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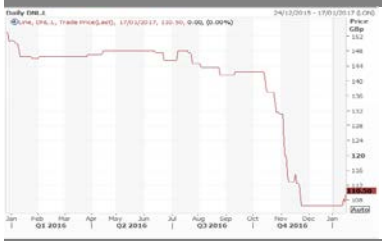
Pharmaceuticals & Biotech



Source: Eikon Thomson Reuters

Market data

EPIC/TKR	DNL
Price (p)	112
12m High (p)	153
12m Low (p)	105
Shares (m)	52.2
Mkt Cap (£m)	58.5
EV (£m)	31.6
Free Float*	17%
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	Richard Bungay
Chairman	Peter Allen

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www.diurnal.co.uk

Key shareholders

Directors	3.3%
IP Group	45.6%
Finance Wales	22.1%
Invesco	12.5%
Oceanwood Capital	7.7%

Diary

27-Oct-16	Hardman initiation
Jun-17	FY-17
4Q-17	Infacort MA expected

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Diurnal Group

Infacort® – On track to market

Diurnal is a clinical stage specialty pharmaceutical company focused on diseases of the endocrine system. It has two lead candidates – Infacort that completed its Phase III in Dec 2016 and Chronocort, currently in Phase III trials – targeted at rare diseases with unmet medical need, and is aiming to build a long-term 'Adrenal Franchise'. The completed Phase III trial confirmed that Infacort is well tolerated, achieved its primary endpoint and received the support of the parents and carers. Infacort will represent the first licenced cortisol replacement therapy for children and is on track to achieve market authorisation in late 2017 and sales in early 2018

- **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 Infacort and Chronocort are established in Europe and the US, the long-term vision is to expand the product offering to other conditions.

- **Phase III clinical trial:** Results from the European Phase III study on children from new-borns to six years of age, showed Infacort to be a paediatric compliant and well tolerated cortisol replacement treatment. No adverse effect was detected and Infacort received support from 95% of parents and carers.

- **Route to market:** These Phase III results represent an important step towards marketing approval in Europe, expected in late 2017. They will support a future study to be performed in the US. Infacort would be the first licenced cortisol treatment in children, hence providing a solution to an unmet medical need.

- **Risks:** As with all drug development companies, there is a risk that products will fail in clinical trials. Diurnal is much lower risk given that its products are formulation variants of well-established drugs. Moreover, with the PUMA dossier already validated by the EMA, Diurnal is in the market authorisation process.

- **Investment summary:** Diurnal is focusing on diseases of the endocrine system. Infacort, a cortisol replacement designed for children and babies, is the first product Diurnal will bring to the market. It will be followed by Chronocort for adults. The cortisol replacement market is for conditions that need life-long treatments, with a potential value of $3.5bn.

Financial summary and valuation

Year end June (£m)	*2014	*2015	2016	2017E	2018E	2019E
Sales	0.00	0.00	0.00	0.00	1.05	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

Infacort® – Update

Following completion of the recent phase III trial, the EMA has already approved a Paediatric Investigation Plan (PIP) for Infacort, setting out the regulatory pathway to market authorisation *via* the PUMA route. If approved, Infacort has the potential to be the first licensed treatment in Europe for paediatric adrenal insufficiency (AI) (including congenital adrenal hyperplasia (CAH)). It will also provide Diurnal with ten years data and market exclusivity from market authorisation. Diurnal is on track to gain market authorisation in late 2017, with product revenues expected from early 2018.

Positive Phase III clinical results

Diurnal recently presented positive results from its European Phase III trial with Infacort in children with Adrenal Insufficiency (AI). Infacort was targeted at this population in a Phase III clinical trial performed in in Europe where there is no licensed treatment available.

Clinical trial design

Regulatory facts

Clinical trials in new-borns and children have strict ethical principles that Diurnal must follow in order to gain 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 reflected in the design, implementation and evaluation of these clinical trials and their findings.

In order to fulfil the regulatory obligation, Diurnal secured a Paediatric Investigation Plan (PIP) up-front with the paediatric committee of the European Medicines Agency.

Design

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 Congenital Adrenal Hyperplasia (CAH), primary adrenal failure, or hypopituitarism. The open label study was carried out at the Charité-Universitätsmedizin in Berlin, Germany and consisted 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 new-borns aged from birth to <28 days will be enrolled

All subjects received their standard treatment, including fludrocortisone (mineralocorticoid activity), other than the dose of hydrocortisone that was substituted by the appropriate intake of Infacort.

The appropriate dose of Infacort used in the trial was determined by specialist endocrinologists, and was in relation to the patient's body weight and previous (unlicensed) dose of hydrocortisone.

Outcomes

Data analysis

No serious adverse events

During the study, no serious adverse events were recorded which, given the clinical knowledge about hydrocortisone, was to be expected. This demonstrated the high tolerability of Infacort in paediatric patients. The bitter taste of hydrocortisone was also shown to be well disguised by the taste masking coating as illustrated with 82% of patients swallowing Infacort with ease.

Primary end-point achieved…

…with average serum cortisol levels of 535nmol/l

The primary end-point – serum cortisol concentration up to 240min (4h) after intake of Infacort – of the study was achieved. Results showed a statistically significant increase in serum cortisol levels at the set time compared to a pre-dose value. Oral intake of Infacort achieved an equivalent morning level of cortisol at 60min post-dose of Infacort compared to healthy children. The average value of 535nmol/L compared to morning reference values for cortisol levels of 193-773nm/L[1]. These results demonstrate the good bioavailability of the drug, achieving one of its main goals as a cortisol replacement therapy.

Patient opinions

95% of parents/carers would give Infacort to their children

As part of the trial, a series of surveys were requested and completed by parents and/or carers, addressing the compliance of Infacort. The following numbers present Infacort on a very positive position with an overwhelming

- 82% of parents/carers found that patients swallow Infacort with ease
- 95% of parents/carers prefer Infacort to the usual unlicensed treatment
- 95% of parents would give Infacort in the future to their child
- 100% of parent/carer in cohort 3 prefer Infacort to the usual treatment

Professional opinions

Infacort received strong support from professionals

Two co-investigators of the Phase III study conducted in Berlin's Charité-Universitätsmedizin, one of the leading paediatric endocrine hospitals in Germany, highlighted the core values of Infacort compared to the unlicensed standard of care.

- Accuracy in the dosing regimen
- Safety of Infacort
- Compliance of the medicine by children

"This carefully controlled study clearly demonstrates, for the first time, the value of a standard dose of hydrocortisone in controlling cortisol levels in children with adrenal insufficiency."

Prof Heiko Krude, director of the Institute for Experimental Paediatric Endocrinology
Source: Diurnal

"These important data suggest that Infacort could be an effective and safe cortisol replacement treatment able to address a significant unmet need for children with adrenal insufficiency. Infacort also has the potential to increase compliance through the product's taste-masking excipients specifically designed to eliminate the bitter taste of hydrocortisone."

Dr Oliver Blankenstein, specialist in endocrinology and metabolism
Source: Diurnal

[1] http://emedicine.medscape.com/article/2088826-overview

Study extension

A majority of patients elected to continue treatment at end of study

Following the formal trial, and based on the recommendation of an independent data monitoring committee, all subjects that had participated were offered the opportunity to continue medication with Infacort in a separated clinical trial. The extension of the Phase III trial is an observational study to identify any adverse events, influence in growth, as well as to measure cortisol levels. Following the very positive outcomes, we believe that a large majority of patients have enrolled to continue treatment.

EMA submission

Diurnal has announced that the regulatory dossier was submitted to the EMA and subsequently validated on the 20th December 2016. This means that the market authorisation process is in full swing and that Diurnal is on track for commercialisation of Infacort at the end of 2017, with first sales in early 2018.

Supporting the US trial

In the US, the intention is to use Infacort in patients from new born until they reach the age of sixteen. From that age, their medication could be switched to Chronocort, when approved, for the remainder of their lives, all based on the recommendation of endocrinologists.

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 children up to the age of sixteen years of age, as well as new-borns and infants. However, as part of the FDA review process, it is expected that they will take into consideration the results from the European trial. The Phase III US study is envisioned to start in mid-2017, with a potential market approval by the end of 2019.

Infacort – Key facts

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

- **Europe** – new-borns and infants up to six years of age
- **US** – new-borns, 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.

Presentation

Multi-layered, and multi-particulate formulation…

Infacort, like Diurnal's Chronocort product, also uses 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

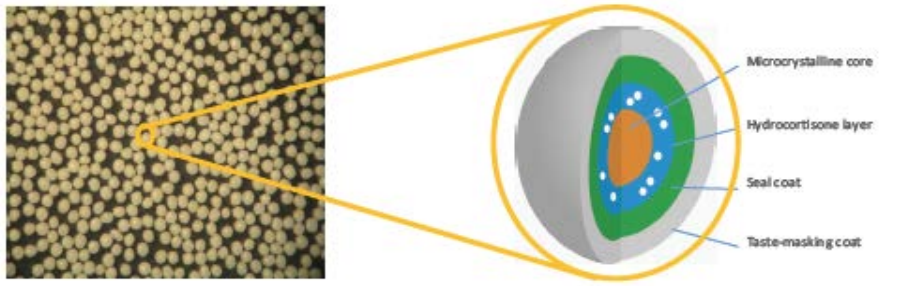
Infacort – four dose levels

Source: Diurnal:

Manufacturing partner Glatt has established a full scale-up process under GMP conditions which enables the manufacture of Infacort in commercial scale 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

Diurnal developed Infacort to fill a space where there is not an approved licensed product in paediatric adrenal insufficiency conditions.

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 non-licensed 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.

Commercial opportunity

Infacort will be the first product Diurnal is attempting to commercialise, initially in Europe, where it would become the first licensed treatment for paediatric adrenal insufficiency (including congenital adrenal hyperplasia). Diurnal has filed for market authorisation with the EMA with the expectation of receiving approval in late 2017. US marketing authorisation is not expected until late 2019.

Infacort – Pipeline timelines

	Indication	Pre-	PI	PII	PIII	Estimated Approval	Annual Addressable Market (Europe & US)
Infacort®	CAH & AI (Under 6 years)					2017	$60m
	CAH & AI (Under 16 years)					2019	

Source: Diurnal

Market exclusivity

Orphan Drug designation

… and Infacort in US for AI

Infacort was granted Orphan Drug designation for paediatric AI in the US (2015), which, 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.

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

Diurnal has a PIP in place in respect of Infacort. The PIP covers the paediatric population from new-borns through to infants and children up to six years of age. A successful PUMA application for Infacort will provide Diurnal with eight years of data exclusivity and ten years of market exclusivity.

Following the positive outcomes of the Phase III trial, Diurnal recently announced that the EMA has accepted the PUMA application for review. This allows Diurnal to reach its target of getting market authorisation in late 2017 and sales in early 2018 for Infacort in Europe.

Sales forecast

Rationale

Infacort is designed for the paediatric sector where there is no licensed therapeutic for adrenal insufficiency available in Europe and the US. We believe that, in view of the positive clinical outcomes from the Phase III trial, coupled with study the supportive parents' and carers' surveys, Infacort will be in a strong position to gain market share relatively quickly.

Population

In our previous report – *Get the rhythm* (dated on the 27th October), we described the pricing policy, with Diurnal expected to match the price of Infacort with that of Plenadren, licensed for adult adrenal insufficiency only (ca. $6,100 annual cost in Europe). In addition, the addressable market for paediatric adrenal insufficiency in CAH and Addison's disease was also described.

Addressable markets			
	Europe	US	Total
Annual price of drug (25mg)	**$6,100**	**$6,800**	
Prevalence			
Paediatric CAH	4,200	7,400	11,600
Paediatric Addison's disease	2,625	1,600	4,225
Market ($m)			
Paediatric CAH	25.6	50.3	75.9
Paediatric Addison's disease	16.0	10.8	26.8
Total market ($m)	**41.6**	**61.1**	**102.7**

Source: Hardman & Co Life Sciences Research

Infacort sales model

Our forecast for Infacort are based around the following core assumptions:

- 0.77% population growth in the US[2] and 0.26% population growth in Europe[3]
- Infacort receiving market authorisation in 2017 and first sales in 2018 in Europe
- Infacort receiving market authorisation in 2019 and first sales in 2020 in the US
- Average wholesaler discounts of 18.5% and 30% in Europe and the US respectively

Applying these assumptions, our sales forecasts for Infacort in Europe and the US are as follows:

Infacort: sales model												
	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029
Europe												
Addressable market	41.8	42.0	42.1	42.2	42.3	42.4	42.5	42.6	42.7	42.8	42.9	43.0
Market share	4%	7%	13%	21%	28%	35%	40%	43%	45%	47%	49%	50%
Sales ($m)	1.67	2.94	5.47	8.85	11.84	14.83	17.00	18.32	19.22	20.12	21.03	21.52
United States												
Addressable market	62.1	62.6	63.1	63.6	64.1	64.6	65.1	65.6	66.1	66.6	67.1	67.6
Market share			5%	15%	25%	33%	40%	42%	44%	46%	48%	50%
Sales ($m)			3.16	9.14	16.02	21.31	26.03	27.54	29.07	30.63	32.21	33.81
Total in-market sales ($m)	1.67	2.94	8.62	18.39	27.86	36.14	43.03	45.86	48.29	50.75	53.24	55.33
Net sales* ($m)	1.36	2.39	6.66	13.89	20.86	27.01	32.07	34.21	36.01	37.84	39.69	41.20
Net sales (£m)	**1.05**	**1.84**	**5.13**	**10.69**	**16.05**	**20.77**	**24.67**	**26.31**	**27.70**	**29.11**	**30.53**	**31.69**

**After average wholesaler discounts*
GBP/US$: 1.300
Source: Hardman & Co Life Sciences Research

Conclusion

Infacort, once approved, will be the first and only licenced product for paediatric adrenal insufficiency available in Europe. With the PUMA dossier already validated by the EMA, Diurnal is in the market authorisation process for Infacort with the aim to start commercialisation in late 2017. With that in mind and the fact that it received very positive appraisal from professional, patients, parents and carers, it would be expected to take market share quickly and reach 50% at peak in both Europe and the US in 2029. On this basis, the market capitalisation of Diurnal is not reflecting this opportunity which will become increasing apparent as event unfold in 2017.

[2] http://www.worldmeters.info/worldpopulation/us-population
[3] http://ec.europa.eu/eurostat

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