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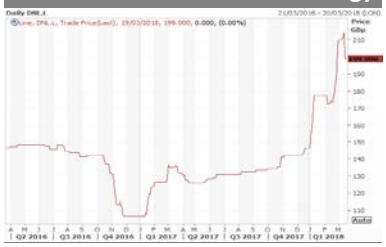
Pharmaceuticals & Biotechnology



Source: Eikon Thomson Reuters

Market data	
EPIC/TKR	**DNL**
Price (p)	199
12m High (p)	216
12m Low (p)	118
Shares (m)	52.6
Mkt Cap (£m)	104.6
EV (£m)	94.3
Free Float*	14%
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. Alkindi has received from the European Commission, with first sales expected in 2Q'18; while Chronocort is in Phase III trials.

Company information

CEO	Martin Whitaker
CFO	Richard Bungay
Chairman	Peter Allen
	+44 (0) 29 2068 2069
	www.diurnal.co.uk

Key shareholders

Directors	3.3%
IP Group	45.3%
Finance Wales	21.9%
Invesco	12.4%
Oceanwood Capital	8.3%

Diary

3rd Apr	General Meeting
3Q'18	US Phase III Chronocort
Sep 18	Full Year Results
4Q'18	Alkindi US reg. submission

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Diurnal Group

Capital increase to support commercial plans

Diurnal (DNL) is a commercial-stage specialty pharmaceutical company focused on diseases of the endocrine system. Its two lead products target rare conditions where medical needs are currently unmet, with the aim of building a long-term 'Adrenal Franchise'. Following regulatory approval, DNL will launch Alkindi in key European markets in 2018 through its own commercial infrastructure. Meanwhile, the company is pushing forward with Alkindi and Chronocort clinical trials in the US. To maintain this positive momentum, DNL has announced a Placing to raise gross new capital of up to £11m and, concomitantly, converting its debt into equity.

- **Strategy:** Diurnal's strategic goal is to create a valuable 'Adrenal Franchise' that can treat patients with chronic cortisol deficiency diseases from birth through to old age. Once Alkindi and Chronocort are established in EU and the US, the long-term vision is to expand its product offering to other related conditions.

- **Interims:** Results were in line with expectations, with planned increases in marketing and R&D, to give an underlying EBIT of -£7.4m (-£5.3m). More important was management's update on the commercial plans for Alkindi in Europe and progress with its EU and US clinical trial programme for Chronocort.

- **Placing:** Just after the interims, DNL announced a conditional Placing to raise up to £11m gross (£10.4m net) to fund its development programmes and to support the launch of Alkindi. Simultaneously, IP Group will convert its outstanding convertible loan into equity, leaving DNL with net cash of ca.£20.0m today.

- **Risks:** While there is a risk with all drugs in development, Diurnal has been considered to have unusually low risk because its products are formulation variants of well-established drugs. This has been validated with the European approval of Alkindi. The main risk now is that of commercial execution.

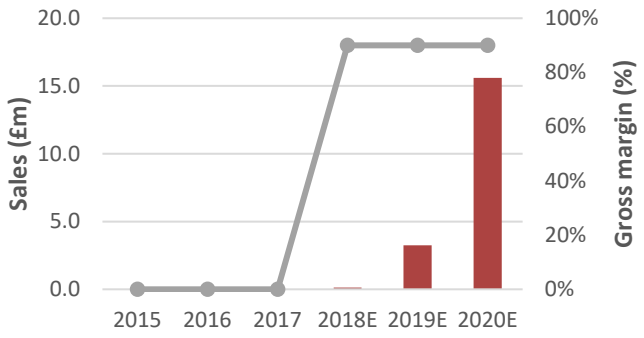
- **Investment summary:** Alkindi, a cortisol replacement therapy designed for babies and children, will be Diurnal's first product on the market. It will be followed soon by Chronocort for adults. The cortisol replacement market is for conditions that need life-long treatments and has a potential value of $3.5bn. DNL will hit a number of valuation inflection points during 2018 with its upcoming newsflow.

Financial summary and valuation

Year-end June (£m)	*2015	2016	2017	2018E	2019E	2020E
Sales	0.00	0.00	0.00	0.13	3.25	15.60
SG&A	-1.00	-1.99	-3.22	-6.03	-7.59	-9.21
R&D	-2.23	-3.89	-8.34	-10.50	-10.00	-7.00
EBITDA	-2.98	-5.87	-11.54	-16.41	-14.66	-2.18
Underlying EBIT	-2.99	-5.88	-11.55	-16.41	-14.66	-2.18
Reported EBIT	-2.99	-6.99	-12.07	-16.96	-15.23	-2.78
Underlying PBT	-3.02	-5.95	-11.64	-16.45	-14.58	-2.15
Statutory PBT	-3.02	-7.06	-12.16	-17.00	-15.15	-2.75
Underlying EPS (p)	-8.49	-12.48	-17.05	-23.86	-18.35	0.22
Statutory EPS (p)	-8.72	-15.02	-18.04	-24.86	-19.28	-0.75
Net (debt)/cash	6.05	26.88	16.37	17.22	4.27	-0.03
Capital increases	9.25	24.52	0.05	14.22	0.00	0.00

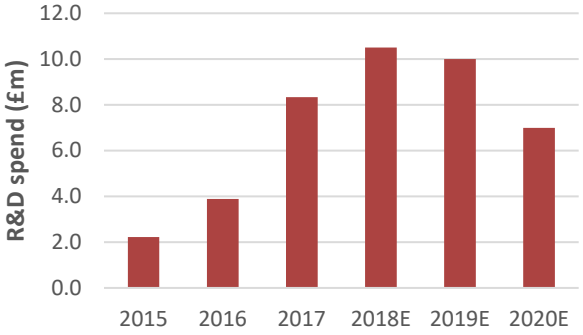
**Year to July; Source: Hardman & Co Life Sciences Research*

Sales & Gross margin



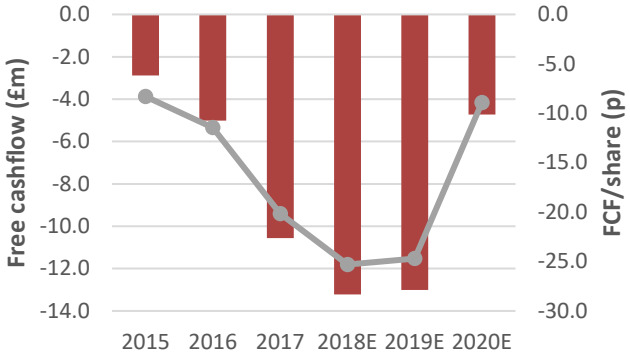
- First sales of Alkindi are anticipated in 2Q'18
- Sales will start in Germany and are expected to roll-out into other countries, with UK and Netherlands in 4Q'18
- Gross margin forecast at ca.90%
- Sales in Israel are expected during 2019

R&D investment



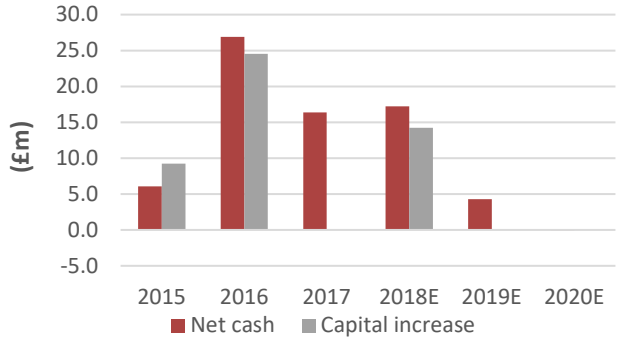
- Increase in R&D costs expected in fiscal 2018 following completion of the European Phase III trial with Chronocort and the US trials for both Alkindi and Chronocort
- R&D investment expected to continue for the foreseeable future

Free cashflow



- The cashflow is driven by the R&D investment and corporate overheads
- A European subsidiary has been established and a sales force of 14 has been recruited through Ashfield for the commercial infrastructure
- Monthly cashburn forecast at ca.£1.5m for the remainder of fiscal 2018.

Net cash and capital increases



- At 31st December 2017, net cash was £10.3m
- Conditional Placing of up to £11m gross (£10.4m net) allocated in 2018, assuming the Broker Options fully exercised, which should conclude early April
- Conversion of the outstanding IP Group loan into equity
- DNL is estimated to have net cash of ca.£20m on conclusion of the funding proposals and after allowing for working capital

Source: Company data; Hardman & Co Life Sciences Research

Interim results

Key features

Operational highlights

- **Alkindi:** The EC has granted a Paediatric Use Marketing Authorisation (PUMA) for Alkindi as a replacement therapy for paediatric in Adrenal Insufficiency (AI) including Congenital Adrenal Hyperplasia (CAH). Use has been extended to include patients up to 18 years of age (originally six years of age). The launch in key European countries is expected in 2Q'18, starting in Germany. In the US, the registration package is moving ahead with the food matrix compatibility study successfully completed, and this will be followed by the next study in healthy adult volunteers in 1H'18. Regulatory package submission to the FDA is expected in late 2018.
- **Chronocort:** Enrolment into the European Phase III Chronocort trial for CAH has been completed, with headline data expected at the end of 2018. In the US, a Phase III trial is due to start in 2H'18, following FDA approval of the protocol. A Phase II trial in AI is expected to commence before the end of the year.
- **Appointment of a specialist CRO:** Worldwide Clinical Trials (WCT) has been appointed for the conduct of the US trials for Chronocort in CAH and AI.
- **Pipeline:** The early stage pipeline is progressing with the ongoing Phase I/II clinical study with the native oral testosterone being evaluated in male patients with hypogonadism.

Commercial highlights

- **Sales infrastructure:** The commercial organisation and supply chain is in place, with Ashfield Healthcare, for the launch of Alkindi in key European territories. Following conclusion of pricing negotiations on a country-by-country basis.
- **Distribution:** Outside its core territories, DNL continues to expand its commercial infrastructure in countries that recognise the Alkindi EU market authorisation dossier, and it is entering into local distribution agreements with specialist partners. This infrastructure will also be used for subsequent products.

Financial highlights

- **R&D:** Investment in 1H'18 was higher than in the same period last year but was slightly lower than forecast at -£4.71m (-£3.96m), reflecting the Phase III programmes and regulatory costs.
- **SG&A:** Administration costs increased 89% to -£2.63m (-£1.39m), reflecting the addition of key personnel from Ashfield (a commercial team of 14) and building up the market access across Europe.
- **Net cash:** At 31st December 2017, net cash on the balance sheet was in line with our forecast at £10.34m. This has been boosted by a Placing of up to £11.0m.

Diurnal interims 2018 – actual vs expectations

Half-year to end June (£m)	1H'17 actual	1H'18 actual	Growth %	1H'18 forecast	Delta Δ
R&D spend	-3.96	-4.71	+19%	-5.00	-0.29
Administration costs	-1.39	-2.63	+89%	-2.45	+0.18
Underlying EBIT	**-5.34**	**-7.35**	**+38%**	**-7.45**	**+0.10**
Net cash/(debt)	22.25	10.34	-	10.35	-0.01

Source: Diurnal; Hardman & Co Life Sciences Research

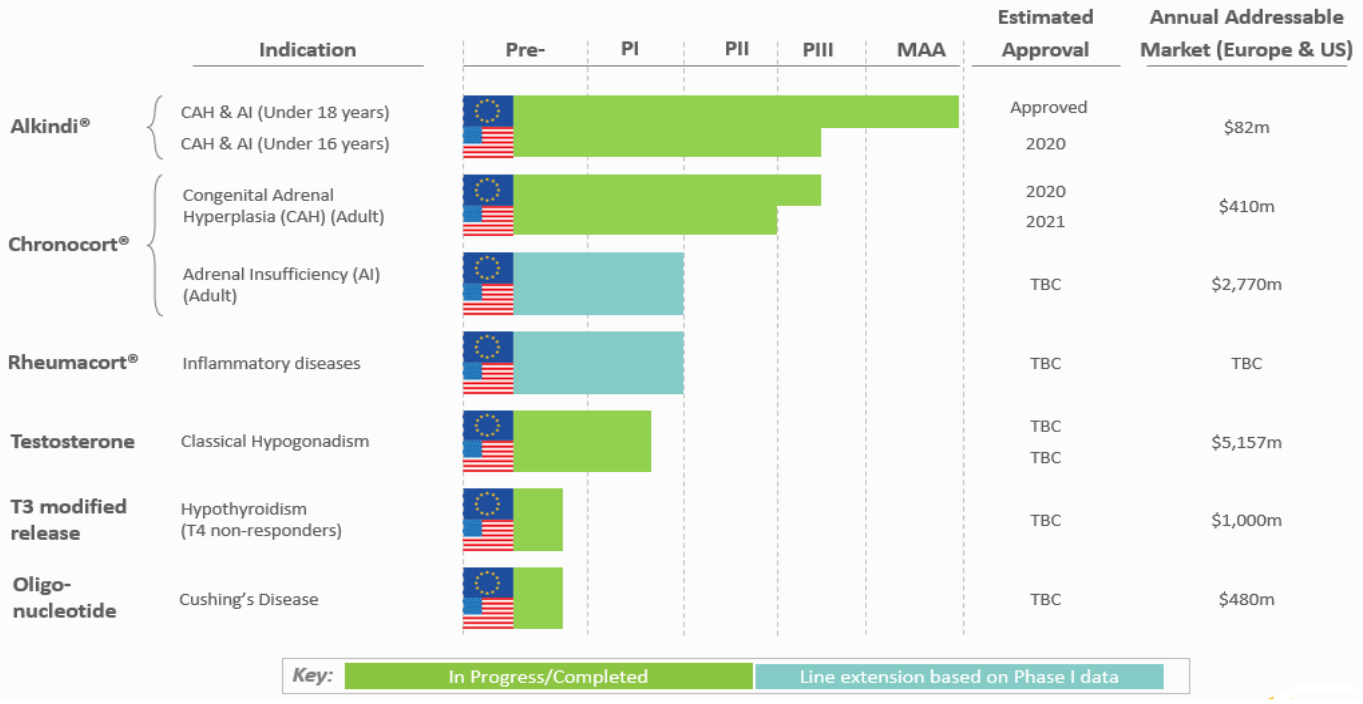
Operational update

Product pipeline

Five products in clinical and two in pre-clinical development

While much of the attention and resources have been focused on its two leading products, Alkindi and Chronocort, DNL has been extending its product pipeline over the last 12 months by advancing products through pre-clinical development and into Phase I. Notably, a line extension of Chronocort into AI and DITEST (testosterone) for hypogonadism. Overall, DNL is progressing five additional programmes, with three products in clinical development and two under pre-clinical evaluation.

Diurnal – product pipeline



Source: Diurnal

Alkindi

European market authorisation

EU approval of Alkindi for both AI and CAH…

On 13th February, following the positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP), Diurnal received Paediatric Use of Marketing Authorisation (PUMA) from the EC for the use of Alkindi in AI and CAH. This drug is being targeted at new-borns and children up to 18 years of age, although the initial focus will be on children up to six years of age.

…making it the first licensed paediatric treatment for these conditions

To date, there is no child-friendly hydrocortisone replacement product for the above age groups in either Europe or the US. Alkindi represents the first-in-class licensed product. From the outset, DNL designed Alkindi to overcome the well-known drawbacks associated with the unlicensed treatments that are used currently to treat this patient population. The goal with Alkindi is to deliver improved compliance, improved disease control and a reduction in disease symptoms caused by the highly variable dosing obtained with current formulations.

First sales

Alkindi will be rolled-out across Europe, starting in Germany in 2Q'18

Despite being a centralised EU authorisation, there will be a staged roll-out of Alkindi influenced by the timetable for agreeing pricing with the relevant authorities in each country. This is normal practice for drugs approved in the EU. The first country for launch is expected to be Germany, where initial sales are anticipated in 2Q'18. This is likely to be followed by further launches in the UK and the Netherlands in 4Q'18.

Establishing supply chain and commercial infrastructure

In Europe, Diurnal will retain the full value of Alkindi through direct commercialisation. The company has been working closely with a number of relevant partners to be ready for commercial launch:

- **Manufacturing:** Already established (since 2012) with the experienced and specialist GMP supplier, Glatt Pharmaceutical Services GmbH, to produce solid pharmaceutical dosage formulations based on multi-particulate systems.
- **Packaging:** Agreement with Sharp Packaging for its expertise in supply chain management.
- **Sales & marketing:** Appointment of Ashfield Healthcare for sales and medical infrastructure support to establish a European network of medical liaison staff.

DNL has built commercial infrastructure over last 12 months

Over the last 12 months, Ashfield Healthcare has been focused on establishing a Europe-wide network of medical liaison staff. Ashfield, together with DNL, has built up a team of 14 commercial staff. A peak sales force of approximately 20-30 (once Chronocort is launched) is considered sufficient, as patients are usually centralised within specialist endocrinology centres. The commercial organisation includes the following:

- Seven medical science liaison staff (covering Germany, the UK, France, Italy and Spain).
- Six key account managers (covering Germany, the UK, Italy and Spain).
- One market access manager.
- A supplements in-house commercial team.

Through Ashfield, DNL has the possibility of establishing a flexible EU commercial organisation that can be modified rapidly if the need arises without the requirement for upfront investment in infrastructure. This same infrastructure will be deployed for Chronocort.

With this in place, DNL becomes a more attractive partner for companies with drugs in the endocrine field that are looking to out-license for commercialisation in Europe.

Pricing

Pricing is likely to be in line with Plenadren at ca.$6,300 p.a.

Diurnal's aim is to price Alkindi in-line with Plenadren, Shire's modified release once-daily formulation of hydrocortisone. The cost of treatment with Plenadren is ca.$6,300 p.a. Pricing negotiations are already taking place in the key European countries. Our previous report '*Alkindi: on route to Europe'*, published on 19th December 2017 following the CHMP opinion, describes the rationale for our Alkindi sales forecasts.

US Phase III trial

The US Phase III trial with Alkindi is expected to complete before the end of the year …

Meanwhile, development is progressing well in the US, with DNL building up the regulatory programme. As part of the registration package, the European dossier will be used, as well as two additional studies, with the first already completed.

- A food matrix study has been completed successfully in healthy volunteers, which confirmed the pharmacokinetics of Alkindi together with safety and tolerability.
- An Investigational New Drug (IND) application is now open in the US, following advice from the FDA, for a bioequivalence study in 24 healthy adult volunteers. This will be a single centre, open-label and single-dose study evaluating the bioavailability of Alkindi compared with Cortef, the US standard-of-care immediate release hydrocortisone tablet. This study is expected to start in 1H'18, with results available before the year-end.

…with estimated approval in 2020

Diurnal is confident that no further studies will be required by the FDA for the US registration of Alkindi, and it is therefore planning to submit the regulatory package by the end of 2018, for an estimated approval in 2020.

Chronocort

Chronocort in CAH patients

European Phase III trial

Recruitment for the EU Phase III trial has been completed, headline data is due by the end of the year

Patient recruitment in the Phase III trial for the treatment of CAH in adults has now been completed. A total of 122 patients across 11 sites (six countries including one site in the US) have been enrolled in the six month study, and the trial will evaluate Chronocort to standard-of-care. Headline data are expected before the end of 2018.

Patients have the possibility of continuing treatment with Chronocort, by enrolling into a subsequent study to assess the long-term effects of the drug and collect additional safety data that include markers of bone turnover, body composition, insulin levels and quality of life. These data will be used in the regulatory dossiers, in both Europe and the US, and will serve also as the basis of price negotiations. DNL has disclosed that a significant proportion of patients has already enrolled into the extension study, and that none of them have dropped-out so far.

US Phase III trial

Recruitment for the US Phase III trial expected to start in 3Q'18…

The US trial is expected to start in 3Q'18 and following discussion with the FDA, it will be slightly different from the EU study. The US regulator has requested that CAH patients are enrolled in a randomised fashion to receive either a single type of medication (immediate-release hydrocortisone thrice-daily) or Chronocort twice-daily. Patients will be treated for 12 months, and a long-term follow-up programme will also be proposed for assessing the long-term safety of Chronocort.

…with headline data due in 2020

Completion of this study is anticipated during 2020, with headline data expected around 2H'20. FDA approval is likely to be at the end of the subsequent year.

Appointment of a US CRO

To support the US Chronocort trials, DNL has appointed Worldwide Clinical Trials (WCT), a global clinical research organisation, which will be responsible for conducting the Phase III CAH study.

Chronocort in AI patients

In order to address the large AI market, DNL intends to start a Phase II trial before the end of 2018, which will also be coordinated by WCT. This trial is expected to be conducted at many of the same sates as the Phase III CAH trial, with headline data available around the beginning of 2021.

Diurnal – development timetable

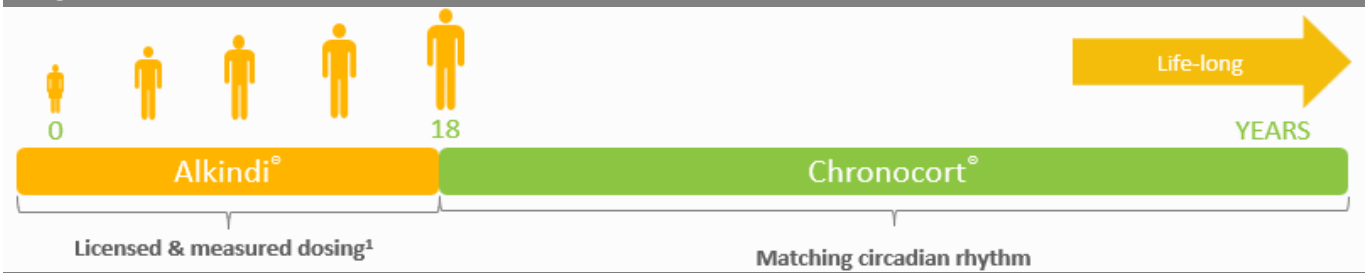
[1] *Subject to confirmation from the FDA*

Source: Diurnal

The adrenal franchise

With Alkindi and Chronocort, the aim is to create a long-life "adrenal franchise", where patients start with Alkindi and will then move on to Chronocort for the rest of their lives. In order to make the transition from Alkindi to Chronocort, DNL is developing a 2mg dose strength of Chronocort, which will be in addition to the existing 5mg, 10mg and 20mg doses.

Long-life adrenal franchise



[1]*Reflects the position in Europe*

Source: Diurnal

Building the endocrine pipeline

Building a pipeline in endocrinology

DNL's vision is "to become a world-leading endocrinology speciality pharma company". It aims to build a commercial franchise and maximise its commercial infrastructure in the niche endocrinology area, which is dominated by small biotech companies. As well as developing internal products, management is considering all available options regarding the acquisition of new products and in-licensing opportunities in order to maximise this opportunity.

In the meantime, DNL is evaluating products for additional endocrine conditions

European Phase I in hypogonadism

DNL is progressing DITEST, a new oral formulation of native testosterone for the treatment of male hypogonadism. The proof-of-concept open-label Phase I study, started in November 2016, was designed to evaluate the pharmacokinetic data and to assess the safety and tolerability in 12 patients with primary and secondary hypogonadism. The first part of the trial is now completed and, following positive results from the first cohort, the second part of the study, involving a higher dose of DITEST in fasted and fed states, has now started. Final results are expected to be communicated during 2018.

Potential treatment for Cushing's disease

DNL is reviewing its options with an oligonucleotide siRNA (silencing RNA) acting on the pituitary gland for a potential treatment of Cushing's disease, a condition characterised by an excess of cortisone secretion. *In vitro* studies, assessing the stability of the molecule in different formulations, are ongoing.

Hypothyroidism

Work on the Tri4Combi formulation, a physiological combination therapy of the T3 and T4 hormones for patients suffering from hypothyroidism, has stopped, as the management considers that the thyroxine (T4) replacement therapy is adequately covered with existing marketed therapies.

Instead, Diurnal has progressed work on the development of a modified-release T3 (triiodothyronine) product, where there remains an unmet medical need.

Patent protection

Continually upgrading and expanding its intellectual property

In addition to market exclusivity granted for Alkindi and Chronocort, Diurnal holds a set of patents granted in key territories, and it is continuously monitoring and upgrading its IP position.

Intellectual property and regulatory exclusivity

	Regulatory exclusivity[4]		Intellectual property	
	EU	US	European Patent	US
Alkindi®	PUMA 10 years	Orphan 7 years	Under review[1] Composition of matter; Under review[2] Medical use	2034 Composition of matter; 2034 Method of treatment (x2); 2032
Chronocort®	Orphan 10 years	Orphan 7 years	Under review[3] Composition of matter & medical use	2033 Composition of matter; 2033 Method of treatment
Oral Testosterone DITEST™	Not an orphan disease	Not an orphan disease	2029 Composition of matter	2030 Composition of matter

1 Granted GB patent number: 2527233; 2 Granted GB patent number 2509663; 3 Granted GB patent numbers: GB 2502402 & 2510754; 4 Conditional and subject to grant of market authorisation (and that the company is the first sponsor to obtain market authorisation for the relevant product).
Source: Diurnal

In addition, DNL announced recently the granting of first patents for Alkindi and Chronocort in Japan, providing protection until 2032 and 2033, respectively.

Commercialisation of Alkindi®

European market authorisation

Alkindi has been granted market authorisation by the EC for the paediatric treatment of AI, including CAH

On 13th February 2018, DNL received commercial authorisation from the EC for Alkindi. Although the approval is from birth through to children up to 18 years of age, DNL will initially focus on children up to six years of age, where no licensed treatment exists.

Currently, there is no child-friendly hydrocortisone replacement product for the above age groups in either Europe or the US. Alkindi represents the first-in-class licensed product. The marketing focus will be on the improved characteristics of Alkindi to obtain better clinical outcomes.

Proposed Alkindi packaging

Source: Diurnal

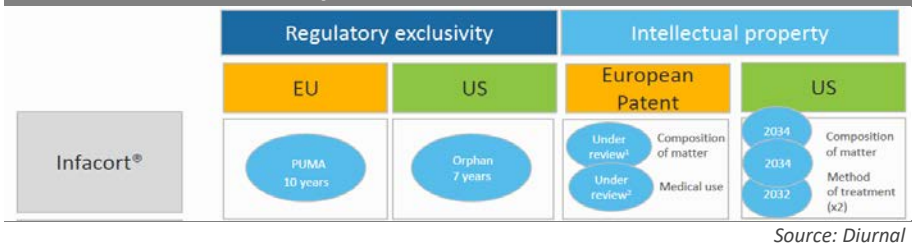
Market exclusivity

Alkindi will have market protection and patent protection in both Europe and the US

Given that hydrocortisone is an old, off-patent drug, DNL acted early in the development process to obtain some form of marketing protection. It has achieved market exclusivity in both Europe and the US through the following applications:

- **Orphan Drug designation:** Infacort was granted Orphan Drug designation for paediatric AI in the US (2015), which will provide commercial exclusivity effective from FDA approval.
- **Paediatric Use of Marketing Authorisation** (PUMA) granted in Europe for Alkindi by the European Commission providing ten years of data and market exclusivity.

Alkindi: market exclusivity & IP



Source: Diurnal

Advantages of Alkindi

Diurnal designed and developed Alkindi to fill a space where there was no approved licensed product in paediatric AI conditions:

- **Accuracy in dosing:** The current practice is for pharmacists to grind (compound) hydrocortisone tablets into a fine powder and then titrate the dose according to the child's weight. The aliquot of powder is put into a capsule or sachet for administration or 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:** Stability studies are in progress. The shelf-life already exceeds two years, which represents superiority over existing non-licensed hydrocortisone products. DNL is still investigating the potential to extend the shelf-life further.
- **Child-friendly preparation:** A key characteristic of Alkindi 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.

Commercialisation agreements

Commercialisation agreements with specialist local in some territories

DNL has the infrastructures in place to commercialise Alkindi in the major European countries with the help of Ashfield. In order to mitigate any potential effect of Brexit, DNL has established a wholly-owned subsidiary Diurnal Europe B.V. in the Netherlands. In key territories, Diurnal is establishing local distribution agreements with partners that intend to submit Diurnal's product for approval to their respective regulatory authorities:

Israel

In March 2016, Diurnal expanded its commercial activity with marketing and distribution agreement with Medison, to make Infacort available in Israel. The deal will also cover Chronocort when it becomes available. The market authorisation submission in Israel will be based on the EMA approval package.

Medison provides a vast spectrum of integrated services, including registration, reimbursement, nursing, distribution and marketing, for companies looking to enter the Israeli healthcare market, and, more specifically, the niche indications. With around 1,000 patients affected, the market opportunity is estimated at $6.4m. First sales are anticipated during 2019.

Australia and New Zealand

Diurnal has licensed exclusive rights to sell Alkindi and Chronocort in Australia and New Zealand to Emerge Health, a specialist hospital pharma company. Around 1,750 patients are affected by Paediatric AI and CAH., giving an estimated market worth $11m. The market authorisation, anticipated in 2020, in both territories will be based on the European dossier, together with published trial data.

Japan

Diurnal is in search of a local partner in Japan where first patents for Alkindi and Chronocort have been granted by the Japanese Patent Office. Japan is a substantial market for Diurnal with around 6,700 patients with CAH and 58,000 with AI, giving an estimated market worth $415m.

Competitive landscape

Direct competition for Alkindi is only in the form of traditional formulations of generically-available hydrocortisone tablet that are crushed up and added to food, leading to the inaccurate dosing mentioned earlier. With Chronocort, Diurnal will be entering a market where competition is low. There will be two main competitors:

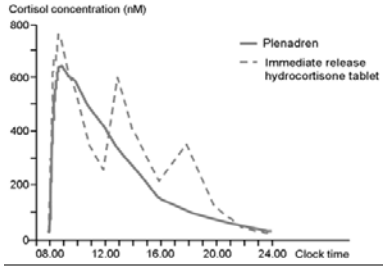
- **Immediate release hydrocortisone** (and synthetic corticosteroids), due to established positions and relatively low costs.
- **Plenadren** as a modified release formulation of hydrocortisone. Plenadren is not licensed for paediatric use in the US and Europe.

Competitive landscape

Product	Mimics circadian rhythm	Indication			Countries	Price
		AI/CAH paediatric[1]	CAH	AI		
Hydrocortisone (generic)	✗	✓ Unlicensed	✓	✓	EU, US	ca. $3.3k p.a.
Plenadren® (modified release)	✗	✗	✗	✓	EU	ca. $6.3k p.a.
Diurnal "Adrenal Franchise"	✓ Chronocort®	✓ Alkindi®	✓ Chronocort®	✓ Chronocort®	EU, US	Targeting $6.3k+ p.a.

[1]Under 18 years in Europe and under 16 years in US
Source: Diurnal

Plenadren profile



Source: www.medecines.org.uk:

Plenadren does not match the natural level of cortisol

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 approved as a prescription-only medicine for the treatment of AI only. The formulation 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, but it does not match the night time build-up in preparation for the energy requirement needed at the start of the day. In contrast, the strategy being used by Diurnal is to have a formulation of Chronocort that matches the circadian rhythm.

Clinical stage products

Apart from DNL, there are three other companies looking to progress products through clinical trials for the treatment of CAH. None of them are in trials for AI. Moreover, they are not based on hydrocortisone, but aim at up-stream targets involved in cortisol production.

Competitive clinical-stage products			
Drug	**Developer**	**Stage**	**Comment**
NBI-74788	Neurocrine Biosciences	Phase II	Non-peptide corticotrophin releasing factor 1 (CRF1) antagonist
Nevanimibe (ATR-101)	Millendo Therapeutics	Phase II	Selective inhibitor of acyl-CoA:Cholesterol acyltransferase 1
SPR001	Spruce Biosciences	Phase II	Headline data are expected in 2018

Source: Hardman & Co Life Sciences Research

NBI-74788

NBI-74788, a CRF antagonist, is in a Phase II trial in the US in CAH patients

In June 2015, Neurocrine Biosciences, a San Diego-based company, announced that it had suspended two planned clinical trials with NBI-77860 in CAH because of new pre-clinical findings. NBI-77860 was a non-peptide corticotrophin releasing factor 1 (CRF1) antagonist, which had been demonstrated to have potent activity in a range of *in vitro* and *in vivo* assays. Neurocrine is now following up with a new CRF antagonist, NBI-74788, which successfully passed a Phase I single ascending dose study in 2017. Neurocrine has now initiated an open label Phase II trial in 20 patients, which will assess two single, ascending doses of NBI-74788.

Nevanimibe (ATR-101)

Millendo has progressed its ACAT1 inhibitor ATR-101 into a Phase II trial in CAH patients

Millendo Therapeutics is a private, Ann Arbor-based company, with a focus on novel endocrine diseases. It is currently advancing the development of nevanimibe for the treatment of CAH as well as Endogenous Cushing's Syndrome. Nevanimibe is claimed to be a potent and selective inhibitor of acyl-CoA:Cholesterol acyltransferase 1 (ACAT1), an enzyme that catalyses the transformation of free cholesterol to cholesterol ester, which serves as a substrate reservoir for steroid biosynthesis. Nevanimibe has been evaluated in a multi-centre, single-blind, multiple dose Phase II proof-of-concept clinical study in 10 patients to assess its efficacy, in addition to corticosteroids, in patients with classic CAH.

At the Endocrine Society's (ENDO) 100th Annual Meeting, being held March 17-20 2018 in Chicago, the company disclosed that only two patents reached the primary endpoint with the reduction of 17-hydroxyprogesterone, a key measure of disease control. Millendo is now planning a subsequent study to assess longer periods of dosing and additional clinical end-points. It has been granted Orphan Drug designation in the US.

SPR001

SPR001 is being assessed by Spruce in a Phase II trial in CAH patients

Spruce Biosciences is a private, San Francisco-based clinical-stage biotechnology company focused on novel therapies for rare endocrine disorders. It is currently developing a small molecule, SPR001, for CAH and for an undisclosed indication. Little information is given on the product other than it is currently in a Phase II clinical trial to assess its safety and efficacy following oral administration in adults with classic CAH. The study is a multiple dose, dose-escalation study to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of SPR001 in adult CAH patients. Headline data are expected in 2018. Spruce has received Orphan Drug designation for SPR001 for the treatment of CAH from both the FDA and the EMA.

Summary

Diurnal is ahead of the competition in Europe and more advanced in the US with Alkindi and Chronocort

DNL is much more advanced than any of the competitor products as far as in Europe is concerned. In the US, given that DNL is preparing to start a pivotal Phase III trial with Chronocort in 2018, we believe that it is more advanced than the competition, which greatly reduces the risk of having its products being blocked from entering the US market.

Funding update

Placing

- On 14th March 2018, the company announced that it had raised £10.0m of gross new capital through the conditional Placing of 5.26m new Ordinary shares @190p with existing and new shareholders.
- In addition, the company has granted a Broker Option to raise a further £1.0m through the issue of up to 0.53m new Ordinary shares at the same price.
- The Placing, representing a minimum 10.0% of the existing share capital, is conditional on the approval of shareholders at a General Meeting to be held on 3rd April 2018.
- The share price represents an 11.2% discount to the mid-market price on 13th March 2017.

Use of proceeds

The conditional Placing of up to £11m, will be used for the commercialisation of Alkindi and to progress the clinical pipeline

The net proceeds, estimated at £10.4m on the basis that all the Broker Option shares are issued, will be used for the commercialisation of Alkindi and to progress the clinical pipeline as follows:

- Complete the European development and regulatory submission of Chronocort.
- Complete the development of Alkindi in the US.
- Commence the pivotal Phase III trial of Chronocort in the US.
- Commence Chronocort indication expansion into AI with a Phase II clinical trial anticipated to start this year.
- Progress the early-stage pipeline into proof-of-principle studies.

Convertible loan conversion

In addition, IP Group is going to convert its loan facility into 3.2m shares

Concomitantly, IP Group (IP2IPO), which provided a £4.65m convertible loan facility available to the company at the time of its IPO in December 2015, is going to convert this into 3.2m Ordinary shares at a price of 144p per share. It should be noted that this portion does not represent any new money, as the loan has been funding the working capital requirement of the group.

In the event that the Broker Option is fully exercised, the enlarged share capital will consist of 61.6m Ordinary shares, with IP Group being the largest shareholder with 43.9%, followed by Invesco with 11.4%. The Directors will hold 3.0%.

Share capital

Type	Shares	Raise
Existing Ordinary shares	**52,580,634**	**-**
EIS/VCT shares	1,578,557	£3.0m
General shares	3,684,600	£7.0m
Broker Option	526,315	£1.0m
Equity raise	**5,789,472**	**£11.0m**
Loan Conversion (IP Group)	3,229,575	-
Enlarged share capital (maximum)	**61,599,681**	

Source: Hardman & Co Life Sciences Research

Following this issue, Diurnal will have net cash of ca.£20.0m. The company has stated that it does not anticipate a further capital increase, at least until the results of the European Chronocort Phase III trial are known (expected at the end of 3Q'18).

Financial summary

No changes have been made to forecasts following the announcement of interim results. Full financial forecasts were published on 14th September 2017 in our report '*Ready to press the button*'[1]. However, the cash position and the number of shares in issue have been adjusted to reflect the capital increase and loan note conversion.

- **SG&A:** Investment will continue to be made in building European infrastructure to maximise the Alkindi commercial opportunity.
- **R&D:** R&D is expected to increase with the pending start for the US clinical trials for Alkindi and Chronocort.
- **Sales:** First sales are expected to be recorded in fiscal 2018 following the launch of Alkindi in Germany.
- **Net cash:** At 31st December 2017, DNL had net cash of £10.34m, comprised £15.8m cash and debt of -£3.7m. This is being boosted by maximum new cash of £10.4m from the conditional Placing, and conversion of all the debt into equity.

Financial overview

Year-end June (£m)	*2015	2016	2017	2018E	2019E	2020E
Profit & Loss						
Sales	0.00	0.00	0.00	0.13	3.25	15.60
COGS	0.00	0.00	0.00	-0.01	-0.32	-1.56
SG&A	-1.00	-1.99	-3.22	-6.03	-7.59	-9.21
R&D	-2.23	-3.89	-8.34	-10.50	-10.00	-7.00
Underlying EBIT	-2.99	-5.88	-11.55	-16.41	-14.66	-2.18
Share-based costs	0.00	-0.49	-0.52	-0.54	-0.57	-0.60
Exceptional items	0.00	-0.62	0.00	0.00	0.00	0.00
Statutory EBIT	**-2.99**	**-6.99**	**-12.07**	**-16.96**	**-15.23**	**-2.78**
U/L pre-tax profit	-3.02	-5.95	-11.64	-16.45	-14.58	-2.15
Tax liability/credit	0.00	0.49	2.73	3.44	3.27	2.29
Weighted average (m)	**34.61**	**43.75**	**52.24**	**54.56**	**61.60**	**61.60**
Underlying basic EPS (p)	-8.49	-12.48	-17.05	-23.86	-18.35	0.22
Balance sheet						
Share capital	0.00	0.00	0.00	0.00	0.00	0.00
Reserves	-9.31	23.32	14.46	15.12	3.24	2.78
Loans/debt	0.02	0.00	0.00	0.00	0.00	0.00
less: Cash	6.07	30.11	19.88	17.22	4.27	-0.03
Invested capital	**-0.01**	**-0.94**	**0.71**	**0.52**	**1.59**	**5.43**
Cashflow						
Trading profit	-2.99	-5.88	-11.55	-16.41	-14.66	-2.18
Working capital	0.02	0.95	1.09	0.12	-1.62	-4.91
Company op. cashflow	**-2.96**	**-5.55**	**-10.72**	**-16.29**	**-16.29**	**-7.08**
Capital expenditure	-0.01	0.00	-0.02	-0.02	-0.02	-0.02
Free cashflow	**-2.88**	**-5.02**	**-10.55**	**-13.23**	**-12.95**	**-4.30**
Share issues	9.25	24.52	0.05	14.22	0.00	0.00
Change in net debt	**6.37**	**20.83**	**-10.51**	**0.85**	**-12.95**	**-4.30**
Opening net cash	-0.34	6.05	26.88	16.37	17.22	4.27
Closing net cash	**6.05**	**26.88**	**16.37**	**17.22**	**4.27**	**-0.03**

**Year to July; Source: Hardman & Co Life Sciences Research*

[1] http://www.hardmanandco.com/docs/default-source/company-docs/diurnal-ltd-documents/14.09.17-ready-to-press-the-button.pdf

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Status of Hardman & Co's research under MiFID II

Some professional investors, who are subject to the new MiFID II rules from 3rd January, may be unclear about the status of Hardman research and, specifically, whether it can be accepted without a commercial arrangement. Hardman's company research is paid for by the companies about which we write and, as such, falls within the scope of 'minor non-monetary benefits', as defined in the Markets in Financial Instruments Directive II.

In particular, Article 12(3) of the Directive states: 'The following benefits shall qualify as acceptable minor non-monetary benefits only if they are' (b) 'written material from a third party that is commissioned and paid for by an[sic] corporate issuer or potential issuer to promote a new issuance by the company, or where the third party firm is contractually engaged and paid by the issuer to produce such material on an ongoing basis, provided that the relationship is clearly disclosed in the material and that the material is made available at the same time to any investment firms wishing to receive it or to the general public;'

The fact that we are commissioned to write the research is disclosed in the disclaimer, and the research is widely available.

The full detail is on page 26 of the full directive, which can be accessed here: http://ec.europa.eu/finance/docs/level-2-measures/mifid-delegated-regulation-2016-2031.pdf

In addition, it should be noted that MiFID II's main aim is to ensure transparency in the relationship between fund managers and brokers/suppliers, and eliminate what is termed 'inducement', whereby free research is provided to fund managers to encourage them to deal with the broker. Hardman is not inducing the reader of our research to trade through us, since we do not deal in any security.

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