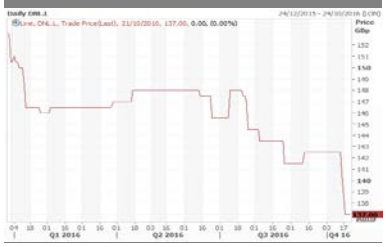
Pharmaceuticals & Biotech



Source: Eikon Thomson Reuters

Market data	
EPIC/TKR	DNL
Price (p)	135
12m High (p)	155
12m Low (p)	132
Shares (m)	52.2
Mkt Cap (£m)	70.5
EV (£m)	43.6
Free Float*	13%
Market	AIM

**As defined by AIM Rule 26*

Description

Diurnal is a UK-based specialty pharma company targeting patient needs in chronic, potentially life threatening, endocrine (hormonal) diseases. It has two products in late-stage clinical trials which are expected to be submitted to the regulators for approval in the next 12 months.

Company information	
CEO	Martin Whitaker
CFO	Ian Ardill
Chairman	Peter Allen
	+44 871 7168848
	www.diurnal.co.uk

Key shareholders	
Directors	3.2%
IP Group	45.6%
Finance Wales	22.1%
Invesco	12.5%
Oceanwood Capital	6.7%
Sarum Investments	3.0%

Next event	
12-Oct	Finals
24-Nov	AGM
4Q-16	Infacort EU filing

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Diurnal Group

Get the rhythm

Diurnal is a clinical stage specialty pharmaceutical company focused on diseases of the endocrine system. It has two lead candidates – Infacort® and Chronocort® – in Phase III trials targeted at rare diseases with unmet medical need with which it aims to build a long-term 'Adrenal Franchise'. The cortisol replacement market is for conditions that need life-long treatments, with a potential value of $3.5bn. Despite this, the market is characterised by few competitors, and Diurnal will target a network of specialist endocrinology centres in Europe and US by itself. Upcoming newsflow on trials and regulatory filings will draw attention to the stock.

- **Strategy**: Diurnal's strategic goal is to create a valuable 'Adrenal Franchise' that can treat patients with chronic cortisol deficiency diseases. Once Infacort and Chronocort are established in Europe and the US, the long-term vision is to expand the product offering to other conditions linked to the endocrine system.

- **Launch timetable:** Infacort will be filed with the EMA in 4Q 2016, allowing a launch in 1Q 2018, with a US Phase III trial programme anticipated to be agreed with the FDA. Chronocort is in Phase III trials in Europe with the expectation of a launch in 2019; the US launch is expected to follow in 2021.

- **Market opportunity:** Diurnal will initially target the orphan conditions of congenital adrenal hyperplasia (CAH) and adrenal insufficiency (AI) which require life-long replacement of cortisol. Based on competitive pricing, Diurnal will be targeting addressable markets of ca.$3.5bn.

- **Risks:** As with all drug development companies, there is a risk that products will fail in clinical trials. However, Diurnal is much lower risk given that its products are formulation variants of well-established drugs. The main risk to forecasts will be management's ability to obtain the desired in-market prices for its drugs

- **Investment summary:** A risk-adjusted DCF model of its two leading products suggests that Diurnal should be trading at 399p per share, with an EV of £208m. This is supported by relative valuation analysis compared to peer group of similar stage development companies in the field of endocrinology, with Corcept (CORT.OQ) being a good example of valuation potential when sales are achieved.

Financial summary and valuation

Year end June (£m)	*2014	*2015	2016	2017E	2018E	2019E
Sales	0.00	0.00	0.00	0.00	1.04	3.43
SG&A	-0.99	-1.55	-1.99	-5.71	-7.43	-9.19
R&D	-0.93	-1.82	-3.89	-8.94	-9.03	-9.12
EBITDA	-0.93	-2.98	-5.87	-14.64	-15.52	-15.22
Underlying EBIT	-0.94	-2.99	-5.88	-14.65	-15.52	-15.22
Reported EBIT	-0.94	-2.99	-6.99	-15.16	-16.06	-15.79
Underlying PBT	-0.98	-3.02	-5.95	-14.76	-15.71	-15.51
Statutory PBT	-0.98	-3.02	-7.06	-15.27	-16.25	-16.08
Underlying EPS (p)	-3.72	-8.49	-12.48	-26.10	-27.91	-27.50
Statutory EPS (p)	-4.13	-8.72	-15.02	-27.09	-28.94	-28.59
Net (debt)/cash	-0.34	6.05	26.88	13.30	-0.86	-15.52
Capital increases	0.00	9.25	24.52	0.00	0.00	0.00

**Year to July*

Source: Hardman & Co Life Sciences Research

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Executive summary

Background

Diurnal focuses on endocrine disorders…

…with two products in Phase III…

… in adults and children

Diurnal is a clinical stage specialty pharmaceutical company focused on endocrine (hormonal) diseases. It was founded in 2004 as a spin-out from the University of Sheffield, supported by IP Fusion (now part of IP Group). An IPO on AIM in 2015 with a concomitant institutional Placing/Loan note raised £30m. The company has two products in Phase III clinical trials that are targeted on endocrine disorders in both adults and children, where the current standard of care has unsatisfactory outcomes.

Evolution of Diurnal

Date	Event
2004	Foundation of Diurnal
2004	Chronocort IP licensed to Phoqus plc
2008	Diurnal re-acquired Chronocort licence
2009	Institutional shareholder base established to develop Chronocort
2012	Glatt manufacturing agreement
2014	£6m funding received
2015	IPO of Diurnal Group plc on AIM
2015	£30m capital increase via an institutional Placing/Convertible loan note

Source: Company reports; Hardman & Co Life Sciences Research

Adrenal franchise

Diurnal is providing speciality services in a niche market with medical unmet needs

Diurnal's strategic goal is to create a valuable 'Adrenal Franchise' that can treat patients with chronic cortisol deficiency diseases. The company is targeting two major indications that could possibly be life-threatening if not correctly treated:

- Adrenal Insufficiency (AI)
- Congenital Adrenal Hyperplasia (CAH)

The adrenal market is characterised by few competitors, specialist providers and known patient groups, making it attractive for niche players providing specialty services. Diurnal is in late-stage development with Chronocort (adults) and Infacort (infants/children) for adrenal conditions. They are capsules containing multi-layered, multi-particulate formulations of hydrocortisone manufactured using specialist multi-particulate technology.

The USP of Chronocort is mimicking the circadian rhythm or cortisol in adults

Infacort is targeted at newborn and young children

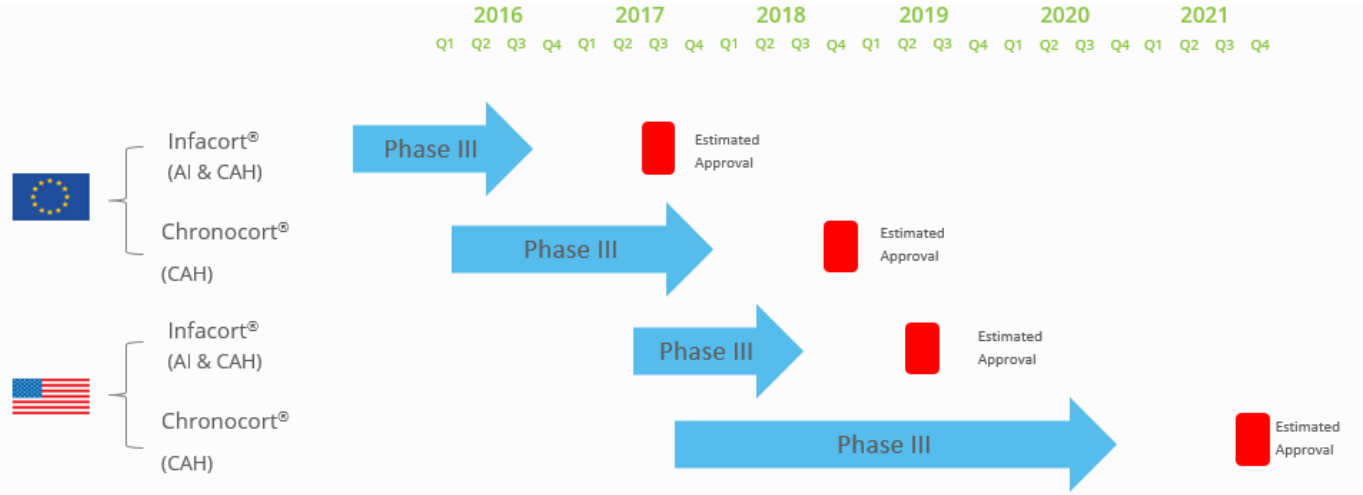
- **Chronocort** – Formulation of hydrocortisone designed to mimic the natural circadian rhythm of cortisol, in Phase III trials targeting adults in Europe and patients >16 in the US
- **Infacort** – An immediate release formulation of hydrocortisone specifically designed to meet the dosing requirement for newborns and young children. Infacort has currently successfully completed Phase III clinical trials in Europe

Diurnal pipeline

Diurnal's first two products Infacort (Phase III completed in Europe) and Chronocort (currently in Phase III in Europe) have anticipated launches in 2018 and 2019, respectively. These will initially be in Europe, followed by the US.

Once established, the long-term vision is to expand the product offering to conditions that are linked to particular endocrine systems, such as the gonads and thyroid, through a new oral testosterone formulation and Tri4Combi, respectively.

Diurnal – Development and approval timetable



[1]*Regulatory programme including a Phase III clinical trial agreed with the FDA*
Source: Diurnal

Commercial opportunity

The adrenal market is estimated at $3.5bn

There are a number of reliable databases available that provide statistics for the prevalence of rare diseases in Europe and the US, Diurnal's target markets. Application of these to 2015 population statistics for adults and children provides the addressable markets. On the basis that Infacort and Chronocort are priced at a similar level to Plenadren®, Shire's modified release formulation of hydrocortisone for adults with adrenal insufficiency, the overall adrenal markets being targeted equate to about $3.5bn.

Addressable markets

$m	Europe	US	Total
Annual price of drug	**$6,100**	**$6,800**	
Paediatric CAH	25.6	50.3	75.9
Adult CAH	256.2	187.0	443.2
Addison's disease	321.9	108.8	430.7
Hypopituitarism	1165.1	1,360.0	2,525.1
Target population	**1,768.8**	**1,706.1**	**3,474.9**

Source: Hardman & Co Life Sciences Research

Commercial exclusivity & strategy

Chronocort has commercial exclusivity with the Orphan Drug designation

Given that the pharmaceutical industry in general has little interest, under normal market conditions, in developing and marketing medicines intended for small numbers of patients, the European and US regulators offer a range of incentives to encourage the development of these medicines, under specific conditions:

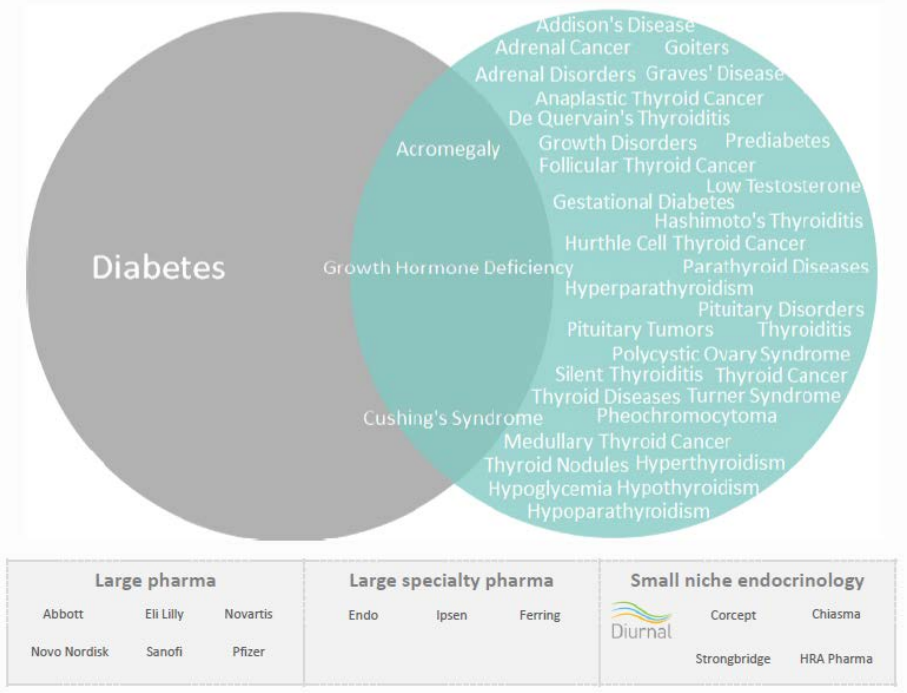
- **Orphan Drug designation** – Provides fast-track approval process and marketing exclusivity (Europe 10 years; US 7 years) from approval

Application for PUMA has been submitted for Infacort

- **PUMA** – The paediatric use of marketing authorisation covers indications and formulations designed for paediatric use, providing data and marketing exclusivity in Europe

Chronocort already has Orphan Drug status in both Europe and the US for both indications. Infacort has been granted Orphan Drug designation in the US for AI. Diurnal will apply for market authorisation through the PUMA route in the Europe for Infacort.

The endocrine market



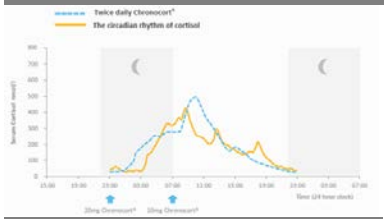
Source: Diurnal

Low competition segments with a poor ability to mimic the circadian rhythm of cortisol

Diurnal will be entering a niche market with Infacort and Chronocort for the indications of CAH and AI, where improvement over the current standard of care is needed and competition is low. There will be two potential lines of competition:

- Immediate release formulations of hydrocortisone (generic) or synthetic corticosteroids (prednisolone and dexamethasone)
- Plenadren – modified release formulation of hydrocortisone

Mimicking circadian rhythm



Source: Diurnal:

Neither of these products have the same ability as Chronocort to mimic the circadian rhythm of cortisol. Proof of improved disease control in clinical trials will provide a considerable marketing edge.

Diurnal's marketing strategy will be to target a network of prescribers practising in specialist endocrinology centres in Europe and the US (120 and 150 centres, respectively). As a consequence, the cost of sales and marketing is expected to be relatively modest.

Investment conclusion

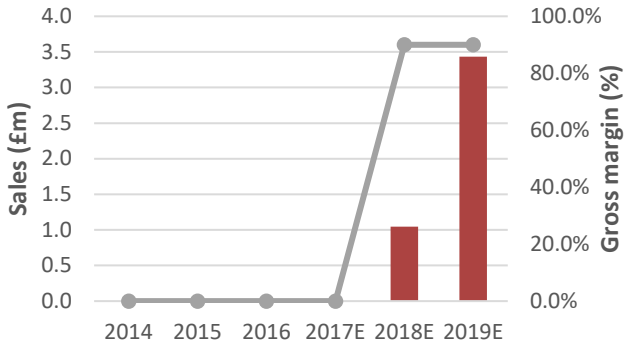
The risk-adjusted NPV of Diurnal is £208m, or 399p per share…

…suggesting that there is plenty of upside potential for shareholders

In a DCF model of Infacort and Chronocort, the net present value of the cashflows that could be generated from these products equates to £316m on the basis that they receive both EMA and FDA approval. Risk-adjusting this to take account of the different stages of development in the two territories reduces this to £208m, or 399p per share. This model allows a very fast assessment of the likely effect on the share price following the announcement of clinical results and also suggests that there is plenty of upside for shareholders.

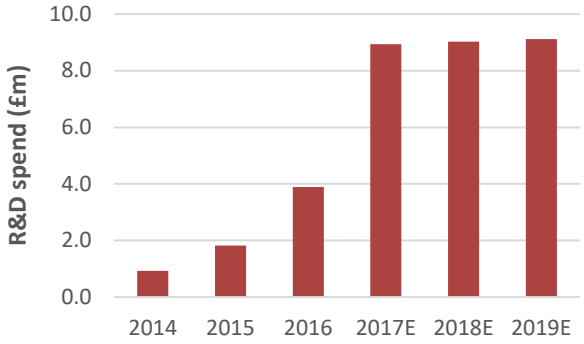
Also, the EV of Diurnal compares well against an international peer group of specialty pharmaceutical companies with putative drugs in late stage clinical trials for endocrine disorders.

Sales & Gross margin



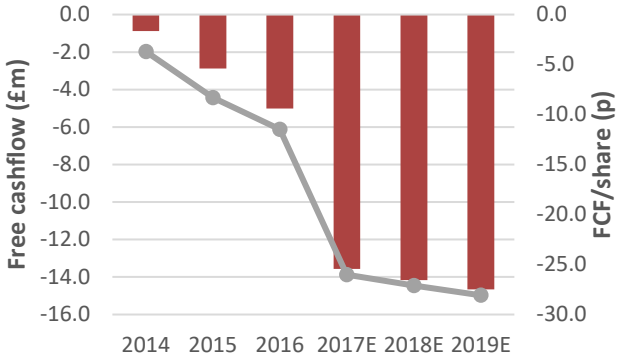
- Diurnal is currently a late-stage drug development company with no sales
- Sales will kick in as soon as products receive regulatory approval
- Initial sales will be in Europe
- The gross margin will be around 90%

R&D investment



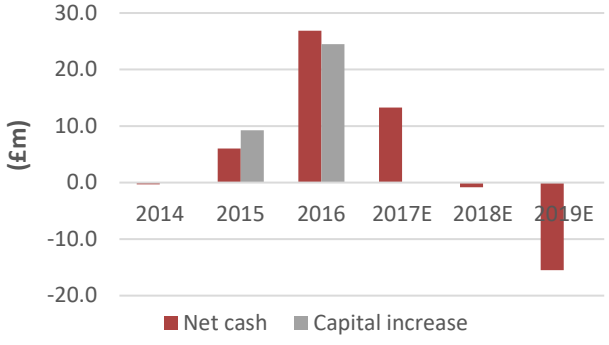
- Investment is being made into Phase III trials for Chronocort and Infacort for EU and US regulatory approval
- Only very modest investment is being made on the next wave of products e.g. testosterone

Free cashflow



- The cashflow is driven entirely by the R&D investment and corporate overhead
- Offset by the tax credit in R&D investment
- There will be some build up for marketing in Europe ahead of regulatory approval of Infacort
- Our cash projections suggest that Diurnal has sufficient cash to complete the Phase III EU trials

Net cash/capital increases



- £30m cash was raised through an institutional placing and convertible loan note at IPO
- At 30th June 2016, Diurnal has net cash and deposits of £26.9m
- Further cash will be required for commercialisation of Chronocort and Infacort in Europe and the US

Source: Company data; Hardman & Co Life Sciences Research

Diurnal – the company

Late-stage specialty pharma company…

Diurnal is a clinical stage specialty pharmaceutical company focused on endocrine (hormonal) diseases. The company targets conditions where the current standard of care results in unsatisfactory patient outcomes, creating an unmet medical need in both adults and children.

Corporate history

…spun out of the University of Sheffield

Diurnal was founded in 2004 as a spin-out from the University of Sheffield, based on the endocrine research of Professor Richard Ross - Professor of Clinical Endocrinology and Head of the Academic Unit of Diabetes, Endocrinology and Metabolism. Diurnal initially focused on the development of Chronocort, a dual layer tablet formulation of hydrocortisone, for adrenal insufficiency (AI).

The manufacturing relationship with Glatt is key

The IP was licensed subsequently to Phoqus plc, which used electrostatic deposition technology to develop its proprietary version of the product, with a once daily dosing regimen in a tablet formulation. However, issues encountered in the manufacturing scale-up led to Phoqus' dissolution and the Chronocort licence was subsequently re-acquired by Diurnal in 2008. Diurnal designed a new version of the product, changing the formulation, dosing regimen and release profile and has entered into a pharmaceutical manufacturing agreement with Glatt GmbH.

Chronocort, a modified release formulation of hydrocortisone, is currently in late stage clinical trials in both the Europe and US for the treatment of Adrenal Insufficiency (AI) and Congenital Adrenal Hyperplasia (CAH). Infacort, a paediatric friendly formulation of hydrocortisone, has completed Phase III trials for the same indications. Through these two products, Diurnal is building its 'Adrenal Franchise' in the disease of cortisol deficiency.

Diurnal is also starting to diversify its offering by targeting other indications affected by cortisol deficiency, as well as other hormone deficiencies like hypothyroidism and hypogonadism.

Evolution of Diurnal

Date	Event
2004	Foundation of Diurnal
2004	Chronocort IP licensed to Phoqus plc
2008	Diurnal re-acquired Chronocort licence
2009	Institutional shareholder base established to develop Chronocort
2012	Glatt manufacturing agreement
2014	£6m funding received
2015	IPO of Diurnal Group on AIM
2015	£30m capital increase via an institutional Placing/Convertible loan note

Source: Company reports; Hardman & Co Life Sciences Research

Strategy

Although the endocrine market is dominated by diabetes drugs…

…there is huge scope for drugs treater the rarer conditions

Diurnal is focused on rare, and chronic, endocrine conditions with high unmet need in order to get fast track approval from the regulatory authorities. The endocrine market was worth more than $39bn in 2015, ruled by major pharmaceutical players, and dominated by insulin replacement products for treatment of diabetes. The other endocrine conditions that affect a significantly smaller proportion of the population, often classified as rare conditions, constitute niches for a number of specialist players, such as Diurnal.

Diurnal – the technology

Chronocort®

Chronocort aims to mimic the natural daily rhythm of cortisol

Chronocort is a hydrocortisone preparation designed to mimic the natural circadian rhythm of cortisol, a life-sustaining adrenal hormone essential for the maintenance of homeostasis (see page 17), when given in a twice daily dosing regimen. The intention is to take the drug at night before sleep and first thing in the morning to mimic the natural cortisol blood levels in healthy individuals. Its name is derived from the contraction of "chronos" (time in Greek) and "cortisone".

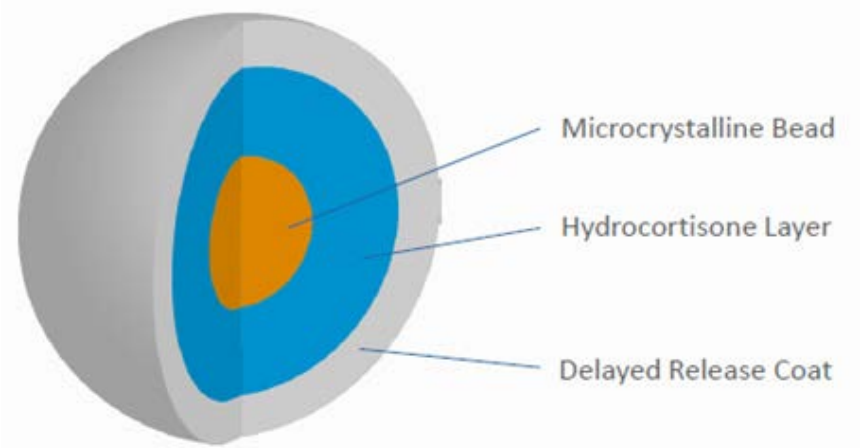
Presentation

Multi-layered, multi-particulate formulation designed for the slow release of hydrocortisone

Chronocort is a multi-layered, multi-particulate, formulation of hydrocortisone containing micro-crystalline beads, using multi particulate manufacturing technology. It is constructed of three essential parts:

- **Core** – an inert microcrystalline bead needed for manufacturing purposes
- **Inner layer** – comprising the active ingredient: hydrocortisone
- **Outer layer** – corresponding to a delayed release coat that will specifically dissolve at the pH found in the gastrointestinal tract, allowing release of the active ingredient where it will be easily absorbed

Chronocort presentation



Source: Diurnal

Chronocort offering

Source: Diurnal

Diurnal is proposing to make Chronocort available in three dosage forms (5mg, 10mg and 20mg) to give endocrinologists the flexibility to adjust the dose to a patient's needs.

Treatment with Chronocort

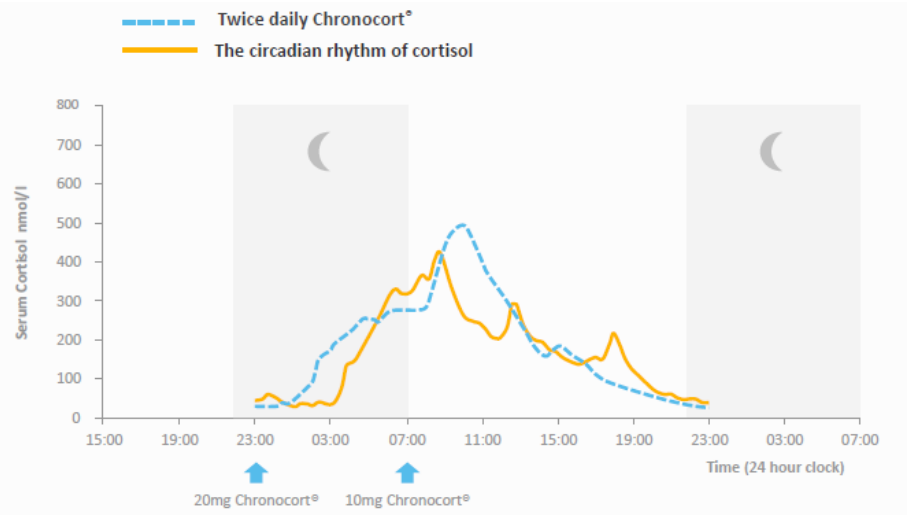
One of the key features of Chronocort is its delayed release coat, which is sensitive to pH. It is deigned to dissolve in the pH environment of the gastrointestinal (GI) tract allowing the slow release of hydrocortisone at a point where the drug can optimally be absorbed into the bloodstream. Due to the short half-life of hydrocortisone, the release mechanism allows a slow, but constant, absorption of drug in order to achieve a therapeutic level that mimics the normal secretion of cortisol.

Twice daily, Chronocort closely matched the natural level of cortisol…

The following graph demonstrates how the natural daily changes in blood levels of cortisol in a healthy individual are closely mimicked by the blood levels of Chronocort with twice a day administration (the dose is dependent of the body weight):

- 20 mg of Chronocort at 11pm, just before going to sleep, that allows the slow release of hydrocortisone during the night
- 10 mg of Chronocort early in the morning to follow the peak of natural cortisol in the morning

Chronocort® – Mimicking the circadian rhythm



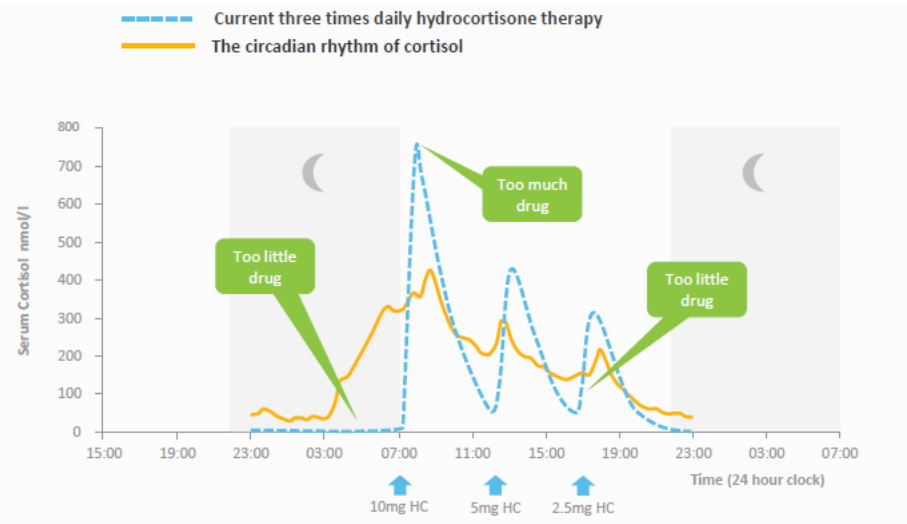
Source: Diurnal

Standard of care

…whereas current standard of care cause big peaks and troughs

The current standard of care is to administer immediate release hydrocortisone twice (20mg at breakfast time, 10mg in early evening) or three times (10mg at breakfast times, 5mg at lunchtime, 2.5mg at supper time) daily, which results in higher short-term blood levels which rapidly decline due to its short half-life.

Hydrocortisone blood levels



Source: Diurnal

It is thought that Chronocort more closely matches natural cortisol levels compared to hydrocortisone for two reasons:

- Manufactured with a better understanding of the circadian rhythm of cortisol
- The modified release features of Chronocort

Endocrinologists will be able to use the different strengths of Chronocort to individualise the dose to each patient's particular needs.

Clinical trial status

Phase II outcomes

A successful Phase II clinical trial[1] enrolling sixteen CAH adult patients was conducted in the US. The six months' pilot study demonstrated that Chronocort was well tolerated and that the cortisol profile was similar to physiologic cortisol secretion. It also showed that Chronocort was able to control androgen (the key clinical measure) excess in CAH patients.

Phase III studies

Europe

The Phase III Chronocort trial is already underway in Europe….

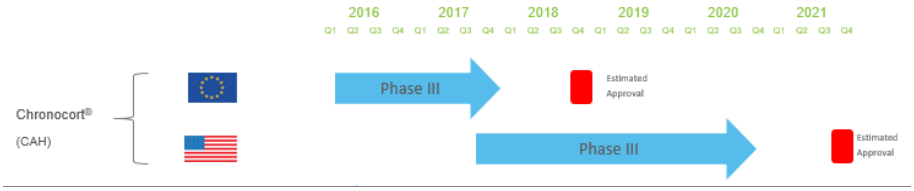
A Phase III clinical trial enrolling 110 CAH patients in Europe started recruiting in February 2016. It will assess the safety, tolerability and clinical benefit of Chronocort compared to standard glucocorticoid therapy. The treatment is randomised, followed by a six month evaluation period, which will measure one androgen (change from baseline in 17-hydroxyprogesterone (17-OHP)) to assess the clinical benefit end-point. A secondary outcome will measure the level of another disease androgen – androstenedione (A4).

US

… and will start recruiting in the US in 2017

A similar Phase III trial, enrolling ca. 150 patients in the US, will commence following the conclusion of protocol discussions with the FDA. For the US regulatory process, the FDA requires a more robust measurement of the clinical benefit, and statistical analyses have yet to be confirmed. The 12 month study will use two androgen measurements to assess the clinical benefit end-point.

Chronocort – Development timetable



Source: Diurnal

At the end of the clinical study, patients will have the choice of whether to stay on Chronocort until market approval or return to their usual standard of care.

Market approval for Chronocort in CAH is expected in 2018 in EU and 2021 in US

Management is expecting to obtain market approval for CAH in Europe by the end of 2018 and in the US by the end of 2021.

[1] Mallappa et al, A Phase 2 study of Chronocort, a modified-release formulation of hydrocortisone, in the treatment of adults with classic congenital adrenal hyperplasia. *The Journal of Clinical Endocrinology & Metabolism,* **2015**, 100(3), 1137-1145.

Chronocort – Pipeline

	Indication	Pre-	PI	PII	PIII	Estimated Approval	Annual Addressable Market (Europe & US)
Chronocort®	Congenital Adrenal Hyperplasia (CAH) (Adult)					2018 2021	$434m
	Adrenal Insufficiency (AI) – Addison's Disease (Adult)					TBC	$555m
	AI – Hypopituitarism (Adult)					TBC	$2,369m

Source: Diurnal

Infacort®

Infacort is a child-friendly form of hydrocortisone for immediate release

Infacort is an immediate release hydrocortisone preparation for the control of Adrenal Insufficiency (AI), including Congenital Adrenal Hyperplasia (CAH) in children and infants. In order to conform to local compliance requirements, Infacort is targeting:

- **Europe** – newborns and infants up to six years of age
- **US** – newborns, infants and children up to the age of sixteen

To date, there is no child-friendly hydrocortisone replacement product for the above age groups in either Europe or the US. Infacort would represent the first-in-class licenced product. The goal with Infacort is to deliver improved compliance, improved disease control and a reduced side effect profile.

Infacort can also potentially be used in elderly patients where dosing with other products might be an issue.

Presentation

Multi-layered, and multi-particulate formulation…

Infacort is also using the multi-particulate manufacturing technology with its multi-layered, multi-particulate formulation, but in this case with four essential components:

…in four dose levels

- **Core** – inert microcrystalline bead needed for manufacturing
- **Inner layer** – comprising the active ingredient: hydrocortisone
- **Second layer** – which acts as a seal
- **Outer layer** – corresponding to a taste masking coat

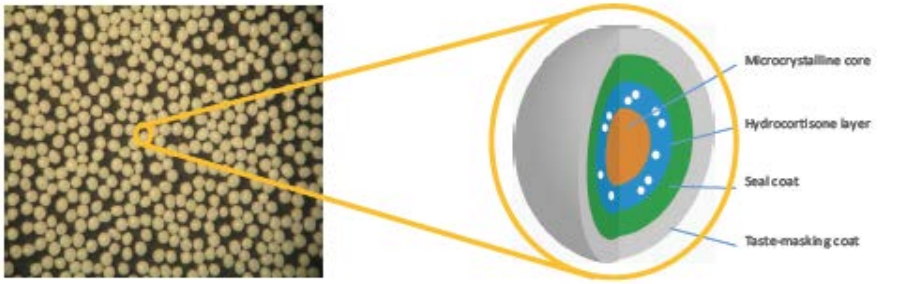
Infacort – four dose levels

Source: Diurnal:

Glatt has established a full scale-up process under GMP conditions which enables the manufacture of Infacort in 190kg batches.

Infacort will be available in capsules containing four different doses of multi-particulates – 0.5mg, 1mg, 2mg and 5mg – again providing endocrinologists with flexibility to individualise the dose according to a patient's needs, which is even more important when treating infants and babies. The capsules can be opened allowing the drug to be mixed/sprinkled with baby/infant food.

Infacort® presentation



Source: Diurnal

Advantages of Infacort

Accuracy in dosing

Infacort allows a high accuracy of dosing…

Current practice for paediatric use is for pharmacists to grind hydrocortisone tablets into a fine powder in order to titrate the dose according to a baby's/infant's weight. The aliquot of powder is then put into a capsule or sachet for administration/mixing with food. The potential for mistakes and weight inaccuracy is inherent with such techniques, leading to poor disease control. The availability of four different doses provides the maximum accuracy and flexibility.

Stability

…with a long shelf-life…

Stability studies on Infacort are in progress. The shelf-life already exceeds two years, which represents superiority over existing hydrocortisone products. Diurnal is still investigating the potential to extend the shelf-life further.

Child friendly preparation

…to aid compliance in children

A key characteristic of Infacort is for the presentation to have an additional taste-masking outer layer, which aims to minimise the bitter taste of hydrocortisone. This makes it very child-friendly for regular administration.

Clinical trial status

Clinical trials in newborns and children have strict ethical principles that Diurnal must follow in order to get market approval in Europe, US and worldwide. Children represent a special population with distinct development and physiological differences from adults. Specific ethical and clinical consideration must also be taken into account when designing, implementing and evaluating these clinical trials and their findings. Diurnal is targeting this population with Infacort in a Phase III clinical trial in Europe.

The EU Phase III trial in newborns and infants met the primary end-points

The European study started in March 2015 and enrolled a total of 24 patients under six years of age requiring replacement therapy for adrenal insufficiency, due to either CAH, primary adrenal failure, or hypopituitarism. It consists of three consecutive cohorts:

- **Cohort 1** – including 12 subjects aged between 2 and <6 years. If no safety concerns emerge, the study will enrol cohort 2
- **Cohort 2** – 6 subjects aged 28 days to <2 years will be enrolled. A review of accumulated data will be undertaken and, again, only if no safety concerns emerge then the study will enrol cohort 3
- **Cohort 3** – 6 newborns aged from birth to <28 days will be enrolled

The primary end-point is the measurement of serum cortisol concentration up to 240 minutes after drug intake. Secondary measures will be the serum concentration up to 6 hours after intake of drug and its palatability. Adverse events will also be recorded.

Infacort – Development timetable

[1] Regulatory programme agreed with FDA including a Phase III clinical trial
Source: Diurnal

Headline results

Infacort is very well tolerated compared to the current standard of care

Initial analysis of the results confirmed that the study met its primary end-point, demonstrating a statistically significant increase in cortisol levels following administration of Infacort compared to pre-dose values. No adverse events were reported. A full evaluation of the data has been performed and shows that a staggering 95% of parents and carers prefer Infacort to current treatment

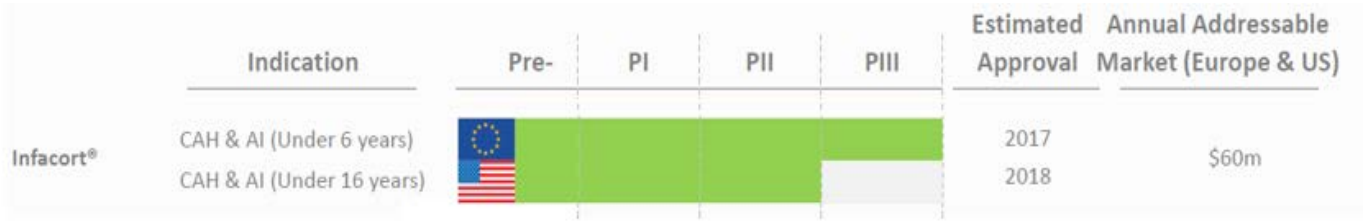
EU approval expected late 2017

Diurnal is planning to file Infacort for European marketing authorisation with the expectation of receiving approval in late 2017.

Expected Phase III in the US

Also, Diurnal is in dialogue with the FDA concerning the design of a US trial. This will require a different design to the European trial as Infacort will be targeted at newborns, infants, and children up to the age of sixteen years of age. However, as part of the FDA review process, it is expected that they will take into consideration the results from the European trial.

Infacort – Pipeline timelines



Source: Diurnal

Manufacturing – Glatt GmbH

Chronocort and Infacort are manufactured by Glatt, a well-known manufacturing company…

In 2012, Diurnal negotiated a development agreement with Glatt, an experienced specialist GMP manufacturing company, based in Germany but with operations across the world. Glatt has four areas of expertise, one of which is Pharmaceutical Services. This division develops and produces solid pharmaceutical dosage formulations based on multi-particulate systems such as pellets, micro-pellets and granules in modern facilities that have been approved by both the FDA and the EMA.

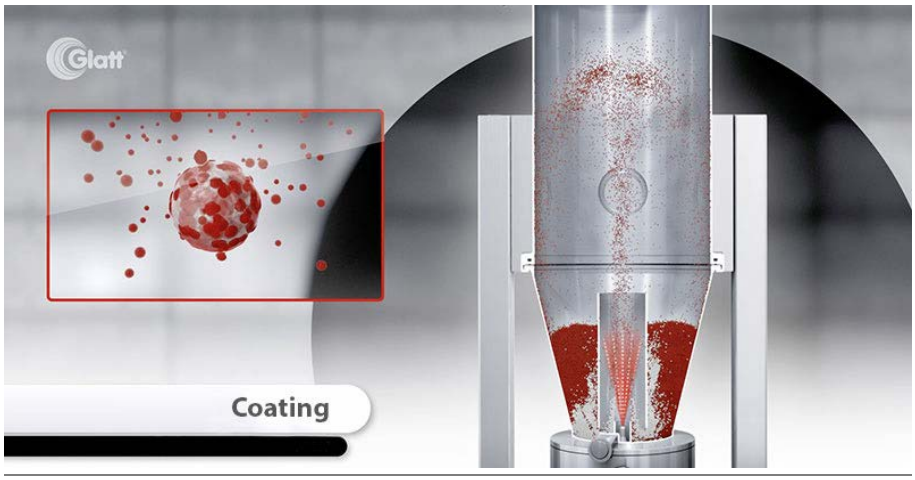
Glatt micro-granule formulation services

Source: Glatt

… with a lot of experience in multi-layered products.

Glatt has over 60 years of experience in the fundamental development of products based on a variety of dosage forms to which it applies innovative technology. One of its specialist areas is in solid dosage forms and includes customised release profiles, enhanced bioavailability and taste masking, which are all applicable to either/both of Diurnal's products. Glatt utilises a fluidised technique to produce the multi-layered micro particles that are fundamental to the construction of both Chronocort and Infacort.

Glatt coating technology

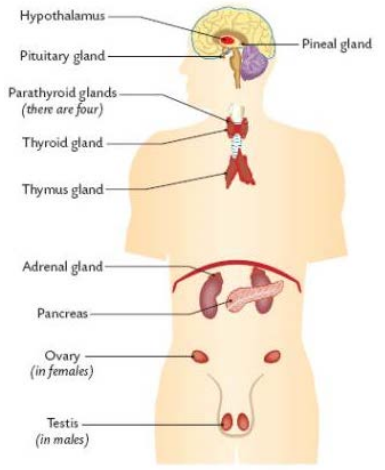


Source: Glatt

Glatt has already developed the scale-up process for commercialisation of both Chronocort and Infacort. Also, Diurnal and Glatt jointly filed a patent application with a priority date of 17 May 2013, in order to protect the formulation of Infacort, subsequently exclusively licenced to Diurnal.

The endocrine system

Major endocrine glands



Source: www.leavingbio.net

The endocrine system describes the collection of glands that produce hormones directly in the circulatory system. It controls the way the body functions and helps to maintain a fine balance in tissues and organs. Secreted hormones are chemical messengers, delivering their messages to specific and distant organs and tissues. The endocrine system produces, stores and releases hormones in response to the body's needs. The glands of the endocrine system are controlled in three ways:

- Directly by stimulation from the nervous system
- Chemical receptors in the blood
- Hormones produced by other glands

By regulating the normal functioning of organs, these glands help to maintain the body's homeostasis and are essential for life.

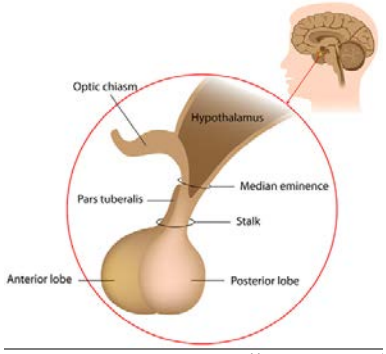
Major endocrine glands

Glands are located throughout the human body and control a host of important functions including cell metabolism, reproduction, response to stress, bone and muscle strength, heart rate, digestion, mood, and energy levels.

Major endocrine glands	
Hypothalamus	Thymus
Pituitary	Adrenal
Pineal	Pancreas
Thyroid	Gonads (Ovary; Testis)

Source: Hardman & Co Life Sciences Research

Pituitary gland



Source: http://cushieblog.com/

The pituitary gland

The pituitary gland (also called hypophysis) is located in the base of the skull, underneath the brain and behind the bridge of the nose. Despite its small size, approximately the size of a pea, the pituitary gland plays a major role in regulating vital body functions and general well-being. It consists of two distinctive parts:

Anterior lobe

The anterior lobe of the pituitary gland is regulated by the hypothalamus and produces the following hormones:

- **Growth hormone** – Stimulates growth of bone and tissue
- **Thyroid-stimulating hormone (TSH)** – Stimulates the thyroid to produce thyroid hormones (a lack of TSH thyroid hormones caused by a defect in the pituitary or the thyroid itself is called hypothyroidism)
- **Adrenocorticotropin hormone (ACTH)** – Stimulates the adrenal gland to produce several related steroid hormones (a lack of ACTH either because of a defect in the pituitary or the thyroid itself is called hypoadrenalism)
- **Luteinizing hormone (LH) & follicle-stimulating hormone (FSH)** – Hormones that control sexual function and production of sex steroids
- **Prolactin** – Hormone that stimulates milk production in females
- **Endorphins** – Produced in response to pain and vigorous effort

Posterior lobe

The posterior lobe is an extension of the hypothalamus. It is responsible for the release of the following two hormones, which are produced by the hypothalamus and carried to the pituitary gland through nerves:

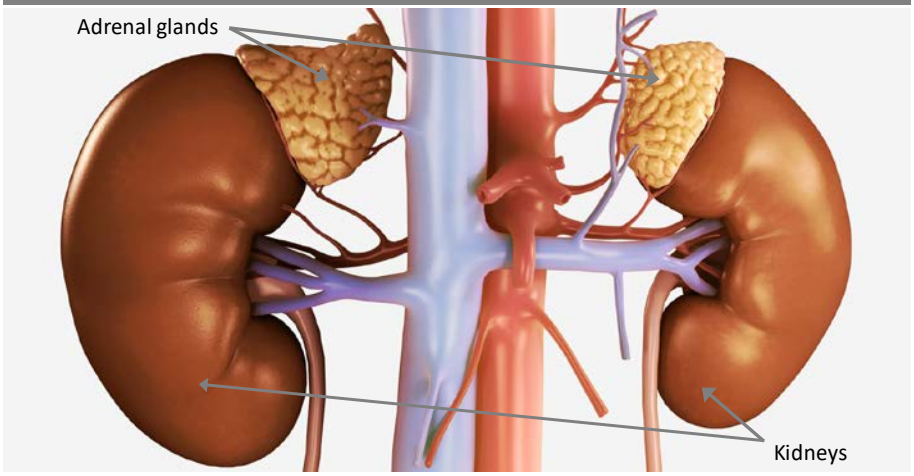
- **Anti-diuretic hormone (vasopressin)** – Controls water loss by the kidneys
- **Oxytocin** – Contracts the uterus during childbirth; stimulates milk production

The adrenal glands

Cortisol is a hormone secreted by the adrenal glands…

The adrenal glands, also known as the suprarenal glands, are a pair of walnut-sized organs situated above the kidneys. They are characterised by one of the greatest blood supply rates per gram of tissue of any organ in the body, helped by a high number of small arteries.

Architecture of the adrenal glands



Source:www.netdoctor.co.uk

… that are regulated by the pituitary gland

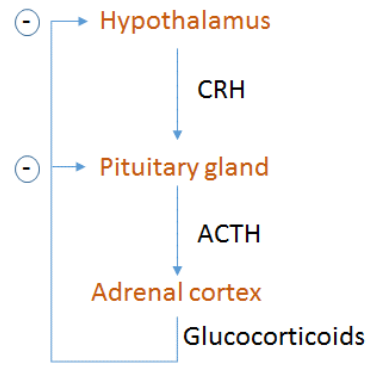
The adrenal glands are regulated by the pituitary gland and adrenocorticotropic hormone (ACTH). They are composed of a cortex (outer part) and a medulla (inner part) that possess distinct functions and produce a number of hormones.

Adrenal cortex

The role of the outer part of the adrenal gland is to produce two main groups of corticoid hormones: glucocorticoids and mineralocorticoids.

- **Glucocorticoids** – hormones, including cortisol, whose secretion is controlled by the hypothalamus-pituitary-adrenal (HPA) axis. The hypothalamus produces corticotrophin-releasing hormone (CRH), which stimulates the pituitary gland to release adrenal corticotrophin hormone (ACTH). This, in turn, triggers the adrenal glands to produce corticosteroid hormones, which also have a negative feedback to both the hypothalamus and the pituitary glands
- **Mineralocorticoids** – these are mediated by signals triggered by the kidney. The main hormone called aldosterone is important in the regulation of salt balance and blood volume, which in turns influences blood pressure.

Glucocorticoid regulation

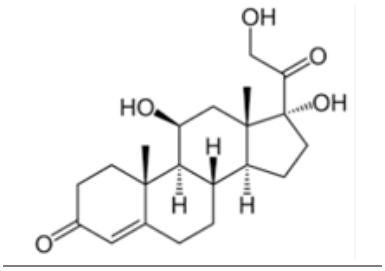


Source: Hardman & Co Life Sciences Research

Adrenal medulla

The role of the inner part of the adrenal gland is to synthesis the hormone adrenaline, a stress hormone, which controls heart rate and blood flow in the muscles.

Cortisol



Source: Hardman & Co Life Sciences Research

Cortisol

Cortisol is a steroid hormone which is a life sustaining adrenal hormone essential for the maintenance of homeostasis and a multitude of other functions, including:

- **Metabolic response** – Regulation of how the body converts fats, proteins and carbohydrate to energy by stimulation of glycogenesis (formation of glucose)
- **Immune response** – Weakens the activity of the immune system by preventing the release of substances that cause inflammation
- **Electrolyte balance** – Acts as a diuretic by increasing the glomerular filtration rate as well as plasma flow from the kidneys, thereby increasing sodium retention and potassium excretion
- Bone formation
- Regulates blood pressure
- Central nervous system activation

The level of cortisol in the plasma has many effects

Cortisol has a short half-life, being cleared from the plasma in about 66 minutes. When it is used as a medication it is known as hydrocortisone.

Effect of circulating cortisol levels

High level of cortisol	Low level of cortisol
Impaired cognitive performance	Low blood pressure
Blood sugar imbalance – hyperglycaemia	Blood sugar imbalance – hypoglycaemia
Decreased bone density – osteoporosis	Fatigue
Lowered immune function	Inflammation
Elevated blood pressure – hypertension	Mild depression
Sleep disturbance	Sleep disturbance
Reduced thyroid function	Low thyroid function
Cushing's syndrome	
Decreased muscle mass	
Increased abdominal fat – weight gain	

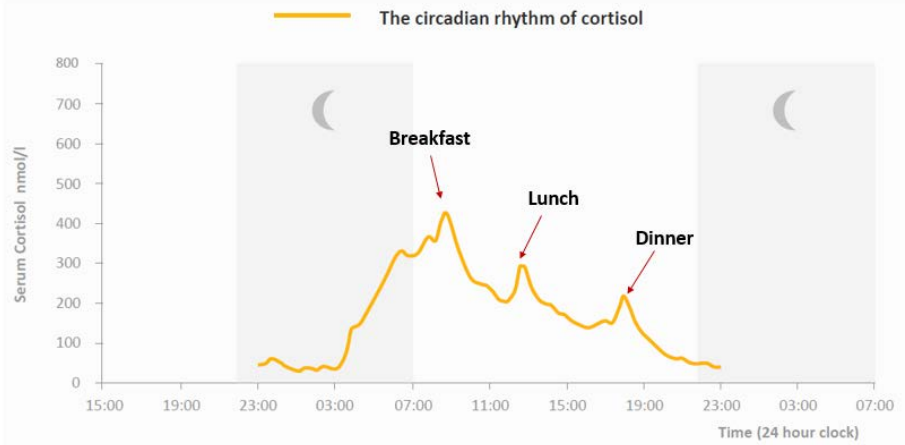
Source: adrenalfatigue.org

The circadian rhythm of cortisol

Cortisol has a naturally circadian rhythm that fluctuates during the day

One of the main characteristics of cortisol is its circadian rhythm – there is a natural daily fluctuation in blood levels, with the same pattern occurring every day. The following serum cortisol data were collected from a healthy individual.

Circadian rhythm of cortisol



Source: Diurnal, Hardman & Co Life Sciences Research

- Cortisol serum levels build up through the night to reach their highest level early in the morning, helping us to have the energy to start the day
- The level of cortisol continues to decrease for the rest of the day apart from small spikes around meals time

The level of cortisol is regulated by the suprachiasmatic nucleus located in the hypothalamus through the release of CRH which, in turn, stimulates the pituitary gland that ultimately stimulates the adrenal gland to produce cortisol.

Absence of cortisol is life threatening

Adrenal insufficiency is a life threatening condition and patients need life-long intake of hydrocortisone

Patients who are deficient in cortisol are known to suffer from adrenal insufficiency (AI), which is a life threatening condition. Patients will die if this defect is not diagnosed and treated effectively. Also, it could be a life-long condition and affected patients will need constant cortisol replacement medication throughout their lives.

The thyroid gland

The thyroid is a butterfly-shaped gland, about 50mm in length, located in the front of the neck below the larynx. It has two lobes, one on each side of the windpipe. This gland makes two thyroid hormones, tri-iodothyronine (T3) and thyroxine (T4). T3 is made from T4 and is the more active, directly affecting the tissues. Thyroid hormones influence the following functions:

Functions controlled by thyroid hormones	
Metabolism	Muscle strength
Growth	Heart and nervous system functions
Brain development	Weight
Breathing/respiration	Menstrual cycle
Body temperature	Fertility

Source: Hardman & Co Life Sciences Research

Thyroid hormone production is regulated by thyroid-stimulating hormone (TSH), which is made by the pituitary gland. When thyroid hormone levels in the blood are low, the pituitary releases more TSH; and vice versa.

The gonads

Longer-term, Diurnal is also interested in products for controlling circulating sex hormones

These reproductive organs produce the male and female gametes, and also the steroid sex hormones needed for growth and development of primary and secondary reproductive organs and structures.

Ovary

The ovary gland produces and secretes five different hormones, but principally:

- **Oestrogens** – a group of sex hormones important for reproduction and development of female sex characteristics
- **Progesterone** – prepares the uterus for conception, involved in ovulation, and stimulates gland development for milk production during pregnancy

The gonads are regulated by gonadotropins – LH and FSH

Testis

Testes are responsible for the development of the male reproductive system, with the main androgen hormone being testosterone:

- **Testosterone** – important for the development of male sex organs and sex characteristics. Also responsible for muscle increase and bone mass.

Targeting the adrenal gland

The main goal of Diurnal is to develop a valuable life-long 'Adrenal Franchise' that can treat patients with cortisol deficiency by targeting chronic adrenal conditions.

Adrenal insufficiency (AI)

Adrenal insufficiency is a condition in which the adrenal glands do not produce a sufficient level of steroid hormones, primarily cortisol, but also aldosterone. The condition was first identified by Dr Thomas Addison in 1849, and can be split into the following two situations:

- **Primary adrenal insufficiency** – direct impairment of the adrenal glands
- **Secondary adrenal insufficiency** – an impairment of the pituitary gland or the hypothalamus having an indirect effect on the adrenal gland

Primary adrenal insufficiency

Adrenal Insufficiency originates from the adrenal glands themselves…

This condition, also called Addison's disease, is caused by a dysfunction of the adrenal glands themselves, which is the result of three possible situations:

- **Immune disorder** (autoimmune adrenalitis) – occurs in 70-80% of cases, where the immune system attacks the adrenal cortex, slowly destroying the tissue and depleting its ability to produce cortisol
- **Tuberculosis** – causative in 10%-20% of cases, and impairs normal functioning of the adrenal glands
- **Other –** infections (mainly fungal), cancer, amyloidosis, medication, bleeding into the adrenal gland or surgical removal of the adrenal glands

In some very rare cases, primary adrenal insufficiency is derived from a genetic disease, when the glands have not formed adequately during development, or genetic mutation.

Secondary adrenal insufficiency

… or upstream…

This condition is not due to a dysfunction of the adrenal glands themselves but to a lack of ACTH, the hormone produced by the pituitary gland that controls the adrenal gland. This impairment may be due to the pituitary gland itself or the hypothalamus, which controls the pituitary gland through the secretion of CRH. The consequence of this indirect mechanism is to influence the release of cortisol.

Hypopituitarism

… with the dysfunction of the pituitary gland

Hypopituitarism is where the pituitary gland is unable to provide sufficient hormones, due to an inability of gland to produce hormones, or due to an insufficient supply of hypothalamic-releasing hormones. Symptoms will depend on the degree of hormone depletion. The most common causes are:

- **Tumours** – mainly due to pituitary adenomas
- **Infections** – meningitis, encephalitis, tuberculosis, syphilis
- **Vascular** – mainly in pregnant women
- **Physical causes** – including brain injury

Temporary adrenal insufficiency

This occurs when the body's natural production and release of cortisol has been down-regulated for a period of time, for example when a person has been treated with corticosteroids. The body naturally adjusts to these synthetic glucocorticoids, which are commonly used to treat inflammatory conditions, by reducing the release of cortisol. On stopping the medication, the body takes times to readjust, causing a temporary shortage of cortisol. This situation is quite common in transplant patients when they start to lower corticosteroid intake about one year after the organ is transplanted.

Surgery

Another cause of hypopituitarism, and hence secondary AI, is the surgical removal of the pituitary gland due to a tumour, the cause of Cushing's syndrome. Cushing's syndrome is characterised by high levels of ACTH, which results in the release of high levels of cortisol production and release from the adrenals. Surgical removal of the tumour results in a sudden loss of ACTH and a consequent reduction in cortisol.

Adrenal crisis

Adrenal crisis is a life threatening event…

Adrenal crisis is a life-threatening condition if not treated promptly, that occurs when the body cannot produce sufficient cortisol in response to stress and illness. An adrenal crisis requires urgent admission to hospital with immediate intravenous or intramuscular administration of high dose hydrocortisone, rehydration and monitoring. A recent survey[2] in 982 patients with Addison's disease found that 8% needed hospital treatment with injected hydrocortisone and/or intravenous fluids over a 12 month period, indicating that the condition is poorly managed.

…that is poorly managed

Symptoms of adrenal insufficiency crisis	
Malaise	Abdominal pain
Fatigue	Low-grade fever
Nausea & vomiting	Muscle pain & cramp
Dehydration	Hypotension

Source: Textbook of Medicine

Current treatment

Current treatment does not meet the needs of patients

Corticosteroids are used to replace the missing or low cortisol secretion in AI. First-line treatment is a daily intake of immediate release hydrocortisone in a dosage regimen designed to mimic the physiological concentration of cortisol. However, given its short half-life, this is not ideal.

Current treatments (for 30 days)

Product	Company	Natural	Synthetic	Comments	Price/month
Hydrocortisone 30mg	Small/generic companies	✓		Requires multiple daily doses Varying formulations	£190
Prednisolone 5mg	Small/generic companies		✓	Minority use	£12
Dexamethasone 5mg	Small/generic companies		✓	Higher incidence of long term consequences Once daily	£157
Plenadren 20mg	Shire	✓		Modified release of hydrocortisone Once daily	£385

Prices for Plenadren and hydrocortisone are based on 25mg daily dose

Source: British National Formulary (Sept. 2015 – Mar. 2016), Hardman & Co Life Sciences Research

[2] White K. and Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. *Eur J Endocrinol*. **2010**, 162(1), 115-120.

Longer-acting prednisolone or dexamethasone are sometimes used in an attempt to improve patient convenience but, unlike hydrocortisone, they have no mineralocorticoid activity.

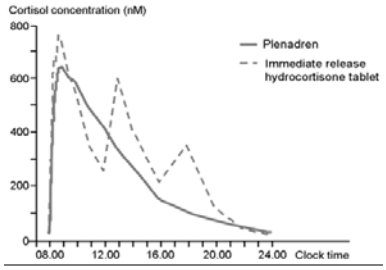
Plenadren

Plenadren (previously DuoCort; Shire) is a once-daily formulation of hydrocortisone designed to be taken in the morning and to provide a therapeutic level of cortisol throughout the day. Plenadren is prescribed for Adrenal Insufficiency patients and not Congenital Adrenal Hyperplasia. Plenadren has two components:

- **Outer layer** – providing an immediate release of hydrocortisone
- **Inner core** – releases hydrocortisone at a slow continuous rate

The graphic on the left compares the plasma cortisol concentration over the course of a day following administration of Plenadren, with that derived from three times daily dosing with immediate release hydrocortisone. Plenadren is able to mimic the day time cortisol. However, it does not match the night time build-up in preparation for the energy requirement needed at the start of the day.

Plenadren



Source: www.medecines.org.uk:

The immediate and slow release of hydrocortisone of Plenadren is not matching the natural level of cortisol

Congenital Adrenal Hyperplasia (CAH)

CAH is a genetic condition that causes enlargement (hyperplasia) of the adrenal gland. It is associated with a decrease in circulating cortisol levels and an increase in the level of male sex hormones in both sexes.

Signs and symptoms of CAH

Congenital Adrenal Hyperplasia is a genetic condition associated with a low level of cortisol secretion…

CAH is an inherited disorder present at birth and occurs in 1:10,000 to 1:18,000 births making it one of the most common endocrine genetic disorders. It occurs equally between boys and girls. In the most common form of CAH, the body is missing an enzyme (21-hydroxylase) that stimulates the adrenal glands to synthesise and release cortisol. Malfunction in the biosynthesis of cortisol causes low levels in the bloodstream, resulting in hormone imbalance. A consequence of the hormonal imbalance is an excess of androgen resulting in an increase of testosterone, bringing early virilisation. Boys will have an enlarged penis, small testicles, early puberty and a deep voice. Girls will have ambiguous genitalia, abnormal or absent periods, a deep voice, early puberty and facial hair. Both boys and girls may appear tall for their age but usually end up being short as adults.

Treatment of CAH

… that affects children

Children with CAH are usually cared for in specialist hospitals by a multidisciplinary team including endocrinologists (hormone specialists) and urologists (genitourinary system specialists). Initially, they will need to be stabilised with intravenous fluids to restore their electrolyte levels. Once stable, cortisol and/or aldosterone replacement therapy will be given with repeated blood tests to monitor hormone levels so the most effective dose can be titrated. Finding the best dose of hydrocortisone that effectively lowers androgens without causing undesirable corticosteroid side effects, such as weight gain and slow growth rate in children, is often difficult to achieve.

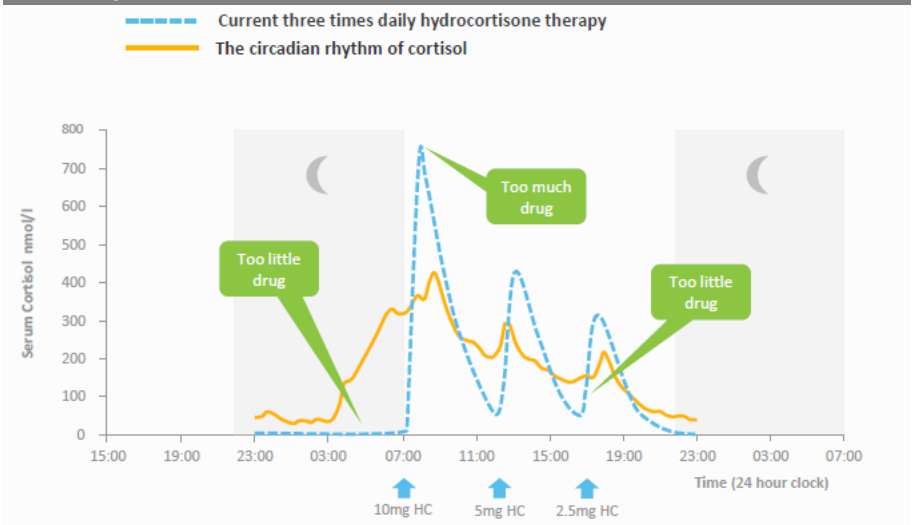
Once stable, children with CAH will need to take replacement cortisol and aldosterone every day for the rest of their lives. If a person with cortisol deficiency becomes very stressed or unwell, either emotionally or physically, they are unable to increase the production of cortisol in their system to help the body cope and this could be life threatening.

Current treatment with hydrocortisone

The current treatment is the use of hydrocortisol…

Stable patients with CAH are usually prescribed hydrocortisone three time a day. Doses are given in a decreasing manner in an attempt to mimic the circadian rhythm of cortisol, which is illustrated in the following graphic.

Serum hydrocortisone levels



Source: Diurnal

… with a poor matching of the natural cortisol level…

- 10 mg of hydrocortisone taken early in the morning is rapidly absorbed to produce an acute peak, corresponding to twice the normal level of cortisol. Due to its short half-life, the concentration decreases sharply below normal levels of cortisol by mid-morning
- 5 mg is given before lunch to mimic the lunchtime spike, which again rapidly decreases by mid-afternoon
- 2.5 mg at dinner time
- Critically, during the night, no cortisol is present in the blood system when harmful androgens build up

Earlier in this note (page 17), we presented the importance of circulating cortisol concentration, where excessively high or low levels present serious health issues. This, together with patient compliance issues, lends itself to poor disease control with the current standard of care.

… with a yoyo movement of hydrocortisone in the serum

The graphic highlights the "yo-yo" movement of hydrocortisone in the serum with current treatment that is not following the circadian rhythm of cortisol. Consequently, the dose and duration of long-term steroid use required to suppress ACTH is well above the normal physiological level of cortisol and results in bone loss, growth impairment, and Cushing's syndrome as common and serious side effects.

Commercial opportunity

Adrenal market

The adrenal market affect adults and children

There are number of reliable databases available with statistics for the prevalence of rare diseases in Europe and the US, which are the target markets for Diurnal. For both paediatric and adult CAH, the numbers consistently average at 1:10,000 of the population. The prevalence of Addison's disease appears to be slightly higher at 1:8,000 of the population.

Prevalence of adrenal disease

	Europe	United States
Paediatric CAH	1:5,000 – 1,15,000[a]	1:10,000[d]
Adult CAH	1:5,000 – 1:15,000[b]	1:10,000 – 1:15,000[e]
Addison's disease	1:7,000 – 1:9,000[b]	40-60/1 million population[e]
Hypopituitarism	45.5/100,000 population[c]	-

[a]NHS; [b]Orphanet; [c]Regal et.al; [d]NIH; [e]NORD
Source: Hardman & Co Life Sciences Research

The prevalence data has then been applied to reliable 2015 population statistics for the major European markets (Eurostat data) and the US (census bureau). Population statistics for children were taken from Eurostat (ages 0-12 years for Europe) and Childstats.gov (0-18 years for the US). This data has been used to calculate the target markets.

Equivalent patient number – From mean prevalence statistics

	Europe	US	Total
Paediatric CAH	4,200	[f]7,400	11,600
Adult CAH	42,000	27,500	69,500
Addison's disease	52,500	16,000	68,500
Hypopituitarism	191,000	[g]<200,000	391,000
Target population	**289,700**	**250,900**	**541,600**

[f]childstats.gov; [g]medscape.com
Source: Hardman & Co Life Sciences Research

Addressable market

Plenadren is used as a benchmark product

Diurnal has indicated that it intends to price Chronocort and Infacort close to the current prices that Shire charges for Planadren. The daily dose of hydrocortisone is usually 20 – 30 mg per patient per day. Therefore, an average daily dose of 25mg has been used in our assumptions – £12.85 per day in UK[3], €14.91 in Europe (assuming same price as in UK), and $18.60 per day in the US. We are aware that Plenadren is not approved in the US, but the drug is available in Canada through the NorthWestPharmacy[4] with a price of CA$1,224 (50 tablets, US$: 930.24) for 25mg, and it is the price we use to assess the US market.

The addressable market is worth $3.5bn

While this would be considerably higher than the price that immediate release hydrocortisone is available for, the argument that cortisol levels would be much more tightly controlled in potentially life threatening conditions should be accepted. On this basis the various addressable markets are shown in the following table. Taken together, the overall target adrenal markets being targeted by Chronocort and Infacort would be just under $3.5bn.

[3] British National Formulary (BNF) Sept 2015- March 2016
[4] NorthWestPharmacy.com

Addressable markets			
$m (EU/USD = 1.12)	Europe	US	Total
Annual price of drug (25mg)	$6,100	$6,800	
Paediatric CAH	25.6	50.3	75.9
Adult CAH	256.2	187.0	443.2
Addison's disease	321.9	108.8	430.7
Hypopituitarism	1,165.1	1,360.0	2,525.1
Target population	**1,768.8**	**1,706.1**	**3,474.9**

Source: Hardman & Co Life Sciences Research

Commercial exclusivity

Since the pharmaceutical industry in general has little interest, under normal market conditions, in developing and marketing medicines intended for small numbers of patients, the Europe and the US offer a range of incentives to encourage the development of these medicines, under specific conditions.

Orphan Drug designation

Chronocort and Infacort have been granted Orphan Drug status…

Regulation 141/2000 states that a drug shall be designated as an Orphan Drug if its sponsor can establish:

- that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in EU or fewer than 200,000 in US when the application is made; or
- that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in EU and US, and that without incentives it is unlikely that the marketing of the drug would generate sufficient return to justify the necessary investment; and
- that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in EU and US, if such method exists, the drug will be of significant benefit to those affected by that condition.

Chronocort

… with Chronocort already designated in US and EU for CAH and AI…

Chronocort has Orphan Drug designation in Europe (2004) and the US (2015) for CAH; and in both Europe (2007) and the US (2015) for AI. Successful completion of clinical trials could be followed by a 'fast track' approval process. This will provide Diurnal marketing exclusivity for 10 years in Europe and seven years in the US with effect from the grant of marketing authorisations by the respective regulatory bodies.

Orphan drug designation exclusivity		
	Europe	US
Patient populations	Less than 5 in 10,000 (1 in 2,000)	Less than 200,000 (1 in 1,500)
Market exclusivity	10 years from approval	7 years from approval
Reduced R&D cost	Assistance with development of the medicine	50% tax credit in clinical trials conducted in the US
	Reduced fees for marketing-authorisation applications	R&D grants for Phase I to Phase III clinical trials
		User fees waived
Regulatory process	Fast track procedure	Fast track procedures

Source: Hardman & Co Life Sciences Research

… and Infacort in US for AI

Infacort

Infacort was granted Orphan Drug designation for paediatric AI in the US (2015), which, again, is expected to provide commercial exclusivity effective from its market authorisation. Given the development programmes and regulatory process, we believe that Infacort will be Diurnal's first product to reach the market.

Paediatric Use of Marketing Authorisation (PUMA)

PUMA is a commercial European scheme targeting the paediatric sector…

PUMA is a type of marketing authorisation covering indications and appropriate formulations for the paediatric population. The development of a PUMA corresponds to a fast route to approval. It must follow a Paediatric Investigation Plan (PIP) agreed up-front with the paediatric committee of the European Medicines Agency.

- Already authorised
- No longer covered by a supplementary protection certificate or a patent
- Exclusively developed for use in children

Diurnal has a PIP in place in respect of Infacort. The PIP covers the paediatric population from newborns through to infants and children up to six years of age. A successful PUMA application for Infacort will provide Diurnal with clear marketing advantages.

… giving 8 years of data exclusivity and 10 years of market exclusivity

- Eight years of data exclusivity
- Ten years of market exclusivity

An application for a PUMA must contain the results of studies performed, and information collected, in compliance with the agreed PIP. Therefore, if the relevant studies are not conducted in accordance with the agreed PIP, a PUMA is unlikely to be obtained. Management intends to secure exclusivity for Infacort in Europe by applying for a PUMA immediately following receipt of regulatory approval.

Diurnal – Commercial exclusivity

Europe	United States	Rest of world
		
✓ Orphan designation granted for CAH & AI (adult) ✓ 10 year exclusivity[1] ✓ Chronocort® UK patent to 2033 – EP patents pending ✓ Infacort® UK patent to 2032 / 2034 – EP patents pending	✓ Orphan designation granted for AI (paediatric and adult) and CAH (adult) ✓ 7 year exclusivity[2] ✓ Chronocort® – US patent pending ✓ Infacort® – US patents pending	✓ Orphan designation applications planned ✓ Chronocort® and Infacort® patents pending

[1]Conditional and subject to grant of market authorisation and PUMA (in EU for Infacort)
[2]Conditional and subject to grant of market authorisation
Source: Diurnal)

Competitive landscape

Low competition for Chronocort and Infacort

Diurnal will be entering a market with Infacort and Chronocort in CAH and AI, where competition is low. There will be two main competitors: Immediate release hydrocortisone (and synthetic corticosteroids), due to established position and low cost; and Plenadren as an advanced modified release formulation of hydrocortisone.

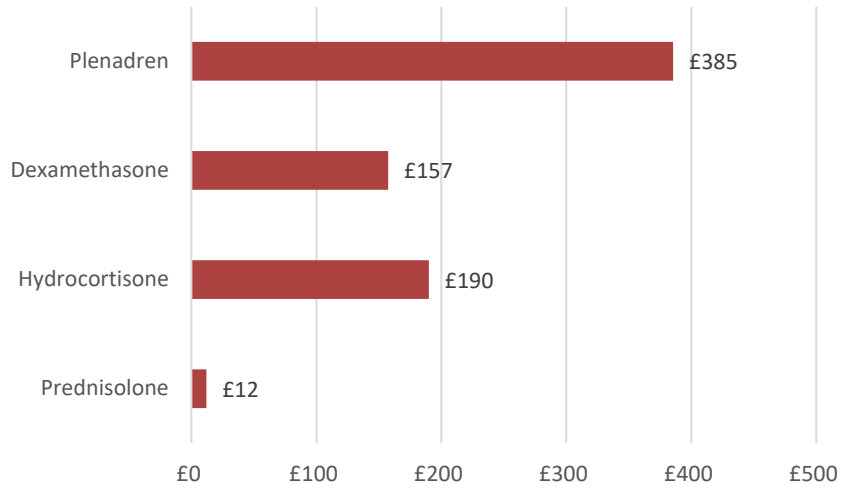
Competitive landscape

Product	Mimics circadian rhythm	Indication			Countries	Price
		AI/CAH paediatric[1]	CAH	AI		
Hydrocortisone	✗	✓ Unlicensed when compounded	✓	✓	EU, US	ca. $2.6k p.a.
Plenadren® (modified release)	✗	✗	✗	✓	EU	ca. $7.0k p.a.
Diurnal "Adrenal Franchise"	✓ Chronocort®	Planned ✓ Infacort®	Planned ✓ Chronocort®	Planned ✓ Chronocort®	Planned EU, US	Targeting $7k+ p.a.

Source: Diurnal

However, neither of these products has the same ability as Chronocort to mimic the circadian rhythm of cortisol. Proof of improved disease control in clinical trials would provide Diurnal with a significant marketing edge over these rivals.

Cost comparison (for 30 days treatment)



Prices for Plenadren and hydrocortisone are based on 25mg daily dose
Source: British National Formulary

Neurocrine Biosciences

In June 2015, San Diego based drug development company, Neurocrine Biosciences, announced that it had suspended two planned clinical trials with NBI-77860 in CAH as a consequence of new pre-clinical findings.

NBI-77860 is a corticotrophin releasing factor (CRF) antagonist that had been demonstrated to have potent activity in a range of *in vitro* and *in vivo* assays. The aim was to block CRF receptors in the pituitary to reduce the release of ACTH, thereby reducing the production of adrenal steroids (cortisol and androgens).

From a safety perspective, Neurocrine halted commencement of its planned trials and notified the FDA. Subsequently, the company was notified by the FDA that the NBI-77860 clinical development programme had been placed on a 'partial clinical hold'. The company is now searching for a new lead candidate.

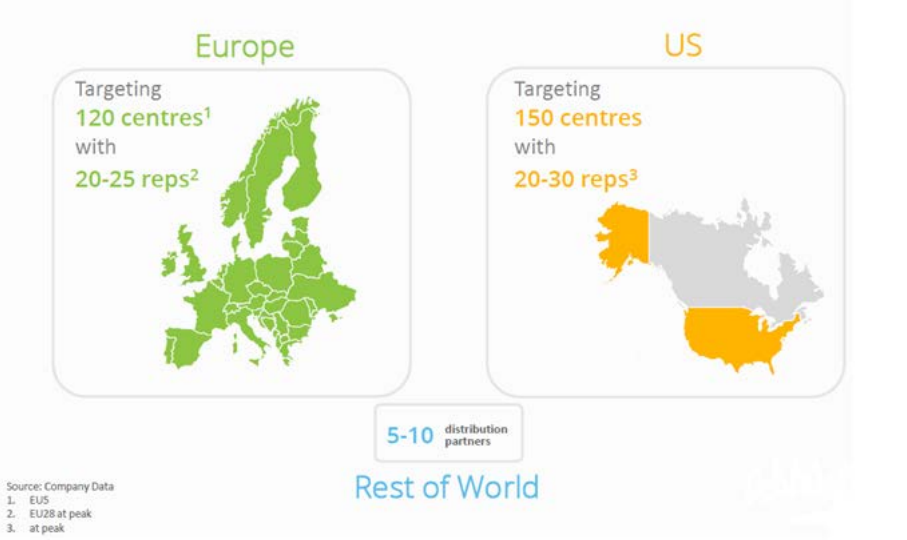
Commercial strategy

Diurnal is ready to lead the market with its 'Adrenal Franchise' for cortisol deficiency

Diurnal's goal is to create a valuable "Adrenal Franchise" that can treat patients with chronic cortisol deficiency diseases. It is anticipated that these products will allow the Group to establish a strong position in cortisol replacement, particularly in CAH and AI. The group then intends to expand the offering to cortisol excess in other disease areas such as Cushing's disease and to create a strong platform across a broader range of adrenal diseases.

Diurnal's marketing strategy is to target a network of prescribers practising in specialist endocrinology centres in Europe and the US (120 and 150 centres, respectively). As a consequence, the cost of sales and marketing is expected to be relatively modest.

Concentrated customer base

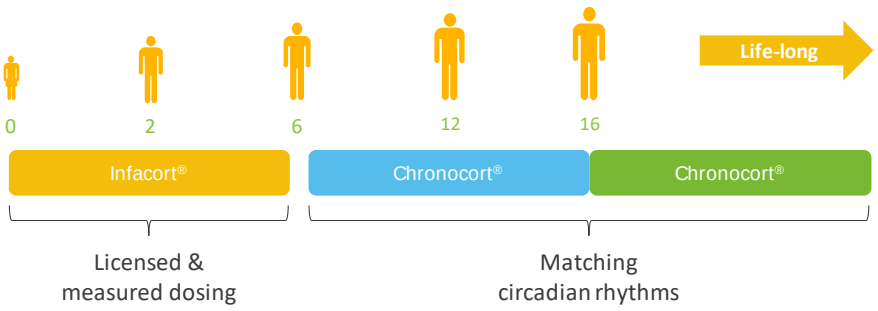


Source: Diurnal

European strategy

In Europe, the use of Infacort is intended for patients from birth to six years of age. At that point in time, the patient would then switch medication to Chronocort and remain on this for the rest of life, following endocrinologists' recommendations.

Building a life-long adrenal franchise



Note: The Company expects further clinical studies will be required for regulatory approval of Chronocort® in the age range 6 – 18 years in Europe

In the US the "Adrenal Franchise" will be Infacort® in the age range 0 – 16 years and Chronocort for 16 years old and above

Source: Diurnal

In US:

In US, the use of Infacort is intended to be used by patients from new born until they reach the age of sixteen. From that age, the medication would again be switched to Chronocort for the remainder of their life, on the recommendation of endocrinologists.

Other indications

Once approved, management will look at alternative indications to CAH and AI where replacement of cortisol is part of the treatment.

Financials & Investment case

On flotation, the company changed its accounting period from July to June. Diurnal is a virtual company with most of its activities being outsourced.

Profit & Loss

In the medium term, the P&L account will be driven by two numbers, the corporate overhead/administration costs and the investment in clinical trials.

- **SG&A** – The underlying corporate overhead is estimated to be about £2.5m p.a. In the run up to launch of Infacort in Europe, there will be investment in marketing infrastructure primarily through a small sales force
- **R&D** – Investment will rise sharply as a consequence of the Phase III trial programme for both Infacort and Chronocort in Europe and the US. Trial costs have been allocated evenly across the expected timelines
- **Tax credit** – Diurnal is accruing and receiving tax credits from the UK government in relation to its R&D spend

Profit & Loss account

Year end June (£m)	*2014	*2015	2016	2017E	2018E	2019E
Sales	0.00	0.00	0.00	0.00	1.04	3.43
COGS	0.00	0.00	0.00	0.00	-0.10	-0.34
SG&A	-0.99	-1.55	-1.99	-5.71	-7.43	-9.19
R&D	-0.93	-1.82	-3.89	-8.94	-9.03	-9.12
EBITDA	-0.93	-2.98	-5.87	-14.64	-15.52	-15.22
Depreciation & Amortis.	-0.01	-0.01	-0.01	-0.01	0.00	0.00
Licensing/Royalties	0.66	0.24	0.00	0.00	0.00	0.00
Underlying EBIT	**-0.94**	**-2.99**	**-5.88**	**-14.65**	**-15.52**	**-15.22**
Share based costs	0.00	0.00	-0.49	-0.51	-0.54	-0.57
Exceptional items	0.00	0.00	-0.62	-0.62	0.00	0.00
Statutory EBIT	**-0.94**	**-2.99**	**-6.99**	-15.16	-16.06	-15.79
Net financials	-0.04	-0.03	-0.07	-0.11	-0.20	-0.29
U/l Pre-tax profit	**-0.98**	**-3.02**	**-5.95**	**-14.76**	**-15.71**	**-15.51**
Reported pre-tax profit	-0.98	-3.02	-7.06	-15.27	-16.25	-16.08
Tax payable/credit	0.00	0.00	0.49	1.13	1.14	1.15
Tax rate	0%	0%	-7%	-7%	-7%	-7%
Underlying net income	**-0.88**	**-2.94**	**-5.46**	**-13.63**	**-14.57**	**-14.36**
Statutory net income	-0.98	-3.02	-6.57	-14.14	-15.11	-14.92
Ordinary shares:						
Period-end (m)	0.00	0.00	52.21	52.21	52.21	52.21
Weighted average (m)	23.76	34.61	43.75	52.21	52.21	52.21
Fully diluted (m)	0.00	23.76	34.61	43.75	52.21	52.21
Underlying Basic EPS (p)	**-3.7**	**-8.5**	**-12.5**	**-26.1**	**-27.9**	**-27.5**
Statutory Basic EPS (p)	-4.1	-8.7	-15.0	-27.1	-28.9	-28.6
U/l Fully-diluted EPS (p)	**-3.7**	**-8.5**	**-12.5**	**-26.1**	**-27.9**	**-27.5**
Stat. Fully-diluted EPS (p)	-4.1	-8.7	-15.0	-27.1	-28.9	-28.6
DPS (p)	0.0	0.0	0.0	0.0	0.0	0.0

**Year to July*

Source: Hardman & Co Life Sciences Research

Balance sheet

- **IPO** – Diurnal raised £30.0m gross proceeds at IPO through a combination of an institutional Placing of Ordinary shares (£24.5m net of expenses) and a Convertible loan note (£4.65m) with IP Group
- **Net cash** – At 30th June 2016, Diurnal had net cash of £26.9m on its balance sheet
- **Convertible loan** – The IP Group loan appears as a combination of capital and equity such that the total capital + interest (@8%) will equate to the gross original loan of £4.76m by the end of fiscal 2021

Balance sheet

at 31st July (£m)	*2014	*2015	2016	2017E	2018E	2019E
Shareholders' funds	5.52	28.64	25.93	11.79	-3.32	-18.24
Cumulated goodwill	0.00	0.00	0.00	0.00	0.00	0.00
Total equity	5.52	28.64	25.93	11.79	-3.32	-18.24
Share capital	0.44	15.35	2.61	2.61	2.61	2.61
Reserves	-0.76	-9.31	23.32	9.18	-5.93	-20.85
Provisions/liabilities	0.00	0.00	0.00	0.00	0.00	0.00
Deferred tax	0.00	0.00	0.00	0.00	0.00	0.00
Long-term loans	0.01	3.11	3.24	3.50	3.78	4.08
Short-term debt	0.02	0.02	0.00	0.00	0.00	0.00
less: Cash	0.95	6.07	16.11	2.80	2.92	-11.44
less: Deposits	-0.23	0.00	14.00	14.00	0.00	0.00
Invested capital	**0.02**	**-0.01**	**-0.94**	**-1.51**	**-2.46**	**-2.73**
Fixed assets	0.00	0.01	0.00	0.00	0.00	0.00
Intangible assets	0.01	0.01	0.01	0.01	0.01	0.01
Inventories	0.00	0.00	0.00	0.00	0.00	0.00
Trade debtors	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*
Other debtors	*0.12*	*0.38*	*0.53*	*0.39*	*0.39*	*0.39*
Tax credit/liability	*0.00*	*0.00*	*0.00*	*0.56*	*1.13*	*1.15*
Trade creditors	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*	*0.00*
Other creditors	*-0.11*	*-0.40*	*-1.48*	*-2.46*	*-3.99*	*-4.27*
Debtors less creditors	0.00	-0.02	-0.95	-1.51	-2.47	-2.73
Invested capital	**0.02**	**-0.01**	**-0.94**	**-1.51**	**-2.46**	**-2.73**
Net cash/(debt)	**-0.34**	**6.05**	**26.88**	**13.30**	**-0.86**	**-15.52**

**Year to July*

Source: Hardman & Co Life Sciences Research

Cashflow

- In the near-term, the cashflow is driven entirely by R&D and SG&A from the P&L account
- Any changes in working capital are simply the result of timing differences between receipt of invoices and payment
- Being a virtual company, there is minimal capital expenditure
- Based on our forecasts, the company has sufficient cash to take it, at least, through to the launch of its first products in Europe

Cashflow						
Year end June (£m)	***2014**	***2015**	**2016**	**2017E**	**2018E**	**2019E**
Trading profit	-1.33	-3.38	-5.88	-14.65	-15.52	-15.22
Depreciation/amort.	0.00	0.00	0.01	0.01	0.00	0.00
Inventories	0.00	0.00	0.00	0.00	0.00	0.00
Working capital	-0.04	0.02	0.95	0.61	0.14	-0.60
Other	0.00	0.00	-0.62	0.00	0.00	0.00
Company op. cashflow	**-0.98**	**-2.96**	**-5.55**	**-14.03**	**-15.38**	**-15.82**
Net interest	0.00	0.00	0.04	-0.11	0.08	0.01
Tax	0.10	0.08	0.49	0.56	1.13	1.15
Operational cashflow	-0.88	-2.88	-5.02	-13.57	-14.16	-14.66
Capital expenditure	0.00	-0.01	0.00	0.00	0.00	0.00
Free cashflow	**-0.88**	**-2.88**	**-5.02**	**-13.57**	**-14.16**	**-14.66**
Dividends	0.00	0.00	0.00	0.00	0.00	0.00
Acquisitions	0.00	0.00	0.00	0.00	0.00	0.00
Disposals	0.00	0.00	0.00	0.00	0.00	0.00
Cashflow after invest.	**-0.88**	**-2.88**	**-5.02**	**-13.57**	**-14.16**	**-14.66**
Share repurchases	0.00	0.00	0.00	0.00	0.00	0.00
Share issues	0.00	9.25	24.52	0.00	0.00	0.00
Change in net debt	**-0.88**	**6.37**	**20.83**	**-13.57**	**-14.16**	**-14.66**
Hardman FCF/share (p)	-3.7	-8.3	-11.5	-26.0	-27.1	-28.1
Opening net cash	0.49	-0.34	6.05	26.88	13.30	-0.86
Closing net cash	**-0.34**	**6.05**	**26.88**	**13.30**	**-0.86**	**-15.52**

**Year to July*

Source: Hardman & Co Life Sciences Research

Valuation

Discounted cashflow

The best approach to valuing biopharmaceutical companies is to prepare detailed discounted cashflow analyses of key products through to patent expiry, and then to risk-adjust the NPV based upon industry standards for the probability of the product reaching the market.

A tried and tested DCF model…

On the basis that Diurnal's strategy is to be a fully-integrated specialist pharmaceutical company, with its own sales force in key territories, a DCF has been prepared based on the following key assumptions:

…that is based on clearly stated assumptions…

- Infacort will develop market shares in EU and US of 27-30% five years' from first launch
- Chronocort will develop market shares in EU and US of 20-25% five years' from first launch for both CAH and AI

…and adjusted for the probability of products reaching the market based on industry standards

- Sales and cashflow forecasts are for the duration of the marketing exclusivity period in each territory after which generic versions could emerge, eliminating any terminal value – this approach may be considered conservative
- WACC is at the cost of equity – the way this type of company is funded – which is 10%
- The risk adjustment – probability of the product reaching the market – for Infacort is 80% and 60% in Europe and the US respectively; and for Chronocort is 60% for both territories. The weighted average is 66%
- No account has been taken of potential future products e.g. sex hormones

Diurnal – DCF valuation summary			
WACC	**NPV**	**Risk-adjusted NPV**	**Risk-adj NPV per share**
8%	£394m	£260m	498p
9%	£353m	£233m	446p
10%	**£316m**	**£208m**	**399p**
11%	£283m	£187m	358p
12%	£253m	£167m	320p

Source: Hardman & Co Life Sciences Research

The risk-adjusted NPV of Diurnal is £208m, or 399p per share…

…suggesting that there is plenty of upside potential for shareholders

Based on our clearly stated assumptions, the net present value of the cashflows that could be generated from Diurnal's first two products alone equate to £316m. Risk-adjustment to take account of their different stages of development in different territories reduced this to £208m, or 399p per share. This model allows a very fast assessment of the likely effect on the share price following the announcement of clinical results and also suggests that there is plenty of upside for shareholders.

Peer group valuation

There are many specialty pharmaceutical companies with a very diverse range of market capitalisations. For our comparative valuation analysis, a group of quoted specialty pharma companies that are working in the field of endocrinology – but not working in diabetes/insulin – have been selected, to provide a guide about the relative valuation of Diurnal. Most of these companies are also at a similar stage of development as Diurnal, although the high valuation of Corcept (CORT.OQ) is likely due to the fact that it has a product on the market generating sales. However, this also provides an indication of valuation uplift potential when Diurnal's products are launched.

- **Corcept** – Korlym (mifepristone) launched in 2012 for patients suffering Cushing's syndrome associated with hyperglycaemia. Looking to extend its use into prostate, ovarian and breast cancers, alcohol dependence and anxiety and stress disorders
- **Ascendis** – Trials with TransCon formulation technology to extend the release properties of growth hormone for use in hypoparathyroidism
- **Versartis** – Development of somavartan for growth hormone deficiency in both paediatrics (Phase III) and adults (Phase II)
- **Viking –** Developing therapeutics for patients suffering from metabolic and endocrine disorders –lead product VK5211 is in Phase II clinical trials

Peer group valuations					
Company	**Ascendis Pharmaceuticals**	**Corcept Therapeutics**	**Diurnal**	**Viking Therapeutics**	**Versartis**
Ticker	**ASND**	**CORT**	**DNL**	**VKTX**	**VSAR**
Local currency (lc)	$	$	£	$	$
Share price	19.0	7.1	135.0	1.0	12.2
Shares in issue (m)	31.5	110.6	52.2	19.3	34.3
Market cap (lc)	599.4	783.0	70.5	19.9	418.7
Mkt cap (£m)	731.0	954.9	70.5	24.2	510.6
Cash	119.6	41.8	30.1	5.2	197.5
Debt	-11.4	18.5	-3.2	-3.7	-8.4
EV (lc)	491.2	722.7	43.6	18.4	229.6
EV (£m)	**402.8**	**592.6**	**43.6**	**15.1**	**188.3**
Relative EV	9.2x	13.6x	-	0.3x	4.3x

Prices taken at close of business on 25th October 2016
Source: Hardman & Co Life Sciences Research

Company matters

Registration

Incorporated in the UK with company registration number: 05237326

UK Headquarters:

Diurnal Limited
Cardiff Medicentre
Heath Park
Cardiff, CF14 4UJ
UK

+44 871 716 8848
www.diurnal.co.uk

Board of Directors

The Board consists of three executive directors, the Chairman, and three non-executive directors. Their representation on the various committees is shown in the following table.

Board of Directors

Position	Name	Remuneration	Audit
Chairman	Peter Allen	M	M
Chief Executive Officer	Martin Whitaker		
Chief Financial Officer	Ian Ardill		
Chief Scientific Officer	Richard Ross		
Non-executive director	John Goddard	M	C
Non-executive director	Alan Raymond	C	M
Non-executive director	Sam Williams	M	M

M = member; C = chair
Source: Company reports

Peter Allen – Non-executive Chairman

Joined Diurnal in July 2015, Peter has a wealth of experience at board level in a wide portfolio of healthcare companies. Currently, non-executive Chairman of Advanced Medical Solutions plc, Future plc, Clinigen plc and Oxford Nanopore Technologies Ltd. Previously, Peter was Chairman and CEO of ProStrakan Group Plc, executing its take-over by Kyowa Hakko Kirin in 2011. Prior to this, he was CFO of Celltech Group plc (1992-2004), and was involved in the strategic acquisitions of Chiroscience Group plc, Medeva plc and Oxford Glycosciences plc. A qualified chartered accountant with a joint degree in Accountancy and Law.

Martin Whitaker – Chief Executive Officer

Joined the Group in January 2008, supporting Fusion IP's investment, and became CEO in 2014. Martin has 18 years' experience in the pharmaceutical industry. Previously, Martin worked for Fusion IP plc with responsibility for commercialising research from the Medical School at the University of Sheffield. Prior to this, Martin was Operations Director of Critical Pharmaceuticals Limited, a drug delivery company spun out of the University of Nottingham. Currently, also a director of D3 Pharma Limited. Trained as a biochemist at the University of Bristol and with a PhD in Pharmaceutical Science from the University of Nottingham.

Ian Ardill – Chief Financial Officer

Joined Diurnal in April 2015, bringing 20 years' experience in senior financial positions, having been CFO at Lombard Medical Technologies plc and Biocompatibles International plc. At Lombard Medical, he was actively involved in fund raising and its listing on NASDAQ. Ian was at Biocompatibles during its transformation from a loss-making to a profitable enterprise, prior to its sale to BTG Plc in 2011. Ian has also worked at Novartis Pharmaceuticals, Compass Group, NHA International and Grant Thornton. Ian is a qualified chartered accountant.

Richard Ross – Chief Scientific Officer

Founding director and Chief Scientific Officer, Richard is contracted to perform work for Diurnal by the Sheffield University pursuant to the terms of secondment and research agreements, where he is Professor of Clinical Endocrinology and Head of the Academic Unit of Diabetes, Endocrinology and Metabolism. Richard's primary research interest is pituitary and adrenal disease and has published over 200 papers and more than 30 granted patents. Richard has been on the editorial boards of Clinical Endocrinology and the Journal of Clinical Endocrinology and Metabolism, and served on the executive committees for the European Society of Endocrinology (Treasurer), the Society for Endocrinology and Growth Hormone Research Society.

John Goddard – Non-Executive Director

Joined Diurnal in November 2015 after a distinguished career in the global pharmaceutical industry, mostly at AstraZeneca, where he was ultimately Head of Group Strategic Planning and Business Development, responsible for M&A and licensing. Currently a non-executive director of Oxford Pharmascience plc and Intas Pharmaceuticals Limited. John is a Fellow of the Institute of Chartered Accountants and a Member of the Association of Corporate Treasurers.

Alan Raymond – Non-Executive Director

An industry veteran with 30 years' international marketing and general management experience. Alan was appointed to the board of Diurnal by Finance Wales in April 2015. Prior to this, he was the Sales and Marketing Director at Aesica Pharmaceuticals Ltd, now part of Consort Medical plc. During his career, Alan has held senior positions in Banner Pharmacaps, RP Scherer, Reckitt & Colman, Lilly, and Merck & Co. Alan holds a PhD in Invertebrate Neurobiology from St. Andrews and was a postdoctoral researcher at the Cardiothoracic Research Institute (London).

Sam Williams – Non-Executive Director

Sam Williams has 18 years' experience in the biotechnology industry, both as an investment banking analyst and, subsequently, as an entrepreneur and Chief Executive. After leaving Lehman Brothers in 2007, he established Modern Biosciences Ltd, an IP Group portfolio company focused on chronic, inflammatory diseases. He continues to oversee the biotechnology portfolio of IP Group. Currently also a board member of the UK BioIndustry Association (BIA) and C4X Discovery Holdings plc, and serves on the Translational Awards Advisory Committee of the British Heart Foundation (BHF). Sam has an MA in Pure and Applied Biology from Oxford University and a PhD from Cambridge University.

Senior management

Diurnal has a number of senior executives that support the Board, providing considerable industry expertise, covering manufacturing and quality control, marketing, R&D and business development.

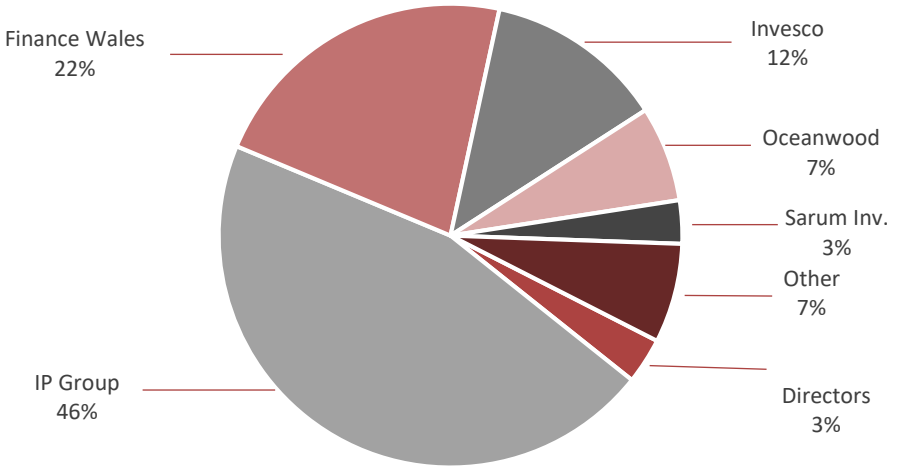
Senior management team	
Name	**Position**
Michael Withe	Commercial Director
Dr John Porter	Medical Affairs Director
Dr Madhu Davies	Medical Director
Dr Daniel Margetson	CMC Director
Linda Roitt	Head of Quality

Source: Company reports

Share capital

The company has 52,210,759 shares in issue.

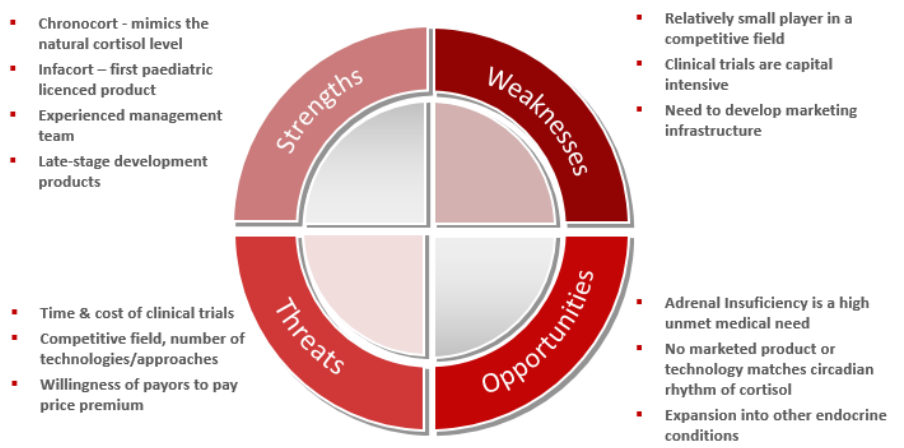
Major shareholders



Source: Company reports

SWOT analysis

SWOT analysis



Source: Hardman & Co Life Sciences Research

Risks

Background

It goes without saying that investments in small early stage companies carry a significant risk and investors must be aware of this fact. In our opinion, the following risks are particularly relevant. Each of them could have an impact on time to reach market, cash flow breakeven and profitability.

Dilution risk

The company has sufficient cash to fund the ongoing European Phase III clinical trial programme for Infacort and Chronocort, and to launch of its first product in Europe. Further capital will be required to repeat this programme for the US market. However, the company and products will be significantly de-risked by this point. There is no guarantee of either the size of any follow-on funding or the share price at which it will be done, raising the risk of dilution.

Commercialisation

The current strategy is to build commercial infrastructure capable of marketing the first two products to specialist endocrinologists in both the EU and the US. An up-front investment is required and there is no certainty that the proposed size of the sales team will be sufficient to visit the leading endocrinologists or the time that it will take to convert them to using new products. However, most clinicians are keen to improve patient outcomes therefore, the success of the commercial programme will be dependent on the quality of the clinical data.

Manufacturing and suppliers

The current strategy is to have all product supply out-sourced. Diurnal is working with a very experienced and globally respected pharmaceutical manufacturer.

Patent robustness

As with all therapeutic products, there is risk that the intellectual property is insufficiently covered by the global patents, allowing a competitor to gain market access. However, in the case of Diurnal, commercial protection is derived mostly from the marketing exclusivity periods associated with either PUMA or Orphan Drug designation in Europe and the US on its first two products for both indications.

Regulatory

As with all pharmaceutical and drug development companies, there is a regulatory risk. Protocols for clinical trials need to be approved. It is important for companies to liaise with regulators on a regular basis throughout the development programme. Protocols for clinical trials need to be planned carefully to ensure that, if the drug works, the results and statistical analysis will deliver the answer being sought. They also need to be approved by the regulators.

Share liquidity

As with many small cap companies listed on AIM, there can be difficulty in buying and shares in volume. Market makers only guarantee prices in a very small number of shares.

Glossary

ACTH	Adrenocorticotropin hormone
AI	Adrenal insufficiency/Addison's disease
CAH	Congenital Adrenal Hyperplasia
FDA	US Food & Drug Administration
NHS	UK National Health Service
NIH	US National Institute of Health
NORD	National Organisation of Rare Diseases
PUMA	Paediatric Use of Marketing Authorisation

References

www.orpha.net

www.childstats.gov

ec.europa.eu/eurostat

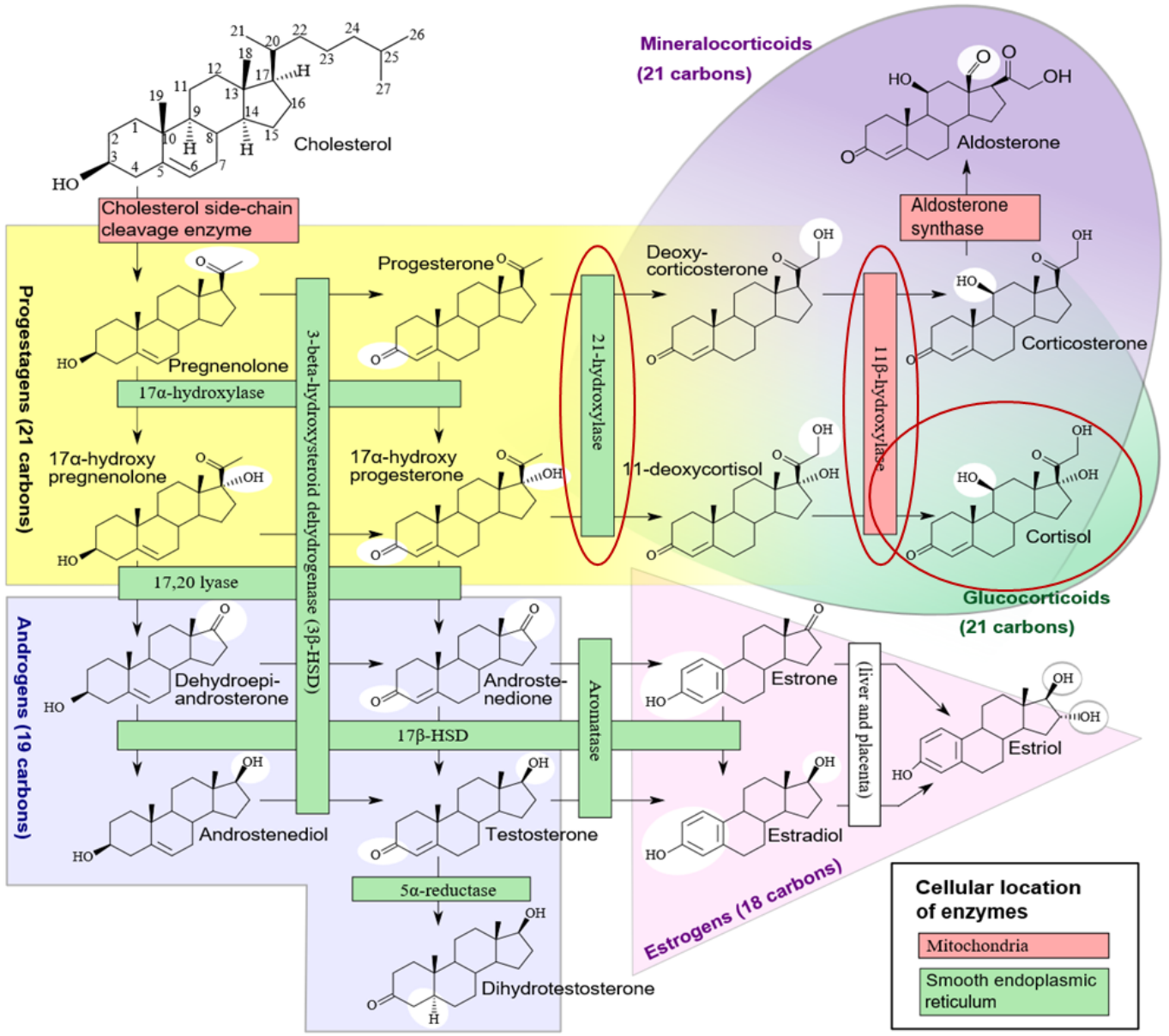
rarediseases.info.nih.gov

rarediseases.org

British National Formulary

Appendix

Biosynthesis of cortisol



Source: Häggström M, Richfield D Wikiversity Journal of Medicine ***1*** *(1).*

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