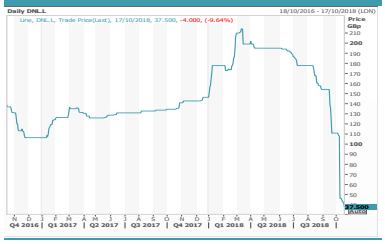
Pharmaceuticals & Biotechnology



Source: Eikon Thomson Reuters

Market data

EPIC/TKR	DNL
Price (p)	36.5
12m High (p)	215.8
12m Low (p)	36.0
Shares (m)	61.3
Mkt Cap (£m)	22.4
EV (£m)	5.1
Free Float*	19%
Market	AIM

**As defined by AIM Rule 26*

Description

Diurnal (DNL) is a UK-based specialty pharma company targeting patient needs in chronic, potentially life threatening, endocrine (hormonal) diseases. Alkindi has received approval from the European Commission, with first sales started in May 2018; Chronocort has completed Phase III trial in Europe.

Company information

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

Key shareholders

Directors	3.0%
IP Group	44.0%
Finance Wales	18.8%
Invesco	11.7%
Oceanwood Capital	7.1%
Polar Capital	3.4%

Diary

4Q'18	Alkindi US reg. feedback
2Q'19	EMA Chrono. Scient. advice
3Q'19	Alkindi US registration subm.

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DIURNAL GROUP

Unexpected Phase III trial outcome

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'. Alkindi is being launched in key EU markets, and this was expected to be followed by Chronocort. However, DNL has received the headline data from its European Phase III trial in CAH, which showed that Chronocort was not superior to standard-of-care, thereby failing to meet its primary end-point. Given the strong Phase II data, this outcome was unexpected. The full data set is now being analysed.

- **Strategy:** DNL'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. The long-term vision, once Alkindi and Chronocort are established in the EU and the US, is to expand the product offering to other related conditions.
- **Phase III results:** Headline data indicated that Chronocort did not meet its primary end-point – superiority over the standard-of-care – in 122 CAH patients enrolled in a European Phase III trial. This was due to the level of androgens being well-controlled in the control arm of the study.
- **Full analysis:** Chronocort did, however, show better control of morning androgen levels compared with standard-of-care and provided the natural overnight cortisol release together with some additional benefits. DNL is reviewing the full data set, alongside interim data from a long-term study for discussion with the regulators.
- **Risks:** While there is a risk with all drugs in development that they might fail clinical trials or not be approved by the regulators, DNL has been considered to have unusually low risk, as its products are formulation variants of well-established drugs. Having been validated with Alkindi, the Chronocort outcome was unexpected.
- **Investment summary:** Alkindi, a cortisol replacement therapy designed for babies and children, is DNL's first product on the market. It had been expected to be followed by Chronocort for adults – a much larger market. The fall in the share price following this unpredictable Chronocort outcome looks overdone, but the price is likely to languish until there is clarity about how to move Chronocort forward from here – probably by adapting the protocol for the US Phase III trial.

Financial summary and valuation

Year-end June (£m)	2016	2017	2018	2019E	2020E	2021E
Sales	0.00	0.00	0.07	1.54	5.53	17.23
SG&A	-1.99	-3.23	-6.21	-7.77	-9.40	-11.13
R&D	-3.89	-8.34	-10.02	-10.83	-7.58	-7.20
EBITDA	-5.87	-11.56	-16.16	-17.28	-11.99	-2.81
Underlying EBIT	-5.88	-11.56	-16.17	-17.29	-12.01	-2.83
Reported EBIT	-6.99	-12.08	-16.98	-18.14	-12.90	-3.76
Underlying PBT	-5.95	-11.64	-16.30	-17.20	-11.99	-2.87
Statutory PBT	-7.06	-12.16	-16.91	-18.05	-12.89	-3.80
Underlying EPS (p)	-12.48	-17.05	-25.68	-22.27	-15.51	-0.83
Statutory EPS (p)	-15.02	-18.04	-26.78	-23.65	-16.96	-2.36
Net (debt)/cash	26.88	16.37	17.28	2.47	-7.79	-11.57
Capital increases	24.52	0.05	13.40	0.00	0.00	0.00

Source: Hardman & Co Life Sciences Research

Chronocort Phase III study in CAH

The news regarding the outcome from its European Phase III study with Chronocort in patients affected by congenital adrenal hyperplasia (CAH) was not what DNL, nor the market, had been anticipating. The primary objective was to demonstrate that Chronocort was superior to standard therapy, which was not met. This was a surprise, given the data from the European Phase II study that *did* show superiority of Chronocort over standard-of-care, which was published in The Journal of Clinical Endocrinology & Metabolism[1]. Further analysis of the data also revealed important differences between the Chronocort and the control arms. In addition, interim data analysis of the open-label extension study has indicated safety over a period of 12 months as well as a sustained benefit from Chronocort treatment. DNL will now await full analysis of the data set. In the meantime, DNL will seek advice from the EMA before the end of 2018, and following its recommendations, intends to submit a Marketing Authorisation Application for Chronocort in Europe in 4Q'19, together with an application for Orphan Drug Designation for the treatment of CAH. In the US, the company has put on 'hold' the US Phase III The market reacted sharply to the news, with the share price correcting by 62% on the day, from 106.5p to 40p.

Phase III study

Rationale

CAH is an inherited disorder due to enzymatic defects in the biosynthetic pathway of cortisol. Nearly 95% of CAH cases are due to an enzyme (21-hydroxylase) deficiency that converts the hormone 17-hydroxyprogesterone (17-OHP) into a precursor of cortisol. The lack of function of the enzyme results in a build-up of 17-OHP in the blood, used as the biomarker, and a deficiency of cortisol. An increase in the level of androgens is associated with increased mortality, infertility and severe developmental defects. Even with standard treatment, patients remain at risk of death through an adrenal crisis.

Phase III trial

The Phase III clinical trial, recorded under the code number NCT02716818 on the ClinicalTrials.gov website, enrolled 122 CAH patients in Europe. It assessed the safety, tolerability and clinical benefit of Chronocort, taken twice daily following a "toothbrush" regimen, compared with three standard glucocorticoid therapies:

- hydrocortisone only;
- prednisone or prednisolone, alone or in combination with hydrocortisone; and
- dexamethasone alone or in combination with any other glucocorticoid.

Treatment was randomised, and followed by a six-month evaluation period, with two key objectives:

Objectives	
Primary	Change from baseline in 17-OHP (time frame: 24 weeks)
Secondary	Change from baseline in A4 (time frame: 24 weeks) Incidence of treatment-emergent adverse event (safety and tolerability) Use and reasons for use of rescue medication (time frame: 24 weeks)

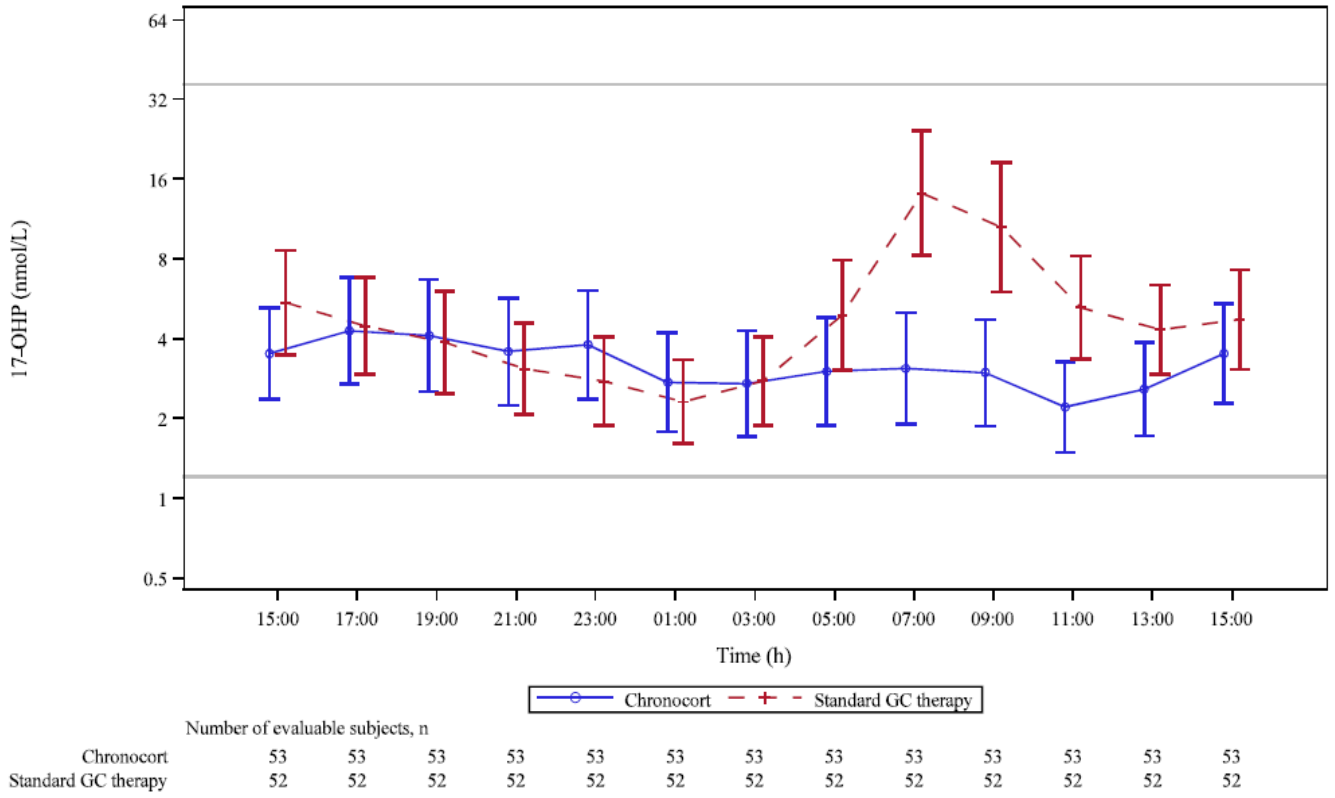
Source: ClinicalTrials.gov website

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.

Results

The following graph shows the average level of the biomarker 17-OHP in the plasma in patients, following the standard therapy (red line) and Chronocort (blue line) over a period of 24 hours. The aim is to have a stable and controlled level of the biomarker within the optimal range, without any build-up of the androgen due to cortisol deficiency.

Phase III: 17-OHP level over 24-hours period: Chronocort vs. standard therapies



Number of evaluable subjects, n													
Chronocort	53	53	53	53	53	53	53	53	53	53	53	53	53
Standard GC therapy	52	52	52	52	52	52	52	52	52	52	52	52	52

17-OHP = 17-hydroxyprogesterone; CI = Confidence interval; GC = Glucocorticoid.
Y-axis is presented on a logarithmic scale.
The grey horizontal lines show the optimal range.

Source: Diurnal

The graph indicates that Chronocort has a strong effect in stabilising the level of 17-OHP, with a consistent value of around 4nmol/L for the whole 24-hour period, and within the optimal range. However, it also shows that the patients receiving one of the three standard treatments also had good control of androgen levels within the optimal range, despite a peak in the 17-OHP value in the early morning at around 16nmol/L, four times higher than the level with Chronocort. It is worth pointing out that differences between the two groups have been 'minimised' by plotting the data on a logarithmic scale on the Y axis. On a linear scale, the amplitude of this morning peak would have been far more pronounced.

This is actually one of the strengths of Chronocort – to be able to control androgen levels during the night and early in the morning – that cannot be obtained with standard therapies. In addition, the company commented that:

- Chronocort achieved the androgen control at a lower dose compared to the standard treatments;
- Chronocort was well tolerated and provided the natural overnight cortisol release;

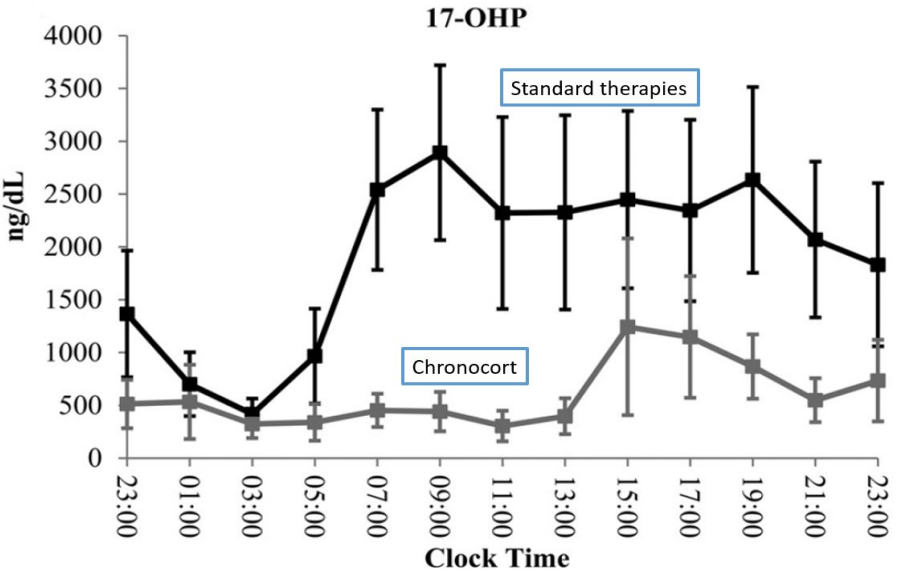
- Chronocort was able to eliminate the early-morning peak of androgen seen using conventional therapies; and
- Chronocort has fewer patients requiring rescue therapies.

In addition, initial data from the ongoing open-label Phase III extension study have indicated that Chronocort has a sustainable safety and benefit record for a period of at least 12 months.

Historical Phase II data

The Phase II data in the 16 CAH patients showed a better disease control with Chronocort, with 94% of the value in the optimal range and a median value of 17-OHP of 5.65nmol/L. This compares with 31% before the Chronocort therapy at a median value of 17-OHP of 70nmol/L. While results from the Chronocort arm are very similar in the two studies, patients receiving the standard regimen in the Phase II study were less well controlled compared with data seen in the Phase III study.

Phase II: 17-OHP level over 24h period: Chronocort vs standard therapies



NB: Y axis units different from Phase III data, with 1nmol/L = 33.05ng/dL
Source: Mallappa et al. J Clin Endocrinol Metab, 2015, 100(3), 1137-1145.

Comparison of the Phase II and Phase III data

Apart from being undertaken in different patients at different times, making a direct comparison between the Phase II and Phase III data is difficult for the following reasons:

- The two graphs showing the results did not start at the same time point (15:00hrs for the Phase III data and 23:00hrs for the Phase II data).
- The units for levels of 17-OHP plotted on the two graphs are different (nmol/L for the Phase III data and ng/dL for the Phase II data).
- The 17-OHP Phase III data have been plotted and presented using a logarithmic scale compared with a linear scale for the Phase II data.

Consequently, we decided to re-plot all the Phase II and Phase III data in a single graph (see page 5), using the same units on a linear scale and starting at the same time point, in order to see how the two sets of results compared.

Standard-of-care data

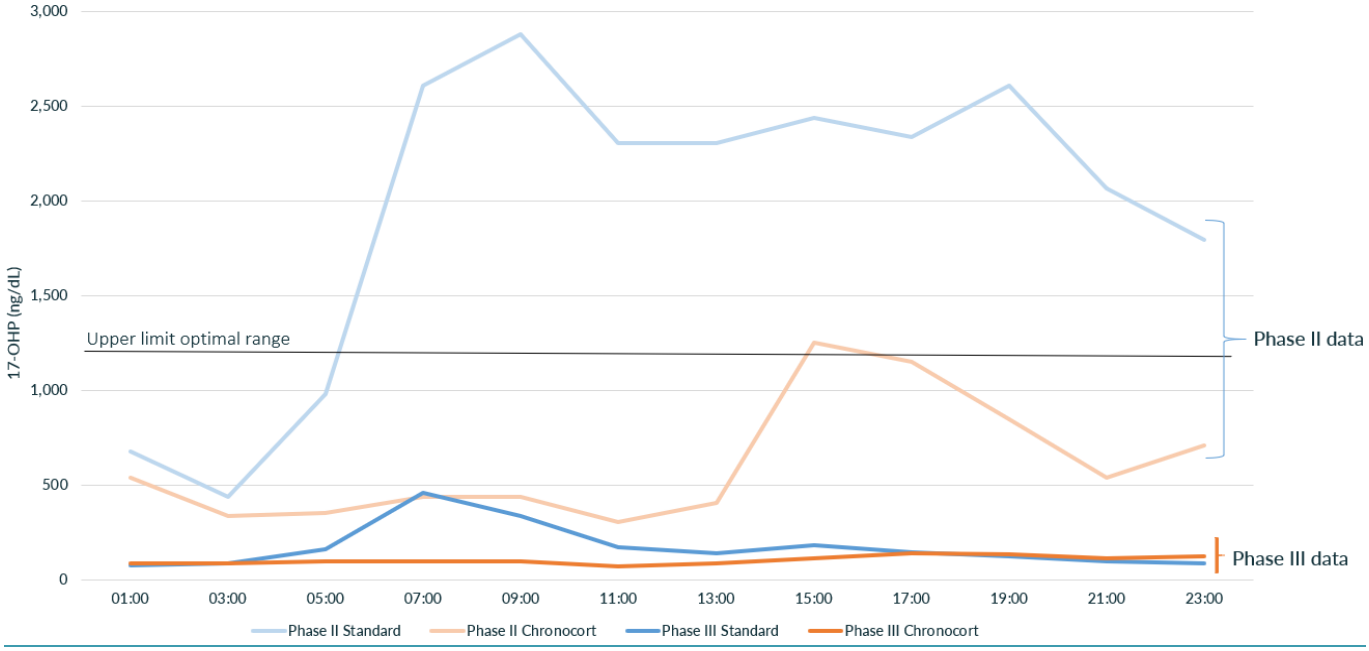
Patients treated with standard therapy are represented by the blue lines. The biomarker concentration in the Phase III data is dramatically different between the two studies, such that in the Phase II study, the level of 17-OHP appears to be poorly controlled (well above the optimal range upper limit), whereas in the Phase III data, it appears to be well controlled. For some unknown reason, the level of the biomarker in the Phase III trial is between one-fifth (at 3:00hrs) and one-twentieth (17:00-23:00hrs) in all the patients, compared with the level seen in the Phase II trial. Interestingly, the profile of the lines is similar, with peaks occurring between 6:00hrs and 8:00hrs.

Chronocort data

Patients treated with Chronocort are represented by the orange lines. The level of biomarker observed throughout the 24-hour period was within the optimal range in both studies (apart from a single point (15:00hrs) in the Phase II study)). Again, the profiles of the two lines are similar, and the levels of the biomarker in the Phase III trial were one-quarter to one-tenth lower than those seen in the Phase II trial.

There is nothing to suggest that Chronocort did not work – only that is was not superior to standard therapy in the Phase III study.

Phase II vs. Phase III: 17-OHP level



Note: values in the graph are approximated
Source: Hardman and Co Life Sciences Research

Next steps

Only a short time has passed since DNL received and announced these results and, although an analysis of the full data set is a top priority, this will take a few months to complete. Meanwhile, the company will continue to assess interim data from the long-term Chronocort study, which will provide additional information to determine whether the effect can be maintained and whether there will be additional clinical benefits. With all this in hand, DNL intends to seek advice with the European regulator before end 2018 and, following the outcome, anticipates submitting a Marketing Authorisation Application in 4Q'19 in Europe for Chronocort, together with an application for Orphan Drug Designation for the treatment of CAH. The outcome of the EMA meeting will also be critical for the future of its US Phase III trial, which has officially been put on 'hold'.

We emphasise that, readers should bear in mind that Chronocort did not fail, it simply did not meet the 'superiority' end-point stipulated in the trial protocol. Indeed, Chronocort generated a very consistent androgen level over the 24-hour test period, and this had less variance to the level seen in patients on current standard-of-care. And also, this result has no implication or impact on the commercial roll-out marketed paediatric product Alkindi across Europe.

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