst*  
[steven@objectivecapital.co.uk](mailto:steven@objectivecapital.co.uk)  
0870 080 2965

Dr. Cheryl Barton, *Analyst*  
[cheryl@objectivecapital.co.uk](mailto:cheryl@objectivecapital.co.uk)  
0870 080 2965

---

---

This report has been prepared by Objective Capital Limited.

Objective Capital is a provider of corporate research. Our research reports provide information, analysis, and estimates and may reference our opinion on the value of highlighted companies. Objective Capital is not registered by any financial authority, and does not provide or purport to provide investment advice or recommendations of any description.

The information in this report is designed to present the opinion of Objective's analysts and what they believe to be the objective prospects of the highlighted company. Where reference is made to estimates of value or relative value of a specific company these are based on standard analysis assuming an "average" investor. There is no guarantee that these estimates are reliable or will eventuate. They should not be relied upon in forming specific investment decisions and readers should seek advice specific to their situation and investment requirements from a person authorized under the Financial Services and Markets Act 2000, before entering into any investment agreement.

Objective Capital's detailed reports are only available to ordinary business investors, market counterparties, high net-worth and sophisticated individual investors.

This report does not constitute an offer or invitation to purchase or acquire any shares in any company or any interest therein, nor shall it form the basis of any contract entered into for the sale of shares in any company.

The information in this report is believed to be correct, but its accuracy or completeness cannot be guaranteed. No representation or warranty, express or implied, is given by any person as to the accuracy or completeness of the information and no responsibility or liability is accepted for the accuracy or sufficiency of any of the information, for any errors, omissions or misstatements, negligent or otherwise.

Objective Capital (including its Directors, employees and representatives) or a connected person may have positions in or options on the securities detailed in this report, and may buy, sell or offer to purchase or sell such securities from time to time, subject to restrictions imposed by internal rules. Objective Capital and its analysts are barred from trading in the shares of companies on which Objective Capital provides coverage.

You are reminded that the value of shares in any company may go up or down. Past performance is not necessarily a guide to future performance.

### About Objective Capital:

Objective Capital is a leading UK provider of objective corporate research.

We offer investors two levels of insight – a regular survey of the complete small and mid-cap segment, highlighting those stocks where attention should be focused, and our detailed institutional-quality, sponsored research coverage. As always, our research doesn't offer trading recommendations or advice but an objective up-to-date assessment of the prospects, and risks, of the companies we cover.

While the companies we cover sponsor our research, it is always written on behalf of our readers. It is of the essence of our research that it be **independent** — that is opinions, estimates and valuations be solely those of Objective's analyst; **objective** — that is based upon verifiable data; and **transparent** — that is based upon explicit assumptions.

Our research complies with all FSA recommendations as may arise out of CP172 and CP176, i.e., that it be independent of any broking or trading interests; and CP205, i.e., that it comply with standards for objectivity.

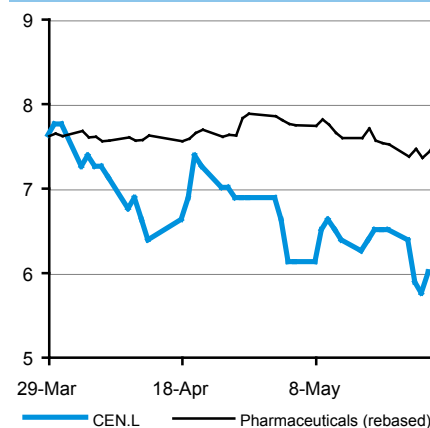
## Key Points

*CeNeS is an emerging drug company focused on developing new therapies for a discrete number of Central Nervous System disorders. It pursues a model which emphasises risk reduction at all levels, managed by a small team of experienced individuals. 2007 should be a pivotal year with further positive news flow expected on its drug pipeline and the likely initiation of its post-operative pain drug (M6G) into the regulatory process through a significant pharmaceutical partnership. This process should lead to further significant pharmaceutical partnerships and the market introduction of M6G from 2008.*

### KEY POINTS

- **The transformation of CeNeS into a 'virtual' specialty pharmaceutical company is complete.** The Company is run by a cohesive team of highly qualified individuals with significant industry experience. The business model devised has moved to a focused 'virtual' one where the team manage development on a totally 'outsourced' basis.
- **Focus on 'low hanging fruit' in CNS disorders**  
CeNeS seeks to reduce business risks by focusing on development candidates in CNS therapeutic areas that have very well characterised drug mechanisms and where improvements create a significant market opportunity.
- **Finely tuned business model in action**  
Alan Goodman, Neil Clark and team have developed an astute, innovative and dynamic business model where the development profile of a drug, its preclinical and clinical results and the financial resources of the Company, drive the team's perception as to the timing of when to outlicense to a Pharma partner. The result is a maximisation of return from the portfolio through payments during development and royalties when the product reaches market.
- **Post-op pain management drug M6G is the spearhead with what appears to be a 'slam-dunk' outcome.** The profile of this morphine metabolite looks extraordinarily promising with all of the cost, side-effect profile and efficacy characteristics pretty much known at this juncture. Failure would be very surprising indeed. With a peak market potential estimated by the Company to be £200 million, the earnings potential for CeNeS is substantial.
- **The rest of the portfolio marches on!**  
CeNeS has a full portfolio of compounds all with significant market potential, which will roll out into licenses with accompanying upfront and milestone payments through 2012. The nearest term prospects are CNS 5161 for neuropathic pain and CNS 7056X a short acting sedative.
- **The paradigm shift in medicine that rates pain as a 'Vital Sign' is a powerful trend for the Company.** Doctors are increasingly being asked to consider treating pain as an obligation they must attend to and cannot ignore. The results of this shift in attitude towards pain has a potentially powerful positive effect on the value of the Company's pipeline.
- **Longer-term prospects could be explosive**  
A novel COMT inhibitor with applications in Parkinson's and cognitive disorders such as schizophrenia, is an internally designed drug with potentially very large market potential (close to £1 billion).

### Price chart – CEN



### Our valuation

Value of equity:	
- Core scenario	£165.9m
- Downside Scenario	£117.8m
Value per share:	28p - 40p

### Company details

Quote	
Ticker - London AIM	CEN.L
- Frankfurt	CQG.F
- Berlin	CQG.BE
- XETRA	CQG.DE
- Pink sheets (US)	CPHAF.PK
Hi-Lo last 12-mos. (p)	9.25 - 5.75
Shares issued (m)	409.76
Market Cap'n (£m)	24.5
Stockbroker:	Canaccord Adams Limited
	+44 (0)20 7518 2777
	<a href="http://www.canaccordadams.com">www.canaccordadams.com</a>
Financial PR:	Northbank Communications
	+44 (0)20 7886 8150
	<a href="http://www.northbankcommunications.com">www.northbankcommunications.com</a>
Website:	<a href="http://www.cenes.com">www.cenes.com</a>

Andy Yeo

Head of Research  
andy@objectivecapital.co.uk  
0870 080 2965

#### Analysts:

Steven Zimmer  
steven@objectivecapital.co.uk

Dr. Cheryl Barton  
cheryl@objectivecapital.co.uk

## Overview

### **CeNeS is a pharma company developing drugs for CNS disorders**

The Company has built a pipeline of 4 'neuro' drugs aimed at post-operative pain (POP), chronic neuropathic pain (NP), sedation, and Parkinson's disease (PD). It is distinguished by its finely tuned model, which enables the Company to maximise the returns from its drug portfolio by:

- minimising the capital needed to exploit each pipeline candidate through a 'virtual' pharma structure that outsources development and regulatory resources; and
- optimising the timing of out-licensing to a larger pharma depending on the nature of the therapeutic target, the characteristics of the clinical trials needed to develop the drug and its perception of the onset of diminishing returns for shareholders.

### **With a messy past it has switched gears and transitioned successfully**

The original CeNeS was a hodge podge of highly risky, mostly biotechnology-driven drug development sprinkled with some cash flow positive contract service companies. An interesting concept (somewhat successfully pulled off by others) but poorly executed in CeNeS's case. After a radical management change, a brutal restructuring and several years of divestments to raise cash, a new management team has been carefully crafted and has built what looks like a very astute business model. With a re-structured, debt-free balance sheet, a relatively low burn rate and a full pipeline of drugs, CeNeS is poised for explosive growth over the next 3-5 years. The ultimate success of this transition will become evident from late 2006 upon completion of the Phase III clinical trials for M6G, the Company's entry into the post-operative pain arena.

### **No 'pie in the sky' stuff; refined focus on high value 'low hanging fruit'**

Banalities aside and skipping over the obvious (i.e., unmet or poorly met medical needs, improved patient and economic outcomes and the like) the Company has deliberately focused on drugs with the following characteristics:

- discrete therapeutic/prophylactic resolutions of common problems in need of an improved solution;
- reasonably well characterised therapeutic pathways;
- superior candidates to the current 'Gold Standard' treatment;
- a sizeable mid-sized market in the £200m+ range;
- the prospect of a significant period of patent or other market protection.

### **How far to market...that is the question**

How far CeNeS wishes to push each of its candidates to market is an exercise in refined analysis of the data at hand and perceptions of the financial resources needed to accomplish the task. To capture more of the value of a particular drug, it may be possible to push certain pipeline drugs in specific applications all the way to market and to retain, in some cases, limited geographic marketing rights to be fulfilled through (another's) outsourced marketing capabilities. The CeNeS team is trying to navigate its way through the minefields of large pharma out-licensing strategies and identify such opportunities. Whether it can do so or not will wholly depend on the data and what large pharma will let them get away with.

Summary of CeNeS's projects								
	Current clinical status	Timeline to first event	Likely partner timing	Partner task	Target launch	Royalty rate est.	Probability success <sup>1</sup>	Peak sales est. (£m)
<b>M6G</b>								
Europe	Phase III	4Q06	mid to late 2007	Reg/Marketing	2009	20%	67%	84
US	IND/PreClinical/ Phase III in mid 07	Partnering in mid 2007	mid 2007	Phase III/Reg/ Marketing	2010	20%	67%	88
<b>CNS 5161</b>								
IV Formulation	Phase IIb/Proof of Concept	1H07 Results	Possible Post PoC trial	Phase II/III Pivotal to Mkt.	2010	15%	30%	167
Transdermal patch	Pre Clinical	Phase I/II Results 4Q07	Completion of PoC Phase II 1H08	Phase III to market	2012	15%	10%	1,000
<b>CNS 7056X</b>								
Short Procedures	US IND in 4Q06	Phase I PoC in US 2007	After PoC/Retention of selected	US Phase II to market	2010	15%	20%	88
Induction/ Maintenance	1H08 Phase I PoC	2H08 Phase I results	Markets	US Phase II to market	2012	10%	10%	95
ICU/CCU	None	None	After PoC/Retention of selected	US Phase II to market	2013	10%	10%	158
<b>COMT Inhibitors</b>								
Parkinson Disease	Preclinical	PoC Phase I in 2008	2008/2009	Phase II to market	2012	8%	10%	480
ADHD	Preclinical	Unclear	Post Phase I trial in PD	Phase II to market	2013	8%	10%	225
schizophrenia	Preclinical	Unclear	Post Phase I trial in PD	Phase II to market	2014	8%	10%	285
<b>Total</b>								<b>2,670</b>

<sup>1</sup> Stewart et al, *Nature Biotechnology*, September 2001

Source: *Objective Capital*

### M6G: the goose that begins to lay the golden eggs

Morphine-6-Glucuronide, a morphine metabolite, appears to be as effective at reducing the level of post-operative pain as its forbear but with a significantly reduced level of uncomfortable and distressing side effects. Potentially, the resultant improved patient and economic outcomes could result in a significant market penetration for this drug in what is today a £2.5bn to £3bn market for narcotic analgesics. The relevant portion of this market is probably in the £500 million range and the Company's estimate of peak sales at circa £200 million seems well founded.

### Golden eggs hatched and futures discounted

The result, is a peak value of their pipeline estimated by the Company to be somewhere in the £800m–£1bn range. This estimate appears conservative, as it does not take into account additional applications of some of the pipeline components.

It appears to us that CeNeS maybe low-balling the value of the various drugs and being conservative about the various applications its pipeline could have. Compared to the wild predictions often conveyed by biotech companies for their pipelines (only to be pulverised when drugs fail in Phase II or III clinicals!), CeNeS's approach is refreshing given the propensity of emerging pharma companies to 'talk up' their pipelines. However investors should not be mistaken, risks still abound as they do elsewhere.

However at a market capitalisation of roughly £25 million, these risks have been heavily discounted both intrinsically and if one compares CeNeS to its biotech brethren. The difference is that the Company has diversified its risk and reduced its technological and clinical risks by the pipeline choices it has made.

# Valuation

CeNeS's strategy and assets are focused on early stage drug development. Our valuation focuses on the Company's ability to grow value through progressing its portfolio of development drugs to the point where it can licence them to a partner. We have therefore approached valuation in two stages:

- calculating the economic potential for the drug should it reach market and given CeNeS's licencing strategy;
- applying risks for the stage of clinical development.

Our analysis suggests an expected monetary value of £170m for CeNeS's drug portfolio. After allowing for overhead, the value of tax losses, and outstanding options we estimate CeNeS to be worth at least £165.9m or 40p per share.

## Estimating Market Potential

In determining the economic potential of each of CeNeS's drugs we have estimated the level of market penetration and price point that could be achieved should the drug live up to its 'advertised' level of efficacy and side-effect profile. We have also recognised the impact of generics on pricing once patent protection expires.

CeNeS plans to "optimise" the point at which it licences each drug so as to maximise its royalty and upfront/milestone payments. We have assumed a royalty level that should be achievable given the stage at which the drug is licenced and likely milestone and upfront payments.

## Applying risks

In calculating the Expected Monetary Value of CeNeS's milestone/upfront and royalty payments we have estimated the likelihood of CeNeS's receiving the revenue based on the current stage of clinical development and the likelihood that development reaches the payment point.

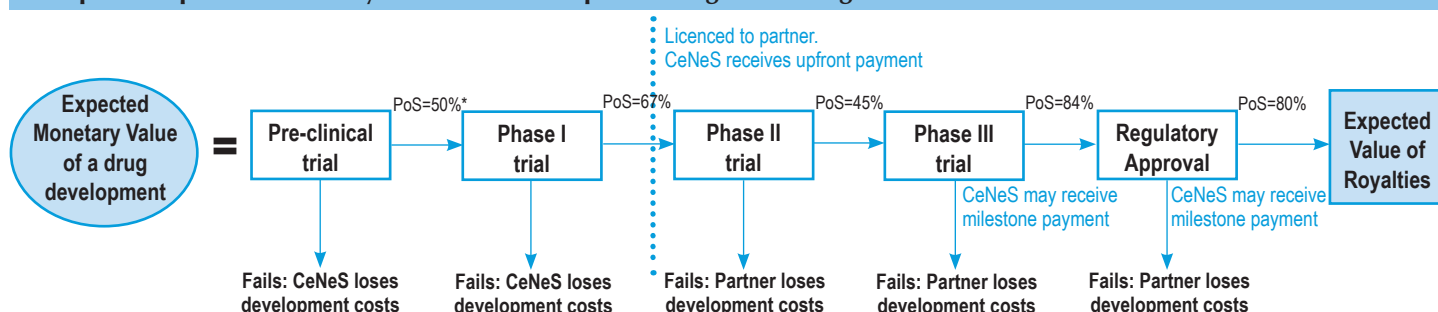
## Valuation

The current valuation is, in our view, a reflection of several factors, which are both historical and current in nature:

- There is a considerable 'show me' attitude for the new team in execution terms and the first corporate partnership to be signed by CeNeS with a significant pharma player is the only event that could alleviate the stock from this stigma.
- The pipeline has minimal credibility and/or visibility at this juncture for the type of investors that invest in AIM. They are prepared to wait until more evidence is in even if they miss the first move in the stock.

As seen in the table opposite, the potential for revaluation compared to strict comparables such as Amarin, Vernalis and Pain Therapeutics is substantial.

### Example of Expected Monetary Value of a development drug – licencing model



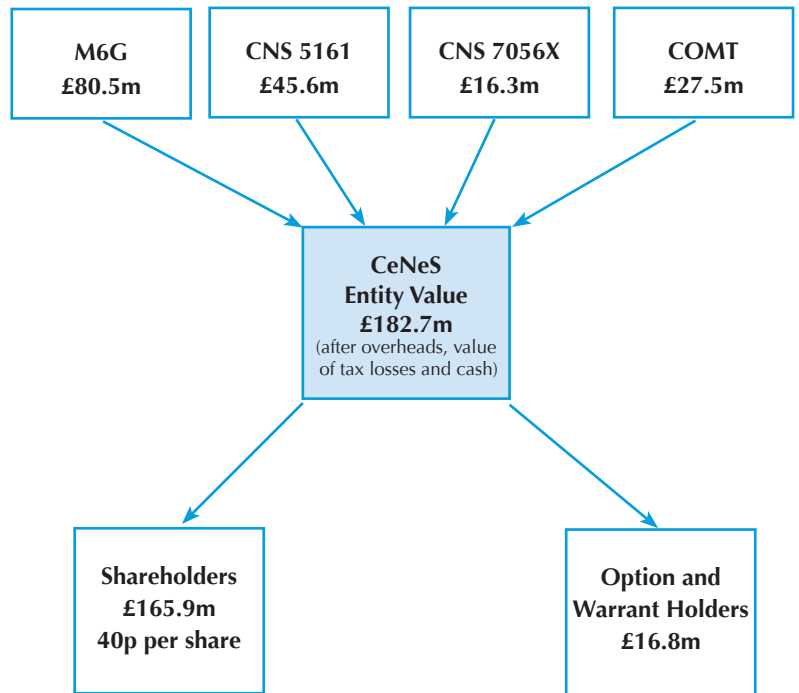
\* industry averages

## Valuation Summary (£m)

	Scenario	
	Core	Downside
M6G	80.5	50.9
CNS 5161	45.6	28.7
CNS 7056X	16.3	16.2
COMT	27.5	20.2
Less: overhead	19.5	19.5
Total Expected Operating Value	150.3	96.5
Add: Cash	10.0	10.0
Add: Tax losses	22.3	22.3
Total Current Value for Firm	182.7	128.8
Less: Bank & Other Debt	0.0	0.0
Total Value to All Equity Claims	182.7	128.8
Less: Alternative Equity Claims - Warrants + Options	16.8	11.3
Total Value Attrib. to Equity Holders	165.9	117.8
Outstanding ordinary shares (m)*	413	413
<b>Value per ordinary shares (£ps)</b>	<b>0.40</b>	<b>0.28</b>

\* includes shares due to GSK for CNS 5161 PoS weighted

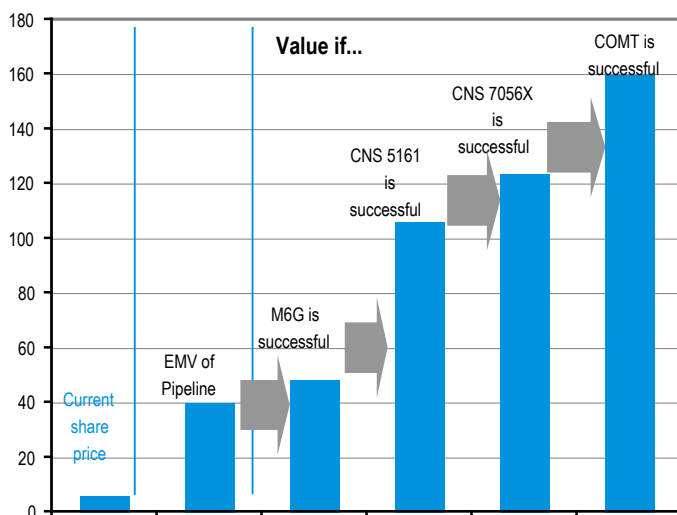
## Components of CeNeS's Entity Value



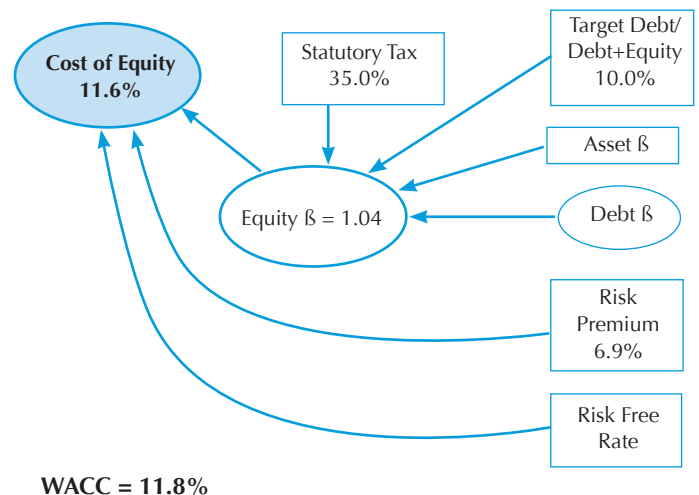
## Comparable speciality pharma companies (CNS speciality)

	Symbol	Market Cap (in millions)	Shares Outstanding (in millions)	Price	Rev Latest	Cash/Equiv latest	Cash/ share	Market Cap to Sales
<b>Dollar Zone</b>								
Acadia Pharmaceuticals	ACAD (Nasdaq)	US\$255.4	24.4	US\$10.49	US\$11.0	US\$55.5	US\$2.28	23
Amarin	AMRN (Nasdaq)	US\$230.0	79.9	US\$2.15	US\$0.5	US\$11.0	US\$0.14	460
Avanir Pharmaceuticals	AVNR (Nasdaq)	US\$309.9	31.2	US\$9.92	US\$16.7	US\$48.3	US\$1.55	19
Cephalon	CEPH (Nasdaq)	US\$3,591.6	60.7	US\$59.14	US\$1,211.0	US\$484.0	US\$7.97	3
Elan Pharmaceuticals	ELN (NYSE)	US\$7,988.5	430.9	US\$18.54	US\$464.0	US\$1,100.0	US\$2.55	17
Endo Pharmaceuticals	ENDP (Nasdaq)	US\$3,931.8	132.9	US\$29.58	US\$270.0	US\$501.0	US\$3.77	15
MGI Pharma	MOGN (Nasdaq)	US\$1,423.7	78.0	US\$18.25	US\$279.0	US\$129.4	US\$1.66	5
<b>Pain Therapeutics</b>	PTIE (Nasdaq)	US\$371.5	44.0	US\$8.45	US\$5.1	US\$212.7	US\$4.84	73
Valeant	VRX (NYSE)	US\$1,545.7	92.8	US\$16.66	US\$822.7	US\$235.1	US\$2.53	2
<b>CeNeS</b>	<b>CEN (AIM)</b>	<b>£24.5</b>	<b>409.0</b>	<b>£0.06</b>	<b>£0.1</b>	<b>£8.4</b>	<b>£0.02</b>	<b>491</b>
Alizyme	AZM (LSE)	£251.6	181.0	£1.39	£0.0	£30.8	£0.17	nm
Antisoma	ASM (LSE)	£84.8	368.7	£0.23	£6.3	£25.0	£0.07	14
Minster Pharmaceuticals	MPM (AIM)	£28.1	1563.0	£0.02	£0.0	£2.8	£0.00	nm
Vernalis	VER (LSE)	£234.4	311.5	£0.75	£14.3	£40.2	£0.13	16
<b>Eurozone</b>								
Lundbeck	LUN.CO (Copenhagen)	€ 1,021.9	58.3	€ 17.53	US\$813.0	US\$361.0	€ 6.19	1.26
Schwartz Pharma	SRZ (Frankfurt)	€ 31.2	46.9	€ 0.67	US\$767.7	US\$206.0	€ 4.39	0.04

## Current EMV of pipeline (p)



## Weighted Cost of Capital



## Key Risks

### **CeNeS has yet to demonstrate successful execution of its new strategy**

On paper, the transition, while brutal, has yielded a conceptually focused and attractive strategy. However, until the M6G Phase III trial is completed and a marketing partnership has been concluded, investors will have no tangible evidence of how the putative value of this reconfigured company will flow down to them. The management team's value is directly correlated to how successful it has been in choosing its pipeline, how able it is to extract an attractive deal from a pharma partner, and how successful the drugs that it has chosen are in the marketplace.

### **The 'how far and when?' strategy does yield uncertainty**

The flexibility inherent in the 'calculated and reasoned opportunism' of the Company's business model has a flipside that makes it difficult for investors to determine the ultimate level of royalties that the Company will exact from partners. While in the case of M6G this is relatively clear, the rest of the pipeline is not far enough along for a judgement to be made. To alleviate this the management of the Company does give some guidance but the uncertainty remains.

### **Success to partnership**

While CeNeS has targeted some relatively lower risk drug targets, the same risks inherent in drug development in general apply. A successful registration of a drug depends on the attainment of certain clinical trial endpoints in a statistically significant fashion. As with any drug, there can be no guarantees that such statistical significance can be achieved. The ability of the Company to successfully negotiate a pharma partnership depends wholly on its ability to complete its targeted Proof of Concept (PoC) trial. CeNeS, by way of its 'virtual model' depends wholly on such partnerships and the success of the Company depends entirely on the ability of its management to successfully negotiate such agreements.

### **Success to market**

Once a partnership has been concluded, the partner must successfully bring the product to market and construct a differentiated and successful marketing campaign for the drug. While CeNeS might be able to negotiate certain performance criteria and/or limited regional or local marketing rights, it will for the most part be dependent on the marketing success of its partners.

**CeNeS** is a specialty pharmaceutical development company focused on the development of drugs for Central Nervous System ('CNS') disorders including post-operative and neuropathic pain, Parkinson's disease and an agent for sedation in short surgical and diagnostic procedures. The Company has adopted a pure 'virtual' model using contracted services directed by an experienced and cohesive management team.

The Company's business model is devised around a highly selective, portfolio-centric, high return-orientated drug screening and selection process. This process is focused on targets with validated mechanisms of action and highly defined gold standards against which improved performance or side-effect profiles can be easily measured.

### **CeNeS has a pipeline of three identifiable drug candidates in phases I to III**

CeNeS' has three identified drug candidates with well-defined milestones and timelines which will result in clear investor-directed news flow (see table on p. 5 and Appendix 1). Success in any of these milestones should have a significant effect on both the perception of the Company's strategy along with knock-on effects on valuation.

### **The pipeline's fourth element represents the icing on the cake!**

Lead compounds as novel COMT (Catechol-O-Methyl Transferase) inhibitors have been identified. The Company is in the final stages of selecting the one to enter Pre-clinical and Phase I trials. This is the first internally developed drug but, again, directed at a well-defined mechanism in a disease where the target is clear and existing agents have severe deficiencies. Higher risk than the rest of the portfolio but potentially higher rewards!

### **Business Model Redux: a 'virtual' specialty pharma drug developer**

CeNeS fits into a category of companies which focus on a disease speciality (in this case CNS drugs) and is 'virtual' by dint of outsourcing all drug development functions to specialists: from 'Regulatory/Clinical' and 'Market Analysis' to Manufacturing; the conduct of clinical trials; the registration process itself; and, in a limited number of cases and for limited geographies, marketing itself. Amongst other similar companies, Pain Therapeutics (Nasdaq: PTIE) and Vernalis (LSE: VER) are the closest examples to CeNeS. The big difference is that they have raised more cash (and therefore have more visible staying power) and they have some deals under their belt.

In CeNeS case, the model operates within its cash constraints by keeping the internal team small (and the burn rate relatively low) which enables the Company to operate efficiently whilst maintaining focus. We see the main issues as:

- managing the outsourced functions;
- overseeing the development/clinical/regulatory process;

- determining the timing of partnering and negotiating partnerships;
- overseeing the partner's development and marketing of the drug;
- acting as a business development team to scrutinise and dissect further pipeline opportunities.

The only drug development function that has been kept in-house is a rational drug design function (computer-driven) which is limited to designing New Chemical Entities (NCE's) in areas of the team's expertise (which is where the COMT inhibitors come from). The class of compounds developed are then synthesized, screened and vetted by a third party under contract, a process that is closely managed and directed by CeNeS.

### **Drug to partner then to market: maximising value for shareholders**

Each drug may have multiple applications within a disease category or might even have different disease applications. This in turn leads to distinct development profiles, which will determine the nature of the clinical trial profile for a particular application. The CeNeS team spends a considerable amount of time and effort modelling these profiles to determine the timing of partnering for each drug application. At which stage a particular drug is partnered and what sort of deal is sought is the crux of the matter. This process while imbued with drug profile analyses, is essentially a value maximisation exercise in its purest form. CeNeS must determine in each case, where the assumption of increased business and financial risk rolls into the potential for diminishing returns given the Company's current structure and financial resources.

### **Cutting and dicing applications and the market**

This is where investors will determine the skills and quality of the management team and the validity of its strategy going forward. The table on the opposite page depicts a list of CNS market participants who could be potential partners or have competitive drugs. For each drug, CeNeS will have to determine the best strategy for partnering. Should the partner be global or regional or a combination thereof? Can CeNeS retain some regional marketing rights? If multiple applications are involved, can they be split or will they be required to partner all at the same time?

### **Market potential for the CeNeS pipeline in the £2.7bn+ range**

A market analysis for each drug has been conducted based on guidance from both the Company and a number of other sources. In the table on p. 5, we have laid out what we feel are peak sales numbers for each pipeline component as well as for each application that the Company has identified. In each case, a probability of success and a putative royalty rate have been estimated. This is based on guidance from CeNeS as to their timelines on when they will seek a partnership as well as pharmaceutical industry analytical norms. We have added our estimate of what the upfront value of each deal might be worth and the probability of suc-

## Some potential partners for CeNeS

Company/Category	Analgescic (narcotic/other)	Neuropathic Pain	Sedative/Hypnotic/ Anaesthesia	Parkinson's Disease	Cognitive impairment/ADHD
<b>Major Pharma</b>					
Abbott	Dilaudid (hydromorphone hydrochloride)		Precedex (dexmedetomidine)		Cylert (pemoline) <sup>1</sup>
Astra Zeneca					Seroquel (quetiapine) <sup>1</sup>
Boehringer Ingelheim	Roxicet (oxycodone), Tramal (tramadol), Oramorph SR (morphine)				
Bristol Myers Squibb				Sinemet (carbidopa-levodopa)	Abilify (aripiprazole) <sup>1</sup>
GSK	Ultiva (remifentanyl)	Paxil (paroxetine) <sup>1</sup>		Requip (ropinirole)	Compazine (prochlorperazine) <sup>1</sup>
Johnson & Johnson	<b>Strong with Durogesic (fentanyl), Alfentanil &amp; Tramadol (now generic)</b>				Risperidal (risperidone) <sup>1</sup>
Lilly	Darvon/Doxelene (dextropropoxyphene)	<b>Cymbalta (duloxetine)</b>			Zyprexa (olanzapine), Strattera (atomoxetine)
Merck				Cogentin (benotropine)	
Novartis	Voltarol/Voltaren (diclofenac)			Strong but branded generic Comtan (entacapone) Stalevo (entacapone/levodopa/carbidopa)	Clozaril (clozapine) <sup>1</sup> , Ritalin (methylphenidate)
Pfizer		<b>Neurontin (gabapentin - generic), Lyrica (pregabalin)</b>		Mirapex (pramipexole)	Geodon (ziprasidone) <sup>1</sup>
Roche	Toradol (ketorolac)		<b>Versed (midazolam)</b>		
Schering Plough	Temgesic (buprenorphine)				
Wyeth	Dolene (dextropropoxyphene)	DVS SR <sup>3</sup>	Ativan (lorazepam), Sonata (zaleplon)		
<b>Specialty Pharma</b>					
Abraxis			Diprivan (propofol - now generic in Europe)		
Allergan	Ketorolac + ALGRX-4965 <sup>3</sup>				
Alpharma	Kadian TR (morphine)				
Alza					Concerta (methylphenidate)
Celltech	Minijet (morphine)				Metadate (methylphenidate HCl)
Cephalon	Actiq (Fentanyl)	OraVescent Fentanyl P3			
Corgentech	Ketorolac + ALGRX-4965 <sup>1</sup>				
Endo	Percocet (oxycodone; acetaminophen)			Symmetrel (amantadine)	
Forest Labs		Namenda (memantine) <sup>2</sup>			
Grunenthal	Zydol (tramadol)				
MGI Pharma			Aquavan <sup>3</sup>		
Napp	OxyNorm (oxycodone) BuTrans & Transtec (buprenorphine) Palladone (hydromorphone)				
Orion Pharma				<b>Comtan (entacapone) market leader COMT inhibitor</b>	Zoleptil (zotepine) <sup>1</sup>
Pain Therapeutics	Remoxy (ORADUR based oxycodone)				
Purdue	Oxycontin (oxycodone), MS Contin (morphine), tramadol				
Shire	Metid (meptazinol)				Adderall (amphetamine-dextroamphetamine)
Valeant Pharmaceuticals				<b>Tasmar (tolcapone)</b>	
<b>European Regionals</b>					
AkzoNobel	ORG-41793/DPI-3290 <sup>3</sup>				
Elan				Permax (pergolide)	
Lundbeck		Namenda (memantine) <sup>2</sup>			
Merz					
UCB	Lortab (hydrocodone)	Keppra (levetiracetam)			

Source: Objective Capital

**Legend:**

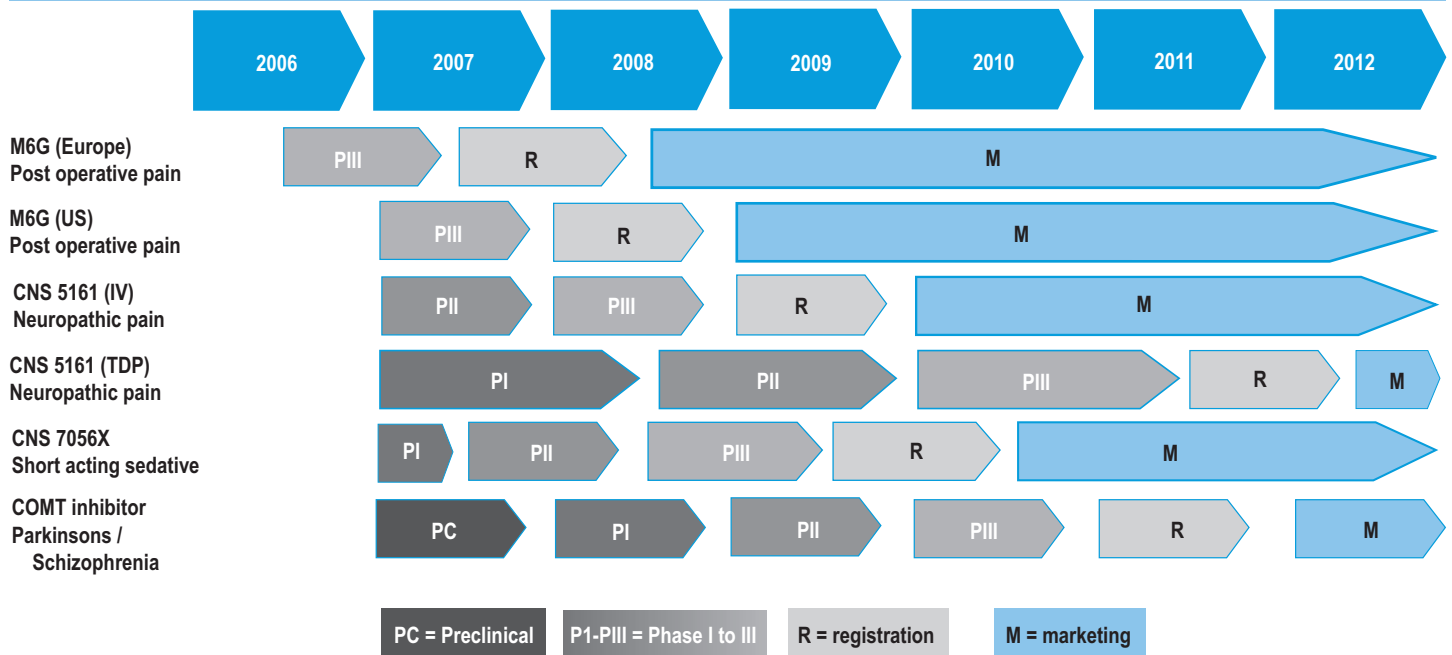
<sup>1</sup> used to treat the symptoms of schizophrenia

<sup>2</sup> drug used off label, being evaluated in clinical trials

<sup>3</sup> in clinical development

**Drugs in bold are key branded products**

## CeNeS's pipeline



Source: Objective Capital

cess of each programme. It does not take a rocket scientist to imagine that if only two of the four drugs were to make it to market, the value implications to CeNeS's stock are potentially significant within a 3-5 year time frame particularly from its current market capitalisation of around £25 million.

### Steady news flow to watch for from the pipeline

As depicted in Appendix 1 from the end of 2006 on, there should be a steady flow of news from this pipeline all of which should give investors a warm tingly feeling. This should also give investors increasing confidence that the transition from a messy, despairingly acquisitive and unfocused company into a targeted, team-driven, value-orientated one with an innovative and effective pharma development strategy has been completed. The rest will be execution, execution and... more execution.

### CeNeS's other carried interests

Asset	Owner/partner	CeNeS's carried interest
Dopamine D1 receptor agonists – Parkinson's research project	Shire Pharmaceuticals Group plc	Milestone payments and royalties
Ion channel library	Scion Pharmaceuticals, Inc.	Stage and milestone payments
Cognitive testing division	Cambridge Cognition Ltd.	Stage and milestone payments
AutoPatch technology and certain ion channel assets	Xention Discovery Ltd.	Minority shareholding, loan note and certain rights to drug candidates
GGF2 – potential treatment for multiple sclerosis	Acorda Therapeutics Inc.	Stage payments and royalties
CEE 03 310 – potential treatment for sleep disorders and substance abuse	Addex Pharmaceuticals SA	Stage payments and royalties

Source: Company

In the CNS arena, there are many conditions and situations where patients remain inadequately or poorly treated with older, as well as newer, drugs that can elicit significant side effects. CeNeS has been able to carefully select a series of drugs that can be best described as high value 'low hanging fruit' therapeutically speaking. Its first major registration candidate will be an opioid narcotic analgesic M6G followed by clinical trial results for CNS 5161, CNS 7056X and then Phase I results for the COMT inhibitor for Parkinson's disease.

### ***M6G: Slam dunk or the holy grail?***

#### **The drug**

Morphine-6-Glucuronide or M6G is a metabolite (i.e., breakdown product in the body) of morphine itself. Appendix 2 provides a detailed analysis of this drug for the benefit of those who wish to delve into the 'nitty gritty' details. Bottom line: we concur with CeNeS that it potentially has a new market entrant in the narcotic analgesic market for the treatment of post operative pain that is as effective as morphine but offers a more attractive side-effect profile.

Specifically, it significantly lowers the rate of nausea and vomiting along with the virtual absence of concomitant respiratory depression. Combined with the fact that it is a longer acting drug than morphine presents surgeons and post-op physicians with what is potentially a safer and superior cost/benefit profile narcotic analgesic. The cost of M6G is projected to be in a price range that is not considered threatening by Hospital Administrators (read relatively inexpensive) and it will certainly hold its own versus much more costly proprietary alternatives such as Johnson & Johnson and Cephalon's fentanyl (in its various formulations).

Although post op pain treatment is the main application, there are other possible (off label) uses that could be contemplated for a medication for moderate to severe pain with a more benign side-effect profile and longer mechanism of action.

#### **Market potential**

CeNeS has conducted an extensive market survey on the potential uses, favourability and pricing of M6G in the six major markets for such drugs. The Company estimates the inpatient operative population is roughly 27 million patients in the US and the same in Europe (excluding Japan and the rest of the world). Of that population a little bit less than half are relevant operations that can result in post op pain. Currently 25% of that population are treated with IV opiates (see Appendix 2).

There is also a sub market for epidural opiates, which surgeons are now increasingly using for post-operative pain. A review of the literature indicates that epidural administration of narcotic analgesics has significant advantages over IV administration in improving patient outcomes. M6G is highly effective via this route although this is not the indication being pursued at this time.

## M6G market potential (£m)

	Total	CeNeS's share	
Addressable IV opiate market	163.70	49.11	Assumes 30% conversion to M6G
IV Morphine	267.10	133.55	Assumes a roughly 50% conv. to M6G
IV Epidural	64.62	32.31	Assumes a 50% conv. rate to M6G
<b>OC estimate of addressable market</b>	<b>495.42</b>	<b>214.97</b>	

Source: Company estimates, Objective Capital

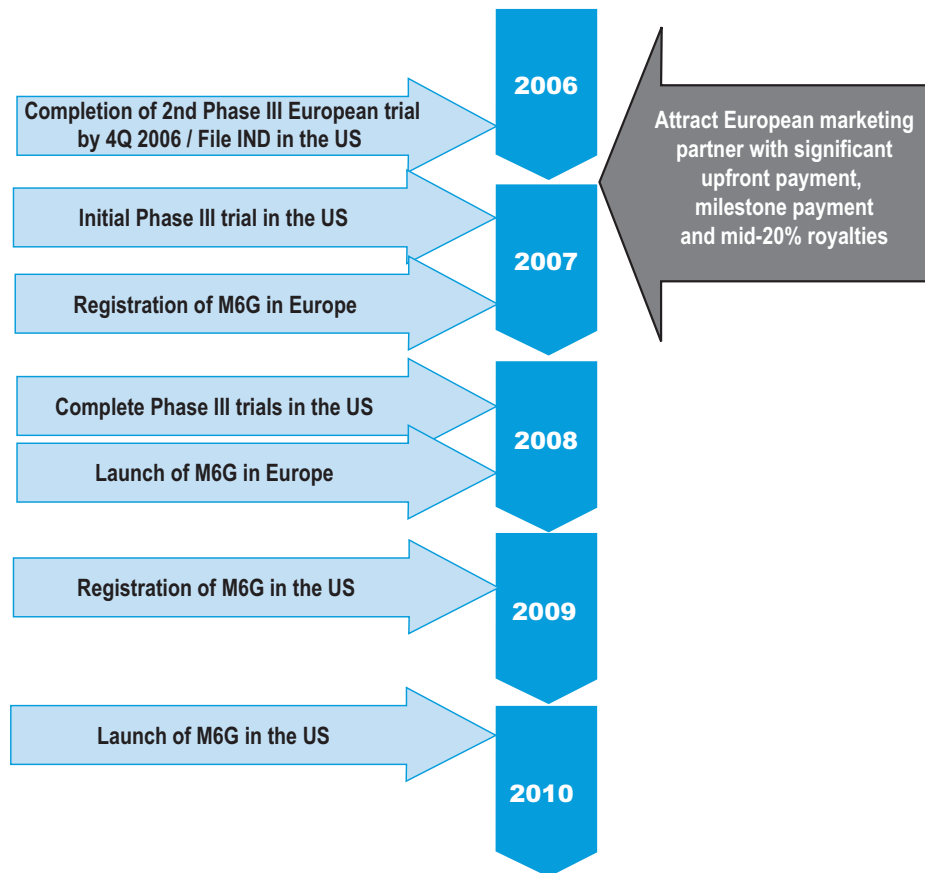
We estimate that the relevant market for post-operative pain is in the £500 million range worldwide. Based on Company guidance, market data and our analysis, we estimate the potential narcotic analgesic market for M6G is somewhere in the £200m-£250m range globally (see Appendix 2 and the table above for details). Evaluate Pharma estimate that sales of morphine alone from different manufacturers are in the £228 million range.

The epidural market within the overall opiate market is estimated to be around £70-80 million or around 30% of the overall opiate-based narcotic analgesic market. Hence CeNeS's projections of peak sales estimated at £200 million are very much in the ballpark if possibly somewhat conservative.

We believe that apart from the morphine segment (IV, PCA and epidural) M6G has the potential to make inroads into many other segments. M6G's promise of a relatively inexpensive, equally efficacious and longer-acting morphine substitute

Exp. monetary value of M6G (pre-corp tax)				Components of core valuation					
£m	Scenario			Core scenario					
	Core	Downside		Expected value of royalties (£ millions)					
<b>EV of Royalties</b>	<b>162.3</b>	<b>94.4</b>		<b>Indication/Market</b>	<b>EV of royalties</b>	<b>Current stage of devlp.</b>	<b>PoS</b>	<b>EMV</b>	<b>% of val.</b>
Likelihood of success (PoS)	67%	67%		- M6G Sales EU	69.8	Phase 3	67%	46.8	29%
<b>EMV of Royalties</b>	<b>108.7</b>	<b>63.3</b>		- M6G Sales US	71.4	Phase 3	67%	47.8	29%
Add: EMV of upfront payments	12.2	12.2		- M6G ROW	21.1	Phase 3	67%	14.2	9%
Add: EMV of milestone payments	7.5	7.5		<b>Total</b>	<b>162.3</b>		<b>67%</b>	<b>108.7</b>	
less: EMV of dev costs	4.7	4.7		<b>Downside risk: lower penetration of market</b>					
<b>EMV of M6G</b>	<b>123.8</b>	<b>78.3</b>		Expected value of royalties (£ millions)					
per share (£ ps)	0.30	0.19		<b>Indication/Market</b>	<b>EV of royalties</b>	<b>Current stage of devlp.</b>	<b>PoS</b>	<b>EMV</b>	<b>% of val.</b>
* see appendix for detailed sales and royalty forecasts				- M6G Sales EU	44.3	Phase 3	67%	29.7	31%
				- M6G Sales US	32.4	Phase 3	67%	21.7	23%
				- M6G ROW	17.7	Phase 3	67%	11.9	13%
				<b>Total</b>	<b>94.4</b>		<b>67%</b>	<b>63.3</b>	
<b>Key Market &amp; Licence Assumptions</b>				<div style="border: 1px solid black; padding: 5px; text-align: center;"> <b>Expected Monetary Value of M6G</b>                      £78.3m - £123.8m                      19p - 30p per share                 </div>					
<b>Indication/Market</b>	<b>Royalty Rate</b>	<b>Impact of Generics</b>							
		<b>Approx Date</b>	<b>Price Impact</b>						
M6G Sales EU	20%	2019	-65%						
M6G Sales US	20%	2017	-45%						
M6G ROW	15%	2019	-70%						
<b>Sensitivity to change in ...</b>				<div style="border: 1px solid black; padding: 5px; text-align: center;"> <b>EMV of upfront payments</b>                      £12.2m                 </div>					
<b>Impact of generics (+ % price decline)</b>				<div style="border: 1px solid black; padding: 5px; text-align: center;"> <b>EMV of milestone payments</b>                      £7.5m                 </div>					
		<b>-20.0%</b>	<b>-10.0%</b>	<b>+0.0%</b>	<b>+10.0%</b>	<b>+20.0%</b>			
Value (£m)	138.6	131.2	123.8	116.4	109.0				
Change in Value	12%	6%	0%	-6%	-12%				
<b>Increase in royalty (+%)</b>									
		<b>-10%</b>	<b>-5%</b>	<b>0%</b>	<b>5%</b>	<b>10%</b>			
Value (£m)	67.1	95.4	123.8	152.2	180.5				
Change in Value	-46%	-23%	0%	23%	46%				

## Developmental programme for M6G



Source: Objective Capital

could become a valuable tool for physicians looking for a better way (read more benign) to control post operative pain and for hospitals who are looking to cut costs and get away from expensive proprietary ethical drug solutions.

At a £215 million market size, our estimates for the direct addressable markets (IV morphine and epidural morphine) could look low if M6G is able to make inroads into the post op pain applications of other drugs such as Oxycodone (Purdue Pharmaceuticals and others) and fentanyl (Johnson & Johnson, Cephalon and others).

### Prospects and news flow

The drug is currently in its pivotal Phase III trials (double blind randomised efficacy and side-effects testing versus morphine), which should be completed by the end of 2006.

CeNeS is already engaged in preliminary discussions with interested parties and will accelerate those discussions into 2006 when the results of the Phase III are in. It is hoped that a licence might be in place (assuming that the pivotal Phase III results come in as planned) somewhere in late 2006 through 2007. CeNeS also plans to initiate a pivotal Phase III trial in the US in 2007, which it will probably do in conjunction with a US partner.

By waiting until Phase III the Company has enabled a licensing strategy, which carries with it a high royalty rate (in the early-20% range most likely). Consequently, substantial upfront and milestone payments are within the realms of possibility.

The Company has 2 choices here:

- if the deals offered by putative European partners are not attractive enough, CeNeS could go 'virtual' (i.e., rent a salesforce) and attempt to register the product itself in the UK and in the EU. It could potentially fund this by doing a regional US deal with a specialty pharma company;
- or it could licence the product to a global company with concomitant worldwide rights (or at least US and Europe) or to a series of regional companies (specialty pharma in the US, pan European and Far East/Japan) possibly retaining limited marketing rights for the UK.

Any combination of these strategies would also work but by developing M6G in this way, CeNeS has the flexibility to be totally opportunistic in the way it licenses the drug while pursuing a value maximisation strategy for the Company and its shareholders.

### **CNS 5161**

CeNeS's second pipeline component has the makings of a significant moneymaker. The treatment of neuropathic pain (see Appendix 3) is one of the holy grails of modern drug development. Pain is now considered to be the 'fifth vital sign' for physicians to focus on and sub optimal efficacies combined with significant side-effects have plagued drugs approved for this indication. It is a testament to the seriousness of the disease that physicians have tried many different drugs off label to find something that works. This category is an umbrella for many different diseases and the number of compounds developed for it that have failed leads us to believe that one needs to be cautious about the ultimate success of this drug.

#### **The drug**

CNS 5161 is a non-competitive NMDA ion channel antagonist similar to a number of drugs that are already on the market for various indications. In other words the mechanism of action and profile of these drugs are well characterised and should not throw up many surprises if efficacy can be confirmed in pivotal trials.

We will not go through the pharmacology, mode of action and clinical profiles of these drugs here but wish to point out where CNS 5161 appears to shine. NMDA receptors are heavily implicated in the induction and maintenance of neuropathic pain and have been a target for much drug development over the past 20 years. The main problem with the current incumbents is that they display sub optimal efficacy for this application. CNS 5161 has displayed efficacy in a Phase IIa proof of concept (PoC) trial without any of the serious side effects seen in this class of drugs. It does not have any psychotomimetic effects (hallucinations and seizures) and is well tolerated at a dose where it has analgesic effects. While it causes some hypertension (increased blood pressure) at the maximum dose in some patients this would only represent a dose limiting effect. Other than that, its side-effect profile appears to be relatively clean.

## CNS 5161 market potential and peak sales estimate

Indication	Administration	Est. number of pts (in million) <sup>2</sup>	Price per Procedure	Total est. market (in millions)	Projected penetration	Peak sales est. (in millions)
Post Operative Pain	Intravenous	23	£25	£575	15%	£86
Cancer	Intravenous	14	£58	£812	10%	£81
Diabetic NP	Transdermal Patch	10	£700	£7,000	10%	£700
Post Surgical Trauma NP <sup>1</sup>	Transdermal Patch	20	£150	£3,000	10%	£300
<b>Total</b>						<b>£1,167</b>

<sup>1</sup> Based on Objective Capital from Company Data and various sources

<sup>2</sup> Based on CDC data on ED admissions grossed up for worldwide

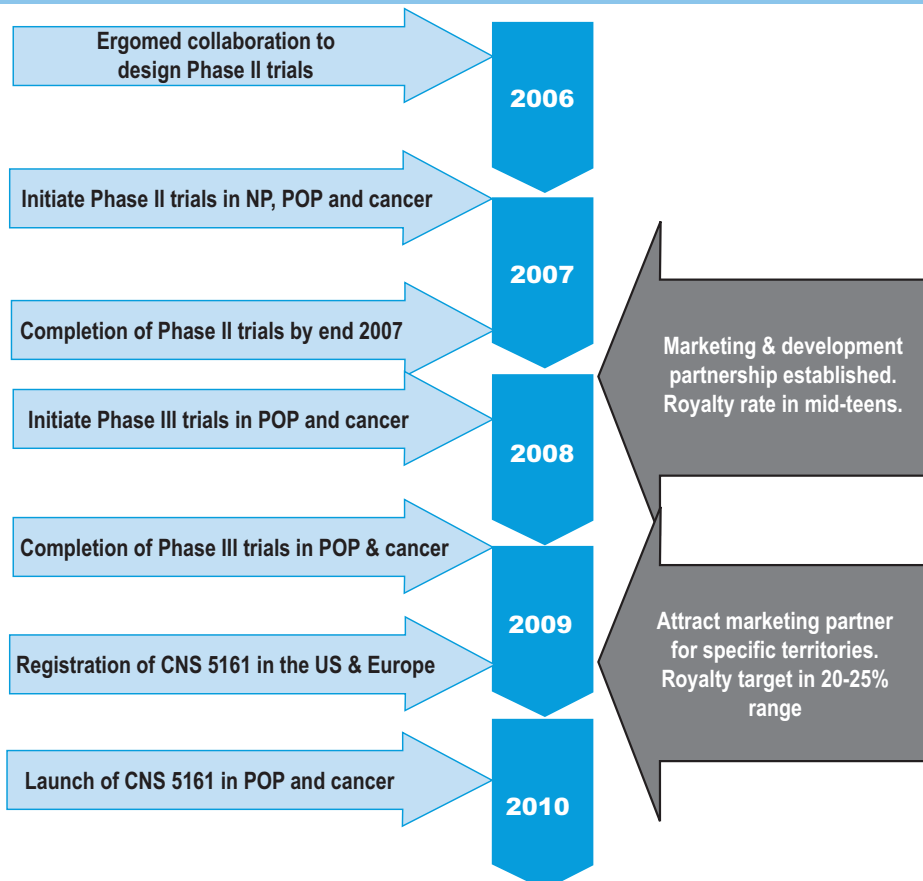
### The market

Competition is fierce in this £1.5bn market and the leaders include Pfizer (with Neurontin and Lyrica) and Lilly (Cymbalta). Ketamine, a non-opioid analgesic, is also a mainstay therapy for certain forms of neuropathic pain<sup>1</sup> but its side-effect profile is relatively nasty and open to abuse. As a result it is used with significant restraint. The presence of generics in the market (e.g., gabapentin and ketamine) provides significant price pressure (although this also indicates that the real market potential for a new entrant is much higher). However, a relatively clean drug that is efficacious could garner a significant market share and in the right formulation, a reasonable price point as well.

CeNeS is testing an intravenous (IV) formulation for its PoC trials but it has also successfully completed feasibility studies for a transdermal patch formulation, which for many forms of neuropathic pain, would be the preferred delivery route.

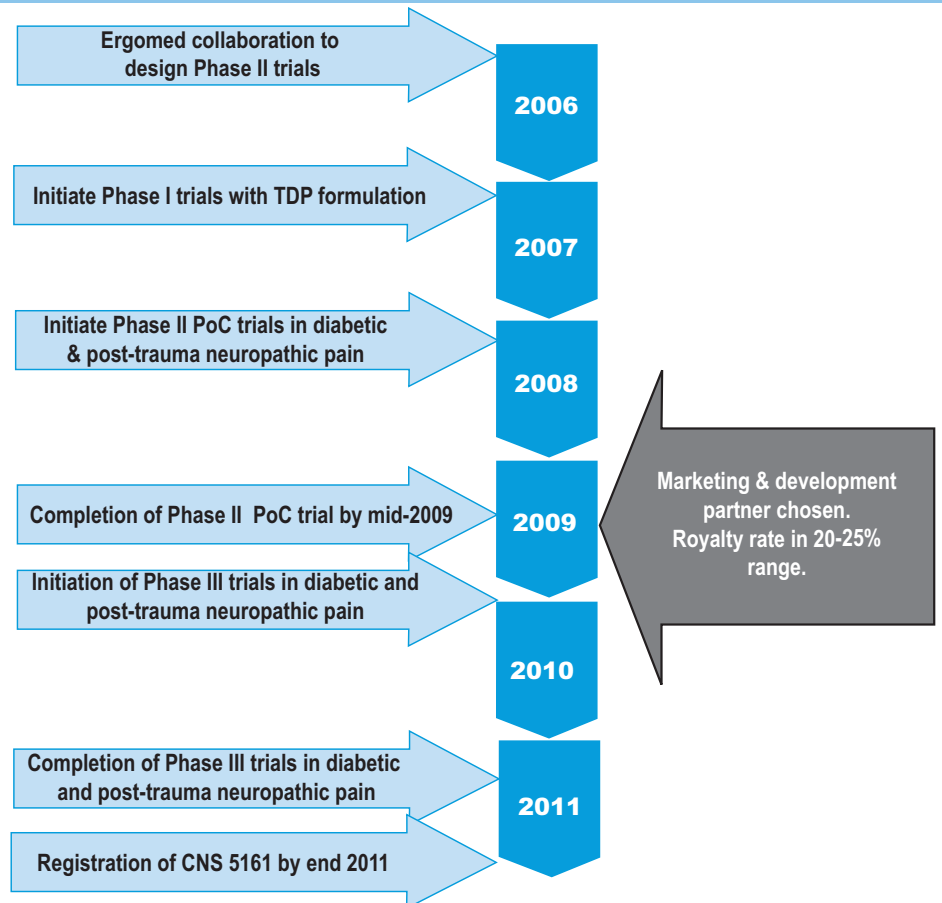
<sup>1</sup> Adjuvants for Neuropathic pain considered essential medicines by WHO: *Cancer relief guidelines* 1986, 1996, 1998.

### Developmental programme for CNS 5161 IV



Source: Objective Capital

## Developmental programme for CNS 5161 TDP



Source: Objective Capital

In the long run, the indications being pursued are diabetic neuropathic pain, post traumatic pain, cancer pain and post-operative pain – each significant markets in their own right.

The table on the previous page summarises the market sizes for each application and, based on our estimates for a reasonable penetration rate, the peak sales attainable for this drug. On that basis, the total sales for this drug would be in the £1.2bn range, which would be attained through a modest 10-15% penetration of the overall market. However, as mentioned above, this indication has been a graveyard of ‘wannabe’s’ and is highly competitive so one must remain cautious as to the prospects.

### News flow and prospects

From the Phase IIa data, we are relatively optimistic about the prospects for CNS 5161. If the patch formulation were to fail and the IV formulation were the only formulation to go to market, the market potential for this drug would be significantly smaller (albeit a respectable £170 million). As a result we are only assigning a 10% chance of success with the patch and with the IV formulation alone we would up that to 30%.

The timelines are not as clear here because many factors will influence the timing of partnerships and what exactly will be partnered away. As seen in the figure on the previous page, the news flow from this drug should be steady over the next 18 months with a Phase IIb PoC trial slated to yield results in late 2007.

## Exp. monetary val. of CNS 5161 (pre-corp tax)

£m	Scenario	
	Core	Downside
<b>EV of Royalties</b>	<b>451.3</b>	<b>231.8</b>
Likelihood of success (PoS)	14%	16%
<b>EMV of Royalties</b>	<b>62.2</b>	<b>36.3</b>
Add: EMV of upfront payments	4.8	4.8
Add: EMV of milestone payments	4.7	4.7
less: EMV of dev costs	1.7	1.7
<b>EMV of CNS 5161</b>	<b>70.0</b>	<b>44.1</b>
per share (£ ps)	0.17	0.11

\* see appendix for detailed sales and royalty forecasts

### Key Market & Licence Assumptions

Indication/Market	Royalty	Impact of Generics	
	Rate	Approx Date	Price Impact
IV Formulation	15%	2016	-45%
Transdermal Patch	15%	2018	-45%

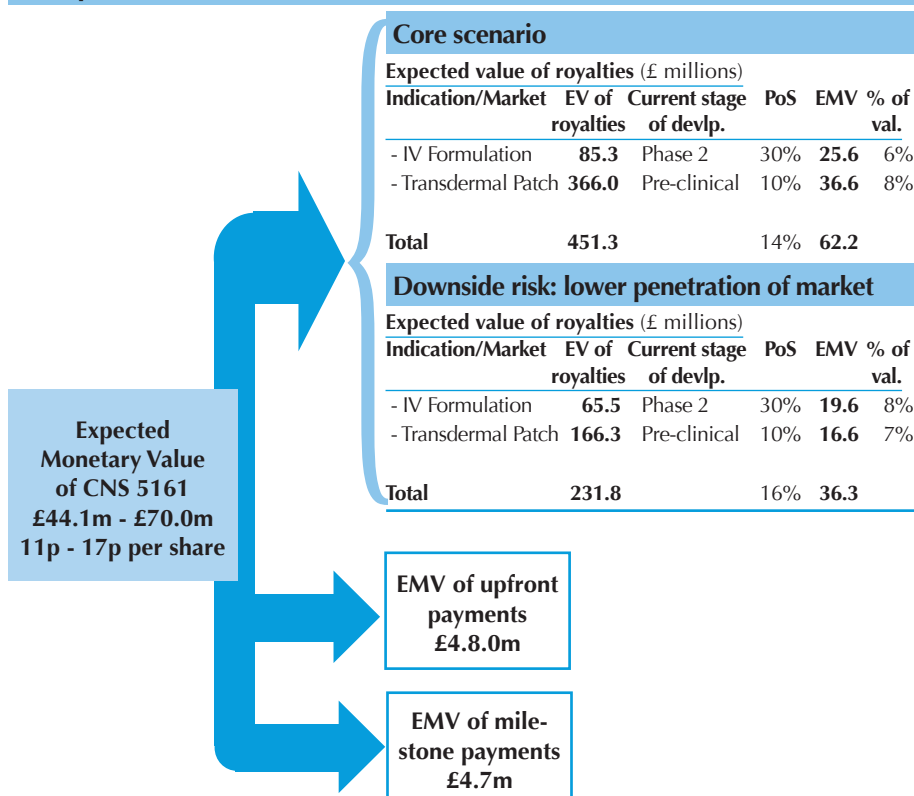
### Sensitivity to change in ...

Impact of generics (+ % price decline)	-20.0%	-10.0%	+0.0%	+10.0%	+20.0%
	Value (£m)	81.6	75.8	70.0	64.3
Change in Value	16%	8%	0%	-8%	-16%

### Increase in royalty (+%)

Value (£m)	-10%	-5%	0%	5%	10%
	Value (£m)	28.6	49.3	70.0	90.8
Change in Value	-59%	-30%	0%	30%	59%

## Components of core valuation



The Company is targeting a 2007 Phase I trial for the patch formulation and a partner-driven Phase II/III trial in 2008 with registration slated for 2011. The IV formulation should yield some interesting data by 4Q07 for cancer and post op indications for which the Company may then seek a partner although it will try to retain certain regional rights. The Transdermal Patch or TDP formulation pathway to market is outlined in the figure on the previous page.

All in all, an exciting pipeline prospect, which would add significant credibility to the Company's strategy longer term.

## CNS 7056X

With the advent of sophisticated minimally invasive endoscopic diagnostic imaging procedures, and ambulatory outpatient surgery, the need for an effective, side-effect free short acting sedative is either required or highly desirable. In ambulatory surgery, the use of such a drug has been shown to improve outcomes and is highly recommended. Again, CeNeS has identified an area with a defined need for a drug with a better efficacy and side-effect profile and has licensed a family of drugs with a very well characterised mechanism of action.

### The drug

CNS 7056X is the lead compound from a family of benzodiazapine derivatives (of which Valium is a well known member) licensed from GSK. CNS 7056X is water-soluble, generates an inactive metabolite and is believed to be truly short acting. This new class of sedatives potentially offers substantial benefits for their targeted

## Summary of market estimates for CNS 7056X applications

Indication	Administration	Drug Price	Procedures (m)	Total est. market (m)	Projected Penetration	Peak Sales est. (m)
Short Procedures (US only) <sup>1</sup>	Intravenous	£8.80	50	£440	20%	£88
Anaesthesia Induction/Maintenance (US Only) <sup>1</sup>	Intravenous	£8.80	27	£237	40%	£95
ICU/CCU (US Only)	Intravenous	£264.00	1.5	£396	40%	£158
<b>Total US Market</b>				<b>£1,074</b>	<b>40%</b>	<b>£341</b>
<b>Worldwide estimate<sup>2</sup></b>				<b>£1,503</b>	<b>40%</b>	<b>£601</b>

<sup>1</sup> assumes a price of US\$15 per procedure

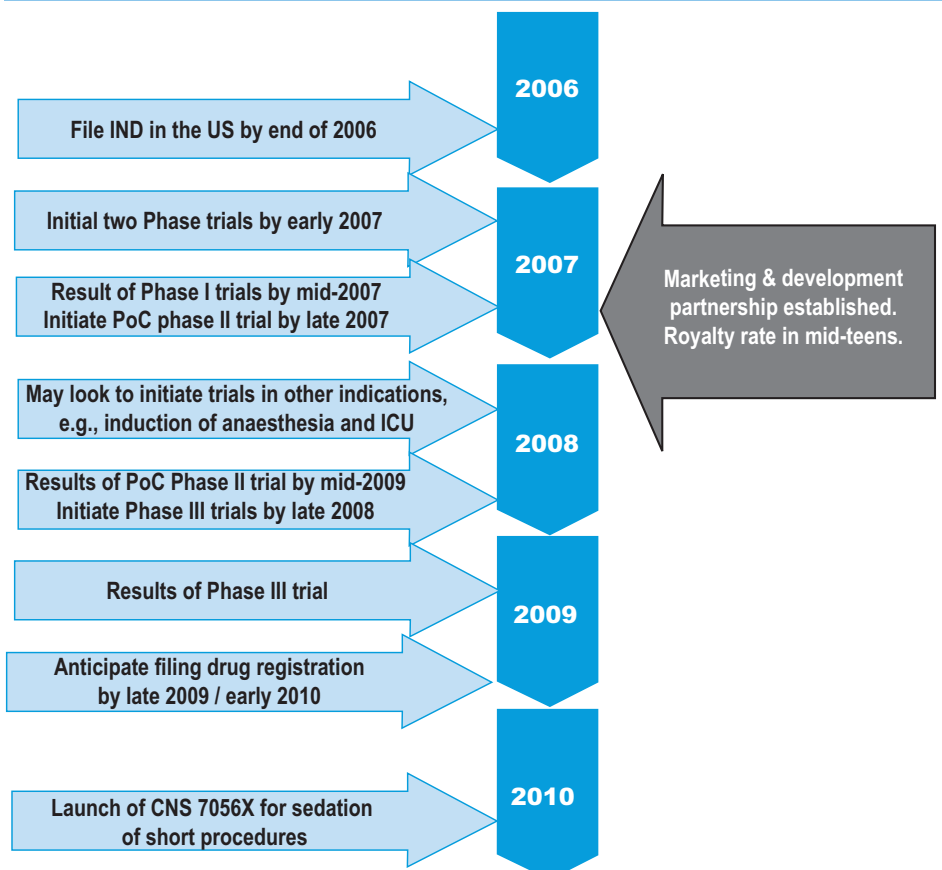
<sup>2</sup> Based on Objective Capital and CDC data, assuming that the US is 60% of the market

use. Additionally, as the drug is primarily a sedative, it may not require an anaesthetist for administration therefore potentially improving the cost/benefit of its use.

The current drugs in use range from benzodiazapines such as midazolam (Roche's Versed) to propofol (Astra Zeneca's Diprivan) and the newer alpha-2 agonist (Abbott Labs' Precedex) all of which are sometimes used in combination with narcotic analgesics such as fentanyl, and remifentanyl (GSK's Ultiva). All have their advantages and disadvantages but the need for a drug with a cleaner side-effect profile is great indeed.

CNS 7056X's initial pre-clinical profile indicates a short onset of action followed by a rapid offset. This would be useful for short procedures such as endoscopy and diagnostic imaging. As there is no clinical data to date, the project remains a high risk one but the Company has reduced the risk by choosing a drug with a well-defined mechanism of action in a clinically well known class of drugs.

## Developmental programme for CNS 7056X



Source: Objective Capital

## The market

The global market for hypnotic/sedatives is estimated to be worth around £1.5 billion in 2005 (Source: Evaluate and Objective Capital estimates). Around £470 million of the total market is thought to have been in anaesthesia (Source: CeNeS). These sales were largely due to two drugs: Roche's Versed (midazolam) and Astra Zeneca's Diprivan (propofol) which together account for around a third of the total market. The US market accounts for 60% of the global total. This latter statistic is consistent with the prevalence of short procedural sedation and ambulatory surgery in the US. The market in Europe is starting to take off and could be a source of future growth as European healthcare systems begin to look to less costly day surgery.

In this market, Abbott's Precedex is a novel alpha-2 agonist, which appears to have a favourable sedation profile. In trials, patients given Precedex (dexmedetomidine) required 80% less Versed (midazolam) for sedation and 50% less morphine for analgesia. Precedex causes little respiratory depression, so patients can be extubated without having to wait for their respiratory function to recover but it does cause hypotension in over 20% of patients, is quite long acting and inadequate alone to provide sedation for procedures.<sup>1</sup>

For ambulatory surgery, short acting sedatives are often used in combination with opioid analgesics such as fentanyl and remifentanyl (Ultiva). We estimate that for short procedures, the market for CNS 7056X is somewhere in the range of £440 million based on an incidence of around 50 million ambulatory and outpatient surgeries per annum in the US and a cost of drug in the neighbourhood of £8.80 per procedure.

CNS 7056X also addresses two other sub markets. CeNeS will pursue an indication for the induction and maintenance of anaesthesia, which is used in the majority of surgical procedures peri-operatively, as well as use in the ICU/CCU environment. These two markets add another £630m in the US. The total US market would then be circa £1.1 billion. As the latter is 60% of the total market, the value of the global market can be estimated at around £1.5 billion.

Assuming that CeNeS is able to demonstrate its targeted profile, it could be expected to penetrate between 20-40% of the estimated market giving it a potential peak sales estimate for this drug of around £600 million worldwide of which £340 million would be in the US.

## News flow and prospects

The Company plans to file a US IND by the end of 2006 followed by two Phase I trials in 2007 that will effectively double as PoC trials. The Company might seek an early partnership on this drug but retain the right to develop certain uses and retain rights to certain geographies. In any case, should CeNeS decide to take this drug through to a Phase II/III clinical trial, we estimate that they could garner a

---

<sup>1</sup> <http://www.australianprescriber.com/upload/pdf/articles/544.pdf>

## Exp. monetary val. of CNS 7056X (pre-corp tax)

£m	Scenario	
	Core	Downside
<b>EV of Royalties</b>	<b>133.7</b>	<b>132.9</b>
Likelihood of success (PoS)	14%	14%
<b>EMV of Royalties</b>	<b>19.0</b>	<b>18.8</b>
Add: EMV of upfront payments	4.8	4.8
Add: EMV of milestone payments	2.5	2.5
less: EMV of dev costs	1.3	1.3
<b>EMV of CNS 7056X</b>	<b>25.0</b>	<b>24.8</b>
per share (£ ps)	0.06	0.06

\* see appendix for detailed sales and royalty forecasts

### Key Market & Licence Assumptions

Indication/Market	Royalty	Impact of Generics	
	Rate	Approx Date	Price Impact
Short Procedures	15%	2020	-45%
Induction/Maint.	10%	2020	-45%
ICU/CCU	10%	2020	-45%

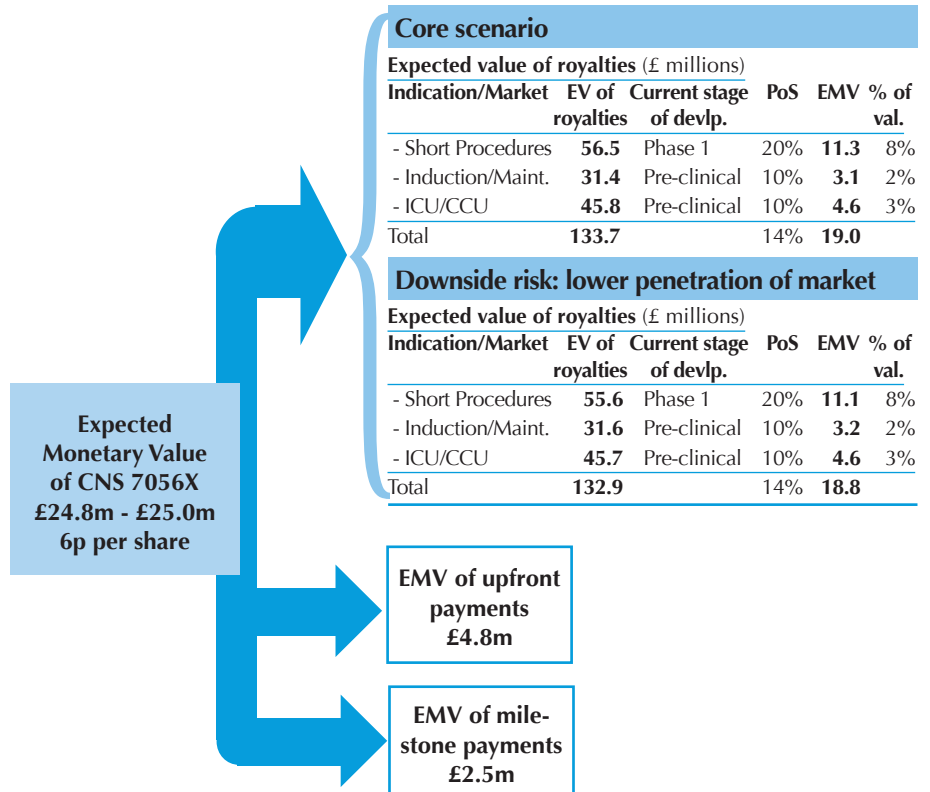
### Sensitivity to change in ...

Impact of generics (+ % price decline)	+ % price decline				
	-20.0%	-10.0%	+0.0%	+10.0%	+20.0%
Value (£m)	27.0	26.0	25.0	24.0	22.9
Change in Value	8%	4%	0%	-4%	-8%

### Increase in royalty (+%)

Value (£m)	+ % price decline				
	-10%	-5%	0%	5%	10%
Value (£m)	9.7	17.4	25.0	32.6	40.2
Change in Value	-61%	-31%	0%	31%	61%

## Components of core valuation



royalty rate in the 15-20% range. However, we believe that they are more likely to attempt to achieve a partnership earlier, which would yield a royalty rate in the low to mid teens.

With a drug in the pre-clinical Phase, it is hard to say what the prospects really are but the news flow should be good for late 2007/early 2008, which would follow on nicely from what will be going on with M6G and CNS 5161. We have assigned a 20% chance of success.

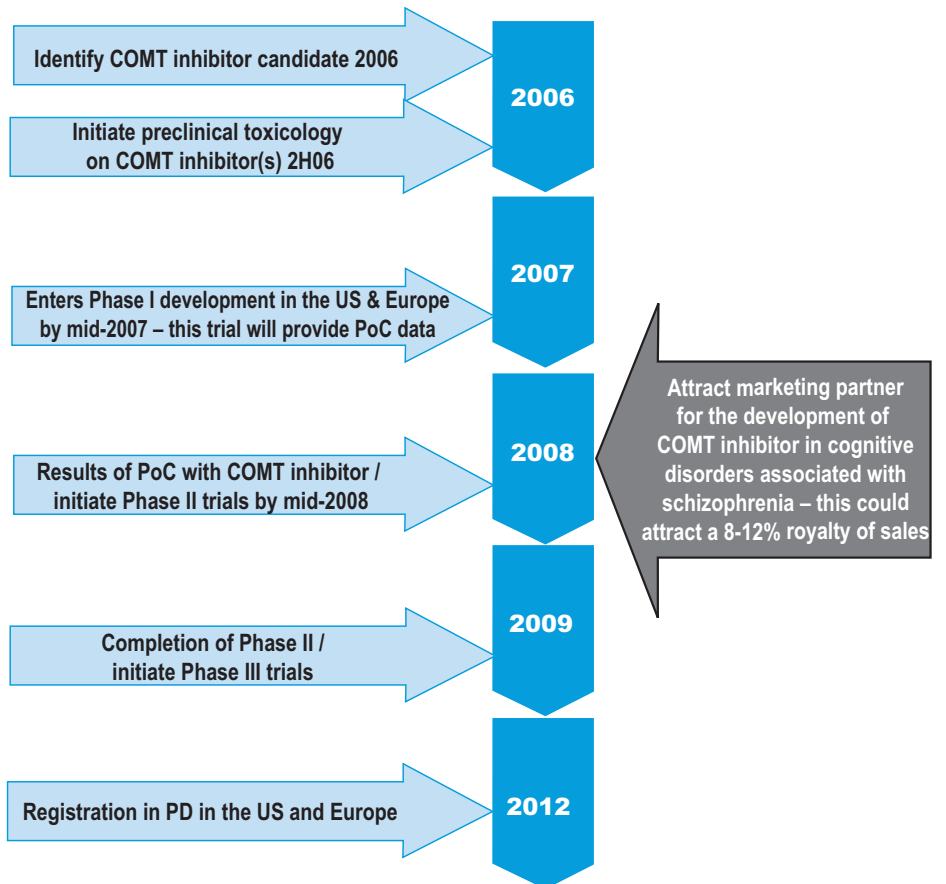
### COMT Inhibitors

This programme has been entirely generated through internal development. With CNS 7056X, the Company has already demonstrated its ability to generate a lead compound able to make it through pre clinical hurdles. With this programme, the company has engaged in developing a family of new chemical entities within a known therapeutic drug class. This programme is clearly the riskiest of CeNeS's portfolio but it also holds the most promise, and in true biotech analytical style we will engage in a crystal ball gazing exercise to assign 'realistic' market prospects to the compounds that will come out of this programme!

To be sure, the programme is risky but there are several COMT inhibitors on the market and the drug mechanisms and clinical effects of drugs in this class are well characterised. Any potential side effects are known and CeNeS has attempted to 'design' these out during the rational drug design process. We assign a 10% probability to this programme but are very excited by it none the less!



## Developmental programme for COMT inhibitors



Source: Objective Capital

It aims to design a drug that:

- displays good inhibition of COMT itself;
- lacks any interaction with liver enzymes and the liver;
- displays good bio-availability to the brain where the disease target lies.

The Company's strategy has been to develop a series of compounds that are a chemically distinct family with features designed into them to deliver the required characteristics. Lead candidates have been identified that display not only the relevant characteristics for activity in PD, but also characteristics that may be applicable to cognitive impairment associated with schizophrenia (CIAS) as well as an indication for attention deficit disorder (ADHD).

### Market

The Global PD market is estimated to be worth around £1.4 billion as of 2005 and is growing rapidly (20%+). Novartis with its PD franchise (Comtan, Comtess and Stalevo) is the market leader representing over 10% of the total market. The other COMT inhibitor Tasmar (tolcapone) marketed by Valeant has had limited success due to its liver toxicity and restrictive label. An effective and less toxic adjunctive therapy (with Sinemet) would have good utility in both early and late-stage PD. Therefore, peak sales of £500 million are certainly achievable here.

We estimate the market for adjunctive CIAS therapy with antipsychotics and cognition associated with ADHD, to be between £1.5bn and £1.9bn. With a modest penetration of 15%, CeNeS could achieve peak sales of £225m and £285m respectively for CIAS and ADHD. Hence the total market potential for a drug in this class, if successful, is beyond the wildest dream of the Company and its investors.

## Exp. monetary val. of COMT (pre-corp tax)

£m	Scenario	
	Core	Downside
<b>EV of Royalties</b>	<b>235.5</b>	<b>124.3</b>
Likelihood of success (PoS)	10%	10%
<b>EMV of Royalties</b>	<b>23.6</b>	<b>12.4</b>
Add: EMV of upfront payments	15.4	15.4
Add: EMV of milestone payments	3.9	3.9
less: EMV of dev costs	0.7	0.7
<b>EMV of COMT</b>	<b>42.2</b>	<b>31.1</b>
per share (£ ps)	0.10	0.08

\* see appendix for detailed sales and royalty forecasts

### Key Market & Licence Assumptions

Indication/Market	Royalty	Impact of Generics	
	Rate	Approx Date	Price Impact
Parkinson's Disease	8%	2023	-75%
Cognitive Impairment	8%	2023	-75%
ADHD	8%	2023	-75%

### Sensitivity to change in ...

#### Impact of generics (+ % price decline)

	-20.0%	-10.0%	+0.0%	+10.0%	+20.0%
Value (£m)	44.5	43.4	42.2	41.0	39.8
Change in Value	6%	3%	0%	-3%	-6%

#### Increase in royalty (+%)

	-10%	-5%	0%	5%	10%
Value (£m)	18.6	27.5	42.2	56.9	71.6
Change in Value	-56%	-35%	0%	35%	70%

## Components of core valuation

### Core scenario

#### Expected value of royalties (£ millions)

Indication/Market	EV of royalties	Current stage of devlp.	PoS	EMV	% of val.
- Parkinson's Disease	127.3	Pre-clinical	10%	12.7	5%
- Cognit. Impairment	51.2	Pre-clinical	10%	5.1	2%
- ADHD	57.0	Pre-clinical	10%	5.7	2%
<b>Total</b>	<b>235.5</b>		<b>10%</b>	<b>23.6</b>	

### Downside risk: lower penetration of market

#### Expected value of royalties (£ millions)

Indication/Market	EV of royalties	Current stage of devlp.	PoS	EMV	% of val.
- Parkinson's Disease	62.5	Pre-clinical	10%	6.3	5%
- Cognit. Impairment	34.3	Pre-clinical	10%	3.4	3%
- ADHD	27.5	Pre-clinical	10%	2.7	2%
<b>Total</b>	<b>124.3</b>		<b>10%</b>	<b>12.4</b>	

**Expected Monetary Value of COMT**  
£31.1m – £42.2m  
8p – 10p per share

**EMV of upfront payments**  
£15.4m

**EMV of milestone payments**  
£3.9m

## News flow and prospects

Nowhere in the portfolio is the risk so high, but CeNeS's management team has worked hard to reduce it and the proof will be revealed in the pre-clinical and Phase I studies to be conducted in late 2006 and 2007. Nevertheless, all of this is in the realm of the possible and although our probability of success here is in the 10% range, we are not ready to discount this programme to zero from a valuation standpoint. We prefer to give investors the choice of how much valuation risk they are willing to endure.

The lead compound for PD should be selected by 2H06 and pre-clinicals initiated by 4Q of 2006. If conclusive, these should lead to a PoC Phase I trial that would put CeNeS in pole position to negotiate a major partnership. It is likely that a number of PD market participants could have an interest in such a drug but one should not forget speciality pharma and regional players as alternative combination partners.

It is likely that royalty rates will be in the 10% range for this drug (see table on p. 5). The schizophrenia applications are likely to be partnered early due to the complexity of clinical trials in this area. As a result, we would anticipate a somewhat lower royalty rate for this – probably in the high single digits. The applications in ADHD are in combination with current treatment regimens and are also likely candidates for early partnering.

# Financials

<b>Balance Sheet</b>						
YE Dec 31, £m	<b>2004</b>	<b>2005</b>	<b>2006F</b>	<b>2007F</b>	<b>2008F</b>	<b>2009F</b>
<b>Fixed Assets</b>						
Intangible	7.50	6.51	5.56	4.61	3.65	2.70
Tangible	0.02	0.04	0.06	0.08	0.10	0.12
<b>Total Fixed Assets</b>	<b>7.52</b>	<b>6.55</b>	<b>5.62</b>	<b>4.68</b>	<b>3.75</b>	<b>2.82</b>
<b>Current Assets</b>						
Debtors	1.44	1.54	1.30	1.30	1.30	1.30
Short term investments	10.00	0.00	0.00	0.00	0.00	0.00
Cash at bank and in hand	4.32	8.46	5.36	8.89	17.57	47.73
<b>Total Current Assets</b>	<b>15.76</b>	<b>10.00</b>	<b>6.66</b>	<b>10.19</b>	<b>18.87</b>	<b>49.03</b>
<b>Current Liabilities</b>						
Short term Notes	2.01	2.00	2.00	2.00	2.00	2.00
Accounts Payable						
<b>Total Current Liabilities</b>	<b>2.01</b>	<b>2.00</b>	<b>2.00</b>	<b>2.00</b>	<b>2.00</b>	<b>2.00</b>
<b>Net Current Assets</b>	<b>13.75</b>	<b>8.00</b>	<b>4.66</b>	<b>8.19</b>	<b>16.87</b>	<b>47.03</b>
<b>Total Asst – Curr. liab.</b>	<b>21.27</b>	<b>14.55</b>	<b>10.28</b>	<b>12.88</b>	<b>20.62</b>	<b>49.85</b>
Other LT liabilities	0.56	0.48	0.50	0.50	0.50	0.50
<b>Net Assets</b>	<b>20.71</b>	<b>14.07</b>	<b>9.78</b>	<b>12.38</b>	<b>20.12</b>	<b>49.35</b>
<b>Shareholders Equity</b>						
Common Stock	8.03	8.00	8.00	8.00	8.00	8.00
Share Prem. Account	113.08	113.08	113.08	113.08	113.08	113.08
Retained Earnings	-126.50	-133.10	-137.39	-134.79	-127.05	-97.82
Other Reserves	26.09	26.09	26.09	26.09	26.09	26.09
<b>Total</b>	<b>20.71</b>	<b>14.07</b>	<b>9.78</b>	<b>12.38</b>	<b>20.12</b>	<b>49.35</b>

<b>Summary Profit and Loss</b>						
YE Dec. 31, £m	<b>2004</b>	<b>2005</b>	<b>2006F</b>	<b>2007F</b>	<b>2008F</b>	<b>2009F</b>
<b>Total Revenues</b>	<b>0.05</b>	<b>0.05</b>	<b>3.00</b>	<b>10.05</b>	<b>15.05</b>	<b>35.05</b>
Royalties	0.00	0.00	0.00	0.00	5.00	25.00
Upfront/Milestone Payments	0.00	0.00	0.00	10.00	10.00	10.00
Other Revenues	0.05	0.05	0.05	0.05	0.05	0.05
Cost of Sales	0.00	0.00	0.00	0.00	0.00	0.00
<b>Gross Profits</b>	<b>£0.05</b>	<b>£0.05</b>	<b>£3.00</b>	<b>£10.05</b>	<b>£15.05</b>	<b>£35.05</b>
G&A	2.43	3.10	3.30	3.50	3.70	3.90
R&D	3.48	4.89	5.00	5.20	5.41	5.62
Other Op Expenses/Income	0.15	0.17	0.17	0.19	0.19	0.19
<b>EBIT</b>	<b>-£5.71</b>	<b>-£7.77</b>	<b>-£5.13</b>	<b>£1.54</b>	<b>£6.13</b>	<b>£25.72</b>
Interest, Net	0.33	0.54	0.34	0.56	1.11	3.02
Other, Net						
<b>Pretax Profit (Loss)</b>	<b>-£5.39</b>	<b>-£7.24</b>	<b>-£4.79</b>	<b>£2.10</b>	<b>£7.24</b>	<b>£28.73</b>
Taxes(credit)	0.47	0.63	0.50	0.50	0.50	0.50
<b>Net Income (Loss)</b>	<b>-£4.92</b>	<b>-£6.61</b>	<b>-£4.29</b>	<b>£2.60</b>	<b>£7.74</b>	<b>£29.23</b>
- Dividends						
Net retained income	-£4.92	-£6.61	-£4.29	£2.60	£7.74	£29.23
Average Shares outst.	282.40	409.76	409.76	409.76	409.76	409.76
<i>Earnings (Loss) per Share</i>	<i>-£0.017</i>	<i>-£0.016</i>	<i>-£0.010</i>	<i>£0.006</i>	<i>£0.019</i>	<i>£0.071</i>
<b>Cashflow analysis and cash position</b>						
£m	<b>2004</b>	<b>2005</b>	<b>2006E</b>	<b>2007E</b>	<b>2008E</b>	<b>2009E</b>
<b>From Operating Activity</b>						
Net Income (loss) from Cont. Operations	-5.71	-7.77	-5.13	1.54	6.13	25.72
Depreciation	0.00	0.01	0.01	0.01	0.01	0.01
Amortization of Intangible Assets	0.95	0.95	0.95	0.95	0.95	0.95
Decrease/Increase in Debtors (Acco. Rec.)	0.22	-0.05	0.24	0.00	0.00	0.00
R&D Tax Credit	0.10	0.52	0.50	0.50	0.50	0.50
<b>Cash From Operations</b>	<b>-4.44</b>	<b>-6.34</b>	<b>-3.43</b>	<b>3.00</b>	<b>7.59</b>	<b>27.18</b>
<b>From Investing Activities</b>						
Capex	-0.02	-0.03	-0.03	-0.03	-0.03	-0.03
Proceeds frm disposal tangible fixed Assts	-0.001					
Proceeds frm disposal of pharma products	0.22					
Decrease/(Increase) in ST deposits at Banks	-2.30	10.00	0.00	0.00	0.00	0.00
Cash Outflow due to changes in debt and finance leasing	-0.06	-0.05	0.02	0.00	0.00	0.00
Net Interest Received	0.32	0.56	0.34	0.56	1.11	3.02
<b>Net Inflow (outflow) from Investments</b>	<b>-1.85</b>	<b>10.48</b>	<b>0.33</b>	<b>0.53</b>	<b>1.08</b>	<b>2.98</b>
<b>From Financing Activities</b>						
Issue of Ordinary Shares	10.67					
Lapse of Share options	-0.27					
Loss on Currency translation	0.00					
Change in Share Capital to be issued		-0.04				
<b>Net Cash Provided for (used in) Financing Activities</b>	<b>10.40</b>	<b>-0.04</b>	<b>0.00</b>	<b>0.00</b>	<b>0.00</b>	<b>0.00</b>
<b>Net Change in Cash</b>	<b>4.12</b>	<b>4.10</b>	<b>-3.10</b>	<b>3.53</b>	<b>8.67</b>	<b>30.16</b>
<b>Cash Position and Cash per share</b>						
Net Funds						
Beginning of Year	7.77	14.25	8.40	5.28	8.82	17.49
End of Year	14.25	8.40	5.28	8.82	17.49	47.65
<b>Cash per share</b>	<b>£0.05</b>	<b>£0.02</b>	<b>£0.01</b>	<b>£0.02</b>	<b>£0.04</b>	<b>£0.12</b>
Average Shares Outstanding	282.40	409.76	409.76	409.76	409.76	409.76

## Appendix 1: News flow and dev. timeline

Year	Newsflow	Significance to stock
2H06	Identify COMT inhibitor leads to enter pre-clinical studies	+
	Completion 2nd EU Phase III trial with M6G	++
	Announcement of EU marketing partner for M6G	+++
	File IND for CNS 7056X in US	+
1H07	File IND for M6G in the US	+
	Announcement of US development/marketing partner for M6G	+++
	Initiate Phase III trial with M6G in the US in post-operative pain (POP)	+++
	Initiate Phase IIb trials with CNS 5161 (IV) in POP & cancer pain	+++
	Initiate Phase I trial with CNS 5161 TDP	++
	Initiate two Phase I trials with CNS 7056X	++
2H07	Registration of M6G in Europe in POP	+++
	Results of Phase IIb CNS 5161 (IV) in POP & cancer	+++
	Results of Phase I trial with CNS 7056X	++
	Phase I PoC of CNS 7056X in short procedures in the US	++
	Initiate PoC Phase I trial with COMT inhibitor for PD	+
	Attract a development partner for CNS 5161 (IV)	+++
	Attract a development/marketing partner for CNS 7056X	+++
1H08	Results of Phase II trials with M6G in the US in POP	+++
	Initiate Phase III trial of CNS 5161 (IV) in POP and Cancer	++
	Initiate Phase II PoC trial with CNS 5161 TDP in NP and PTNP	++
	Initiate Phase II trials of CNS 7056X in induction/maintenance of anaesthesia and or sedation in ICU	++
	Attract developmental partner for COMT inhibitor in CIAS	+++
	Attract developmental partner for COMT inhibitor in PD	+++
2H08	Launch M6G in Europe in POP	+++
	Results of Phase II PoC trial with CNS 7056X	+++
	Initiate Phase III trial of CNS 7056X in short procedures in the US	++
	Results of PoC trial with COMT inhibitor	+++
	Initiate Phase II trials with COMT inhibitor in PD	++
Attract development/marketing partner for COMT inhibitor in ICAS	+++	
1H09	Registration of M6G in the US in POP	+++
	Results of Phase III CNS 5161 (IV) in POP and cancer	+++
	Results of PoC with CNS 5161 TDP	+++
	Results of CNS 7056X Phase III trial sedation in short procedures	+++
	Attract a marketing/developmental partner for CNS 5161 TDP	+++
2H09	Registration of CNS 5161 (IV) in US/EU in POP & cancer	+++
	Initiate Phase III trial with CNS 5161 TDP in NP and PTNP	+++
	Registration of CNS 7056X for sedation in short procedures in the US	+++
	Completion of Phase II trial with COMT inhibitor in PD	+++
	Initiate Phase III trial with COMT Inhibitor in PD	++
	Attract marketing partner for CNS 5161 (IV)	+++
1H10	Launch M6G in the US in POP	+++
	Registration of COMT inhibitor in PD (EU and US)	+++
2H10	Launch of CNS 5161 (IV) in US/EU in POP and cancer pain	+++
	Launch of CNS 7056X for sedation in short procedures	+++
1H11	Results of Phase III CNS 5161 (TDP) in NP and PTNP	+++
	Launch COMT inhibitor as adjunct for PD	+++
2H11	Registration of CNS 5161 TDP in NP	++

## Overview

Morphine-6-glucuronide (M6G) is an active potent metabolite of morphine. M6G is an opioid agonist, which acts on Mu receptors in the brain to elicit its analgesic effect. It is administered initially as an intravenous bolus followed by patient controlled analgesia (PCA) for at least 24 hours post-surgery. It is in Phase III clinical development for the acute treatment of post-operative pain (POP) but may have additional use in chronic pain.

Whilst morphine formulations are currently the gold standard treatment for the relief of moderate to severe post-operative pain, acute administration is associated with nausea and vomiting and may result in life-threatening respiratory depression. In addition, between 40–100% of patients treated with morphine continue to experience moderate to severe pain following surgery, highlighting there is a clear need for new and effective treatments for post-operative pain. M6G hydrophilic properties indicate it might have a low abuse potential compared to the parent compound and therefore lend itself to prescription in chronic pain.

In summary, M6G appears to be as efficacious as morphine in post-operative pain it offers several advantages over morphine due to its long lasting action, improved safety profile (reduced nausea, vomiting, sedation and respiratory depression) and low abuse potential.

## Market Analysis

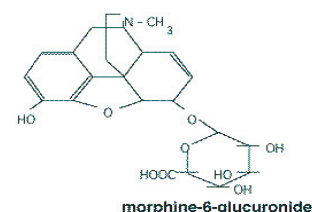
The narcotic analgesic market is worth between £2.5bn-£3bn (source: Evaluate) whilst the post-operative pain market is estimated to be worth over £500 million (US\$1 billion, source: Datamonitor) with sales driven by the increasing demand for surgical procedures, which rose to around 130 million in 2004 (in the seven major markets). Opioids remain the cornerstone of treatment of POP with morphine sulphate the current gold standard and a value of £260 million (US\$450million) in 2004 in the US morphine market alone (Source: Phosphagenics).<sup>1</sup> The table over the page details our analysis of the Narcotic Analgesic market:

### SWOT analysis of market

<p><b>Strengths</b></p> <ul style="list-style-type: none"> <li>• Proven clinical concept               <ul style="list-style-type: none"> <li>• Improved safety</li> </ul> </li> <li>• Limited respiratory depression</li> </ul> <p>Strong IP with respect to manufacturing process</p>	<p><b>Opportunities</b></p> <ul style="list-style-type: none"> <li>• Current drugs not optimal</li> <li>• Market expanding through increase in surgical procedures</li> <li>• Potential for premium pricing based on cost-benefit analysis of using anti-emetics agents etc.</li> </ul>
<p><b>Weaknesses</b></p> <ul style="list-style-type: none"> <li>• Physician education to switch from morphine</li> <li>• Morphine intolerant patients</li> </ul>	<p><b>Threats</b></p> <ul style="list-style-type: none"> <li>• Competitive market with major player's e.g., JNJ, GSK, Novartis               <ul style="list-style-type: none"> <li>• Generic morphine IV available</li> </ul> </li> <li>• New POP drugs and formulations in development</li> </ul>

## Appendix 2: M6G drug profile

### M6G molecular structure



## M6G market analysis

USA		Europe	
Total inpatient procedures	27	Total inpatient procedures	26.3
Relevant procedures	10	Relevant procedures	12
IV Opiate treated	6.90	IV Opiate treated	7.50
Epidural Opiate	2.07	Epidural Opiate	2.25
IV Morphine	4.28	IV Morphine	4.66
PCA Morphine	2.76	PCA Morphine	2.4
<b>Market Size (£m)</b>		<b>Market Size (£m)</b>	
IV opiate	220.80	IV opiate	210
Non-Morphine segment	83.90	Non-Morphine segment	79.8
% addressable by M6G (30%)	67.12	% addressable by M6G	63.84
IV Morphine	136.90	IV Morphine	130.2
with formulary penetration level	109.52	with formulary penetration level	104.16
Epidural Opiate (50% penetration)	33.12	Epidural Opiate	31.5
with formulary penetration	26.50	with formulary penetration	25.2
<b>Total Addressable US market</b>	<b>203.14</b>	Total Addressable European market	193.2
<b>Est M6G price per procedure</b>	<b>32</b>	<b>Est M6G price per procedure</b>	<b>28</b>
<b>Total US + Europe</b>	<b>396.34</b>		
<b>Total Worldwide</b>	<b>495.42</b>		

Source: CeNeS and Market Data/Objective Capital Estimates

Several other parenteral analgesics are routinely used for short procedures including: Alfentanil (Janssen-Ortho), Fentanyl (Johnson & Johnson) and Remifentanyl (GlaxoSmithKline), as well as Ketorolac (Allergan) Oxycodone (Purdue Pharmaceuticals) and Tramadol (Johnson & Johnson). These drugs offer some advantages over morphine with regard to nausea and vomiting but may result in cardiovascular issues and respiratory depression.<sup>2</sup> In addition there are several new analgesics and formulations in development including: bicifadine (DOV pharmaceuticals), ALGRX-4965 (Allergan), APF-112 (AP Pharma), ORG-41793 (Akzo Nobel) and REN-213/nalbuphine + naloxone (Renovis).

In clinical trials to date M6G causes fewer side effects than morphine but has equal analgesic efficacy – a potentially attractive alternative for patients and healthcare providers. Based on M6G's current efficacy and safety data M6G has the ability to gain a substantial share of the morphine IV market (with potential upside if it penetrates competitor market share). Cost-benefit analysis suggests that CeNeS may be able to charge a price premium resulting in a cost of between £28 to £34 per procedure enabling it to generate peak sales of over £215 million. Potential upside to sales forecasts, assuming use as an epidural in chronic pain, could generate sales of £67 million without taking into consideration its potential development in other formulations.

### Clinical Status and Development Timeline

The first European Phase III in 167 patients undergoing major joint replacement was completed in September 2004. This study demonstrated that: M6G has analgesic potency similar to that of morphine; previous Phase II data showed a lower incidence of respiratory depression rates, i.e., morphine group (27%) compared

<sup>1</sup> <http://www.phosphagenics.com/documents/Phosphagenics%20October%202004%20newsletter.pdf> (page 8)

<sup>2</sup> <http://www.anaesthetist.com/anaes/drugs/opioids.htm>

with the M6G group (6%); less sedation in the M6G group in the immediate post-operative period and at 24 hours; and a lower incidence of nausea (41% vs. 21%) post-operatively.

A second pivotal European Phase III trial in patients suffering from moderate to severe post-operative pain (hysterectomy, major gastrointestinal, bowel and urological surgery) commenced in September 2005. This study compares M6G and morphine over a 24-hour period and aims to demonstrate that patients on M6G achieve equivalent analgesia to those on morphine, but improved safety (less nausea and vomiting). Data is expected in 2H06 and following completion of this programme, CeNeS plans an initial European marketing authorisation application for the use of M6G in the treatment of moderate to severe acute post-operative pain. CeNeS also plans to carry out supportive clinical studies, such as Phase I drug distribution studies, in parallel with this pivotal Phase III study.

### Partnering

CeNeS anticipates signing a marketing/development partner in Europe following the completion of the second European Phase III trial. The European partner will be responsible for completing the drug file and marketing procedures by late 2007/early 2008. Positive data from the European trial will ensure CeNeS achieves a significant royalty of up to 25% from sales outside its territories.

CeNeS also intends to file an Investigational New Drug (IND) application in the US in 2H06 to enable M6G to enter into pivotal Phase III studies in the US in early 2007 and anticipates attracting a US developmental partner following positive Phase III European trials. Big Pharma or a specialist pain pharmaceutical company are the most likely candidates for acquiring the rights to develop/market M6G and include: Allergan, Akzo Nobel, Bayer, GlaxoSmithKline, Novartis and Johnson & Johnson.


### Sales and royalty forecasts for M6G (£m)

#### Forecast sales

Market	Dec-07	Dec-08	Dec-09	Dec-10	Dec-11	Dec-12	Dec-13	Dec-14	Dec-15	Dec-16	Dec-17	Dec-18	Dec-19	Total
M6G Sales EU			13.0	39.0	60.8	73.6	79.5	83.8	83.8	83.8	83.8	83.8	29.3	714.5
M6G Sales US			10.0	15.0	48.8	71.2	82.6	86.7	88.1	89.5	49.2	49.2	49.2	639.5
M6G ROW					10.6	31.8	38.8	41.5	42.3	43.0	43.0	43.0	12.9	306.9
<b>Total</b>	<b>0.0</b>	<b>0.0</b>	<b>23.0</b>	<b>54.0</b>	<b>120.2</b>	<b>176.6</b>	<b>200.9</b>	<b>212.0</b>	<b>214.3</b>	<b>216.3</b>	<b>176.1</b>	<b>176.1</b>	<b>91.5</b>	<b>1660.9</b>
<i>M6G Sales EU YoY Growth</i>				200%	56%	21%	8%	5%	0%	0%	0%	0%	-65%	
<i>M6G Sales US YoY Growth</i>				50%	225%	46%	16%	5%	2%	2%	-45%	0%	0%	
<i>M6G ROW YoY Growth</i>					200%	22%	7%	2%	2%	2%	0%	0%	-70%	

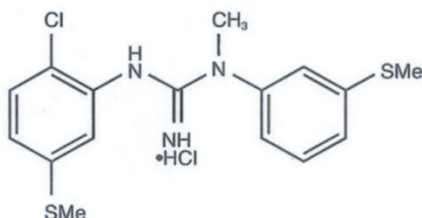
#### M6G Licence Revenue to CeNeS

Revenue	Dec-07	Dec-08	Dec-09	Dec-10	Dec-11	Dec-12	Dec-13	Dec-14	Dec-15	Dec-16	Dec-17	Dec-18	Dec-19	Total
<b>Upfront and Milestone Payments</b>														
- Upfront Payment	10.0	10.0												20.0
- Milestones		5.0	5.0	5.0										15.0
Total upfront & milestones payments	10.0	15.0	5.0	5.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	35.0
<b>Royalties</b>														
- M6G Sales EU			2.6	7.8	12.2	14.7	15.9	16.8	16.8	16.8	16.8	16.8	5.9	178.6
- M6G Sales US			2.0	3.0	9.8	14.2	16.5	17.3	17.6	17.9	9.8	9.8	9.8	127.9
- M6G ROW			0.0	0.0	1.6	4.8	5.8	6.2	6.4	6.4	6.4	6.4	1.9	46.0
Total Royalties			4.6	10.8	23.5	33.7	38.2	40.3	40.7	41.1	33.1	33.1	17.6	352.6
<b>Total licence revenue</b>	<b>10.0</b>	<b>15.0</b>	<b>9.6</b>	<b>15.8</b>	<b>23.5</b>	<b>33.7</b>	<b>38.2</b>	<b>40.3</b>	<b>40.7</b>	<b>41.1</b>	<b>33.1</b>	<b>33.1</b>	<b>17.6</b>	<b>35.0</b>
Average royalty rate	-	-	20.0%	20.0%	19.6%	19.1%	19.0%	19.0%	19.0%	19.0%	18.8%	18.8%	19.3%	21.2%

Key: Peak market penetration =  Impact of generics = 

## Appendix 3: CNS 5161 drug profile

### CNS 5161 molecular structure



Source: CeNeS

### Overview

CNS 5161 is a potent and non-competitive N-methyl-D-aspartate (NMDA) ion channel antagonist. In animal models NMDA antagonists have been shown to be antinociceptive as NMDA receptors are thought to be involved in the development and maintenance of neuropathic pain. NMDA-antagonists also have a significant impact on the development of tolerance to opioid analgesics. Consequently, NMDA-receptor antagonists may represent a new class of analgesics and may have potential as co-analgesics when used in combination with opioids.

CNS 5161 is being evaluated in two formulations: as an intravenous infusion for acute treatment of opioid-refractory cancer pain and post-operative pain and as a transdermal patch (TDP) formulation for chronic treatment of diabetic and post-trauma neuropathic pain.

Several NMDA-receptor antagonists are commercially available such as ketamine, dextromethorphan, memantine (Namenda), and amantadine. Ketamine is increasingly being used in post-operative pain (particularly patients refractory to morphine) and cancer, e.g., chemotherapy, however its use is limited by its risk of inducing psychotomimetic effects such as hallucinations. This does not appear to be the case for CNS 5161.

### Market analysis

The post-operative pain market is estimated to be worth over £500 million (US\$1 billion; source: Datamonitor). Neuropathic pain (NP) affects over 26 million people and its treatment generated some £1.4 billion (US\$2.5 billion) in 2003 and is estimated to reach around £2.9 billion (US\$5 billion) by 2010 (Source: Espicom). The most commonly prescribed drugs are the antiepileptic agents, Neurontin and Lyrica (Pfizer), which generated sales of around £540 million (US\$930 million)

### SWOT analysis of market

<p><b>Strengths</b></p> <ul style="list-style-type: none"> <li>• Proven clinical concept</li> <li>• IV and patch formulation</li> <li>• No psychotomimetic side-effects <ul style="list-style-type: none"> <li>• Strong IP position</li> </ul> </li> </ul>	<p><b>Opportunities</b></p> <ul style="list-style-type: none"> <li>• Current drugs not optimal</li> <li>• Large &amp; expanding market following DTC marketing of Pfizer – increased patient awareness</li> <li>• Chronic use in diabetic NP and post-trauma NP for TDP formulation</li> <li>• Acute use in chronic pain e.g. cancer and post-operative pain as IV formulation</li> </ul>
<p><b>Weaknesses</b></p> <ul style="list-style-type: none"> <li>• Cause hypertension when given IV</li> <li>• Variable clinical data from competitors in diabetic neuropathy/ diabetic peripheral neuropathy</li> <li>• May require substantial investment in clinical trials and patient education <ul style="list-style-type: none"> <li>• Not orally bioavailable</li> </ul> </li> </ul>	<p><b>Threats</b></p> <ul style="list-style-type: none"> <li>• Competitive market with major players e.g. Pfizer, Eli Lilly, Lundbeck <ul style="list-style-type: none"> <li>• Generic gabapentin</li> </ul> </li> </ul>

in 2005 – approximately 55% of sales being derived from the treatment of NP (c. £300 million). [Note that Neurontin generated peak sales of c. £1.5 billion in 2004 before going generic].

In September 2004 Eli Lilly's antidepressant Cymbalta was approved for the treatment of diabetic peripheral neuropathic pain. Cymbalta generated £105 million (US\$183 million) in sales in 2005 and we estimate that approximately 20% of sales were derived from the treatment of NP (c. £20 million). These drugs are generally well tolerated but they are not effective in all forms of neuropathic pain and long-term use may be associated with weight gain and somnolence.

A number of NMDA Antagonists are in various stages of clinical development for the treatment of NP and include: AV-1-1 (VistaGen), Dexanabinol (Pharmos), EVT102/103 (Evotec), Oral Glycine (AstraZeneca) Neurodex (Avanir Pharmaceuticals), Traxoprodil (Pfizer), Perzinfotel (Wyeth) and V3381 (Vernalis)

There is considerable room to improve analgesic control in post-operative pain and cancer – both these conditions are significantly under treated and inadequately controlled with current drugs in part due to sub-optimal drugs, inadequate protocols, and patient/medical education. We forecast that approval of CNS 5161 IV as an analgesic for POP and cancer could generate sales of £167 million.

There are considerable opportunities within the neuropathic pain market as only a handful of drugs are approved, each drug is approved within a subset of the neuropathic pain population and their long-term use may be limited by their side-effect profiles. We forecast that approval of a CNS 5161 Transdermal patch as an analgesic for neuropathic pain, namely diabetic and post-trauma, could generate sales of around £1 billion.

### **Clinical Status and Development Timeline**

A European Phase IIa dose-finding study in 48 patients suffering from intractable chronic neuropathic pain (such as diabetic neuropathy and post-traumatic neuropathy) was completed in June 2005. This study compared CNS 5161 (at levels of 125, 250, 500 and 750 µg) to placebo to determine a maximum tolerated dose (MTD). Results showed that 500 µg of CNS 5161 was associated with a clear trend to improvements in pain levels (measured using a Visual Analogue Scale (VAS)) at two, six and twelve hours after the start of the intravenous infusion when compared to placebo. The analgesic effects of CNS 5161 at 250 µg and above, were predominantly in patients with diabetic neuropathy and most evident at 24 hours. There were no psychotomimetic side effects with CNS 5161.

CeNeS plans to finalize the design of the Phase II study and initiate it by the end of 2006/early 2007. In addition, it has already performed an assessment of the feasibility of developing a TDP formulation with two US companies and intends to initiate a Phase I trial in early 2007.

### Partnering


Following the completion of a Phase II study in late 2007 we would anticipate CeNeS could partner CNS 5161 IV and that it would be filed with the regulatory authorities by the end of 2009. The company anticipates attracting a marketing partner to evaluate CNS 5161 in the acute treatment of cancer and post-operative pain and may choose to carve out its own territories and receive a royalty of up to 25% from sales outside its territories.

In contrast, the Company is targeting a 2007 Phase I trial for the patch formulation and following a positive PoC Phase II in TDP formulation CeNeS anticipates seeking a developmental/marketing partner to evaluate CNS 5161 in the chronic treatment of diabetes and post-traumatic surgical pain. Phase II/III trials would be initiated in 2008. This could attract upfront payments of 30-40% of NPV sales, milestone payments and royalties of up to 15%. CNS 5161 TDP could be filed with the regulatory authorities by the end of 2011.

We would anticipate CNS 5161 IV could be attractive to a wide variety of companies from pain specialists to CNS orientated specialty and regional pharma whilst the licensing of CNS 5161 TDP may be more attractive to larger pharma players such as AstraZeneca, Bristol Myers Squibb, GlaxoSmithKline, Novartis and Johnson & Johnson.

### Sales and royalty forecasts for CNS 5161 (£m)

Forecast sales														
Market	Dec-07	Dec-08	Dec-09	Dec-10	Dec-11	Dec-12	Dec-13	Dec-14	Dec-15	Dec-16	Dec-17	Dec-18	Dec-19	Total
IV Formulation			0.0	23.0	82.8	124.2	137.9	147.5	167.5	92.1	92.1	92.1	92.1	1051.2
Transdermal Patch			0.0	0.0	0.0	50.0	250.0	425.0	658.8	889.3	1000.0	550.0	550.0	4373.1
<b>Total</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>23.0</b>	<b>82.8</b>	<b>174.2</b>	<b>387.9</b>	<b>572.5</b>	<b>826.2</b>	<b>981.4</b>	<b>1092.1</b>	<b>642.1</b>	<b>642.1</b>	<b>5424.3</b>
<i>IV Formulation YoY Growth</i>					260%	50%	11%	7%	14%	-45%	0%	0%	0%	
<i>Transdermal Patch YoY Growth</i>							400%	70%	55%	35%	12%	-45%	0%	
CNS 5161 Licence Revenue to CeNeS														
Revenue	Dec-07	Dec-08	Dec-09	Dec-10	Dec-11	Dec-12	Dec-13	Dec-14	Dec-15	Dec-16	Dec-17	Dec-18	Dec-19	Total
<b>Upfront and Milestone Payments</b>														
- Upfront Payment		5.0		15.0										20.0
- Milestones			3.0	3.0	10.0	10.0								26
Tot. upfront & milestone paymnts	0.0	5.0	3.0	18.0	10.0	10.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	46.0
<b>Royalties</b>														
- IV Formulation			0.0	3.5	12.4	18.6	20.7	22.1	25.1	13.8	13.8	13.8	13.8	157.7
- Transdermal Patch			0.0	0.0	0.0	7.5	37.5	63.8	98.8	133.4	150.0	82.5	82.5	656.0
Total Royalties			0.0	3.5	12.4	26.1	58.2	85.9	123.9	147.2	163.8	96.3	96.3	813.6
<b>Total licence revenue</b>	<b>0.0</b>	<b>5.0</b>	<b>3.0</b>	<b>21.5</b>	<b>22.4</b>	<b>36.1</b>	<b>58.2</b>	<b>85.9</b>	<b>123.9</b>	<b>147.2</b>	<b>163.8</b>	<b>96.3</b>	<b>96.3</b>	<b>46.0</b>
<i>Average royalty rate</i>	-	-	-	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%	15.0%

Key: Peak market penetration = 

Impact of generics = 

**Overview**

CNS 7056X is a short-acting benzodiazepine. Benzodiazepines act at the GABA<sub>A</sub> receptor to reduce anxiety and provide sedation. It is being developed in an intravenous formulation for use in procedural sedation, the induction and maintenance of anaesthesia and for sedation of patients in intensive care.

Benzodiazepines are widely used for intravenous sedation and midazolam (Versed) has largely superseded diazepam (Valium) and lorazepam (Ativan) due to its ease of administration and relatively short duration of action. However, midazolam can induce prolonged sedation due to the production of active metabolites. Low doses of the anaesthetic agent, Diprivan (propofol) is increasingly being used as a sedative for diagnostic and short procedures however it should only be administered by an anaesthetist/anaesthesiologist which results in additional costs – estimated at around US\$250 per procedure equating to approximately 25-30% of endoscopy procedural costs (Source: CeNeS).

Benzodiazepines are also widely used in anesthesia in combination with other drugs such as midazolam-narcotic, ketamine-diazepam and tiletamine-zolazepam, and for induction of general anesthesia and for short procedures.

**Market analysis**

The global market for hypnotics/sedatives is estimated to be worth around £1.6 billion in 2005, +20% YoY (Source: Evaluate). Intravenous (IV) anaesthesia accounted for around £450 million with sales largely derived from two products midazolam (Roche/generic) and propofol (AstraZeneca/Generic) (Source: CeNeS). The US is the largest segment of the market and accounts for a 60% share by value and market research indicates that the US is the major and growing market for short procedures requiring sedatives (Source: CDC, 2005).

SWOT analysis of market	
<p><b>Strengths</b></p> <ul style="list-style-type: none"> <li>• Proven clinical concept</li> <li>• Predictable on-set and off-set of action</li> <li>• Minimal CV and respiratory effects                             <ul style="list-style-type: none"> <li>• No active metabolites</li> </ul> </li> <li>• Not reliant on liver/kidney for metabolism</li> </ul>	<p><b>Opportunities</b></p> <ul style="list-style-type: none"> <li>• Current drugs not optimal</li> <li>• Increased use in procedural sedation                             <ul style="list-style-type: none"> <li>• Potential use in intensive care patients (ICP)</li> </ul> </li> <li>• Potential use for induction and maintenance of anaesthesia</li> </ul>
<p><b>Weaknesses</b></p> <ul style="list-style-type: none"> <li>• More expensive than generics</li> <li>• Not tested in the clinic</li> </ul>	<p><b>Threats</b></p> <ul style="list-style-type: none"> <li>• Competitive market - 3 key IV benzodiazepines (Versed, Ativan, Valium)</li> <li>• Widespread use propofol (Diprivan)                             <ul style="list-style-type: none"> <li>• Reimbursement issues</li> </ul> </li> <li>• Generics</li> </ul>

## Sales and royalty forecasts for CNS 7056X (£m)

### Forecast sales

Market	Dec-07	Dec-08	Dec-09	Dec-10	Dec-11	Dec-12	Dec-13	Dec-14	Dec-15	Dec-16	Dec-17	Dec-18	Dec-19	Total
Short Procedures			0.0	15.0	45.0	58.5	67.3	74.0	88.0	89.8	91.6	93.4	95.3	717.7
Induction/Maintenance						15.0	45.0	68.0	82.2	91.3	95.0	96.9	98.9	592.3
ICU/CCU							25.0	75.0	122.0	142.0	153.0	158.4	161.6	837.0
<b>Total</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>15.0</b>	<b>45.0</b>	<b>73.5</b>	<b>137.3</b>	<b>217.0</b>	<b>292.2</b>	<b>323.0</b>	<b>339.6</b>	<b>348.7</b>	<b>355.7</b>	<b>2147.0</b>
<i>Short Procedures YoY Growth</i>					200%	30%	15%	10%	19%	2%	2%	2%	2%	
<i>Induction/Maintenance YoY Growth</i>							200%	51%	21%	11%	4%	2%	2%	
<i>ICU/CCU YoY Growth</i>								200%	63%	16%	8%	4%	2%	

### CNS 7056X Licence Revenue to CeNeS

Revenue	Dec-07	Dec-08	Dec-09	Dec-10	Dec-11	Dec-12	Dec-13	Dec-14	Dec-15	Dec-16	Dec-17	Dec-18	Dec-19	Revenue Total
<b>Upfront and Milestone Payments</b>														
- Upfront Payment	5.0			5.0	5.0									15.0
- Milestones		2.0	2.0	3.0	3.0	3.0								13.0
Tot. upfront & milestone paymnts	5.0	2.0	2.0	8.0	8.0	3.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	28.0
<b>Royalties</b>														
- Short Procedures			0.0	2.3	6.8	8.8	10.1	11.1	13.2	13.5	13.7	14.0	14.3	107.7
- Induction/Maintenance			0.0	0.0	0.0	1.5	4.5	6.8	8.2	9.1	9.5	9.7	9.9	59.2
- ICU/CCU			0.0	0.0	0.0	0.0	2.5	7.5	12.2	14.2	15.3	15.8	16.2	83.7
Total Royalties			0.0	2.3	6.8	10.3	17.1	25.4	33.6	36.8	38.5	39.5	40.3	250.6
<b>Total licence revenue</b>	<b>5.0</b>	<b>2.0</b>	<b>2.0</b>	<b>10.3</b>	<b>14.8</b>	<b>13.3</b>	<b>17.1</b>	<b>25.4</b>	<b>33.6</b>	<b>36.8</b>	<b>38.5</b>	<b>39.5</b>	<b>40.3</b>	<b>28.0</b>
<i>Average royalty rate</i>	-	-	-	15.0%	15.0%	14.0%	12.5%	11.7%	11.5%	11.4%	11.3%	11.3%	11.3%	11.7%

Key: Peak market penetration = 

At its peak IV midazolam generated sales of c. £260 million (CHF840 million) in 1999 ahead of generic erosion in 2000. Versed is also available in a syrup formulation for use in pediatrics. Now IV propofol is the world's best selling intravenous anaesthetic and generated peak sales of £285 million (US\$500 million) in 2004 - sales declined to £210 million (US\$369 million) in 2005 following the impact of generics.

In pre-clinical studies CNS 7056X is rapidly metabolized by tissues esterase to an inactive metabolite. This enables it to have a predictable onset/offset of action with a shorter duration of action than midazolam (pre-clinical data). In addition, it is anticipated CNS 7056X will have limited drug-drug interactions compared to midazolam due to its route of metabolism. Unlike propofol, it does not require administration by an anaesthetist due to its sedative profile thereby reducing potential administration costs.

In the clinic, midazolam is associated with severe respiratory depression, acute pulmonary insufficiency and gastrointestinal disturbance (nausea and vomiting) following sedation. CNS 7056X has yet to be evaluated in the clinic.

## Clinical Status and Development Timeline

CeNeS anticipates filing an Investigational New Drug (IND) application with the US authorities by the end of 2006 and anticipates initiating two Phase I trials early in 2007.

The Phase I trial will evaluate CNS 7056X's pharmacological profile (fast onset/offset) compared with midazolam through simple measures of sedation. Importantly, PoC would be established in Phase I and assuming smooth transition of the product CeNeS would anticipate filing for registration late 2009/2010.

## Partnering

Following positive Phase I data the company anticipates developing this drug through to late stage development as an IV sedative for short procedures and may look to attract a co-development/marketing partner in the US at an early stage - if this were the case we would anticipate that they may negotiate a royalty rate of up to 10% if CeNeS drives development to Phase I/III but should the company develop it to Phase II/III clinical trial, they could attract a royalty rate of up to 25%.

In addition, there is potential to evaluate CNS 7056X in other indications including: induction of anaesthesia and more chronically within the intensive care unit (ICU). In both cases it is possible that CeNeS could:

- choose to develop the drug to late stage and out-licence it and command a significant upfront payment, milestone payments and a royalty;
- it may co-market it and choose specific territories in which to market the drug and receive royalties from other territories.

We would anticipate that several specialist anaesthetic suppliers might be interested in acquiring the rights to CNS 7056X to complement their existing hospital-based portfolio such as Allergan, Cephalon and Purdue or big pharma who already have a vested interest in this market such as Abbott, Roche and Wyeth.

## Appendix 5: COMT inhibitors drug profile

### Overview

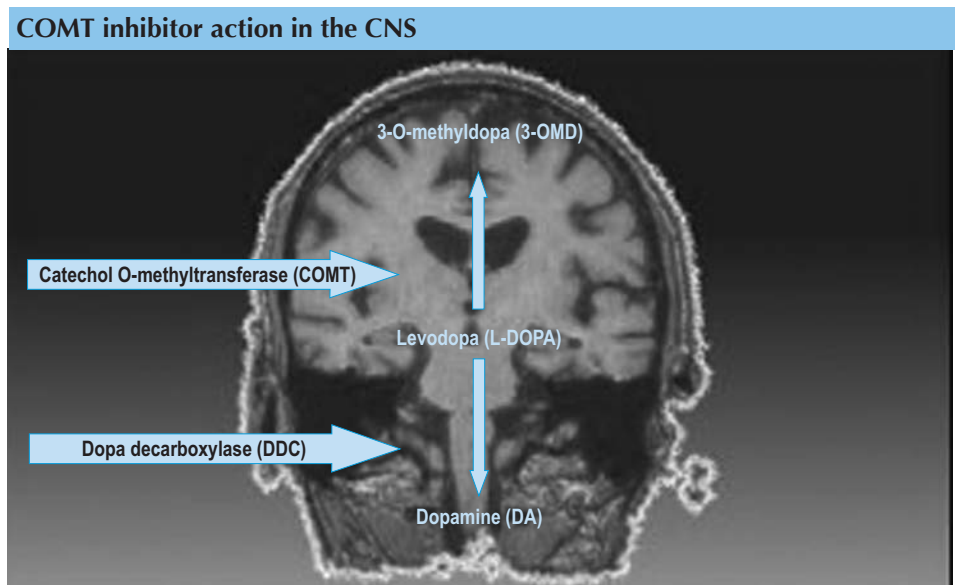
Catechol-O-methyltransferase inhibitors (COMT inhibitors) minimize the metabolism of levodopa (L-DOPA) by COMT, thereby prolonging the action of L-DOPA (See figure).

Two orally active COMT inhibitors entacapone (comtan) and tolcapone (Tasmar) are prescribed in combination with levodopa and carbidopa in moderate to severe Parkinson's disease. They do not alter the progression of the disease but are L-DOPA sparing prolonging the effectiveness of L-DOPA.

Clinical data is mounting to suggest that levodopa combinations may delay the onset of motor complications, such as dyskinesias, and combination use may be more effective if prescribed earlier during the course of the disease. Results to support this are expected in 2007/2008 following the completion of the pivotal STRIDE study using Stalevo (entacapone/levodopa/carbidopa).

Preliminary data suggests that COMT inhibitors may be useful in cognitive disorders and improve attention and therefore have utility as adjuvants in cognitive impairment associated with schizophrenia (CIAS) and Attention Deficit Disorder (ADHD). These are considerable markets as it is estimated that up to 60% of schizophrenics suffer with cognitive impairment (Datamonitor, 2005) and anti-psychotic therapies generated sales of £7.7 billion in 2005 (Evaluate) versus £1.7 billion for ADHD treatments (source: Espicom).

Levodopa remains the most effective treatment of Parkinson's disease following its introduction over 30 years ago. The majority of patients (c.75%) are only prescribed levodopa/carbidopa therapy due to side-effects associated with adjunctive therapies such as COMT inhibitors. There remains a high unmet clinical need to identify candidates for more efficacious and less toxic adjunct therapies which



Source: CeNeS

## SWOT analysis of market

<b>Strengths</b> <ul style="list-style-type: none"><li>• Proven clinical concept<ul style="list-style-type: none"><li>• Levodopa sparing</li></ul></li><li>• Reduce motor fluctuations<ul style="list-style-type: none"><li>• Uncompetitive market</li></ul></li></ul>	<b>Opportunities</b> <ul style="list-style-type: none"><li>• Current drugs not optimal</li><li>• More aggressive use in early stages of PD</li><li>• Potential in cognitive disorders associated with schizophrenia and attention deficient disorder (ADHD)</li></ul>
<b>Weaknesses</b> <ul style="list-style-type: none"><li>• Do not modify disease progression<ul style="list-style-type: none"><li>• In pre-clinical development</li></ul></li><li>• Unknown pharmacokinetic profile</li></ul>	<b>Threats</b> <ul style="list-style-type: none"><li>• Increase uptake of combination<ul style="list-style-type: none"><li>• Triple therapies</li></ul></li><li>• Launch of new therapy classes<ul style="list-style-type: none"><li>• Generics</li></ul></li></ul>

may have utility for both early and late-stage PD. CeNeS has identified a series of non-nitrocatechol containing COMT inhibitors which are expected to be associated with improved toxicity and absorption/metabolism profiles.

### Market analysis

The global market for anti-Parkinsonian agents was estimated to be worth £1.4 billion in 2005 (+20% YoY). The COMT inhibitors are a small segment of the market and accounted for £200m (source: Evaluate). Novartis is the market leader through the promotion of its Comtan franchise (Comtan/Comtess/Stalevo) which generated sales of £160 million (US\$278 million, +38% YoY) compared to £3.3 million (US\$5.8 million, +64 YoY) from Tasmar sales marketed by Valeant Pharmaceuticals (acquired in June 2004).<sup>1</sup>

Current COMT inhibitors are sub-optimal: tolcapone requires liver enzyme monitoring due to toxicity issues whilst entacapone has limited brain penetration and therefore is less efficacious. The development of a brain penetrating COMT inhibitor with improved toxicity profile would lead to an increased uptake of COMT inhibitors within the PD patient pool potentially earlier in treatment. As far as we are aware there are no other COMT inhibitor candidates in clinical development.

### Clinical Status and development timeline

The company is currently optimizing leads to identify candidates for pre-clinical development in Parkinson's disease and cognitive disorders within 2006. Following positive pre-clinical data CeNeS would anticipate entering Phase I clinical development by mid-2007. Importantly, Phase I data will provide proof of concept (PoC) data equivalent to Phase II. This should be available by mid-2008.

<sup>1</sup> <http://www.valeant.com/mediaCenter/newsArticle/newsArticle.jspf?objectId=4142>

### Potential marketing partners for COMT inhibitors in CIAS/ADHD

Company	Antipsychotic	Patent expiration	Psycho-stimulant	Patent Expiration
AstraZeneca / Fujisawa	Seroquel	Sept 2011		
Bristol Myers Squibb / Otsuka			Abilify	Oct 2014
Celltech			Metadate	expired
Eli Lilly	Zyprexa	April 2011	Strattera	2015
Johnson & Johnson	Risperdal	Dec. 2007	Concerta	expired
Pfizer	Geodon	Mar. 2007		
Shire	Equetro	Jul. 2011	Adderall	expired
Novartis	Clozaril	expired	Ritalin Focalin	2019 expired

Source: Company data, FDA Orange Book

### Partnering

CeNeS would anticipate attracting a developmental & marketing partner for the development of COMT inhibitors for the treatment of Parkinson's disease as an adjunct therapy to levodopa/carbidopa early in the clinical trial programme – potentially following PoC data which is expected mid-2008. Further development of COMT inhibitors is likely to require the development of a combination pill, e.g., COMT inhibitor plus levodopa/carbidopa to aid market penetration and ease pill burden. This will incur additional formulation costs. A drug at this stage of development should attract royalties of between 10% and 20% of sales.

CeNeS anticipates identifying a second COMT inhibitor for clinical development and evaluation in CIAS due in part to the differential pricing of Parkinson's drugs versus antipsychotics, i.e., PD agents are priced at a discount to schizophrenia drugs. CeNeS is unlikely to develop its COMT inhibitors in-house for cognitive disorders associated with schizophrenia and attention deficit disorder and anticipates attracting a developmental/marketing partner following PoC data which is due mid-2008.

We would anticipate that several of the large pharma companies might be interested in acquiring the rights to COMT inhibitors to complement their existing antipsychotic portfolio, to increase their stronghold in the market, and aid the life-cycle management of their branded drugs. Potentially partners could include Johnson & Johnson, Novartis and Shire (see Table above).

## Sales and royalty forecasts for COMT (£m)

### Forecast sales

Market	Dec-07	Dec-08	Dec-09	Dec-10	Dec-11	Dec-12	Dec-13	Dec-14	Dec-15	Dec-16	Dec-17	Dec-18	Dec-19	Total
Parkinson's Disease						90.0	289.8	388.3	446.6	464.4	480.0	489.6	499.4	3148.2
Cognitive Impairment							43.0	129.0	180.6	207.7	218.1	225.0	229.5	1232.9
ADHD								60.0	180.0	252.0	272.2	280.3	285.0	1329.5
<b>Total</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>0.0</b>	<b>90.0</b>	<b>332.8</b>	<b>577.3</b>	<b>807.2</b>	<b>924.1</b>	<b>970.2</b>	<b>994.9</b>	<b>1013.9</b>	<b>5710.5</b>
<i>Parkinson's Disease YoY Growth</i>								222%	34%	15%	4%	3%	2%	2%
<i>Cognitive Impairment YoY Growth</i>								200%	40%	15%	5%	3%	2%	
<i>ADHD YoY Growth</i>									200%	40%	8%	3%	2%	

### COMT Licence Revenue to CeNeS

Revenue	Dec-07	Dec-08	Dec-09	Dec-10	Dec-11	Dec-12	Dec-13	Dec-14	Dec-15	Dec-16	Dec-17	Dec-18	Dec-19	Total
<b>Upfront and Milestone Payments</b>														
- Upfront Payment			25.0	25.0	25.0									75.0
- Milestones				10.0	10.0	10.0	10.0							40.0
Tot. upfront & milestone paymnts	0.0	0.0	25.0	35.0	35.0	10.0	10.0	0.0	0.0	0.0	0.0	0.0	0.0	115.0
<b>Royalties</b>														
- Parkinson's Disease						7.2	23.2	31.1	35.7	37.2	38.4	39.2	40.0	251.9
- Cognitive Impairment						0.0	3.4	10.3	14.4	16.6	17.4	18.0	18.4	98.6
- ADHD						0.0	0.0	4.8	14.4	20.2	21.8	22.4	22.8	106.4
Total Royalties						7.2	26.6	46.2	64.6	73.9	77.6	79.6	81.1	456.8
<b>Total licence revenue</b>	<b>0.0</b>	<b>0.0</b>	<b>25.0</b>	<b>35.0</b>	<b>35.0</b>	<b>17.2</b>	<b>36.6</b>	<b>46.2</b>	<b>64.6</b>	<b>73.9</b>	<b>77.6</b>	<b>79.6</b>	<b>81.1</b>	<b>115.0</b>
<i>Average royalty rate</i>	-	-	-	-	-	8.0%	8.0%	8.0%	8.0%	8.0%	8.0%	8.0%	8.0%	8.0%

Key: Peak market penetration = 

## Appendix 6: Management

### **Alan Goodman**, *Chairman*

Medeva & founder of Acambis, Oxford Biomedica , CeNeS

### **Neil Clark**, *CEO*

CFO then COO, led restructuring & promoted to CEO in 2005

### **Terry Smith**, PhD, *Clinical*

25 years of R&D in neuro drugs. Wellcome, BTG and CeNeS

### **Simon Kerr**, *Commercial*

20 years in business development, marketing/sales including with Beecham and Wellcome

### **Gavin Kilpatrick**, PhD, *Discovery*

Glaxo, Roche, Co-founder of TheraSci

### **Gary Tilbrook**, PhD, *Chemistry*

Kings College, London and co-founder of TheraSci.

### **Tony Osbourne**, *ACA, Finance*

10 years in Biotech. Joined Cobra Therapeutics & CeNeS in 2004

## **Non Exec Directors**

### **Ron Irwin**

Former Chairman of Marion Merrell Dow. ICI, Sterling Winthrop & British Biotech

### **Dr Peter Johnson**

Wellcome, Hoechst, SmithKline, Fisons & Astra, Chair of Oxford Biomedica

### **Alan Smith**, CIPFA

Chairman of Acambis, Chair/Avlar Bioventures, former Group MD of Anglian Water

## **Scientific Advisory Board**

### **Ann Hayes**, PhD (Chair)

Former Head of Drug Discovery, Glaxo. Founder of Ionix and TheraSci

### **David J Brooks**, MD, DSc

Professor of Neurology at Imperial College School of Medicine

### **Mick Serpell**, MB, ChB

Head of Clinical Trial Unit at Pain Clinic at Gartnavel, a Neuropathic Pain Specialist

### **David Brown**, PhD

Former Head of Drug Discovery at Roche. Co-Inventor of Viagra & key to Relpax development.

We are pleased to bring you this report on **CeNeS Pharmaceuticals plc**.



Objective was founded so that issuers can ensure that the market and their investors always have access to quality research through sponsoring indepth, proactive coverage.

While our research is sponsored by the companies we cover, it is always written on behalf of our readers. We offer you an objective, independently prepared view of the opportunity, the risks and what the value might be to an average investor in the companies we cover.

As we are unconflicted by corporate finance or PR/IR agendas, our analysts are always free to give their true opinion of the businesses we cover.

As always, I welcome your comments and feedback on our research!

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.

**Dr Cheryl Barton**

Cheryl has over 15 years experience in industry and as senior equity analyst for ABN Amro. Cheryl is a former scientist with Merck and previously lead analyst on AstraZeneca, Roche and Sanofi-Synthelabo.

---

**About our relationship with CeNeS Pharmaceuticals plc**

Objective Capital has been sponsored by the company to provide research coverage of CeNeS Pharmaceuticals plc.

Objective will provide proactive, indepth coverage for a period of more than one year. The typical fee for the quality and level of coverage offered by Objective is £20,000 per annum. Objective does not accept payment in any form of equity.

Unless otherwise noted, the opinions expressed in our reports are entirely those of our analysts. Objective's analysts are contractually protected to be able to always provide their opinion on the businesses they write on.

# Objective Corporate Research

Call us today to find out  
how our sponsored research  
can benefit you

## **Objective Capital Limited**

2nd floor, 145 St. John St.  
London EC1V 4PY  
Tel: +44-(0)870-080-2965  
Fax: +44-(0)870-116-0839  
sales@objectivecapital.com

Internationally:  
Phone: +44-20-7754 5994

US Toll-Free:  
1-888-802-7215

For Marketing & Sales:  
Token House  
11-12 Tokenhouse Yard  
London EC2R 7AS

Corporate: [www.ObjectiveCapital.com](http://www.ObjectiveCapital.com)  
Research: [www.ObjectiveCapital.co.uk](http://www.ObjectiveCapital.co.uk)